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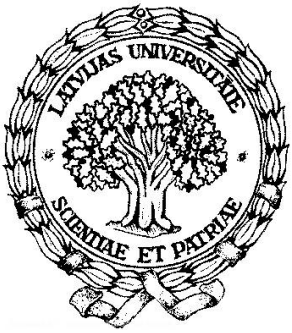

Edgars Paegle

KONDENSĒTI SELENOFĒNI: STRATĒĢIJA UN PERSPEKTĪVAS

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Rīga, 2018

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3) *Dr. habil. chem*. Andris Zicmanis, LU.

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ANOTĀCIJA

Kondensēti selenofēni: stratēģija un perspektīvas. Paegle E., zinātniskais vadītājs Dr. ķīm. Arsenjans P. Promocijas darbs, 83 lappuses, 42 attēli, 40 literatūras avoti. Latviešu un angļu valodā.

Darbā ir veikta aril(hetaril)alkīnu ciklizēšnas reakcijas selēnbromēšanas apstākļos pielietojamības robežu paplašināšana, izmantojot alkēna piedevu. Alkēna piedevas klātienē būtiski samazinās vai pilnīgi tiek novērsta blakusreakcija, kas saistīta ar izejvielas trīskāršās saites bromēšanos, kā rezultātā aril(hetaril)alkīnu selēnbromēšana ir kļuvusi par efektīvu metodi plaša spektra 3-brombenz[*b*]selenofēna atvasinājumu iegūšanai, kā arī pirmo reizi metode ir pielietojama selenofēntiofēna atvasinājumu iegūšanai. Ir pētīts diarilalkīnu selēnbromēšanas mehānisms, sniedzot padziļinātu izpratni par ciklizēšanās procesa norisi un reģioselektivitātes avotu nesimetrisku substrātu reakcijās. Uzlabotā arilalkīnu selēnbromēšanas metode ir izmantota kā atslēgas stadija raloksifēna (selektīvs estrogēna receptoru modulators) selēna analogu sintēzei, kā arī kombinācijā ar skābes inducētu 3,2-arilgrupas migrāciju iegūta rinda dabisku polifenola antioksidantu inspirētu benz[*b*]selenofēna atvasinājumu.

SELĒNS, BENZ[b]SELENOFĒNS, SELENOFĒNTIOFĒNS, SELĒNBROMĒŠANA, RALOKSIFĒNS.

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IEVADS

200 gadu ir pagājuši kopš zviedru ķīmiķis Jenss Jākobs Bercēliuss (Jöns Jacob Berzelius) 1818. gādā atklāja ķīmisko elementu selēnu. Pirmais iespaids par šo elementu nebija pievilcīgs, jo bija zināms, ka tas spēj izraisīt dažādas veselības problēmas, kā arī tika novēroti toksiski efekti pētījumos ar dzīvniekiem[1]. Neskatoties uz to, interese par selēna bioķīmisko nozīmi sāka palielināties 20. gs. 50-ajos gados, kad novēroja, ka daži baktēriju paveidi vairojās ātrāk ar selēnu bagātinātā vidē[1a]. Nozīmīgākais sasniegums, kas ļāva noskaidrot selēna bioķīmisko nozīmi zīdītāju organismos, tika paveikts 1973. gadā, kad izdevās atklāt selēncisteīna (Sec) klātbūtni antioksidanta enzīma glutationa peroksidāzes (GPx) aktīvajā centrā[1a]. Mūsdienās cilvēku organismā ir atklāti vismaz 25 selēnu saturoši proteīni, bet darbības mehānisms ir noskaidrots tikai dažiem no tiem[2]. Neskaitot plaši pazīstamo GPx, ir atklātas arī citas svarīgas prokariotu organismos neaizstājamas selēnenzīmu klases; to skaitā jodtironīna dejodināzes (Ids), tioredoksīna reduktāzes (TrxRs), selēnfosfāta sintāze un selēnproteīns P[1a].

Lai gan selēnu saturoši savienojumi lielā mērā savu ķīmisko un fizikālo īpašību ziņā ir ļoti līdzīgi attiecīgajiem sēra analogiem, kopumā red/oks potenciāli selēna savienojumiem ir zemāki nekā atbilstošajiem sēra savienojumu pārstāvjiem, kas noved pie selēna savienojumu paaugstinātas reaģētspējas salīdzinājumā ar sēra savienojumiem[1a]. Šī varētu būt nozīmīgākā atšķirība starp sēra un selēna analogiem savienojumiem, kā rezultātā selēns, pretēji sēram, organismā spēj darboties kā mikroelements. Faktiski vairāku pētījumu rezultāti ir apstiprinājuši, ka nepietiekams selēna daudzums ikdienas diētā var novest pie dažādu nevēlamu saslimšanu parādīšanos, tajā skaitā vēža, diabēta, sirds saslimšanām un ar īmūnsistēmas darbību saistītiem traucējumiem[2].

Gan dabiskus, gan sintētiski iegūtus selēna atvasinājumus, balstoties uz to darbības lomu organismā, varētu iedalīt trīs lielās grupās:

1) Selēna savienojumi, kuri spēj metabolizēties līdz ūdeņraža selenīdam (HSe^-), tādējādi kalpojot par selēna avotu, kas var tikt iesaistīts selēnproteīnu sintēzē;
2) Selēnenzīmu mimētiķi;
3) Selēnu saturoši savienojumi, kuriem piemīt bioloģiska aktivitāte, bet tā nav tieši saistīta ar selēnu.

Pirmājā grupā ietilpst, piemēram, selenīts (SeO_3^{2-}), selenāts (SeO_4^{2-}) un Sec. Interesanti, ka Sec netiek tieši iekļauts proteīnu biosintēzē, lai gan tā ir galvenā selēna forma selēnproteīnu aktīvajos centros. Vispirms Sec tiek

metabolizēts līdz ūdeņraža selenīdam (HSe^-), un tikai pēc tam tas piedalās ģenētiski iekodētā selēnproteīnu sintēzē, kas to padara par patiesu 21. neaizstājamo aminoskābi[2]. Turpretī otras grupas pārstāvji ir tieši atbildīgi par konkrētajam selēnenzīmam līdzīgu aktivitāti. Labākie sasniegumi šo savienojumu vidū ir sasniegti GPx mimētiķu saimē (*Ebselen* ir visplašāk pazīstamais piemērs)[3], tomēr sasniegumu citu selēnenzīmu mimētiķu meklējumos praktiski nav.

Šīs disertācijas kontekstā 3. savienojumu grupa ieņem vislielāko nozīmi, jo pastāv ļoti maza iespēja, ka benz[*b*]selenofēna atvasinājumi varētu tikt metabolizēti līdz ūdeņraža selenīdam, kā arī tieši darboties kā GPx mimētiķi. Lai gan benz[*b*]selenofēna heterocikliskā sistēma līdz šim nav atrasta dabas savienojumu sastāvā, tas tiek uzskatīts par naftalīna, benz[*b*]furāna, benz[*b*]tiofēna un indola bioizostēru[4]. Pētījumi ir parādījuši, ka milfasartāna (milfasartan) un eprosartāna (eprosartan) (savienojumi, kas tiek izmantoti asins spiediena pazemināšanai) benz[*b*]selenofēna analogi ir efektīvi AT_1 receptoru antagonisti, un selēna analogi uzrāda augstāku aktivitāti nekā attiecīgie benz[*b*]tiofēna atvasinājumi[5]. Arī mūsu pašu pētījumi par 2,3-aizvietotu benz[*b*]selenofēna atvasinājumu sintēzi un bioloģisko aktivitāti ir parādījuši, ka šiem savienojumiem piemīt vidējs vai vājš citotoksiskais efekts uz normālām šūnām, neizraisot izmaiņas šūnu morfoloģijā[6]. Tā rezultātā jau zināmu preparātu selēna analogu sintēzi, kā arī jaunas bioloģiskās aktivitātes meklējumus benz[*b*]selenofēna atvasinājumu rindā esam izraudzījušies kā ļoti perspektīvu pētījumu virzienu.

Tādēļ par pētījuma galveno **mērķi** tika izvirzīta pieejamo metožu loka paplašināšana nepieciešamās struktūras benz[*b*]selenofēna atvasinājumu sintēzei, kā arī pētījumā izstrādātās metodes pielietot izvirzīto mērķu sasniegšanai medicīnas ķīmijā.

Lai sasniegtu mērķi, tika izvirzīti sekojoši **uzdevumi**:

1) Uzlabot jau zināmo arilalkīnu ciklizēšanas metodi selēnbromēšanas apstākļos, lai paplašinātu 3-brombenz[*b*]selenofēna atvasinājumu sintēzei pieejamo substrātu loku, kā arī piemērot metodi selenofēntiofēnu iegūšanai.
2) Veikt selēnbromēšanas mehānisma pētījumus, lai noteiktu reģioselektivitātes avotu nesimetrisku diaril(hetaril)alkīnu ciklizēšanā un veicinātu dziļāku izpratni par substrātu noteiktu struktūras elementu ietekmi uz reakciju iznākumu.

3) Iegūt raloksifēna (selektīvs estrogēna receptoru modulators) selēna analogu, lai novērotu, kādu efektu uz savienojumu bioloģisko aktivitāti atstāj sēra atoma aizvietošana pret selēnu.
4) Polihidroksi benz[*b*]selenofēna atvasinājumu kā potenciālu antioksidantu un pretvēža aģentu sintēze.

Pētījuma zinātniskā novitāte:

- Ir izstrādāta aril(hetaril)alkīnu ciklizēšanas metode reakcijās ar *in situ* iegūtu $SeBr_4$. Alkēna piedevas kā broma "savācēja" izmantošana ļauj viegli iegūt funkcionalizētus benz[*b*]selenofēna un selenofēntiofēna atvasinājumus no komerciāli pieejamām vai viegli sintezējamām izejvielām. Reakcijas norisinās atvērtā atmosfērā, neizmantojot mitruma jutīgus reaģentus, sausus šķīdinātājus vai inertu atmosfēru. Reakcijas mehānisma pētījumi apstiprina, ka ciklizēšanās sākas ar reģioselektīvu *anti* 1,2-pievienošanos selēnbromēšanas stadijā un noslēdzas ar sekojošu elektrofīlu aizvietošanos aromātiskajā gredzenā.
- Selēna dibromīda reakcijas ar 1-(aril(tienil)etīnil)pirolidīn-2-ona atvasinājumiem sniedz alternatīvu sintētisko ceļu jauna tipa hipervalentu 10-Se-3 sistēmas cviterjonu iegūšanai.
- Uzlabotā arilalkīnu ciklizēšanas metode selēnbromēšanas reakcijās ir izmantota kā atslēgas stadija raloksifēna (selektīvs estrogēna receptoru modulators, kas tiek izmantots sieviešu osteoporozes ārstēšanai postmenopauzes periodā un krūts vēža rašanās riska mazināšanai) selēna analogu sintēzei. Tādējādi sēra atoma aizvietošana ar selēnu ievērojami paaugstina savienojuma citotoksisko efektu uz dažādām vēža šūnu līnijām, tai pat laikā uzrādot zemāku bazālo toksicitāti nekā oriģinālā zāļu viela.
- Uzlabotā arilalkīnu ciklizēšana kombinācijā ar skābes inducētu 3,2-arilgrupas migrāciju tika izmantota kā vispārēja metode polihidroksi 2- un 3-arilbenz[*b*]selenofēna atvasinājumu iegūšanai, izmantojot kopīgas izejvielas. Ir pētītas iegūto savienojumu red/oks īpašības, brīvo radikāļu savākšanas spēja un citotoksicitāte uz dažādām vēža šūnu līnijām. Iegūtie rezultāti ir izmantoti struktūras – aktivitātes likumsakarību (SAR) noteikšanai, kā rezultātā ir noteikti struktūras elementi, kas nodrošina augsto peroksilradikāļu savākšanas spēju.

PUBLIKĀCIJU SARAKSTS

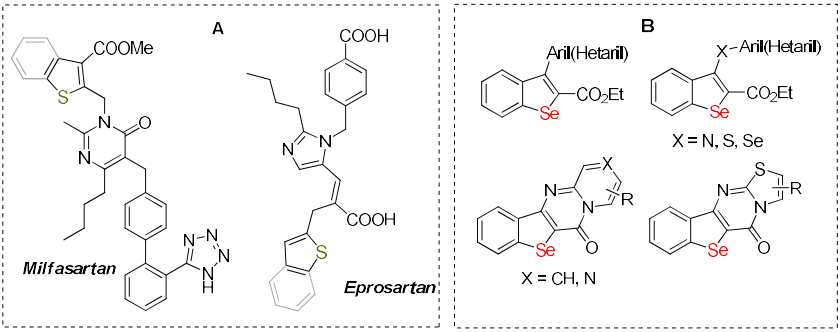
Sintēzes metožu izstrāde un pielietojums ir pilnībā publicēti 5 zinātniskajos rakstos, tādēļ promocijas darbs noformēts kā publikāciju kopa:

1) Paegle, E.; Domracheva, I.; Turovska, B.; Petrova, M.; Kanepe-Lapsa, I.; Gulbe, A.; Liepinsh, E.; Arsenyan, P. "Natural-Antioxidant-Inspired Benzo[*b*]selenophenes: Synthesis, Redox Properties, and Antiproliferative Activity" *Chem. Asian J*. **2016**, *11*, 1929-1938.
2) Paegle, E.; Belyakov, S.; Petrova, M.; Liepinsh, E.; Arsenyan, P. "Cyclization of Diaryl(hetaryl)alkynes under Selenobromination Conditions: Regioselectivity and Mechanistic Studies" *Eur. J. Org. Chem*. **2015**, *20*, 4389-4399.
3) Paegle, E.; Belyakov, S.; Kirsch, G.; Arsenyan, P. "Addition of selenium(II) bromide to arylalkynylamides – a route to hypervalent T-shaped 10–Se–3 systems" *Tetrahedron Lett*. **2015**, *56*, 4554-4557.
4) Arsenyan, P.; Paegle, E.; Domracheva, I.; Gulbe, A.; Kanepe-Lapsa, I.; Shestakova, I. "Selenium analogues of raloxifene as promising antiproliferative agents in treatment of breast cancer" *Eur. J. Med. Chem.* **2014**, *87*, 471-483.
5) Paegle, E.; Belyakov, S.; Arsenyan, P. "An Approach to the Selenobromination of Aryl(thienyl)alkynes: Access to 3-Bromobenzo[*b*]selenophenes and Selenophenothiophenes" *Eur. J. Org. Chem*. **2014**, *18*, 3831-3840.

1. NODAĻA. PĒTĪJUMA KONCEPCIJA

1.1. Pamatojums benz[*b*]selenofēna heterocikliskās sistēmas iekļaušanai bioloģiski aktīvu savienojumu struktūrās

Pēdējā laikā paaugstināta interese par benz[*b*]selenofēniem tiek izrādīta gan medicīnas ķīmijā[5,6], gan materiālzinātnē[7-9]. Lai gan benz[*b*]selenofēna heterocikliskā sistēma līdz šim nav atrasta dabas savienojumu sastāvā, benz[*b*]selenofēns tiek uzskatīts par naftalīna, benz[*b*]furāna, benz[*b*]tiofēna un indola bioizostēru.[4] Pētījumi ir parādījuši, ka milfasartāna (*milfasartan*) un eprosartāna (*eprosartan*) (savienojumi, kas tiek izmantoti asinsspiediena pazemināšanai; 1.1. attēls, **A**) benz[*b*]selenofēna analogi ir lieliski AT_1 receptoru antagonisti, turklāt selēna analogi ir aktīvāki par attiecīgajiem benz[*b*]tiofēna atvasinājumiem.[5] Arī mūsu pašu pētījumi par 2,3-aizvietotu benz[*b*]selenofēna atvasinājumu sintēzi un bioloģisko aktivitāti ir parādījuši, ka šie savienojumi ir vidēji vai vāji citotoksiski uz normālām šūnām, neizraisot izmaiņas šūnu morfoloģijā (1.1. attēls, **B**).[6]

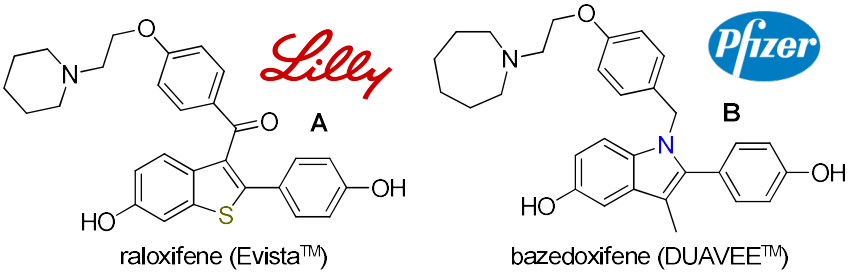


1.1. attēls. **Milfasartāna (*milfasartan*) un eprosartāna (*eprosartan*) molekulārās struktūras (A) un 2,3-aizvietoti benz[*b*]selenofēni (B)**.

Benz[*b*]selenofēna atvasinājumu zemā citotoksicitāte[6] un to bioizostēriskums attiecībā pret saviem sēra analogiem[5] ir pamudinājis mūs pievērsties jau zināmu preparātu selēna analogu sintēzei, lai novērotu, kādu efektu sniedz šāda sēra aizvietošana pret selēnu uz savienojumu bioloģisko aktivitāti.

1.2. Izaicinājumi raloksifēna selēna analoga sintēzes stratēģijā

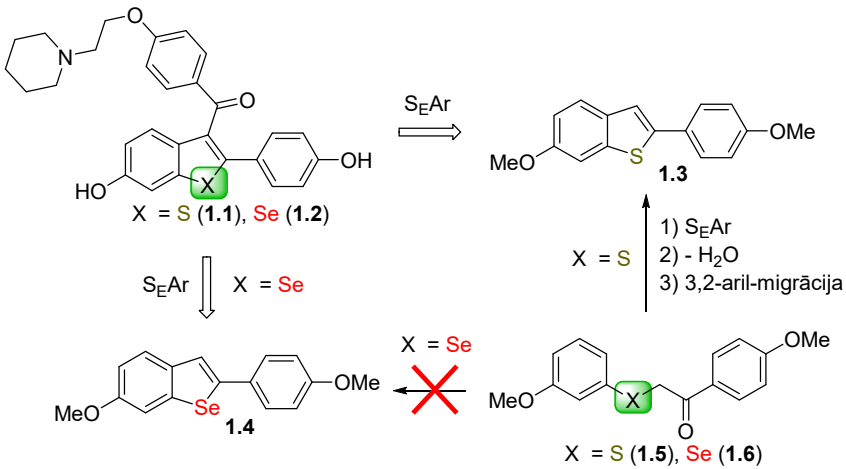
Viena no farmaceitisko vielu saimēm, kuru struktūra ir balstīta uz benz[*b*]tiofēna vai indola heterocikliskās sistēmas un plaši tiek izrakstīta pacientiem, ir selektīvi estrogēna receptoru modulatori (SERMs)[10] (1.2. attēls). Šīs zāles pārsvarā tiek izmantotas sieviešu osteoporozes ārstēšanai postmenopauzes periodā, krūts vēža rašanās riska samazināšanai, kā arī citu ar menopauzi saistītu simptomu ārstēšanai. Saistībā ar to, ka benz[*b*]selenofēns un tā sēra analogs ir līdzīgi fizikālo īpašību (šķīdība, polaritāte, telpiskais novietojums utt.) ziņā, varētu prognozēt, ka sintezētie selēna analogi saglabātu oriģinālās zāļvielas SERM aktivitāti. Tomēr nelielas atšķirības šo struktūru noteiktās īpašībās, tādās kā pazemināts selenofēna gredzena aromātiskums salīdzinājumā ar tiofēnu, kā rezultātā savienojumi varētu vieglāk oksidēties un piedalīties arī citās ķīmiskās pārvērtībās, potenciāli varētu novest pie būtiskām izmaiņām bioloģiskajā aktivitātē. Tādēļ mēs fokusējām savu uzmanību uz raloksifēna selēna analoga sintēzi (1.2. attēls, **A**).



1.2. attēls. **Benz[*b*]tiofēna un indola heterocikliskās sistēmas saturošu SERMs molekulārās struktūras**.

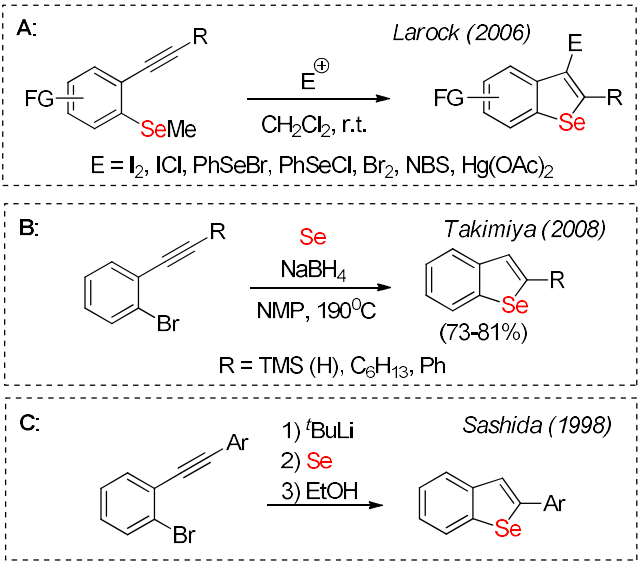
Aplūkojot raloksifēna **1.1** sintēzes metodes, vistiešākais ceļš uz atslēgas intermediāta **1.3** iegūšanu ir tioetanona atvasinājuma **1.5** ciklizēšana skābā vidē (1.3. attēls)[11]. Šis ciklizēšanās process sevī ietver skābes katalizētu elektrofīlu aizvietošanos aromātiskā gredzenā (S_EAr), tiofēna gredzena aromatizāciju pēc ūdens molekulas atšķelšanas un sekojošu skābes inducētu 3,2-arilgrupas migrāciju, iegūstot 2-arilbenz[*b*]tiofēna atvasinājumu **1.3**. Diemžēl selēna analoga **1.6** gadījumā šāda stratēģija nav piemērota, jo eksperimentu rezultātā noskaidrojām, ka izejviela **1.6** skābā vidē, kas ir nepieciešama S_EAr stadijas

norisei, pilnībā sadalās, šķeļoties Se–C(sp^3) saitei. Tā rezultātā bija nepieciešams meklēt citas alternatīvas savienojuma **1.4** vai tā ekvivalenta iegūšanai.



1.3. attēls. **Raloksifēna sintēzes stratēģija**.

Visproduktīvākās pieejas 3-neaizvietotu vai 2-aril-3-halogēnbenz[*b*]selenofēnu sintēzei ir Laroka[12] (*Larock*) 1-(1-alkīnil)-2-(alkilselēn)arēnu elektrofīlā ciklizēšana (1.4. attēls, **A**), Takimijas[13] (*Takimiya*) *o*-halogēnarilalkīnu reakcijas ar *in situ* iegūtu nātrija selēnīdu (1.4. attēls, **B**) un Sašidas[14] (*Sashida*) arillitija savienojumu ciklizēšana reakcijās ar elementāru selēnu (1.4. attēls, **C**). Laroka elektrofīlā ciklizēšana norisinās ļoti maigos apstākļos, reģiospecifiski un ar augstu produkta iznākumu, bet ar selenofēnu kondensētā benzola gredzena aizvietotāju diverifikācija ir vai nu ķēpīgs, vai arī finansiāli neizdevīgs process, jo nepieciešamo *o*-jodanilīnu iegūšna ir ļoti sarežģīta vai arī tie ir ļoti dārgi. Līdzīgi trūkumi piemīt arī Takimijas un Sašidas metodēm, bet papildus iepriekš minētajiem trūkumiem Takimijas ciklizācijas tiek veiktas ļoti augstās temperatūrās, savukārt Sašidas reakcijām gluži pretēji ir nepieciešama zemas temperatūras kontrole, tiek izmantoti viegli uzliesmojoši un mitruma jutīgi litija organiskie reaģenti, sausi šķīdinātāji un inerta atmosfēra.

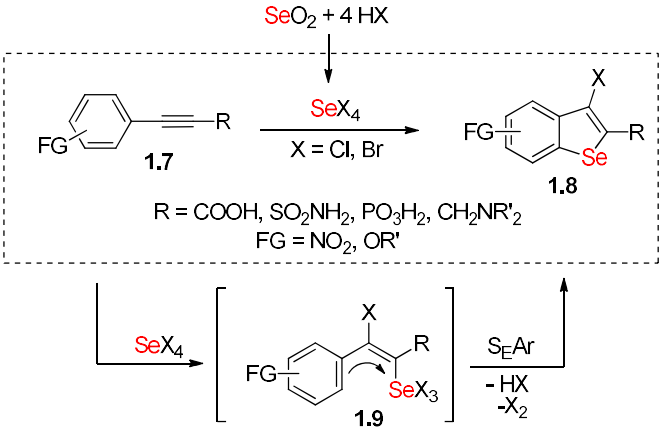


1.4. attēls. **Visplašāk izmantotās metodes 2-arilbenz[*b*]selenofēna atvasinājumu sintēzei**.

1.3. Arilalkīnu selēnbromēšana kā piemērota atslēgas stadija raloksifēna selēna analogu sintēzē

Bez iepriekš minētajām metodēm (1.4. attēls), 3-halogēnbenz[*b*]selenofēni **1.8** ir iegūstami arī, ciklizējot arilalkīnus **1.7** selēnbromēšanas apstākļos (1.5. attēls). Benz[*b*]selenofēna atvasinājumu sintēzes vēsture selēna halogenīdu reakcijās ar fenilacetilēna atvasinājumiem ilgst no pirmās publikācijas[15] 1963. Gadā līdz pēdējai 1998. Gadā. Tomēr sākotnējie pētījumi[15-18] šajā pētījumu laukā nespēja radīt efektīvas metodes vēlamo produktu iegūšanai, jo to iznākumi (balstoties uz izmantotā arilalkīna daudzumu) pat visveiksmīgākajos piemēros nepārsniedza 40 %. Vērā ņemams progress tika sasniegts, ieviešot selēnbromēšanu divfāžu (fāžu pārneses) apstākļos[19], kur tiek izmantots izejvielas arilalkīna šķīdums organiskajā fāzē (parasti dietilētera vai dioksāna šķīdums) un SeX_4 (X = Cl vai Br) ūdens šķīdums, kas viegli tiek pagatavots no selēna dioksīda un attiecīgās halogēnūdeņražskābes (HCl vai HBr). Tā rezultātā ir publicēti vēl daži raksti[20-24], lai parādītu metodes pielietojamības robežas.

Lai gan divfāžu metode ir ievērojami efektīvāka par iepriekš izmantoto „vienfāzes" pieeju, tomēr šīs stratēģijas limitējošais faktors ir nepieciešamība izmantot tikai substrātus ar elektroniem nabadzīgām trīskāršajām saitēm. Tādēļ efektīva ciklizācija ir izdevusies tikai ar fenil- un naftilpropiolskābēm[19-21], fenilpropiolskābes amīdu[22] un sulfonamīdu[19], feniletīnilfosfonskābi[23] un fenilpropargilamīniem[24]. Lai gan iepriekš literatūrā[15-24] tas nav bijis minēts, mūsu pašu pētījumi noveda pie secinājuma, ka elektroniem bagātu trīskāršo saišu izmantošana cieta neveiksmi tādēļ, ka reakcijas pirmajā stadijā selēnhalogenēšanas vietā norisinājās konkurējoša halogenēšanās, tādējādi „saindējot" izejvielu (1.5. attēls).

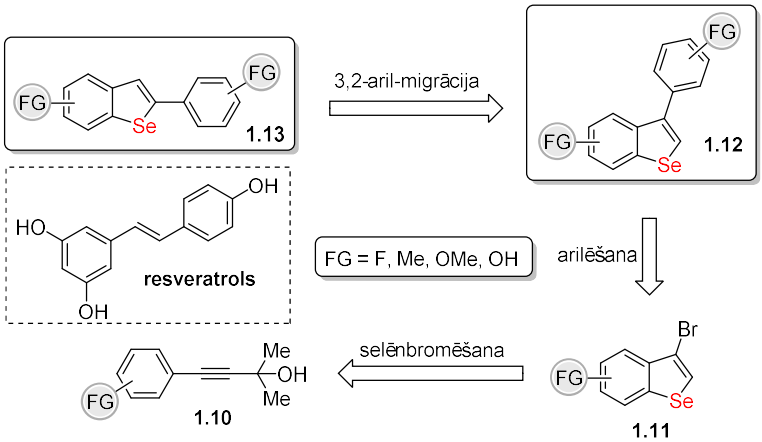


1.5. attēls. **3-Halogēnbenz[*b*]selenofēna atvasinājumu sintēze, izmantojot arilalkīnu selēnhalogenēšanu**.

Saistībā ar to, ka dažādi fenilacetilēna atvasinājumi ir komerciāli pieejami vai viegli iegūstami no attiecīgajiem arilhalogenīdiem (pseidohalogenīdiem) un terminālajiem alkīniem, mēs bijām motivēti šīs metodes tālākai attīstīšanai. Tā kā attiecīgie broma atvasinājumi ir plašāk pielietojami tālākai modificēšanai dažādās pārejas metālu katalizētu reakcijās, tad savu uzmanību esam koncentrējuši uz selēnbromēšanu (1.5. attēls, X = Br).

1.4. Dabisku polifenolu inspirētu benz[*b*]selenofēna atvasinājumu konstruēšana

Mūsdienās ir novērojama pieaugoša interese par antioksidantiem. Jo īpaši būtu jāizceļ dabiskiem polifenoliem līdzīgi savienojumi, un resveratrols ir iespējams visvairāk pētītais šīs antioksidantu saimes pārstāvis (1.6. attēls).[25] Mūsu pētījumu turpinājumā esam centušies vienā struktūrā apvienot polifenolu[26-28] un selēna[29-31] spēju aizsargāt pret saslimšanu ar vēzi ar to oksidatīvā stresa modulēšanas aktivitāti karcinoģenēzes procesā. Tā kā Se-raloksifēna **1.2** pamatstruktūra ietver abus minētos struktūras elementus, tad radās motivācija pētīt, kā hidroksilgrupu skaits un novietojums ietekmē sintezēto polihidroksibenz[*b*]selenofēna atvasinājumu citotoksicitāti un radikāļu ķeršanas aktivitāti.



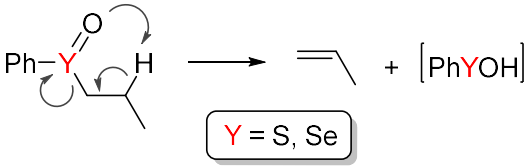
1.6. attēls. **Sintēzes stratēģija dabisku polifenolu inspirētu polihidroksibenz[*b*]selenofēna atvasinājumu iegūšanai**.

Nepieciešamo polihidroksibenz[*b*]selenofēna atvasinājumu **1.12** un **1.13** konstruēšanai kā atslēgas stadijas izvēlējāmies izmantot uzlabotās arilalkīnu ciklizēšanas selēnbromēšanas apstākļos un skābes inducētas 3,2-arilgrupas migrācijas kombināciju, kas ļautu iegūt vēlamos produktus no vienām izejvielām.

1.5. Atšķirības starp sēra un selēna savienojumu ķīmiskajām īpašībām[1b]

Autori *Hans J. Reich* un *Robert J. Hondal* 2016. gadā ir publicējuši apskata rakstu[1b], cenšoties atbildēt uz jautājumu, kāpēc daba ir izvēlējusies selēnu? Savā ziņā tas sasaucas ar jautājumu, kāpēc mēs esam izvēlējušies sintezēt benz[*b*]tiofēna selēna analogus. Minētais apskata raksts sniedz plašu ieskatu līdz šim atklātajā selēna lomā bioloģiskajos procesos, koncentrējoties uz atšķirībām no sava tuvākā radinieka – sēra. Šajā promocijas darba sadaļā tiks sniegta tikai būtiskākā informācija par atšķirībām šo elementu un to atvasinājumu starpā, tāpēc detalizētākas informācijas iegūšanai rekomendēju iepazīties ar iepriekš minēto rakstu.

Sēram un selēnam piemīt ļoti līdzīgas ķīmiskās un fizikālās īpašības, raugoties no dažādiem aspektiem. Tiem ir kopīgas visas oksidācijas pakāpes, kā arī funkcionālo grupu tipi. Analoģisku savienojumu struktūras ir tik līdzīgas, ka šie savienojumi daudzos gadījumos viegli kokristalizējas. Vairākas no būtiskākajām atšķirībām sēra un selēna ķīmiskajās īpašībās ir saistītas ar vispārzināmām likumsakarībām, kas iezīmējas pārejā no vieglākiem uz smagākiem elementiem. Smagāki elementi parasti ir vieglāk polarizējami, kas parasti noved pie ātrākām gan elektrofīlās, gan nukleofīlās aizvietošanās reakcijām. Lielākā daļa saišu ar selēnu stipruma ziņā ir vājākas nekā attiecīgās saites ar sēru, kā rezultātā pie selēna vieglāk norisinās saites šķelšanās reakcijas. Tas nozīmē, ka Se–X saites σ* orbitāle ir zemākas enerģijas nekā attiecīgā S–X saites σ* orbitāle, kā rezultātā Se–X saite ir efektīvāks elektronu akceptors. Tādējādi selēns visās savās oksidācijas pakāpēs ir elektrofīlāks par sēra analogiem. Piemēram, visplašāk zināmā selēna reakcija organiskajā sintēzē ir selēna oksīda eliminēšana, veidojot alkēnus (1.7. attēls). Selēna gadījumā eliminēšanās notiek aptuveni 100 000 reižu ātrāk nekā analoga sēra oksīda atšķelšana.



1.7. attēls. **Selēna oksīda eliminēšana, veidojot alkēnus**.

Ir zināma arī vispārēja likumsakarība, ka smagākiem elementiem parasti ir mazāk stabilas augstas osidācijas pakāpes formas, un šāda parādība ir spēkā arī selēna un sēra gadījumā. Selēns kā smagāks elements ir vairāk tolerants arī pret hipervalentiem saišu stāvokļiem. Viens no nedaudzajiem piemēriem, kad Se–X saites ir spēcīgākas nekā attiecīgās S–X saites, ir šo elementu hipervalenti savienojumi. Piemēram, selēnāni (R_4Se) veidojas daudz vieglāk nekā sulfurāni (R_4S), un tie ir daudz stabilāki. Analoģiska relatīvā stabilitāte ir vērojama arī āta kompleksos R_3Se^- un R_3S^-.

Aciditāte. Lielāks atoma izmērs un līdz ar to vājāka saite ar ūdeņradi, kā arī lielāka polarizējamība noved pie selenolāta anjona vājāka bāziskuma salīdzinājumā ar attiecīgu tiolātu, pK_a vērtībām atšķiroties pat par 3-4 vienībām. Tādējādi selēncisteīns neitrālā pH ir praktiski pilnīgi jonizēts, kamēr cisteīns pastāv praktiski tikai tiola formā. Tā kā selenolāti ir mazāk bāziski par tiolātiem, tad parasti selenolāti ir arī labākas aizejošās grupas.

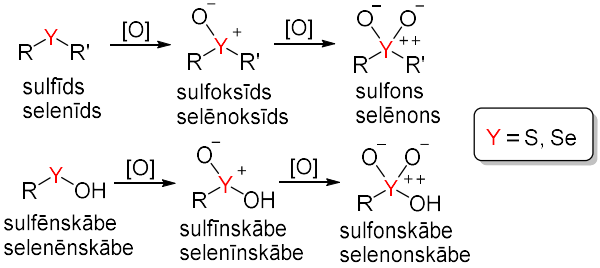
Nukleofilitāte. Pretstatā vājākam bāziskumam, selenolāta anjoni ir aptuveni par kārtu aktīvāki nukleofīli par attiecīgajiem tiolāta anjoniem. To skaidro ar selēna lielāku polarizējamību. Ieguldījumu selenolāta anjona pastiprinātā nukleofilitātē protiskos šķīdinātājos sniedz arī vājākas ūdeņraža saišu akceptora īpašības salīdzinājumā ar to sēra analogiem. Vislielākā atšķirība selēna un sēra nukleofilitātē novērojama fizioloģiska pH robežās, kad selenoli pretēji tioliem ir praktiski pilnīgi jonizēti.

Elektrofilitāte. Selēna lielāka tolerance pret hipervalentiem stāvokļiem atstāj nozīmīgu iespadu uz selēna elektrofilitāti, jo nukleofīls uzbrukums selēnam parasti norisinās, veidojot hipervalentus starpsavienojumus (R_4Se vai R_3Se^-). Tādēļ šāda tipa reakcijas ar selēnu norisinās daudz straujāk nekā ar sēru, un visu tipu selēna savienojumi ir labāki elektrofīli nekā attiecīgie sēra analogi.

Vājas π-saites. Selēnam salīdzinājumā ar sēru ir lielāks atoma rādiuss un līdz ar to lielākas hibridizētās orbitāles. Kombinācijā ar lielākiem saišu garumiem tas izraisa vājāku π-saišu veidošanos. Piemēram, šāda selēna īpašība izraisa selēnesteru ievērojami zemāku stabilitāti par attiecīgajiem tioesteriem, jo selēna rezonanse ar karbonilgrupu ir apgrūtināta. Tādējādi selēnesterus var izmantot kā efektīvus acilgrupas pārneses aģentus.

Red/oks ķīmija. Vislielākā atšķirība starp sēru un selēnu novērojama tieši abu elementu oksidēšanās un reducēšanās procesos, un atšķirības ir būtiskas gan viena, gan divu elektronu pārneses procesos. Lai gan labākas

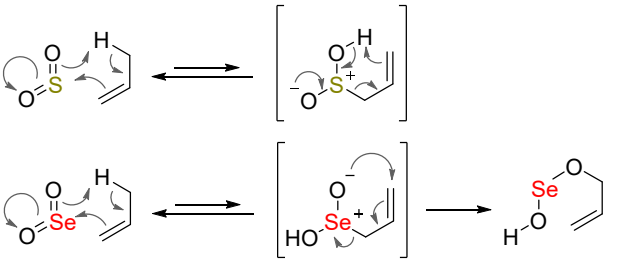
uztveramības dēļ halkogēna-skābekļa saites bieži vien tiek attēlotas kā dubultsaites, sevišķi selēna gadījumā, korektāk būtu izmantot vienkāršu σ-saiti ar daļlādiņiem uz atomu centriem, jo vājās π-saišu veidošanas spējas dēļ Y–O saites ir ļoti polarizētas (1.8. attēls). Iespējams tādēļ, ka skābekļa atoma nedalītā elektronu pāra atgriezensikās saites veidošana ar akceptora orbitāli (σ* vai d orbitāles) uz selēna ir mazāk efektīva nekā sēra gadījumā, Y–O datīvās saites selēnoksīdos, selenonos, selenīnskābēs un selenonskābēs ir vājākas un vairāk polarizētas nekā attiecīgajos sēra analogos. Šīs atšķirības parādās daudzos aspektos, ja salīdzina sēra un selēna ķīmiskās īpašības. Piemēram, alkilselenoni ir lieliski alkilēšanas aģenti, bet sulfoniem šāda reaģētspēja praktiski nepiemīt. Turklāt dimetilselēnoksīds ir ievērojami bāziskāks par dimetilsulfoksīdu. Tādējādi skābes katalizētā reakcijā selēnoksīda gadījumā aktīvās protonētās formas koncentrācija ir aptuveni 10^4 reizes lielāka nekā sulfoksīda gadījumā. Tā kā selēns pats par sevi jau ir elektrofīlāks par sēru Se–O saites palielinātas polarizācijas dēļ, tad šādas papildu aktivācijas rezultātā selēna elektrofilitātes pārākums pār sēru pieaug vēl dramatiskāk. Arī selēnoksīdu racemizācija norisinās daudzkārt ātrāk nekā tas notiek ar sulfoksīdiem, un racemizācijas mehānisms abos gadījumos ir atšķirīgs.



1.8. attēls. **Sēra un selēna atvasinājumi dažādās oksidācijas pakāpēs**.

Bieži sastopams efekts, salīdzinot vieglākus elementus ar smagākiem, ir smagāko elementu lielāka tieksme pēc pastāvēšanas zemākā oksidācijas pakāpē, un selēns šajā ziņā nav izņēmums. Piemēram, selēnoksīdi spēj oksidēt sulfīdus par sulfoksīdiem. Atšķiras arī sēra dioksīda (SO_2) un selēna dioksīda (SeO_2) īpašības. SO_2 tiek uzskatīts par maigu reducētāju, turpretī SeO_2 – par maigu oksidētāju (*Riley* oksidēšana). Abi savienojumi reaģē ar alkēniem, veidojot attiecīgos alilsulfīnskābes un alilselenīnskābes intermediātus (1.9.

attēls). Tomēr SO_2 gadījumā notiek atgriezeniska reakcija, kā rezultātā eliminējas SO_2 un no jauna veidojas alkēns, sēram saglabājot savu augstāko oksidācijas pakāpi. Savukārt selenīnskābes intermediāts iesaistās [2,3]sigmatropā pārgrupēšanās reakcijā, veidojot divalenta selēna esteri, kas ļoti ātri hidrolizējas par alilspirtu.



1.9. attēls. **Sēra dioksīda (SO_2) un selēna dioksīda (SeO_2) reakcijas ar alkēniem**.

Atšķirības sēra un selēna oksīdu elektroniskajās struktūrās izraisa arī būtiskas atšķirības šo savienojumu oksidēšanas un reducēšanas reakciju ātrumos. Lai gan pirmais oksidēšanas solis no sulfīda/selenīda par sulfoksīdu/selēnoksīdu ātruma ziņā ir ļoti līdzīgs, nedaudz ātrāk reakcijai notiekot ar selēnu, būtiska atšķirība parādās otrajā oksidēšanas stadijā, kur selēnona veidošanās notiek daudz grūtāk nekā attiecīgā sulfona. Tas lielā mērā saistīts ar Se–O saites lielāku polarizāciju un selēna nedalītā elektronu pāra mazāku nukleofilitāti. Salīdzinot tiolu un selenolu oksidēšanās ātrumu par attiecīgajiem disulfīdiem un diselenīdiem, jāsecina, ka diselenīdu veidošanās notiek daudz ātrāk. Kopumā tiolu un selenolu oksidēšanās procesiem raksturīgas iepriekš apskatīto sulfīdu un selēnīdu oksidēšanās reakcijām piemītošās likumsakarības. Runājot par viena elektrona oksidēšanās procesiem, svarīgi pieminēt, ka selenilradikāļi ir ievērojami stabilāki par tiilradikāļiem.

Kopsavilkums. Apkopojot šajā nodaļā izklāstīto informāciju, var secināt, ka praktiski visas selēna atvasinājumu reakcijas notiek ātrāk nekā ar attiecīgajiem sēra analogiem. Apskata raksta autori secina, ka šādu novērojumu dēļ ir vilinoši teikt, ka daba ir izvēlējusies selēnu sēra vietā, jo selēna paaugstinātā aktivitāte dažādās ķīmiskās reakcijās ļauj paātrināt enzimātiskus procesus. Tomēr autoru patiesā atbilde uz jautājumu, kāpēc daba ir izvēlējusies selēnu, balstās uz selēna spēju apgriezeniski mijiedarboties ar skābekļa

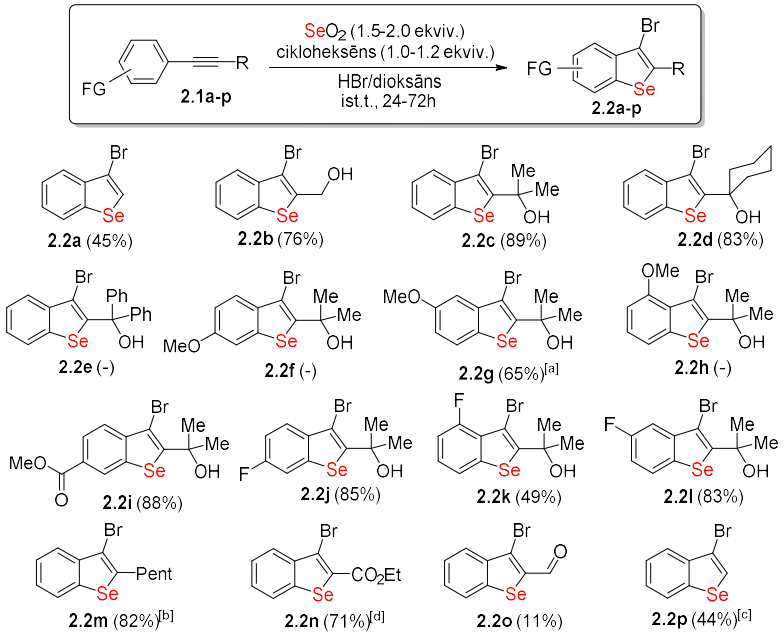
aktīvajām formām (SAF). Gan sērs, gan selēns ir efektīvi nukleofīli, kas reakcijās ar SAF divu elektronu pārneses procesos oksidējas. Sēra un selēna oksīdu ievērojami atšķirīgo elektronisko struktūru dēļ dramatiski atšķiras to ķīmiskās īpašības. Tā rezultātā selēna oksīdi daudz vieglāk spēj atgūt reducēto formu. Parādību, ka selēns spēj viegli oksidēties un viegli reducēties atpakaļ izejas stāvoklī, mēdz saukt par „selēna paradoksu". Turklāt selenilradikāļa ievērojami augstākā stabilitāte salīdzinājumā ar tiilradikāļa stabilitāti nodrošina selēnu saturošiem proteīniem paaugstinātu noturību viena elektrona oksidētāju klātienē.

2. NODAĻA. PĒTĪJUMA REZULTĀTU KOPSAVILKUMS

2.1. Aril(hetaril)alkīnu selēnbromēšana

Kā jau tika minēts 1.3. apakšnodaļā, nozīmīgākais limitējošais faktors arilalkīnu selēnbromēšanas izmantošanai benz[*b*]selenofēna atvasinājumu sintēzē ir izejvielas trīskāršās saites bromēšana, kas konkurē ar vēlamo selēnbromēšanu. Šāda blakus reakcija ne tikai samazina produktu iznākumu, bet arī rada grūti atdalāmus piemaisījumus, no kuriem atbrīvoties ir sarežģīti pat tad, ja to saturs ir relatīvi niecīgs. Tā kā tika pieņemts, ka izejvielas trīskāršās saites „saindēšanās" notiek reakcijā ar molekulāro bromu, kas izdalās ciklizēšanās procesā (1.5. attēls), mēs uzsākām selektīva broma ķērāja meklējumus. Veiksmīgā kārtā vienkāršas alkēna piedevas izmantošana izrādījās pietiekami efektīva, lai būtiski paplašinātu izmantojamo substrātu loku 3-brombenz[*b*]selenofēna atvasinājumu sintēzei (2.1. attēls)[32].

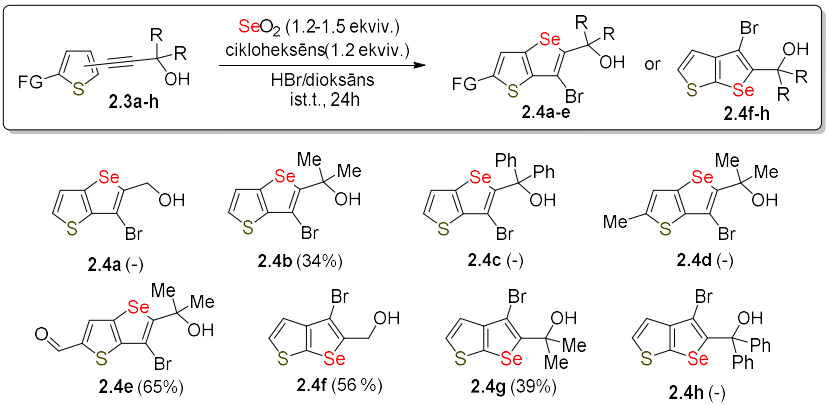
Ir svarīgi pieminēt to, ka bez alkēna piedevas izmantošanas visos 2.1. attēlā parādītajos piemēros kā piemaisījumi lielākā vai mazākā mērā veidojas attiecīgie trīskāršās saites bromēšanas produkti, bet, pateicoties alkēna piedevas izmantošanai, daudzos gadījumos tie praktiski nav detektējami. Ļoti tīri reakcijas norisinās ar benzola gredzenā neaizvietotiem substrātiem **2.1a-d**,**m**,**n**, kā rezultātā attiecīgie ciklizēšanās produkti **2.2a-d**,**m**,**n** ir iegūti ar ļoti labiem iznākumiem. Lieliski rezultāti ir iegūti arī *p*-elektronakceptorās grupas saturošā **2.1i** un fluoraizvietoto **2.1j-l** ciklizēšanā, kur ļoti nozīmīgs faktors ir *m*-fluoraizvietotā atvasinājuma **2.1l** pilnīgi reģioselektīvā ciklizēšanās. Neskatoties uz to, ka iepriekš minētajos piemēros ir sasniegts būtisks progress salīdzinājumā ar selēnbromēšanu bez alkēna piedevas, *o*- un *p*-elektrondonoru aizvietotāju klātesamība substrātu benzola gredzenos pat alkēna klātbūtnē neļauj novērst trīskāršās saites bromēšanu. Tādējādi substrātu **2.1f**,**h** gadījumos blakusreakcija kļūst par galveno reakciju. Savukārt *m*-metoksiatvasinājums **2.1g** neveido attiecīgo dibromatvasinājumu, bet ciklizējas ar nepilnīgu reģioselektivitāti (aptuveni 90 %) S_EAr stadijā.



2.1. attēls. **Arilalkīnu selēnbromēšana alkēna piedevas klātienē**. [a] Produkts iegūts ar 10 % attiecīgā 7-metoksiatvasinājuma piemaisījumu. [b] Kā alkēna piedeva izmantots cikloheks-2-ēnons. [c] Savienojumā **1.1p** R = TMS; izmantoti 2.0 ekvivalenti selēna dioksīda un 2.0 ekvivalenti cikloheks-2-ēnona, un pilnīga desililēšana panākta, izmantojot 0.5 ekvivalentus TBAF.

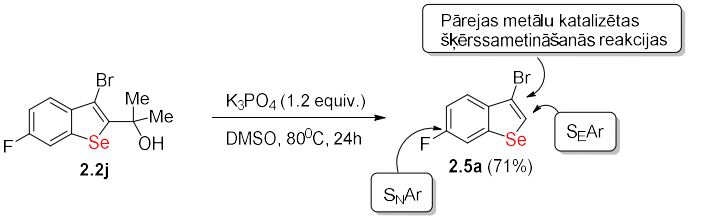
Ar mērķi iegūt attiecīgos selenofēn[3,2-*b*]tiofēna **2.4a-e** un selenofēn[2,3-*b*]tiofēna atvasinājumus **2.4f-h**, līdzīgus apstākļus piemērojām tienilalkīnu **2.3a-h** ciklizēšanai (2.2. attēls)[32]. Diemžēl 6-bromselenofēn[3,2-*b*]tiofēna atvasinājumu rindā vienīgais tīras reakcijas un preparatīva iznākuma piemērs ir formilatvasinājuma **2.3e** ciklizēšana, bet 4-bromselenofēn[2,3-*b*]tiofēnus **2.4f**,**g** izdevās iegūt ar viduvējiem iznākumiem. Zemāki iznākumi salīdzinājumā ar radniecīgajiem benzola analogiem (2.1. attēls) rodas papildus blakus reakcijas dēļ. Tā ir daļēja tiofēna gredzena *α*-pozīcijas bromēšana, kas nopietni apgrūtina ciklizēšanās produktu attīrīšanu. Šādu apsvērumu dēļ efektīvas selenofēntiofēnu sintēzes panākšanai tienilalkīnu selēnbromēšanas

apstākļos ir absolūti nepieciešama tiofēna gredzenu *α*-pozīcijas „aizsargāšana" ar elektronakceptoru aizvietotāju.



2.2. attēls. **Tienilalkīnu selēnbromēšana alkēna piedevas klātienē**.

Propān-2-ola atvasinājumi **2.2j-l** ir ļoti daudzpusīgi mazi „būvbloki" sarežģītākas struktūras benz[*b*]selenofēna atvasinājumu sintēzei. Piemēram, deacetonējot **2.2j**, iegūst 3-brom-6-fluorbenz[*b*]selenofēnu (**2.5a**) (2.3. attēls)[32]. Savienojumam **2.5** ir iespējams plašs tālāko pārvērtību spektrs, jo C–Br saite ir izmantojama dažādās pārejas metālu katalizētās reakcijās, C–2 pozīcija ir aktīva elektrofīlai aizvietošanai, un ir labi zināms, ka fluora atoms ir ļoti laba aizejošā grupa nukleofīlai aizvietošanai aromātiskā gredzenā, kas ļautu ciklizēšanās procesā „aizliegtās" pozīcijās ieviest elektrondonorus aizvietotājus (piemēram, alkoksigrupas). Visas minētās pārvērtības ir demonstrētas praksē, sintezējot „apgrieztos" raloksifēna selēna analogus (skat. 2.5. apakšnodaļu) un dabisku polifenolu inspirētos benz[*b*]selenofēnus (skat. 2.6. apakšnodaļu).



2.3. attēls. **Plaši pielietojama maza būvbloka 3-brom-6-fluorbenz[*b*]selenofēna (2.5) sintēze**.

2.2. Diaril(hetaril)alkīnu selēnbromēšana

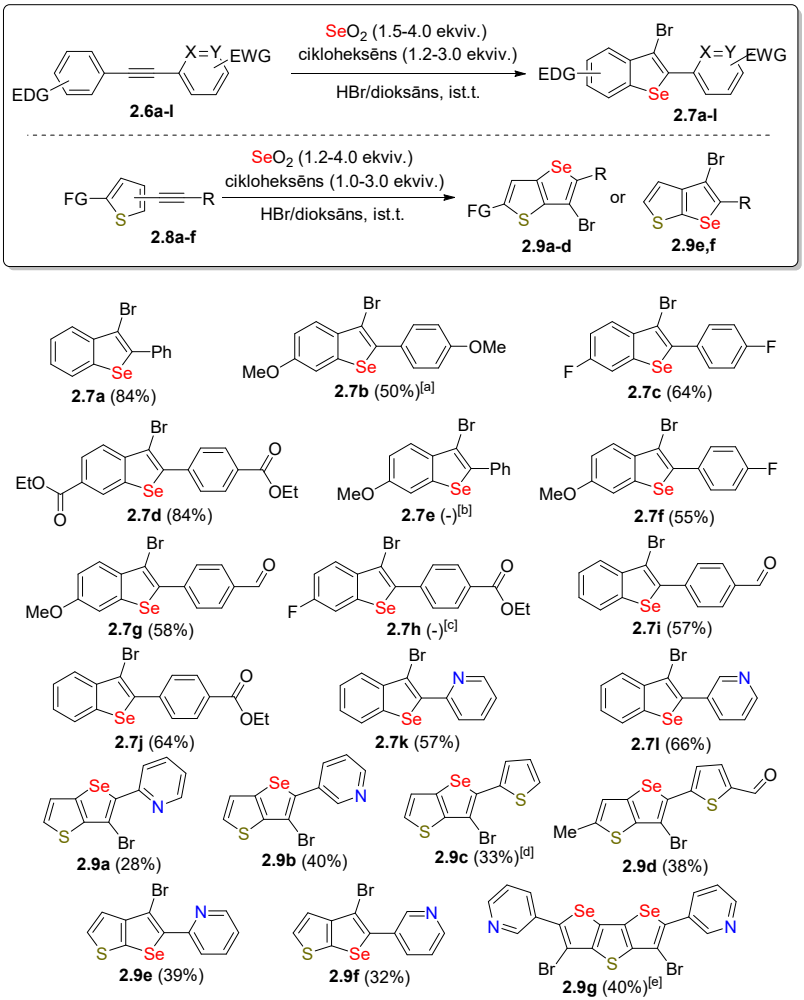
Izstrādātā aril(tienil)alkīnu ciklizēšanas metode[32] (skat. 2.1. apakšnodaļu) tālāk tika izmantota diaril(hetaril)alkīnu ciklizēšanai (2.4. attēls)[33], un tā ir arī atslēgas stadija raloksifēna selēna analoga sintēzei (skat. 2.5. apakšnodaļu). Tā rezultātā ieguvām dažādus gan jaunus, gan iepriekš zināmus 2-aril-3-brombenz[*b*]selenofēna un selenofēntiofēna atvasinājumus.

Sekmīga ciklizēšanās norisinās ne tikai simetrisku substrātu **2.6a-d** gadījumos, bet arī nesimetriskie substrāti reģioselektīvi ciklizējas, veidojot attiecīgos kondensētos selenofēnus (2.4. attēls). Tomēr reakciju reģioselektivitāti stipri ietekmē aromātisko gredzenu elektroniskās īpašības, t.i., stiprāk polarizēta trīskāršā saite veicina augstāku reģioselektivitāti. Tādējādi izriet sekojoša likumsakarība: selenofēna gredzena veidošanās notiek pie elektroniem bagātākā aromātiskā gredzena. Elektrondonori aizvietotāji un/vai stipri polarizēta trīskāršā saite izraisa pastiprinātu izejvielas bromēšanu, bet selēna tetrabromīda pārākuma izmantošana kombinācijā ar alkēna piedevu spēj būtiski samazināt blakusreakcijas īpatsvaru. Šajā kontekstā svarīgi ir atzīmēt elektroniem bagāto diarilalkīnu **2.6b**, kura sekmīga ciklizēšana ļāva iegūt attiecīgo raloksifēna selēna analoga sintēzes atslēgas intermediātu **2.7b**.

Ļoti atšķirīgi uzvedas stipru elektronakceptoru aizvietotāju saturoši substrāti, piemēram, diarilalkīns **2.6d**, kurš ciklizējas ļoti tīri pat bez alkēna piedevas. Gluži pretēji, alkīna **2.6d** reakcija ar selēna tetrabromīdu cikloheksēna klātienē praktiski nenotiek, jo selēna tetrabromīds ātrāk bromē cikloheksēnu, nekā pievienojas izejvielas trīskāršajai saitei.

Lai panāktu pilnīgu reģioselektivitāti nesimetrisko diarilalkīna atvasinājumu gadījumā, nepietiek tikai ar spēcīgu *p*-elektronu donoru vai elektronu akceptoru vienā no aromātiskajiem gredzeniem. Lai gan alkīnu **2.6i**,**j** ciklizēšana nenotiek absolūti reģioselektīvi, pārākumā esošos reģioizomērus **2.7i**,**j** var samērā vienkārši attīrīt un izdalīt ar viduvējiem iznākumiem. Diemžēl vienu elektrondonoru saturošā substrāta **2.6e** ciklizēšanā papildus nepilnīgajai reģioselektivitātei rodas arī trīskāršās saites bromēšanas produkti, kā rezultātā tīru produktu **2.7e** izdalīt nebija iespējams. Tomēr pat salīdzinoši vāji induktīvi elektronakceptora fluora atoma ievadīšana otrā aromātiskajā gredzenā (savienojums **2.6f**) ļauj sasniegt pilnīgu reģioselektivitāti un attiecīgo ciklizēšanās produktu izdalīt ar 55 % iznākumu.

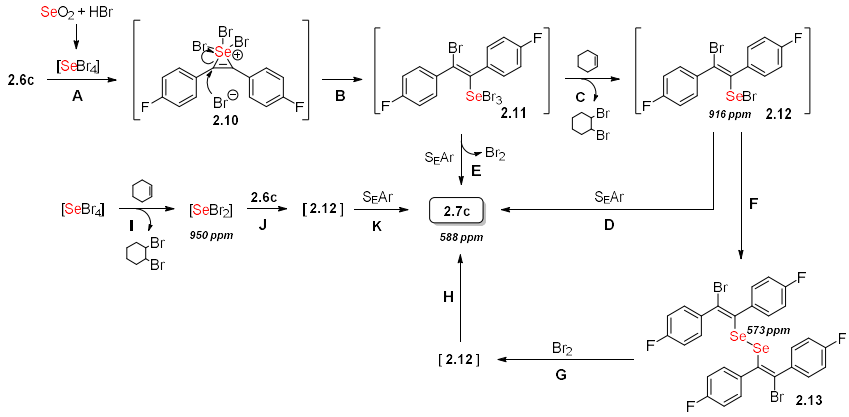
Arī feniletīnil- un tieniletīnilpiridīna atvasinājumu **2.6k**,**l** un **2.8a**,**b**,**e**,**f** ciklizēšanās norisinās pilnīgi reģioselektivi, veidojot benz[*b*]selenofēnus **2.7k**,**l** un selenofēntiofēna atvasinājumus **2.9a**,**b**,**e**,**f**. Nozīmīgs sasniegums ir bis-ciklizēšanas piemērs **2.9g**.



2.4. attēls. **Diaril(hetaril)alkīnu ciklizēšana selēnbromēšanas apstākļos**.
[a] Izmantota Et_3N (4.0 ekviv.) piedeva. [b] Tika iegūts neatdalāmu produktu maisījums. [c] Iegūts divu neatdalāmu reģioizomēru maisījums. [d] Cikloheksēna vietā izmantots cikloheks-2-ēnons (1.5 ekviv.) Et_3N (1.0 ekviv.) piedevas klātienē. [e] Kā izejviela izmantots 2,5-bis(pirid-3-iletīnil)tiofēns.

2.3. Arilalkīnu selēnbromēšanas mehānisma pētījumi

Difluoraizvietotā diarilalkīna **2.6c** neparasti lēnā reakcija deva lielisku iespēju pētīt pakāpenski notiekošo ciklizēšanās procesu (2.5. attēls)[33]. Fluora atomu klātiene izejvielā **2.6c**, starpsavienojumā **2.12** un produktā **2.7c** ļāva tieši novērot reakcijas norisi ūdeni saturošā dioksānā, izmantojot ^{19}F KMR spektroskopiju. Veicot **2.6c** ciklizāciju bez alkēna piedevas, reakcija beidzas jau 24 h laikā, un kā produktus iegūst benz[*b*]selenofēnu **2.7c** un attiecīgo trīskāršās saites bromēšanas aduktu. Tādējādi mums neizdevās detektēt nevienu starpsavienojumu. Tomēr, reakcijai izmantojot 2.0 ekviv. SeO_2 un 1.0 ekviv. Cikloheksēna, ciklizācijas process ievērojami palēninājās.



2.5. attēls. **Savienojuma 2.6c iespējamais ciklizēšanās mehānisms**.

Šādā veidā noskaidrojām, ka pēc 24 h maisīšanas istabas temperatūrā rekacijas maisījums satur praktiski tikai starpsavienojumu **2.12** (apstiprināts ar ^{1}H, ^{13}C, ^{19}F un ^{77}Se KMR spektroskopijas datiem; 2.5. attēls). Balstoties uz *Poleschner* un *Seppelt*[34] pētījumiem, ir pamatots iemesls apgalvot, ka selēna tetrabromīda pievienošanās izejvielas **2.6c** trīskāršajai saitei norisinās caur selēnirēnija tipa katjonu intermediātu **2.10** (2.5. attēls, **A**, **B**), savukārt vinilselenilbromīda starpsavienojuma **2.12** veidošanās varētu būt izskaidojama ar sekojošu broma pārnesi no **2.11** uz cikloheksēnu (2.5. attēls, **C**). Noslēgumā starpsavienojums **2.12** lēnām ciklizējas, veidojot vēlamo produktu **2.7c**, kas norisinās pēc elektrofīlas aizvietošanas aromātiskā gredzenā mehānisma (2.5. attēls, **D**).

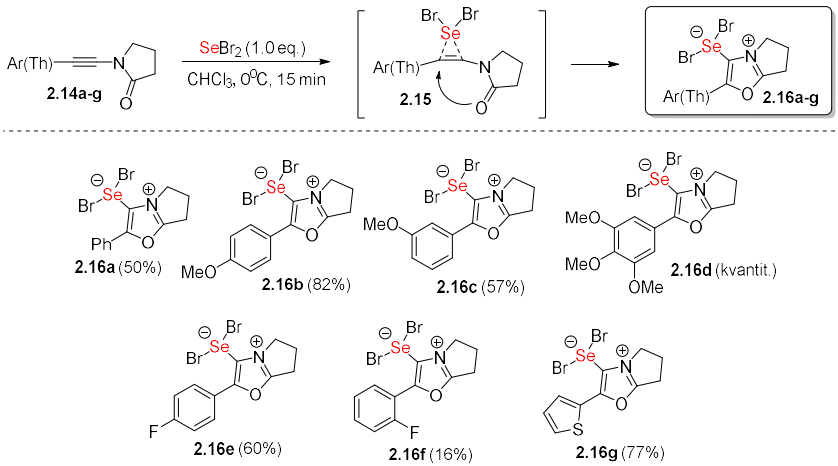
Apstrādājot reakcijas maisījumu ar piesātinātu nātrija hlorīda ūdens šķīdumu un etilacetātu pēc 24 h maisīšanas, kā galveno reakcijas produktu ar 42 % iznākumu izdalīja diselenīdu **2.13** (2.5. attēls, **F**). Acīmredzami šādos apstākļos starpsavienojums **2.12** disproporcionējas, kā rezultātā veidojas Se–Se saite. Tā kā diselenīds **2.13** tika izdalīts kā tīrs *E*,*E*-stereoizomērs (apstiprināts, izmantojot monokristālu rentgendifraktometriju), ir iegūts neapgāžams pierādījums stereospecifiskai *anti* 1,2-pievienošanai selēnbromēšanas stadijā (2.5. attēls, **A**, **B**). Papildus pierādījumi starpsavienojuma **2.12** eksistencei tika iegūti, oksidatīvi pievienojot 1.0 ekviv. Br_2 diselenīda **2.13** dioksāna šķīdumam (2.5. attēls, **G**). Mazāk nekā stundas laikā diselenīds **2.13** pārvērtās vinilselenilbromīdā **2.12**, un atkal novēroja lēnu **2.12** ciklizēšanos, veidojot produktu **2.7c** (2.5. attēls, **H**).

Ievērojamā ciklizācijas reakcijas ātruma atšķirība (24 h vai 72 h) atkarībā no tā, vai alkēna piedevu izmanto vai nē, varētu būt izskaidrojama ar elektrofīlāka Se^{IV} starpsavienojuma **2.11** piedalīšanos S_EAr stadijā, ja alkēns netiek izmantots (2.5. attēls, **E**). Tā kā $SeBr_4$ var tieši reaģēt arī ar alkēna piedevu, bromējot tā dubultsaiti (2.5. attēls, **I**), $SeBr_2$ klātieni reakcijas maisījumā nevajadzētu kategoriski izslēgt. Saistībā ar to, ka 3-brom-2-fenilbenz[*b*]selenofēna sintēzes piemērs $SeBr_2$ reakcijā ar difeniletīnu ir demonstrēts jau iepriekš[35], tad daļēja šāda reakcijas norises ceļa (2.5. attēls, **J**, **K**) iespējamība kopējā ciklizēšanās procesā ir izvērtējama.

2.4. 1-(Aril(tienil)etīnil)pirolidīn-2-onu reakcijas ar $SeBr_2$[36]

Lai gan alkīnilamīdu **2.14a-g** reakcijās ar $SeBr_2$ benz[*b*]selenofēni neveidojas, šīs disertācijas tēmas kontekstā tika iegūta ļoti vērtīga informācija. Papildus tam, ka negaidīti tika atrasts alternatīvs paņēmiens jauna tipa hipervalentu T-veida 10-Se-3 sistēmu **2.16** iegūšanai (2.6. attēls), iegūtos savienojumus **2.16a-g** varētu uzskatīt arī par „notvertiem" intermediāta **2.12** (2.5. attēls) analogiem. Savienojumu **2.16a-g** struktūra parāda, ka vispirms $SeBr_2$ selēna atoms mijiedarbojas ar attiecīgās izejvielas **2.14** trīskāršo saiti, visdrīzāk veidojot selēnirēna tipa starpsavienojumu **2.15**, un sekojošs iekšēja skābekļa nukleofīla uzbrukums broma anjona vietā noved pie cviterjonu **2.16** izgulsnēšanos. Visticamāk, savienojumos **2.16** selēns nav pietiekami elektrofīls, lai iesaistītos elektrofīlā aizvietošanā aromātiskā gredzenā, kā rezultātā neveidojas benz[*b*]selenofēna heterocikliskā sistēma. Hipervalenta selēna eksistence savienojumu **2.16** struktūrās ir apstiprināta gan kristāliskā stāvoklī,

gan šķīdumā, izmantojot monokristālu rentgendifraktometrijas un ^{77}Se KMR spektroskopijas datus.



2.6. attēls. **Alkīnilamīdu 2.14a-g reakcijas ar $SeBr_2$.**

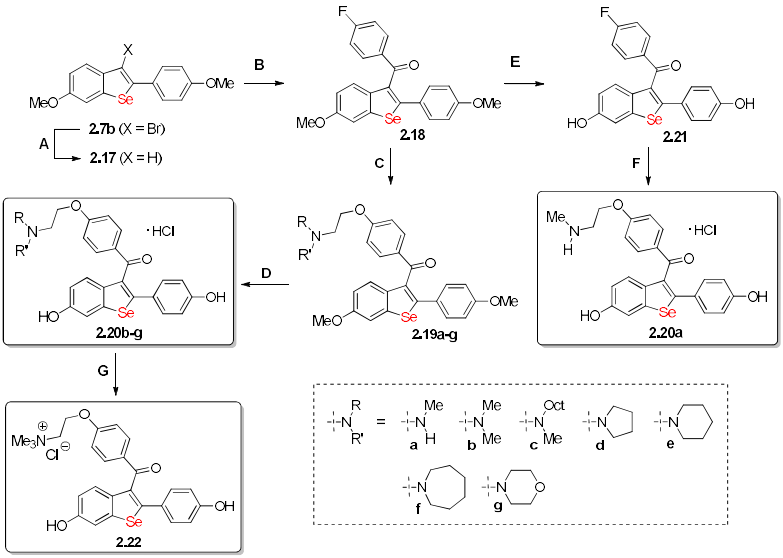
Diemžēl visi $SeBr_4$ izmantošanas mēģinājumi beidzās ar neveiksmi, jo reakciju rezultātā ieguvām sarežģītus produktu maisījumus.

2.5. Raloksifēna selēna analogu sintēze

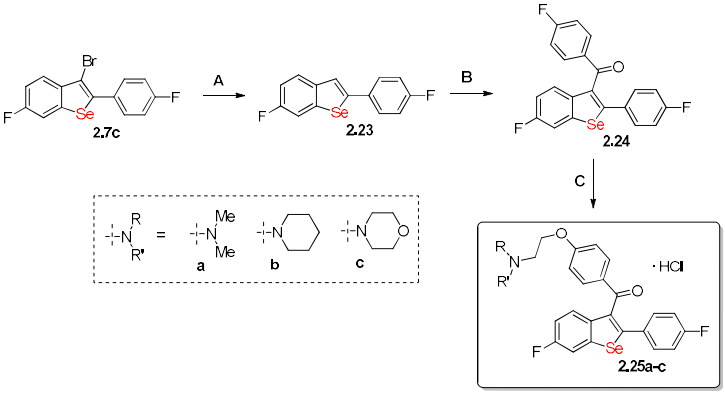
Kā atslēgas prekursors raloksifēna selēna analoga **2.20e** un citu atvasinājumu ar modificētiem amīna fragmentiem sintēzei tika izvēlēts savienojums **2.7b** (2.7. attēls)[37]. Apstrādājot **2.7b** ar cinka pulveri 80 % etiķskābē, ar teicamu iznākumu iegūst 2-neaizvietotu prekursoru **2.17** (2.7. attēls, **A**). Tā kā benz[*b*]selenofēns **2.17** ir analogs benz[*b*]tiofēna atvasinājumam, kas ir izmantots raloksifēna iegūšanai, tad atlikusī shēmas daļa ir analoģiska oriģinālpreparāta sintēzei[38], un produktu iznākumi ir līdzīgi tiem, kādi ir iegūti sēra analoga gadījumā. Tādējādi savienojuma **2.17** Fridela–Kraftsa benzoilēšana ar labu iznākumu ļāva iegūt ketonu **2.18** (2.7. attēls, **B**), un sekojošas fluora atoma nukleofīlas aizvietošanas rezultātā ar 65-91 % iznākumu ieguva prekursorus **2.19a-g** (2.7. attēls, **C**). Visbeidzot, pēc fenola fragmentu aizsarggrupu noņemšanas ar BBr_3 (2.7. attēls, **D**) tika iegūti nepieciešamie selēna analogi **2.20b-g**. Saistībā ar to, ka prekursora **2.19a**

demetilēšana noveda pie sarežģīta produktu maisījuma, kārotais **2.20a** tika iegūts, samainot vietām nukleofīlās aizvietošanas un aizsardzības noņemšanas stadijas (2.7. attēls, **E** un **F**). Savukārt savienojuma **2.20b** dimetilamino-fragmenta kvaternizēšana ļāva iegūt holīna atvasinājumu **2.22** (2.7. attēls, **G**). Līdzīgu sintēzes stratēģiju izmantojām, lai iegūtu raloksifēna selēna analogus **2.25a-c**, kuros hidroksilgrupas ir aizstātas ar fluora atomiem (2.8. attēls)[37].

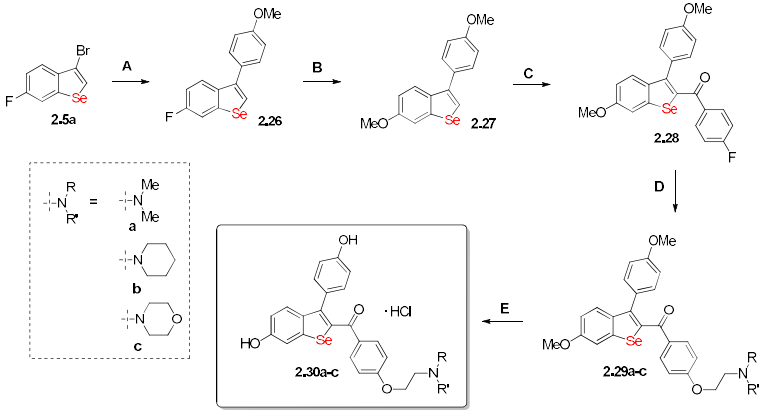
2-Benzoil-3-arilatvasinājumi **2.30a-c** (apgrieztie analogi) tika iegūti piecās stadijās, kā izejvielu izmantojot iepriekš minēto (skat. 2.1. apakšnodaļu) **2.5a** (2.9. attēls)[37]. Savienojuma **2.5a** Suzuki–Mijaura šķērssametināšanās reakcijā ar 4-metoksifenilborskābi ar teicamu iznākumu ieguva **2.26**, un sekojoša **2.26** metoksilēšana ļāva iegūt 3-arilatvasinājumu **2.27** (2.9. attēls, **A** un **B**). Prekursora **2.27** Fridela–Kraftsa benzoilēšana (2.9. attēls, **C**) norisinās ievērojami lēnāk un ar zemāku iznākumu nekā attiecīgā 2-arilatvasinājuma **2.17** gadījumā (2.7. attēls, **B**), tomēr ar viduvēju iznākumu ketonu **2.28** iegūt izdevās. Visbeidzot, pēc attiecīgā etanolamīna fragmenta ievadīšanas un savienojumu **2.29a-c** demetilēšanas ieguva „apgrieztos" analogus **2.30a-c**, produktu iznākumam svārstoties no viduvēja līdz labam (2.9. attēls, **D** un **E**).



2.7. attēls. **Raloksifēna selēna analoga 2.20e un citu amīna fragmentā modificētu atvasinājumu sintēze**. Reakciju norises apstākļi: **A**: Zn (5.0 ekviv.), 80% AcOH, 105ºC, 24h, 93 % iznākums; **B**: 4-fluorbenzoilhlorīds (2.0 ekviv.), $AlCl_3$ (2.0 ekviv.), DCM, 0ºC – r.t., 2h, 73 % iznākums; **C**: attiecīgais 2-aminoetanola atvasinājums (2.0 ekviv.), NaH (2.2 ekviv.), DMF, Ar, ist.t., 2 h, 65-91 % iznākums; **D**: 1) BBr_3 (6.0 ekviv.), DCM, 0 ºC, Ar, 1h, 2) HCl/Et_2O, 29-86 % iznākums; **E**: BBr_3 (6.0 ekviv.), DCM, 0 ºC, Ar, 1h, 47 % iznākums; **F**: 1) 2-metilaminoetanols (4.0 ekviv.), NaH (4.0 ekviv.), DMF, Ar, ist.t., 2 h; 2) HCl/Et_2O, 25 % iznākums; **G**: 1) MeI (10 ekviv.), dioksāns, ist.t., 20 h, 2) jonu apmaiņa, 85 % iznākums.



2.8. attēls. **Fluoraizvietoto raloksifēna selēna analogu sintēze**. Reakciju norises apstākļi: **A**: Zn (10 ekviv.), 80 % AcOH, 110 ºC, 48 h, 87 % iznākums; **B**: 4-fluorbenzoilhlorīds (2.0 ekviv.), $AlCl_3$ (2.0 ekviv.), DCM, 0 ºC – ist.t., 4 h, 75 % iznākums; **C**: attiecīgais 2-aminoetanola atvasinājums (2.0 ekviv.), NaH (2.0 ekviv.), DMF, Ar, r.t., 2 h, 63-77 % iznākums.



2.9. attēls. **Apgriezto raloksifēna selēna analogu sintēze**. Reakciju norises apstākļi: **A**: 4-metoksifenilborskābe (2.0 ekviv.), $Pd(Oac)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 ekviv.), ksilols/^{i}PrOH (2:1), 110 °C, Ar, 12 h, 94 % iznākums; **B**: MeOH (6.0 ekviv.), NaH (6.0 ekviv.), NMP, 140 °C, Ar, 3 h, 81 % iznākums; **C**: 4-fluorbenzoilhlorīds (2.0 ekviv.), $AlCl_3$ (2.5 ekviv.), DCM, 0 ºC – r.t., 72 h, 52 % iznākums; **D**: attiecīgais 2-aminoetanola atvasinājums (3.0 ekviv.), NaH (3.0 ekviv.), DMF, Ar, 50 °C; 5 h, 48-68 % iznākums; **E**: 1) BBr_3 (6.0 ekviv.), DCM, 0 ºC, Ar, 1 h, 2) HCl/Et_2O, 31-90 % iznākums.

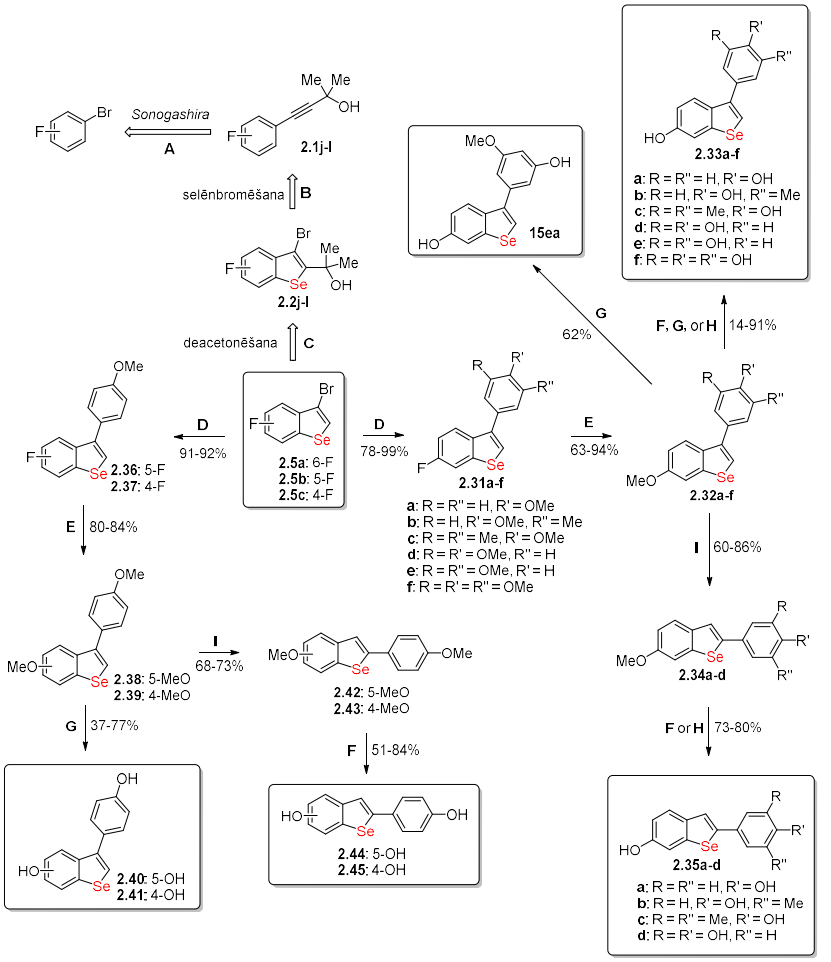
2.6. Dabisku antioksidantu inspirētu polihidroksi benz[*b*]selenofēnu sintēze[39]

Kombinējot arilalkīnu ciklizēšanu selēnbromēšanas apstākļos ar skābes inducētu 3,2-arilgrupas migrāciju, ir izstrādāta vispārīga sintētiskā stratēģija, kas ļauj iegūt polihidroksi 2- un 3-arilbenz[*b*]selenofēna atvasinājumus, izmantojot vienas un tās pašas izejvielas (2.10. attēls).

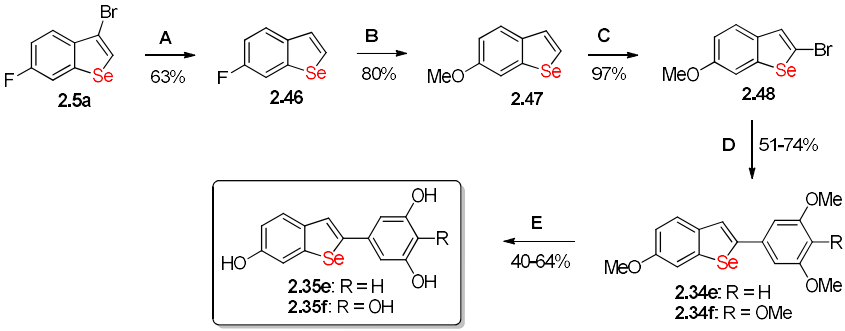
Tādējādi, izmantojot komerciāli pieejamus izejmatreiālus, stratēģiskās izejvielas **2.5a-c** ar labiem iznākumiem ieguva trīs stadijās (2.10. attēls, **A**, **B**, un **C**). Atslēgas stadijas 3-arilbenz[*b*]selenofēna atvasinājumu **2.33a-f**, **2.40** un **2.41** iegūšanai ir savienojumu **2.5a-c** 3. Pozīcijas Suzuki arilēšana (2.10. attēls, **D**), attiecīgā fluora atoma aizvietošana ar metoksigrupu (2.10. attēls, **E**) un sekojoša aizsardzības noņemšana fenola fragmentiem, izmantojot piemērotu demetilēšanas metodi (2.10. attēls, **F**, **G** vai **H**). Lai iegūtu attiecīgos 2-arilatvasinājumus **2.35a-d**, **2.44** un **2.45**, tika veikta pārgrupēšanās metoksiaizvietoto prekursoru **2.32a-d**, **2.38** un **2.39** struktūrās, inducējot 3,2-arilgrupas migrāciju skābes klātienē (2.10. attēls, **I**). Pēc hidroksilgrupu aizsardzības noņemšanas prekursoros **2.34a-d**, **2.42** un **2.43** ieguva kārotos polihidroksi 2-arilbenz[*b*]selenofēna atvasinājumus **2.35a-d**, **2.44** un **2.45** (2.10. attēls, **F** vai **H**).

Tā kā 3-arilatvasinājumu **2.32e**,**f** pārgrupēšanās nenotika (2.10. attēls, **I**), tad attiecīgo 2-arilizostēru **2.35e**,**f** iegūšanai ir izstrādāta alternatīva sintēzes shēma (2.11. attēls). Tās pamatā ir 2-bromatvasinājuma **2.48** sintēze (2.11. attēls, **A**, **B** un **C**), jo to ir iespējams tieši arilēt 2. Pozīcijā, kā rezultātā tiek iegūtas nepieciešamās 2-arilbenz[*b*]selenofēna molekulārās platformas **2.34e**,**f** (2.11. attēls, **D**). Šeit parādās acīmredzamas priekšrocības 3,2-arilgrupas migrācijai pārgrupēšanās stadijā (2.10. attēls, **I**), jo liekās debromēšanas/bromēšanas stadijas (2.11. attēls, **A** un **C**) ir iespējams no sintēzes shēmas izslēgt.

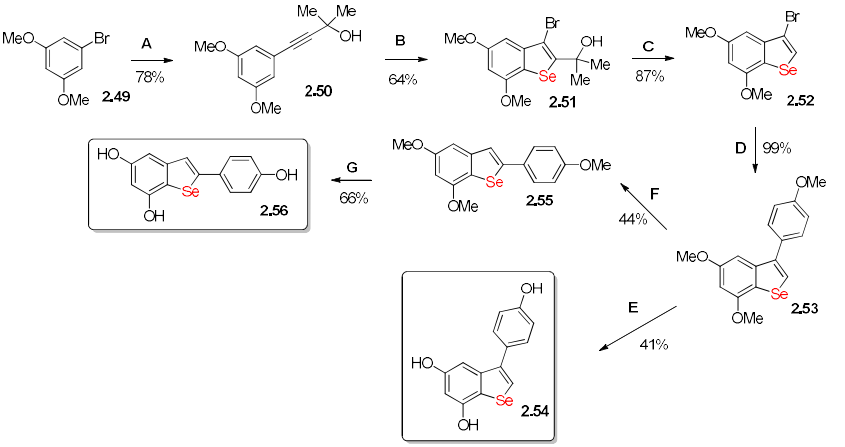
Izmantojot ļoti līdzīgu pieeju iepriekš aprakstītajai sintētiskajai stratēģijai (2.10. attēls), mēģinājām iegūt arī resveratrola analogu **2.56** un tā izomēro 3-arilatvasinājumu **2.54** (2.12. attēls). Vienīgā atšķirība ir tāda, ka pateicīgais hidroksilgrupu izvietojums kārotajos benz[*b*]selenofēnos pieļāva tiešu metoksi-aizvietotā arilalkīna **2.50** izmantošanu ciklizēšanas stadijā (2.12. attēls, **B**).



2.10. attēls. **Polihidroksibenz[*b*]selenofēna atvasinājumu sintēzes stratēģija**. Reakciju norises apstākļi: **A**: 2-metilbut-3-īn-2-ols (1.5 ekviv.), $PdCl_2$ (5.0 mol-%), PPh_3 (10 mol-%), CuI (10 mol-%), $^{i}Pr_2NH$ (4.0 ekviv.), DMF, 60 °C, Ar, 24 h; **B**: SeO_2 (1.5-2.0 ekviv.), cikloheksēns (1.0-1.2 ekviv.), 48 % HBr (0.43 ml uz 1.0 mmol SeO_2), dioksāns, ist.t., 24-72 h; **C**: K_3PO_4 (1.2 ekviv.), DMSO, 80 °C, Ar, 24 h; **D**: attiecīgā arilborskābe (2.0 equiv.), $Pd(Oac)_2$ (10 mol-%), (*o*-Tol)$_3$P (30 mol-%), K_3PO_4 (3.5 ekviv.), ksilols/^{i}PrOH (2:1), 110 °C, Ar, 1 h; **E**: MeOH (6.0 ekviv.), NaH (6.0 ekviv.), NMP, 140 °C, Ar, 1h; **F**: BBr_3 (6.0 ekviv.), DCM, 0 ºC – ist.t., Ar, 12 h; **G**: *n*-dodekāntiols (6.0 ekviv.), NaH (6.0 ekviv.), NMP, 100 °C, Ar, 24 h; **H**: Py · HCl, 220 °C, 6 h; **I**: $MeSO_2OH$ (0.4 M), toluols, 90 °C, 4h.



2.11. attēls. **2-Arilatvasinājumu 35e un 35f sintēze**. Reakciju norises apstākļi: **A**: Zn (20 ekviv.), 80 % AcOH, 110 °C, 24 h; **B**: MeOH (6.0 ekviv.), NaH (6.0 ekviv.), NMP, 140 °C, Ar, 1h; **C**: NBS (1.1 ekviv.), DMF, 0 °C – ist.t., 12 h; **D**: attiecīgā arilborskābe (2.0 ekviv.), $Pd(Oac)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 ekviv.), ksilols/^{i}PrOH (2:1), 110 °C, Ar, 1 h; **E**: Py · HCl, 220 °C, 6 h.



2.12. attēls. **Resveratrola analogu 2.54 un 2.56 iegūšana**. Reakciju norises apstākļi: **A**: 2-metilbut-3-īn-2-ols (1.5 ekviv.), $PdCl_2$ (5.0 mol-%), PPh_3 (10 mol-%), CuI (10 mol-%), $^iPr_2NH$ (4.0 ekviv.), DMF, 60 °C, Ar, 24 h; **B**: SeO_2 (1.2 ekviv.), cikloheksēns (1.2 ekviv.), 48% HBr (0.43 ml uz 1.0 mmol SeO_2), dioksāns, ist.t., 24 h; **C**: K_3PO_4 (2.4 ekviv.), DMSO, 90 °C, Ar, 24 h; **D**: 4-metoksifenilborskābe (2.0 ekviv.), $Pd(OAc)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 ekviv.), ksilols/^{i}PrOH (2:1), 110 °C, Ar, 1 h; **F**: $MeSO_2OH$ (0.4 M), toluols, 90 °C, 8 h; **G**: Py · HCl, 220 °C, 6 h; **E**: BBr_3 (20 ekviv.), DCM, 0 ºC – ist.t., Ar, 12 h.

Ir pētītas iegūto savienojumu red/oks īpašības, brīvo radikāļu ķeršanas spēja un citotoksicitāte uz dažādām audzēju šūnu līnijām (MCF-7, MDA-MB-231, HepG2 un 4T1), un iegūtie rezultāti ir izmantoti struktūras–aktivitātes likumsakarību (SAR) noteikšanai. Tā rezultātā ir noskaidroti struktūras elementi, kas ir pamatā ļoti augstajai peroksilradikāļu ķeršanas aktivitātei.

SECINĀJUMI

1. Alkēna piedeva būtiski samazina aril(hetaril)alkīnu trīskāršās saites bromēšanos selēnbromēšanas apstākļos, tādējādi paaugstinot ciklizēšanās produktu iznākumu. Uzlabotā ciklizēšanas metode ir visātrākais paņēmiens plaša spektra 3-brombenz[*b*]selenofēna atvasinājumu iegūšanai, un pirmo reizi selēnbromēšana ir pielietojama arī selenofēntiofēna atvasinājumu sintēzei.
2. Eksperimentāli iegūti pierādījumi apstiprina, ka ciklizēšanās mehānisma pamatnorises ir stereospecifiska *anti* 1,2-pievienošanās selēnbromēšanas stadijā, kam seko elektrofīla aizvietošana aromātiskā gredzenā. Tādēļ stiprāk polarizēta trīskāršā saite ir pamatā augstākai reģioselektivitātei nesimetrisku diaril(hetaril)alkīnu ciklizēšanā, un kā vispārīga likumsakarība – priekšroka tiek dota ciklizēšanās norisei elektroniem bagātākā aromātiskā gredzena virzienā.
3. Aril(hetaril)alkīnu ciklizēšanas metodes pielietojamības robežu būtiskākais limitējošais faktors ir stipru elektrondonoru aizvietotāju klātiene substrātu aromātiskajos gredzenos. Zemu reģioselektivitāti S_EAr stadijā novēro *meta*-aizvietotu izejvielu gadījumā, bet *orto*- un *para*-aizvietoto substrātu reakcijās pat alkēna piedevas klātienē paaugstinās trīskāršās saites bromēšanas īpatsvars.
4. 1-Etīnilpirolidīn-2-onu reakcijas ar selēna dibromīdu paver iespējas jauna tipa hipervalentu 10-Se-3 sistēmas cviterjonu iegūšanai. Turklāt hipervalento cviterjonu struktūra norāda uz to, ka selēna centra elektrofīls uzbrukums trīskāršajai saitei ir aril(hetaril)alkīnu selēnbromēšanas procesa pirmā stadija.
5. Relatīvi zemo izmaksu un vienkāršo veicamo manipulāciju dēļ 1,2-bis(4-metoksifenil)etīna (**2.6b**) selēnbromēšana ir šobrīd piemērotākā atslēgas stadija raloksifēna selēna analoga sintēzei.
6. Sēra aizstāšana ar selēnu raloksifēnā izraisa paaugstinātu citotoksicitāti uz dažādām vēža šūnu līnijām *in vitro*, tai pat laikā saglabājot augstāku vēža/normālu šūnu selektivitāti.
7. Arilalkīnu selēnbromēšana kombinācijā ar skābes inducētu 3,2-arilgrupas migrāciju ir sekmīgi izmantojama 2- un 3-arilpolihidroksibenz[*b*]selenofēna atvasinājumu iegūšanai, izmantojot vienas un tās pašas izejvielas.
8. Polihidroksibenz[*b*]selenofēni ir jauna un perspektīva antioksidantu un pretaudzēju aģentu saime. Iespējas piemērotās pozīcijās ievadīt papildus hidroksilgrupu/-as ļauj nākotnē cerēt uz vēl aktīvāku atvasinājumu radīšanu.

9. Izteikta korelācija struktūras – aktivitātes likumsakarībās (SAR) tika konstatēta tikai peroksilradikāļu ķeršanas eksperimentos, un iegūtie aktivitātes dati pilnībā atbilst savienojumu struktūru elektroniskajām īpatnībām, kas ir novērotas savienojumu KMR spektrometrijas pētījumos.
10. Benz[*b*]selenofēna atvasinājumu augstā stabilitāte, zemā toksicitāte un struktūras diversificēšanai pastāvīgi pieaugošais metožu klāsts tuvākajā nākotnē ļauj cerēt uz jauniem zāļu vielu kandidātiem šo savienojumu saimē.

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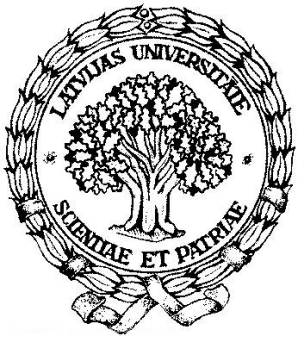

Edgars Paegle

FUSED SELENOPHENES: STRATEGY AND PERSPECTIVES

DOCTORAL THESIS
Submitted for the Degree of Doctor of Chemistry
Subfield of Organic Chemistry

Riga, 2018

The doctoral thesis was carried out at Latvian Institute of Organic Synthesis from 2010 to 2016.


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ABSTRACT

Fused Selenophenes: Strategy and Perspectives. Paegle E., supervisor Dr. chem. Arsenjans P. Doctoral thesis, 82 pages, 42 figures, 40 literature references. In Latvian and English.

The scope of aplicability for the cyclization of aryl(hetaryl)alkynes under selenobromination conditions has been extended by introduction of an alkene additive. The presence of the alkene additive substantially suppresses or completely prevents side reaction asociated with bromination of the starting material's triple bond. Thus, selenobromination of aryl(hetaryl)alkynes has become an effective methodology for the preparation of wide variety of 3-bromobenzo[*b*]selenophenes, and for the first time the methodology is applicable for the synthesis of selenophenothiophenes. Mechanistic studies for the cyclization of diarylalkynes have been done, providing deeper understanding about the cyclization process and origin of the regioselectivity upon the cyclization of unsymmetric substrates. The improved cyclization of arylalkynes has been used as a key step for the synthesis of selenium analogues of raloxifene (selective estrogen receptor modulator), and, in combination with acid induced 3,2-aryl migration, a series of natural polyphenol antioxidant-inspired benzo[*b*]selenophene derivatives was obtained.

SELENIUM, BENZO[*b*]SELENOPHENE, SELENOPHENO-THIOPHENE, SELENOBROMINATION, RALOXIFENE.

INTRODUCTION

200 years have passed since the discovery of selenium by Swedish chemist Jöns Jacob Berzelius in 1818. The first impression about this element was not appealing as it was known that selenium is able to cause certain health problems and toxic effects in animal experiments were also observed[1]. Nevertheless, the biochemical role of selenium started to gain more attention in 1950s, when Pincent discovered that some types of bacteria grow faster in selenium-fortified media[1a]. The major breakthrough for the establishment of biochemical role of selenium in the functioning of mammalian organisms was achieved in 1973 by discovering that antioxidant enzyme glutathione peroxidase (GPx) contains selenocysteine (Sec) residue in its active site[1a]. Nowadays, at least 25 selenoproteins have been discovered in humans, but the mechanism of their action is known for only few of them[2]. In addition to the very well-known GPx, other important selenoenzyme classes essential for prokaryotic organisms have been found; those include iodothyronine deiodinases (IDs), thioredoxin reductases (TrxRs), selenophosphate synthetase, and selenoprotein P[1a].

Although selenium compounds resemble many physical and chemical properties of analogous sulfur containing substances, in general, redox potentials of selenium compounds are lower than in the case of corresponding sulfur analogues, leading to higher reactivity of selenium compounds compared to sulfur ones[1a]. This might be the most important aspect in the differences between selenium und sulfur derivatives, which in contrast to sulfur allows selenium to function as a microelement in the living organisms. As a matter of fact, numerous studies have shown that insufficient amount of selenium in daily diet can lead to development of various undesired health conditions, including cancer, diabetes, heart diseases, and immune system disorders[2].

Regarding the biochemical role of both naturally occurring and synthetic selenium compounds, based on their action mechanism, they could be divided in three major groups:

1) Selenium compounds that can be metabolized to hydrogen selenide (HSe^-), and, therefore, be able to serve as selenium source to be incorporated in selenoproteins;
2) Synthetic mimics of known selenoenzymes;
3) Selenium compounds possessing biologic activity that is not directly related to selenium itself.

Members of the first group are for example selenite (SeO_3^-), selenate (SeO_4^-), and Sec. Interestingly, Sec is not directly incorporated in the biosynthesis of selenoproteins, even though it is the form of selenium in most of the active sites of selenoenzymes. Therefore, at first, it has to be metabolized to hydrogen selenide (HSe^-) and only afterwards it participates in genetically encoded selenoprotein synthesis, which makes it a true 21th essential amino acid[2]. On contrary, members of the second group are directly responsible for the enzyme like activity. The best achievements have been reached in the field of GPx mimics (ebselen being the most famous example)[3], but in the case of other selenoenzyme mimicking the success is close to none.

In the context of the present thesis, the third group of selenium compounds becomes the most important one, as there is small possibility that benzo[*b*]selenophenes could either be metabolized to hydrogen selenide or directly act as GPx mimics. Although the heterocyclic system of benzo[*b*]selenophene has not been found in natural compounds, it is considered to be a bioisostere of naphthalene, benzo[*b*]furan, benzo[*b*]thiophene, and indole[4]. It has been shown that benzo[*b*]selenophene analogues of *milfasartan* and *eprosartan* (compounds used for treatment of hypertension) are excellent AT1 receptor antagonists, and the selenium analogues exhibit higher activity than the corresponding benzo[*b*]thiophene derivatives[5]. Our own research on the synthesis and antiproliferative activity studies of 2,3-disubstituted benzo[*b*]selenophene derivatives has shown that these compounds exhibit medium or low acute cytotoxic effect on normal cells without causing changes in cell morphology[6]. Consequently, selenium analogue synthesis of existing pharmaceuticals as well as seeking for biologic activity in the series of benzo[*b*]selenophene derivatives was chosen as a highly perspective research direction to be explored.

Therefore, the main **aim** of the current research was to broaden the scope of available tools for the synthesis of appropriately substituted benzo[*b*]selenophenes, and to apply the developed methodologies to the requirements of medicinal chemistry purposes.

To achieve the goal, the following **tasks** were proposed:

1) Improvement of the known methodology for the cyclization of arylalkynes under selenobromination conditions to broaden the available substrate scope for the synthesis of 3-bromo-benzo[*b*]selenophenes, and to extend the capability of the methodology in the synthesis of selenophenothiophenes.

2) Exploration of the selenobromination mechanism to confirm the regioselectivity origin in the reactions of unsymmetrically substituted diaryl(hetaryl)alkynes and to gain a better understanding of the influence of particular structural features of the substrates on the outcome of the reactions.
3) Synthesis of selenium analogues of raloxifene (selective estrogen receptor modulator) to observe the effect of sulfur substitution by selenium on biological activity of the corresponding analogues.
4) Preparation of natural polyphenol inspired benzo[*b*]selenophenes as potential antioxidants and antiproliferative agents.

The scientific novelty of the present research:

- Cyclization of aryl(hetaryl)alkynes with *in situ* prepared $SeBr_4$ is elaborated. The use of an alkene additive as a bromine scavenger provides simple access to functionalized benzo[*b*]selenophene and selenophenothiophene derivatives from commercially available or easily accessible starting materials. Reactions can be performed open to air without the use of moisture sensitive reagents, dry solvents, or an inert atmosphere. Mechanistic studies confirm regioselective *anti* 1,2-addition in selenobromination step and subsequent electrophilic substitution in aromatic ring to complete the cyclization.
- Reactions of selenium(II) bromide with 1-(aryl(thienyl)ethynyl)pyrrolidin-2-one derivatives offer alternative way towards new type of zwitterionic hypervalent T–shaped 10-Se-3 systems.
- The improved cyclization of arylalkynes under selenobromination conditions was used as the key step for the preparation of selenium analogues of raloxifene (selective estrogen receptor modulator used for treatment of osteoporosis in postmenopausal women and for prevention of breast cancer). Thus, replacement of sulfur atom by selenium led to highly pronounced antiproliferative effect against malignant cell lines and considerably lower basal toxicity than it was recorded for the original drug.
- Improved cyclization of arylalkynes under selenobromination conditions combined with acid induced 3,2-aryl shift was employed to provide general synthetic pathway for the preparation of polyhydroxy 2- and 3-arylbenzo[*b*]selenophenes from the same starting materials. Redox properties, free radical scavenging ability, and cytotoxicity against malignant cell lines (MCF-7, MDA-MB-231, HepG2, and

4T1) of the synthesized compounds were explored, and the obtained results were subjected to discussion of the structure–activity relationships (SAR). Consequently, structural features responsible for the highly potent peroxyl radical scavenging activity were established.

LIST OF PUBLICATIONS

The development and application of synthetic methodologies are fully published in 5 scientific papers, therefore, the PhD thesis is prepared in the form of collection of publications:

1) Paegle, E.; Domracheva, I.; Turovska, B.; Petrova, M.; Kanepe-Lapsa, I.; Gulbe, A.; Liepinsh, E.; Arsenyan, P. "Natural-Antioxidant-Inspired Benzo[*b*]selenophenes: Synthesis, Redox Properties, and Antiproliferative Activity" *Chem. Asian J.* **2016**, *11*, 1929-1938.
2) Paegle, E.; Belyakov, S.; Petrova, M.; Liepinsh, E.; Arsenyan, P. "Cyclization of Diaryl(hetaryl)alkynes under Selenobromination Conditions: Regioselectivity and Mechanistic Studies" *Eur. J. Org. Chem*. **2015**, *20*, 4389-4399.
3) Paegle, E.; Belyakov, S.; Kirsch, G.; Arsenyan, P. "Addition of selenium(II) bromide to arylalkynylamides – a route to hypervalent T-shaped 10–Se–3 systems" *Tetrahedron Lett*. **2015**, *56*, 4554-4557.
4) Arsenyan, P.; Paegle, E.; Domracheva, I.; Gulbe, A.; Kanepe-Lapsa, I.; Shestakova, I. "Selenium analogues of raloxifene as promising antiproliferative agents in treatment of breast cancer" *Eur. J. Med. Chem.* **2014**, *87*, 471-483.
5) Paegle, E.; Belyakov, S.; Arsenyan, P. "An Approach to the Selenobromination of Aryl(thienyl)alkynes: Access to 3-Bromobenzo[*b*]selenophenes and Selenophenothiophenes" *Eur. J. Org. Chem*. **2014**, *18*, 3831-3840.

CHAPTER 1. CONCEPT OF THE RESEARCH

1.1. Justification for the introduction of benzo[*b*]selenophene's heterocyclic system in biologically active compounds

Recently, benzo[*b*]selenophenes have attracted increasing attention in both medicinal chemistry[5,6] and materials science[7-9]. Although, benzo[*b*]selenophene's heterocyclic system so far has not been found in natural compounds, it is considered to be a bioisoster of naphthalene, benzothiophene, and indole.[4] It has been shown that benzo[*b*]selenophene analogues of *milfasartan* and *eprosartan* (compounds used for treatment of hypertension; Figure 1.1., **A**) are excellent AT_1 receptor antagonists and selenium analogue exhibits higher activity than the corresponding benzo[*b*]thiophene derivative.[5] Besides, our own research on the synthesis and investigation of the cytotoxic activity of 2,3-substituted benzo[*b*]selenophene derivatives has shown that these compounds exhibit medium or low acute cytotoxic effect on normal cells without causing changes in cell morphology (Figure 1.1., **B**).[6]

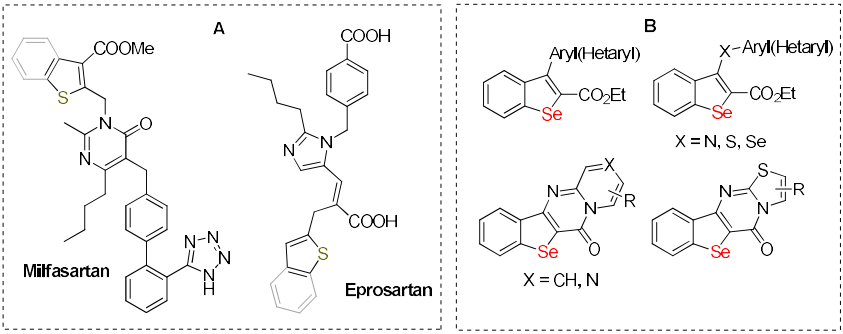

Figure 1.1. **Molecular structures of milfasartan and eprosartan (A) and 2,3-substituted benzo[*b*]selenophenes (B)**.

The low cytotoxicity of benzo[*b*]selenophene derivatives[6] and the bioisosteric nature of benzo[*b*]selenophenes relative to their corresponding sulfur analogues[5] inspired us to enter in the field of selenium analogue synthesis of known pharmaceuticals in order to explore the effect of such sulfur substitution by selenium on the bioactivity of these compounds.

1.2. Challenges in synthetic strategy for the preparation of selenium analogues of raloxifene

One of widely prescribed families of pharmaceuticals containing a core structure based on the heterocyclic system of benzo[*b*]thiophene or indole is selective estrogen receptor modulators (SERMs)[10] (Figure 1.2.). These drugs are mostly used for treatment of osteoporosis in postmenopausal women, prevention of breast cancer, and for lowering of other symptoms associated with menopause. Due to the close resemblance of benzo[*b*]selenophene and its sulfur analogue in terms of physical properties (solubility, polarity, spatial arrangement, etc.) it might be expected that the synthesized selenium analogues would retain the SERM activity of the original drug. However, due to the minor differences in certain characteristics of these structures, such as lowered aromaticity of the selenophene ring relative to thiophene and consequently elevated susceptibility towards oxidation and other chemical transformations, could lead to major differences in biological activity of these compounds. Therefore, we focused our attention on the synthesis of selenium analogues of raloxifene (Figure 1.2., **A**).

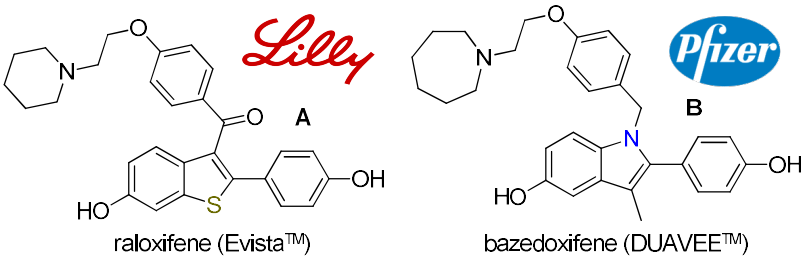

Figure 1.2. **Molecular structures of SERMs containing benzo[*b*]thiophene and indole core structures**.

Regarding the synthesis of raloxifene **1.1**, the most straightforward way towards the key intermediate **1.3.** is cyclization of thioethanone derivative **1.5** under acidic conditions (Figure 1.3.)[11]. The cyclization process involves acid catalyzed electrophilic substitution in the aromatic ring (S_EAr), elimination of water molecule to aromatize the thiophene ring, and subsequent acid induced

3,2-aryl migration to produce 2-arylbenzo[*b*]thiophene derivative **1.3**. Unfortunately, in the case of selenium analogue **1.6** this strategy is not appropriate, since we found that under acidic conditions required for the S_EAr step the starting material **1.6** was completely decomposed by cleavage of Se–C(sp^3) bond. Therefore, it was necessary to find other suitable synthetic pathway for the preparation of **1.4** or its equivalent.

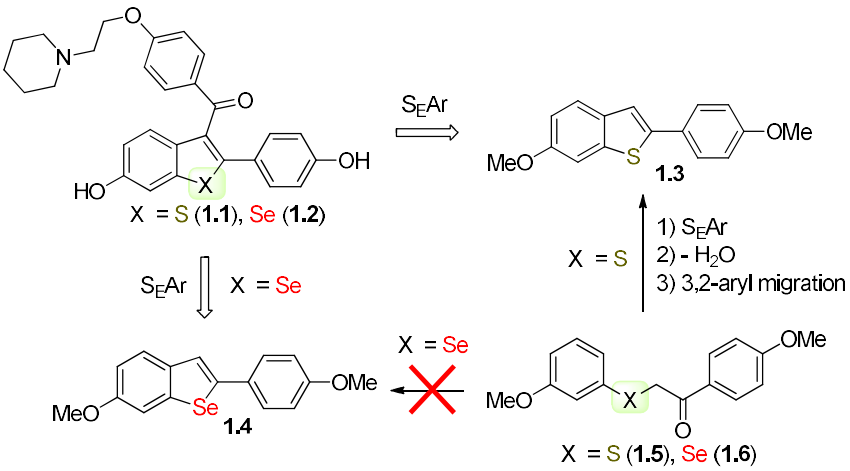

Figure 1.3. **Synthetic strategy for the preparation of raloxifene**.

The most powerful tools for the preparation of 3-unsubstituted- or 3-halo-2-arylbenzo[*b*]selenophenes are Larock's[12] electrophilic cyclization of 1-(1-alkynyl)-2-(alkylseleno)arenes (Figure 1.4., **A**), Takimiya's[13] reactions of *o*-haloarylalkynes with *in situ* formed sodium selenide (Figure 1.4., **B**), and Sashida's[14] cyclization of aryllithium reagents by electrophilic trapping of elemental selenium (Figure 1.4., **C**). The Larock's electrophilic cyclization is very mild, regiospecific, and high yielding approach, but diversification of the substitution pattern in the benzene ring condensed to the selenophene is either tedious or very costly, because the required appropriately substituted *o*-iodoanilines are very expensive or difficult to prepare. Similar advantages and disadvantages apply to the Takimiya's and Sashida's protocols, but, additionally, very high temperature requirement stands in the case of Takimiya's cyclization and, on contrary, Sashida's methodology involves low

temperature, highly moisture sensitive and easily flammable organolithium reagents, dry solvents, and inert atmosphere.

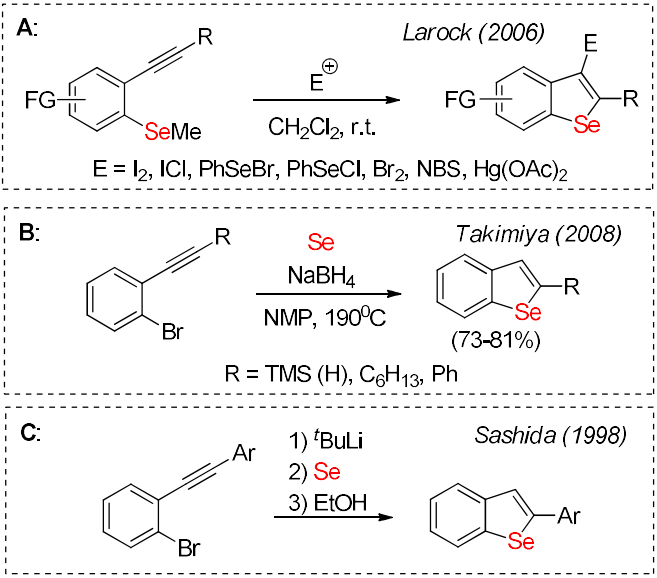

Figure 1.4. **The most widely used methodologies for the preparation of 2-arylbenzo[*b*]selenophenes.**

1.3. Selenobromination of arylalkynes as convenient key step in the synthesis of selenium analogue of raloxifene

Besides the previously mentioned methodologies (Figure 1.4.), 3-halo-benzo[*b*]selenophenes **1.8** also can be obtained by cyclization of arylalkynes **1.7** under selenohalogenation conditions (Figure 1.5.). The history of selenium halide ($SeCl_4$ and $SeBr_4$) reactions with phenylacetylene derivatives in order to obtain benzo[*b*]selenophenes spans from the first publication[15] in 1963 till 1998. However, the pioneering research[15-18] in this field did not provide efficient procedures for the preparation of desired compounds as the yields of the products (based on the arylalkyne) did not exceed 40 % even in the most successful examples. Considerable progress was achieved by introduction of selenohalogenation under two-phase (phase transfer) conditions[19], consisting of

the arylalkyne starting material in organic phase (in general, Et_2O or dioxane solution) and aqueous solution of SeX_4, easily prepared from selenium dioxide and the corresponding conc. Aq. HX (X = Cl, Br). Consequently, several other publications[20-24] appeared to show the range of applicability of the methodology.

Although the two-phase protocol has substantial advantage over the previously used "one-phase" approach, the methodology was limited to the use of substrates with electron-deficient triple bonds. Thus, efficient cyclization was achieved only with phenyl- and naphthylpropiolic acids[19-21], phenylpropiolic acid amide[22] and sulfonamide[19], phenylethynylphosphonic acid[23], and phenylpropargylic amines[24]. Despite the fact that it was never mentioned in the literature[15-24], our own research led to conclusion that the electron rich triple bonds were challenging because of the "poisoning" of the starting material by competitive alogenations instead of selenohalogenation in the first step of the reaction (Figure 1.5.).

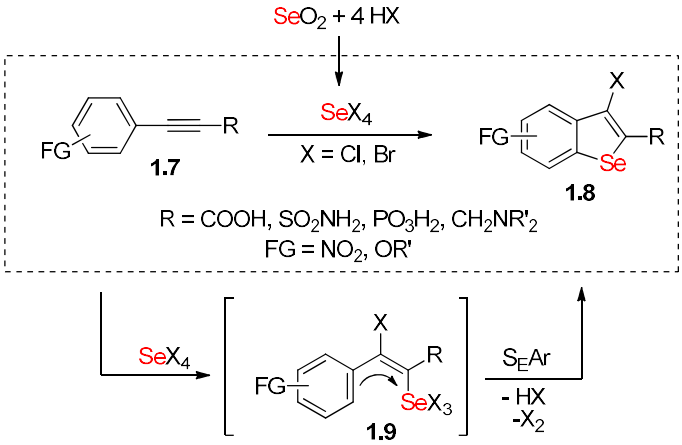

Figure 1.5. **Synthesis of 3-halo-benzo[*b*]selenophenes by selenohalogenation of arylalkynes**.

Due to various phenylacethylene derivatives are commercially available or easily prepared from the corresponding arylhalogenides and terminal alkynes we were inspired to further develop this protocol. As corresponding bromoderivatives are more useful for further modification through different

kinds of transition metal catalyzed reactions, we focused our attention on the cyclization under selenobromination conditions (Figure 1.5., X = Br).

1.4. Construction of natural polyphenol inspired benzo[*b*]selenophenes

Nowadays, there is an increased interest in antioxidants, especially in natural polyphenol-like derivatives, and resveratrol is probably the most widely studied representative (Figure 1.6.).[25] Consequently, in continuation of our research we tried to merge cancer preventive abilities of polyphenols[26-28] and selenium[29-31] with their oxidative stress modulating activity during carcinogenesis. As the core structure of Se-raloxifene **1.2** contains both ingredients, we were encouraged to study how the number and displacement of hydroxyl groups affects the cytotoxicity and radical scavenging activity of the synthesized polyhydroxy benzo[*b*]selenophenes.

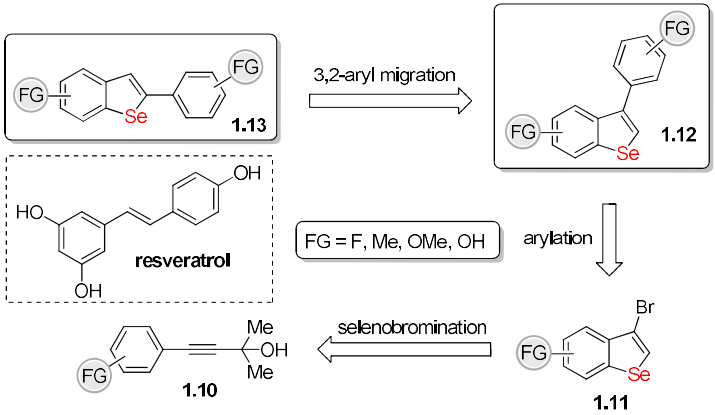

Figure 1.6. **Synthetic strategy towards natural polyphenol inspired polyhydroxy benzo[*b*]selenophenes**.

Therefore, the improved cyclization of arylalkynes under selenobromination conditions combined with acid induced 3,2-aryl shift was chosen to construct desired polyhydroxy 2- and 3-arylbenzo[*b*]selenophenes **1.12** and **1.13** from the same starting materials.

1.5. Differences in chemical properties of sulfur and selenium compounds[1b]

In 2016 Hans J. Reich and Robert J. Hondal have published a review paper[1b] devoted to the question „why nature has chosen selenium?". In some sense, it resembles the question, why we decided to prepare selenium analogues of benzo[*b*]thiophene derivatives. The mentioned review provides a deep and concentrated overlook on the biologic role of selenium discovered so far, keeping the main focus on the differences between selenium and its closest relative – sulfur. In this section of the thesis only the most important differences between sulfur and selenium compounds will be covered. Therefore, in order to obtain more detailed information on the subject, reading of the full article is recommended.

In many aspects, sulfur and selenium have very similar chemical and physical properties. They share all oxidation states and functional group types. Structures of analogous compounds are so similar that in many cases they can be co-crystallized. Numerous differences between both chalcogens originate from common observations upon comparison of lighter and heavier elements. Heavier elements usually are more easily polarized thus leading to faster nucleophilic and electrophilic reactions. Most bonds with selenium are less strong than the corresponding bonds to sulfur, therefore, bond cleavage reactions at the selenium center are more favored. It means that the σ* orbital of Se–X bond is lower in energy than the corresponding σ* orbital of S–X bond. As a result, Se–X bond is a better electron acceptor. Thus, selenium in all of its oxidation states is more electrophilic than sulfur. For example, the most common selenium reaction in organic synthesis is selenium oxide elimination to form alkene (Figure 1.7.). In the case of selenium, the reaction proceeds 100 000 times faster than the analogous sulfur oxide elimination.

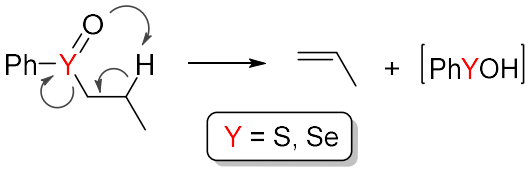

Figure 1.7. **Selenium oxide elimination to form alkene**.

Another common characteristic of heavier elements is lowered stability in high oxidation states and selenium versus sulfur is not an exception. Additionally, selenium is more tolerant towards hypervalent bonding situations. Consequently, one of the rare cases when Se–X bonds are stronger than the corresponding S–X bonds is hypervalent bonding. For example, selenanes (R_4Se) are formed much more easily than sulfuranes (R_4S) and they are considerably more stable. Analogous relative stability is observed in the corresponding ate complexes R_3Se^- and R_3S^-.

Acidity. The larger atomic radius and consequently weaker bonding to hydrogen as well as greater polarizability leads to lower basicity of selenolate anion compared to thiolate, and the corresponding pK_a values differ by 3 to 4 units. Thus, selenocycteine at a neutral pH is nearly completely ionized while cysteine exists almost exclusively in its thiol form. As selenolates are less basic than thiolates, usually they are better leaving groups as well.

Nucleophilicity. Contrary to the lower basicity, selenolate anions are by order of magnitude stronger nucleophiles than thiolates. It is attributed to the greater polarizability of selenium. Additional gain in nucleophilicity in protic solvents is caused by weaker hydrogen bond acceptor properties of selenolate compared to thiolate. The most significant difference in nucleophilicity of sulfur and selenium is observed in the range of physiological pH, because of the nearly complete ionization of selenols while thiols remain mostly undissociated.

Electrophilicity. The greater tolerance of selenium towards hypervalent bonding states strongly influences electrophilicity of selenium. It is explained by the fact that nucleophilic attack on selenium usually involves hypervalent intermediates (R_4Se vai R_3Se^-). Therefore, this type of reactions occurs much faster with selenium than sulfur, and all types of selenium compounds are better electrophiles than the corresponding sulfur analogues.

Weak π-bonding. Selenium compared to sulfur has larger atomic radius and consequently larger hybridized orbitals. In combination with longer bonds it leads to weaker π-bonding. For example, such characteristic of selenium causes considerably lower stability of selenoesters compared to thioesters, as the resonance between selenium and carbonyl group is less effective. Therefore selenoesters are useful acyl group transfer agents.

Red/oks chemistry. The greatest difference between sulfur and selenium is observed in the oxidation and reduction processes of both elements,

and the divergence is substantial in both – one and two electron transfer reactions. Although, for the convenience purposes chalcogen–oxygen bonds often are depicted as double bonds, especially in the case of selenium, more correct approach would be use of single σ-bond and partial charges on the elements (Figure 1.8.). Because of weaker π-bonding Y–O bonds are extensively polarized. Probably because of less effective back-donation of loan pair electrons on oxygen to an acceptor orbital (σ* or d orbitals) on selenium, Y–O dative bonds of selenoxides, selenones, seleninic acids, and selenonic acids are weaker and more polarized, than in the corresponding sulfur analogues. These distinctions can be seen in many aspects when the chemical properties of sulfur and selenium are compared. For example, alkyl selenones are useful alkylating agents, but alkyl sulfones are not. Furthermore, dimethyl selenoxide is considerably more basic than dimethyl sulfoxide. Thus, the concentration of active protonated form in acid catalyzed reactions of selenoxides is 10^4 times higher than in the case of sulfoxides. As selenium on its own is more electrophilic than sulfur, such additional activation increases its electrophilicity even more dramatically. The racemization of selenoxides is much faster than it is for sulfoxides as well, and the racemization mechanism is different in each case.

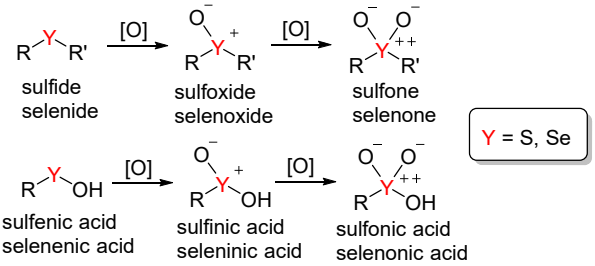

Figure 1.8. **Sulfur and selenium compounds in various oxidation states**.

Common effect observed upon comparison of heavier and lighter elements is the preference of heavier elements to exist in lower oxidation state, and selenium is not an exception. For example, selenoxides can oxidize sulfides to give sulfoxides. Another example is different reactivity exerted by sulfur dioxide (SO_2) and selenium dioxide (SeO_2) (Figure 1.9.). SO_2 is considered as a mild reducing agent, while SeO_2 is a mild oxidant (Riley oxidation). Both

oxides react with alkenes and form the corresponding alylsulfinic and alylseleninic acid intermediates. However, in the case of sulfur dioxide, the reaction is reversible. As a result, SO_2 and alkene are regenerated, and sulfur remains its higher oxidation state. On the other hand, seleninic acid intermediate undergoes [2,3]sigmatropic rearrangement to give divalent selenium ester, which is rapidly hydrolyzed to the corresponding allyl alcohol.

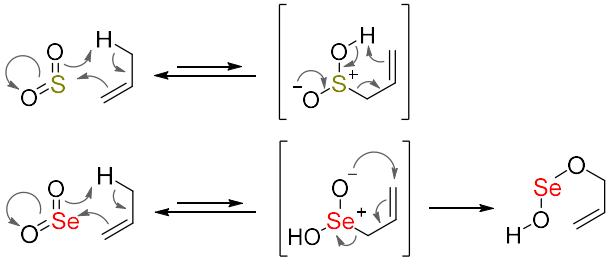

Figure 1.9. **Reactions of sulfur dioxide (SO_2) and selenium dioxide (SeO_2) with alkenes**.

The differences in the electronic structures of sulfur and selenium oxides cause substantial distinctions in the rate of oxidation and reduction reactions. Although rate of the first oxidation step from sulfides/selenides to sulfoxides/selenoxides is comparative, slightly faster occurring in the case of selenides, huge difference appears in the second oxidation step, as formation of the corresponding selenone is much slower, than in the case of sulfone. Mostly it is associated with the more polarized Se–O bond and the decreased nucleophilicity of the lone electron pair on selenium. Oxidation of thiols and selenols in to the disulfides and diselenides occurs much faster in the case of selenium derivatives, but, overall, oxidation of thiols and selenols follows similar tendencies as the oxidation of sulfides and selenides. Concerning the one electron transfer processes, it is important to mention that selenyl radicals are much more stable than thiyl radicals.

Conclusion. Regarding the information presented in this section, it can be concluded that nearly all reactions of selenium compounds are faster than the same reactions of sulfur derivatives. Authors of the review conclude that based on such observation it is tempting to say that nature has chosen selenium,

because the increased activity of selenium in different types of chemical reactions allows to speed up enzymatic processes. However, their true answer on the question “why nature choose selenium” is that selenium can interact with reactive oxygen species (ROS) in a readily reversible manner. Both sulfur and selenium are excellent nucleophiles that react with ROS and thus get oxidized in two electron transfer processes. Nevertheless, due to the distinctions in the electronic structures of sulfur and selenium oxides, their chemical properties differ significantly. Thus, selenoxides are able to regain the reduced state more easily. The phenomenon that selenium compounds can easily oxidize and reduce back to the original state is frequently called “selenium paradox”. Furthermore, the greater stability of selenyl radicals compared to thiyl radicals provides enhanced persistence of selenium containing proteins in the presence of one electron oxidants.

CHAPTER 2. SUMMARY OF THE RESEARCH RESULTS

2.1. Selenobromination of aryl(hetaryl)alkynes

Like it was mentioned in the section 1.3., the main limitation for the use of selenobromination of arylalkynes in the synthesis of benzo[*b*]selenophenes is competitive bromination of the starting materials triple bond instead of its selenobromination. Such a side reaction leads not only to a diminished yield of the desired product, but also produces premixes that are extremely difficult to remove even at relatively small quantities. Since it was postulated that the "poisoning" of the starting arylalkyne was caused by the molecular bromine expelled during the cyclization process (Figure 1.5.), we started our quest for a selective bromine scavenger. Fortunately, a simple alkene additive was efficient enough to substantially broaden the scope of appropriate substrates for the synthesis of desired 3-bromo-benzo[*b*]selenophene derivatives (Figure 2.1.)[32].

It is important to mention that in the absence of alkene additive cyclization of all examples shown in Figure 2.1. occurs by more or less pronounced formation of premixes due to the bromination of the starting material's triple bond, but by use of alkene additive in many cases the premixes practically can not be detected. Very clean reactions were observed upon cyclization of in benzene ring unsubstituted substrates **2.1a-d**,**m**,**n**. As a rezult, the corresponding benzo[*b*]selenophenes **2.2a-d**,**m**,**n** were obtained in very good yields. Additionally, excellent results were obtained in the cyclization of *p*-EWG containing **2.1i** and fluorosubstituted **2.1j-l**. An important moment to emphasize here is the complete regioselectivity upon cyclization of *m*-fluoro substituted **2.1l**. Despite the fact that considerable progress has been achieved in the previously mentioned examples, compared to the cyclization in the absence of alkene, *o*- and *p*-EDG bearing substrates do not allow to suppress the side reaction efficiently enough even in the presence of alkene additive. Thus, in the cases of **2.1f**,**g** the side reaction becoms the main one. Whereas, *m*-methoxy derivative **2.1g** does not form the corresponding dibromoderivative, but cyclize by incomplete (approximately 90 %) regioselectivity in the S_EAr step.

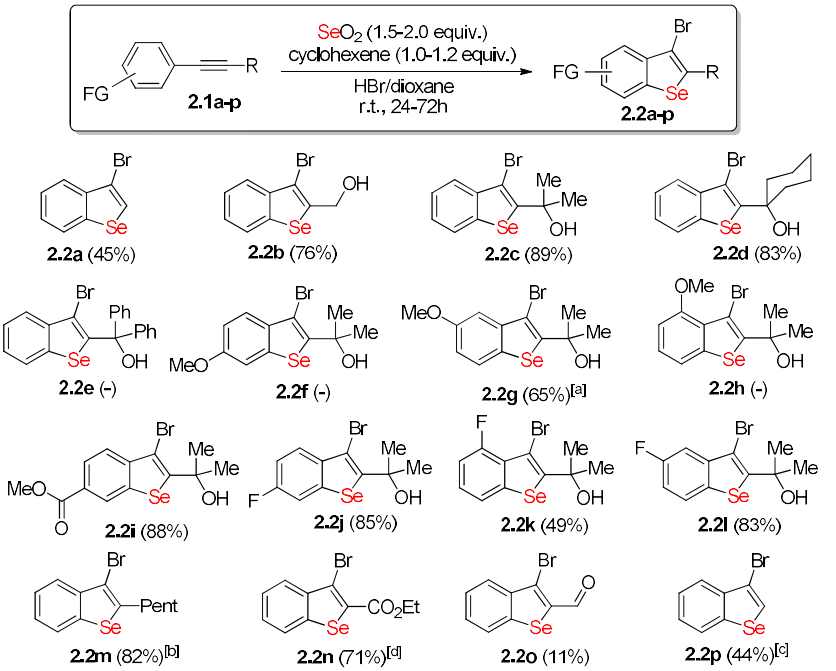

Figure 2.1. **Selenobromination of arylalkynes in the presence of alkene additive**. [a] Product was isolated with 10% premix of corresponding 7-methoxy derivative. [b] Cyclohex-2-enone was used as alkene additive. [c] In **1.1p** R = TMS, 2.0 equivalents of selenium dioxide and 2.0 equivalents of cyclohex-2-enone were used, and complete desilylation was achieved by 0.5 equivalents of TBAF.

To obtain the corresponding selenopheno[3,2-*b*]thiophenes **2.4a-e** and selenopheno[2,3-*b*]thiophenes **2.4f-h**, similar conditions were applied for the cyclization of thienylalkynes **2.3a-h** (Figure 2.2.)[32]. Unfortunately, in the series of 6-bromoselenopheno[3,2-*b*]thiophenes **2.4a-e**, clean reaction and preparative yield was achieved only in the case of EWG aldehyde group bearing **2.4e**, but 4-bromoselenopheno[2,3-*b*]thiophenes **2.4f**,**g** were obtained in moderate yields. Lowered yields, relative to the parent benzene derivatives (Figure 2.1.), were obtained because of additional side reaction – partial bromination in the *α*-position of the thiophene ring, leading to substantially more tedious purification

of the desired products. Therefore, α-protection of thiophene ring by EWG is crucial to achieve efficient synthesis of selenophenothiophenes.

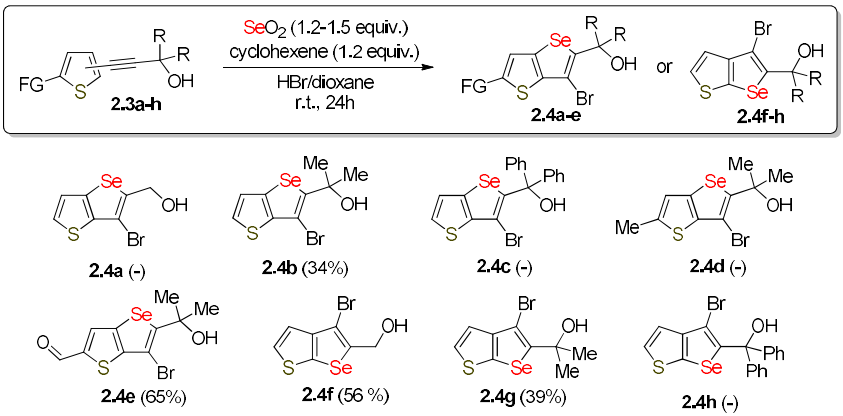

Figure 2.2. **Selenobromination of thienylalkynes in the presence of alkene additive**.

Propan-2-ol derivatives **2.2j-l** are highly versatile small building blocks for the synthesis of more complex benzo[*b*]selenophene derivatives. For example, deacetonation of **2.2j** leads to 3-bromo-6-fluorobenzo[*b*]selenophene (**2.5a**) (Figure 2.3.)[32]. Wide range of possible modifications can be envisioned for **2.5a**, as C–Br bond is available for different kinds of transition metal catalyzed proceses, C–2 is active in electrophilic aromatic substitution, and it is very well known that fluorine atom is excellent leaving group for nucleophilic aromatic substitution, which would allow insertion of EDG (for example alkoxy groups) in positions that are forbidden during the cyclization process. All of these transformations are demonstrated in the synthesis of reversed selenium analogues of raloxifene (see section 2.5.) and natural antioxidant inspired polyhydroxybenzo[*b*]selenophenes (see section 2.6.).

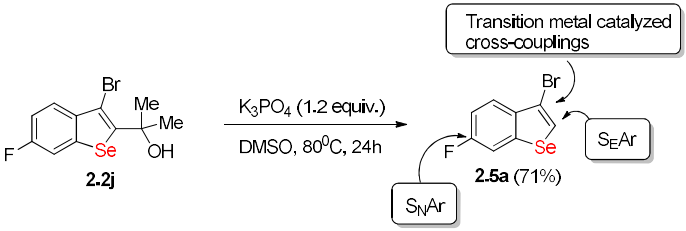

Figure 2.3. **Synthesis of 3-bromo-6-fluorobenzo[*b*]selenophene (2.5) as a versatile small building block**.

2.2. Selenobromination of diaryl(hetaryl)alkynes

The elaborated cyclization of aryl(hetaryl)alkynes[32] (see section 2.1.) was further applied for the cyclization of diaryl(hetaryl)alkynes (Figure 2.4.)[33], and it is also a key step in the synthesis of selenium analogue of raloxifene (see section 2.5.). As a result, a series of new and previously reported 2-aryl(hetaryl)-3-bromobenzo[*b*]selenophenes and selenophenothiophenes was obtained.

Cyclization successfully occurs not only in the case of symmetrical substrates **2.6a-d**, but also the unsymmetrical substrates provide regioselective cyclization to give the corresponding condensed selenophenes (Figure 2.4.). Nevertheless, the regioselectivity of the reactions is strongly affected by the electronic nature of the aromatic rings, e.g., more polarized triple bond leads to higher regioselectivity. Thus, a general rule can be formulated: the selenophene ring is formed at the more electron-rich aromatic ring. EDGs and/or strongly polarized triple bond causes pronounced bromination of the starting material, though, excessive amount of selenium tetrabromide in combination with alkene additive can significantly suppress the side reaction. In this context, it is important to mention that successfull cyclization of electron-rich substrate **2.6b** allowed to obtain the key intermediate in the synthesis of selenium analogue of raloxifene **2.7b**.

EWG bearing substrates exhibit exceedingly different behaviour, as, for example, cyclization of diarylalkyne **2.6d** proceeds very cleanly even in the absence of the alkene additive. Quite the contrary, reaction of **2.6d** with selenium tetrabromide in the presence of cyclohexene does not take place practically at all, because selenium tetrabromide brominates cyclohexene faster than it adds to the triple bond.

Strong *p*-electron acceptor or donor in only one aromatic ring is not enough to achieve complete regioselectivity in the cyclization of unsymmetric diarylalkynes. Although complete regioselectivity is not achieved by cyclization of alkynes **2.6i**,**j**, the major regioisomers **2.7i**,**j** can be relatively easily purified and isolated in moderate yields. Unfortunately, upon cyclization of one *p*-electron donor containing substrate **2.6e** the incomplete regioselectivity was accompained by partial bromination of the triple bond. Therefore, isolation of pure **2.7e** was not possible. However, insertion of fluorine atom (considerably weak inductive acceptor) in the other aromatic ring of substrate **2.6f** allowed to achieve complete regioselectivity, and the corresponding cyclization product **2.7f** was isolated in 55 % yield.

Cyclization of phenylethynyl- and thienylethynylpyridine derivatives **2.6k**,**l** and **2.8a**,**b**,**e**,**f** also proceeds with complete regioselectivity to give the corresponding benzo[*b*]selenophenes **2.7k**,**l** and selenophenothiophene derivatives **2.9a**,**b**,**e**,**f**. Quite important achievment is the exapmle of bis-cyclization **2.9g**.

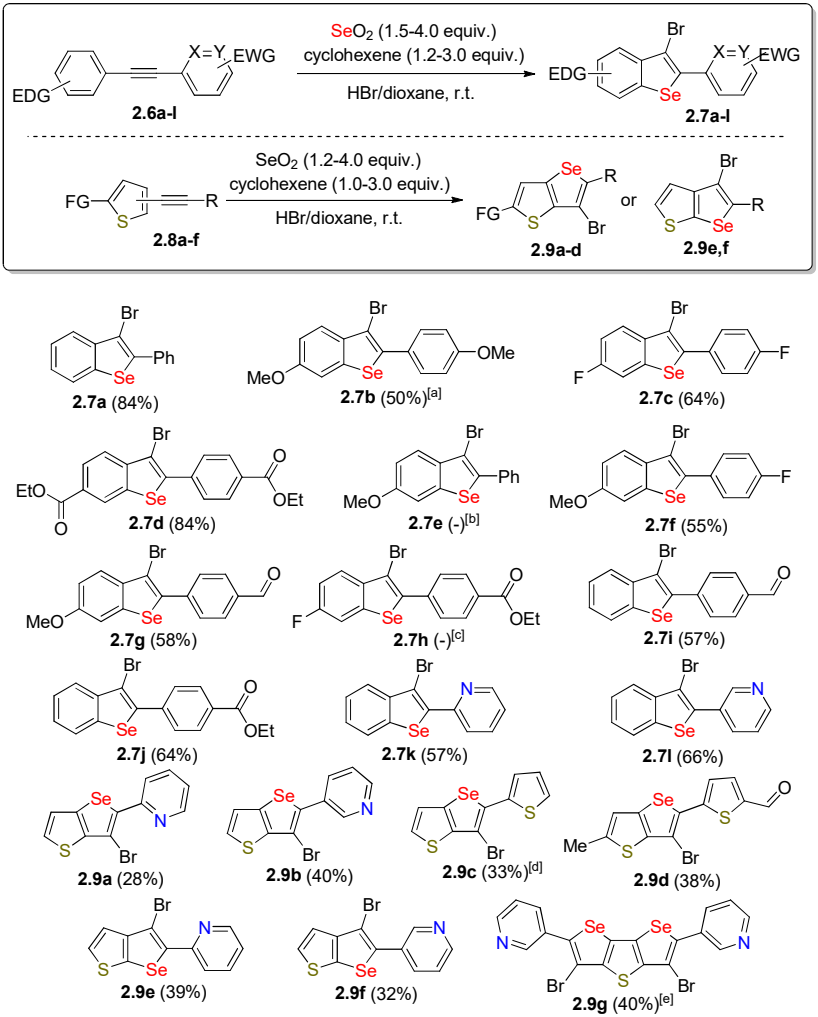

Figure 2.4. **Cyclization of diaryl(hetaryl)alkynes under selenobromination conditions**. [a] Et_3N (4.0 equiv.) additive was used. [b] Inseparable mixture of products was obtained. [c] A mixture of two inseparable regioisomers was obtained. [d] Cyclohex-2-enone (1.5 equiv.) was used instead of cyclohexene in the presence of Et_3N (1.0 equiv.) additive. [e] 2,5-Bis(pyridin-3-ylethynyl)thiophene was used as a starting material.

2.3. Mechanistic studies of selenobromination of arylalkynes

Exceptionally slow reaction of difluorosubstituted **2.6c** provided an excellent opportunity to study the stepwise mechanism of the cyclization process (Figure 2.5)[33]. The presence of fluorine atoms in the structures of starting material **2.6c**, intermediate **2.12**, and the product **2.7c** allowed us to directly monitor the progress of the reaction in water containing dioxane by ^{19}F NMR spectroscopy using D_2O as an external standard. The reaction of **2.6c** in the absence of an alkene additive reached completion after 24 h, and a mixture of cyclization product **2.7c** and the corresponding triple bond bromination adduct was obtained. Furthermore, we were not able to detect any intermediate compounds. However, when the reaction was performed in the presence of 2.0 equiv. of SeO_2 and 1.0 equiv. of cyclohexene, the cyclization process was significantly slowed down.

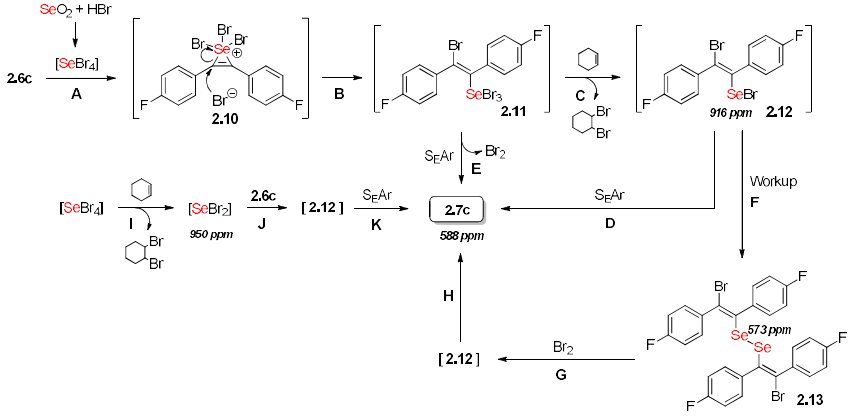

Figure 2.5. **Proposed mechanism for the cyclization of 2.6c**.

We found that after 24 h of stirring at r.t. intermediate **2.12** (confirmed by ^{1}H, ^{13}C, ^{19}F, and ^{77}Se NMR spectroscopy) was formed almost exclusively (Figure 2.5.). According to the study by Poleschner and Seppelt,[34] there is a good reason to believe that the addition of $SeBr_4$ to a triple bond of **2.6c** occurs through a cationic selenirenium type intermediate **2.10** (Figure 2.5., **A**, **B**), and the vinylselenylbromide intermediate **2.12** might be formed after subsequent bromine transfer from **2.11** to cyclohexene (Figure 2.5., **C**). Consequently,

intermediate **2.12** is slowly converted into the desired product **2.7c** through intramolecular electrophilic substitution in the aromatic ring (Figure 2.5., **D**).

By quenching the reaction mixture with brine and ethyl acetate after 24 h of stirring, diselenide derivative **2.13** was isolated in 42% yield. Apparently, an aqueous workup led to the disproportionation of intermediate **2.12** and subsequent Se–Se bond formation. Because diselenide **2.13** was isolated solely as an *E*,*E*-stereoisomer (confirmed by single crystal X-ray diffraction), it provides unambiguous evidence of stereospecific *anti* 1,2-addition in the selenobromination step (Figure 2.5., **A**, **B**). More evidence confirming the existence of intermediate **2.12** was provided by the oxidative addition of 1.0 equiv. of Br_2 to the dioxane solution of diselenide **2.13** (Figure 2.5., **G**). Diselenide **2.13** was completely converted into vinylselenylbromide **2.12** in less than 1 h, and the slow formation of the cyclization product **2.7c** (Figure 2.5., **H**) was observed again.

The significant difference concerning the speed of reaction in the absence and in the presence of an alkene additive (24 h versus 72 h) might be explained by the participation of more electrophilic Se^{IV} species (**2.11**) in the S_EAr step (Figure 2.5., **E**) in the absence of alkene. However, $SeBr_4$ can react directly with the alkene additive by bromination of the double bond (Figure 2.5., **I**). Thus, the presence of $SeBr_2$ species in the reaction mixture should not be categorically denied. As example of 3-bromo-2-phenylbenzo[*b*]selenophene synthesis in the reaction of diphenylethyne with $SeBr_2$ has been demonstrated previously[35], partial participation of this pathway (Figure 2.5., **J**, **K**) should be under consideration.

2.4. Reactions of 1-(aryl(thienyl)ethynyl)pyrrolidin-2-ones with $SeBr_2$[36]

Despite that reactions of alkynylamides **2.14a-g** with $SeBr_2$ did not lead to formation of benzo[*b*]selenophenes, highly valuable information was obtained in the context of the present thesis. Apart from the fact that unexpectedly was found an alternative route to new type of hypervalent T–shaped 10-Se-3 systems **2.16** (Figure 2.6.), the obtained compounds **2.16a-g** could be regarded as "trapped" analogues of intermediate **2.12** (Figure 2.5.). The structure of **2.16a-g** reveals that selenium center of $SeBr_2$ species first interacts with the triple bond of the corresponding starting material **2.14**, presumably forming the selenirene type intermediate **2.15**, and subsequent attack of internal oxygen nucleophile instead of bromide anion leads to precipitation of zwitterionic compounds **2.16**. Apparently, the selenium center

in the structures **2.16** is not electrophilic enough to take part in to the S_EAr step and, consequently, does not lead to formation of the heterocyclic system of benzo[*b*]selenophene. The existence of hypervalent selenium in both the solid state and solution of **2.16** has been supported by single crystal x-ray analysis and ^{77}Se NMR spectroscopy data.

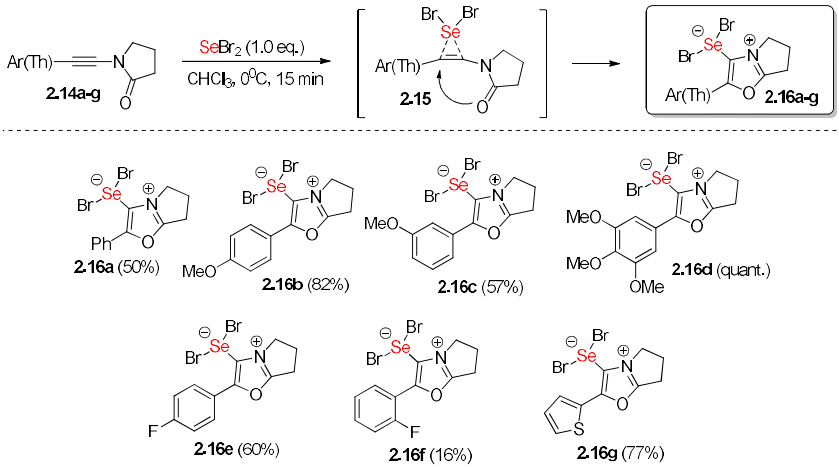

Figure 2.6. **Reactions of alkynylamides 2.14a-g with $SeBr_2$.**

Unfortunately, all attempts to use $SeBr_4$ were unsuccessful, as complex mixtures of products were obtained.

2.5. Synthesis of selenium analogues of raloxifene

The key precursor chosen for the synthesis of selenium analogue of raloxifene **2.20e** and other derivatives with modified amine fragment is compound **2.7b** (Figure 2.7.)[37]. Treatment of **2.7b** by zinc powder in 80% acetic acid provided 3-unsubstituted precursor **2.17** in excellent yield (Figure 2.7., **A**). Since benzo[*b*]selenophene **2.17** is an analogue of benzo[*b*]thiophene derivative which has been used for the synthesis of raloxifene, further steps are analogous to preparation of the original drug[38], and the corresponding yields are very similar to those obtained in reactions of the sulphur analogue. Thus, Friedel–Crafts benzoylation of **2.17** led to ketone **2.18** in a good yield (Figure 2.7., **B**), and subsequent nucleophilic substitution of

fluorine atom provided precursors **2.19a-g** in 65-91 % yield (Figure 2.7., **C**). Finally, after deprotection of the phenol moieties by BBr_3 (Figure 2.7., D), the desired selenium analogues **2.20b-g** were obtained. As demethylation of precursor **2.19a** gave a complex mixture of products, the desired **2.20a** was prepared by reversing the nucleophilic substitution and deprotection steps (Figure 2.7., **E** and **F**). Finally, quaternisation of the dimethylamino-fragment of **2.20b** led to the choline derivative **2.22** (Figure 2.7., **G**). Similar synthetic strategy was also applied for the preparation of selenium analogues of raloxifene **2.25a-c** in which hydroxyl groups are substituted by fluorine atoms (Figure 2.8.)[37].

Synthesis of 2-benzoyl-3-arylderivatives **2.30a-c** (reversed analogues) was accomplished in five steps starting from previously mentioned (see section 2.1.) **2.5a** (Figure 2.9.)[37]. Suzuki–Miyaura cross-coupling of **2.5a** with 4-methoxyphenyl boronic acid gave **2.26** in excellent yield, and subsequent methoxylation of **2.26** led to 3-aryl derivative **2.27** (Figure 2.9., **A** and **B**). Friedel–Crafts benzoylation of **2.27** (Figure 2.9, **C**) was considerably slower and lower yielding than analogous reaction of 2-arylderivative **2.17** (Figure 2.7., **B**), but nevertheless the ketone **2.28** was successfully obtained in moderate yield. Finally, after insertion of the corresponding ethanolamine fragment and demethylation of **2.29a-c** provided **2.30a-c** in moderate to good yields (Figure 2.9., **D** and **E**).

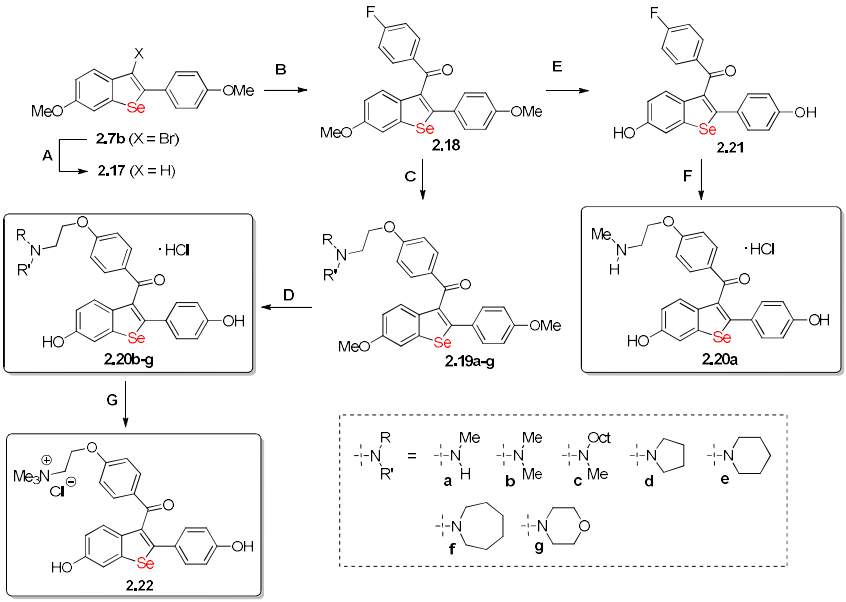

Figure 2.7. **Synthesis of exact selenium analogue of raloxifene 2.20e and other derivatives with modified amine fragment**. Conditions: **A**: Zn (5.0 equiv.), 80% AcOH, 105ºC, 24h, 93 % yield; **B**: 4-fluorobenzoyl chloride (2.0 equiv.), $AlCl_3$ (2.0 equiv.), DCM, 0ºC – r.t., 2h, 73 % yield; **C**: corresponding 2-aminoethanol derivative (2.0 equiv.), NaH (2.2 equiv.), DMF, Ar, r.t., 2h, 65-91 % yield; **D**: 1) BBr_3 (6.0 equiv.), DCM, 0ºC, Ar, 1h, 2) HCl/Et_2O, 29-86 % yield; **E**: BBr_3 (6.0 equiv.), DCM, 0ºC, Ar, 1h, 47 % yield; **F**: 1) 2-methylaminoethanol (4.0 equiv.), NaH (4.0 equiv.), DMF, Ar, r.t., 2h; 2) HCl/Et_2O, 25 % yield; **G**: 1) MeI (10 equiv.), dioxane, r.t., 20h, 2) ion exchange, 85 % yield.

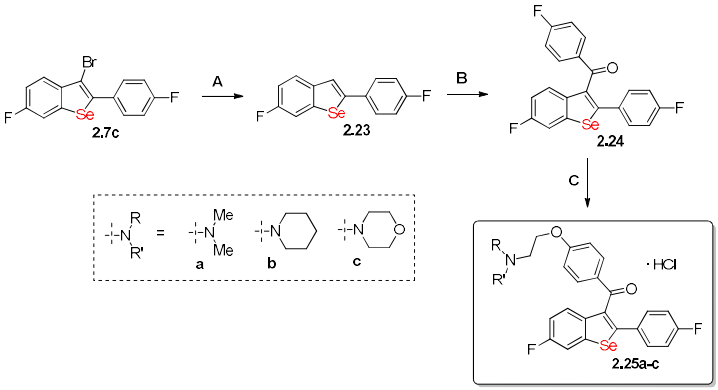

Figure 2.8. **Synthesis of fluoro-substituted selenium analogues of raloxifene**. **A**: Zn (10 equiv.), 80% AcOH, 110ºC, 48 h, 87 % yield; **B**: 4-fluorobenzoyl chloride (2.0 equiv.), $AlCl_3$ (2.0 equiv.), DCM, 0ºC – r.t., 4h, 75 % yield; **C**: corresponding 2-aminoethanol derivative (2.0 equiv.), NaH (2.0 equiv.), DMF, Ar, r.t., 2h, 63-77 % yield.

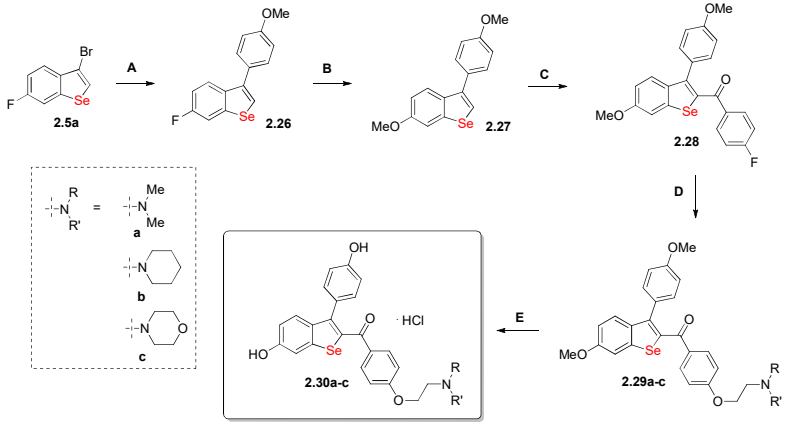

Figure 2.9. **Synthesis of reversed selenium analogues of raloxifene**. **A**: 4-methoxyphenylboronic acid (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 equiv.), xylene/*i*PrOH (2:1), 110 °C, Ar, 12h, 94 % yield; **B**: MeOH (6.0 equiv.), NaH (6.0 equiv.), NMP, 140 °C, Ar, 3h, 81 % yield; **C**: 4-fluorobenzoyl chloride (2.0 equiv.), $AlCl_3$ (2.5 equiv.), DCM, 0ºC – r.t., 72h, 52 % yield; **D**: corresponding 2-aminoethanol derivative (3.0 equiv.), NaH (3.0 equiv.), DMF, Ar, 50 °C; 5h, 48-68 % yield; **E**: 1) BBr_3 (6.0 equiv.), DCM, 0ºC, Ar, 1h, 2) HCl/Et_2O, 31-90 % yield.

2.6. Synthesis of natural antioxidant inspired polyhydroxy benzo[*b*]selenophenes[39]

Cyclization of arylalkynes under selenobromination conditions combined with acid induced 3,2-aryl shift was elaborated, providing general synthetic pathway for the preparation of polyhydroxy 2- and 3-arylbenzo[*b*]selenophenes from the same starting materials (Figure 2.10.).

Thus, the strategic starting materials **2.5a-c** were prepared in three high yielding steps from commercially available substances (Figure 2.10., **A**, **B**, and **C**). The key steps for the preparation of the corresponding 3-aryl polyhydroxy benzo[*b*]selenophenes **2.33a-f**, **2.40**, and **2.41** are Suzuki arylation in the 3rd position of **2.5a-c** (Figure 2.10., **D**), substitution of the corresponding fluorine atom by methoxy group (Figure 2.10., **E**), and subsequent deprotection of phenol moieties employing appropriate demethylation approach (Figure 2.10., **F**, **G**, or **H**). To obtain the corresponding 2-aryl derivatives **2.35a-d**, **2.44**, and **2.45**, the methoxy substituted precursors **2.32a-d**, **2.38**, and **2.39** were rearranged by acid induced 3,2-aryl migration (Figure 2.10., **I**). After deprotection of the phenol moieties of **2.34a-d**, **2.42**, and **2.43**, the desired 2-aryl polyhydroxy benzo[*b*]selenophenes **2.35a-d**, **2.44**, and **2.45** were prepared (Figure 2.10., **F** or **H**).

As 3-aryl derivatives **2.32e**,**f** did not undergo the rearrangement step (Figure 2.10., **I**), alternative synthetic pathway was developed to obtain the corresponding 2-aryl isosteres **2.35e**,**f** (Figure 2.11.). This strategy is based on the synthesis of 2-bromoderivative **2.48** (Figure 2.11., **A**, **B**, and **C**), which can be directly arylated to afford the necessary 2-arylbenzo[*b*]selenophene molecular scaffold **2.34e**,**f** (Figure 2.11., **D**). Consequently, the obvious advantage of the 3,2-aryl shift in the rearrangement step (Figure 2.10., **I**) can be appreciated, since the quite "silly" debromination/bromination steps (Figure 2.11., **A** and **C**) can be eliminated.

Finally, synthesis of resveratrol analogue **2.56** and its isomeric 3-aryl derivative **2.54** was attempted (Figure 2.12.), employing very similar synthetic strategy to the previously described (Figure 2.10). The only difference is that, the appreciative displacement of hydroxy groups in the desired benzo[*b*]selenophenes allowed direct use of methoxy substituted arylalkyne **2.50** in the cyclization step (Figure 2.12., **B**).

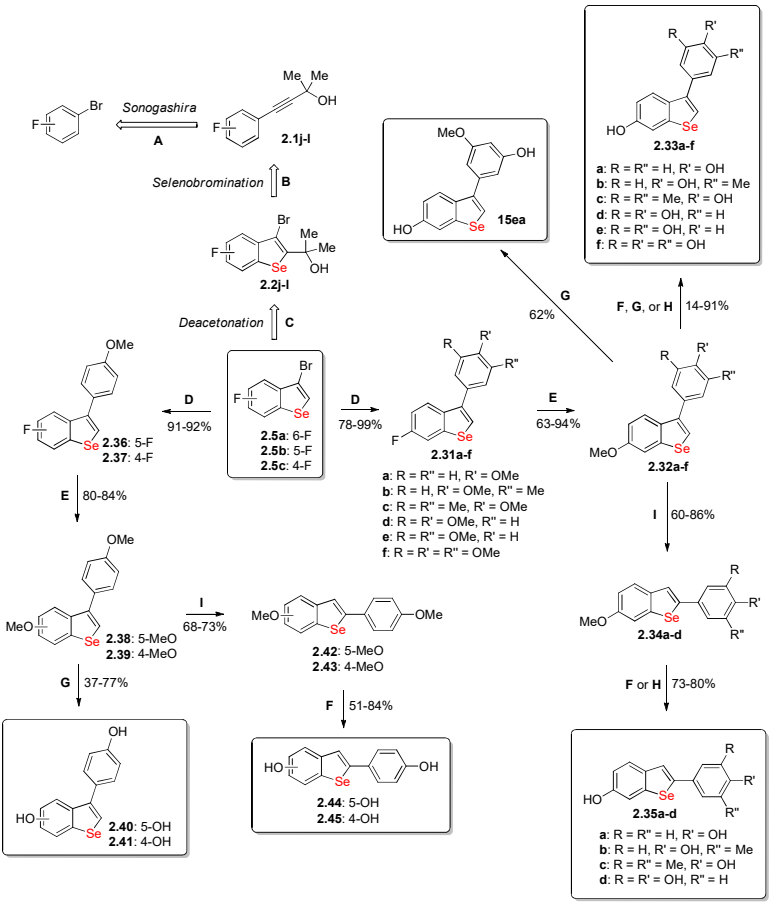

Figure 2.10. **Synthetic strategy for the synthesis of polyhydroxybenzo[*b*]selenophenes**. Reaction conditions: **A**: 2-methylbut-3-yn-2-ol (1.5 equiv.), $PdCl_2$ (5.0 mol-%), PPh_3 (10 mol-%), CuI (10 mol-%), $^{i}Pr_2NH$ (4.0 equiv.), DMF, 60 °C, Ar, 24 h; **B**: SeO_2 (1.5-2.0 equiv.), cyclohexene (1.0-1.2 equiv.), 48 % HBr (0.43 ml per 1.0 mmol of SeO_2), dioxane, r.t., 24-72 h; **C**: K_3PO_4 (1.2 equiv.), DMSO, 80 °C, Ar, 24 h; **D**: corresponding arylboronic acid (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), (*o*-Tol)$_3$P (30 mol-%), K_3PO_4 (3.5 equiv.), xylene/^{i}PrOH (2:1), 110 °C, Ar, 1 h; **E**: MeOH (6.0 equiv.), NaH (6.0 equiv.), NMP, 140 °C, Ar, 1h; **F**: BBr_3 (6.0 equiv.), DCM, 0 ºC – r.t., Ar, 12 h; **G**: *n*-dodecanethiol (6.0 equiv.), NaH (6.0 equiv.), NMP, 100 °C, Ar, 24 h; **H**: Py · HCl, 220 °C, 6 h; **I**: $MeSO_2OH$ (0.4 M), toluene, 90 °C, 4h.

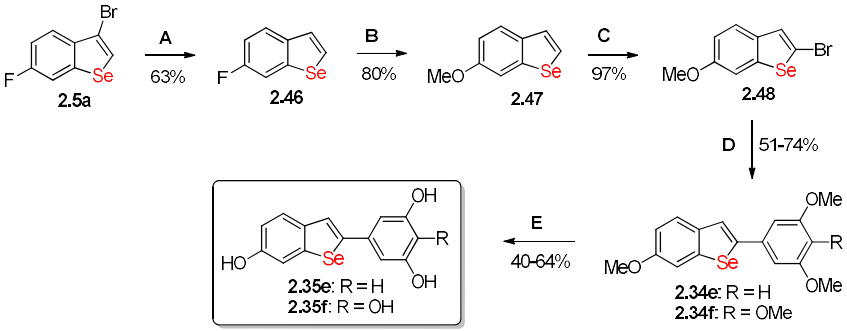

Figure 2.11. **Synthesis of 2-arylderivatives 35e and 35f**. Reaction conditions: **A**: Zn (20 equiv.), 80 % AcOH, 110 °C, 24 h; **B**: MeOH (6.0 equiv.), NaH (6.0 equiv.), NMP, 140 °C, Ar, 1h; **C**: NBS (1.1 equiv.), DMF, 0 °C – r.t., 12 h; **D**: corresponding arylboronic acid (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 equiv.), xylene/^{i}PrOH (2:1), 110 °C, Ar, 1 h; **E**: Py · HCl, 220 °C, 6 h.

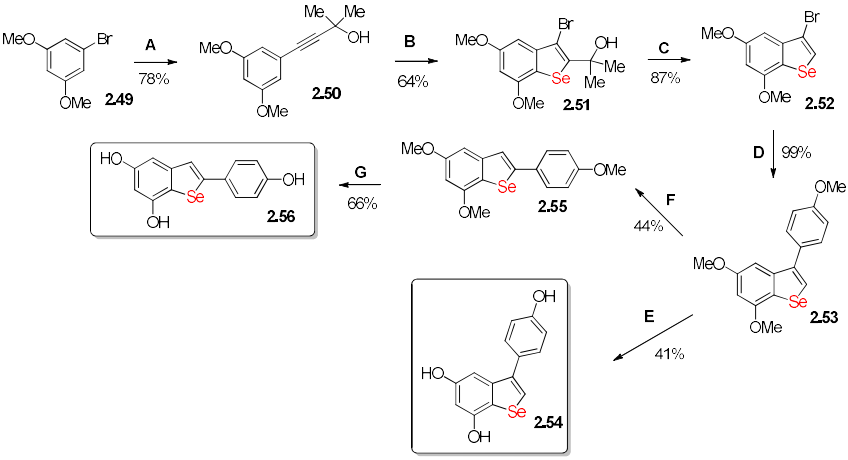

Figure 2.12. **Preparation of the resveratrol analogues 2.54 and 2.56**. Reaction conditions: **A**: 2-methylbut-3-yn-2-ol (1.5 equiv.), $PdCl_2$ (5.0 mol-%), PPh_3 (10 mol-%), CuI (10 mol-%), $^i Pr_2NH$ (4.0 equiv.), DMF, 60 °C, Ar, 24 h; **B**: SeO_2 (1.2 equiv.), cyclohexene (1.2 equiv.), 48% HBr (0.43 ml per 1.0 mmol of SeO_2), dioxane, r.t., 24 h; **C**: K_3PO_4 (2.4 equiv.), DMSO, 90 °C, Ar, 24 h; **D**: 4-methoxyphenylboronic acid (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 equiv.), xylene/^{i}PrOH (2:1), 110 °C, Ar, 1 h; **F**: $MeSO_2OH$ (0.4 M), toluene, 90 °C, 8h; **G**: Py · HCl, 220 °C, 6 h; **E**: BBr_3 (20 equiv.), DCM, 0 ºC – r.t., Ar, 12 h.

Redox properties, free radical scavenging ability, and cytotoxicity against malignant cell lines (MCF-7, MDA-MB-231, HepG2, and 4T1) of the synthesized compounds were explored, and the obtained results were subjected to discussion of the structure–activity relationships (SAR). Consequently, structural features responsible for the highly potent peroxyl radical scavenging activity were established.

CONCLUSIONS

1. Alkene additive substantially suppresses bromination of aryl(hetaryl)alkyne's triple bond, thus, elevating yields of cyclization products under selenobromination conditions. The improved cyclization procedure provides the shortest synthetic pathway to wide variety of 3-bromobenzo[*b*]selenopenes, and for the first time selenobromination is applicable for the preparation of selenophenothiophenes.
2. Experimental evidence confirms stereospecific *anti* 1,2-addition in the selenobromination step and subsequent intramolecular electrophilic substitution on the aromatic ring as the main contributors in the cyclization mechanism. Thereby, more polarized triple bond leads to higher regioselectivity in the cyclization of diaryl(hetaryl)alkynes. As a general rule, cyclization is favored on the side of the more electron-rich aromatic ring.
3. The main limitations of the cyclization of aryl(hetaryl)alkynes under selenobromination conditions are substrates containing strong electron donors in the aromatic ring. In the case of *meta*-substituted derivatives poor regioselectivity in S_EAr step is obtained, but *ortho*- and *para*-substituted substrates cause pronounced bromination of the triple bond even in the presence of alkene additive.
4. Reactions of 1-ethynylpyrrolidin-2-ones with selenium dibromide provide novel synthetic pathway towards new type of zwitterionic hypervalent 10-Se-3 systems. Additionally, structure of the hypervalent products supports electrophilic attack of selenium center on the triple bond as the first step in selenobromination of aryl(hetaryl)alkynes.
5. Due to cost efficiency and simplicity of necessary manipulations, selenobromination of 1,2-bis(4-methoxyphenyl)ethyne (**2.6b**) is the most convenient key step for the synthesis of selenium analogue of raloxifene to date.
6. Substitution of sulfur by selenium in the core structure of raloxifene leads to pronounced *in vitro* cytotoxicity on variety of cancer cells, in the same time providing higher cancer/normal cell selectivity.
7. Selenobromination of arylalkynes combined with acid induced 3,2-aryl migration can be successfully applied for the synthesis of 2- and 3-aryl polyhydroxy benzo[*b*]selenophenes employing the same starting materials.

8. Polyhydroxybenzo[*b*]selenophenes emerge as a new family of highly potent antioxidants and antiproliferative agents. The positive effect of introduction of additional electron donors in the proper positions holds the future potential of developing even more active derivatives.
9. Strong correlation in the structure-activity relationships (SAR) was found only in the case of peroxyl radical scavenging, and the obtained activity data is in full agreement with the observations made in the NMR study.
10. High stability, low toxicity, and the growing arsenal of available tools for the structural diversification of benzo[*b*]selenophenes allows to anticipate new drug candidates among this family in the near future.

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An Approach to the Selenobromination of Aryl(thienyl)alkynes: Access to 3-Bromobenzo[*b*]selenophenes and Selenophenothiophenes

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Keywords: Heterocycles / Selenophenes / Selenium / Bromination / Cyclization

A novel approach for the cyclization of arylalkynes with selenium(IV) bromide prepared in situ has been elaborated. The use of an alkene additive as a bromine scavenger provides a convenient synthetic pathway for the synthesis of a wide variety of 3-bromobenzo[*b*]selenophenes. Reactions can be performed open to air without the use of moisture-sensitive reagents, anhydrous solvents, or an inert atmosphere. Selenobromination of ethynylthiophenes has been applied for the preparation of selenopheno[3,2-*b*]- and selenopheno[2,3-*b*]thiophenes. The molecular structures of representative derivatives have been confirmed by X-ray crystallographic analysis.

Introduction

During the last decade benzo[*b*]selenophenes have attracted increasing attention in both medicinal chemistry and materials science. Although the benzo[*b*]selenophene heterocyclic system has not been found in natural compounds, it is considered to be a bioisoster of naphthalene, benzofurane, benzothiophene, and indole.[1] It has been shown that benzo[*b*]selenophene analogues of *milfasartan* and *eprosartan* (compounds used for treatment of hypertension) are excellent AT_1 receptor antagonists, and selenium analogues exhibit higher activity than the corresponding benzo[*b*]thiophene derivatives.[2] Our own research work on synthesis and antiproliferative activity studies of 2,3-disubstituted benzo[*b*]selenophene derivatives has shown that these compounds exhibit medium or low acute cytotoxic effect on normal cells without causing changes in cell morphology.[3a,3b] Furthermore, fused selenophene ring containing systems have attracted much interest because of their potential application as organic semiconductors in various optoelectronic devices.[4]

Although there are a number of more or less general methods for the preparation of benzo[*b*]selenophenes,[5–10] only two methods are applicable for the synthesis of 3-halo derivatives, which are extremely useful for further modifications through different kinds of cross-coupling protocols. In 2006, Larock and co-workers published their studies on the cyclization of 1-(1-alkynyl)-2-(methylseleno)arenes in the presence of iodine and other electrophiles.[6a] The most important advantages of this methodology are mild reaction conditions, regioselectivity, and high product yields, and it is the only general method available for the preparation of 3-iododerivatives. However, starting materials for this cyclization are prepared by using a rather low yielding, three-step procedure. Moreover, only a limited number of the required iodoanilines are commercially available, and the synthesis of appropriately substituted substrates is quite complex. Another option is the reaction of phenylacetylene derivatives with selenium tetrahalogenides ($SeCl_4$ and $SeBr_4$) generated in situ.[9] This methodology has been known for more than 30 years, but the scope of useful substrates remains quite poor. Cyclizations have been achieved by using phenyl- and naphthylpropiolic acids,[9a,9c,9e] phenylpropiolic acid amide[9f] and sulfonamide,[9a] phenylethynylphosphonic acid,[9d] and phenylpropargylic amines.[9b] The cyclization reaction is regarded as a two-step process (Scheme 1).[9e] The first step involves *anti* addition of selenium tetrahalide ($SeCl_4$ or $SeBr_4$) to a triple bond, forming a selenohalogenated intermediate, followed by intramolecular cyclization through an S_EAr mechanism, while one equivalent of hydrogen halide and halogen molecule is expelled.

Based on the above idea and on our experience with thiophene and selenophene chemistry,[3c,3d] in the present study we focused on the construction of benzo[*b*]selenophene, selenopheno[3,2-*b*]- and -[2,3-*b*]thiophene rings by treatment of ethynylarenes with $SeBr_4$ prepared in situ. Because a range of phenylacetylene derivatives are either commercially available or easily prepared from the corresponding arylhalogenides and terminal alkynes, we were inspired to develop this protocol. Considering that the corresponding bromo derivatives are more useful for further modifications through different types of transition-metal-catalyzed reactions, we focused our attention on cyclization under selenobromination conditions.

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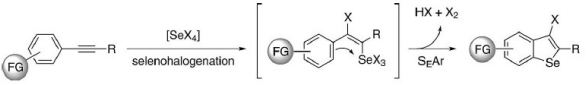


Scheme 1. Ethynylarenes cyclization mechanism under selenohalogenation conditions.

Results and Discussion

As previously[9a] mentioned, cyclization of phenylacetylene derivatives in the presence of water is higher yielding and less time-consuming than the corresponding reactions under anhydrous conditions.[11] The standard protocol involves dropwise addition of arylalkyne solution in ethers (diethyl ether or dioxane) to a freshly prepared aqueous solution of selenium(IV) bromide, or vice versa. The aqueous solution of selenium(IV) bromide is simply prepared by treatment of selenium dioxide with an appropriate amount of concentrated hydrobromic acid.

Because phenylacetylene (**1**) is the simplest and most readily available arylalkyne, and because no successful examples of its cyclization under the given conditions have been shown so far, we selected this compound as our first model (Scheme 2, Table 1). Brief examination of this reaction under previously described conditions[9e] led us to conclude that four main products were formed (Table 1, entry 1). Simultaneously with the expected cyclization product **2**, both stereoisomers of dibromo derivative **2a** and divinyl selenide **2b** were formed (approximate mass ratio 2:2:1). Moreover, considerable amounts of minor unidentified side products were detected, and all attempts to isolate pure **2** from such a complex mixture were unsuccessful. Although alteration of the addition sequence did not affect cyclization of phenylpropargylic amines,[9b] in this case it was important that the solution of **1** in dioxane was added to aqueous $SeBr_4$ solution, because the reverse addition led to a more complex mixture of products accompanied by more pronounced formation of **2b**. Because the structure of **2b** corresponds to addition of two phenylacetylene (**1**) units to one selenium(IV) bromide molecule, more diluted conditions were employed (Table 1, entries 2–4). In this way, the appearance of minor side products was completely prevented and the formation of divinyl selenide **2b** was suppressed to a minimum (Table 2, entry 4). Further dilution did not considerably reduce the formation of **2b** further. Notably, use of diethyl ether instead of dioxane drastically increased the amount of **2a** formed (Table 1, entry 5). Despite the fact that the formation of **2a** was suppressed by approximately 8% by performing the reaction in tetrahydrofuran (THF) (Table 1, entry 6), cleaner reaction was achieved by using dioxane as solvent (Table 1, entry 4). All attempts to separate **2** from **2a** were unsuccessful, so it was crucial to find a methodology that would avoid formation of **2a**.

Table 1. Optimization of reaction conditions for the cyclization of **1**.[a]

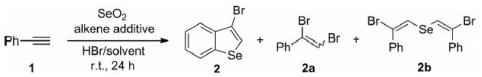
Entry	SeO_2 [equiv.]	Alkene additive (equiv.)	Product mass ratio [%][h] **2**	**2a**	**2b**
1[b]	1.2	–	43	39	18
2[c]	1.2	–	55	40	5
3[d]	1.2	–	59	38	3
4	1.2	–	60	38	2
5[e]	1.2	–	34	61	5
6[f]	1.2	–	68	28	4
7[g]	1.2	cyclohexene (1.0)	96 (45)	< 1	3
8	1.2	cyclohexene (0.8)	90	4	6
9	1.2	cyclohexene (0.6)	82	10	8
10	1.2	cyclohexene (0.4)	75	21	4
11	1.2	allyl alcohol (1.0)	52	45	3
12	1.2	3,4-dihydro-2*H*-pyran (1.0)	92	4	4
13	1.2	cyclohex-2-enone (1.0)	97 (46)	< 1	2
14	1.5	cyclohex-2-enone (1.2)	97 (51)	< 1	2
15	2.0	cyclohex-2-enone (1.0)	97 (60)	< 1	2
16	1.2	isophorone (1.0)	70	26	4

[a] Reaction conditions (unless otherwise stated): phenylacetylene **1** (200 mg), dioxane (12 mL), 48% HBr (0.43 mL), selenium dioxide (1.0 mmol). [b] Reaction performed in 3 mL dioxane. [c] Reaction performed in 6 mL dioxane. [d] Reaction performed in 9 mL of dioxane. [e] Et_2O was used as solvent. [f] THF was used as solvent. [g] For isolation of **2** the reaction was performed on a 5.0 g scale of **1**. [h] Determined by GC–MS. [i] Isolated yield shown in parentheses.

Table 2. Optimization of reaction conditions for cyclization of **3a**.[a]

Entry	SeO_2 [equiv.]	Cyclohexene [equiv.]	Product mass ratio [%][b] **4a**[c]	**5**	**6**
1	1.2	–	62 (42)	38	–
2	1.2	1.0	99 (62)	1	–
3	1.5	1.2	> 99 (76)	< 1	–
4	2.0	–	72 (48)	11	17
5	4.0	–	73 (46)	1	26

[a] Reaction conditions (unless otherwise stated): **3a** (300 mg), dioxane (6 mL), 48% HBr (0.43 mL), selenium dioxide (1.0 mmol). [b] Determined by GC–MS. [c] Isolated yield is shown in parentheses.



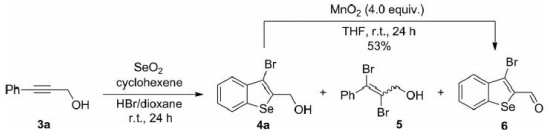
Scheme 2. Cyclization of **1**.

Because the formation of **2a** could be explained by reaction of **1** with the bromine expelled during the cyclization process (Scheme 1), we examined the use of a selective bromine scavenger that, under the given reaction conditions, would be inactive to $SeBr_4$. We were pleased to find that, in the presence of one equivalent of cyclohexene, formation of **2a** was almost completely prevented and, as a result, a nearly 1:1 mixture of **2** and 1,2-dibromocyclohexane was obtained (Table 1, entry 7). Although, separation of these compounds by chromatographic methods turned out to be rather difficult, **2** was isolated in high purity by distillation under reduced pressure. We noticed that the use of a decreased amount of cyclohexene led to the formation of larger quantities of **2a** (Table 1, entries 8–10). On the other hand, when a larger amount of alkene additive was employed, no **2a** formed, however, the yield of **2** decreased. In the presence of 2.0 equiv. cyclohexene almost no cyclization product was observed, and 1,2-dibromocyclohexane was formed as a main product, which indicates that under the given reaction conditions the alkene additive reacts with $SeBr_4$. Because, in this case, no cyclization took place, it was presumed that selenium(IV) bromide itself could serve as a brominating agent. Such a hypothesis was confirmed by performing the reaction in the absence of **1**. As a result, 1,2-dibromocyclohexane was obtained as almost sole product. To adapt the methodology for small-scale synthesis, we looked for alternative bromine scavengers that would form more polar adducts that would be easier to separate from **2** (Table 1, entries 11–16). Allyl alcohol turned out to be rather ineffective because a large amount of **2a** as well as other unidentified side products were formed (Table 1, entry 11). 2,3-Dihydropyrane appeared to be slightly less active than cyclohexene and, consequently, only 4% **2b** was formed (Table 1, entry 12). Finally, cyclohexenone showed excellent activity and selectivity, providing easy isolation of pure **2** in 46% yield (Table 1, entry 13). Notably, the use of 1.5 equiv. SeO_2 and 1.2 equiv. cyclohexenone did not dramatically alter the product yield (Table 1, entry 14). However, when the amount of selenium dioxide was increased to 2.0 equiv. and only 1.0 equiv. cyclohexenone was used, **2** was isolated in 60% yield (Table 1, entry 15). With the aim of finding a less expensive alternative to cyclohexenone, we attempted to use isophorone but, presumably for steric reasons, this turned out to be ineffective (Table 1, entry 16).

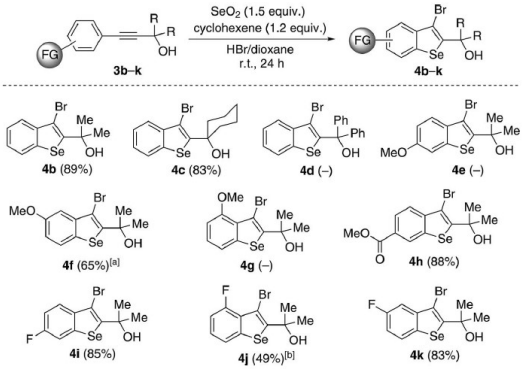
Thus, a potential precursor for the synthesis of more complex benzo[*b*]selenophene derivatives can be obtained in a single step directly from commercially available materials without the use of anhydrous solvents or an inert atmosphere. The last time the synthesis of **2** was reported (1974),[11b] the approach employed selective debromination of 2,3-dibromobenzo[*b*]selenophene.

Recently, two papers[12] have been published by Braverman and co-workers regarding reactions of propargyl alcohols with selenium di- and tetrahalides under anhydrous conditions, but no successful results were obtained for the preparative synthesis of benzo[*b*]selenophenes. Because highly versatile substrates could be obtained for further modifications, we were encouraged to explore the cyclization of these derivatives. Commercially available 3-phenylpropargyl alcohol (**3a**) was chosen as a model compound for optimization of the reaction conditions (Scheme 3, Table 2). As expected, a large amount of the corresponding dibromo derivative **5** was formed in the absence of alkene additive (Table 2, entry 1). Although the separation of **4a** from **5** was rather complex, pure **4a** was isolated in 42% yield. Nevertheless, in the presence of one equivalent of cyclohexene, the formation of **5** was nearly completely prevented and product **4a** was obtained (62%) (Table 2, entry 2). When 1.5 equiv. selenium(IV) oxide and 1.2 equiv. cyclohexene were used, the yield of **4a** increased to 76% (Table 1, entry 3). We found that the formation of **5** could be effectively prevented when a large excess of SeO_2 was used (Table 2, entries 4 and 5). Such an approach is not only economically disadvantageous, but also another side product, **6**, was formed as a result of oxidation of the hydroxymethyl group of **4a**. Aldehyde **6** was also obtained by oxidation of **4a** with manganese(IV) oxide (Scheme 3).

Optimized reaction conditions (Table 2, entry 3) were applied to the cyclization of substituted phenylpropargyl alcohols (Scheme 4). Arylalkynes **3b**, **3c**, and **3e**–**i** were successfully obtained in a single step from the corresponding aryl bromides and terminal alkynes by using Sonogashira cross-coupling reactions (see the Supporting Information). By cyclization of dimethyl-substituted **3b** and cyclohexyl derivative **3c**, the corresponding benzo[*b*]selenophenes **4b** and **4c** were obtained in very good yields. Although the formation of **4d** was detected by GC–MS, all attempts to isolate pure product were unsuccessful; failure in this case can possibly be explained by steric hindrance imparted by the phenyl groups. As previously reported,[9e] the outcome of the reaction depends strongly on the nature of the substituents in the aromatic ring. Even in the presence of an alkene additive, cyclization of *para*-methoxy-substituted **3e** led to the formation of an inseparable mixture of **4e** and the corresponding dibromo derivative. In the case of *ortho*-



Scheme 3. Cyclization of **3a** and oxidation of **4a** to **6**.



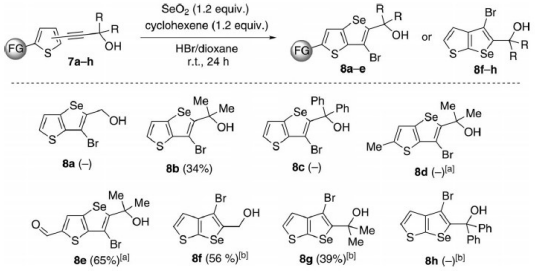
Scheme 4. Cyclization of phenylpropargyl alcohols **3b**–**j**. Reaction conditions (unless otherwise stated): **3b**–**j** (300 mg), dioxane (6 mL), 48% HBr (0.43 mL), selenium dioxide (1.0 mmol). [a] Product was isolated with 10% premix of 7-methoxy isomer. [b] SeO_2 (2.0 equiv.) and cyclohexene (1.0 equiv.) were used and reaction time was 72 h.

methoxy-substituted **3g**, only a trace amount of the cyclization product **4g** was detected (GC–MS), with the major product being the corresponding dibromo derivative. No bromination of the triple bond of the starting material was observed in the cyclization of **3f** but, unfortunately, the reaction suffered from a lack of complete regioselectivity. Compound **4f** was formed as a major regioisomer (approximately 90%), but we were not able to separate this from the corresponding 7-methoxy derivative. The presence of the other regioisomer could not be established by GC–MS analysis because the mixture appears as a single signal, but it could be readily recognized by ^{1}H NMR spectroscopy. A strongly electron-withdrawing group in the *para*-position of **3h** favors the corresponding cyclization product, and **4h** was easily isolated in 88% yield. Similarly, *para*-fluoro derivative **3i** underwent clean cyclization to give **4i** in very good yield. Interesting results were found in the cyclization of *ortho*-fluoro-substituted **3j**. Although seven days were required for complete consumption of starting material, no formation of the corresponding dibromo derivative was observed. Use of 2.0 equiv. SeO_2 and 1.0 equiv. cyclohexene reduced the reaction time to 72 h, and **4j** was isolated in 49% yield. In the case of *meta*-fluoro-substituted **3k**, the reaction proceeded with complete regioselectivity and the corresponding cyclization product **4k** was isolated in 83% yield.

From the results obtained for the cyclization of substituted phenylpropargyl alcohol derivatives **3a**–**k** (Scheme 4), it is quite clear that the failure of the cyclization of *para*- and *ortho*-methoxy substituted compounds **3e** and **3g** is not due to deactivation towards the intramolecular S_EAr step (Scheme 1), as reported[9e] for the cyclization of phenylpropiolic acid derivatives. More likely, the presence of an electron-donating group increases the electron density on the C≡C triple bond of the starting material, thus making it more attractive for attack by the bromine molecule. Particularly, in the case of **3g**, direct bromination of the triple bond almost completely overcomes the selenobromination.

To broaden the substrate scope of the reaction further, we attempted the cyclization of thienylpropargyl alcohols, which could lead to formation of selenopheno[3,2-*b*]- and selenopheno[2,3-*b*]thiophenes (Scheme 5). Although electrophilic cyclization of 3-alkynyl-2-organylselenothiophenes[13] serves as a powerful tool for the preparation of 4-haloselenopheno[2,3-*b*]thiophenes, no convenient methodologies are available for the synthesis of 6-haloselenopheno[3,2-*b*]thiophenes.

Similarly to phenylpropargyl alcohols **3b**, **3c**, and **3e**–**j**, substrates **7a**–**h** were prepared in one step from the corresponding bromothiophenes and terminal alkynes under the Sonogashira protocol (see the Supporting Information). When previously optimized reaction conditions (Table 2, entry 3) were applied to the cyclization of **7a**, a complex mixture of products was obtained. Along with cyclization product **8a**, not only was a large amount of the corresponding dibromo derivative formed, but bromination at the α-position of thiophene ring was also detected. No better results were obtained by increasing the amount of alkene additive, however, α-bromination was almost completely prevented when only 2.4 equiv. of hydrogen bromide was used per 1.0 equiv. SeO_2. In this case, formation of the corresponding dibromo derivative was also considerably suppressed, however, formation of $SeBr_4$ in situ is open to question. The isolation of pure **8a** was unsuccessful, but treatment of **7b** with selenium(IV) oxide (1.2 equiv.) and cyclohexene (1.2 equiv.) led to the formation of selenopheno[3,2-*b*]thiophene derivative **8b** in 34% yield. As expected, formation of the cyclization product **8c** was not detected, probably because of steric hindrance. When α-



Scheme 5. Cyclization of thienylpropargyl alcohols **7a**–**h**. Reaction conditions (unless otherwise stated): **7a**–**h** (300 mg), dioxane (6.0 mL), 48% HBr (0.27 mL), selenium dioxide (1.0 mmol). [a] Reaction conditions were those used for the cyclization of phenylpropargyl alcohols **3a**–**i**. [b] During addition of thienylethynyl alcohol **7f**–**g** solution to $SeBr_4$ the reaction mixture was cooled to 0 °C.

methyl-substituted **7d** was submitted to the conditions used for cyclization, only a trace amount of **8d** was observed by GC–MS, and the corresponding dibromo derivative was formed as a major product. Because in this case no α-bromination could take place, we tried to employ reaction conditions analogous to the cyclization of phenylpropargyl alcohol derivatives (Table 2, entry 3), but no better results were achieved. In general, the reactivity of 2-alkynylthiophenes **7a**–**d** was similar to methoxy-substituted **3e** and **3g** (Scheme 4). On the other hand, the presence of a strongly electron-withdrawing formyl group activates **7e** towards cyclization. As a result, under previously optimized conditions (Table 2, entry 3) cyclization of **7e** proceeded without formation of the corresponding dibromo derivative and product **8e** was isolated in 66% yield. Completely different reactivity was observed in the case of 3-alkynylthiophenes **7f** and **7g**. Although α-bromination in the thiophene ring was not completely avoided, no formation of the corresponding dibromo derivative was observed, and selenopheno[2,3-*b*]thiophenes **8f** and **8g** were obtained in moderate yields. As expected, diphenyl-substituted **7h** did not form any cyclization product.

For representative derivatives **4b**, **8b**, and **8g** single-crystal X-ray analysis data were obtained. Molecular structures with thermal ellipsoids and atomic labels are shown in Figure 1. The crystal structures of **4b**, **8b**, and **8g** are isomorphous and each asymmetric unit consists of two independent molecules. These compounds form tetramers by means of O–H···O′ and O′–H′···O intermolecular hydrogen bonds. The lengths of these bonds in the structures of **4b**, **8b**, and **8g** are 2.742(4)/2.801(4) Å, 2.740(7)/2.787(7) Å, and 2.729(7), 2.803(8) Å, respectively.

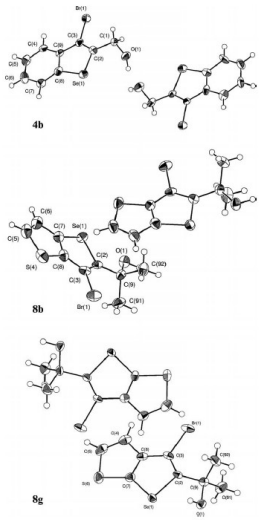
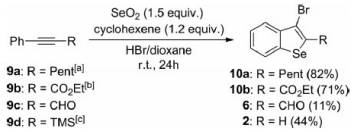


Figure 1. Molecular structures of **4b**, **8b**, and **8g**.

Other C(sp)-substituted arylalkynes were also subjected to cyclization (Scheme 6). Very good yield was obtained by selenobromination of hept-1-ynylbenzene (**9a**). Because of the low polarity of **10a**, cyclohex-2-enone was used as alkene additive. Considerably slower reaction was observed in the cyclization of ethyl phenylpropiolate (**9b**). By using 2.0 equiv. selenium dioxide and 1.2 equiv. cyclohexene the reaction proceeded for 36 h and ester derivative **10b** was isolated in 71% yield.

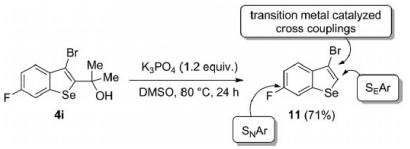
The longer reaction time required for these reactions is probably a result of the decrease in nucleophilicity of the triple bond in the initial compounds. It should be noted that previously reported[9e] cyclization of the corresponding methyl ester provided the cyclization product in only 17% yield. Although no bromination of the C≡C triple bond of



Scheme 6. Cyclization of C(sp)-substituted arylalkynes **10a**–**d**. Reaction conditions (unless otherwise stated): arylalkyne **10a**–**d** (200 mg), 48% HBr (0.43 mL), SeO_2 (1.0 mmol). [a] Cyclohex-2-enone was used as alkene additive. [b] SeO_2 (2.0 equiv.) and cyclohexene (1.2 equiv.) were used and the reaction time was 36 h. [c] SeO_2 (2.0 equiv.) and cyclohex-2-enone (2.0 equiv.) were used; complete desilylation was achieved by the use of TBAF (0.5 equiv.).

the starting material was observed, cyclization of aldehyde **9c** led to aldehyde derivative **6** in only 11% yield, which is close to that previously reported.[9e] Nevertheless, aldehyde **6** can be obtained in better yield by using a two-step procedure (Scheme 3). Finally, cyclization of phenylethynyltrimethylsilane (**9d**) was attempted, however, as expected, the TMS group was not sufficiently stable to survive under the given reaction conditions, so partial desilylation occurred. Complete desilylation was achieved by treatment of the reaction mixture with 0.5 equiv. tetrabutylammonium fluoride (TBAF). As a result, 2-unsubstituted 3-bromobenzo[*b*]selenophene (**2**) was obtained in 44% yield. In this case, it was essential to use equimolar amounts of SeO_2 and alkene additive, because in the presence of a subequimolar amount of alkene additive the TMS group was partially replaced by bromine, leading to a premix of the corresponding 2,3-dibromo derivative.

Propan-2-ole derivatives **4b** and **4h**–**k** can serve as powerful precursors for 2-unsubstituted frameworks. For example, by deacetonation[14] of **4i**, 3-bromo-6-fluorobenzo[*b*]-selenophene (**11**) was obtained in good yield (Scheme 7).



Scheme 7. Deacetonation of **4i**.

A wide range of modifications can be envisioned for **11**, because the C–Br bond is available for different kinds of transition-metal-catalyzed processes, C-2 is active in electrophilic aromatic substitution, and it is well-known that fluorine is an excellent leaving group for nucleophilic aromatic substitution, which would allow insertion of electron-donating groups (for example alkoxy) in positions that are forbidden during cyclization process.

Conclusions

A new approach for the cyclization of readily accessible aryl(thienyl)alkynes under selenobromination conditions has been elaborated. The method provides convenient synthetic access to a wide variety of 3-bromobenzo[*b*]selenophenes and, for the first time, selenobromination is applicable for the preparation of selenophenothiophenes. By cyclization of commercially available substrates, the 3-bromobenzo[*b*]selenophene heterocyclic framework can be obtained in one step without the use of anhydrous solvents or an inert atmosphere. A significant limitation of the elaborated methodology is extensive bromination of the C≡C triple bond of the starting material, or lack of regioselectivity, when electron-donating groups bearing aryl(tienyl)alkynes are subjected to cyclization. Nevertheless, unsubstituted and ethynyl arenes bearing an electron-withdrawing group are highly favored and even *meta*-fluoro derivative **3k** was cyclized with complete regioselectivity in very good yield. The presence of an electron-withdrawing group in the α-position of the thiophene ring is essential for highly efficient preparation of 6-bromoselenopheno[3,2-*b*]thiophenes. So far, this is the only methodology available for the preparation of this type of derivative.

Further work in this area will be directed towards to bis- and tris-cyclizations, as well as to regioselective cyclization of diaryl(hetaryl)alkynes.

Experimental Section

General Remarks: Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using MERCK Silica gel 60 F254 plates and visualized by UV (254 nm) fluorescence. ZEOCHEM silica gel (ZEOprep 60/35–70 microns – SI23501) was used for column chromatography. ^1H, ^{13}C, ^{19}F, and ^{77}Se NMR spectra were recorded with a Varian 400 Mercury spectrometer at 400.0, 100.58, 376.21, and 76.37 MHz, respectively, at 298 K in $CDCl_3$. The ^1H chemical shifts are given relative to residual $CHCl_3$ signal (δ = 7.26 ppm), ^{13}C shifts are relative to $CDCl_3$ (δ = 77.0 ppm), and ^{77}Se relative to dimethyl selenide (δ = 0.0 ppm). The melting points were determined with a "Digital melting point analyser" (Fisher), and the results are given without correction. Diffraction data were collected with a Nonius Kappa CCD diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The crystal structures were solved by direct methods and refined by full-matrix least-squares.

Large-Scale Procedure Using Cyclohexene as Alkene Additive: Selenium dioxide (6.52 g, 58.8 mmol) was dissolved in 48% hydrogen bromide (25.3 mL) and stirred at room temp. for 15 min. A solution of **1** (5.00 g, 49.0 mmol) and cyclohexene (4.03 g, 49.0 mmol) in dioxane (300 mL) was added dropwise, and the reaction mixture was stirred at room temp. for 24 h. Then reaction was quenched with ethyl acetate (500 mL) and water (200 mL). After stirring for 15 min, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 150 mL). The combined organic phases were washed with brine (200 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography on sil-

ica gel (petroleum ether) to give a mixture of **2** and 1,2-dibromocyclohexane (approximately 1:1) as a colorless oil. Product **2** (5.73 g, 45%) was isolated by fractionated distillation.

3-Bromobenzo[*b*]selenophene (2):[15] Colorless oil; b.p. 120 °C (10 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, $^2J_{H,Se}$ = 44.8 Hz, 1 H, 2-CH), 7.88–7.94 (m, 2 H, 4,7-CH), 7.46–7.52 (m, 1 H, 6-CH), 7.34–7.40 (m, 1 H, 5-CH) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 139.4, 139.2, 125.7, 125.4, 125.3, 125.2, 124.7, 109.4 ppm. ^{77}Se NMR (76.37 MHz, $CDCl_3$): δ = 533.8 (s) ppm. MS (EI, 70 eV): *m/z* (%) = 260 (100) $[M]^+$. C_8H_5BrSe (259.99): calcd. C 36.96, H 1.94; found C 36.54, H 1.79.

Small-Scale Procedure Using Cyclohex-2-enone as Alkene Additive: Selenium dioxide (435 mg, 3.92 mmol) was dissolved in 48% hydrogen bromide (1.69 mL) and stirred at room temp. for 15 min. A solution of **1** (200 mg, 1.96 mmol) and cyclohex-2-enone (188 mg, 1.96 mmol) in dioxane (12 mL) was added dropwise, and the reaction mixture was stirred at room temp. for 24 h. The reaction was quenched with ethyl acetate (50 mL) and water (20 mL). After stirring for 15 min, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic phases were washed with brine (40 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether) to give **2** (306 mg, 60%).

Cyclization of Phenylpropargylalcohol Derivatives 3a–c, 3f, 3h, 3i, and 3k: Typical Procedure for 3a: Selenium dioxide (378 mg, 3.41 mmol) was dissolved in 48% hydrogen bromide (1.47 mL) and stirred at room temp. for 15 min. A solution of **3a** (300 mg, 2.27 mmol) and cyclohexene (223 mg, 2.72 mmol) in dioxane (6.0 mL) was added dropwise, and the reaction mixture was stirred at room temp. for 24 h. The reaction was quenched with ethyl acetate (80 mL) and water (30 mL). After stirring for 15 min, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 40:1→5:1) to give **4a** (501 mg, 76%).

(3-Bromobenzo[*b*]selenophen-2-yl)methanol (4a):[16] White solid; m.p. 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.87 (m, 2 H, 4,7-CH), 7.42–7.48 (m, 1 H, 6-CH), 7.29–7.35 (m, 1 H, 5-CH), 4.99 (s, 2 H, CH_2), 2.26 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 143.3, 140.1, 138.2, 125.6, 125.4, 125.3, 125.0, 105.7, 62.2 ppm. MS (EI, 70 eV): *m/z* (%) = 290 (64) $[M]^+$, 183 (100). C_9H_7BrOSe (290.02): calcd. C 37.27, H 2.43; found C 37.20, H 2.46.

2-(3-Bromobenzo[*b*]selenophen-2-yl)propan-2-ol (4b): Eluent: petroleum ether/ethyl acetate (40:1→5:1), yield 89%; white solid; m.p. 119–121 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.80 (m, 2 H, 4,7-CH), 7.47–7.40 (m, 1 H, 6-CH), 7.34–7.28 (m, 1 H, 5-CH), 2.63 (br. s, 1 H, OH), 1.82 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 153.5, 141.9, 137.0, 125.1 (2 C), 125.0, 101.7, 74.3, 29.2 ppm. ^{77}Se NMR (76.37 MHz, $CDCl_3$): δ = 548.2 ppm (s) ppm. MS (EI, 70 eV): *m/z* (%) = 318 (45) $[M]^+$, 303 (100) $[M - CH_3]^+$. $C_{11}H_{11}BrOSe$ (318.07): calcd. C 41.54, H 3.49; found C 41.49, H 3.51.

1-(3-Bromobenzo[*b*]selenophen-2-yl)cyclohexanol (4c): Eluent: petroleum ether/ethyl acetate (40:1→5:1), yield 83%; white solid; m.p. 67–68 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.81 (m, 2 H, 4′,7′-CH), 7.48–7.41 (m, 1 H, 6′-CH), 7.34–7.27 (m, 1 H, 5′-CH), 2.62 (br. s, 1 H, OH), 2.59–2.44 (m, 2 H, 2,6-CH), 1.87–1.96 (m, 2 H, 2,6-CH), 1.68–1.82 (m, 5 H, 3,4,5-CH), 1.30–1.47 (m, 1 H, 4-CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 154.0, 142.1, 137.1, 125.1, 125.0 (2 C), 124.9, 101.4, 75.4, 35.6, 24.9, 21.7 ppm. MS (EI, 70 eV): *m/z* (%) = 358 (57) $[M]^+$, 236 (100). $C_{14}H_{15}BrOSe$ (358.14): calcd. C 46.95, H 4.22; found C 46.85, H 4.25.

2-(3-Bromo-5-methoxybenzo[*b*]selenophen-2-yl)propan-2-ol (4f): Eluent: petroleum ether/ethyl acetate (40:1→5:1); isolated with premix of minor regioisomer (approximately 10%); Overall yield: 65%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 [d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7-CH], 7.32 [d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 4-CH], 6.95 [dd, $^4J_{H,H}$ = 2.5, $^3J_{H,H}$ = 8.6 Hz, 1 H, 6-CH], 3.90 (s, 3 H, OCH_3), 2.64 (br. s, 1 H, OH), 1.83 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 155.0, 143.0, 128.5, 125.9, 114.9, 107.9, 104.9, 101.3, 74.3, 55.6, 29.2 ppm. ^{77}Se NMR (76.37 MHz, $CDCl_3$): δ = 537.8 ppm. MS (EI, 70 eV): *m/z* (%) = 348 (11) $[M]^+$, 330 (100) $[M - H_2O]^+$. $C_{10}H_9BrO_2Se$ (320.04): calcd. C 37.53, H 2.83; found C 37.44, H 2.94.

Methyl 3-Bromo-2-(2-hydroxypropan-2-yl)benzo[*b*]selenophene-6-carboxylate (4h): Eluent: petroleum ether/ethyl acetate (20:1→10:3), yield 88%; white solid; m.p. 137–138 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 [dd, $^5J_{H,H}$ = 0.6, $^4J_{H,H}$ = 1.6 Hz, 1 H, 7-CH], 8.07 [dd, $^4J_{H,H}$ = 1.6, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-CH], 7.85 [dd, $^5J_{H,H}$ = 0.6, $^3J_{H,H}$ = 8.4 Hz, 1 H, 4-CH], 3.96 (s, 3 H, OCH_3), 2.77 (br. s, 1 H, OH), 1.84 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 166.9, 158.6, 145.5, 136.8, 127.0, 126.5, 126.0, 124.8, 101.6, 74.5, 52.3, 29.0 ppm. MS (EI, 70 eV): *m/z* (%) = 376 (43) $[M]^+$, 361 (100) $[M - CH_3]^+$. $C_{13}H_{13}BrO_3Se$ (376.11): calcd. C 41.52, H 3.48; found C 41.58, H 3.49.

2-(3-Bromo-6-fluorobenzo[*b*]selenophen-2-yl)propan-2-ol (4i): Eluent: petroleum ether/ethyl acetate (40:1→10:1); Yield: 85%; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, $^4J_{H,F}$ = 5.0, $^3J_{H,H}$ = 8.9 Hz, 1 H, 4-CH), 7.53 (dd, $^4J_{H,H}$ = 2.4, $^3J_{H,F}$ = 8.1 Hz, 1 H, 7-CH), 7.16 (ddd, $^4J_{H,H}$ = 2.4, $^3J_{H,H}$ = 8.9, $^3J_{H,F}$ = 8.9 Hz, 1 H, 5-CH), 2.60 (br. s, 1 H, OH), 1.82 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 160.8 (d, $^1J_{C,F}$ = 247.6 Hz), 153.0 (d, $^4J_{C,F}$ = 3.5 Hz), 138.4 (d, $^5J_{C,F}$ = 1.6 Hz), 137.8 (d, $^3J_{C,F}$ = 9.0 Hz), 126.3 (m), 113.8 (m), 111.4 (m), 100.8 (d, $^6J_{C,F}$ = 0.8 Hz), 74.3, 29.2 ppm. ^{19}F NMR (376.21 MHz, $CDCl_3$): δ = –116.7 (m) ppm. MS (EI, 70 eV): *m/z* (%) = 336 (8) $[M]^+$, 318 (66) $[M - H_2O]^+$, 159 (100). $C_{11}H_{10}BrFOSe$ (336.06): calcd. C 39.31, H 3.00; found C 39.18, H 3.05.

2-(3-Bromo-5-fluorobenzo[*b*]selenophen-2-yl)propan-2-ol (4k): Eluent: petroleum ether/ethyl acetate (40:1→10:1), yield 83%; white crystalline solid; m.p. 84–85 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, $^4J_{H,F}$ = 5.0, $^3J_{H,H}$ = 8.7 Hz, 1 H, 7-CH), 7.53 (dd, $^4J_{H,H}$ = 2.5, $^3J_{H,F}$ = 10.0 Hz, 1 H, 4-CH), 7.06 (ddd, $^4J_{H,H}$ = 2.5, $^3J_{H,H}$ = 8.7, $^3J_{H,F}$ = 8.7 Hz, 1 H, 6-CH), 2.57 (br. s, 1 H, OH), 1.83 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 161.6 (d, $^1J_{C,F}$ = 242.1 Hz), 156.6, 143.5 (d, $^3J_{C,F}$ = 9.0 Hz), 131.9 (d, $^4J_{C,F}$ = 1.9 Hz), 126.4 (d, $^3J_{C,F}$ = 9.0 Hz), 113.7 (d, $^2J_{C,F}$ = 24.5 Hz), 111.1 (d, $^2J_{C,F}$ = 24.1 Hz), 100.9 (d, $^4J_{C,F}$ = 4.3 Hz), 74.4, 29.1 ppm. ^{19}F NMR (376.21 MHz, $CDCl_3$): δ = –117.4 (m) ppm. MS (EI, 70 eV): *m/z* (%) = 336 (45) $[M]^+$, 321 (100) $[M - CH_3]^+$. $C_{11}H_{10}BrFOSe$ (336.06): calcd. C 39.31, H 3.00; found C 39.22, H 3.04.

Cyclization of 3j: Methodology was analogous to cyclization of **3a** except SeO_2 (2.0 equiv.) and cyclohexene (1.0 equiv.) were used and the reaction was run for 72 h.

2-(3-Bromo-4-fluorobenzo[*b*]selenophen-2-yl)propan-2-ol (4j): Eluent: petroleum ether/ethyl acetate (40:1→10:1), yield 49%; white

solid; m.p. 103–104 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, $^4J_{H,H}$ = 0.9, $^3J_{H,H}$ = 7.9 Hz, 1 H, 7-CH), 7.22 (ddd, $^4J_{H,F}$ = 4.5, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 7.9 Hz, 1 H, 6-CH), 7.06 (ddd, $^4J_{H,H}$ = 0.9, $^3J_{H,H}$ = 7.9, $^3J_{H,F}$ = 12.4 Hz, 1 H, 5-CH), 2.54 (br. s, 1 H, OH), 1.84 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 158.5 (d, $^1J_{C,F}$ = 256.5 Hz), 154.5 (d, $^5J_{C,F}$ = 1.2 Hz), 139.7 (d, $^4J_{C,F}$ = 2.7 Hz), 130.0 (d, $^3J_{C,F}$ = 9.7 Hz), 125.5 (d, $^3J_{C,F}$ = 7.8 Hz), 121.1 (d, $^4J_{C,F}$ = 4.7 Hz), 111.6 (d, $^2J_{C,F}$ = 21.8 Hz), 95.9 (d, $^4J_{C,F}$ = 4.3 Hz), 74.7, 28.8 ppm. ^{19}F NMR (376.21 MHz, $CDCl_3$): δ = –117.7 (m) ppm. MS (EI, 70 eV): *m/z* (%) = 336 (46) $[M]^+$, 321 (100) $[M - CH_3]^+$. $C_{11}H_{10}BrFOSe$ (336.06): calcd. C 39.31, H 3.00; found C 39.25, H 3.04.

Cyclization of 2-Methyl-4-thiophen-2-ylbut-3-yn-2-ol (7b): Selenium dioxide (240 mg, 2.16 mmol) was dissolved in 48% hydrogen bromide (0.60 mL) and stirred at room temp. for 15 min. A solution of **7b** (300 mg, 1.80 mmol) and cyclohexene (177 mg, 2.16 mmol) in dioxane (6.0 mL) was added dropwise to a cooled (10 °C) solution of selenium(IV) bromide, and the reaction mixture was stirred at room temp. for 24 h. The reaction was quenched with ethyl acetate (80 mL) and water (30 mL). After stirring for 15 min, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2× 50 mL). The combined organic phases were washed with brine (50 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 50:3) and recrystallized (petroleum ether) to give **8b** (198 mg, 34%).

2-(6-Bromoselenopheno[3,2-*b*]thiophen-5-yl)propan-2-ol (8b): Pale-yellow crystalline solid; m.p. 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H, 2-CH), 7.30 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H, 3-CH), 2.49 (br. s, 1 H, OH), 1.80 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 154.5, 144.2, 133.0, 125.6, 123.4, 95.9, 74.1, 29.4 ppm. MS (EI, 70 eV): *m/z* (%) = 324 (39) $[M]^+$, 309 (100) $[M - CH_3]^+$. $C_9H_9BrOSSe$ (324.09): calcd. C 33.35, H 2.80; found C 33.28, H 2.84.

Cyclization of 5-(3-Hydroxy-3-methylbut-1-ynyl)thiophene-2-carbaldehyde (7e): Methodology was analogous to the cyclization of **3a**.

6-Bromo-5-(2-hydroxypropan-2-yl)selenopheno[3,2-*b*]thiophene-2-carbaldehyde (8e): Eluent: petroleum ether/ethyl acetate (40:1→4:1), yield 66%; pale-yellow solid; m.p. 127–128 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H, cabonyl-CH), 7.97 (s, 1 H, 3-CH), 2.72 (br. s, 1 H, OH), 1.81 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 183.2, 162.6, 151.4, 142.9, 132.7, 132.6, 96.6, 74.5, 29.0 ppm. MS (EI, 70 eV): *m/z* (%) = 352 (38) $[M]^+$, 337 (100) $[M - CH_3]^+$. $C_{10}H_9BrO_2SSe$ (352.10): calcd. C 34.11, H 2.58; found C 34.00, H 2.60.

General Method for Cyclization of 8f and 8g: Methodology was analogous to cyclization of **8b**, except the reaction mixture was cooled to 0 °C (ice bath) during addition of dioxane solution, then slowly (within 2 h) allowed to reach room temp. and stirred for an additional 24 h.

(4-Bromoselenopheno[2,3-*b*]thien-5-yl)methanol (8f): Eluent: petroleum ether/ethyl acetate (40:1→10:1); Yield: 56%; white crystalline solid; m.p. 92–93 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H, 2-CH), 7.23 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H, 3-CH), 4.90 (d, $^3J_{H,H}$ = 4.8 Hz, 2 H, CH_2), 2.23 (t, $^3J_{H,H}$ = 4.8 Hz, 1 H, OH) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 147.5, 144.8, 132.6, 128.9, 121.6, 101.3, 61.8 ppm. MS (EI, 70 eV): *m/z* (%) = 296 (100) $[M]^+$. $C_7H_5BrOSSe$ (296.04): calcd. C 28.40, H 1.70; found C 28.40, H 1.78.

2-(4-Bromoselenopheno[2,3-*b*]thiophen-5-yl)propan-2-ol (8g): Eluent: petroleum ether/ethyl acetate (40:1→10:1), yield 39%; white crystalline solid; m.p. 103–104 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H, 2-CH), 7.21 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H, 3-CH), 2.50 (br. s, 1 H, OH), 1.80 (s, 6 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 155.1, 149.5, 130.6, 128.2, 122.1, 74.3, 29.4 ppm. MS (EI, 70 eV): *m/z* (%) = 324 (8) $[M]^+$, 306 (71) $[M - H_2O]^+$, 147 (100). $C_9H_9BrOSSe$ (324.09): calcd. C 33.35, H 2.80; found C 33.30, H 2.81.

Cyclization of Hept-1-yn-1-ylbenzene (9a): Method was analogous to cyclization of **3a**, except cyclohex-2-enone was used as alkene additive.

3-Bromo-2-pentylbenzo[*b*]selenophene (10a): Eluent: petroleum ether, yield 82%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.78 (m, 2 H, 4,7-CH), 7.45–7.40 (m, 1 H, 6-CH), 7.30–7.26 (m, 1 H, 5-CH), 3.03–2.96 (m, 2 H, 1′-CH_2), 1.79–1.69 (m, 2 H, 2′-CH_2), 1.48–1.33 (m, 4 H, 3′,4′-CH_2), 0.95–0.89 (m, 3 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 144.3, 140.3, 125.3, 125.2, 125.0, 124.9, 107.4, 32.2, 31.3, 30.8, 22.4, 14.0 ppm. MS (EI, 70 eV): *m/z* (%) = 330 (39) $[M]^+$, 273 (100) $[M - C_4H_9]^+$. $C_{13}H_{15}BrSe$ (330.13): calcd. C 47.30, H 4.58; found C 47.38, H 4.43.

Cyclization of Ethyl 3-Phenylpropiolate (9b): Method was analogous to cyclization of **3a**, except SeO_2 (2.0 equiv.) and cyclohexene (1.2 equiv.) were used and the reaction was run for 36 h.

Ethyl 3-Bromobenzo[*b*]selenophene-2-carboxylate (10b): Eluent: petroleum ether/ethyl acetate (1:0→40:1); Yield: 71%; white solid; m.p. 177–178 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.06 (m, 1 H, 4-CH), 7.89–7.85 (m, 1 H, 7-CH), 7.53–7.44 (m, 2 H, 5,6-CH), 4.42 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2),1.43 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 162.5, 140.7, 140.4, 129.6, 128.1, 127.8, 125.8, 125.6, 116.3, 61.9, 14.3 ppm. MS (EI, 70 eV): *m/z* (%) = 332 (81) $[M]^+$, 287 (100) $[M - OC_2H_5]^+$. $C_{11}H_9BrO_2Se$ (332.05): calcd. C 39.79, H 2.73; found C 39.71, H 2.77.

Cyclization of 3-Phenylpropiolaldehyde (9c): Method was analogous to the cyclization of **3a**.

3-Bromobenzo[*b*]selenophene-2-carbaldehyde (6):[17] Eluent: petroleum ether/ethyl acetate (1:0→40:1), yield 11%; pale-yellow solid; m.p. 106–107 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.20 (s, 1 H, carbonyl-CH), 8.13–8.08 (m, 1 H, 4-CH), 7.94–7.90 (m, 1 H, 7-CH), 7.46–7.55 ppm (m, 2 H, 5,6-CH) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 186.1, 141.2, 140.1, 139.5, 129.1, 127.2, 126.3, 126.1, 120.3 ppm. MS (EI, 70 eV): *m/z* (%) = 288 (100) $[M]^+$. C_9H_5BrOSe (288.00): calcd. C 37.53, H 1.75; found C 37.46, H 1.83.

Cyclization of Trimethyl(phenylethynyl)silane (9d): Selenium dioxide (255 mg, 2.30 mmol) was dissolved in 48% hydrogen bromide (0.99 mL) and stirred at room temp. for 15 min. A solution of **9d** (200 mg, 1.15 mmol) and cyclohex-2-enone (221 mg, 2.30 mmol) in dioxane (6.0 mL) was added dropwise, and the reaction mixture was stirred at room temp. for 24 h. The reaction was quenched with ethyl acetate (50 mL) and water (20 mL). After stirring for 15 min, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2× 20 mL). The combined organic phases were washed with brine (20 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in dioxane (5.0 mL), tetrabutylammonium fluoride (150 mg, 0.575 mmol) was added and reaction mixture was stirred at 110 °C overnight. After complete desilylation (monitored by

GC–MS), solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether) to give **2** (132 mg, 44%).

Oxidation of (3-Bromobenzo[*b*]selenophen-2-yl)methanol (4a): A solution of **4a** (200 mg, 0.690 mmol) in anhydrous THF (10 mL) was added dropwise to a stirred suspension of manganese(IV) oxide (240 mg, 2.76 mmol) and stirring was continued at room temp. for 24 h. Precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 1:0→40:1) to give **6** (106 mg, 53%).

Deacetonation of 2-(3-Bromo-6-fluorobenzo[*b*]selenophen-2-yl)propan-2-ol (4i): A mixture of **4i** (0.760 g, 2.26 mmol) and anhydrous potassium phosphate (0.575 g, 2.71 mmol) in anhydrous DMSO (8.0 mL) was barbotated with argon and stirred at 80 °C for 24 h. After usual workup, the crude product was purified by flash chromatography on silica gel (petroleum ether) to give **11** (0.446 g, 71%).

3-Bromo-6-fluorobenzo[*b*]selenophene (11): White solid; m.p. 50–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, $^2J_{H,Se}$ = 45.8 Hz, 1 H, 2-CH), 7.82 (dd, $^4J_{H,F}$ = 5.0, $^3J_{H,H}$ = 8.8 Hz, 1 H, 4-CH), 7.61 (dd, $^4J_{H,H}$ = 2.4, $^3J_{H,F}$ = 8.1 Hz, 1 H, 7-CH), 7.22 (ddd, $^4J_{H,H}$ = 2.4, $^3J_{H,H}$ = 8.8, $^3J_{H,F}$ = 8.8 Hz, 1 H, 5-CH) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 161.1 ($^1J_{C,F}$ = 248.3 Hz), 140.2 (d, $^3J_{C,F}$ = 9.3 Hz), 135.8 (d, $^5J_{C,F}$ = 1.6 Hz), 126.5 (d, $^3J_{C,F}$ = 9.0 Hz), 124.2 (d, $^4J_{C,F}$ = 3.5 Hz), 114.1 (d, $^2J_{C,F}$ = 24.1 Hz), 112.0 (d, $^2J_{C,F}$ = 24.9 Hz), 108.7 (d, $^6J_{C,F}$ = 0.8 Hz) ppm. ^{19}F NMR (376.21 MHz, $CDCl_3$): δ = –116.2 (m) ppm. MS (EI, 70 eV): *m/z* (%) = 278 (90) $[M]^+$, 199 (45) $[M - Br]^+$, 107 (100). C_8H_4BrFSe (277.98): calcd. C 34.57, H 1.45; found C 34.53, H 1.51.

Crystallographic Data: Diffraction data were collected at low temperature with a Nonius Kappa CCD diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The crystal structures of **4b**, **8b** and **8g** were solved by direct methods[18a] and refined by full-matrix least-squares.[18b,18c]

CCDC-967670 (for **4b**), -967165 (for **8b**), and -967166 (for **8g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Methods for the preparation of ethynylarenes, copies of the ^{1}H, ^{13}C, ^{19}F, ^{77}Se NMR spectra, and crystallographic data for compounds **4b**, **8b**, and **8g**.

Acknowledgments

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Preliminary communication

Selenium analogues of raloxifene as promising antiproliferative agents in treatment of breast cancer

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ABSTRACT

Synthetic protocols for the preparation of selenium analogues of raloxifene were elaborated. General aim of the current research is to improve the positive impact of selenium atom introduction in drug design. Antiproliferative activity on CCL-8 (mouse sarcoma), MDA-MB-435s (human melanoma), MES-SA (human uterus sarcoma), MCF-7 (human breast adenocarcinoma), HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) tumor cell lines, and normal cell line NIH 3T3 (mouse fibroblasts) was studied. Influence of aminoethoxy "tail" and benzoyl group position on SAR was discussed. Results of *in vivo* studies on BALB/c female mice with 4T1 cell induced breast cancer model showed that selenium analogue of raloxifene is able to suppress estrogen-depending tumor growth.

1. Introduction

Estrogen-sensitive cancers are one of the most frequently diagnosed diseases and a leading cause of cancer deaths [1]. The significant difference in the effectiveness of the existing treatment of cancer causes the necessity to discover new, more targeted drugs. One of the best ways to deal with the creation of malignant tumors is to support mechanisms of preventing their formation or destruction in the early stages. It is known that estrogen can be both a beneficial and a harmful molecule [2]. This compound programs the breast and uterus for sexual reproduction, controls cholesterol level in the coronary arteries, and preserves bone strength by helping to maintain the proper balance between bone build-up and breakdown [3]. Unluckily, estrogen can be also harmful due to its ability to promote the proliferation of cells in the breast and uterus increasing a chance for the development of malignant cells. Cancer is caused by DNA damage in genes that regulate cell growth and division. Since high level of estrogen in tissues can promote the formation of cancer in the breast and uterus first steps to solve this problem were made by searching drugs that block the action of estrogen. So-called antiestrogens block estrogen receptors in this way preventing genes activation responsible for specific growth-promoting proteins. In the further research was found that antiestrogen drugs usually block the action in certain tissues, but activate estrogen activity in others [4]. New generation of drugs was discovered and called as selective estrogen receptor modulators (SERMs), due to they selectively stimulate or inhibit the estrogen receptors in different tissues. SERMs can be used to treat women both before and after menopause. The most commonly used SERM drugs are tamoxifen, toremifene, arzoxifene, and raloxifene [5]. These compounds block the action of estrogen in breast tissue by binding to the estrogen receptors and are used as medicines in postmenopausal osteoporosis, treatment of breast cancer, and potentially in hormone replacement therapy [6]. Unfortunately, SERMs simultaneously may cause side effects, such as uterine cancer risk growth, hot flashes, chest pain, vision changes, etc., in recent years various modifications of these types of compounds have been intensively developed [7].

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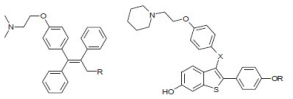


Tamoxifen (R=H)
Toremifene (R=Cl)

Raloxifene (X=CO, R=H)
Arzoxifene (X=O, R=Me)

Furthermore, in the last decades selenium has attracted growing interest as an essential element and certain diseases have been eradicated by dietary supplementation of this element. Supplemental dietary selenium is associated with reduced incidence of many cancers, including breast cancer [8a–i]. However, harmful effect of selenium overdose on human health also should be mentioned. The recommended dietary allowance of selenium for adults is up to 55 μg per day. In extreme conditions humans could survive by taking up to 400 μg per day, anything above that is considered an overdose. It may cause bad breath, hair loss, fever, leg cramps, and rush, nausea, liver, kidney and heart problems. At high enough levels, selenium could cause death [8j–n]. In continuation of our studies in the field of selenium containing compounds as antitumor agents [9] the present research is connected with the elaboration of synthetic protocols for the synthesis of selenium analogues of raloxifene, antiproliferative activity studies on various tumor cell lines depending by modifying of aminoethoxy "tail" and position of benzoyl group, and *in vivo* studies on BALB/c female mice with 4T1 cell induced breast cancer model. General purpose of the current research is to improve the positive impact of selenium atom introduction in drug design.

2. Results and discussion

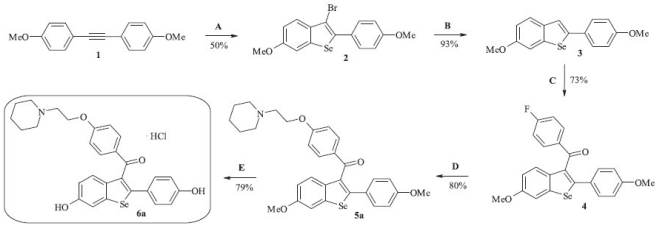
2.1. Chemistry

During the last decade benzo[*b*]selenophenes have attracted increasing attention in both medicinal chemistry and materials science. From synthetic point of view chemistry of selenium usually is quite complicated. Particularly preparation of 2-arylbenzo[*b*]selenophenes requires multistep protocols, complex reaction conditions, and use of toxic and hazardous chemicals [10].

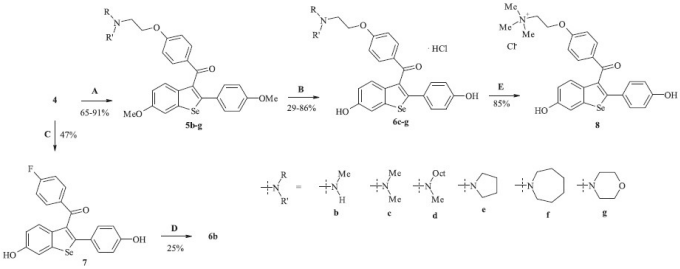
On the other hand, recently we have elaborated a new approach for cyclization of arylalkynes under selenobromination conditions [11], which was used as a key tool for straightforward construction of the 2-arylbenzo[*b*]selenophene's molecular scaffold (Scheme 1). The cyclization step (**A**) involves addition of *in situ* prepared selenium(IV) bromide to a starting materials triple bond and subsequent intramolecular electrophilic substitution in the aromatic ring. Due to extensive bromination of the triple bond reaction was performed in the presence of an alkene additive as a bromine scavenger. Furthermore, we have found that the use of triethylamine in equimolar amount with selenium(IV) oxide completely prevents precipitation of elemental selenium after quenching of the reaction mixture. This way isolation of pure product **2** becomes considerably more effortless. Treatment of **2** by zinc powder in 80% acetic acid provided 3-unsubstituted precursor **3** in excellent yield (Scheme 1, B). As benzo[*b*]selenophene **3** is an analogue of benzo[*b*]thiophene derivative which has been used for synthesis of raloxifene, further steps are analogous to preparation of an original drug [12]. Besides, corresponding yields are very similar to those obtained in reactions of the sulphur analogue. Thus, Friedel–Crafts benzoylation of **3** led to ketone **4** in a good yield (Scheme 1, C), and subsequent nucleophilic substitution of fluorine atom provided precursor **5a** in 80% yield (Scheme 1, D). Finally, deprotection of phenol moieties by BBr_3 was employed and, after treatment of the corresponding free base form with HCl/Et_2O the hydrochloride of raloxifene's selenium analogue **6a** was obtained in 79% yield (Scheme 1, E). The overall yield starting from diarylalkyne **1** in six subsequent steps was 21%.

Following the same synthetic strategy other derivatives of raloxifene's selenium analogue **6a** were obtained (Scheme 2). Precursors **5b**–**g** were prepared from **4** in good yields by nucleophilic aromatic substitution of fluorine atom (Scheme 2, A), and subsequent deprotection of **5c**–**g** provided corresponding analogues **6c**–**g** in moderate to good yields (Scheme 2, B). Unfortunately, demethylation of **5b** using BBr_3 in DCM (dichloromethane) gave complex mixture of products and we were not able to isolate pure **6b**. Therefore, we slightly modified synthetic approach by simply exchanging sequence of nucleophilic aromatic substitution and deprotection steps. Demethylation of **4** led to hydroxy substituted benzo[*b*]selenophene derivative **7** in moderate yield (Scheme 2, C). Nucleophilic aromatic substitution of fluorine atom in the presence of unprotected hydroxyl groups and subsequent treatment of corresponding free base form with HCl/Et_2O gave **6b** in relatively low yield (Scheme 2, D). The free base form of **6c** was further modified by quaternization of nitrogen atom with methyl iodide. After iodide anion exchange to chloride using anion-exchange resins choline derivative **8** was obtained in good yield (Scheme 2, E).

Similar synthetic strategy was also applied for the preparation of selenium analogues of raloxifene in which hydroxyl groups are substituted by fluorine atoms (Scheme 3). Cyclization of diarylalkyne **9** under selenobromination conditions led to 3-



Scheme 1. A: SeO_2 (4.0 equiv.), cyclohexene (3.0 equiv.), Et_3N (4.0 equiv.), HBr/dioxane, r.t., 24 h; B: Zn (5.0 equiv.), 80% AcOH, 105 °C, 24 h; C: 4-fluorobenzoyl chloride (2.0 equiv.), $AlCl_3$ (2.0 equiv.), DCM, 0 °C – r.t., 2 h; D: 2-piperidin-1-ylethanol (2.0 equiv.), NaH (2.2 equiv.), DMF, Ar, r.t., 2 h; E: 1) BBr_3 (6.0 equiv.), DCM, 0 °C, Ar, 1 h, 2) HCl/Et_2O.



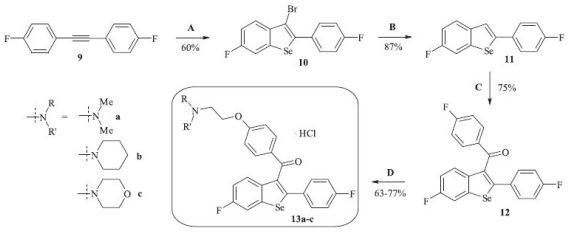
Scheme 2. A: corresponding 2-aminoethanol derivative (2.0 equiv.), NaH (2.2 equiv.), DMF, Ar, r.t., 2 h; B: 1) BBr_3 (6.0 equiv.), DCM, 0 °C, Ar, 1 h, 2) HCl/Et_2O; C: BBr_3 (6.0 equiv.), DCM, 0 °C, Ar, 1 h; D: 1) 2-methylaminoethanol (4.0 equiv.), NaH (4.0 equiv.), DMF, Ar, r.t., 2 h; 2) HCl/Et_2O; E: 1) MeI (10 equiv.), dioxane, r.t., 20 h, 2) ion exchange.

bromoderivative **10** in moderate yield (Scheme 3, A). Cyclization of **9** occurred much cleaner than analogous reaction of **1** (Scheme 1, A) and as a result less excessive amount of selenium reagent and alkene additive was required. On the other hand, larger excess of zinc powder and slightly elevated temperature was necessary for successive debromination of **10** (Scheme 3, B) than it was necessary in the case of corresponding derivative **2** (Scheme 1, B). Nevertheless, 2-unsubstituted precursor **11** was obtained in very good yield. Due to electron withdrawing effect of fluorine atoms also the Friedel–Crafts benzoylation step was quite slow, however, desired ketone **12** was obtained in 75% yield (Scheme 3, C). Finally, by regioselective nucleophilic substitution of activated fluorine atom of precursor **12** and subsequent treatment with HCl/Et_2O corresponding products **13a–c** were prepared in good yields (Scheme 3, D).

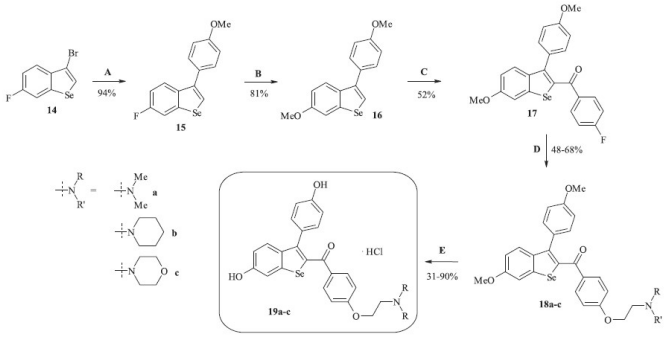
Synthesis of 2-benzoyl-3-arylderivatives **19a–c** (reversed analogues) was accomplished in five steps starting from previously described 3-bromo-6-fluorobenzo[*b*]selenophene (**14**) [11a] (Scheme 4). Suzuki–Miyaura cross-coupling of **14** with 4-methoxyphenyl boronic acid gave 3-arylderivative **15** in excellent yield (Scheme 4, A). Insertion of methoxy group in **16** was achieved by nucleophilic aromatic substitution of fluorine atom of **15** (Scheme 4, B). Due to the absence of activating groups substitution occurred effectively only in the presence of a large excess of nucleophile at 140 °C. Friedel–Crafts benzoylation of **16** was considerably slower and lower yielding than analogous reaction of 2-arylderivative **3** (Scheme 1, C), but nevertheless ketone **17** was successfully obtained in moderate yield (Scheme 4, C). Fluorine atom of **17** also is slightly less reactive than fluorine atom of **4** (Scheme 1, D). Slightly elevated reaction temperature was required for insertion of ethanolamine "tail" in precursors **18a–c** (Scheme 4, D). Finally, demethylation of **18a–c** and preparation of the corresponding hydrochlorides provided **19a–c** in moderate to good yields (Scheme 4, E).

2.2. Cytotoxic activity

In vitro cytotoxicity caused by raloxifene and novel selenium analogues was tested on monolayer tumor cell lines: CCL-8 (mouse sarcoma), MDA-MB-435s (human melanoma), MES-SA (human uterus sarcoma), MCF-7 (human breast adenocarcinoma, estrogen-positive), HT-1080 (human connective tissue fibrosarcoma), and MH-22A (mouse hepatoma). The borderline concentration, relevant to the highest tolerated dose, was determined for each compound using the NIH 3T3 (Mouse Swiss Albino embryo fibroblasts) cell line. The basal cytotoxicity was used to predict starting doses for *in vivo* acute oral LD_{50} values in rodent [13]. The results of these experiments are summarized in Table 1. Sodium selenite (Na_2SeO_3) and raloxifene were used as references. Despite the fact that raloxifene is widely used drug for breast cancer prevention, *in vitro* results showed more than a modest activity on studied tumor cell lines ($IC_{50} = 6.8 \div 50$ μM) with simultaneously quite high toxic effect



Scheme 3. A: SeO_2 (2.0 equiv.), cyclohexene (1.5 equiv.), HBr/dioxane, r.t., 72 h; B: Zn (10 equiv.), 80% AcOH, 110 °C, 24 h; C: 4-fluorobenzoyl chloride (2.0 equiv.), $AlCl_3$ (2.0 equiv.), DCM, 0 °C – r.t., 4 h; D: corresponding 2-aminoethanol derivative (2.0 equiv.), NaH (2.0 equiv.), DMF, Ar, r.t., 2 h.



Scheme 4. Synthesis of 3-aryl-2-carbonyl derivatives. Reaction conditions: A: 4-methoxyphenylboronic acid (2.0 equiv.), $Pd(OAc)_2$ (10 mol-%), $(o\text{-Tol})_3P$ (30 mol-%), K_3PO_4 (3.5 equiv.), xylene/*i*PrOH (2:1), 110 °C, Ar, 12 h; B: MeOH (6.0 equiv.), NaH (6.0 equiv.), NMP, 140 °C, Ar, 3 h; C: 4-fluorobenzoyl chloride (2.0 equiv.), $AlCl_3$ (2.5 equiv.), DCM, 0 °C – r.t., 72 h; D: corresponding 2-aminoethanol derivative (3.0 equiv.), NaH (3.0 equiv.), DMF, Ar, 50 °C; 5 h; E: 1) BBr_3 (6.0 equiv.), DCM, 0 °C, Ar, 1 h, 2) HCl/Et_2O.

against normal cell line (NIH 3T3, IC_{50} = 7.8 μM). Also, sodium selenite, a compound used as a source of selenium in various dietary supplements worldwide, exhibits a medium toxicity on NIH 3T3 cells (IC_{50} = 23 μM). Notably, raloxifene has a slight cytotoxic effect on estrogen-positive human breast adenocarcinoma MCF-7 (IC_{50} = 50 μM) and human uterus sarcoma MES-SA (IC_{50} = 37 μM). However, introduction of selenium into a molecule of raloxifene showed extremely positive influence on

Table 1
In Vitro cytotoxicity in monolayer tumor cell lines [CCL-8 (mouse sarcoma), MDA-MB-435s (human melanoma) MES-SA (human uterus sarcoma), MCF-7 (human breast adenocarcinoma, estrogen-positive), HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and normal cell line NIH 3T3 (mouse fibroblasts) caused by selenium analogues of raloxifene.

Nr.	NR_2	CCL-8	MDA-MB-435s	MES-SA	MCF-7	HT-1080	MG-22A	3T3	
		IC_{50}[a]	IC_{50}[a]	IC_{50}[a]	IC_{50}[a]	IC_{50}[a]	IC_{50}[a]	IC_{50}[a]	LD_{50},mg/kg
Na_2SeO_3		8	12	29	17	1.7	64	23	105
Raloxifene		27	26	37	50	34	6.8	7.8	255
6a		5.4	3.6	56	35	12	5.4	22	446
6b	MeHN	46	17	42	12	6	6	32	452
6c	Me_2N	28	26	51	22	48	9	20	413
8	Me_3N^+	*	*	*	*	131	124	452	1540
6d	OctMeN	4.7	4	4	4.7	4.7	3.2	8	308
6e		34	43	32	33	36	21	42	543
6f		36	14	39	40	27	5.2	14	400
6g		9.8	32	61	38	46	8.0	36	553
13a	Me_2N	3.8	3.5	3.8	6.7	4.8	3.8	11	313
13b		3.6	3.6	4.5	11.6	4.5	4.5	9	280
13c		25	168	53	121	27	21	363	1407
19a	Me_2N	3.8	3.8	5.8	17.3	5.8	3.9	31	674
19b		3.6	32	14.3	25	30	3.6	28	615
19c		3.4	15.5	6.9	31	8.6	5.2	16	465

[a] IC_{50} – Concentration (μM) providing 50% cell killing effect [(CV + MTT)/2].

antiproliferative activity. Selenium analogue of raloxifene **6a** exhibits impressive cytotoxicity against tumor cell lines in all conducted *in vitro* experiments compared to raloxifene. Maximal differences were found on mouse sarcoma CCL-8 (**6a**, $IC_{50} = 5.4$ μM; raloxifene, $IC_{50} = 27$ μM) and human melanoma MDA-MB-435a (**6a**, $IC_{50} = 3.6$ μM; raloxifene, $IC_{50} = 26$ μM). Selenium analogue **6a** is more potent than raloxifene even on estrogen positive MCF-7 cell line (**6a**, $IC_{50} = 35$ μM). It should be noted that Se-raloxifene **6a** exhibits lower cytotoxicity on NIH 3T3, therefore lower acute toxicity (**6a**, $LD_{50} = 446$ mg/kg; raloxifene, $LD_{50} = 255$ mg/kg), than the original drug. Next, we studied series of raloxifene's selenium analogues **6b**–**6g** and **8** with modified aminoethoxy "tails" by purpose to investigate how this fragment can affect cytotoxic effect. *N*-Methylaminoethoxy derivative **6b** and *N*,*N*-dimethylamninoethoxy analogue **6c** (similar to tamoxifen and toremifene "tails") exhibited medium antiproliferative effect on all studied cell lines, except HT-1080 and MG-22A cells. In the case of **6b** IC_{50} value increased up to 6.0 μM. Surprisingly, introduction of a choline motive in molecule (**8**) led to complete loss of a cytotoxic effect, and also Se-raloxifene **8** showed very low acute toxicity ($LD_{50} = 1540$ mg/kg). Conversely, introduction of a long lipophilic substituent led to increased antiproliferative effect on all tumor cell lines. *N*-Methyl-*N*-octylaminomethylethoxy derivative **6d** has an IC_{50} in a range from 3.2 to 4.7 μM without expressed sensitivity to any tumor. In general, both reduction and increase of the size of piperidine ring in selenium analogue **6a** by one methylene group (pirrolidine derivative **6e** and azepan analogue **6f**) decreased the activity against most of the tested cell lines ($IC_{50} = 5.2 \div 40.0$ μM). Likewise, morpholyl analogue **6g** exhibited lower antiproliferative effect simultaneously with lower acute toxicity ($LD_{50} = 553$ mg/kg) compared to **6a**.

Due to fluoro substituent sterically is similar to hydroxyl group, but without the ability to form strong hydrogen bonds, next, we investigated how this modification affects a target molecule's antiproliferative activity against cancer cell lines. It was found that selenium analogues with tamoxifen and raloxifene "tails" (**13a** – *N*,*N*-dimethylamninoethoxy, **13b** – piperidylethoxy) exhibited even more pronounced cytotoxic effect on all cell lines than Se-raloxifene **6a**. Particularly should be mentioned very high effect on human breast adenocarcinoma MCF-7 cell line ($IC_{50} = 6.7 \div 11.6$ μM). Furthermore, the LD_{50} values determined for fluoro substituted derivatives are still higher than in the case of raloxifene (**13a**, $LD_{50} = 313$ mg/kg; **13b**, $LD_{50} = 280$ mg/kg). Notably, morpholyl analogue **13c** showed medium level of *in vitro* antiproliferative activity.

With the aim to study the influence of spatial orientation of hydroxyl and aminoethoxybenzoyl substituents of Se-raloxifenes we switched positions of 4-hydroxyphenyl and benzoyl groups attached to the benzo[*b*]selenophene core. *N*,*N*-Dimethylaminoethoxy analogue **19a** showed high potency to suppress cancer cells. Especially good results (up to $IC_{50} = 3.8$ μM) received on mouse sarcoma CCL-8 and human melanoma MDA-MB-435s, however, the value of IC_{50} on MCF-7 cell line was lower than for **6c**. Moreover, derivative **19a** possesses considerably lower acute toxicity ($LD_{50} = 674$ mg/kg) compared with **6c**. Reversed selenium analogue of raloxifene **19b** exhibits more extended activity against sarcomas CCL-8 and MES-SA, besides, more melanoma MDA-MB-435s cells were able to survive after a treatment with **19b** than **6a**. Also, acute toxicity for reversed Se-raloxifene **19b** was lower ($LD_{50} = 615$ mg/kg). Unexpectedly, morpholyl derivative **19c** showed very good antiproliferative activity compared not only with other morpholyl substituted analogues **6g** and **13c**, but also with a series of all studied Se-raloxifenes. The most impressive results were found on CCL-8, MES-SA, and MG-22A cell lines (up to $IC_{50} = 3.4$ μM). Cytotoxicity against breast adenocarcinoma MCF-7 was comparable with raloxifene's selenium analogue **6a** ($IC_{50} = 31$ μM).

2.3. In vivo antitumor activity

Results from the trial data on raloxifene's influence on breast cancer come almost exclusively from the Multiple Outcomes of Raloxifene Evaluation (MORE) study, in which 7705 postmenopausal women with osteoporosis were randomized to raloxifene at 60 or 120 mg/day (5129 women) or placebo (2576 women) for 4 years and monitored for breast cancer development from the safety database. As a result significant breast cancer risk reduction in postmenopausal women treated with raloxifene was approved [14].

In continuation of our research we decided to compare the ability of inhibition of breast cancer growth caused by raloxifene and its selenium analogue **6a**. Experiments were made on BALB/c female mice group (5–7) animals with 4T1 tumors in 2 doses (1.8 mg/kg and 15.0 mg/kg). Drug injection was started 24 h after tumor transplantation on even days (9 times). Total time of experiment was 18 days. The 4T1 cells grow as adherent epithelial type *in vitro*, and are characterized as murine mammary carcinoma cells (American Type Culture Collection (ATCC) catalogue no. CRL-2539, 2004). When injected into BALB/c mice, 4T1 cells rapidly multiply resulting in highly metastatic tumors. Because these tumors closely imitate human breast cancer, the 4T1 cell line serves as an animal model for stage IV breast cancer [15]. According to our results (Fig. 1) after a course of injections of raloxifene in both doses on day 18 the volume of a primary tumor was bigger, than in control group: 70% in 1.8 mg/kg and 113% in 15 mg/kg doses. Other researchers have observed similar effect on mice with 4T1 cell induced breast cancer model also. It could be connected with the effect of estrogen on tumor growth rate and expression of 4T1 tumor estrogen receptor [16]. On the other hand, treatment of mice with selenium analogue **6a** in 1.8 mg/kg dose showed volume of tumor variance comparable with a control (4% inhibition). More interesting results received in 15.0 mg/kg dose. Average tumor volume decreased by 30% after the treatment with **6a** in 18 days. Thus in comparison with raloxifene we had statistically significant difference. Analysing the effect caused by raloxifene selenium analogue **6a** individually for each mouse in a group of 7 animals with a dose of 15.0 mg/kg (Fig. 2), we observed that in 3 animals the tumor was not growing at all, animals were healthy and active, weight loss wasn't visually detected. At the same time, the four animals that developed tumors stayed at the control level. Definitely, discovered effect requires further in-depth study. Perhaps, the large scatter in the obtained data could be explained by the fact that the mice in group are at various stages of hormonal cycle.

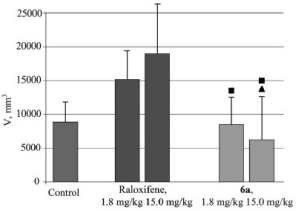


Fig. 1. Tumor sizes of the groups after 18 days of treatment. ▲ $P < 0.5$ vs. control group. ■ $P < 0.05$ vs. raloxifene group.

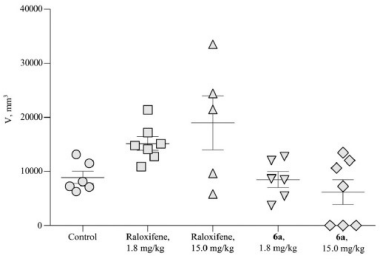


Fig. 2. 4T1 tumor growth inhibition caused by raloxifene and **6a** (tumor volume showed individually for each mouse).

Possible effects of the compounds depend on hormone levels or affect hormone levels. So, it could be concluded that widely used raloxifene could prevent the formation of breast cancer, but, possibly, not that effective in treatment of already existing tumors, however, its selenium analogue **6a** is promising antiproliferative agent in the treatment and/or prevention of breast cancer.

Additionally, antitumor activity of raloxifene and its selenium analogue **6a** against estrogen independent sarcoma S-180 was determined for male ICR mice (six weeks old, 18–20 g). Results showed no significant influence on tumor growth inhibition or activation after 9 days of treatment by both raloxifene and its selenium analogue **6a**.

3. Conclusions

Convenient synthetic protocols for the preparation of various selenium analogues of raloxifene were successfully elaborated. Summarizing all the above-mentioned bioactivity data it can be concluded that the pharmacophore of raloxifenes molecule is very sensitive to any structural modifications. Introduction of selenium atom into the molecule led to increased antiproliferative activity. Moreover, acute toxicity decreased for all selenium-containing compounds compared with raloxifene. Any modifications in aminoethoxy "tail' in some cases led to tangible or even complete loss of activity. Replacement of hydroxyl groups by fluoro substituents in general increased cytotoxicity against tumor cell lines, especially MCF-7. Antiproliferative activity data obtained for reversed analogues of Se-raloxifene showed interesting direction for further research. *In vivo* experiments showed the ability to inhibit 4T1 breast cancer growth in 15.0 mg/kg by 30%, besides, raloxifene was ineffective in the same model. Finally, it can be concluded that obtained data opens a way to further modifications in a series of selenium analogues of raloxifene and other SERM drugs with the purpose to find a leading compound with extended antitumor activity in treatment of breast cancer.

4. Experimental section

4.1. Chemistry

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using MERCK Silica gel 60 F254 plates and visualized by UV (254 nm) fluorescence. ZEOCHEM silica gel (ZEOprep 60/35-70 microns – SI23501) was used for column chromatography. ^{1}H, ^{13}C, ^{19}F, and ^{77}Se NMR spectra were recorded on a Varian 400 Mercury spectrometer at 400.0, 100.58, 376.21, and 76.37 MHz, respectively, at 298 K in $CDCl_3$. The ^{1}H chemical shifts are given relative to residual $CHCl_3$ signal (7.26 ppm), ^{13}C – relative to $CDCl_3$ (77.0 ppm), and ^{77}Se – relative to dimethyl selenide (0.0 ppm). The melting points were determined on a "Digital melting point analyser" (Fisher), and the results are given without correction.

4.1.1. 3-Bromo-6-methoxy-2-(4-methoxyphenyl)benzo[b] selenophene (**2**)

Selenium(IV) oxide (9.32 g, 84.0 mmol) was dissolved in 48% hydrobromic acid (36.0 ml) and stirred at room temperature for 15 min. A solution of **1** (5.00 g, 21.0 mmol), cyclohexene (5.18 g, 63.0 mmol), and triethylamine (11.7 ml, 84.0 mmol) in dioxane (100 ml) was added dropwise, and the reaction mixture was stirred for 24 h. Then reaction mixture was quenched with EtOAc (ethyl acetate) (400 ml) and brine (100 ml). After stirring for additional 15 min, organic phase was separated and aqueous phase was extracted with EtOAc (2 × 200 ml). Combined organic phases were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of petroleum ether and EtOAc (40:1) as eluent. Note: not collectable solid precipitates appear in first fractions. After evaporation of solvents, pale yellow oil was obtained, which slowly crystallizes upon standing at room temperature. After recrystallization from a mixture of petroleum ether and EtOAc (5:1), compound **2** was obtained in 50% yield (4.16 g) as a white crystalline solid; mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.87 (3H, s, O$\underline{CH_3}$), 3.89 (3H, s, O$\underline{CH_3}$), 6.96–7.00 (2H, m, 3′,5′-C$\underline{H}$), 7.07 (1H, dd, 5-C$\underline{H}$, $^{4}J_{(H,H)}$ = 2.3 Hz, $^{3}J_{(H,H)}$ = 8.8 Hz), 7.35 (1H, d, 7-C$\underline{H}$, $^{4}J_{(H,H)}$ = 2.3 Hz), 7.59–7.64 (2H, m, 2′,6′-C$\underline{H}$), 7.79 (1H, d, 4-C$\underline{H}$, $^{3}J_{(H,H)}$ = 8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.4 (O$\underline{CH_3}$), 55.7 (O$\underline{CH_3}$), 105.3, 108.4, 114.0, 114.5, 126.5, 127.4, 131.0, 134.9, 137.4, 139.7, 158.1, 159.7; ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 571.3; MS (EI, 70 eV): *m*/*z* (%): 396 (100) $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{13}BrO_2Se$ [396.14]: C 48.51, H 3.31; found: C 48.42, H 3.51.

4.1.2. 6-Methoxy-2-(4-methoxyphenyl)benzo[b]selenophene (**3**)

To a suspension of **2** (10.5 mmol, 4.16 g) in 80% acetic acid (40 ml) zinc powder (52.5 mmol, 3.43 g) was added in one portion and resulting mixture was stirred at 105 °C for 24 h. After cooling to room temperature, DCM (800 ml) and water (200 ml) were added and resulting mixture was stirred for additional 30 min. Aqueous phase was separated and organic phase was washed with water (2 × 200 ml) and aqueous solution of saturated Na_2CO_3 (100 ml). After drying over anhydrous Na_2SO_4, solvent was evaporated to give crude **3** (3.10 g) as a white amorphous solid in 93% yield. Without further purification it was used for preparation of **4**. mp 97–98 °C (recrystallized from mixture of petroleum ether and EtOAc (4:1)); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.85 (3H, s, O$\underline{CH_3}$), 3.87 (3H, s, O$\underline{CH_3}$), 6.90–6.95 (2H, m, 3′,5′-C$\underline{H}$), 6.95 (1H, dd, 5-C$\underline{H}$, $^{4}J_{(H,H)}$ = 2.3 Hz, $^{3}J_{(H,H)}$ = 8.6 Hz), 7.36 (1H, d, 7-C$\underline{H}$, $^{4}J_{(H,H)}$ = 2.3 Hz), 7.49 (1H, s, 3-C$\underline{H}$), 7.51–7.55 (2H, m, 2′,,6′-C$\underline{H}$), 7.62 (1H, d, 4-C$\underline{H}$, $^{3}J_{(H,H)}$ = 8.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.4 (O$\underline{CH_3}$), 55.6 (O$\underline{CH_3}$), 108.7, 114.3, 121.2, 125.5, 127.8, 129.1, 133.9, 137.3, 141.9, 144.5, 157.1, 159.5; ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 517.6; MS (EI, 70 eV): *m*/*z* (%): 318 (100) $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{14}O_2Se$ (317.24): C 60.58, H 4.45; found: C 60.52, H 4.61.

4.1.3. (4-Fluorophenyl) (6-methoxy-2-(4-methoxyphenyl)benzo[b] selenophen-3-yl)methanone (**4**)

To at 0 °C cooled solution of **3** (3.00 g, 9.46 mmol) in dry DCM (600 ml) aluminium(III) chloride (2.52 g, 18.9 mmol) was added in

one portion and resulting mixture was stirred at 0 °C for 30 min (the reaction mixture slowly changed colour from colourless to deep violet). Then, solution of 4-fluorobenzoyl chloride (3.00 g, 18.9 mmol) in dry DCM (40 ml) was added dropwise and stirring was continued at room temperature for 2 h. The reaction mixture was poured on ice (approximately 300 g) and stirred till all ice was molten. Organic phase was separated and aqueous phase was extracted with DCM (2 × 100 ml). Combined organic phases were washed with brine (200 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of petroleum ether and EtOAc (40:1 → 10:1) as eluent to give **4** (3.03 g) in 73% yield as greenish yellow solid. mp 83–84 °C (recrystallized from mixture of petroleum ether and EtOAc (5:1)); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.73 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.70–6.75 (2H, m, 3′,5′-CH), 6.90–6.96 (2H, m, 3,5-CH), 6.96 (1H, dd, 5″-CH, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.9 Hz), 7.25–7.29 (2H, m, 2′,6′-CH), 7.40 (1H, d, 7″-CH, $^4J_{(H,H)}$ = 2.3 Hz), 7.52 (1H, d, 4″-CH, $^3J_{(H,H)}$ = 8.9 Hz), 7.78–7.83 (2H, m, 2,6-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.2 (OCH_3), 55.6 (OCH_3), 108.3, 114.0, 114.3, 115.5 (d, 3,5-C, $^2J_{(C,F)}$ = 22.0 Hz), 125.7, 127.7, 130.3, 132.5 (d, 2,6-C, $^3J_{(C,F)}$ = 9.3 Hz), 133.3, 133.7 (d, 1-C, $^4J_{(C,F)}$ = 2.7 Hz), 135.7, 142.0, 146.6, 157.7, 159.8, 165.7 (d, 4-C, $^1J_{(C,F)}$ = 255.5 Hz), 194.0 (C=O); ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 546.4; MS (EI, 70 eV): *m/z* (%): 440 (78) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{17}FO_3Se$ (439.34): C 62.88, H 3.90; found: C 62.71, H 4.00.

4.1.4. General method for preparation of ***5a–g***

To a suspension of NaH (60% suspension in mineral oil, 60 mg, 1.50 mmol) in dry DMF (0.50 ml) under argon atmosphere solution of the corresponding 2-aminoethanol (1.37 mmol) in DMF (1.0 ml) was added dropwise and resulting mixture was stirred at room temperature for 15 min. Then, solution of **4** (300 mg, 0.683 mmol) in DMF (3.0 ml) was added and stirring was continued for 2 h. The reaction mixture was quenched with EtOAc (400 ml) and brine (80 ml) and resulting mixture was stirred for additional 30 min. After separation of aqueous phase, organic phase was washed with brine (4 × 80 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of DCM and EtOH as eluent to give **5a–g** in 65–91% yield as greenish yellow glass like solids.

*4.1.4.1. (6-Methoxy-2-(4-methoxyphenyl)benzo[b]selenophen-3-yl) (4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone (**5a**).* 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.39–1.47 (2H, m, 4-CH_2), 1.55–1.63 (4H, m, 3,5-CH_2), 2.43–2.51 (4H, m, 2,6-CH_2), 2.73 (2H, t, NCH_2, $^3J_{(H,H)}$ = 6.0 Hz), 3.74 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.08 (2H, t, OCH_2, $^3J_{(H,H)}$ = 6.0 Hz), 6.71–6.79 (4H, m, 3,5,3″,5″-CH), 6.92 (1H, dd, 5′-CH, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.9 Hz), 7.28–7.34 (2H, m, 2,6-CH), 7.39 (1H, d, 7′-CH, $^4J_{(H,H)}$ = 2.4 Hz), 7.44 (1H, d, 4′-CH, $^3J_{(H,H)}$ = 8.9 Hz), 7.75–7.80 (2H, m, 2″,6″-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 24.1 (4-CH_2), 25.8 (3,5-CH_2), 55.0 (2,6-CH_2), 55.2 (OCH_3), 55.6 (OCH_3), 57.6 (NCH_2), 66.2 (OCH_2), 108.3, 114.0, 114.1, 114.2, 125.7, 127.9, 130.2 (2C), 132.3, 133.9, 136.1, 141.8, 144.9, 157.5, 159.6, 163.0, 194.4 (C=O); MS (EI, 70 eV): *m/z* (%): 550 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{30}H_{31}NO_4Se$ (548.53): C 65.69, H 5.70, N 2.55; found: C 65.52, H 5.89, N 2.51.

*4.1.4.2. (6-Methoxy-2-(4-methoxyphenyl)benzo[b]selenophen-3-yl) (4-(2-(methylamino)-ethoxy)phenyl)methanone (**5b**).* 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.49 (3H, s, NCH_3), 2.98 (2H, t, NCH_2, $^3J_{(H,H)}$ = 5.1 Hz), 3.10 (1H, br s, NH), 3.72 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.07 (2H, t, OCH_2, $^3J_{(H,H)}$ = 5.1 Hz), 6.70–6.79 (4H, m, 3,5,3″,5″-CH), 6.91 (1H, dd, 5′-CH, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 7.28–7.33 (2H, m, 2,6-CH), 7.38 (1H, d, 7′-CH, $^4J_{(H,H)}$ = 2.3 Hz), 7.43 (1H, d, 4′-CH, $^3J_{(H,H)}$ = 8.8 Hz), 7.74–7.79 (2H, m, 2″,6″-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 35.8 (NCH_3), 50.1 (NCH_2), 55.2 (OCH_3), 55.6 (OCH_3), 66.6 (OCH_2), 108.3, 114.0, 114.1, 114.2, 125.7, 127.9, 130.2, 130.4, 132.3, 133.8, 136.0, 141.9, 144.9, 157.6, 159.6, 162.8, 194.4 (C=O); MS (EI, 70 eV): *m/z* (%): 496 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{26}H_{25}NO_4Se$ (494.44): C 63.16, H 5.10, N 2.83; found: C 62.95, H 5.24, N 2.74.

*4.1.4.3. (4-(2-(Dimethylamino)ethoxy)phenyl) (6-methoxy-2-(4-methoxyphenyl)benzo[b]selenophen-3-yl)methanone (**5c**).* 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.31 (6H, s, 2 × NCH_3), 2.70 (2H, t, NCH_2, $^3J_{(H,H)}$ = 5.7 Hz), 3.73 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.04 (2H, t, OCH_2, $^3J_{(H,H)}$ = 5.7 Hz), 6.70–6.80 (4H, m, 3,5,3′,5′-CH), 6.92 (1H, dd, 5″-CH, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 9.0 Hz), 7.28–7.33 (2H, m, 2′,6′-CH), 7.39 (1H, d, 7″-CH, $^4J_{(H,H)}$ = 2.3 Hz), 7.45 (1H, d, 4″-CH, $^3J_{(H,H)}$ = 9.0 Hz), 7.75–7.80 (2H, m, 2,6-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 45.8 (2 × NCH_3), 55.2 (OCH_3), 55.6 (OCH_3), 58.0 (NCH_2), 66.1 (OCH_2), 108.3, 114.0, 114.1, 144.2, 125.7, 127.9, 130.2 (2C), 132.2, 133.9, 136.1, 141.8, 145.0, 157.5, 159.6, 163.0, 194.4 (C=O); MS (EI, 70 eV): *m/z* (%): 510 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{27}H_{27}NO_4Se$ (508.47): C 63.78, H 5.35, N 2.75; found: C 63.64, H 5.49, N 2.73.

*4.1.4.4. (6-Methoxy-2-(4-methoxyphenyl)benzo[b]selenophen-3-yl) (4-(2-(methyl(octyl)amino)ethoxy)phenyl)methanone (**5d**).* 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 0.87 (3H, t, 8-CH_3, $^3J_{(H,H)}$ = 6.8 Hz), 1.20–1.34 (10H, m, 3-7-CH_2), 1.41–1.50 (2H, m, 2-CH_2), 2.30 (3H, s, NCH_3), 2.37–2.43 (2H, m, 1-CH_2), 2.75 (2H, t, NCH_2, $^3J_{(H,H)}$ = 5.9 Hz), 3.74 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.04 (2H, t, OCH_2, $^3J_{(H,H)}$ = 5.9 Hz), 6.71–6.79 (4H, m, 3,5,3″,5″-CH), 6.92 (1H, dd, 5′-CH, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.9 Hz), 7.29–7.34 (2H, m, 2,6-CH), 7.39 (1H, d, 7′-CH, $^4J_{(H,H)}$ = 2.4 Hz), 7.45 (1H, d, 4′-CH, $^3J_{(H,H)}$ = 8.9 Hz), 7.75–7.80 (2H, m, 2″,6″-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 14.1, 22.6, 27.2, 27.4, 29.2, 29.5, 31.8, 43.0, 55.2 (OCH_3), 55.6 (OCH_3), 55.9, 58.4, 66.4 (OCH_2), 108.3, 114.0, 114.1, 114.2, 125.7, 127.9, 130.2, 132.2 (2C), 133.9, 136.1, 141.8, 144.9, 157.6, 159.6, 163.1, 194.4 (C=O); MS (EI, 70 eV): *m/z* (%): 608 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{34}H_{41}NO_4Se$ (606.65): C 67.31, H 6.81, N 2.31; found: C 67.15, H 6.94, N 2.25.

*4.1.4.5. (6-Methoxy-2-(4-methoxyphenyl)benzo[b]selenophen-3-yl) (4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)methanone (**5e**).* 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.76–1.84 (4H, m, 3,4-CH_2), 2.59–2.67 (4H, m, 2,5-CH_2), 2.89 (2H, t, NCH_2, $^3J_{(H,H)}$ = 5.8 Hz), 3.73 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.10 (2H, t, OCH_2, $^3J_{(H,H)}$ = 5.8 Hz), 6.71–6.80 (4H, m, 3,5,3″,5″-CH), 6.92 (1H, dd, 5′-CH, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.9 Hz), 7.29–7.33 (2H, m, 2,6-CH), 7.38 (1H, d, 7′-CH, $^4J_{(H,H)}$ = 2.4 Hz), 7.44 (1H, d, 4′-CH, $^3J_{(H,H)}$ = 8.9 Hz), 7.75–7.79 (2H, m, 2″,6″-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 23.4 (3,4-CH_2), 54.7 (2,5-CH_2, NCH_2), 55.2 (OCH_3), 55.6 (OCH_3), 67.1 (OCH_2), 108.3, 114.0, 114.1, 114.2, 125.7, 127.9, 130.2 (2C), 132.2, 133.9, 136.1, 141.8, 144.9, 157.5, 159.6, 163.0, 194.4 (C=O); MS (EI, 70 eV): *m/z* (%): 536 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{29}H_{29}NO_4Se$ (534.50): C 65.17, H 5.47, N 2.62; found: C 65.10, H 2.70, N 2.59.

*4.1.4.6. (4-(2-(Azepan-1-yl)ethoxy)phenyl) (6-methoxy-2-(4-methoxyphenyl)benzo[b]-selenophen-3-yl)methanone (**5f**).* 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.55–1.69 (8H, m, 3-6-CH_2), 2.72–2.79 (4H, m, 2,7-CH_2), 2.93 (2H, t, NCH_2, $^3J_{(H,H)}$ = 6.1 Hz), 3.74 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.05 (2H, t, OCH_2, $^3J_{(H,H)}$ = 6.1 Hz), 6.71–6.79 (4H, m, 3,5,3′,5′-CH), 6.92 (1H, dd, 5″-CH, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.9 Hz), 7.29–7.34 (2H, m, 2′,6′-CH), 7.39 (1H, d, 7″-CH, $^4J_{(H,H)}$ = 2.4 Hz), 7.44 (1H, d, 4″-CH,

$^3J_{(H,H)}$ = 8.9 Hz), 7.75–7.80 (2H, m, 2,6-C<u>H</u>); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 27.0 (4,5-C<u>H</u>$_2$), 27.8 (3,6-C<u>H</u>$_2$), 55.2 (O<u>C</u>H$_3$), 55.6 (O<u>C</u>H$_3$), 55.8, 56.0, 66.6 (O<u>C</u>H$_2$), 108.3, 114.0, 114.1, 114.2, 125.7, 127.9, 130.1, 130.2, 132.3, 133.9, 136.1, 141.8, 144.8, 157.5, 159.6, 163.1, 194.4 (<u>C</u>=O); MS (EI, 70 eV): *m/z* (%): 564 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{31}H_{33}NO_4Se$ (562.56): C 66.19, H 5.91, N 2.49; found: C 65.94, H 6.00, N 2.42.

*4.1.4.7. (6-Methoxy-2-(4-methoxyphenyl)benzo[b]selenophen-3-yl)(4-(2-morpholinoethoxy)phenyl)methanone (**5g**).* 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.52–2.59 (4H, m, 2,6-C<u>H</u>$_2$), 2.78 (2H, t, NCH$_2$, $^3J_{(H,H)}$ = 5.6 Hz), 3.69–3.73 (4H, m, 3,5-C<u>H</u>$_2$), 3.73 (3H, s, O<u>C</u>H$_3$), 3.86 (3H, s, O<u>C</u>H$_3$), 4.09 (2H, t, O<u>C</u>H$_2$, $^3J_{(H,H)}$ = 5.6 Hz), 6.71–6.78 (4H, m, 3,5,3″,5″-C<u>H</u>), 6.92 (1H, dd, 5′-C<u>H</u>, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.9 Hz), 7.29–7.33 (2H, m, 2,6-C<u>H</u>), 7.39 (1H, d, 7′-C<u>H</u>, $^4J_{(H,H)}$ = 2.4 Hz), 7.44 (1H, d, 4′-C<u>H</u>, $^3J_{(H,H)}$ = 8.9 Hz), 7.75–7.80 (2H, m, 2″,6″-C<u>H</u>); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 54.0, 55.2 (O<u>C</u>H$_3$), 55.6 (O<u>C</u>H$_3$), 57.3, 65.9, 66.8 (O<u>C</u>H$_2$), 108.3, 114.0, 114.2 (2C), 125.7, 127.9, 130.2, 130.3, 132.3, 133.8, 136.0, 141.9, 144.9, 157.6, 159.6, 162.8, 194.4 (<u>C</u>=O); MS (EI, 70 eV): *m/z* (%): 552 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{29}H_{29}NO_5Se$ (550.50): C 63.27, H 5.31, N 2.54; found: C 63.11, H 5.38, N 2.21.

*4.1.5. General method for preparation of **6a,c–g***

To a solution of corresponding precursor **5** (0.35 mmol) in dry DCM (cooled in ice/water bath) was added 0.5 M solution of HCl in dry Et_2O till all the starting material was converted to the corresponding hydrochloride (controlled by TLC). After removal of solvents and excess of HCl, obtained salt was dried by adding and evaporating dry toluene (3 × 10 ml). Then, to a homogeneous solution of prepared salt in DCM at 0 °C under argon atmosphere 1 M solution of BBr_3 in DCM (2.10 ml, 2.10 mmol) was added dropwise. After stirring at 0 °C for 1 h reaction mixture was poured in to a stirred mixture of EtOAc (200 ml), EtOH (10 ml), and saturated aqueous solution of Na_2CO_3 (100 ml) and stirring was continued for additional 30 min. Organic phase was separated and aqueous phase was extracted with 5% EtOH solution in EtOAc (2 × 100 ml). Combined organic phases were washed with brine (60 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Crude product was purified by flash chromatography on silica gel using a mixture of dichloromethane and MeOH as eluent. EtOH was added to a suspension of isolated product in DCM (50 ml) till homogeneous solution was obtained. By cooling in ice/water bath 0.5 M solution of HCl in dry Et_2O was added dropwise till the entire free base was converted in corresponding hydrochloride (controlled by TLC). After evaporation of solvents and excess of HCl, products **6a,c–g** were obtained in 29–86% yield as white to pale yellow amorphous solids.

*4.1.5.1. 1-(2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)ethyl)piperidin-1-ium chloride (**6a**).* mp 202–203 °C; 79% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.29–1.42 (1H, m, 4-C<u>H</u>), 1.62–1.81 (5H, m, 4-C<u>H</u>, 3,5-C<u>H</u>$_2$), 2.89–3.01 (2H, m, NC<u>H</u>$_2$), 3.40–3.49 (4H, m, 2,6-C<u>H</u>$_2$), 4.39–4.45 (2H, m, OC<u>H</u>$_2$), 6.64–6.70 (2H, m, 3,5-C<u>H</u>), 6.82 (1H, dd, 5′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 6.95–7.01 (2H, m, 2″,6″-C<u>H</u>), 7.11–7.15 (2H, m, 2,6-C<u>H</u>), 7.15 (1H, d, 4′-C<u>H</u>, $^3J_{(H,H)}$ = 8.8 Hz), 7.47 (1H, d, 7′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz), 7.68–7.72 (2H, m, 3″,5″-C<u>H</u>), 9.80 (1H, br s, O<u>H</u>), 9.82 (1H, br s, O<u>H</u>), 10.33 (1H, br s, N<u>H</u>); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 21.1 (4-C<u>H</u>$_2$), 22.2 (3,5-C<u>H</u>$_2$), 54.4 (2,6-C<u>H</u>$_2$), 62.4 (NC<u>H</u>$_2$), 66.3 (O<u>C</u>H$_2$), 111.0, 114.6, 114.7, 115.6, 124.8, 125.6, 129.6, 130.0, 131.6, 132.7, 134.2, 141.0, 143.0, 155.4, 157.7, 161.7, 193.9 (<u>C</u>=O); ^{77}Se NMR (76.37 MHz, DMSO-d_6) δ (ppm): 530.9; MS (EI, 70 eV): *m/z* (%): 522 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{28}H_{27}NO_4Se \times 1.3$ HCl (567.88): C 59.22, H 5.03, N 2.47; found: C 59.15, H 5.11, N 2.41.

*4.1.5.2. 2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)-N,N-dimethylethylamonium chloride (**6c**).* mp 189–190 °C; 29% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.79 (6H, s, 2 × NC<u>H</u>$_3$), 3.47 (2H, t, NC<u>H</u>$_2$, $^3J_{(H,H)}$ = 4.9 Hz), 4.39 (2H, t, OC<u>H</u>$_2$, $^3J_{(H,H)}$ = 4.9 Hz), 6.66–6.71 (2H, m, 3,5-C<u>H</u>), 6.83 (1H, dd, 5′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.7 Hz), 6.96–7.01 (2H, m, 2″,6″-C<u>H</u>), 7.10–7.17 (3H, m, 2,6-C<u>H</u>, 4′-C<u>H</u>), 7.48 (1H, d, 7′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz), 7.67–7.73 (2H, m, 3″,5″-C<u>H</u>), 9.85 (1H, br s, O<u>H</u>), 9.86 (1H, br s, O<u>H</u>), 10.66 (1H, br s, N<u>H</u>); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 42.6 (2 × NCH$_3$), 54.9 (NCH$_2$), 62.4 (OCH$_2$), 111.0, 114.7 (2C), 115.6, 124.8, 125.6, 129.6, 130.1, 131.6, 132.7, 134.2, 141.0, 143.0, 155.4, 157.7, 161.7, 193.9 (<u>C</u>=O); MS (EI, 70 eV): *m/z* (%): 482 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{25}H_{23}NO_4Se \times 1.2$ HCl (524.16): C 57.28, H 4.66, N 2.67; found: C 57.10, H 4.71, N 2.65.

*4.1.5.3. (2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)ethyl)methyloctylammonium chloride (**6d**).* mp 127–128 °C; 76% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.79–0.88 (3H, m, 8-CH$_3$), 1.16–1.32 (10H, m, 3-7-CH$_2$), 1.59–1.71 (2H, m, 2-CH$_2$), 2.76 (3H, s, NCH$_3$), 2.98–3.14 (2H, m, 1-CH$_2$), 3.40–3.52 (2H, m, NCH$_2$), 4.35–4.46 (2H, m, OCH$_2$), 6.64–6.72 (2H, m, 3,5-C<u>H</u>), 6.82 (1H, dd, 5′-C<u>H</u>, $^4J_{(H,H)}$ = 2.1 Hz, $^3J_{(H,H)}$ = 8.7 Hz), 6.93–7.01 (2H, m, 2″,6″-C<u>H</u>), 7.09–7.18 (3H, m, 2,6-C<u>H</u>, 4′-C<u>H</u>), 7.48 (1H, d, 7′-C<u>H</u>, $^4J_{(H,H)}$ = 2.1 Hz), 7.66–7.74 (2H, m, 3″,5″-C<u>H</u>), 9.84 (1H, br s, O<u>H</u>), 9.85 (1H, br s, O<u>H</u>), 10.57 (1H, br s, N<u>H</u>); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 13.9, 22.0, 23.1, 25.9, 28.4 (2C), 31.1, 39.9, 53.3, 55.4, 62.5 (OCH$_2$), 111.0, 114.6, 114.7, 115.6, 124.8, 125.6, 129.6, 130.1, 131.6, 132.7, 134.2, 141.0, 143.0, 155.4, 157.7, 161.7, 193.9 (C=O); MS (EI, 70 eV): *m/z* (%): 580 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{32}H_{37}NO_4Se \times 1.8$ HCl (644.23): C 59.66, H 6.08, N 2.17; found: C 59.54, H 6.19, N 2.05.

*4.1.5.4. 1-(2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)-ethyl)pyrrolidin-1-ium chloride (**6e**).* mp 154–155 °C; 72% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.78–2.05 (4H, m, 3,4-CH$_2$), 3.00–3.12 (2H, m, NCH$_2$), 3.50–3.61 (4H, m, 2,5-CH$_2$), 4.32–4.38 (2H, m, OCH$_2$), 6.64–6.69 (2H, m, 3,5-C<u>H</u>), 6.81 (1H, dd, 5′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 6.97–7.02 (2H, m, 2″,6″-C<u>H</u>), 7.12–7.16 (2H, m, 2,6-C<u>H</u>), 7.15 (1H, d, 4′-C<u>H</u>, $^3J_{(H,H)}$ = 8.8 Hz), 7.46 (1H, d, 7′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz), 7.68–7.73 (2H, m, 3″,5″-C<u>H</u>), 9.75 (1H, br s, O<u>H</u>), 9.78 (1H, br s, O<u>H</u>), 10.25 (1H, br s, N<u>H</u>); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 22.4 (3,4-CH$_2$), 52.3 (2,5-CH$_2$), 53.6 (NCH$_2$), 63.4 (OCH$_2$), 111.0, 114.6, 114.7, 115.6, 124.7, 125.6, 129.6, 130.0, 131.6, 132.6, 134.2, 140.9, 143.0, 155.3, 157.6, 161.7, 193.9 (<u>C</u>=O); MS (EI, 70 eV): *m/z* (%): 508 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{27}H_{25}NO_4Se \times 1.3$ HCl (553.85): C 58.55, H 4.80, N 2.53; found: C 58.31, H 4.92, N 2.38.

*4.1.5.5. 1-(2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)-ethyl)azepan-1-ium chloride (**6f**).* mp 159–160 °C; 86% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.50–1.68 (4H, m, 4,5-CH$_2$), 1.73–1.86 (4H, m, 3,6-CH$_2$), 3.14–3.24 (2H, m, NCH$_2$), 3.36–3.44 (2H, m, 2,7-CH$_2$), 4.38–4.55 (2H, m, 2,7-C<u>H</u>), 4.39 (2H, t, OCH$_2$, $^3J_{(H,H)}$ = 5.0 Hz), 6.64–6.69 (2H, m, 3,5-C<u>H</u>), 6.81 (1H, dd, 5′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 6.96–7.01 (2H, m, 2″,6″-C<u>H</u>), 7.12–7.15 (2H, m, 2,6-C<u>H</u>), 7.15 (1H, d, 4′-C<u>H</u>, $^3J_{(H,H)}$ = 8.8 Hz), 7.46 (1H, d, 7′-C<u>H</u>, $^4J_{(H,H)}$ = 2.3 Hz), 7.69–7.73 (2H, m, 3″,5″-C<u>H</u>), 9.75 (1H, br s, O<u>H</u>), 9.78 (1H, br s, O<u>H</u>), 10.06 (1H, br s, N<u>H</u>); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 22.6 (4,5-CH$_2$), 25.9 (3,6-CH$_2$), 54.2, 54.6, 62.6 (OCH$_2$), 111.0, 114.7 (2C), 115.6, 124.8, 125.7, 129.6, 130.1, 131.7, 132.7, 134.3, 141.0, 143.0, 155.4, 157.7, 161.7, 193.9 (<u>C</u>=O); MS (EI, 70 eV): *m/z* (%): 536 (100) $[M+1]^+$; elemental

analysis calcd (%) for $C_{29}H_{30}ClNO_4Se$ (570.96): C 59.11, H 5.23, N 2.38; found: C 59.02, H 5.26, N 2.31.

4.1.5.6. 4-(2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)-ethyl)morpholin-4-ium chloride (**6g**).

mp 172–173 °C; 64% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.08–3.23 (2H, m, NC$\underline{H}_2$), 3.39–3.58 (4H, m, 2,6-C$\underline{H}_2$), 3.73–3.97 (4H, m, 3,5-C$\underline{H}_2$), 4.40–4.48 (2H, m, OC$\underline{H}_2$), 6.64–6.70 (2H, m, 3,5-C$\underline{H}$), 6.81 (1H, dd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 6.95–7.01 (2H, m, 2″,6″-C$\underline{H}$), 7.10–7.17 (3H, m, 2,6-C$\underline{H}$, 4′-C$\underline{H}$), 7.47 (1H, d, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz), 7.68–7.73 (2H, m, 3″,5″-C$\underline{H}$), 9.80 (1H, br s, O$\underline{H}$), 9.82 (1H, br s, O$\underline{H}$), 11.19 (1H, br s, N$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 51.6, 54.6, 62.4, 63.1, 111.0, 114.7 (2C), 115.6, 124.8, 125.7, 129.6, 130.1, 131.6, 132.7, 134.2, 141.0, 142.9, 155.4, 157.6, 161.7, 193.9 (C=O); MS (EI, 70 eV): *m/z* (%): 524 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{27}H_{25}NO_5Se \times 1.7$ HCl (584.43): C 55.48, H 4.61, N 2.40; found: C 55.27, H 4.62, N 2.32.

4.1.6. (4-Fluorophenyl) (6-hydroxy-2-(4-hydroxyphenyl)benzo[b] selenophen-3-yl)methanone (**7**)

demethylation of **4** is analogous to demethylation of **5a,c**–**g** (see preparation of **6a,c**–**g**), except preparation of the corresponding hydrochloride is not necessary. Mixture of DCM and EtOAc (5:1) was used as eluent to isolate **7** in 47% yield. White solid; mp 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.61–6.66 (2H, m, 3′,5′-C$\underline{H}$), 6.83 (1H, dd, 5″-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.7 Hz), 7.07–7.13 (2H, m, 2′,6′-C$\underline{H}$), 7.15–7.22 (2H, m, 3,5-C$\underline{H}$), 7.27 (1H, d, 4″-C$\underline{H}$, $^3J_{(H,H)}$ = 8.7 Hz), 7.47 (1H, d, 7″-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz), 7.71–7.77 (2H, m, 2,6-C$\underline{H}$), 9.72 (1H, br s, O$\underline{H}$), 9.77 (1H, br s, O$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 111.0, 114.8, 115.5, 115.7 (d, 3,5-$\underline{C}$H, $^2J_{(C,F)}$ = 22.2 Hz), 125.0, 125.5, 129.9, 132.1, 132.2 (d, 2,6-$\underline{C}$H, $^3J_{(C,F)}$ = 9.7 Hz), 133.4 (d, 1-$\underline{C}$, $^4J_{(C,F)}$ = 2.7 Hz), 134.0, 141.2, 145.1, 155.4, 157.7, 165.0 (d, 4-$\underline{C}$F, $^1J_{(C,F)}$ = 252.6 MHz), 193.6 ($\underline{C}$=O); MS (EI, 70 eV): *m/z* (%): 411 (100) $[M-1]^+$; elemental analysis calcd (%) for $C_{21}H_{13}FO_3Se$ (411.28): C 61.33, H 3.19; found: C 61.12, H 3.31.

4.1.7. (2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)ethyl)methylammonium chloride (**6b**)

Methodology is analogous to preparation of **5a**–**g**, except 4.0 equivalents of 2-methylaminoethanol and 4.0 equivalents of NaH were used. mp 212–213 °C; 25% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.58 (3H, s, NC$\underline{H}_3$), 3.25–3.31 (2H, m, NC$\underline{H}_2$), 4.24–4.29 (2H, m, OC$\underline{H}_2$), 6.64–6.70 (2H, m, 3,5-C$\underline{H}$), 6.82 (1H, dd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.2 Hz, $^3J_{(H,H)}$ = 8.7 Hz), 6.94–7.00 (2H, m, 2″,6″-C$\underline{H}$), 7.10–7.18 (3H, m, 2,6-C$\underline{H}$, 4′-C$\underline{H}$), 7.47 (1H, d, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.2 Hz), 7.67–7.73 (2H, m, 3″,5″-C$\underline{H}$), 8.95 (2H, br s, N$\underline{H}_2$), 9.82 (2H, br s, O$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 32.7 (N$\underline{C}$H$_3$), 47.0 (N$\underline{C}$H$_2$), 63.6 (O$\underline{C}$H$_2$), 111.0, 114.6, 114.7, 115.6, 124.8, 125.7, 129.6, 130.0, 131.7, 132.7, 134.3, 141.0, 143.1, 155.4, 157.7, 161.9, 193.9 ($\underline{C}$=O); MS (EI, 70 eV): *m/z* (%): 468 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{24}H_{21}NO_4Se \times 1.4$ HCl (517.43): C 55.71, H 4.37, N 2.71; found: C 55.66, H 4.31, N 2.65.

4.1.8. (2-(4-(6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]selenophene-3-carbonyl)phenoxy)ethyl)trimethylammonium chloride (**8**)

To a solution of **6c** (free base form) (100 mg, 0.208 mmol) in dry dioxane (5.0 ml) iodomethane (295 mg, 2.08 mmol) was added and reaction mixture was stirred for 20 h. After evaporation of solvent, iodide anion was replaced by chloride using ion exchange resins (IRA 400 Cl^- form) to give **8** in 85% yield. mp 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.16 (9H, s, 3 × NC$\underline{H}_3$), 3.75–3.81 (2H, m, NC$\underline{H}_2$), 4.46–4.52 (2H, m, OC$\underline{H}_2$), 6.66–6.72 (2H, m, 3,5-C$\underline{H}$), 6.82 (1H, dd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 6.96–7.02 (2H, m, 2″,6″-C$\underline{H}$), 7.11–7.17 (3H, m, 2,6-C$\underline{H}$, 4′-C$\underline{H}$), 7.48 (1H, d, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz), 7.68–7.74 (2H, m, 3″,5″-C$\underline{H}$), 9.88 (2H, br s, 2 × O$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 53.0 (3 × N$\underline{C}$H$_3$), 61.8 (N$\underline{C}$H$_2$), 63.8 (O$\underline{C}$H$_2$), 111.1, 114.7, 115.6, 124.7, 125.6, 129.5, 130.0, 131.6, 132.7, 134.2, 141.0, 142.7, 155.4, 157.7, 161.6, 194.0 ($\underline{C}$=O); MS (EI, 70 eV): *m/z* (%): 496 (100) $[M]^+$; elemental analysis calcd (%) for $C_{26}H_{26}ClNO_4Se$ (530.90): C 58.82, H 4.94, N 2.64; found: C 58.71, H 4.97, N 2.58.

4.1.9. 3-Bromo-6-fluoro-2-(4-fluorophenyl)benzo[b]selenophene (**10**)

Cyclization of **9** is analogous to cyclization of **1**, except 2.0 equivalents of selenium dioxide and 1.5 equivalents of cyclohexene were used without triethylamine additive. Reaction was completed in 72 h and petroleum ether was used as eluent to give **10** in 60% yield. White amorphous solid; mp 108–109 °C (recrystallized from petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.13–7.19 (2H, m, 2′,6′-C$\underline{H}$), 7.23 (1H, ddd, 5-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,H)}$ = 8.8 Hz, $^3J_{(H,F)}$ = 8.8 Hz), 7.57 (1H, dd, 7-C$\underline{H}$, $^4J_{(H,H)}$ = 2.3 Hz, $^3J_{(H,F)}$ = 8.0 Hz), 7.61–7.66 (2H, m, 3′,5′-C$\underline{H}$), 7.88 (1H, dd, 4-C$\underline{H}$, $^4J_{(H,F)}$ = 5.1 Hz, $^3J_{(H,H)}$ = 8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 111.6 (d, $^2J_{(C,F)}$ = 25.3 Hz), 114.3 (d, $^2J_{(C,F)}$ = 23.7 Hz), 115.7 (d, $^2J_{(C,F)}$ = 21.8 Hz), 127.3 (d, $^3J_{(C,F)}$ = 9.0 Hz), 130.7 (d, $^4J_{(C,F)}$ = 3.5 Hz), 131.6 (d, $^3J_{(C,F)}$ = 8.2 Hz), 137.3 (d, $^4J_{(C,F)}$ = 1.9 Hz), 138.9 (d, $^4J_{(C,F)}$ = 3.5 Hz), 139.4 (d, $^3J_{(C,F)}$ = 9.3 Hz), 161.1 (d, $^1J_{(C,F)}$ = 248.7 Hz), 162.2 (m), 162.9 (d, $^1J_{(C,F)}$ = 249.5 Hz); ^{19}F NMR (376.21 MHz, $CDCl_3$) δ (ppm): −115.4 (m, 6-C$\underline{F}$), −112.1 (m, 4′-C$\underline{F}$); ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 588.5 (dd, *J* = 2.1 Hz, *J* = 17.8 Hz); MS (EI, 70 eV): *m/z* (%): 372 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_7BrF_2Se$ (372.07): C 45.19, H 1.90; found: C 45.01, H 1.98.

4.1.10. 6-Fluoro-2-(4-fluorophenyl)benzo[b]selenophene (**11**)

Methodology is analogous to preparation of **3**, except 10 equivalents of zinc were used and reaction was completed in 48 h mp 171–172 °C; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.07–7.14 (3H, m, 2′,6′-C$\underline{H}$, 3-C$\underline{H}$), 7.53–7.59 (4H, m, 5,7-C$\underline{H}$, 3′,5′-C$\underline{H}$), 7.69 (1H, dd, 4-C$\underline{H}$, $^4J_{(H,F)}$ = 5.2 Hz, $^3J_{(H,H)}$ = 8.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 111.8 (d, $^2J_{(C,F)}$ = 24.5 Hz), 113.6 (d, $^2J_{(C,F)}$ = 23.7 Hz), 116.0 (d, $^2J_{(C,F)}$ = 22.2 Hz), 122.2 (m), 126.1 (d, $^3J_{(C,F)}$ = 9.0 Hz), 128.4 (d, $^3J_{(C,F)}$ = 8.2 Hz), 132.2 (d, $^4J_{(C,F)}$ = 3.1 Hz), 139.6 (d, $^5J_{(C,F)}$ = 1.9 Hz), 141.7 (d, $^3J_{(C,F)}$ = 9.3 Hz), 145.8 (d, $^4J_{(C,F)}$ = 3.9 Hz), 160.3 (d, $^1J_{(C,F)}$ = 241.3 Hz), 162.8 (d, $^1J_{(C,F)}$ = 243.3 Hz); ^{19}F NMR (376.21 MHz, $CDCl_3$) δ (ppm): −116.9 (m, 6-C$\underline{F}$), −113.3 (m, 4′-C$\underline{F}$); MS (EI, 70 eV): *m/z* (%): 294 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_8F_2Se$ (293.17): C 57.36, H 2.75; found: C 57.31, H 2.86.

4.1.11. (6-Fluoro-2-(4-fluorophenyl)benzo[b]selenophen-3-yl) (4-fluorophenyl) methanone (**12**)

Methodology is analogous to preparation of **4**, except reaction was proceeded for 4 h and mixture of petroleum ether and EtOAc (1:0 → 20:1) was used as eluent to give **12** in 75% yield. Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 6.88–6.99 (4H, m, 2,3,5,6-C$\underline{H}$), 7.12 (1H, ddd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.8 Hz, $^3J_{(H,F)}$ = 8.8 Hz), 7.30–7.36 (2H, m, 3″,5″-C$\underline{H}$), 7.58–7.63 (2H, m, 4′,7′-C$\underline{H}$), 7.75–7.80 (2H, m, 2″,6″-C$\underline{H}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 111.6 (d, $^2J_{(C,F)}$ = 24.9 Hz), 114.2 (d, $^2J_{(C,F)}$ = 23.7 Hz), 115.7 (d, $^2J_{(C,F)}$ = 22.2 Hz), 115.9 (d, $^2J_{(C,F)}$ = 21.8 Hz), 126.5 (d, $^3J_{(C,F)}$ = 9.0 Hz), 130.9 (d, $^3J_{(C,F)}$ = 8.6 Hz), 131.0 (d, $^4J_{(C,F)}$ = 3.5 Hz), 132.5 (d, $^3J_{(C,F)}$ = 9.7 Hz), 133.4 (d, $^4J_{(C,F)}$ = 2.7 Hz), 134.2 (m), 138.0 (d, $^5J_{(C,F)}$ = 1.9 Hz), 141.7 (d, $^3J_{(C,F)}$ = 9.0 Hz), 147.5 (d, $^4J_{(C,F)}$ = 3.5 Hz), 160.7 (d, $^1J_{(C,F)}$ = 248.7 Hz), 162.9 (d, $^1J_{(C,F)}$ = 250.7 Hz), 165.9 (d, $^1J_{(C,F)}$ = 256.5 Hz), 193.4 ($\underline{C}$=O); ^{19}F NMR (376.21 MHz, $CDCl_3$) δ (ppm): −115.3 (m, 6′-C$\underline{F}$), −111.7 (m, 4-C$\underline{F}$), −103.6 (m, 4″-C$\underline{F}$); MS (EI, 70 eV): *m/z* (%): 416 (42) $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{11}F_3OSe$ (415.27): C 60.74, H 2.67; found: C 60.66, H 2.82.

4.1.12. General method for preparation of ***13a–c***

To a suspension of NaH (60% suspension in mineral oil, 39 mg, 0.964 mmol) in dry DMF (0.40 ml) under argon atmosphere solution of the corresponding 2-aminoethanol (0.964 mmol) in DMF (0.50 ml) was added dropwise and resulting mixture was stirred at room temperature for 15 min. Then, solution of **12** (200 mg, 0.482 mmol) in DMF (2.0 ml) was added and stirring was continued for 2 h. The reaction mixture was quenched with EtOAc (400 ml) and brine (80 ml) and resulting mixture was stirred for additional 30 min. After separation of aqueous phase, organic phase was washed with brine (4 × 80 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of DCM and EtOH as eluent to give a corresponding free base form of **13a–c**. Corresponding hydrochlorides were prepared by dropwise addition of 0.5 M HCl solution in dry diethyl ether to a cooled (ice/water bath) solution of free base form in DCM. After evaporation of solvents and excess of HCl under reduced pressure, products **13a–c** were obtained in 63–77% yield as white amorphous powders.

*4.1.12.1. 2-(4-(6-Fluoro-2-(4-fluorophenyl)benzo[b]selenophene-3-carbonyl)phenoxy)-N,N-dimethylethylamonium chloride (**13a**).* mp 217–218 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 2.80 (6H, s, 2 × NC$\underline{H}_3$), 3.45–3.50 (2H, m, NC$\underline{H}_2$), 4.35–4.40 (2H, m, OC$\underline{H}_2$), 6.97–7.02 (2H, m, 2″,6″-C$\underline{H}$), 7.15–7.22 (2H, m, 3,5-C$\underline{H}$), 7.27 (1H, ddd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.5 Hz, $^3J_{(H,H)}$ = 8.9 Hz, $^3J_{(H,F)}$ = 8.9 Hz), 7.39–7.45 (3H, m, 2,6-C$\underline{H}$, 4′-C$\underline{H}$), 7.69–7.75 (2H, m, 3″,5″-C$\underline{H}$), 8.14 (1H, dd, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.5 Hz, $^3J_{(H,F)}$ = 8.9 Hz), 10.30 (1H, br s, N$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d$_6$) δ (ppm): 42.5 (2 × N$\underline{C}$H$_3$), 54.8 (N$\underline{C}$H$_2$), 62.5 (O$\underline{C}$H$_2$), 112.4 (d, $^2J_{(C,F)}$ = 25.7 Hz), 114.0 (d, $^2J_{(C,F)}$ = 23.7 Hz), 114.8, 115.9 (d, $^2J_{(C,F)}$ = 21.8 Hz), 125.9 (m), 129.7, 130.6 (d, $^3J_{(C,F)}$ = 8.6 Hz), 130.9 (d, $^4J_{(C,F)}$ = 3.5 Hz), 131.8, 134.1, 137.9 (d, $^5J_{(C,F)}$ = 1.6 Hz), 141.4 (d, $^3J_{(C,F)}$ = 9.7 Hz), 145.7 (d, $^4J_{(C,F)}$ = 3.9 Hz), 159.7 (d, $^1J_{(C,F)}$ = 230.1 Hz), 162.0, 162.1 (d, $^1J_{(C,F)}$ = 232.0 Hz), 193.0 (C=O); ^{19}F NMR (376.21 MHz, DMSO-d$_6$) δ (ppm): −115.7 (m, 6′-C$\underline{F}$), −112.3 (m, 4-C$\underline{F}$); MS (EI, 70 eV): *m/z* (%): 486 (100) [M+1]$^+$; elemental analysis calcd (%) for $C_{25}H_{21}F_2NO_2Se \times 1.1$ HCl (524.51): C 57.24, H 4.26, N 2.67; found: C 57.21, H 4.29, N 2.60.

*4.1.12.2. 1-(2-(4-(6-Fluoro-2-(4-fluorophenyl)benzo[b]selenophene-3-carbonyl)phenoxy)ethyl)piperidin-1-ium chloride (**13b**).* mp 208–209 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 1.29–1.42 (1H, m, 4-C$\underline{H}$), 1.62–1.82 (5H, m, 3,5-C$\underline{H}_2$, 4-C$\underline{H}$), 2.89–3.01 (2H, m, NC$\underline{H}_2$), 3.41–3.50 (4H, m, 2,6-C$\underline{H}_2$), 4.39–4.45 (2H, m, OC$\underline{H}_2$), 6.97–7.03 (2H, m, 2″,6″-C$\underline{H}$), 7.15–7.22 (2H, m, 3,5-C$\underline{H}$), 7.27 (1H, ddd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.5 Hz, $^3J_{(H,H)}$ = 9.0 Hz, $^3J_{(H,F)}$ = 9.0 Hz), 7.39–7.45 (3H, m, 2,6-C$\underline{H}$, 4′-C$\underline{H}$), 7.70–7.75 (2H, m, 3″,5″-C$\underline{H}$), 8.14 (1H, dd, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.5 Hz, $^3J_{(H,F)}$ = 9.0 Hz), 10.20 (1H, br s, N$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d$_6$) δ (ppm): 21.1 (4-$\underline{C}$H$_2$), 22.2 (3,5-$\underline{C}$H$_2$), 52.4 (2,6-$\underline{C}$H$_2$), 54.3 (N$\underline{C}$H$_2$), 62.5 (O$\underline{C}$H$_2$), 112.4 (d, $^2J_{(C,F)}$ = 25.7 Hz), 114.0 (d, $^2J_{(C,F)}$ = 24.1 Hz), 114.8, 115.9 (d, $^2J_{(C,F)}$ = 21.8 Hz), 125.9 (m), 129.7, 130.6 (d, $^3J_{(C,F)}$ = 9.0 Hz), 130.9 (d, $^4J_{(C,F)}$ = 3.1 Hz), 131.8, 134.1, 137.9 (d, $^5J_{(C,F)}$ = 1.6 Hz), 141.4 (d, $^3J_{(C,F)}$ = 9.7 Hz), 145.7 (d, $^4J_{(C,F)}$ = 3.5 Hz), 159.7 (d, $^1J_{(C,F)}$ = 230.1 Hz), 162.0, 162.1 (d, $^1J_{(C,F)}$ = 231.6 Hz), 193.0 (C=O); ^{19}F NMR (376.21 MHz, DMSO-d$_6$) δ (ppm): −115.7 (m, 6′-C$\underline{F}$), −112.3 (m, 4-C$\underline{F}$); MS (EI, 70 eV): *m/z* (%): 526 (100) [M+1]$^+$; elemental analysis calcd (%) for $C_{28}H_{25}F_2NO_2Se \times 1.3$ HCl (571.86): C 58.80, H 4.65, N 2.45; found: C 58.92, H 4.65, N 2.39.

*4.1.12.3. 4-(2-(4-(6-Fluoro-2-(4-fluorophenyl)benzo[b]selenophene-3-carbonyl)phenoxy)ethyl)morpholin-4-ium chloride (**13c**).* mp 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 3.09–3.22 (2H, m, NC$\underline{H}_2$), 3.41–3.58 (4H, m, 2 × NC$\underline{H}_2$), 3.70–3.81 (2H, m, OC$\underline{H}_2$), 3.89–3.99 (2H, m, OC$\underline{H}_2$), 4.39–4.47 (2H, m, OC$\underline{H}_2$), 6.97–7.03 (2H, m, 2″,6″-C$\underline{H}$), 7.15–7.22 (2H, m, 3,5-C$\underline{H}$), 7.27 (1H, ddd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.5 Hz, $^3J_{(H,H)}$ = 9.0 Hz, $^3J_{(H,F)}$ = 9.0 Hz), 7.38–7.45 (3H, m, 2,6-C$\underline{H}$, 4′-C$\underline{H}$), 7.69–7.75 (2H, m, 3″,5″-C$\underline{H}$), 8.14 (1H, dd, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.5 Hz, $^3J_{(H,F)}$ = 9.0 Hz), 10.80 (1H, br s, N$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d$_6$) δ (ppm): 51.5 (2 × N$\underline{C}$H$_2$), 54.5 (N$\underline{C}$H$_2$), 62.4 (O$\underline{C}$H$_2$), 63.0 (2 × O$\underline{C}$H$_2$), 112.4 (d, $^2J_{(C,F)}$ = 25.3 Hz), 114.0 (d, $^2J_{(C,F)}$ = 23.7 Hz), 114.8, 116.0 (d, $^2J_{(C,F)}$ = 22.2 Hz), 125.9 (m), 129.7, 130.6 (d, $^3J_{(C,F)}$ = 8.6 Hz), 130.9 (d, $^4J_{(C,F)}$ = 3.5 Hz), 131.8, 134.1, 137.9 (d, $^5J_{(C,F)}$ = 1.9 Hz), 141.5 (d, $^3J_{(C,F)}$ = 9.7 Hz), 145.7 (d, $^4J_{(C,F)}$ = 3.5 Hz), 159.7 (d, $^1J_{(C,F)}$ = 230.1 Hz), 161.9, 162.1 (d, $^1J_{(C,F)}$ = 232.4 Hz), 193.0 (C=O); ^{19}F NMR (376.21 MHz, DMSO-d$_6$) δ (ppm): −115.7 (m, 6′-C$\underline{F}$), −112.3 (m, 4-C$\underline{F}$); MS (EI, 70 eV): *m/z* (%): 528 (100) [M+1]$^+$; elemental analysis calcd (%) for $C_{27}H_{23}F_2NO_3Se \times 1.1$ HCl (566.54): C 57.24, H 4.30, N 2.47; found: C 57.09, H 4.31, N 2.36.

*4.1.13. 6-Fluoro-3-(4-methoxyphenyl)benzo[b]selenophene (**15**)*

A suspension of 3-bromo-6-fluorobenzo[*b*]selenophene (2.00 g, 7.19 mmol), Pd(OAc)$_2$ (161 mg, 0.719 mmol), tri(*o*-tolyl)phosphine (657 mg, 2.16 mmol), and K_3PO_4 (5.35 g, 25.2 mmol) in dry xylene (40 ml) was barbotated with argon and stirred at 40 °C for 15 min. Then, a suspension of 4-methoxyphenyl boronic acid (2.19 g, 14.4 mmol) in isopropanol (20 ml) was added by syringe and reaction mixture was stirred at 110 °C over night. After cooling to room temperature, reaction mixture was quenched with EtOAc (300 ml) and water (100 ml). Resulting mixture was stirred for 15 min and organic phase was separated. Aqueous phase was extracted with EtOAc (2 × 100 ml) and combined organic phases were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Crude product was purified by flash chromatography using mixture of petroleum ether/EtOAc (100:1) as eluent to give **14** (2.05 g) in 94% yield as white solid. mp 76–77 °C (recrystallized from mixture of petroleum ether/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$/TMS) δ (ppm): 3.88 (3H, s, OC$\underline{H}_3$), 6.99–7.04 (2H, m, 3′,5′-C$\underline{H}$), 7.12 (1H, ddd, 5-C$\underline{H}$, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.8 Hz, $^3J_{(H,F)}$ = 8.8 Hz), 7.41–7.46 (2H, m, 2′,6′-C$\underline{H}$), 7.64 (1H, dd, 7-C$\underline{H}$, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,F)}$ = 8.4 Hz), 7.71 (1H, dd, 4-C$\underline{H}$, $^4J_{(H,F)}$ = 5.2 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 7.75 (1H, s, 2-C$\underline{H}$, $^2J_{(H,Se)}$ = 48 Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 55.3 (O$\underline{C}$H$_3$), 112.2 (d, $^2J_{(C,F)}$ = 24.5 Hz), 113.1 (d, $^2J_{(C,F)}$ = 23.4 Hz), 114.1, 124.4 (d, $^4J_{(C,F)}$ = 3.5 Hz), 125.9 (d, $^3J_{(C,F)}$ = 9.0 Hz), 129.7, 129.9, 137.2 (d, $^5J_{(C,F)}$ = 1.9 Hz), 140.5 (m), 142.6 (d, $^3J_{(C,F)}$ = 9.0 Hz), 159.2, 160.5 (d, 6-C$\underline{F}$, $^1J_{(C,F)}$ = 246.4 Hz); ^{19}F NMR (376.21 MHz, CDCl$_3$) δ (ppm): −117.9 (m); MS (EI, 70 eV): *m/z* (%): 306 (100) [M]$^+$; elemental analysis calcd (%) for $C_{15}H_{11}FOSe$ (305.21): C 59.03, H 3.63; found: C 58.91, H 3.66.

*4.1.14. 6-Methoxy-3-(4-methoxyphenyl)benzo[b]selenophene (**16**)*

To a cooled (0 °C) suspension of NaH (60% suspension in mineral oil, 676 mg, 16.9 mmol) in dry NMP (6.0 ml) under argon atmosphere dry MeOH (0.98 ml, 16.9 mmol) was added dropwise. Resulting white suspension was stirred at the same temperature for additional 5 min and for 10 min at room temperature. Then a solution of **15** (860 mg, 2.82 mmol) in dry NMP (4.0 ml) was added and reaction mixture was stirred at 140 °C for 3 h. After cooling to room temperature, reaction mixture was quenched with EtOAc (500 ml) and water (100 ml). Resulting mixture was stirred for 30 min and aqueous phase was separated. Organic phase was washed with water (4 × 100 ml) and brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Crude product was purified by flash chromatography using mixture of petroleum ether/EtOAc (1:0 → 40:1) as eluent to give **16** (729 mg) in 81% yield as pale yellow sticky liquid. ^{1}H NMR (400 MHz, CDCl$_3$/TMS) δ (ppm): 3.87 (3H, s, OC$\underline{H}_3$), 3.89 (3H, s, OC$\underline{H}_3$), 6.98 (1H, dd, 5-C$\underline{H}$, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 6.98–7.02 (2H, m, 3′,5′-C$\underline{H}$), 7.43–7.47 (2H, m, 2′,6′-C$\underline{H}$), 7.46 (1H, d,

7-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.62 (1H, s, 2-CH, $^{2}J_{(H,Se)}$ = 47 Hz), 7.67 (1H, d, 4-CH, $^{3}J_{(H,H)}$ = 8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.3 (OCH_3), 55.6 (OCH_3), 109.0, 113.8, 114.0, 122.1, 125.5, 129.9, 130.1, 134.6, 140.6, 143.2, 157.4, 159.1; ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 502.18; MS (EI, 70 eV): *m/z* (%): 318 (100) $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{14}O_2Se$ (317.24): C 60.58, H 4.45; found: C 60.32, H 4.54.

*4.1.15. (4-Fluorophenyl) (6-methoxy-3-(4-methoxyphenyl)benzo[b] selenophen-2-yl)methanone (**17**)*

Methodology is analogous to preparation of **4** except 2.5 equiv. of aluminium(III) chloride were used and reaction was completed in 72 h. 52% yield; greenish yellow glace like solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 3.75 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.70–6.74 (2H, m, 3′,5′-CH), 6.75–6.82 (2H, m, 3,5-CH), 7.00 (1H, dd, 5″-CH, $^{4}J_{(H,H)}$ = 2.4 Hz, $^{3}J_{(H,H)}$ = 8.8 Hz), 7.10–7.15 (2H, m, 2′,6′-CH), 7.45 (1H, d, 7″-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.50–7.56 (2H, m, 2,6-CH), 7.59 (1H, d, 4″-CH, $^{3}J_{(H,H)}$ = 8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.3 (OCH_3), 55.7 (OCH_3), 108.2, 113.7, 114.7 (d, 3,5-CH, $^{2}J_{(C,F)}$ = 21.7 Hz), 115.1, 128.1, 128.3, 131.5, 131.9 (d, 2,6-CH, $^{3}J_{(C,F)}$ = 9.4 Hz), 134.1 (d, 1-C, $^{4}J_{(C,F)}$ = 3.0 Hz), 136.1, 138.8, 144.3, 144.4, 159.4, 159.5, 164.6 (d, 4-C, $^{1}J_{(C,F)}$ = 253.5 Hz), 191.3 (C=O); ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 562.7; MS (EI, 70 eV): *m/z* (%): 440 (100) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{17}FO_3Se$ (439.34): C 62.88, H 3.90; found: C 62.53, H 4.00.

*4.1.16. General method for preparation of **18a–c***

To a suspension of NaH (60% suspension in mineral oil, 82 mg, 2.05 mmol) in dry DMF (2.0 ml) under argon atmosphere solution of the corresponding 2-aminothenol derivative (2.05 mmol) in DMF (1.5 ml) was added dropwise and resulting mixture was stirred at room temperature for 15 min. Then, solution of **17** (300 mg, 0.683 mmol) in DMF (3.0 ml) was added and stirring was continued at 50 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with EtOAc (400 ml) and brine (80 ml) and resulting mixture was stirred for 30 min. After separation of aqueous phase, organic phase was washed with brine (4 × 80 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of DCM and EtOH as eluent to give **18a–c** in 48–68% yield as greenish yellow glass like solids.

*4.1.16.1. (4-(2-(Dimethylamino)ethoxy)phenyl) (6-methoxy-3-(4-methoxyphenyl)benzo[b]selenophen-2-yl)methanone (**18a**).* 48% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.32 (6H, s, 2 × NCH_3), 2.70 (2H, t, NCH_2, $^{3}J_{(H,H)}$ = 5.6 Hz), 3.73 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.01 (2H, t, OCH_2, $^{3}J_{(H,H)}$ = 5.6 Hz), 6.62–6.67 (2H, m, 3′,5′-CH), 6.71–6.76 (2H, m, 3,5-CH), 6.97 (1H, dd, 5″-CH, $^{4}J_{(H,H)}$ = 2.4 Hz, $^{3}J_{(H,H)}$ = 8.8 Hz), 7.15–7.19 (2H, m, 2′,6′-CH), 7.43 (1H, d, 7″-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.54–7.59 (2H, m, 2,6-CH), 7.58 (1H, d, 4″-CH, $^{3}J_{(H,H)}$ = 8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 45.8 (2 × NCH_3), 55.2 (OCH_3), 55.6 (OCH_3), 58.0 (NCH_2), 66.0 (OCH_2), 108.1, 113.6 (2C), 114.8, 127.9, 128.3, 130.4, 131.4, 131.8, 135.9, 138.7, 143.1, 143.8, 159.0, 159.2, 161.9, 191.4 (C=O); ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 564.7; MS (EI, 70 eV): *m/z* (%): 510 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{27}H_{27}NO_4Se$ (508.47): C 63.78, H 5.35, N 2.75; found: C 63.71, H 5.40, N 2.66.

*4.1.16.2. (6-Methoxy-3-(4-methoxyphenyl)benzo[b]selenophen-2-yl) (4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone (**18b**).* 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.40–1.49 (2H, m, 4-CH_2), 1.57–1.64 (4H, m, 3,5-CH_2), 2.45–2.53 (4H, m, 2,6-CH_2), 2.73 (2H, t, NCH_2, $^{3}J_{(H,H)}$ = 6.1 Hz), 3.75 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.05 (2H, t, OCH_2, $^{3}J_{(H,H)}$ = 6.1 Hz), 6.61–6.67 (2H, m, 3,5-CH), 6.72–6.77 (2H, m, 3″,5″-CH), 6.98 (1H, dd, 5′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz, $^{3}J_{(H,H)}$ = 8.9 Hz), 7.16–7.21 (2H, m, 2,6-CH), 7.44 (1H, d, 7′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.55–7.60 (2H, m, 2″,6″-CH), 7.59 (1H, d, 4′-CH, $^{3}J_{(H,H)}$ = 8.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 23.9 (4-CH_2), 25.6 (3,5-CH_2), 54.9 (2,6-CH_2), 55.2 (OCH_3), 55.6 (OCH_3), 57.4 (NCH_2), 65.8 (OCH_2), 108.1, 113.6, 113.7, 114.8, 127.9, 128.3, 130.4, 131.4, 131.9, 136.0, 138.7, 143.1, 143.8, 159.0, 159.2, 161.8, 191.3 (C=O); ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 564.5; MS (EI, 70 eV): *m/z* (%): 550 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{30}H_{31}NO_4Se$ (548.53): C 65.69, H 5.70, N 2.55; found: C 65.42, H 5.84, N 2.42.

*4.1.16.3. (6-Methoxy-3-(4-methoxyphenyl)benzo[b]selenophen-2-yl) (4-(2-morpholinoethoxy)phenyl)methanone (**18c**).* 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.51–2.58 (4H, m, 2 × NCH_2), 2.75 (2H, t, NCH_2, $^{3}J_{(H,H)}$ = 5.8 Hz), 3.69–3.75 (4H, m, 2 × OCH_2), 3.74 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.05 (2H, t, OCH_2, $^{3}J_{(H,H)}$ = 5.8 Hz), 6.60–6.66 (2H, m, 3,5-CH), 6.71–6.76 (2H, m, 3″,5″-CH), 6.98 (1H, dd, 5′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz, $^{3}J_{(H,H)}$ = 8.9 Hz), 7.15–7.20 (2H, m, 2,6-CH), 7.43 (1H, d, 7′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.54–7.59 (2H, m, 2″,6″-CH), 7.58 (1H, d, 4′-CH, $^{3}J_{(H,H)}$ = 8.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 54.0 (2 × NCH_2), 55.2 (OCH_3), 55.6 (OCH_3), 57.3 (NCH_2), 65.8 (OCH_2), 66.8 (2 × OCH_2), 108.1, 113.6 (2C), 114.8, 127.9, 128.3, 130.4, 131.4, 131.8, 135.9, 138.7, 143.1, 143.8, 159.0, 159.1, 161.7, 191.3 (C=O); ^{77}Se NMR (76.37 MHz, $CDCl_3$) δ (ppm): 564.2; MS (EI, 70 eV): *m/z* (%): 552 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{29}H_{29}NO_5Se$ (550.50): C 63.27, H 5.31, N 2.54; found: C 63.01, H 5.42, N 2.18.

*4.1.17. General method for preparation of **19a–c***

Methodology is analogous to preparation of **6a,c–g**. Derivatives **19a–c** were obtained in 31–90% yield as white to pale yellow amorphous solids.

*4.1.17.1. 2-(4-(6-Hydroxy-3-(4-hydroxyphenyl)benzo[b]selenophene-2-carbonyl)phenoxy)-N,N-dimethylethylamonium chloride (**19a**).* mp > 230 °C; 78% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.82 (6H, s, 2 × NCH_3), 3.44–3.50 (2H, m, NCH_2), 4.29–4.36 (2H, m, OCH_2), 6.59–6.66 (2H, m, 3,5-CH), 6.77–6.84 (2H, m, 2″,6″-CH), 6.93 (1H, dd, 5′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz, $^{3}J_{(H,H)}$ = 8.8 Hz), 6.99–7.06 (2H, m, 2,6-CH), 7.45 (1H, d, 4′-CH, $^{3}J_{(H,H)}$ = 8.8 Hz), 7.50 (1H, d, 7′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.49–7.53 (2H, m, 3″,5″-CH), 9.57 (1H, br s, OH), 10.09 (1H, br s, OH), 10.17 (1H, br s, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 42.8 (2 × NCH_3), 55.2 (NCH_2), 62.4 (OCH_2), 111.2, 114.0, 115.0, 115.4, 126.2, 127.9, 130.6, 131.3, 131.5, 134.3, 136.5, 143.0, 143.6, 157.0, 157.2, 160.3, 190.8 (C=O); MS (EI, 70 eV): *m/z* (%): 482 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{25}H_{23}NO_4Se$ × 1.2 HCl (524.16): C 57.28, H 4.66, N 2.67; found: C 57.15, H 4.54, N 2.57.

*4.1.17.2. 1-(2-(4-(6-Hydroxy-3-(4-hydroxyphenyl)benzo[b]selenophene-2-carbonyl)phenoxy)ethyl)piperidin-1-ium chloride (**19b**).* mp > 230 °C; 90% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.30–1.45 (1H, m, 4-CH), 1.62–1.85 (5H, m, 4-CH, 3,5-CH_2), 2.90–3.03 (2H, m, NCH_2), 3.40–3.50 (4H, m, 2,6-CH_2), 4.31–4.39 (2H, m, OCH_2), 6.59–6.65 (2H, m, 3,5-CH), 6.78–6.84 (2H, m, 2″,6″-CH), 6.93 (1H, dd, 5′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz, $^{3}J_{(H,H)}$ = 8.8 Hz), 7.01–7.06 (2H, m, 2,6-CH), 7.45 (1H, d, 4′-CH, $^{3}J_{(H,H)}$ = 8.8 Hz), 7.50 (1H, d, 7′-CH, $^{4}J_{(H,H)}$ = 2.4 Hz), 7.49–7.55 (2H, m, 3″,5″-CH), 9.54 (1H, br s, OH), 9.77 (1H, br s, NH), 10.06 (1H, br s, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 21.0 (4-CH_2), 22.2 (3,5-CH_2), 52.5 (2,6-CH_2), 54.4 (NCH_2), 62.3 (OCH_2), 111.1, 113.8, 114.9, 115.3, 126.0, 127.7, 130.5, 131.2, 131.4, 134.2, 136.4, 142.9, 143.5, 157.0, 157.2, 160.2, 190.6 (C=O); MS (EI, 70 eV): *m/z* (%): 522 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{28}H_{27}NO_4Se$ × 1.2 HCl (564.23): C 59.53, H 5.04, N 2.48; found: C 59.46, H 5.10, N 2.39.

*4.1.17.3. 4-(2-(4-(6-Hydroxy-3-(4-hydroxyphenyl)benzo[b]selenophene-2-carbonyl)phenoxy)ethyl)morpholin-4-ium chloride (**19c**).* mp 221–222 °C; 31% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.09–3.24 (2H, m, NC$\underline{H}_2$), 3.41–3.60 (4H, m, 2,6-C$\underline{H}_2$), 3.68–4.01 (4H, m, 3,5-C$\underline{H}_2$), 4.32–4.42 (2H, m, OC$\underline{H}_2$), 6.59–6.66 (2H, m, 3,5-C$\underline{H}$), 6.78–6.85 (2H, m, 2″,6″-C$\underline{H}$), 6.93 (1H, dd, 5′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.4 Hz, $^3J_{(H,H)}$ = 8.8 Hz), 7.00–7.06 (2H, m, 2,6-C$\underline{H}$), 7.45 (1H, d, 4′-C$\underline{H}$, $^3J_{(H,H)}$ = 8.8 Hz), 7.50 (1H, d, 7′-C$\underline{H}$, $^4J_{(H,H)}$ = 2.4 Hz), 7.49–7.54 (2H, m, 3″,5″-C$\underline{H}$), 9.55 (1H, br s, O$\underline{H}$), 10.06 (1H, br s, O$\underline{H}$), 10.56 (1H, br s, N$\underline{H}$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm): 51.8, 54.9, 62.4, 63.2, 111.1, 113.9, 115.0, 115.4, 126.1, 127.8, 130.5, 131.2, 131.4, 134.2, 136.4, 142.9, 143.4, 157.0, 157.2, 160.3, 190.7 (C=O); MS (EI, 70 eV): *m/z* (%): 524 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{27}H_{25}NO_5Se \times 1.5$ HCl (577.14): C 56.19, H 4.64, N 2.43; found: C 56.12, H 4.66, N 2.32.

4.2. Biological evaluation

4.2.1. In vitro cytotoxicity assay

Monolayer tumor cell line: CCL-8 (mouse sarcoma), MDA-MB-435s (human melanoma) MES-SA (human uterus sarcoma), MCF-7 (human breast adenocarcinoma, estrogen-positive), HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and normal cell line NIH 3T3 (mouse fibroblasts) were cultured in standard medium DMEM (Dulbecco's modified Eagle's medium) without an indicator ("Sigma"). All cells obtained from the American Type Culture Collection. After the ampoule was thawed the cells from 1 to 4 passages were used. About $2-10\cdot10^4$ cells/mL (depending on line nature) were placed in 96-well plates immediately after compounds were added to the wells. The control cells without test compounds were cultured on separate plate. The plates were incubated for 72 h, 37 °C, 5% CO_2. The number of surviving cells was determined using tri(4-dimethylaminophenyl)methyl chloride (Crystal Violet) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolinium bromide (MTT). MTT-test: after incubating with preparations culture medium was removed and 200 μL fresh medium with 10 mM HEPES was added in each well of the plate, than 20 μL MTT (2 mg/mL in HBSS) was added. After incubation (3 h, 37 °C, 5% CO_2) the medium with MTT was removed and 200 μL DMSO and 25 μL glycine buffer pH 10.5 were added at once to each sample. The samples were tested at 540 nm on Anthos HT II photometer. CV-test: after incubating with preparations cell culture was removed and 100 ml 1% glutaraldehyde in HBSS was added to each well. After incubation (15 min) the HBSS with glutaraldehyde the samples washed off H_2O (1 time) and 0.05% crystal violet were added. After incubation with dye (15 min) the samples washed off H_2O (3 times) and citrate buffers pH 4.2 and EtOH (1:1) was added. The samples were tested at 540 nm.

4.2.2. In vivo assays

The compounds were tested *in vivo* against 4T1 mammary carcinoma cells obtained from the American Type Culture Collection. The cells were grown in standard medium DMEM (Dulbecco's modified Eagle's medium) ("Sigma") supplemented with 10% fetal bovine serum (Sigma). Six-to eight-week-old female BALB/c mice (15–25 g) were used. The mice were housed in a temperature-controlled facility on a 12-h photoperiod. The mice were acclimated for 1 week before use and maintained throughout the study in a controlled environment: 24 ± 2 °C, 50 ± 10% relative humidity, and a 12-h light/dark cycle. The mice were given food and water *ad libitum*. Litter used from the company "Basic Micro" (Holland) and food supplied by the firm "Lactamin" (Sweden). *In vivo* experimental protocol is accepted by the Food and Veterinary Service (Republic of Latvia), and the Latvian Science Council's Ethics Commission.

Measurement of tumour growth: in the prevention experiment, female mice were randomized into four groups of 5–7 animals each. Mice were subcutaneously inoculated with 5×10^5 4T1 cells in PBS harvested from culture by treatment with 0.25% trypsin in the mid-back region. Drugs were administered i.p. Drug injection was started 24 h after tumor transplantation on even days (9 times). The daily dose was 15 and 1.8 mg/kg. Total time of experiment was 18 days.

The compounds were tested *in vivo* against sarcoma S-180 cells. Sarcoma S-180 (5×10^6) cells were inoculated s.c. into male ICR mice (six weeks old, 18–20 g) on day 0. Drugs were administered i.p.; the treatment was started 24 h after tumor transplantation. The number of mice used in each group was between 6 and 10. The daily dose was 15 mg/kg; duration of treatment was nine days.

The mice were monitored and weighed, and the sizes of the tumors were recorded by measuring tumor diameters. Tumor size was measured with callipers, and tumor volume was calculated by the formula ($V = 4\pi ab^2/3$), where b is the smaller radius and a is the larger radius.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.09.088.

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III

Paegle, E.; Belyakov, S.; Kirsch, G.; Arsenyan, P.
”Addition of selenium(II) bromide to arylalkynylamides – a route to hypervalent T-shaped 10–Se–3 systems”
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Addition of selenium(II) bromide to arylalkynylamides—a route to hypervalent T-shaped 10-Se-3 systems

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ABSTRACT

A route for the generation of hypervalent T-shaped 10-Se-3 systems is described involving an interaction between in situ prepared selenium(II) bromide and an aryl alkynyl amide derivative. The existence of hypervalent selenium in both the solid and solution states has been supported by X-ray analysis and ^{77}Se NMR data.

Selenium is able to form highly versatile organic and inorganic hypervalent compounds due to its wide range of oxidative states and its unoccupied valence d orbitals.[1] Trivalent selenium compounds bearing a formal positive charge on the selenium atom have been extensively described,[1] but much less is known about the negatively charged T-shaped trivalent selenium groups. These type of compounds, which feature a linear X–Se–X or X–Se–Y moiety (X = Cl, Br, I; Y = CN), are frequently designated as a 10-Se-3 system, which means that 10 electrons are associated with the central selenium atom but only six (3 pairs) are involved in bonding.[2] The most widely used method for the formation of T-shaped selenium moieties containing a C–Se bond involves an oxidative addition of halogens (Cl_2,[3] Br_2,[3a,c,4] I_2[3a,c,4a,5]), interhalogens (IBr),[6] or pseudohalogens (ICN)[7] to the selenium atom of the corresponding selone derivative. However, generation of such a system has also been accomplished by the addition of selenium halides to an *N*-heterocyclic carbene[8] or by reaction of diaryldiselenide derivatives with an excessive amount of the corresponding dihalogen.[9] Herein, we report an alternative method for the synthesis of a new type of oxazolinium derived hypervalent T-shaped 10-Se-3 system utilizing the addition of selenium(II) bromide to the triple bond of the corresponding *N*-aryl(hetaryl)alkynyl pyrrolidinone.

As the selenohalogenation of aryl(thienyl)alkynes[10] is one of the most straightforward synthetic pathways for the preparation of benzo[*b*]selenophenes and selenophenothiophenes, we were inspired to further expand the existing protocol. Because almost nothing was known about the selenohalogenation of aryl alkyne derivatives bearing heteroatoms directly attached to the triple bond, we decided to pursue this research direction. Aryl alkynyl amides were found to be suitable substrates for this investigation due to their stability and relatively simple preparation. The initial alkynyl amides **3a–g** were prepared by a two-step procedure (Scheme 1). Benzaldehydes **1a–f** and thiophene-2-carbaldehyde (**1g**) were converted to the corresponding dibromovinylbenzenes(thiophene) **2a–g** by the Corey–Fuchs[11] protocol. Subsequent CuI/DMEDA (*N*,*N*′-dimethylethylenediamine) catalyzed coupling[12] of **2a–g** with pyrrolidin-2-one led to the desired alkynyl amides **3a–g**. Next, alkynyl amides **3a–g** were treated with in situ prepared selenium(II) bromide[13] in $CHCl_3$. Unexpectedly, the reaction of phenylethynyl amide **3a** with $SeBr_2$ failed to yield the corresponding 3-bromobenzo[*b*]selenophene derivative, instead generating a new type of 10-Se-3 system **4a**. Since selenirenium species have been widely[14] postulated as the key intermediates in reactions of selenium electrophiles with C≡C triple bonds, we propose that the reaction begins with the coordination of $SeBr_2$ to the triple bond of **3a**, forming selenirenium type adduct **A**, which induces an intramolecular nucleophilic attack of oxygen onto the carbon of the triple bond to form a five-membered cycle.

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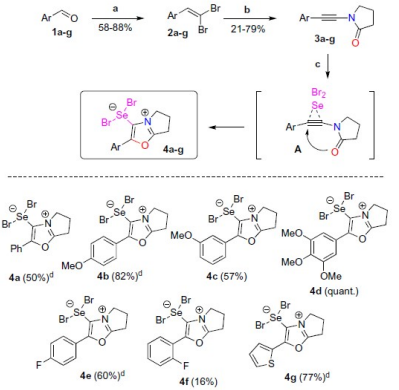

Scheme 1. Synthetic procedure for the preparation of hypervalent T-shaped compounds **4a–g**. Reagents and conditions: (a) **1a–g** (1.0 equiv), CBr_4 (1.5 equiv), PPh_3 (3.0 equiv), CH_2Cl_2, 0 °C, 2 h; (b) **2a–g** (1.0 equiv), pyrrolidin-2-one (1.0 equiv), CuI (12 mol %), DMEDA (18 mol %), Cs_2CO_3 (4.0 equiv), dioxane, 60 °C, 24 h; (c) **3a–g** (1.0 equiv), $SeBr_2$ (1.0 equiv), $CHCl_3$, 0 °C, 15 min. [a]To achieve complete precipitation of the corresponding products **4a**, **b**, **e**, and **g** the reaction mixture was stirred at room temperature for an additional 24 h.

The intramolecular nucleophilic attack of the carbonyl oxygen seems to be favored over the expected selenobromination. Product **4a** began to precipitate as a yellow amorphous solid during the addition of alkynyl amide **3a** to the selenium(II) bromide solution. Complete consumption of the starting material was observed in 15 min (TLC), then the reaction was left to stir overnight to achieve complete precipitation of the product, which was isolated in 50% yield after filtration. In a similar manner, a series of hypervalent selenium compounds **4b–g** were prepared in moderate to high yields. It was concluded that electron-rich substrates were generally more suitable for these reactions, thus enabling the desired products to be obtained in higher yields. This was exemplified by the low yield obtained for *o*-fluorosubstituted **3f** and quantitative yield using trimethoxy substituted **3d**. A modified isolation procedure was required to obtain **4c**, **d**, and **f** as these products did not precipitate directly from the reaction mixture, even after stirring for 24 h. Thus, the reaction mixture was evaporated under reduced pressure after stirring for 15 min at 0 °C, and the corresponding product was successfully precipitated by stirring in a mixture of petroleum ether and $CHCl_3$. The modified procedure also worked well for the other products, but highly pure compounds were more easily obtained by direct precipitation from the reaction mixture. To the best of our knowledge, this is a new route for preparation of zwitterionic T-shaped trivalent selenium derivatives.

The chemical shift values in the ^{77}Se NMR spectra for known analogous trivalent systems are found in the range of approximately 300 to 400 ppm,[3a,4b,c] showing considerably higher shielding than in the case of the corresponding divalent PhSeBr system (888 ppm in dioxane). The ^{77}Se chemical shifts for the new derivatives **4a–g** ranged from 344 ppm for **4g** to 374 ppm for **4d**. These results suggest the hypervalent state of selenium in solution. Compounds **4a–g** were relatively stable and could be stored in a closed system at room temperature for several months without any signs of decomposition, however, the slow appearance of red selenium was observed in the presence of air. These compounds are insoluble in nonpolar organic solvents but slightly soluble in acetonitrile and acetone. In highly polar solvents (DMSO, DMF, and water), these substances quickly decompose which was accompanied by the precipitation of amorphous selenium. Because of their thermal instability, no melting points were obtained. In general, upon heating above 100 °C, compounds **4a–g** decompose, as evidenced by a color change.

The structures of **4a**, **b**, **e**, and **g** were unambiguously confirmed by X-ray analysis (Fig. 1). Monocrystals of **4a** were obtained by crystallization from an oversaturated solution in acetone, but in the cases of **4b**, **e**, and **g**, acetonitrile was used as a solvent. In the crystal structures of **4a** and **4g**, strong intermolecular σ-hole interactions between the T-shaped selenium atom and the bromine of another molecule were observed. By means of these interactions, centrosymmetric molecular pseudodimers containing square-planar coordinated selenium atoms were formed. The corresponding intermolecular Se···Br distances are equal to 3.4439(8) Å and 3.3374(5) Å for **4a** and **4g**, respectively. A perspective view of the molecular pseudodimer of the thiophene derivative **4g** is illustrated in Figure 1A. Similar centrosymmetric pseudodimers formed by Se···Br σ-hole interactions have also been observed in previously reported crystal structures;[15] however, the same interactions were weaker, and their lengths fell in the range of 3.491–3.610 Å. Unlike the crystal structures of phenyl derivative **4a** and thienyl analogue **4g** (Fig. 1A), the Se···Br σ-hole interactions in 4-fluorophenyl substituted **4e** did not lead to the formation of analogous centrosymmetric pseudodimers (Fig. 1B). Because of the elevated electronegativity of C-5, strong intermolecular CH···F type hydrogen bonds are present, leading to the formation of molecular chains along the screw axes 2_1 parallel to the lattice parameter ***a*** (space group is *Pbca*). In this case, the distance of the intermolecular Se···Br interaction is 3.556(1) Å, and the length of the hydrogen bonds is 2.948(9) Å. A similar type of packing for the 10-Se-3 system has been shown by Mugesh[4a] and coworkers in the crystal structure of dibromo(1-methyl-3-benzylimidazolium-2-yl)selenide. This compound forms molecular chains along the screw axes 2_1 parallel to the lattice parameter ***b*** (space group *Pbca*) supported by the corresponding Se···Br σ-hole interactions with a distance equal to 3.507(1) Å.

In contrast to the crystal structures of **4a**, **4e**, and **4g**, no shortened intermolecular Se···Br contacts were found in the crystal structure of **4b**. Instead, the selenium atom formed a moderate intermolecular Se···O σ-hole bond (3.232(5) Å) with the oxygen atom of the methoxy group, which leads to the continuation of molecular chains along the crystallographic direction [101] (Fig. 1C). As a result, similar to 4-fluorophenyl substituted **4e**, no centrosymmetric pseudodimers were observed in the crystal structure of 4-methoxyphenyl derivative **4b**. Considering that the crystal structure of **4b** belongs to space group *Pn*, non-centrosymmetric physical properties described by third-rank tensors (piezoelectricity, second harmonic generation, etc.) could be expressed. Due to their symmetry, all components of the third-rank tensors for centrosymmetric crystals are zero.[16] The main geometric parameters characterizing the square-planar coordination of selenium in compounds **4a**, **4e**, and **4g** are listed in Table 1. It should be noted that the length of the Se···Br σ-hole interaction in thienyl derivative **4g** is the shortest among all known hypervalent T-shaped 10-Se-3 systems. However, it seems that the nature of the substituent has a slight influence on the σ-hole interaction length. This length is most strongly affected by the crystal packing effect and temperature.[17] The packing coefficients for **4a**, **4b**, **4e**, and **4g** were calculated based on Kitaigorodsky's[18] approach (Table 1). A consistent correlation between the packing coefficient and the length of the

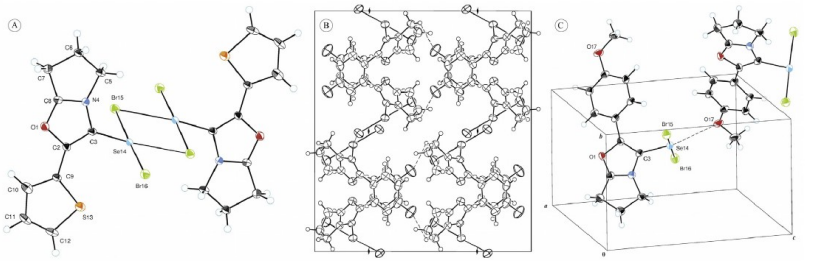

Figure 1. A: view of molecular pseudodimers formed by **4g**, showing the atom-numbering scheme; B: projection of the crystal structure of **4e** along crystallographic direction [100], showing the screw axes of second order, unit cell outlines, σ-hole, and hydrogen bonds; C: Partial crystal structure of **4b**, showing the formation of a σ-hole interaction and unit cell outlines. Displacement ellipsoids are drawn at 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Table 1
Geometrical parameters of square-planar coordinated selenium in **4a**, **4b**, **4e**, and **4g**

	4a	4b	4e	4g
C3–Se14, Å	1.906(3)	1.904(5)	1.870(5)	1.894(3)
Se14–Br15, Å	2.6356(8)	2.534(1)	2.586(1)	2.6199(5)
Se14–Br16, Å	2.5569(8)	2.637(1)	2.600(1)	2.5724(5)
Se14···Br15, Å	3.4439(8)	3.232(5)[a]	3.556(1)	3.3374(5)
C3–Se14···Br15#1,°	173.5(1)	164.4(3)[b]	156.6(2)	168.5(1)
Br15–Se14–Br16,°	63.2(1)	85.1(2)	81.9(2)	65.6(1)
C6 deviation, Å	0.152(5)	0.244(6)	0.070(5)	0.256(4)
Packing coefficient	0.713	0.709	0.677	0.736

[a] Se14···O17 σ-hole bond length.
[b] C3–Se14···O17 angle.

Se···Br σ-hole interaction in **4a**, **4b**, and **4g** was observed, meaning that denser crystal structures yield weaker intermolecular interactions. In the structures studied, the atomic lines Br15–Se14–Br16 have considerable angles with the oxazolinium plane. Overall, the tricyclic systems in the molecular structures are nearly planar; the carbon atom of C6 insignificantly deviates from the oxazolinium planes. The dihedral angles between the aryl rings and the oxazolinium planes are as follows: 1.6(4)° (**4a**), 14.4(5)° (**4b**), 25.1(5)° (**4e**), and 4.4(3)° (**4f**). It should be noted that the crystal structure **4f** features static disorder in the thienyl group.

An alternative method for the generation of zwitterionic hypervalent T-shaped 10-Se-3 systems *via* the treatment of *N*-ethynylpyrrolidinones with $SeBr_2$ in moderate to high yields has been described. The existence of hypervalent selenium in both the solid state and solution has been unambiguously confirmed by X-ray analysis and ^{77}Se NMR data. Future research dedicated to studying the reactions of aryl alkynyl amides with other selenium halides and the use of other aryl alkynyl derivatives containing heteroatoms directly attached to the triple bond is in progress.

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Supplementary data

Experimental data, copies of the ^{1}H, ^{19}F, and ^{13}C NMR spectra of all compounds, and crystallographic data for compounds **4a**, **4b**, **4e** and **4g**.[19] Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.026. These data include MOL files and InChiKeys of the most important compounds described in this article.

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19. Diffraction data were collected on an automatic diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The crystal structures were solved by direct methods and refined by full-matrix least squares. The main crystallographic data and refinement parameters of the crystal structures are listed in the ESI. For further details, the crystallographic data for **4a** (CCDC 1047477), **4b** (CCDC 1045665), **4e** (CCDC 1045663), and **4f** (CCDC 1045664) is deposited with the Cambridge Crystallographic Data Centre as Supplementary Publications. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

IV

Paegle, E.; Belyakov, S.; Petrova, M.; Liepinsh, E.; Arsenyan, P.
"Cyclization of Diaryl(hetaryl)alkynes under Selenobromination Conditions: Regioselectivity and Mechanistic Studies"
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Cyclization of Diaryl(hetaryl)alkynes under Selenobromination Conditions: Regioselectivity and Mechanistic Studies

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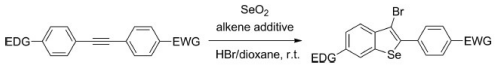
Keywords: Synthetic methods / Cyclization / Selenium / Heterocycles / Alkynes / Regioselectivity

The cyclization of substituted diaryl(hetaryl)alkynes with in-situ-prepared $SeBr_4$ has been achieved. The use of an alkene additive as a bromine scavenger gives simple access to functionalized benzo[*b*]selenophene and selenophenothiophene derivatives from commercially available or easily accessible starting materials. The reactions can be performed in air without the use of moisture-sensitive reagents, dry solvents, or an inert atmosphere. Mechanistic studies confirmed a regioselective *anti* 1,2-addition in the selenobromination step, and a subsequent electrophilic substitution in the aromatic ring to complete the cyclization.

Introduction

In both medicinal chemistry[1] and materials science,[2] fused selenophene-ring-containing systems have been intriguing subjects of research. Although the heterocyclic benzo[*b*]selenophene system has not been found in natural compounds to date, it is regarded as a bioisostere of naphthalene, benzofuran, benzothiophene, and indole.[3] Recently,[1a] it has been shown that the selenium analogue of raloxifene, which is a selective estrogen-receptor modulator (SERM) that is used for the prevention of osteoporosis in postmenopausal women and to reduce the incidence of breast cancer, shows a considerably higher cytotoxic activity against various cancer cell lines, while also providing better normal/malignant cell selectivity than the original drug. Furthermore, the results of in vivo studies on BALB/c female mice with the 4T1 cell induced breast cancer model showed that the selenium analogue of raloxifene is able to suppress estrogen-dependent tumor growth, whereas no such effect was observed for raloxifene itself. Additionally, in materials science, the potential applicability of these systems as organic semiconductors in various optoelectronic devices has been an inspiration for numerous studies.[2]

Since the introduction of alkene additives as bromine scavengers,[4] the cyclization of aryl(thienyl)alkyne derivatives in the presence of in-situ-prepared $SeBr_4$ (SeO_2 + HBr) has become one of the most straightforward methods for the synthesis of a wide variety of benzo[*b*]selenophenes and selenophenothiophenes. Nevertheless, no studies on the cyclization of symmetrically or unsymmetrically substituted diaryl(hetaryl)alkynes (Scheme 1) have been reported to date. Electrophilic selenium reagents, including selenium halides, react with C≡C triple bonds by 1,2-addition, but the regio- and stereoselectivity strongly depends on the substitution patterns of the substrates and the reaction conditions. In the case of PhSeCl(Br),[5] *anti* 1,2-addition was observed, and the corresponding halovinylselenylbenzenes were usually formed with a substantial excess of one regioisomer due to regioselectivity. Nevertheless, the addition of PhSeCl to arylferrocenylethynes[6a] led to the formation of two regioisomers in different ratios, and no regioselectivity was observed in reactions of phenylselenylfluoride[6b] with unsymmetrical alkynes. Additional contradictory results have been reported in the case of selenium halides. Quite recently, Amosova[7] and coworkers showed that selenium mono-, di-, and tetrahalides react with acetylene in a stereoselective manner to give the corresponding *anti* ad-



Scheme 1. Cyclization of diarylalkynes under selenobromination conditions (EWG = electron-withdrawing group; EDG = electron-donating group).

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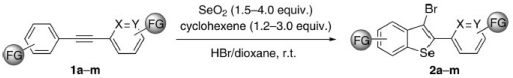
dition products. On the other hand, in Braverman's[8] studies, the addition of $SeCl_2$, $SeBr_2$, or $SeCl_4$ to propargyl alcohols involved *syn* stereochemistry and an anti-Markovnikov orientation. Furthermore, reactions of selenium halides with diethynylsilane and germane systems[9] can lead to sequential intermolecular *anti* and intramolecular *syn* additions. Regarding the mechanism of the selenohalogenation step, cationic selenirenium species have been widely[5a,5e,6a,10] postulated as a key intermediates, and their existence has been proved by single-crystal X-ray diffraction analysis.[5a] Additionally, it has been suggested that the formation of the selenophene heterocyclic system by the cyclization of aryl(hetaryl)alkyne derivatives under selenohalogenation conditions[4,11] involves the regioselective *anti* 1,2-addition of the selenium halide to the C≡C triple bond, and subsequent intramolecular electrophilic substitution in the aromatic ring. However, no mechanistic studies have been performed to date to prove this claim.

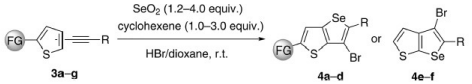
Considering that the cyclization of commercially available or easily prepared diaryl(hetaryl)alkynes could provide direct access to the corresponding 2-aryl(hetaryl)benzo[*b*]-selenophenes, and that the cyclization of unsymmetric substrates would provide useful information concerning the regioselectivity of the selenobromination step, we were motivated to further explore this topic.

Results and Discussion

To investigate the reactions of in-situ-prepared $SeBr_4$ (SeO_2 + HBr) with various substituted diaryl(hetaryl)alkynes, compounds **1a**–**m** and **3a**–**g** were used as substrates (Schemes 2 and 3). The required diaryl(hetaryl)alkynes (i.e., **1b**–**l**, **3a**–**g**), and (cyclohex-1-en-1-ylethynyl)benzene (**1m**) were easily prepared by Sonogashira-type coupling protocols (for the procedure used to prepare the starting materials, see the Supporting Information), and the results of the cyclization reactions are summarized in Table 1. Analogously to recently reported reactions of phenylpropargyl alcohol derivatives,[4] selenobromination of commercially available 1,2-diphenylethyne (**1a**) in the absence of a cyclohexene additive as a bromine scavenger led to the formation of a nearly inseparable mixture (approximately 9:1) of the desired cyclization product [i.e., 3-bromo-2-phenylbenzo[*b*]-selenophene (**2a**)] and a side-product originating from bromination of the triple bond of the starting material. Nonetheless, using 1.5 equiv. of SeO_2 and 1.0 equiv. of cyclohexene, and allowing the reaction to proceed for 24 h at room temperature, **2a** was formed exclusively, and was easily isolated in 84% yield (Table 1, entry 1). As expected, the electronic nature of the substituents attached to the aromatic rings strongly influenced the progress of the reaction. Thus, upon cyclization of dimethoxy derivative **1b** in the absence of the alkene additive, an approximately 1:1 mixture of the desired benzo[*b*]selenophene derivative (i.e., **2b**) and the corresponding product of bromination of the triple bond was obtained, and conditions analogous to the cyclization of **1a** did not sufficiently suppress the side reaction. It seems that the presence of strongly electron-donating methoxy groups and the resulting increase in electron density on the triple bond drives the equilibrium towards bromination. The optimal reaction conditions were achieved when 4.0 equiv. of SeO_2 and 3.0 equiv. of cyclohexene were used, providing cyclization product **2b** in 50% yield (Table 1, entry 2). Inspired by the fact that the cyclization of phenylpropargylamines[11g] proceeds without bromination of the triple bond in the starting material, even in the absence of an alkene additive, we attempted the cyclization of **1b** in the presence of triethylamine as an external base. However, no significant changes in the product yield or the ratio of selenobromination to bromination were observed. However, because such an excessive amount of SeO_2 was used for the cyclization of **1b**, a large amount of elemental selenium precipitated upon quenching of the reaction mixture. Nevertheless, in the presence of triethylamine (4.0 equiv.), no precipitation was observed, which facilitated the isolation of product **2b**. It should be mentioned that **2b** has been used elsewhere as a key precursor for the preparation of selenium analogues of raloxifene.[1a] A very distinctive reaction was observed in the case of difluoro derivative **1c**. Despite the fact that the use of 2.0 equiv. of SeO_2 and 1.5 equiv. of cyclohexene resulted in the complete consumption of the starting material (i.e., **1c**) after stirring at room temperature for 3 d, no bromination of the triple bond of the starting material was observed, and product **2c** was easily isolated in 64% yield (Table 1, entry 3). This observation can be explained by the decreased nucleophilicity of the triple bond resulting from the inductive electron-withdrawing effect of the fluorine atoms. This conclusion was further supported



Scheme 2. Cyclization of diaryl(hetaryl)alkynes **1a**–**l** and (cyclohex-1-en-1-ylethynyl)benzene (**1m**).



Scheme 3. Cyclization of dihetarylalkynes **3a**–**g**.

Table 1. Cyclization of diaryl(hetaryl)alkynes **1a**–**l** and **3a**–**g** and (cyclohex-1-en-1-ylethynyl)benzene (**1m**).[a]

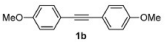
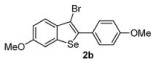
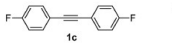
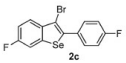
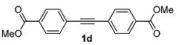
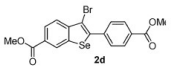
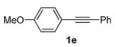
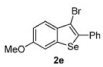
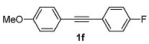
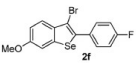
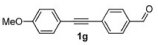
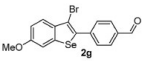
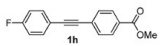
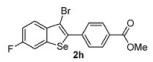
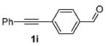
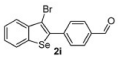
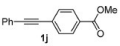
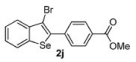
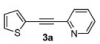
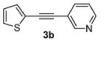
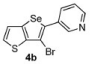
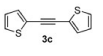
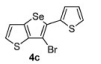
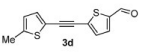
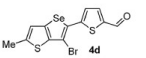
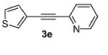
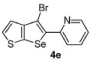
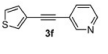
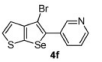
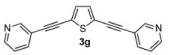
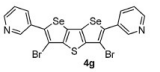
Entry	Starting material	SeO_2 [equiv.]	Cyclohexene [equiv.]	Reaction time [h]	Product	Isolated yield [%]
1	**1a**	1.5	1.2	24	 **2a**	84
2[b]	 **1b**	4.0	3.0	24	 **2b**	50
3	 **1c**	2.0	1.5	72	 **2c**	64
4	 **1d**	1.5	-	24	 **2d**	84
5[c]	 **1e**	4.0	3.0	24	 **2e**	-
6	 **1f**	3.0	3.0	24	 **2f**	55
7	 **1g**	4.0	3.0	24	 **2g**	58
8[d]	 **1h**	1.5	-	24	 **2h**	-
9	 **1i**	1.5	1.2	30	 **2i**	57
10	 **1j**	1.5	1.2	30	 **2j**	64
11	 **1k**	4.0	3.0	24	 **2k**	57
12	 **1l**	4.0	3.0	24	 **2l**	66
13[e]	 **1m**	3.0	1.5	1	 **2m**	58
14	 **3a**	1.2	1.5	24	 **4a**	28

Table 1. *(Continued)*

Entry	Starting material	SeO_2 [equiv.]	Cyclohexene [equiv.]	Reaction time [h]	Product	Isolated yield [%]
15	 **3b**	1.2	1.5	24	 **4b**	40
16[f,g]	 **3c**	1.5	1.5	15	 **4c**	33
17	 **3d**	4.0	3.0	24	 **4d**	38
18[f]	 **3e**	1.2	1.2	24	 **4e**	39
19[f]	 **3f**	1.2	1.5	24	 **4f**	32
20	 **3g**	3.0	2.4	96	 **4g**	40

[a] Reactions were carried out on a scale of up to 1.12 mmol of **1a**–**1m** and **3a**–**3g**; 0.43 mL of HBr (48%) was used per 1.0 mmol of selenium dioxide. [b] Et_3N (4.0 equiv.) additive was used. [c] An inseparable mixture of products was obtained. [d] A mixture of two inseparable regioisomers was obtained. [e] Cyclohex-2-enone (1.5 equiv.) was used instead of cyclohexene. [f] 0.27 mL of HBr (48%) was used per 1.0 mmol of selenium dioxide. [g] Cyclohex-2-enone (1.5 equiv.) was used instead of cyclohexene in the presence of Et_3N (1.0 equiv.) additive.

by the negligible reaction of diarylalkyne **1d** in the presence of an alkene additive. We have previously shown[4] that $SeBr_4$ can react directly with an alkene additive by brominating the double bond, which may be the main reaction in the case of the strongly deactivated **1d**. Nevertheless, when the reaction was conducted in the absence of cyclohexene, no bromination of the triple bond of the starting material was detected, and the corresponding cyclization product (i.e., **2d**) was isolated in very good yield (84%; Table 1, entry 4). Next, we examined the cyclization of unsymmetrically substituted diarylalkynes, which can theoretically lead to the formation of two regioisomers (Table 1, entries 5–13). In the case of methoxy-substituted derivative **1e**, a large amount of the product of bromination of the triple bond was observed, as well as poor regioselectivity. As a result, a complex mixture of inseparable products was obtained (Table 1, entry 5). Nevertheless, even the slightly electron-accepting fluorine atom in **1f** promoted complete regioselectivity, and product **2f** was obtained in 55% yield (Table 1, entry 6). However, such polarized triple bonds also have a quite pronounced affinity for the addition of bromine; therefore, 3.0 equiv. of SeO_2 and 3.0 equiv. of cyclohexene were used to achieve the optimal reaction conditions. Very similar results were obtained in the case of diarylalkyne **1g**, which gave benzo[*b*]selenophene derivative **2g** in a 58% yield (Table 1, entry 7). Next, we tried to achieve the cyclization of substrates bearing two different electron-withdrawing groups. As was expected in the case of the cyclization of **1h**, no bromination of the triple bond of the starting material was observed, but very poor regioselectivity led to the formation of both possible regioisomers, which we were not able to separate (Table 1, entry 8). Additionally, complete regioselectivity of the cyclization was not achieved in the presence of one strongly electron-withdrawing group (Table 1, entries 9 and 10). Thus, the cyclizations of substrates **1i** and **1j** led to the formation of 5:1 and 10:1 mixtures of regioisomers, respectively. However, the minor regioisomers were easily separated by recrystallization, and the corresponding cyclization products (i.e., **2i** and **2j**) were obtained in moderate yields. The cyclization of phenylethynyl pyridines **1k** and **1l** proceeded with complete regioselectivity, and the corresponding products (i.e., **2k** and **2l**) were isolated in 57 and 66% yields, respectively (Table 1, entries 11 and 12). Finally, we attempted the cyclization of **1m**, which contains an aromatic C(sp^2) on one side of the triple bond, and an aliphatic C(sp^2) on the other. An unexpected outcome was obtained in this case, as complete regioselectivity was achieved, and the selenophene ring formed towards the nonaromatic side of substrate **1m**. As a result, the corresponding 3-bromo-2-phenyl-4,5,6,7-tetra-

hydrobenzo[*b*]selenophene (**2m**) was obtained in 58% yield (Table 1, entry 13).

The reactions of dihetarylalkynes **3a**–**3g** were regiospecific in all cases, and as a result, the corresponding selenophenothiophene derivatives (i.e., **4a**–**4g**) were obtained in moderate yields (Table 1, entries 14–20). For **3a** and **3b**, optimal reaction conditions were achieved when 1.2 equiv. of SeO_2 and 1.5 equiv. of cyclohexene were used. Although no bromination of the triple bond of the starting material was detected, slight α-bromination of the thiophene ring was observed. Nevertheless, the corresponding cyclization products (i.e., **4a** and **4b**) were isolated in 28 and 40% yields, respectively (Table 1, entries 14 and 15). Even more pronounced α-bromination occurred in the cyclization of **3c**, but the reaction was somewhat cleaner in the presence of 1.0 equiv. of trimethylamine. As a result, selenophenothiophene derivative **4c** was obtained in a 33% yield (Table 1, entry 16). To simplify the isolation of pure **4c**, cyclohex-2-enone was used instead of cyclohexene as a bromine scavenger. In the case of unsymmetrically substituted derivative **3d**, the α-positions of the thiophene rings are blocked, preventing the bromination of the thiophene rings. However, similarly to what was observed for the cyclization of diarylalkynes **1f** and **1g** (Table 1, entries 6 and 7), quite pronounced bromination of the triple bond of the starting materials occurred. Therefore, a greater excess of SeO_2 (4.0 equiv.) and cyclohexene (3.0 equiv.) was necessary, and the corresponding cyclization product (i.e., **4d**) was isolated in 38% yield (Table 1, entry 17). Although slight α-bromination of the thiophene ring also occurred during the cyclization of **3e** and **3f**, selenopheno[2,3-*b*]thiophene derivatives **4e** and **4f** were obtained in moderate yields (39 and 32%, respectively) (Table 1, entries 18 and 19). The cyclization of 2,5-bis(pyridin-3-ylethynyl)thiophene (**3g**) provided a successful example of biscyclization. In the presence of 3.0 equiv. of SeO_2 and 2.4 equiv. of cyclohexene, the reaction proceeded for 4 d, and fused heterocyclic system **4g** was obtained in 40% yield (Table 1, entry 20). No chromatographic methods were necessary for the purification of the product, and the structure of **4g** was unambiguously confirmed by X-ray analysis. Figure 1 shows a projection of two interacting molecules of **4g** along the monoclinic axis. In the crystal structure, the molecules lie in general positions, and the symmetrical parts of the molecules have different surroundings. For one of the pyridyl groups, all of the intermolecular contacts correspond to sums of the van der Waals radii, whereas the second pyridine ring participates in a strong σ-hole N-1′···Br-1 bonding with a distance of 3.034(3) Å. There are also weak intermolecular σ-hole interactions between selenium (Se-7) and bromine (Br-2) atoms, with a distance of 3.607(2) Å. These interactions lead to the formation of molecular chains along the [100] crystallographic direction.

The exceptionally slow reaction of difluoro-substituted derivative **1c** provided an excellent opportunity to study the stepwise mechanism of the cyclization process under conditions identical to those described in Table 1. The presence of fluorine atoms in the structures of starting material **1c**,

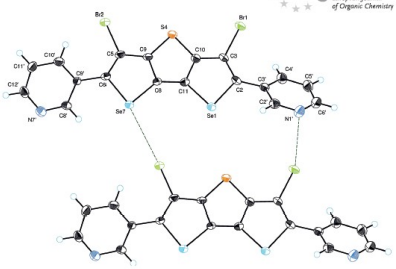


Figure 1. Molecular structure of 3,3′-(3,5-dibromodiselenopheno[3,2-*b*:2′,3′-*d*]thiophene-2,6-diyl)dipyridine (**4g**). Displacement ellipsoids are drawn at the 50% probability level, and hydrogen atoms are shown as small spheres of arbitrary radius.

intermediate **7**, and product **2c** allowed us to directly monitor the progress of the reaction by ^{19}F NMR spectroscopy in dioxane using D_2O as an internal standard (Figure 2, Scheme 4). In the absence of an alkene additive, the reaction of **1c** reached completion after 24 h, and a mixture of cyclization product **2c** and the corresponding triple bond bromination adduct was obtained. Furthermore, we were not able to detect any intermediates. However, when the reaction was performed in the presence of 2.0 equiv. of SeO_2 and 1.0 equiv. of cyclohexene, the cyclization process was significantly slowed. The complete disappearance of the resonance at $\delta = -111.31$ ppm due to starting material **1c** (Figure 2, A) was observed after 24 h. At this point, only one major product was observed in the reaction mixture

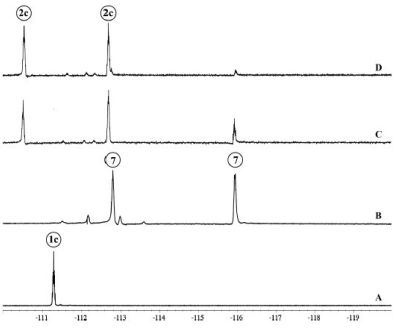
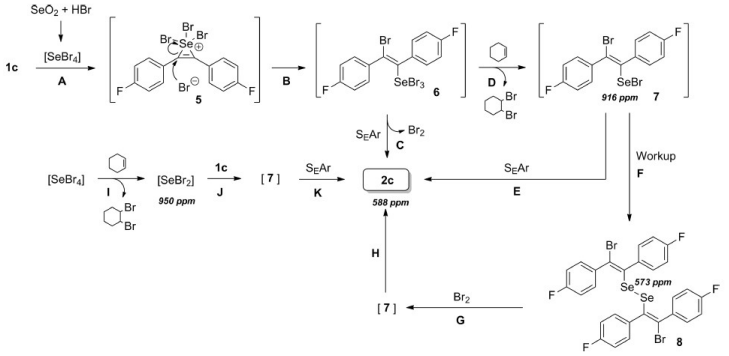


Figure 2. Cyclization of **1c** monitored by ^{19}F NMR spectroscopy in dioxane using D_2O as an internal standard. A) resonance signal due to starting material **1c**; B) ^{19}F NMR spectrum of the reaction mixture after 24 h, showing intermediate **7** as the major component; C) ^{19}F NMR spectrum of the reaction mixture after 48 h; D) ^{19}F NMR spectrum of the reaction mixture after 72 h, showing cyclization product **2c** as the major component.



Scheme 4. Proposed mechanism for the cyclization of **1c**.

(Figure 2, B). This product showed two resonances at δ = –112.84 and –116.04 ppm in the ^{19}F NMR spectra (Figure 2, B). In addition, the ^{77}Se NMR spectrum of the reaction mixture was recorded, and only one major resonance at δ = 916 ppm was observed. The similarity of the chemical shift of this resonance to that of commercially available PhSeBr (δ = 888 ppm in dioxane/D_2O) led us to conclude that after 24 h of stirring, vinylselenylbromide intermediate **7** had been formed almost exclusively. After 48 h of stirring, the slow disappearance of intermediate **7** and the formation of cyclization product **2c** was observed (Figure 2, C). Finally, after 72 h, benzo[*b*]selenophene derivative **2c** was the major component of the reaction mixture (Figure 2, D). Product **2c** also shows two distinct resonances in its ^{19}F NMR spectrum at δ = –110.64 and –112.80 ppm.

The experimental data discussed above allowed us to confirm certain aspects of the cyclization mechanism under selenobromination conditions (Scheme 4). Considering the study of Poleschner and Seppelt,[5a] there is good reason to believe that the addition of $SeBr_4$ to a triple bond of **1c** occurs through a cationic selenirenium type intermediate **5** (Scheme 4, A). As the presence of this type of intermediate can only be detected by low-temperature techniques,[5a] it is not surprising that intermediate **5** was not detected during our room-temperature experiments. Unfortunately, due to the relatively high melting point of dioxane, low-temperature studies are not feasible in this case. The selenobromination step (Scheme 4, A,B) is crucial for achieving a regioselective synthesis in the case of unsymmetrical substrates. It seems that the nucleophilic attack of the bromide anion occurs at the carbon bearing the lowest electron density. A more polarized triple bond leads to more pronounced regioselectivity. The faster cyclization in the absence of an alkene additive (Scheme 4, C) could be explained by the fact that more electrophilic Se^{IV} species **6** are involved in the S_EAr step compared to the corresponding Se^{II} intermediate **7**. Nevertheless, the equivalent of molecular bromine expelled during the cyclization process poisons starting material **1c** by bromination of the triple bond. On the other hand, in the presence of cyclohexene, the equivalent of bromine formed from intermediate **6** is transferred to the scavenger, and 1,2-dibromocyclohexane is formed along with the vinylselenylbromide intermediate **7** (Scheme 4, D). The structure of intermediate **7** was confirmed by ^{1}H, ^{13}C, ^{19}F, and ^{77}Se NMR spectroscopic data. The formation of 1,2-dibromocyclohexane was observed by GC–MS analysis of the reaction mixture, and it was also isolated in pure form. By quenching the reaction mixture with brine and ethyl acetate after 24 h of stirring, diselenide derivative **8** was isolated in 42% yield. Apparently, an aqueous work-up led to the disproportionation of intermediate **7**, and subsequent Se–Se bond formation. The fact that diselenide **8** was isolated solely as an *E*,*E* stereoisomer (Figure 3) provides unambiguous evidence of stereospecific *anti* 1,2-addition in the selenobromination step (Scheme 4, A,B). As observed by monitoring the cyclization of **1c** using ^{19}F NMR spectroscopy (Figure 2, C,D), intermediate **7** is slowly converted into the desired product (i.e, **2c**) through intramolecular electrophilic substitution in the aromatic ring. More evidence for the existence of intermediate **7** was provided by the oxidative addition of Br_2 to diselenide **8** (Scheme 4, G). When 1.0 equiv. of Br_2 was added to a dioxane solution of diselenide **8**, the diselenide was completely converted into vinylselenylbromide **7** in less than 1 h, and the slow formation of the cyclization product **2c** (Scheme 4H) was observed again. Moreover, no side-products were formed during this experiment. Finally, as mentioned previously, $SeBr_4$ can react directly with an alkene additive by bromination of the double bond (Scheme 4I). Thus, the presence of $SeBr_2$ species in the reaction mixture should not be categorically denied. To confirm the formation of selenium(II) bromide, the reaction was monitored directly in an NMR

tube. After the reactants [in-situ-prepared selenium(IV) bromide and cyclohexene] were mixed, a broad resonance at δ = 950 ppm in the ^{77}Se NMR spectra was observed. This signal can probably be assigned to $SeBr_2$. The selenium(II) bromide was unstable in aqueous dioxane, and disproportionated over the next 0.5 h. Then ^{77}Se signals at δ = 728, 411, and 406 ppm were detected, and could be assigned to selenium polybromides Se_nBr_m.[12,13] Because an example of 3-bromo-2-phenylbenzo[*b*]selenophene synthesis in the reaction of diphenylethyne with $SeBr_2$ has been demonstrated previously,[11e] partial participation of this pathway (Scheme 4, J,K) should be under consideration.

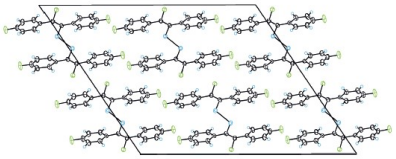


Figure 3. Molecular structure of 1,2-bis[(*E*)-2-bromo-1,2-bis(4-fluorophenyl)vinyl] diselenide (**8**). Displacement ellipsoids are drawn at the 50% probability level, and hydrogen atoms are shown as small spheres of arbitrary radius.

Conclusions

The first examples of regioselective addition of in-situ-prepared $SeBr_4$ to diaryl(hetaryl)alkynes are reported. This approach represents the most straightforward access to 2-aryl(hetaryl)-3-bromobenzo[*b*]selenophenes and selenophenothiophenes. The regioselectivity is strongly affected by the electronic nature of the aromatic rings. A more polarized triple bond leads to higher regioselectivity, and as a general rule, cyclization is favoured on the side of the more electron-rich aromatic ring. The presence of electron-donating groups or a strongly polarized triple bond leads to an increased tendency for bromination, but a greater excess of $SeBr_4$ can significantly suppress the poisoning of the starting material. On the other hand, strongly electron-withdrawing groups completely prevented the bromination of the triple bond of the starting material, even in the absence of an alkene additive. Experimental evidence confirmed stereospecific *anti* 1,2-addition in the selenobromination step and subsequent intramolecular electrophilic substitution on the aromatic ring to be the main contributors to the cyclization mechanism.

Further work in this research field will be dedicated to the application of the developed method to the construction of more advanced selenophene-ring-containing molecular scaffolds as core structures of potential nonlinear optical materials.

Experimental Section

General Remarks: Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using Merck Silica gel 60 F254 plates, which were visualized using UV (254 nm) fluorescence. Zeochem silica gel (ZEOprep 60/35–70 microns –SI23501) was used for column chromatography. ^{1}H, ^{13}C, ^{19}F, and ^{77}Se NMR spectra were recorded with a Varian 400 Mercury spectrometer at 400.0, 100.58, 376.21, and 76.37 MHz, respectively, at 298 K in $CDCl_3$. The ^{1}H chemical shifts were calibrated using the residual $CHCl_3$ signal (δ = 7.26 ppm), ^{13}C shifts were calibrated using the $CDCl_3$ signal (δ = 77.0 ppm), and ^{77}Se shifts were calibrated using the dimethyl selenide signal (δ = 0.0 ppm). Melting points were determined with a "digital melting-point analyser" (Fisher).

3-Bromo-2-phenylbenzo[*b*]selenophene (2a):[14] Selenium dioxide (186 mg, 1.68 mmol) was dissolved in hydrogen bromide (48%; 0.72 mL), and the mixture was stirred at room temperature for 15 min. A solution of diphenylethyne (**1a**; 200 mg, 1.12 mmol) and cyclohexene (110 mg, 1.34 mmol) in dioxane (4.0 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with ethyl acetate (50 mL) and water (20 mL). The mixture was stirred for 15 min at room temperature, then the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using petroleum ether as eluent to give **2a** (315 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.93 (m, 1 H, 4-C*H*), 7.89–7.85 (m, 1 H, 7-C*H*), 7.72–7.67 (m, 2 H, 2′,6′-C*H*), 7.52–7.39 (m, 4 H, 6,3′,4′,5′-C*H*), 7.39–7.33 (m, 1 H, 5-C*H*) ppm.

3-Bromo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]selenophene (2b):[1a] Selenium dioxide (373 mg, 3.36 mmol) was dissolved in hydrogen bromide (48%; 1.44 mL), and the mixture was stirred at room temperature for 15 min. A solution of bis(4-methoxyphenyl)-ethyne (**1b**; 200 mg, 0.839 mmol), cyclohexene (207 mg, 2.52 mmol), and triethylamine (0.47 mL, 3.36 mmol) in dioxane (4.0 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with ethyl acetate (50 mL) and water (20 mL). The mixture was stirred for 15 min at room temperature, then the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic phases were dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (40:1) as eluent. In the first fractions, a solid precipitate appeared, which was not collected (almost exclusively contained the corresponding dibromo derivative). After evaporation of the solvents, a pale yellow oil was obtained, which slowly crystallized upon standing at room temperature. This material was recrystallized from a mixture of petroleum ether and ethyl acetate to give **2b** (166 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, 1 H, $^3J_{H,H}$ = 8.8 Hz, 4-C*H*), 7.64–7.59 (m, 2 H, 2′,6′-C*H*), 7.35 (d, 1 H, $^4J_{H,H}$ = 2.3 Hz, 7-C*H*), 7.07 (dd, 1 H, $^4J_{H,H}$ = 2.3, $^3J_{H,H}$ = 8.8 Hz, 5-C*H*), 7.00–6.96 (m, 2 H, 3′,5′-C*H*), 3.89 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3) ppm.

3-Bromo-6-fluoro-2-(4-fluorophenyl)benzo[*b*]selenophene (2c):[1a] Starting from bis(4-fluorophenyl)ethyne (**1c**), and following a method analogous to that used for the cyclization of **1a**, but using 2.0 equiv. of selenium dioxide and 1.5 equiv. of cyclohexene, and running the reaction for 72 h gave **2c** (222 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, 1 H, $^4J_{H,F}$ = 5.1, $^3J_{H,H}$ = 8.8 Hz, 4-C*H*), 7.66–7.61 (m, 2 H, 3′,5′-C*H*), 7.57 (dd, 1 H, $^4J_{H,H}$ = 2.3, $^3J_{H,F}$ = 8.0 Hz, 7-C*H*), 7.23 (ddd, 1 H, $^4J_{H,H}$ = 2.3, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,F}$ = 8.8 Hz, 5-C*H*), 7.19–7.13 (m, 2 H, 2′,6′-C*H*) ppm.

Methyl 3-Bromo-2-[4-(methoxycarbonyl)phenyl]benzo[*b*]selenophene-6-carboxylate (2d): Selenium dioxide (57 mg, 0.510 mmol) was dissolved in hydrogen bromide (48%; 0.22 mL), and the mixture was stirred at room temperature for 15 min. A suspension of dimethyl 4,4′-(ethyne-1,2-diyl)dibenzoate (**1d**; 100 mg, 0.340 mmol) in dioxane (6.0 mL) was added, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with ethyl acetate (100 mL) and water (40 mL). The mixture was stirred for 15 min at room temperature, then the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using mixture of petroleum ether, dichloromethane, and ethyl acetate (13:7:1) as eluent to give **2d** (130 mg, 84%) as a white solid, m.p. 175–176 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.59 (dd, 1 H, $^5J_{H,H}$ = 0.6, $^4J_{H,H}$ = 2.4 Hz, 7′-*CH*), 8.15 (dd, 1 H, $^4J_{H,H}$ = 2.4, $^3J_{H,H}$ = 12.6 Hz, 5′-*CH*), 8.16–8.12 (m, 2 H, 3,5-*CH*), 8.00 (dd, 1 H, $^5J_{H,H}$ = 0.6, $^3J_{H,H}$ = 12.6 Hz, 4′-*CH*), 7.80–7.75 (m, 2 H, 2,6-*CH*), 3.98 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 166.6, 166.5, 144.2, 143.5, 139.0, 138.7, 130.4, 129.8 (2 C), 127.5, 127.0, 126.6, 126.1, 107.6, 52.4, 52.3 ppm. MS (EI, 70 eV): *m/z* (%) = 452 (100) $[M]^+$. $C_{18}H_{13}BrO_4Se$ (452.16): calcd. C 47.81, H 2.90; found C 47.60, H 2.95.

3-Bromo-2-(4-fluorophenyl)-6-methoxybenzo[*b*]selenophene (2f): Starting from 1-fluoro-4-[(4-methoxyphenyl)ethynyl]benzene (**1f**), and following a method analogous to that used for the cyclization of **1a**, but using 3 equiv. of selenium dioxide and cyclohexene. A mixture of petroleum ether and dichloromethane (0:1→20:3) was used as eluent. The product was then recrystallized from a mixture of petroleum ether and ethyl acetate to remove traces of the corresponding dibromo derivative, to give **2f** (187 mg, 55%) as a white solid, m.p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.67–7.60 (m, 2 H, 3′,5′-*CH*), 7.36 (d, 1 H, $^4J_{H,H}$ = 2.3 Hz, 7-*CH*), 7.18–7.11 (m, 2 H, 2′,6′-*CH*), 7.08 (dd, 1 H, $^4J_{H,H}$ = 2.3 Hz, $^3J_{H,H}$ = 8.8 Hz, 5-*CH*), 3.90 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 162.6 (d, $^1J_{C,F}$ = 249.1 Hz), 158.4, 139.9, 136.2, 134.6, 131.6 (d, $^3J_{C,F}$ = 8.2 Hz), 131.1 (d, $^4J_{C,F}$ = 3.5 Hz), 126.7, 115.6 (d, $^2J_{C,F}$ = 21.8 Hz), 114.7, 108.4, 106.3 (d, $^5J_{C,F}$ = 0.8 Hz), 55.7 ppm. ^{19}F NMR (376.21 MHz, $CDCl_3$): δ = –112.7 (tt, $^4J_{H,F}$ = 5.5, $^3J_{H,F}$ = 8.5 Hz) ppm. MS (EI, 70 eV): *m/z* (%) = 384 (100) $[M]^+$. $C_{15}H_{10}BrFOSe$ (384.11): calcd. C 46.90, H 2.62; found C 46.82, H 2.69.

4-(3-Bromo-6-methoxybenzo[*b*]selenophen-2-yl)benzaldehyde (2g): Starting from 4-[(4-methoxyphenyl)ethynyl]benzaldehyde (**1g**), and following a method analogous to that used for the cyclization of **1b**, but without using the triethylamine additive, and using a mixture of petroleum ether and dichloromethane (1:1) as eluent gave **2g** (194 mg, 58%) as a pale grey solid, m.p. 154–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1 H, *CHO*), 7.97–7.92 (m, 2 H, 2,6-*CH*), 7.87–7.83 (m, 2 H, 3,5-*CH*), 7.84 (d, 1 H, $^3J_{H,H}$ = 8.8 Hz, 4′-*CH*), 7.37 (d, 1 H, $^4J_{H,H}$ = 2.3 Hz, 7′-*CH*), 7.10 (dd, 1 H, $^4J_{H,H}$ = 2.3, $^3J_{H,H}$ = 8.8 Hz, 5′-*CH*), 3.90 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 191.5, 158.7, 141.1, 140.3, 135.6, 135.5, 134.7, 130.3, 129.8, 127.1, 115.0, 108.3, 107.5, 55.7 ppm. MS (EI, 70 eV): *m/z* (%) = 394 (100) $[M]^+$. $C_{16}H_{11}BrO_2Se$ (394.13): calcd. C 48.76, H 2.81; found C 48.44, H 3.01.

4-(3-Bromobenzo[*b*]selenophen-2-yl)benzaldehyde (2i): Starting from **1i**, and following a method analogous to that used for the cyclization of **1a**, except that the reaction was run for 30 h, and a mixture of petroleum ether and ethyl acetate (1:0→40:1) was used as eluent. To remove the minor regioisomer, the product was recrystallized from a mixture of petroleum ether and ethyl acetate to give **2i** (201 mg, 57%), m.p. 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.08 (s, 1 H, *CHO*), 8.00–7.95 (m, 3 H, 2,6-CH, 4′-*CH*), 7.91–7.85 (m, 3 H, 3,5-*CH*, 7′-*CH*), 7.55–7.49 (m, 1 H, 6′-*CH*), 7.43–7.37 (m, 1 H, 5′-*CH*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 191.6, 141.0, 140.8, 139.2, 138.8, 135.9, 130.5, 129.8, 126.4, 126.3, 125.8, 125.2, 108.1 ppm. MS (EI, 70 eV): *m/z* (%) = 364 (100) $[M]^+$. $C_{15}H_9BrOSe$ (364.10): calcd. C 49.48, H 2.49; found C 49.30, H 2.51.

Methyl 4-(3-Bromobenzo[*b*]selenophen-2-yl)benzoate (2j): Starting from **1j**, and following a method analogous to that used for the cyclization of **1a**, except that the reaction was run for 30 h, and a mixture of petroleum ether and ethyl acetate (1:0→40:1) was used as eluent. To remove the minor regioisomer, the product was recrystallized from a mixture of petroleum ether and ethyl acetate to give **2j** (214 mg, 64%), m.p. 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.08 (m, 2 H, 2,6-*CH*), 7.99–7.93 (m, 1 H, 4′-*CH*), 7.90–7.84 (m, 1 H, 7′-*CH*), 7.81–7.73 (m, 2 H, 3,5-*CH*), 7.54–7.47 (m, 1 H, 6′-*CH*), 7.41–7.34 (m, 1 H, 5′-*CH*), 3.96 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 166.6, 140.8, 139.5, 139.2, 139.1, 130.0, 129.8, 129.7, 126.3, 126.1, 125.7, 125.2, 107.7, 52.2 ppm. MS (EI, 70 eV): *m/z* (%) = 394 (100) $[M]^+$. $C_{16}H_{11}BrO_2Se$ (394.13): calcd. C 48.76, H 2.81; found C 48.67, H 3.15.

General Method for the Cyclization of Phenylethynylpyridines 1k and 1l: Selenium dioxide (497 mg, 4.48 mmol) was dissolved in hydrogen bromide (48%; 1.92 mL), and the mixture was stirred at room temperature for 15 min. A solution of **1k** or **1l** (200 mg, 1.12 mmol) and cyclohexene (276 mg, 3.36 mmol) in dioxane (4.0 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with dichloromethane (100 mL) and saturated aqueous sodium hydrogen carbonate solution (50 mL). The mixture was stirred for 30 min at room temperature, then the organic phase was separated, and aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using mixture of petroleum ether and ethyl acetate (20:1→5:1) as eluent to give **2k** or **2l**.

2-(3-Bromobenzo[*b*]selenophen-2-yl)pyridine (2k): White solid (214 mg, 57%), m.p. 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65–8.62 (m, 1 H, 6-*CH*), 8.61–8.56 (m, 1 H, 3-*CH*), 7.99–7.94 (m, 1 H, 4′-*CH*), 7.90–7.86 (m, 1 H, 7′-*CH*), 7.80 (ddd, 1 H, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 8.0 Hz, 4-*CH*), 7.49–7.44 (m, 1 H, 6′-*CH*), 7.39–7.34 (m, 1 H, 5′-*CH*), 7.27 (ddd, 1 H, $^4J_{H,H}$ = 0.8, $^3J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 8.0 Hz, 5-*CH*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 152.7, 149.6, 142.9, 142.1, 139.1, 136.4, 126.2, 125.3 (2 C), 123.1, 121.7, 106.1 ppm. MS (EI, 70 eV): *m/z* (%) = 337 (100) $[M]^+$. HRMS (ESI): calcd. for $C_{13}H_9BrNSe^+$ [M + H]$^+$ 337.9078; found 337.9090. $C_{13}H_8BrNSe$ (337.08): calcd. C 46.32, H 2.39, N 4.16; found C 46.13, H 2.52, N 4.08.

3-(3-Bromobenzo[*b*]selenophen-2-yl)pyridine (2l): White solid (248 mg, 66%), m.p. 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (d, 1 H, $^4J_{H,H}$ = 2.0 Hz, 2-*CH*), 8.65 (dd, 1 H, $^4J_{H,H}$ = 1.6, $^3J_{H,H}$ = 4.9 Hz, 6-*CH*), 8.03–7.99 (m, 1 H, 4-*CH*), 7.97–7.94 (m, 1 H, 4′-*CH*), 7.90–7.86 (m, 1 H, 7′-*CH*), 7.54–7.49 (m, 1 H, 6′-*CH*), 7.42–7.37 (m, 2 H, 5,5′-*CH*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 150.2, 149.4, 140.6, 139.1, 137.0, 136.3, 131.3, 126.3, 126.1, 125.8, 125.2, 123.2, 108.3 ppm. MS (EI, 70 eV): *m/z* (%) = 337 (100) $[M]^+$. HRMS (ESI): calcd. for $C_{13}H_9BrNSe^+$ [M + H]$^+$

337.9078; found 337.9080. $C_{13}H_8BrNSe$ (337.08): calcd. C 46.32, H 2.39, N 4.16; found C 46.20, H 2.45, N 4.02.

3-Bromo-2-phenyl-4,5,6,7-tetrahydrobenzo[*b*]selenophene (2m): Starting from (cyclohex-1-en-1-ylethynyl)benzene (**1m**), and following a method analogous to that used for the cyclization of **1a**, but 3.0 equiv. of SeO_2 and 1.5 equiv. of cyclohex-2-enone were used, and the reaction was run for 1 h. A mixture of petroleum ether and dichloromethane (50:1) was used as eluent to give **2m** (216 mg, 58%) as a pale grey amorphous solid, m.p. 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.55 (m, 2 H, 2′,6′-C*H*), 7.43–7.31 (m, 3 H, 3′,4′,5′-C*H*), 2.90–2.82 (m, 2 H, 4-CH_2), 2.60–2.53 (m, 2 H, 7-CH_2), 1.91–1.82 (m, 4 H, 5,6-CH_2) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 141.3, 138.3, 137.0, 135.5, 129.3, 128.3, 127.8, 110.4, 28.2, 27.8, 23.7, 22.5 ppm. MS (EI, 70 eV): *m/z* (%) = 340 (100) $[M]^+$. $C_{14}H_{13}BrSe$ (340.12): calcd. C 49.44, H 3.85; found C 49.55, H 4.01.

General Method for the Cyclization of Thiophen-2-ylethynylpyridines 3a and 3b: Following a method analogous to that used for the cyclization of **1k** and **1l**, but using 1.2 equiv. of selenium dioxide and 1.5 equiv. of cyclohexene.

2-(6-Bromoselenopheno[3,2-*b*]thiophen-5-yl)pyridine (4a): Pale yellow solid (104 mg, 28%), m.p. 158–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58–8.54 (m, 1 H, 6-C*H*), 8.46–8.43 (m, 1 H, 3-C*H*), 7.75 (ddd, 1 H, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 7.8 Hz, 4-C*H*), 7.42 (d, 1 H, $^3J_{H,H}$ = 5.3 Hz, 2′-C*H*), 7.39 (d, 1 H, $^3J_{H,H}$ = 5.3 Hz, 3′-C*H*), 7.22 (ddd, 1 H, $^4J_{H,H}$ = 0.8, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 7.8 Hz, 5-C*H*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 152.6, 149.6, 144.9, 144.2, 136.4 (2 C), 127.8, 123.8, 122.7, 119.6, 100.0 ppm. MS (EI, 70 eV): *m/z* (%) = 343 (100) $[M]^+$. HRMS (ESI): calcd. for $C_{11}H_7BrNSSe^+$ $[M + H]^+$ 343.8642; found 343.8639. $C_{11}H_6BrNSSe$ (343.10): calcd. C 38.51, H 1.76, N 4.08, S 9.35; found C 38.38, H 1.83, N 3.79, S 9.26.

3-(6-Bromoselenopheno[3,2-*b*]thiophen-5-yl)pyridine (4b): Pale grey solid (148 mg, 40%), m.p. 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (d, 1 H, $^4J_{H,H}$ = 2.2 Hz, 2-C*H*), 8.62 (dd, 1 H, $^4J_{H,H}$ = 1.6, $^3J_{H,H}$ = 4.9 Hz, 6-C*H*), 8.01–7.97 (m, 1 H, 4-C*H*), 7.46 (d, 1 H, $^3J_{H,H}$ = 5.2 Hz, 2′-C*H*), 7.40 (d, 1 H, $^3J_{H,H}$ = 5.2 Hz, 3′-C*H*), 7.40–7.36 (m, 1 H, 5-C*H*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 149.7, 149.2, 143.6, 137.9, 136.3, 135.4, 131.3, 127.4, 123.3, 101.8 ppm. MS (EI, 70 eV): *m/z* (%) = 343 (100) $[M]^+$. HRMS (ESI): calcd. for $C_{11}H_7BrNSSe^+$ $[M + H]^+$ 343.8642; found 343.8645. $C_{11}H_6BrNSSe$ (343.10): calcd. C 38.51, H 1.76, N 4.08, S 9.35; found C 38.33, H 1.81, N 3.92, S 9.16.

6-Bromo-5-(thiophen-2-yl)selenopheno[3,2-*b*]thiophene (4c): Selenium dioxide (175 mg, 1.58 mmol) was dissolved in hydrogen bromide (48%; 0.43 mL), and the mixture was stirred at room temperature for 15 min, then the solution was cooled to 15 °C. A solution of bis(thiophen-2-yl)ethyne (**3c**; 200 mg, 1.05 mmol), cyclohex-2-enone (152 mg, 1.58 mmol), and triethylamine (146 µL, 1.05 mmol) in dioxane (4.0 mL) was added dropwiseto the cooled selenium tetrabromide solution, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with ethyl acetate (50 mL) and water (20 mL). The mixture was stirred for 15 min at room temperature, then the organic phase was separated, and aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic phases were dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using petroleum ether as eluent. The resulting fractions were divided into three parts. The first contained brominated products, but the last ones were pure product. After evaporation of the solvent, **4c** (121 mg, 33%) was obtained as a greenish yellow oil that slowly crystallized upon standing at room temperature to give a greenish yellow solid, m.p. 56–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 3 H, 2,3′,5′-C*H*), 7.34 (d, 1 H, $^3J_{H,H}$ = 5.2 Hz, 3-C*H*), 7.10 (dd, 1 H, $^3J_{H,H}$ = 3.8, $^3J_{H,H}$ = 5.2 Hz, 4′-C*H*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 143.7, 136.7, 135.2, 133.7, 127.3, 127.2, 127.1, 126.7, 123.2, 100.6 ppm. MS (EI, 70 eV): *m/z* (%) = 348 (100) $[M]^+$. $C_{10}H_5BrS_2Se$ (348.13): calcd. C 34.50, H 1.45, S 18.42; found C 34.31, H 1.41, S 18.14.

5-(6-Bromo-2-methylselenopheno[3,2-*b*]thiophen-5-yl)thiophene-2-carbaldehyde (4d): Starting from 5-[(5-methylthiophen-2-yl)ethynyl]thiophene-2-carbaldehyde (**3d**), and following a method analogous to that used for the cyclization of **1b**, but without the triethylamine additive, and using a mixture of petroleum ether and ethyl acetate (40:1→10:1) as eluent, gave **4d** (129 mg, 38%) as a yellow solid, m.p. 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (s, 1 H, C*H*O), 7.70 (d, 1 H, $^3J_{H,H}$ = 4.0 Hz, 3-C*H*), 7.42 (d, 1 H, $^3J_{H,H}$ = 4.0 Hz, 4-C*H*), 7.03 (q, 1 H, $^4J_{H,H}$ = 1.2 Hz, 3′-C*H*), 2.61 (d, 3 H, $^4J_{H,H}$ = 1.2 Hz, CH_3) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 182.7, 146.6, 144.7, 142.6, 142.3, 136.1, 135.3, 131.7, 127.0, 121.4, 103.4, 16.4 ppm. MS (EI, 70 eV): *m/z* (%) = 390 (100) $[M]^+$. $C_{12}H_7BrOS_2Se$ (390.17): calcd. C 36.94, H 1.81, S 16.44; found C 36.80, H 1.85, S 16.21.

2-(4-Bromoselenopheno[2,3-*b*]thiophen-5-yl)pyridine (4e): Selenium dioxide (144 mg, 1.30 mmol) was dissolved in hydrogen bromide (48%; 0.36 mL), and the mixture was stirred at room temperature for 15 min. The resulting selenium tetrabromide solution was cooled to 0 °C, and a solution of 2-(thiophen-3-ylethynyl)pyridine (**3e**; 200 mg, 1.08 mmol) and cyclohexene (108 mg, 1.30 mmol) in dioxane (4.0 mL) was added dropwise. Then the reaction mixture was slowly allowed to reach room temperature, and stirring was continued at room temperature for 24 h. The reaction mixture was quenched with dichloromethane (100 mL) and saturated aqueous sodium hydrogen carbonate solution (50 mL). The mixture was stirred for 30 min at room temperature, then the organic phase was separated, and aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried with anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (1:0→40:1) as eluent to give **4e** (mixed with a small amount of the α-brominated product; 144 mg, 39%) as a pale yellow solid, m.p. 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (ddd, 1 H, $^5J_{H,H}$ = 1.0, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 4.9 Hz, 6-C*H*), 8.51–8.47 (m, 1 H, 3-C*H*), 7.75 (ddd, 1 H, $^4J_{H,H}$ = 1.8, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 7.8 Hz, 4-C*H*), 7.43 (d, 1 H, $^3J_{H,H}$ = 5.3 Hz, 2′-C*H*), 7.31 (d, 1 H, $^3J_{H,H}$ = 5.3 Hz, 3′-C*H*), 7.22 (ddd, 1 H, $^4J_{H,H}$ = 1.2, $^3J_{H,H}$ = 4.9 Hz, $^3J_{H,H}$ = 7.8 Hz, 5-C*H*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 152.7, 150.1, 149.5, 145.3, 136.5, 134.8, 128.7, 122.7 (2 C), 119.6, 101.0 ppm. MS (EI, 70 eV): *m/z* (%) = 343 (100) $[M]^+$. HRMS (ESI): calcd. for $C_{11}H_7BrNSSe^+$ $[M + H]^+$ 343.8642; found 343.8646. $C_{11}H_6BrNSSe$ (343.10): calcd. C 38.51, H 1.76, N 4.08, S 9.35; found C 38.13, H 1.68, N 3.78, S 9.12.

3-(4-Bromoselenopheno[2,3-*b*]thiophen-5-yl)pyridine (4f): Starting from 3-(thiophen-3-ylethynyl)pyridine (**3f**), and following a method analogous to that used for the cyclization of **3a** and **3b**, except that upon addition of the dioxane solution to the solution of selenium tetrabromide, the reaction mixture was cooled to 0 °C, and then slowly allowed to reach room temperature, gave **4f** (118 mg, 32%) as a pale yellow solid, m.p. 137–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89–8.85 (m, 1 H, 2-C*H*), 8.63 (dd, 1 H, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 4.8 Hz, 6-C*H*), 7.96 (ddd, 1 H, $^4J_{H,H}$ = 2.0, $^4J_{H,H}$ = 2.0 Hz, $^3J_{H,H}$ = 8.0 Hz, 4-C*H*), 7.49 (d, 1 H, $^3J_{H,H}$ = 5.2 Hz, 2′-C*H*), 7.38

(dd, 1 H, $^3J_{H,H}$ = 4.8, $^3J_{H,H}$ = 8.0 Hz, 5-C*H*), 7.33 (d, 1 H, $^3J_{H,H}$ = 5.2 Hz, 3′-C*H*) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 149.9, 149.3, 148.5, 138.5, 136.5, 133.3, 131.2, 129.2, 123.3, 122.4, 103.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 343 (100) $[M]^+$. $C_{11}H_6BrNSSe$ (343.10): calcd. C 38.51, H 1.76, N 4.08, S 9.35; found C 38.15, H 1.90, N 3.97, S 9.01.

3,3′-(3,5-Dibromodiselenopheno[3,2-*b*:2′,3′-*d*]thiophene-2,6-diyl)-dipyridine (4g): Selenium dioxide (234 mg, 2.10 mmol) was dissolved in hydrogen bromide (48%; 0.90 mL), and the mixture was stirred at room temperature for 15 min. A solution of **3g** (200 mg, 0.698 mmol) and cyclohexene (114 mg, 1.40 mmol) in dioxane (12 mL) was then added dropwise, and the resulting mixture was stirred at room temperature for 96 h. The reaction mixture was quenched with dichloromethane (300 mL) and aqueous NaOH solution (1 M; 100 mL). The mixture was stirred at room temperature for 1 h, then the organic phase was separated, and the aqueous phase was extracted with dichloromethane (100 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by adding ethyl acetate (30 mL), and stirring at room temperature for 30 min. After decantation of the solvent, this washing procedure was repeated twice. The resulting pure product was dried under vacuum to give **4g** (170 mg, 40%) as a yellow solid, m.p. > 245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, 1 H, $^4J_{H,H}$ = 2.0 Hz, 2,2′-Py-C*H*), 8.66 (dd, 1 H, $^4J_{H,H}$ = 1.6, $^3J_{H,H}$ = 4.9 Hz), 8.05 (ddd, 1 H, $^4J_{H,H}$ = 2.0, $^4J_{H,H}$ = 2.0, $^3J_{H,H}$ = 8.0; 4 Hz, 4′-Py-C*H*), 7.44 (dd, 1 H, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 8.0; 5 Hz, 5′-Py-C*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 149.5, 149.4, 144.3, 138.0, 136.5, 131.6, 131.0, 123.5, 102.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 603 (100) [M + 1]$^+$. HRMS (ESI): calcd. for $C_{18}H_9Br_2N_2SSe_2^+$ [M + H]$^+$ 602.7178; found 602.7185. $C_{18}H_8Br_2N_2SSe_2$ (602.06): calcd. C 35.91, H 1.34, N 4.65, S 5.33; found C 35.87, H 1.28, N 4.63, S 5.17.

1,2-Bis[(*E*)-2-bromo-1,2-bis(4-fluorophenyl)vinyl] Diselenide (8): Following a method analogous to that used for the cyclization of **1c**, but running the reaction for 24 h, and using a mixture of petroleum ether and dichloromethane (10:1) as eluent gave **8** (146 mg, 42%) as a pale yellow crystalline solid, m.p. 196–197 °C (crystallized from dichloromethane by slow evaporation at room temperature). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 4 H), 7.00–7.08 (m, 12 H) ppm. ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 162.9 (d, $^1J_{C,F}$ = 250.5 Hz), 162.1 (d, $^1J_{C,F}$ = 248.6 Hz), 136.3 (d, $^4J_{C,F}$ = 3.6 Hz), 136.2 (d, $^4J_{C,F}$ = 3.6 Hz), 131.4 (d, $^3J_{C,F}$ = 8.4 Hz), 131.2 (d, $^3J_{C,F}$ = 8.7 Hz), 131.2 (d, $^5J_{C,F}$ = 0.6 Hz), 116.7 (m), 115.4 (d, $^2J_{C,F}$ = 21.7 Hz), 115.0 (d, $^2J_{C,F}$ = 21.7 Hz) ppm. ^{19}F NMR (376.21 MHz, $CDCl_3$): δ = –110.6 (tt, $^4J_{H,F}$ = 5.5, $^3J_{H,F}$ = 8.5 Hz), –112.7 (tt, $^4J_{H,F}$ = 6.1, $^3J_{H,F}$ = 8.2 Hz) ppm. ^{77}Se NMR (76.37 MHz, dioxane/D_2O): δ = 575.7 ppm. $C_{28}H_{16}Br_2F_4Se_2$ (746.15): calcd. C 45.07, H 2.16; found C 44.78, H 2.31.

Crystallographic Data: Diffraction data were collected at low temperature with a Nonius KappaCCD diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The crystal structures of **2b**, **2f**, **2k**, **2l**, **4g**, and **8** were solved by direct methods[15a] and refined by full-matrix least-squares.[15b,15c]

CCDC-1048489 (for **2b**), 1048491 (for **2f**), 1048490 (for **2k**), 1048492 (for **2l**), 1048495 (for **4g**), 048493 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): methods for the preparation of starting materials, copies of the ^{1}H, ^{13}C, ^{19}F, ^{77}Se NMR spectra, and crystallographic data for compounds **2b**, **2f**, **2k**, **2l**, **4g**, and **8**.

Acknowledgments

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Selenophenes

Natural-Antioxidant-Inspired Benzo[*b*]selenophenes: Synthesis, Redox Properties, and Antiproliferative Activity

Edgars Paegle, Ilona Domracheva, Baiba Turovska, Marina Petrova, Iveta Kanepe-Lapsa, Anita Gulbe, Edvards Liepinsh, and Pavel Arsenyan*[a]

Abstract: The cyclization of arylalkynes under selenobromination conditions, combined with an acid-induced 3,2-aryl shift, was elaborated as a general synthetic pathway for the preparation of polyhydroxy-2- and -3-arylbenzo[*b*]selenophenes from the same starting materials. The redox properties, free-radical-scavenging ability, and cytotoxicity against malignant cell lines (MCF-7, MDA-MB-231, HepG2, and 4T1) of the synthesized compounds were explored, and the obtained results were used to consider the structure–activity relationships (SARs) in these compounds. Consequently, the structural features that were responsible for the highly potent peroxyl-radical-scavenging activity were established.

Introduction

Recent interest in polyphenols, such as flavonoids, gallic acid, curcumin, and resveratrol, has stemmed from the fact that they exhibit antioxidant and anticancer activities on various types of cancers. Indeed, polyphenols are promising chemopreventive agents for cancer management, because they restore normal cell growth by modulating proliferation, apoptosis, angiogenesis, metastasis, and inflammation and by targeting several of the molecular and biochemical pathways that have been implicated in tumor development.[1] On the other hand, selenium-containing compounds exhibit significant ability to modulate the activity of various redox enzymes, including the glutathione peroxidases family, glutathione reductase, and thioredoxin, by the depletion and formation of cellular glutathione, the modulation of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) levels, and the stimulation of oxygen consumption. Owing to their interactions with glutathione, these compounds hold great potential for application in the therapy of oncological diseases.[2] Because polyhydroxybenzo[*b*]selenophenes contain both of the structural features mentioned above, the development of procedures for their synthesis and the evaluation of their activities is an intriguing area of research.

From a synthetic point of view, the preparation of 2- and 3-arylbenzo[*b*]selenophenes that contain the desired hydroxy substitution pattern in both benzene rings is not a simple task. One of the most-powerful tools for the synthesis of 2-arylbenzo[*b*]selenophenes is the electrophilic cyclization of 1-(1-alkynyl)-2-(methylseleno)arenes developed by Larock and co-workers.[3] The advantages of this method are the use of mild reaction conditions, high yields of the products, and controllable regioselectivity. Disappointingly, however, the starting materials are only afforded in quite low yields, following a multistep preparation, whilst only a limited range of the necessary *o*-iodoanilines are commercially available. Furthermore, the synthesis of appropriately substituted iodoanilines can be extremely laborious. Another efficient strategy involves the lithiation of 1-bromo-2-(arylethynyl)benzene derivatives and subsequent electrophilic trapping by selenium powder;[4] however, again, the required starting materials are expensive or difficult to synthesize. Very recently, a two-step procedure that involved the reaction of arylzinc reagents with alkynes to form *o*-iodoalkenylarenes and subsequent cyclization upon treatment with elemental selenium in the presence of a catalytic amount of CuI was published as an alternative route to the desired benzo[*b*]selenophenes.[5] Nevertheless, this strategy involved two steps that demanded high regioselectivities for an expedient synthesis. One example of 2-arylbenzo[*b*]selenophene and some of the corresponding sulfur analogues were obtained by using this method, but all of the products were limited to a 3-alkyl substitution pattern, which didn't suit the requirements for our investigation.

Recently, we reported a new approach for the selenobromination of aryl and heteroaryl alkynes,[6a] which, for many cases, represents the most-straightforward synthetic pathway to 2-arylbenzo[*b*]selenophenes or their 3-bromo-2-unsubstituted derivatives, which can be directly used in the high-yielding preparation of the corresponding 3-aryl derivatives.[7] On the other hand, rearrangement of 3-arylbenzo[*b*]thiophenes into their corresponding 2-aryl derivatives by 3,2-aryl-group migration

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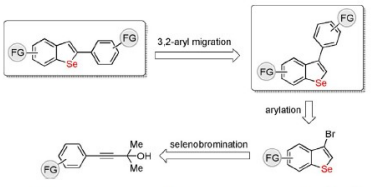


Scheme 1. Retrosynthetic strategy for the preparation of 2-aryl and 3-aryl-benzo[*b*]selenophenes. FG = functional group.

was used in the synthesis of the core structure of raloxifene.[8] By taking the advantages of both methods (Scheme 1), we overcame the regioselectivity issues that faced the direct cyclization of diarylalkynes,[9] thereby providing a general approach for the synthesis of the desired functionalized 2- and 3-aryl-benzo[*b*]selenophenes.

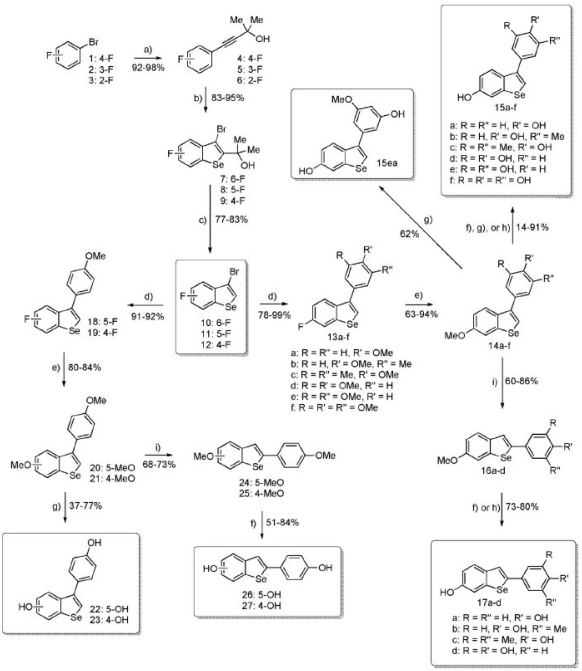
Results and Discussion

Synthesis of Polyhydroxybenzo[*b*]selenophenes

The preparation of hydroxy-substituted benzo[*b*]selenophenes involved a six-step procedure to obtain the 3-aryl derivatives, but an additional step was required for the preparation of the 2-aryl compounds (Scheme 2). We employed the cyclization of the corresponding phenylpropargyl alcohol derivatives (**4**–**6**) under selenobromination conditions as a key step in our construction of the benzo[*b*]selenophene heterocyclic system (Scheme 2b).[6] Thus, the starting materials (**4**–**6**) were prepared from fluoro-substituted bromobenzenes **1**–**3** in excellent yields by employing standard Sonogashira coupling conditions (Scheme 2a). The cyclization reactions proceeded very smoothly, even on a multigram scale (up to 20 g), and the desired benzo[*b*]selenophenes (**7**–**9**) were obtained in 83–95% yields. The corresponding 2-unsubstituted derivatives (**10**–**12**) were successfully obtained from a high-yielding deacetonation step (Scheme 2c). We previously reported[6a,7] that 3-bromo-6-fluoro-benzo[*b*]selenophene (**10**) is a versatile substrate for the preparation of more-complex target compounds, through the insertion of alkoxy substituents at the 6-position by nucleophilic substitution of the fluorine atom and arylation at the 3-position through a Suzuki coupling reaction. Herein, we also obtained the corresponding 5- and 4-fluoro derivatives (**11** and **12**, respectively).

Suzuki coupling of compound **10** with appropriate arylboronic acids (Scheme 2d) and subsequent methoxylation through nucleophilic substitution of the fluorine atom in compounds **13a**–**13f** afforded the corresponding 6-methoxy precursors (**14a**–**14f**) in good yields (Scheme 2e). Subsequent deprotection furnished the corresponding 3-aryl compounds (**15a**–**15f**; Scheme 2f–h). Three different demethylation methods were employed because, in some cases, treatment with BBr_3 in CH_2Cl_2 afforded undesired rearrangement products that were extremely difficult to separate from the target products. However, this method worked quite well for substrates **14a** and **14c**, thereby providing dihydroxy derivatives **15a** and **15c** in 89 and 91% yield, respectively (Scheme 2f). Dimethyl-substituted compound **15c** was also obtained by using thiolate demethylation (Scheme 2g), but in considerably lower yield (58%) compared with the BBr_3 method (91%). However, deprotection with dodecanethiolate allowed easier purification of the desired products. Disappointingly, thiolate deprotection was not effective for trimethoxy derivatives **14d** and **14e** or tetramethoxy derivative **14f**, because complete demethylation could not be achieved, even in a large excess of thiolate or at elevated temperature. Thus, the reaction of trimethoxy-substituted compound **14e** with 6.0 equivalents of dodecanethiolate led to the isolation of methoxy-substituted compound **15ea** in moderate yield (Scheme 2g). As a result, compounds **15d** and **15e** were obtained by deprotection with BBr_3 in quite low yields (32 and 14%, respectively), owing to the tedious purification process. Complete demethylation was achieved for tetramethoxy-substituted compound **14f** by heating at 220 °C in pyridine hydrochloride and, as a result, tetrahydroxy-substituted compound **15f** was isolated in 68% yield (Scheme 2h). Disappointingly, this method was not suitable for the deprotection of other 3-aryl precursors (**14a**–**14e**), as partial rearrangement into the corresponding 2-aryl derivatives was observed.

The standard conditions for the cyclization/rearrangement sequence in the synthesis of the core structure of raloxifene[8] involve heating the starting material in polyphosphoric acid. However, we found the later modification of these conditions,[10] which utilizes a 0.4 M solution of methanesulfonic acid in toluene, much more appealing than the original conditions (Scheme 2i). Thus, on heating compound **14a** at 90 °C for 4 h, we obtained the rearranged 6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]selenophene (**16a**) in 86% yield. In an analogous manner, 2-aryl derivatives **16b**–**16d** were prepared in moderate-to-good yields. Prolonged reaction times were typically unsuitable, and we observed undesired transformations of the starting materials or products, such as acid-induced polymerization of the starting materials. Pleasingly, considerably lower solubilities of the rearranged products compared to the corresponding 3-aryl starting materials allowed us to isolate compounds **16a**–**16d** in excellent purity by simple recrystallization. This method was unsuitable for trimethoxy-substituted compound **14e** and tetramethoxy-substituted compound **14f**, and prolonged reaction times and elevated temperatures did not induce their rearrangement. We expected that two strongly electron-donating substituents at the *meta* positions to the bond between the aryl ring and the heterocyclic system of benzo[*b*]selenophene caused a significant decrease in the electron density on the C1 atom of the aryl ring, which could lead to less-favored protonation at the 3-position of benzo[*b*]selenophene and lower nucleophilicity of the migrating aryl fragment. To the best of our knowledge, the rearrangement of compounds **14a**–**14d** into compounds **16a**–**16d** are the first examples of such a transformation in benzo[*b*]selenophene chemistry. Finally, deprotection of compounds **16a**–**16d**, either by using BBr_3 or pyridine hydrochloride, provided the target products (**17a**–**17d**) in good yields.

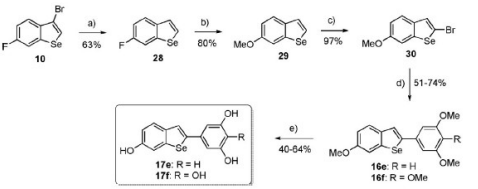


Scheme 2. Synthetic strategy for the preparation of polyhydroxybenzo[*b*]selenophenes. Reagents and conditions: a) 2-methylbut-3-yn-2-ol (1.5 equiv), $PdCl_2$ (5.0 mol%), PPh_3 (10 mol%), CuI (10 mol%), iPr_2NH (4.0 equiv), DMF, 60 °C, Ar, 24 h; b) SeO_2 (1.5–2.0 equiv), cyclohexene (1.0–1.2 equiv), HBr (48%, 0.43 mL per 1.0 mmol arylalkyne), 1,4-dioxane, RT, 24–72 h; c) K_3PO_4 (1.2 equiv), DMSO, 80 °C, Ar, 24 h; d) corresponding arylboronic acid (2.0 equiv), $Pd(OAc)_2$ (10 mol%), (*o*-Tol)$_3$P (30 mol%), K_3PO_4 (3.5 equiv), xylene/*i*PrOH (2:1, v/v), 110 °C, Ar, 1 h; e) MeOH (6.0 equiv), NaH (6.0 equiv), NMP, 140 °C, Ar, 1 h; f) BBr_3 (6.0 equiv), CH_2Cl_2, 0 °C–RT, Ar, 12 h; g) *n*-dodecanethiol (6.0 equiv), NaH (6.0 equiv), NMP, 100 °C, Ar, 24 h; h) Py·HCl, 220 °C, 6 h; i) $MeSO_2OH$ (0.4 M), toluene, 90 °C, 4 h. DMF = dimethylformamide, NMP = *N*-methylpyrrolidone, Py = pyridine.

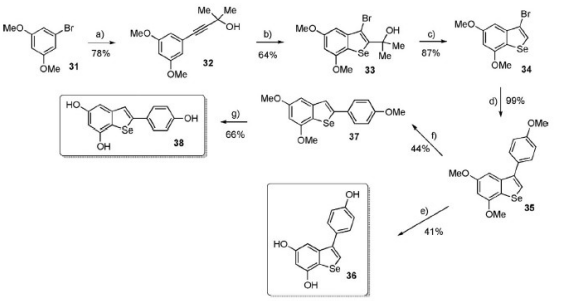
In a similar manner, we obtained the corresponding 5-hydroxy and 4-hydroxy isosteres (**22**, **23**, **26**, and **27**; Scheme 2). The rearrangement of 4-methoxy-substituted compound **21** was the only substrate for which complete consumption of the starting material was observed. In this case, steric interactions between the aryl group and the methoxy substituent at the 4-position of compound **21** could be an additional driving force for the 3,2-shift of the aryl group.

Because 3-aryl derivatives **14e** and **14f** did not undergo the rearrangement step (Scheme 2i), we developed an alternative synthetic pathway to obtain the corresponding 2-aryl isosteres (**17e** and **17f**; Scheme 3). This strategy was based on the synthesis of 2-bromo derivative **30**, which could be directly arylated to afford the necessary 2-arylbenzo[*b*]selenophene molecular scaffold. Thus, reductive debromination of compound **10**, followed by methoxylation of compound **28** and regioselective bromination of compound **29**, furnished the desired 2-bromo derivative (**30**; Scheme 3a–c). Subsequent Suzuki coupling of compound **30** and the deprotection of precursors **16e** and **16f** in the final step afforded the desired trihydroxy- and tetrahydroxy-substituted 2-aryl derivatives (**17e** and **17f**, respectively; Scheme 3d,e).

Finally, we attempted the synthesis of resveratrol analogue **38** and its isomeric 3-aryl derivative (**36**; Scheme 4), by employing a very similar synthetic strategy to the conditions described above. As we reported previously,[6a] an electron-donating substituent at the *meta* position relative to the triple bond did not promote regiospecific cyclization, but an electron-do-



Scheme 3. Synthesis of 2-aryl-derivatives **17 e** and **17 f**. Reagents and conditions: a) Zn (20 equiv), 80% AcOH in water, 110 °C, 24 h; b) MeOH (6.0 equiv), NaH (6.0 equiv), NMP, 140 °C, Ar, 1 h; c) NBS (1.1 equiv), DMF, 0 °C–RT, 12 h; d) corresponding arylboronic acid (2.0 equiv), $Pd(OAc)_2$ (10 mol%), (*o*-Tol)$_3$P (30 mol%), K_3PO_4 (3.5 equiv), xylene/*i*PrOH (2:1, v/v), 110 °C, Ar, 1 h; e) Py·HCl, 220 °C, 6 h. NBS = *N*-bromosuccinimide.



Scheme 4. Preparation of resveratrol analogues **36** and **38**. Reagents and conditions: a) 2-methylbut-3-yn-2-ol (1.5 equiv), $PdCl_2$ (5.0 mol%), PPh_3 (10 mol%), CuI (10 mol%), *i*Pr$_2$NH (4.0 equiv), DMF, 60 °C, Ar, 24 h; b) SeO_2 (1.2 equiv), cyclohexene (1.2 equiv), 48% HBr (0.43 mL per 1.0 mmol arylalkyne), 1,4-dioxane, RT, 24 h; c) K_3PO_4 (2.4 equiv), DMSO, 90 °C, Ar, 24 h; d) 4-methoxyphenylboronic acid (2.0 equiv), $Pd(OAc)_2$ (10 mol%), (*o*-Tol)$_3$P (30 mol%), K_3PO_4 (3.5 equiv), xylene/*i*PrOH (2:1, v/v), 110 °C, Ar, 1 h; e) BBr_3 (20 equiv), CH_2Cl_2, 0 °C–RT, Ar, 12 h; f) $MeSO_2OH$ (0.4 M), toluene, 90 °C, 8 h; g) Py·HCl, 220 °C, 6 h. DMSO = dimethyl sulfoxide.

nating substituent at the *ortho*- or *para* positions led to overbromination of the triple bond. As such, the direct application of the methoxy-substituted substrates used in our previous strategy (Scheme 2) was not possible. In this case, symmetrical arrangement of the methoxy groups in compound **32** eliminated the regiospecificity issues and decreased the electron density on the triple bond, which prevented its bromination under the cyclization conditions. Notably, compound **38** was synthesized by the direct cyclization of resveratrol on treatment with selenium(II) chloride.[11] However, this was not a general approach, because, in this case, the substrate underwent regioselective electrophilic substitution on the aromatic ring, presumably as the first step of the cyclization process. Furthermore, the product was obtained as a mixture with the chlorinated adduct.

Structure Elucidation by Using NMR Spectroscopy

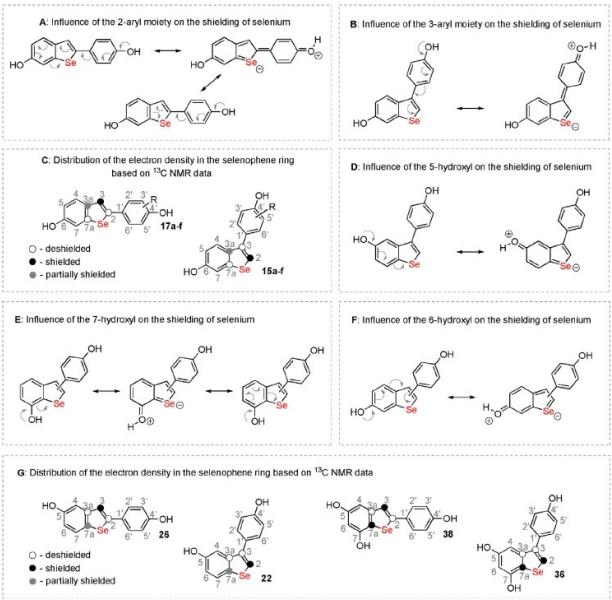
^{77}Se NMR chemical shifts are highly sensitive towards small changes in the electronic structure around the selenium atom. Thus, the ^{77}Se NMR resonance signal of benzo[*b*]selenophene ($\delta = 526$ ppm) was upfield shifted by approximately $\Delta\delta = 80$ ppm, compared to the selenophene itself ($\delta = 605$ ppm). The introduction of a phenyl group at the 2- or 3-positions of the benzo[*b*]selenophene heterocyclic system resulted in upfield shifts of the selenium signal to $\delta = 515$ and 505 ppm, respectively, whilst the ^{77}Se NMR shifts for the 2-arylbenzo[*b*]selenophenes were typically shifted downfield by approximately $\Delta\delta = 10$ ppm compared to their 3-phenyl analogues.[12]

The same trend was observed for 2-aryl derivatives **17 a–17 f** and **27**, and their corresponding 3-aryl isomers **15 a–15 f** and **23**, respectively. Although only electron-donating substituents were present in the synthesized molecules, the ^{77}Se NMR chemical shifts fell within a range of about 55 ppm, which suggested that systematic analysis of the relationship between the substituent (at a defined position) and the selenium atom could provide highly valuable information about the positions that provide the most-efficient electron donation to the selenium atom.

More importantly, because selenium itself is an electron donor, the reverse effect (electron donation towards the hydroxy groups) should also be investigated, which would be almost impossible to evaluate from the ^{13}C NMR signals of the corresponding *C*–OH moieties, owing to the lower sensitivity of ^{13}C versus ^{77}Se NMR spectroscopy. This information is crucial in the context of radical-scavenging activity, as correlation between these data would allow us to specify the mechanisms involved in the exhibited activity. A full discussion on the NMR study, as well as other topics, is presented in the Supporting Information; herein, we will only emphasize the most-important aspects of this investigation.

Thus, in the individual series of 2-aryl derivatives (**17a–17f**) and their 3-aryl isomers (**15a–15f**), the range of ^{77}Se NMR shifts was very small ($\leq$5 ppm). In fact, the typical range was even narrower than this, because the derivative without a 4′-hydroxy group (**17e** and **15e**, respectively) acted as an outlier in each series. The downfield shift of approximately $\Delta\delta =$ 10 ppm on going from 3-phenyl- to 2-phenyl-substituted benzo[*b*]selenophenes was attributed to more-effective transfer of the π-electron density from the phenyl substituent at the 3-position compared to that at the 2-position, as illustrated by their corresponding resonance structures (Scheme 5a, b).

In contrast to the insignificant influence of the substitution pattern of the aryl moiety, a more-pronounced influence of the substitution position of the hydroxy group in the benzo[*b*]selenophene benzene ring was observed. Thus, the ^{77}Se NMR shift of 5-hydroxy derivative **26** ($\delta =$ 490.5 ppm) was downfield shifted by $\Delta\delta =$ 12.5 ppm compared to parent compound **17a** ($\delta =$ 503 ppm). The *para* interaction between the 5-hydroxy and selenium groups through the benzene ring (Scheme 5d) was so efficient that its influence on the ^{77}Se NMR shift became considerably less significant ($\Delta\delta =$ 4.5 ppm) on switching from the 2-aryl isomer (**26**) to the 3-aryl isomer (**22**) than for the 6-hydroxy analogues ($\Delta\delta \approx$ 10 ppm). More-pronounced shielding of the selenium atom was observed on the introduction of an additional hydroxy group at the 7-position. The ^{77}Se NMR shift of compound **38** ($\delta =$ 462.8 ppm) was downfield shifted by an additional $\Delta\delta =$ 27.7 ppm compared to that of compound **26**; likewise, in the case of compound **26**, the difference between the ^{77}Se NMR shifts of the corresponding 2-aryl and 3-aryl isomers (**38** and **36**; $\delta =$ 458 ppm) was approximately halved ($\Delta\delta =$ 4.8 ppm). In this case, the outstanding shielding was attributed not only to the highly efficient *ortho* interaction between the 7-hydroxy and selenium groups (Scheme 5e), but the upfield ^{77}Se NMR shifts of compounds **38** and **36** could



Scheme 5. Electronic effects in the 2- and 3-arylbenzo[*b*]selenophenes.

also be owing to the steric effects of the 7-hydroxy group, which is typical of the influence of closely positioned substituents on the chemical shifts of heavy atoms.

Comparison of 6-hydroxy derivatives **15a** and **17a** with 4-hydroxy derivatives **23** and **27** revealed that the hydroxy group at the 6-position led to slightly better shielding of the selenium atom than substitution at the 4-position. In both instances, the ^{77}Se NMR shifts were downfield shifted compared to the 5- and 7-hydroxy analogues because the hydroxy group was *meta*-substituted relative to the selenium atom, as illustrated in Scheme 5 with the 6-hydroxy derivative.

In addition to information concerning the electron density on the selenium center that was obtained from analysis of the ^{77}Se NMR data, ^{13}C NMR analysis revealed significant differences between the relative distributions of electron density throughout the selenophene ring (Scheme 5). In 2-aryl derivatives **17a–17f**, both carbon atoms adjacent to the selenium center were relatively deshielded ($\delta_{C2} \approx 146.1$ ppm and $\delta_{C7a} \approx 143.8$ ppm), but, in the case of the 3-aryl analogues, the C2 atom was shielded ($\delta_{C2} \approx 122.7$ ppm) and the C7a atom was deshielded ($\delta_{C7a} \approx 145.4$ ppm). Considering the resonance contributors for the 3-aryl derivatives (Scheme 5b), the interactions between the 3-aryl moiety and the selenium atom were expected to mostly occur through the shielded C2 atom (Scheme 5c). On the contrary, for 2-aryl derivatives **17a–17f**, the same interactions should preferentially take place through the deshielded C7a atom (Scheme 5a,c). The relative distribution of electron density in the selenophene ring of 4-hydroxy derivatives **23** and **27** was analogous to that in 6-hydroxy benzo[*b*]selenophenes **17a–17f** and **15a–15f** (Scheme 5c). However, in compounds **22**, **26**, **36**, and **38**, opposite shielding of the C3a and C7a atoms was observed, which led to higher electron density on the C7a atom and a deshielded C3a atom. As expected, the presence of the 7-hydroxy group strongly increased the shielding of the C7a atom.

Electrochemical Studies

The protective action of phenolic compounds as antioxidants has been proposed to occur through two general mechanisms:[13] The first mechanism involves the abstraction of a hydrogen atom by a free radical from the antioxidant (ArOH), which itself becomes a radical (ArO$^{\bullet}$). In this regard, the O–H bond-dissociation energy (BDE) is highly informative, as the weaker the O–H bond, the more effective the inactivation of the free radical becomes. In the second mechanism, inactivation of the free radical takes place by single-electron transfer (SET) from the antioxidant to the free radical. In this regard, a particularly important parameter is the ionization potential (IP) of the antioxidant. Because a lower IP value means stronger electron-donating ability, molecules that possess the lowest IPs should be the most-potent antioxidants through the SET mechanism. Therefore, we turned our attention to the redox properties of our synthesized polyhydroxybenzo[*b*]selenophenes. Electrochemical redox reactions of these compounds were studied by using cyclic voltammetry (CV) in MeCN.

Because one of the most-widely studied phenolic antioxidants is a naturally occurring stilbene, resveratrol, we used this compound as a reference molecule for estimating the oxidation potentials of our synthesized benzo[*b*]selenophenes. Thus, resveratrol itself underwent irreversible electrochemical oxidation at 1.10 V. The main factor in facilitating the removal of the first electron was likely the relative stability of the generated cation radical (ArOH$^{\bullet+}$). Because inductive and/or mesomeric effects of the substituents are responsible for stabilizing the cation radicals, the abstraction of an electron from the *para*-hydroxyphenyl moiety should be less energy consuming than the resorcinol-type moiety.[14] This assumption was supported by the fact that the obtained value was within the characteristic potential range for *para*-substituted phenols.[15] In the cyclic voltammogram of resveratrol, the first oxidation peak was followed by a second peak that was rather poorly defined and significantly less intense than the first peak. We also encountered reproducibility issues with the second peak, even when using freshly polished electrode. Furthermore, the potential difference between these two steps was too small to attribute the second peak to oxidation of the resorcinol moiety. As numerous possible transformations can be proposed for the generated cation radical (e.g. further oxidation, dimerization, and polymerization) and no preparative oxidation experiments were performed to establish the actual structures of the oxidation products, the discussion below is solely based on the first oxidation peak (oxidation potential, OP) in the corresponding cyclic voltammograms, which could be regarded as being closely related to the IP of the given compound.

The OP values of the synthesized benzo[b]selenophenes were within the range 0.85–1.34 V. As expected, for the 6,4′-hydroxy-containing compounds (**15a–15d**, **15f** and **17a–17d**, **17f**), in all cases, switching from the 2-aryl derivatives to the corresponding 3-aryl derivatives caused the OP to increase by approximately 100 mV, with the most-pronounced increase for compounds **17c** and **15c** (230 mV). This change could be explained by extended delocalization of the electron-deficient site between the aryl moiety and the heterocyclic system of the benzo[b]selenophene in the 2-aryl derivatives (**17a–17d** and **17f**), which was significantly disrupted in the corresponding 3-aryl isomers (**15a–15d** and **15f**).

Another unifying feature of the 2-aryl derivatives that contained 6,4′-hydroxy groups (**17a–17d**, **17f**, and **39**) was a reversible/quasi-reversible first oxidation step if the potential scan was reversed immediately after the first peak in the corresponding CV. This observation showed that, at least for this family of compounds, the removal of the first electron led to the formation of a sufficiently stable cation radical, whilst the second (irreversible) oxidation peak in the corresponding CV could be attributed to the removal of another electron from the already generated cation radical, thereby leading to the formation of a two-electron-oxidation product. On the contrary, all of the other derivatives underwent irreversible oxidation, thus indicating high reactivity of the generated cation radical, which might lead to the previously mentioned side reactions. Consequently, these compounds provided similar CVs to resveratrol itself.

For the selenium analogues of resveratrol (**17e** and **38**), in both cases, abstraction of the first electron took place slightly more anodically (1.18 V) than for resveratrol itself. The difference between the OPs of compound **17e** and resveratrol was too small to ascribe it to the removal of an electron from the resorcinol-type moiety. Thus, the formation of a more-stabilized cation radical could be envisaged by the removal of an electron from the heterocyclic system of benzo[b]selenophene. On the contrary, the ionization of compound **38** was much less predictable, because the 4-hydroxyphenyl moiety was still present and an *ortho*/*para*-substitution pattern of the 5,6-hydroxyl groups relative to the electron-donating selenium atom could provide substantial stabilization of cation radicals that were generated by the removal of an electron from the benzene ring of the benzo[b]selenophene moiety. Interestingly, by switching to the corresponding 3-aryl derivatives (**15e** and **36**), the OP changed in the opposite direction. For compound **36**, the lower OP (1.08 V) could be owing to stronger interactions between the 3-(4′-hydroxyphenyl) moiety and the selenium atom, thereby providing extra stabilization of the generated cation radical. However, it might also suggest that the removal of the first electron in both compounds **36** and **38** took place on the *para*-substituted phenol moiety and that the difference between the observed OPs was predominantly governed by the stabilizing effect of the selenium atom.

Finally, no significant change in the OP was determined upon substituting the selenium atom of compound **17a** (1.04 V) with a sulfur atom in compound **39** (1.02 V), thus suggesting that neither selenium nor sulfur was directly involved in the oxidation process.

Radical-Scavenging Activity and In Vitro Cytotoxicity

One of our main research interests is the discovery of promising selenium-containing antiproliferative agents.[7,16] In this context, especially impressive results were obtained by synthesizing the selenium analogue of raloxifene (a well-known selective estrogen-receptor modulator).[7] Thus, the replacement of the sulfur atom by a selenium atom led to a highly pronounced antiproliferative effect against malignant cell lines and considerably lower basal toxicity. In contrast to the original drug, the selenium analogue inhibited the growth of breast cancer cells (mammary carcinoma 4T1) by 30% in vivo. On the other hand, there is increased interest in antioxidants, in particular in "nature-mimicking" polyphenol derivatives, and resveratrol is probably the most-widely studied representative of this family.[11] Consequently, as a continuation of our research in this area, we attempted to merge the cancer-preventive abilities of polyphenols[17] and selenium[18] with their oxidative-stress-modulating activity during carcinogenesis. Because the core structure of selenium raloxifene contained both ingredients, we were encouraged to study how the number and substitution pattern of hydroxy groups affected the cytotoxicity and radical-scavenging activity of the synthesized polyhydroxybenzo[*b*]selenophenes. Screening results of radical-scavenging activity on free radicals, superoxide, and peroxyl radicals and an evaluation of the malignant-cell-proliferation suppression are listed in Table 1.

By comparison of the peroxyl-radical-scavenging activity of the synthesized benzo[*b*]selenophenes, the structural features that provided the highest activities were established. We found that, in all cases, the 3-aryl derivatives were more active than the corresponding 2-aryl isomers. The only exceptions were the compounds that contained 5-hydroxy and 5,7-dihydroxy groups (**22** and **26**, and **36** and **38**). In particular, increased activity was observed in the presence of 5-hydroxy- and 7-hydroxy-substituents, with resveratrol analogue **38** ($IC_{50}=0.02$ μM) the most-active compound of the examined derivatives. Furthermore, the introduction of an additional hydroxy group at the *ortho* position relative to the 4′-hydroxy group provided an opportunity to significantly increase the scavenging capacity. Thus, the presence of a 3′-hydroxy group in compound **15d** ($IC_{50}=0.04$ μM) led to a 20-fold increase in activity of compound **15a** ($IC_{50}=0.8$ μM). In the case of the corresponding 2-aryl isomers (**17a** and **17d**), the effect was similar, but considerably less pronounced.

On the contrary, in all cases, compounds that contained an additional electron donor at the 5′-position (compounds **15c**, **15f**, **17c**, and **17f**) were less activating than their 5′-unsubstituted isosteres (**15b**, **15d**, **17b**, and **17d**) and, in some cases, even strongly deactivating (**15c** and **17f**). Following careful analysis of the ^{77}Se NMR data (see the Supporting Information), we found that *meta*-substituted electron-donating (hydroxy) groups in the aryl moiety, with implied mesomeric effects, acted in a distinctive manner, depending on whether the phenyl group was attached to the C2 or C3 atom of the selenophene ring. These observations correlated remarkably well with the scavenging activity of the corresponding derivatives towards peroxyl radicals. Because electron-donating substituents at the *ortho* and *para* positions relative to the phenolic hydroxy group decreased the O–H bond dissociation enthalpy (BDE), thereby providing faster transfer of the hydrogen atom to the peroxyl radical,[19] slightly higher scavenging activity of selenium-containing compound **17a** ($IC_{50}=2.2$ μM) towards peroxyl radicals compared to the corresponding sulfur analogue (**39**; $IC_{50}=3.5$ μM) was observed, which indicated that selenium was a better electron donator than sulfur.

Disappointingly, no reasonable correlation between the structural elements of the synthesized molecules and their ability to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and superoxide was observed. However, of the studied compounds, the most-potent scavengers for DPPH radicals were compounds **15a–15c**, **15f**, **17e**, **17f**, **23**, and **27** ($IC_{50}=8$–15 μM), whereas the most-potent scavengers for superoxide radicals were compounds **15ea**, **15f**, **17e**, **36**, and **38** ($IC_{50}=$ 7–25 μM).

As mentioned above, despite the fact that only electron-donating substituents were present in the synthesized benzo[*b*]-selenophenes, a wide range of chemical shifts was observed in the ^{77}Se NMR spectra, thus indicating that appropriately positioned electron-donating groups could significantly increase the vulnerability of selenium towards oxidation. We hypothesized that the derivatives that contained the most-shielded se-

Table 1. Radical-scavenging activity and in vitro cytotoxicity on monolayer tumor cell lines MCF-7 (human breast adenocarcinoma, estrogen-positive), MDA-MB-231 (human breast adenocarcinoma, estrogen-negative), HepG2 (human liver hepatocellular carcinoma), and 4T1 (mammary carcinoma; IC_{50}), and basal toxicity (LD_{50}) of the synthesized polyhydroxybenzo[*b*]selenophenes, resveratrol, and compound **39**.

Compound	IC_{50} [μM]							LD_{50} [mg kg^{-1}]
	DPPH radical	Superoxide radical	Peroxyl radical	MCF-7	MDA-MB-231	HepG2	4T1	
resveratrol	12	17	1	118	105	105	17.5	571
15a	15	>1000	0.8	86	100	21	69	364
17a	41	>1000	2.2	27	17	17	3.5	188
15b	11	n/a	0.2	131	9.4	12.5	25	382
17b	45	n/a	0.63	28	59	19	18	324
15c	8	n/a	2.1	66	8.9	8.9	8.9	374
17c	334	324	1.75	51	21	63	8.9	178
15d	76	n/a	0.04	72	85	78	9.8	171
17d	104	>1000	0.44	92	16	72	39	117
15e	61	314	0.17	127	248	118	98	427
15ea	92	10	0.63	93	93	93	12.5	271
17e	9	9	2.11	75	98	68	23	214
15f	8	25	0.11	227	143	168	28	707
17f	10	851	9.6	104	121	22	62	771
22	244	115	2.4	134	96	96	103	243
26	50	804	0.15	110	141	45	6.9	335
23	9	78	0.75	100	93	107	48	405
27	10	217	1.5	96	65	41	69	252
36	54	18	0.55	131	238	98	91	171
38	43	7	0.02	16.3	49	29	39	305
39	28	110	3.5	37	25	20	3.3	70

lenium atoms could potentially be susceptible towards oxidation by hydroperoxides, which could lead to glutathione peroxidase (GPx)-like activity in the presence of thiols.[20] However, upon stirring compound **38** in the presence of 10 equivalents of hydrogen peroxide or *tert*-butyl peroxide in MeOH at 40 °C for 20 h, no reaction took place. In fact, somehow, the opposite effect was observed, as the oxidation of thiols by hydrogen peroxide into their corresponding disulfides partially occurred, even without a catalyst, owing to a radical-induced process that was caused by the partial decomposition of hydrogen peroxide; however, in the presence of a catalytic amount of compound **38**, the formation of the corresponding disulfide was partially prevented, thus indicating antioxidative behavior, owing to its radical scavenging ability.

Finally, all of the products were subjected to cytotoxicity assays versus four different cancer cell lines, and their basal toxicities were also determined (Table 1). The core structure of raloxifene **39** and its selenium analogue (**17a**) exhibited similar behavior towards verified cancer cells, with the highest cytotoxicity versus the 4T1 (mammary carcinoma) cell line (IC_{50} = 3.5 and 3.3 μM, respectively). Nevertheless, the basal toxicity of compound **17a** (LD_{50} = 188 mg kg^{-1}) was considerably lower than that of sulfur analogue **39** (LD_{50} = 70 mg kg^{-1}).

A notable decrease in cytotoxicity against cancer cells was observed for the corresponding 3-aryl derivative (**15a**), with a simultaneous increase in LD_{50} value (364 mg kg^{-1}). A similar correlation was observed between methylated derivatives **17b** and **17c** and their corresponding 3-aryl analogues (**15b** and **15c**). Notably, the LD_{50} value of compound **17b** (324 mg kg^{-1}) was approximately double that of compound **17a** (188 mg kg^{-1}), whilst the activities of compounds **15b** and **15c** (IC_{50} = 9.4 and 8.9 μM, respectively) were 10-times higher versus the estrogen-negative human breast adenocarcinoma MDA-MB-231 cell line than compound **15a**. The introduction of another hydroxy group adjacent to the 4′-OH moiety (**17d**) did not lead to significant changes in the antiproliferative activity, except for lower activity against carcinoma 4T1 cells (39 μM) than compound **17a** (3.5 μM). The opposite effect was observed for the corresponding 3-aryl derivative (**15d**), which exhibited seven-times-higher activity against 4T1 cells than compound **15a**. Compounds **17d** and **15d** exhibited increased basal toxicity (LD_{50} = 117 and 171 mg kg^{-1}, respectively) compared to parent compounds **17a** and **15a** (LD_{50} = 188 and 364 mg kg^{-1}, respectively). The cytotoxic effects of 3′,5′-dihydroxyphenylderivatives **17e** and **15e** on all studied cancer cell lines were diminished, although monomethylated **15ea** exhibited higher cytotoxicity towards all cancer cell lines and elevated basal toxicity compared with compound **15e**.

Despite the fact that, in general, tetrahydroxy-substituted compounds **17f** and **15f** were less cytotoxic than compounds **17a** and **15a**, their LD_{50} values were significantly higher. A very similar trend was observed for 5,4′- and 4,4′-dihydroxy derivatives **22**, **23**, **26**, and **27**, but the quite high cytotoxic effect towards 4T1 cells (6.9 μM) exhibited by compound **26** was preserved. Furthermore, in the case of 5,4′-dihydroxy derivatives **26** and **22**, switching from the 2-aryl isomer to the 3-aryl one resulted in a considerable increase in basal toxicity (LD_{50} = 335 and 243 mg kg^{-1}, respectively). Finally, the cytotoxicity data for the selenium analogue of resveratrol (**38**) revealed that, in general, it was a less-potent antiproliferative pharmacophore than

4′,6-dihydroxy derivative **17a**; however, moderate cytotoxicity of compound **38** towards the MCF-7 cell line (16.3 μM) was observed. The cytotoxicity exhibited by 3-aryl isomer **36** was even less promising than 2-aryl derivative **38**. Moreover, the basal toxicity of compound **36** was much higher than that of compound **38**. Upon comparison of resveratrol with its selenium analogue (**38**), we concluded that the introduction of selenium notably increased the antiproliferative activity of the compound, but simultaneously increased its basal toxicity. The remarkable activity of resveratrol on mammary carcinoma 4T1 cells (IC_{50} = 17.5 μM) should be mentioned; in this case, the introduction of selenium decreased the activity of the compound.

Conclusion

The cyclization of arylalkynes under selenobromination conditions, combined with an acid-induced 3,2-aryl shift, was elaborated as a general synthetic pathway for the preparation of functionalized 2- and 3-arylbenzo[*b*]selenophenes from the same starting materials. This approach overcame the regioselectivity issues that limited the scope of the direct cyclization of asymmetrical diarylalkynes. The limitations of the rearrangement step were resolved by preparing 2-bromo-6-methoxybenzo[*b*]selenophene (**30**), which was arylated in high yields, thereby furnishing the otherwise-inaccessible 2-aryl derivatives. Nevertheless, the clear advantage of the 1,2-aryl shift in the rearrangement step allowed the quite "silly" debromination/bromination steps to be eliminated.

NMR analysis revealed highly valuable information about the interactions between different structural motifs in the synthesized molecules. Hydroxy groups at the 5- and 7-positions provided the strongest electron donation to the selenium atom, and an analogously substituted aryl moiety at the 3-position led to more-efficient shielding of the selenium center than the 2-substituted structure. A similar effect was expected for the selenium atom as an electron donor, but in the opposite direction, as supported by recently published results[11] on O–H BDE calculations for Se–resveratrol **38**. Because the electron-donating effect of the selenium atom facilitated homolytic cleavage of the O–H bonds, the 5,7-hydroxy-substituted derivatives and their corresponding 3-aryl isomers exhibited the best peroxyl-radical-scavenging activity.

The 6,4′-hydroxy-substituted 2-aryl isomers had the lowest OPs among the studied compounds, owing to more-efficient stabilization of the generated cation radicals. Because we could not find any correlation between the OP and the radical-scavenging activity, we concluded that a SET mechanism was either not predominant or did not participate at all in this process.

In general, we only observed strong correlations in the structure–activity relationships (SARs) for the peroxyl-radical scavenging, and the obtained activity data were in full agreement with the observations made from the NMR study. Disappointingly, the mechanisms of free-radical and superoxide scavenging were less clear, owing to the lower activity of the studied compounds.

We observed no direct correlation between the radical-scavenging activities of the compounds and their cytotoxic activities on cancer cell lines, which indicated that the highly cytotoxic effects on tumor cells were not necessarily caused by the antioxidant properties of the particular compounds. Furthermore, a direct role of the selenium atom in the increased antiproliferative activity was also questionable. We found that, despite the high electron density on the selenium atom, the synthesized compounds did not possess any hydroperoxide-scavenging (GPx-mimicking) ability, as was recently suggested by Panzella, Capperuci, and co-workers.[11] In addition, the sulfur-containing core structure of raloxifene (**39**) was even more cytotoxic on the evaluated cancer cell lines than its selenium analogue (**17a**). However, the positive influence of replacing the sulfur atom with a selenium atom on the basal toxicity should not be discounted.

To conclude, polyhydroxybenzo[*b*]selenophenes have emerged as a new family of highly potent antioxidants and antiproliferative agents. The positive effect of introducing additional electron donors at judicious positions on the scaffold holds great potential for developing even-more-active derivatives. Moreover, we anticipate that the high stability, low toxicity, and growing collection of available tools for the structural diversification of benzo[*b*]selenophenes will lead to the development of new candidate drug molecules from this family of compounds in the near future.

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Keywords: antiproliferative activity · cytotoxicity · radicals · redox chemistry · selenophenes

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Ar savu parakstu apliecinu, ka pētījums veikts patstāvīgi, izmantoti tikai tajā norādītie informācijas avoti un iesniegtā darba elektroniskā kopija atbilst izdrukai.

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