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# Synthesis, physicochemical characterization, cytotoxicity, antimicrobial, anti-inflammatory and psychotropic activity of new *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl] alkanamides

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ABSTRACT

A series of new *N*-[(benzo)thiazol-2-yl]-2/3-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethan/propanamide derivatives was synthesized and characterized by $^{1}H$, $^{13}C$ NMR and IR spectroscopy and mass-spectrometry. A single crystal X-ray study of *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide is reported to determine its conformational feature. The investigated compounds were found to be active in psychotropic *in vivo*, anti-inflammatory *in vivo* and cytotoxicity *in vitro* screening. They possess marked sedative action, reveal high anti-inflammatory activity, have selective cytotoxic effects and NO-induction ability concerning tumour cell lines. Some of the compounds synthesized demonstrate antimicrobial action. An attempt was made to correlate the biological results with their structural characteristics and physicochemical parameters. Some specific combinations of types of activities for the synthesized compounds have been revealed.



## 1. Introduction

Among pharmacologically important heterocyclic compounds, thiazole and tetrahydroisoquinoline derivatives have been well known in medicinal chemistry because of their wide spectrum of biological activities and the presence of their structural moieties in molecules of naturally occurring compounds.

Thiazole core is present in many biologically relevant molecules, which are in therapeutical use, such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug), Tiazofurin (antineoplastic agent), Meloxicam (non-steroidal anti-inflammatory drug), Nitazoxanide (antiprotozoal agent) etc. Many natural products containing thiazole ring were isolated and most of them exhibit considerable cytotoxicity and antitumour potential [1–4]. Thiazole and its derivatives are found to be associated with various biological activities such as anti-inflammatory [5–7], antimicrobial [8–12], antitubercular [13], antitumour activities [14–18], enzyme inhibition [19,20] and also find application in the drug development for the treatment of allergies [21], schizophrenia [22] and as hypnotics [23]. Some coumarins incorporating thiazolyl semicarbazones act as anticonvulsant agents [24]. Thiazole derivatives were reported to possess antidegenerative activity and coupling with other heterocyclic system form new biologically active compounds [25–27].

The tetrahydroisoquinoline ring system is an important structural motif [28,29], which is commonly encountered in naturally occurring alkaloids with interesting biological activities. Typical examples include indenoisoquinoline (topoisomerase I inhibitor) [30], saframycin-B [31], narciclasine [32] and ecteinascidin-743 (antitumour agents) [33]. In this regard, the tetrahydroisoquinoline framework has become widely identified as a “privileged” structure with representation in several medicinal agents of diverse therapeutic action and are the potential drug candidates [34–37]. Tetrahydroisoquinoline derivatives have been discussed as affine

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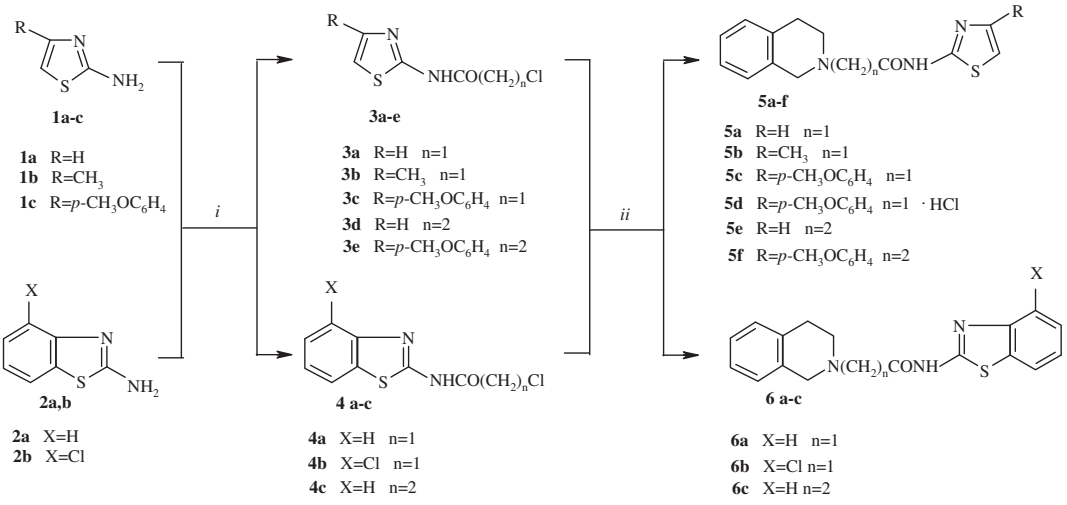



*i*: $Cl(CH_2)_nCOCl/C_6H_6/80^oC$

*ii*: $Et_3N/C_6H_6/80^oC$ (A); $K_2CO_3/EtOH/78^oC$ (B); [**3** or **4**]:[Tetrahydroisoquinoline] = 1:2.5/$C_6H_6/80^oC$ (C)

**Scheme 1.** Synthesis of *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides (**5a**–**f** and **6a**–**c**).

ligands for CNS receptors [38–41] and possess sedative [42–44] and antitumour properties [45–47]. Besides hydrogenated quinoline moieties are present as structural fragments in Amsacrine, Bruneomycinum, Vincristine and Vinblastinum widely used in oncology [14,48].

Taking into account the importance of heterocyclic compounds in creating drug [49], the successful application of fragment-based analysis in the design of new biologically active substances [50] and regarding the pharmacological properties of tetrahydroquinoline and thiazole derivatives, it was envisaged to synthesize some new bis-heterocyclic compounds as possible prodrugs and to evaluate their biological potentials. Coupling of tetrahydroquinoline and thiazole ring in a single frame for the development of new chemical entities, in which the one could reinforce or modify the biological effects of the other, was carried out by using peptide link as a spacer.

This approach, called "dual action prodrug approach" or "mutual prodrug approach" [51,52] has several advantages, such as synchronous delivery of active agents, slower development of resistance, improved formulation, improved chemical stability, reduced potential steric and/or electronic issues associated with biological target interaction and decreased toxicity [53].

In this paper, we propose the synthesis of novel *N*-[(benzo) thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamide derivatives, in order to generate compounds with high biological activity and low toxicity, and evaluation of their biological action, namely, *in vitro* inhibiting properties on tumour cells (human fibrosarcoma HT-1080 and mouse hepatoma MG-22A), normal mouse fibroblasts (NIH 3T3), bacterial (two Gram-positive, *Staphylococcus aureus* and *Bacillus cereus*, and three Gram-negative, *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus mirabilis*) and fungal strains (*Candida albicans* and *Aspergillus niger*), as well as their *in vivo* anti-inflammatory properties against carrageenin mouse paw oedema and psychotropic activity along a number of tests. In addition, we report on a single crystal X-ray study of *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide to understand its conformational feature and supramolecular assembly. It helps in understanding the mechanism of action of the drug and also in docking studies with various receptors. An attempt was made to correlate the biological results with their structural characteristics and physicochemical parameters.

## 2. Results and discussion

As mentioned above, the aim of our work is to get potential dual action prodrugs with low toxicity by combining conventional pharmacophores in one molecule. New compounds, containing two biologically active heterocycles (1,2,3,4-tetrahydroisoquinoline and 1,3-thiazole), namely, 2(3)-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl)- and -(1,3-benzothiazol-2-yl)ethan/propanamides have been synthesized, characterized by various physicochemical methods and evaluated for some types of biological action.

### 2.1. Chemistry

The synthesis of the title compounds is outlined in Scheme 1.

The strategy for the synthesis of *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides (**5a**–**f** and **6a**–**c**) involved the preparation of the ethanamido **3a**–**e** and propanamido intermediates **4a**–**c** [54], which were further used as alkylating agents in reaction with 1,2,3,4-tetrahydroisoquinoline to afford a series of the desired compounds.

Initially, three different synthetic modifications were followed for the synthesis of 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl)ethanamide (**5a**): interaction of equimolar amounts of the 1,2,3,4-tetrahydroisoquinoline and 2-chloro-*N*-(1,3-thiazol-2-yl)ethanamide (**3a**) in boiling benzene in presence of triethylamine (A), alkylation of the appropriate amine in boiling alcohol in presence of potassium carbonate with a little access of the amine (B) and reaction between the reactants in boiling benzene using 2.5 molar excess of the amine (C). The yields of product **5a** along the methods A, B and C were 31, 24 and 44%, correspondingly. Taking into account the possibility to recover the heterocyclic amine from the reaction mixture, method C was the optimal alkylation procedure among the examined ones. Therefore, the latter reaction conditions were applied for the synthesis of all the other title compounds. The yields of the synthesized *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides ranged from moderate to high (44–87%).

The structure of the compounds was confirmed by element analysis, IR, $^1H$ and $^{13}C$ NMR spectroscopy, GC- and LC-mass-

spectrometry and X-ray diffraction analysis (for compound **6a**). Analysis of IR spectra showed that they had absorption bands typical for amide bond.

### 2.2. Biological activities

The biological activity of the title compounds, namely, *in vivo* psychotropic action along a number of tests, *in vivo* anti-inflammatory effects using the functional model of carrageenin-induced mouse paw oedema (CPE), antimicrobial activity against different Gram-positive, Gram-negative and fungi strains, using the agar dish diffusion method, and cell cytotoxicity on two monolayer tumour cell lines (HT-1080 and MG-22A) and normal mouse fibroblasts NIH 3T3 have been investigated.

#### 2.2.1. *In vivo* psychotropic activity

Psychotropic activity of the title compounds was examined on mice under intraperitoneal administration in doses of 5 mg $kg^{-1}$ and the action of the substances on the CNS was evaluated on indicators of phenamine hyperactivity, hypoxia, hexenal and ethanol anaesthesia and corazole convulsions. The results of the study of neurotropic properties are presented in Table 1.

The investigated compounds possessed marked sedative action. The structure–activity study was carried out comparing the influence of heterocycle nature and alkyl chain length on the psychotropic activity indicators.

All of the tested compounds at dose of 5 mg $kg^{-1}$ are synergists of hexenal and ethanol, reliably extending their narcotic action by 35–60% and by 22–53%, respectively. The most reliable extension of narcotic action, by 1.6 times for hexenal was noted for thiazolyl propanamide **5e** without substituent in the $C_4$ position of the molecule.

All the compounds studied revealed anticonvulsive action in the test of corazole induced convulsions (clonic and tonic) increasing their threshold by 26–61% in the clonic and by 26–62% in the tonic phase. 2-[3,4-Dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl) ethanamide (**5a**) possessed the greatest anticonvulsive activity and was the stronger anticonvulsant in comparison with its benzothiazolyl analogue **6a**. The investigated substances did not display protective properties in test of maximal electroshock.

Almost all the investigated compounds acted as phenamine antagonists, reducing the locomotor activity caused by administration of phenamine by 49–59%. The greatest antagonistic effect on interacting with phenamine was observed for thiazolyl- (**5e**), (4-methoxyphenyl)thiazolyl- (**5f**) propanamides and (4-methoxyphenyl)thiazolylethananamide hydrochloride (**5d**). In the case of **5d** the sedative action appeared later, after an hour. Benzothiazolyl compounds **6a** and **6b** were less active in this respect. The only compounds strengthening the action of phenamine by 15–29% (synergists of phenamine) were thiazolyl ethanamides **5b** and **5c**, containing 4-methyl or 4-methoxyphenyl substituent correspondingly.

Study of the effect of some substances on memory processes showed that the greatest activity was displayed by (4-methoxyphenyl)thiazolyl propanamide (**5f**), which at dose of 5 mg $kg^{-1}$ completely (100%) prevented retrograde amnesia.

Psychotropic action of compounds **5d–f** on the central nervous system was also assessed by effect on motor coordination and muscle tone along a number of tests, namely, rotating rod, tube, traction, on body temperature, by analgetic and antispasmodic effect to electroshock (Table 2).

In *in vivo* acute toxicity experiments, the examined compounds did not cause toxic effects. The acute toxicity depended on the presence of the substituent in $C_4$ position. The toxicity of (4-methoxyphenyl)thiazolyl propanamide (**5f**) was lower at least by twice in comparison with the analogue without 4-methoxyphenyl substituent (**5e**). Depriming activity in rotating rod, tube and traction tests was expressed weakly. However, thiazolyl propanamide **5e** possessed clearly expressed depriming activity and analgetic action.

As the result of the carried out investigations a dominant display of a definite type of neurotropic properties was shown depending on the nature of the heterocyclic fragment (thiazolyl benzothiazolyl), alkyl chain length between two heterocycles and also on the presence of a substituent in the $C_4$ position of the molecule. Thiazolyl propanamides possessed tranquilizing/sedative (phenamine antagonism), antihypoxic (increasing of lifespan under conditions of hypoxia) and hypnotic (elongation in duration of sleep caused by hexenal) action. Anticonvulsive effect in corazole induced convulsions test was mostly expressed in thiazolyl and benzothiazolyl ethanamides without $C_4$ substituent.

It can be concluded, that the investigated compounds possessed marked neurotropic activity, such as antihypoxic, hypnotic and anticonvulsive effects, and acted as phenamine antagonists. Thiazolyl derivatives **5a–f** displayed higher psychotropic activity in comparison with benzothiazolyl analogues **6a**, **b**.

#### 2.2.2. *In vivo* anti-inflammatory activity

The *in vivo* anti-inflammatory effects of 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl)ethanamide (**5a**), 3-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl)propanamide (**5e**), and the corresponding 4-*p*-methoxyphenyl-substituted analogues **5c** and **5f** were assessed by using the functional model of carrageenin induced mouse paw oedema (CPE)

**Table 1**
*In vivo* neurotropic activity of compounds **5a–f** and **6a**,**b** with respect to control (100%).

| No. | Test, M ± m, % to control (100%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Phenamine hyperthermia[a] | | Phenamine induced hyperactivity | | Hypoxic hypoxia | Ethanol induced narcosis | Hexenal induced narcosis | Corazole induced convulsions | | Retrograde amnesia |
| | 30 min | 60 min | 30 min | 60 min | | | | Clonic | Tonic | |
| **5a** | 100.8 | 98.5 | 80 | 88 | n | n | **135*** | **161*** | **162*** | n |
| **5b** | 98.6 | 99.8 | 129 | 117 | n | n | 111 | **132*** | 116* | n |
| **5c** | 99.7 | 100.6 | 115 | 117 | n | n | 86 | 105 | **143*** | n |
| **5d** | −0.8 | −0.6 | 80 | **46*** | 115 | **153*** | **140*** | **130*** | **135*** | 80 |
| **5e** | −0.4 | −0.6 | **51*** | **49*** | 105 | 105 | **160*** | 115* | 116* | 80 |
| **5f** | −0.7 | −0.2 | **41*** | **49*** | **139*** | **122*** | 100 | **126*** | **124*** | **100*** |
| **6a** | 99.8 | 102 | 70 | 64 | n | n | **141*** | **127*** | **150*** | n |
| **6b** | 96.7 | 98 | 95 | 95 | n | n | 111 | 114 | **126*** | n |

*Differences in relation to control are statistically reliable at $P < 0.05$.
[a] M ± m, % to control (100%) for compounds **5a–c** and **6a**,**b** or °C for compounds **5d–f**.

**Table 2**
Effect of compounds **5d–f** on the tone of skeletal musculature and motor coordination.

| Compound | $LD_{50}$, mg $kg^{-1}$ | Test, $ED_{50}$, mg $kg^{-1}$ | | | | | |
|---|---|---|---|---|---|---|---|
| | | Rotating rode | Tube | Rectal temperature | Narcosis | Analgesia | Traction |
| **5d** | >500 | 224 | >250 | >250 | >250 | 141 | >250 |
| **5e** | 258 | >200 | >200 | >200 | >200 | 44.7 | 70.8 |
| **5f** | >500 | >500 | >500 | >500 | >500 | 103 | >500 |

[26,55] and are presented in Table 3, as percent inhibition of carrageenin induced mouse oedema.

All the studied compounds after 3.5 h at dose of 0.2 mmol $kg^{-1}$ body weight exhibited high anti-inflammatory activity protecting *in vivo* against the carrageenin induced paw oedema formation (50.2%–75.8%).

Analyzing the data obtained it was revealed that 4-(*p*-methoxyphenyl)thiazolyl propanamide (**5f**) provided the lowest protection (50.2%), which was about similar one to the reference drug indomethacin (57.2%). In its turn, 4-(*p*-methoxyphenyl)thiazolyl ethanamide (**5c**) caused the highest inhibition among the tested compounds (75.8%) followed by compounds without substituent in the $C_4$ position – thiazolyl ethanamide **5a** (70.4%) and thiazolyl propanamide **5e** (62.4%).

It was interesting, that the distance elongation between tetrahydroisoquinolyl and thiazolyl moieties influenced the biological response – compare compounds **5a** and **5c** ($n = 1$) with compounds **5e** and **5f** ($n = 2$). Both thiazolyl- and 4-(*p*-methoxyphenyl)thiazolyl ethanamides possessed higher inhibition in comparison with their propanamide analogues, which was mostly expressed between $C_4$-substituted compounds **5c** and **5f**, where the difference in inhibition was about 25%.

Lipophilicity is a significant physicochemical property, determining distribution, bioavailability, metabolic activity and elimination. This parameter was theoretically calculated as *c*log *P* value in *n*-octanol-buffer system [56]. Herein the role of lipophilicity is marginal (**5a** > **5e**, **5c** > **5f**), and the values could not be used as successful indicators of the biological activity. It can be attributed to the presence of basic nitrogen atoms in the examined compounds, which could disturb the absorption/desorption process.

It was found that among tested compounds the alkyl chain length between two heterocycle moieties is more essential for anti-inflammatory display than the presence of the bulky substituent in $C_4$ position of thiazole ring.

It can be concluded that the studied compounds possessed high anti-inflammatory activity, which in almost all cases was higher or close to that of the reference drug indomethacin.

### 2.2.3. *In vitro antimicrobial activity*

The antimicrobial activity of the title compounds has been investigated against two Gram-positive, *S. aureus* (SA) and *B. cereus* (BC), three Gram-negative *E. coli* (EC), *P. aeruginosa* (PA) and *P. mirabilis* (PM), and two fungi strains, *C. albicans* (CA) and *A. niger* (AN), using the agar dish diffusion method [57,58] and was examined quantitatively by measuring of the inhibition zone diameter in comparison with gentamicin and fluconazole as the reference compounds. The investigation of antimicrobial screening (Table 4) revealed that almost all the newly synthesized compounds (**5a–c**, **5e**,**f** and **6a**,**b**) showed selective antibacterial activity against Gram-negative *P. aeruginosa* with diameter of inhibition zones ranged from 17 to 20 mm, and moderate antibacterial activities against some other Gram-negative and Gram-positive bacteria with inhibition zones of 9–15 mm. Thiazolyl derivatives were also potent against Gram-positive SA (compounds **5a**, **5c**, **5e** and **5f**) and BC bacteria (compounds **5b**, **5c** and **5e**). Almost all the compounds were also potent against Gram-negative bacterial EC and PM and fungal CA strains.

3-[3,4-Dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-benzothiazol-2-yl) propanamide (**6c**), possessing weak antibacterial activity against Gram-positive and being non active against Gram-negative bacterial strains, showed strong antifungal activity for *C. albicans* and very strong for *A. niger* with inhibition zones of 17 and 26 mm correspondingly.

It can be concluded, that almost all synthesized compounds showed good selective antibacterial activity against Gram-negative *P. aeruginosa*, and benzothiazolyl derivative **6c** – against tested fungi.

### 2.2.4. *In vitro antitumour activity*

Cell cytotoxicity of the title compounds was tested on two monolayer tumour cell lines: HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), and normal mouse fibroblasts (NIH 3T3). The experimental evaluation of cytotoxic properties is presented in Table 5. Analysis of structure–activity data for the cytotoxic action clearly indicates the influence of the heterocyclic substituent nature on the *in vitro* toxic effect. Between thiazolyl (**5a**) and benzothiazolyl (**6a**) ethanamides, **6a** was more effective, exhibiting high cytotoxic effect concerning mouse hepatoma MG-22A and the moderate one concerning human fibrosarcoma HT-1080. Introduction of bulky substituent *p*-$CH_3O$–$C_6H_4$ at $C_4$ position of thiazolyl ring (compounds **5c** and **5f**) had a positive impact on antitumour properties of thiazolyl alkanamides in comparison with their unsubstituted analogues (**5a** and **5e**), which provided specificity concerning mouse hepatoma MG-22A cells, increasing the cytotoxicity up to 8.6 times for **5c**. Benzothiazolyl containing compounds **6a–c** revealed high cytoxicity concerning human fibrosarcoma HT-1080 or mouse hepatoma MG-22A. Compound **6b** possessed good cytotoxic properties, high NO-induction ability (MG-22A cell line) and was non-toxic compound ($LD_{50} = 1879$ mg $kg^{-1}$).

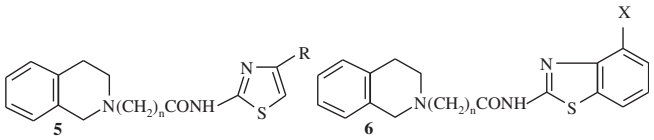
**Table 3**
*In vivo* anti-inflammatory activity (carrageenin mouse paw oedema inhibition, CPE) of compounds **5a**, **5c**, **5e** and **5f** and theoretically calculated lipophilicity (*c*log *P*).

**5**

| Compound | | | *c*log *P*[a] | CPE inhibition, % |
|---|---|---|---|---|
| No | *n* | R | | |
| **5a** | 1 | H | 2.543 | 70.4* |
| **5c** | 1 | *p*-MeOPh | 4.659 | 75.8* |
| **5e** | 2 | H | 2.777 | 62.4* |
| **5f** | 2 | *p*-MeOPh | 4.894 | 50.2* |
| Indomethacin | | | – | 57.2 |

*Differences in relation to control are statistically reliable at $P \leq 0.05$.
[a] Theoretically calculated values using the *c*log *P* program from Biobyte [56].

**Table 4**
*In vitro* antibacterial and antifungal activity data of compounds **5a–c**, **5e**, **5f** and **6a–c**.




| Compound | | | Diameter of zones showing complete inhibition of growth (mm)[a] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *SA* | | *BC* | | *EC* | | *PA* | | *PM* | | *CA* | | *AN* | |
| No | *n* | R or X | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 |
| **5a** | 1 | H | – | 13 | n | – | – | 12 | 11 | 19 | n | 12 | 12 | n | n | n |
| **5b** | 1 | Me | – | – | 10 | – | 9 | 11 | 16 | 18 | 14 | 9 | 11 | 9 | n | n |
| **5c** | 1 | *p*-MeOPh | 11 | 14 | 12 | – | – | 12 | 13 | 18 | – | 10 | 12 | 11 | n | n |
| **5e** | 2 | H | – | 14 | 14 | – | – | 12 | 12 | 17 | – | 14 | 11 | 11 | n | n |
| **5f** | 2 | *p*-MeOPh | – | 15 | n | – | – | 12 | 13 | 20 | n | 14 | – | n | n | n |
| **6a** | 1 | H | 12 | 9 | 9 | – | 11 | 12 | 16 | 18 | 12 | – | 11 | 12 | n | n |
| **6b** | 1 | Cl | 10 | 9 | 9 | – | 10 | 12 | 16 | 18 | 13 | 9 | 11 | 11 | n | n |
| **6c** | 2 | H | – | 8 | 9 | 9 | – | – | – | – | – | – | 13 | 17 | 26 | 15 |
| Gentamicin | | | 25 | 27 | 19 | 22 | 21 | 23 | 40 | 42 | 20 | 21 | n | n | n | n |
| Fluconazole | | | | | | | | | | | | | | | | |
| 2.0 mg ml$^{-1}$ | | | n | n | n | n | n | n | n | n | n | n | 10 | | | |
| | | | | | | | | | | | | | | | 11 | |
| 0.2 mg ml$^{-1}$ | | | n | n | n | n | n | n | n | n | n | n | – | | – | |

"–" ≤ 4 mm (no inhibition).
"n" – not-determined.
[a] Diameter of a ditch for substances – 7 mm.

Among the synthesized compounds, in general possessing moderate cytotoxicity, the specific action of some ones concerning tumour cell lines has been revealed. Thiazolyl (**5c**) and benzothiazolyl (**6a**) containing derivatives exhibited high cytotoxic activity against mouse hepatoma MG-22A (5/7 and 4/4 μg ml$^{-1}$, CV/MTT tests correspondingly). The elongation of alkyl chain length between tetrahydroisoquinolyl and thiazolyl moieties ($n$ = 1 for compounds **5a** and **5c**; $n$ = 2 for compounds **5e** and **5f**) led to cytotoxicity decrease from 21/60 to 45/65 μg ml$^{-1}$ against mouse hepatoma MG-22A in the case of compounds **5a** and **5e** without substituent in the $C_4$ position, and from 5/7 to 21/50 μg ml$^{-1}$ in the case of **5c** and **5f**, containing bulky $C_4$ substituent. The opposite effect was revealed against human fibrosarcoma HT-1080 for compounds **5a** and **5e**, when the cytotoxicity increased by up to 5 times with alkyl chain elongation (100/24 and 100/18 μg ml$^{-1}$, CV/MTT tests correspondingly).

It can be concluded, that all the compounds, to more or less extend, revealed selective cytotoxicity concerning examined tumour cells lines.

As a result of biological investigation of the synthesized *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides it was revealed, that the synthesized compounds were active in psychotropic *in vivo*, anti-inflammatory *in vivo*, antitumour *in vitro* and antimicrobial *in vitro* screening. Generally the high *in vivo* anti-inflammatory activity was combined with high *in vivo* psychotropic activity. For all the tested compounds the high *in vivo* anti-inflammatory activity was matched with moderate *in vitro* antimicrobial activity (either antibacterial or antifungal) and also with moderate ($LC_{50}$ = 18–21 μg/ml) or high ($LC_{50} \leq 5$ μg/ml) selective cytotoxicity against tumour cell lines according to CV or MTT tests. In the group of compounds, containing thiazole moiety, the moderate selective cytotoxicity ($LC_{50}$ = 18–41 μg/ml) was combined with moderate antimicrobial activity, but for all the compounds possessing benzothiazole residue the high selective cytotoxicity ($LC_{50}$ = 2–6 μg/ml) was accompanied by low antibacterial action and moderate or high antifungal activity.

### 2.3. X-ray crystallographic study

X-ray diffraction study was carried out for *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide (**6a**) to determine its conformational feature and possibility of molecular assembly. The crystal data and the refinement details are given in Table 6.

Table 7 lists the values of bond lengths and principal valence angles.

The molecular structure of compound **6a** is shown in Fig. 1.

Fig. 1 shows a perspective view of the molecular structure. There is the strong intramolecular hydrogen bond of N(14)–H···N(2) in the structure. The lengths of this bond is equal to 2.599(7) Å (N(2)···H = 1.85 Å, angle N(2)···H–N(14) = 132°). The hydrogen bond determines the molecular conformation: the torsion angle of N(2)–C(11)–C(12)–N(14) is 12.3(5)°. The atomic plane of C(11), C(12), O(13), N(14) is almost coplanar with benzothiazole system. The conformation for heterocycle of isoquinoline system is near to envelope. The deviation of the atom N(2) from the mean plane of C(1), C(3), C(4), C(10), C(11) is 0.693(5) Å.

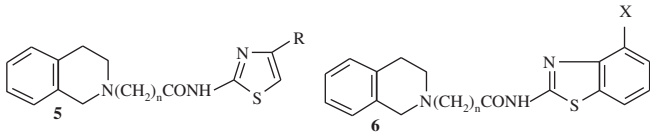
Fig. 2 illustrates the molecular packing of the crystal structure on the crystallographic plane *yz*. There are no intermolecular hydrogen bonds in the crystal structure. All the intermolecular contacts correspond to sums of van der Waals radii.

## 3. Conclusions

The study revealed, that the synthesized *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides, which combine two heterocyclic rings, tetrahydroisoquinoline and thiazole or benzothiazole, in one molecule were active in psychotropic *in vivo*, anti-inflammatory *in vivo*, antitumour *in vitro* and antimicrobial *in vitro* screening. Both *in vivo* anti-inflammatory and *in vivo* psychotropic activities were more expressed.

A dominant display was shown of a definite type of neurotropic properties depending on the nature of the heterocyclic fragment,

**Table 5**
*In vitro* antitumour activity and intracellular NO generation caused by compounds **5a–f** and **6a–c**.




| Compound/test | | | HT-1080 | | | MG-22A | | | NIH 3T3 | |
|---|---|---|---|---|---|---|---|---|---|---|
| No | *n* | R or X | $LC_{50}$ CV[a] | $LC_{50}$ MTT[b] | NO CV[c] | $LC_{50}$CV[a] | $LC_{50}$MTT[b] | NOCV[c] | $LC_{50}$NR[d] | $LD_{50}$, mg $kg^{-1}$ |
| **5a** | 1 | H | 100 | 100 | 18 | 21 | 60 | 38 | n | n |
| **5b** | 1 | Me | 96 | – | 17 | 41 | 42 | 54 | 158 | 948 |
| **5c** | 1 | *p*-MeOPh | 28 | 74 | 77 | 5 | 7 | 182 | 59 | 723 |
| **5d** | 1 | *p*-MeOPh, HCl | 76 | 1 | 22 | 58 | 73 | 23 | n | n |
| **5e** | 2 | H | 24 | 18 | 550 | 45 | 65 | 6 | n | n |
| **5f** | 2 | *p*-MeOPh | 40 | 20 | 114 | 21 | 50 | 133 | n | n |
| **6a** | 1 | H | 34 | 28 | 100 | 4 | 4 | 90 | 37 | 517 |
| **6b** | 1 | Cl | 6 | 10 | 20 | >100 | 10 | 233 | 600 | 1879 |
| **6c** | 2 | H | 2 | 12 | 100 | 10 | 9 | 33 | 15 | 371 |

n – non-determined.
"–" no cytotoxic effect.
[a] Concentration (μg/ml) providing 50% cell killing effect (CV:coloration).
[b] Concentration (μg/ml) providing 50% cell killing effect (MTT:coloration).
[c] NO concentration (CV:coloration), determined according to Ref. [59].
[d] Concentration (μg/ml) providing 50% cell killing effect (NR:coloration).

alkyl chain length between two heterocycles and also on the presence of a substituent in the $C_4$ position of the molecule. All the synthesized compounds revealed marked anticonvulsive properties. Antiphenamine action was mostly expressed for thiazolyl propanamide derivatives.

Anti-inflammatory effect of the tested compounds surpassed the same one of indomethacin, and alkyl chain length between two heterocycle moieties was essential for its display. The manifestation of anti-inflammatory properties of the tested compounds was combined with their moderate antibacterial and high antifungal properties. It has been revealed, that 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-[4-(*p*-methoxy)phenyl-1,3-thiazol-2-yl]ethanana-mide, which possessed the highest anti-inflammatory activity among thiazolyl derivatives, was also potent selective cytotoxic agent against mouse hepatoma cell line. Some specific combinations of types of activities for the synthesized compounds have been revealed. The data obtained show the expediency of the chosen approach to the construction of new biologically active substances.

**Table 6**
The main crystallographic and structure refinement data of compound **6a**.

| | |
|---|---|
| Brutto-formula | $C_{18}H_{17}N_3OS$ |
| Formula weight | 323.418 |
| Crystal description | Prism (0.12 × 0.17 × 0.28 mm) |
| Crystal system | Orthorhombic |
| Space group | *P* 21 *n b* |
| *Cell dimensions* [Å]: | |
| *a* | 4.8526(2) |
| *b* | 13.0104(5) |
| *c* | 25.6052(12) |
| Unit cell volume [$Å^3$] | 1616.6(1) |
| Molecular multiplicity (*Z*) | 4 |
| Crystal density [g $cm^{-3}$] | 1.329 |
| F(000) | 680 |
| Absorption coefficient [$mm^{-1}$] | 0.208 |
| Maximum 2$\theta$ (°) | 52.0 |
| Total number of reflections | 3046 |
| Number of reflections with $I > 2\sigma(I)$ | 1736 |
| Number of refined parameters | 208 |
| Final *R*-factor | 0.0669 |

## 4. Experimental

### 4.1. Chemistry

$^1H$ and $^{13}C$ NMR spectra were recorded on Varian Mercury 200 or 400 (200 and 50 MHz or 400 and 100 MHz correspondingly) at 303 K with $CDCl_3$ as a solvent using hexamethyldisiloxane (HMDSO) as internal standard. Mass spectra under electron impact conditions were recorded on a Agilent Technologies mass-spectrometer 5975C (GC 7890A, 70 eV) and on Waters mass-spectrometer 3100 (LC Alliance Waters 2695). Infrared spectra (films as Nujol mulls) were recorded with Shimadzu IR Prestige-21.

**Table 7**
The main bond lengths (Å) and angles (°) of compound **6a**.

| Main bond lengths (Å) | | Principal valence angles (°) | |
|---|---|---|---|
| C(1)–N(2) | 1.472(8) | N(2)–C(1)–C(9) | 110.6(6) |
| N(2)–C(3) | 1.480(9) | C(1)–N(2)–C(3) | 110.5(5) |
| C(3)–C(4) | 1.532(11) | C(1)–N(2)–C(11) | 111.6(5) |
| C(5)–C(6) | 1.425(13) | C(3)–N(2)–C(11) | 112.6(5) |
| C(6)–C(7) | 1.379(13) | N(2)–C(3)–C(4) | 107.6(6) |
| C(8)–C(9) | 1.400(10) | C(3)–C(4)–C(10) | 112.8(6) |
| C(11)–C(12) | 1.515(9) | N(2)–C(11)–C(12) | 112.3(6) |
| C(12)–N(14) | 1.359(9) | C(11)–C(12)–O(14) | 124.4(6) |
| C(15)–S(16) | 1.751(6) | O(13)–C(12)–N(14) | 123.5(6) |
| S(16)–C(17) | 1.752(7) | C(12)–N(14)–C(15) | 128.6(5) |
| C(17)–C(22) | 1.394(10) | N(14)–C(15)–S(16) | 121.7(4) |
| C(19)–C(20) | 1.367(11) | N(14)–C(15)–N(23) | 120.2(5) |
| C(21)–C(22) | 1.410(10) | S(16)–C(15)–N(23) | 118.1(5) |
| C(1)–C(9) | 1.510(11) | C(15)–S(16)–C(17) | 87.7(3) |
| N(2)–C(11) | 1.463(9) | C(15)–N(23)–C(22) | 109.0(6) |
| C(4)–C(10) | 1.516(11) | | |
| C(5)–C(10) | 1.378(11) | | |
| C(8)–C(7) | 1.378(11) | | |
| C(9)–C(10) | 1.408(10) | | |
| C(12)–O(13) | 1.214(9) | | |
| N(14)–C(15) | 1.385(8) | | |
| C(17)–C(18) | 1.281(8) | | |
| C(18)–C(19) | 1.382(9) | | |
| C(20)–C(21) | 1.384(11) | | |
| C(20)–C(21) | 1.377(10) | | |
| C(22)–N(23) | 1.393(8) | | |

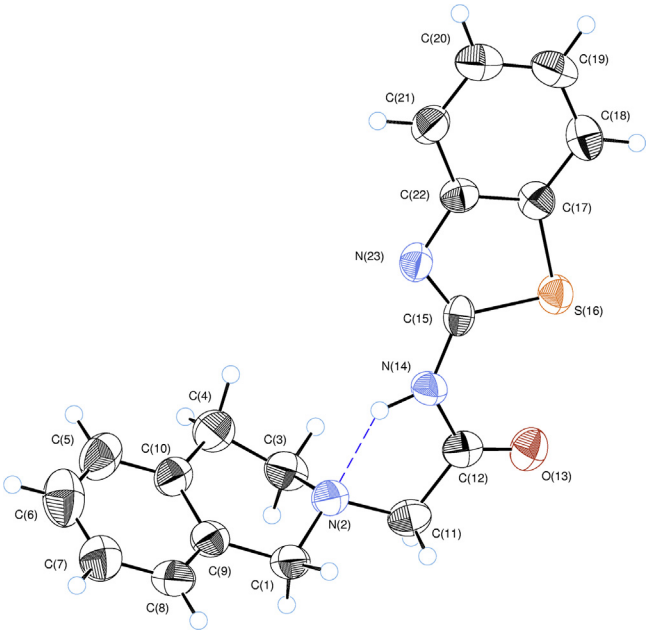



**Fig. 1.** Molecular structure of *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide (**6a**).

Nonius KappaCCD was used for X-ray crystallographic study. Elemental analyses (C, H, N) were performed on CARLO ERBA 1108 elemental analyzer. Melting points were determined on a Boetius melting point apparatus and were taken uncorrected.

Analytical thin-layer chromatography was performed on 60 $F_{254}$ Merck silica gel plates and Macherey–Nagel silica gel plastic plates, with visualization under UV (254 nm). Column chromatography was performed using Merck silica gel (0.040–0.063 nm). Solvents and reagents were purchased from Acros and Sigma–Aldrich Corporation.

#### *4.1.1. General procedure for the synthesis of 2-chloro-N-[1,3-(benzo)thiazol-2-yl]ethanamides (**3a**–**e**) and 3-chloro-N-[1,3-(benzo)thiazol-2-yl]propanamides (**4a**–**c**) [54]*

To a solution of 2-aminothiazole or 2-aminobenzothiazole, 4-substituted 2-aminothiazole or 2-aminobenzothiazole (0.025 mol) in dry benzene a cooled solution of chloroacetyl or 3-chloropropionyl chloride (0.041 mol) in dry benzene (9 ml) was added dropwise. The reaction mixture was stirred for 3 h at reflux temperature, and then solvent and surplus of chloroacetyl or 3-chloropropionyl chloride were removed in vacuum. The residue was washed with 5% aqueous sodium bicarbonate solution followed by cold water. The crude product was dried and crystallized from ethanol.

#### *4.1.2. 2-[3,4-Dihydroisoquinolin-2(1H)-yl]-N-(1,3-thiazol-2-yl) ethanamide (**5a**)*

Three different procedures (A, B and C) were used for the synthesis of compound **5a**.

(A): A mixture of 1,2,3,4-tetrahydroisoquinoline (182 mg, 1.37 mmol), 2-chloro-*N*-(1,3-thiazol-2-yl)ethanamide **3a** (241 mg, 1.37 mmol) and triethylamine (1 ml) in benzene (6 ml) was heated at 65–75 °C for 4 h. The formed precipitate was isolated by filtration. The solvent from filtrate was removed by distillation and the residue was washed with hexane and dried to afford **5a** (116 mg, 31%) as a light beige powder. M.p. 63–65 °C. IR, $\nu$ $cm^{-1}$: 1687 (C=O), 1527 (N–H), 1276 (C–N). $^1$H NMR, $\delta$ ppm: 2.8–3.2 (m, 4H, 3′,4′-$CH_2$), 3.42 (s, 2H, $COCH_2N$), 3.80 (s, 2H, 1′-$CH_2N$), 6.98 (d, $J$ = 3.6 Hz, 1H, 5-CH), 7.0–7.2 (m, 4H, ArH), 7.42 (d, $J$ = 3.7 Hz, 1H, 4-CH), 10.4 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.88 (4′-$CH_2$), 51.52, 56.02 (1′,3′-$CH_2N$), 60.73 ($COCH_2N$), 113.62 (5-C), 125.91, 126.39, 126.60, 128.73 (5′,6′,7′,8′-Ar), 133.22, 133.32 (9′,10′-Ar), 137.51 (4-C), 157.39 (2-C), 168.47 (CO). LC–MS, $m/z$ (%): 273 ($M^+$, 20), 173 ($M^+$–thiazole–NH, 20), 146 ($M^+$–thiazole–NHCO (100). Anal. calcd for $C_{14}H_{15}N_3OS$: C 61.51, H 5.53, N 15.37, S 11.73. Found: C 61.20, H 5.47, N 15.28, S 11.61.

(B): A mixture of 2-chloro-*N*-(1,3-thiazol-2-yl)ethanamide **3a** (220 mg, 1.25 mmol) and 1,2,3,4-tetrahydroisoquinoline (197 mg, 1.48 mmol) in absolute ethanol (10 ml) was heated at 70 °C until clear solution was obtained. Then anhydrous potassium carbonate (314 mg, 2.96 mmol) was added, and the reaction mixture was stirred under heating for 12 h, cooled to room temperature and washed with 5% sodium bicarbonate solution (20 ml). The product was extracted from water solution with chloroform (3 × 10 ml), and the organic layer was dried over sodium sulphate and concentrated under reduced pressure, and the crude product was purified by column chromatography on silica-gel using chloroform/methanol (100:1) as eluent to afford **5a** (82 mg, 24%) as light beige powder.

(C): A mixture of 2-chloro-*N*-(1,3-thiazol-2-yl)ethanamide **3a** (220 mg, 1.25 mmol) and 1,2,3,4-tetrahydroisoquinoline (415 mg, 3.12 mmol) in benzene (12 ml) was heated for 8 h in a water bath. After that, the mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure, and the residue was treated with hexane to afford pure **5a** (150 mg, 44%) as light beige powder.

#### *4.1.3. 2-[3,4-Dihydroisoquinolin-2(1H)-yl]-N-(4-methyl-1,3-thiazol-2-yl)ethanamide (**5b**)*

*Procedure* C. Crude product was purified by column chromatography using ethyl acetate as eluent to afford pure **5b**. Yield 51%, light beige crystalline powder, m.p. 128–130 °C. IR, $\nu$ $cm^{-1}$: 1700 (C=O), 1527 (N–H), 1263 (C–N). $^1$H NMR, $\delta$ ppm: 2.10 (3H, s, 4-$CH_3$), 2.9–3.0 (m, 4H, 3′,4′-$CH_2$), 3.41 (s, 2H, $COCH_2N$), 3.78 (s, 2H, 1′-$CH_2N$), 6.52 (s, 1H, 5-CH), 7.0–7.2 (m, 4H, ArH), 10.4 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 16.97 ($CH_3$), 26.95 (4′-$CH_2$), 51.55, 56.12 (1′,3′-$CH_2N$), 60.85 ($COCH_2N$), 108.14 (5-C), 125.97, 126.46, 126.68, 128.77 (5′,6′,7′,8′-Ar), 133.28, 133.37 (9′,10′-Ar), 147.23 (4-C), 156.72 (2-C), 168.50 (CO).

Anal. calcd for $C_{15}H_{17}N_3OS$: C 62.69, H 5.96, N 14.62, S 11.16. Found: C 62.70, H 6.01, N 14.67, S 11.10.

#### *4.1.4. 2-[3,4-Dihydroisoquinolin-2(1H)-yl]-N-[4-(p-methoxy) phenyl-1,3-thiazol-2-yl]ethanamide (**5c**)*

*Procedure* C. Yield 80%, orange-coloured crystalline powder, m.p. 124–125 °C. IR, $\nu$ $cm^{-1}$: 1685 (C=O), 1538 (N–H), 1249 (C–N). $^1$H NMR, $\delta$ ppm: 2.9–3.0 (m, 4H, 3′,4′-$CH_2$), 3.44 (s, 2H, $COCH_2N$), 3.82 (m, 5H, $OCH_3$ + 1′-$CH_2N$), 6.91 (d, $J$ = 8.0 Hz, 2H, PhH), 6.99 (s, 1H, 5-CH), 7.0–7.2 (m, 4H, ArH), 7.72 (d, $J$ = 8.0 Hz, 2H, PhH), 10.4 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.79 (4′-$CH_2$), 51.51, 55.98 (1′,3′-$CH_2N$), 55.26 ($OCH_3$), 60.71 ($COCH_2N$), 105.96 (5-C), 113.99 (*m*-Ph), 125.98, 126.48, 126.65, 128.77 (5′,6′,7′,8′-Ar), 127.29 (*o*-Ph), 133.29, 133.37 (9′,10′-Ar), 149.79 (4-C), 156.89 (2-C), 159.44 (*p*-Ph), 168.51 (CO). Anal. calcd for $C_{21}H_{21}N_3O_2S$: C 66.47, H 5.58, N 11.07, S 8.45. Found: C 66.10, H 5.52, N 11.01, S 8.41.

#### *4.1.5. 2-[3,4-Dihydroisoquinolin-2(1H)-yl]-N-[4-(p-methoxy) phenyl-1,3-thiazol-2-yl]ethanamide hydrochloride (**5d**)*

The product was isolated from the reaction mixture when the reaction was carried out analogously to procedure B without the work up by potassium carbonate. Yield 31%, light orange-coloured crystalline powder, m.p. 135–137 °C. IR, $\nu$ $cm^{-1}$: 1684 (C=O), 1539 (N–H), 1248 (C–N). $^1$H NMR, $\delta$ ppm: 2.9–3.0 (m, 4H, 3′,4′-$CH_2$), 3.43 (s, 2H, $COCH_2N$), 3.82 (m, 5H, $OCH_3$ + 1′-$CH_2N$), 6.90 (d, $J$ = 8.9 Hz,

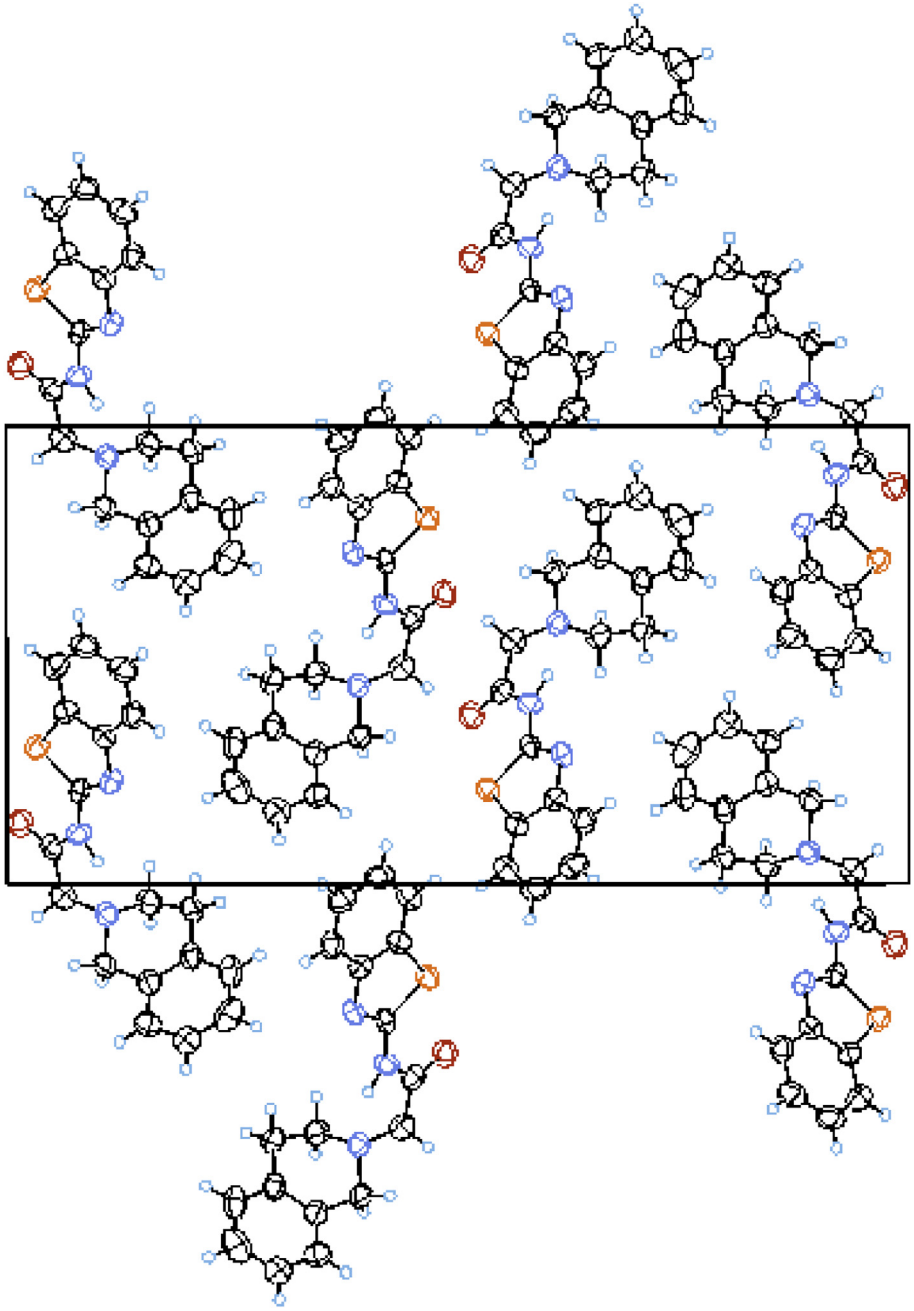


**Fig. 2.** Molecular packing of the crystal structure of *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide (**6a**).

2H, PhH), 6.99 (s, 1H, 5-CH), 7.0–7.2 (m, 4H, ArH), 7.72 (d, $J = 8.9$ Hz, 2H, PhH), 10.4 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$, ppm: 28.90 (4′-$CH_2$), 51.55, 56.07 (1′,3′-$CH_2$N), 55.25 ($OCH_3$), 60.89 ($COCH_2$N), 105.94 (5-C), 113.99 (*m*-Ph), 125.96, 126.48, 126.62, 128.78 (5′,6′,7′,8′-Ar), 127.28 (*o*-Ph), 133.30, 133.45 (9′,10′-Ar), 149.80 (4-C), 156.86 (2-C), 159.41 (*p*-Ph), 168.68 (CO). Anal. calcd for $C_{21}H_{22}ClN_3O_2S$: C 60.64, H 5.33, N 10.10, S 7.71. Found: C 60.97, H 5.26, N 10.17, S 7.81.

#### 4.1.6. 3-[3,4-Dihydroisoquinolin-2(1H)-yl]-N-(1,3-thiazol-2-yl) propanamide (**5e**)

*Procedure* C. Yield 87%, light yellow powder, m.p. 125–127 °C. IR, $\nu$ cm$^{-1}$: 1710 (C=O), 1543 (N–H), 1280 (C–N). $^1$H NMR, $\delta$ ppm: 2.73 (t, $J = 6.3$ Hz, 2H, $COCH_2$), 2.9–3.0 (m, 4H, 3′,4′-$CH_2$), 3.01 (t, $J = 6.2$ Hz, 2H, $CH_2$N), 3.83 (s, 2H, 1′-$CH_2$N), 6.90 (d, $J = 3.8$ Hz, 1H, 5-CH), 7.0–7.2 (m, 4H, ArH), 7.36 (d, $J = 3.9$ Hz, 1H, 4-CH), 12.3 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.57 (4′-$CH_2$), 32.00 ($COCH_2$), 50.39, 52.97, 54.90 (1′,3′,$\alpha$-$CH_2$N), 113.28 (5-C), 125.93, 126.47, 126.52, 128.76 (5′,6′,7′,8′-Ar), 133.16, 133.74 (9′,10′-Ar), 137.28 (4-C), 158.24 (2-C), 169.93 (CO). Anal. calcd for $C_{15}H_{17}N_3OS$: C 62.69, H 5.96, N 14.62, S 11.16. Found: C 62.41, H 5.96, N 14.53, S 11.12.

#### 4.1.7. 3-[3,4-Dihydroisoquinolin-2(1H)-yl]-N-[4-(p-methoxy) phenyl-1,3-thiazol-2-yl]propanamide (**5f**)

*Procedure* C. Yield 52%, white crystalline powder, m.p. 125–127 °C. IR, $\nu$ cm$^{-1}$: 1684 (C=O), 1539 (N–H), 1248 (C–N). $^1$H NMR, $\delta$ ppm: 2.65 (t, $J = 6.0$ Hz, 2H, $COCH_2$), 2.90 (m, 4H, 3′,4′-$CH_2$), 3.05 (t, $J = 6.0$ Hz, 2H, $CH_2$N), 3.78 (s, 2H, 1′-$CH_2$N), 3.79 (s, 3H, $OCH_3$), 6.87 (d, $J = 8.8$ Hz, 2H, PhH), 6.93 (s, 1H, 5-CH), 7.05–7.2 (m, 4H,

ArH), 7.67 (d, $J$ = 8.8 Hz, 2H, PhH), 12.1 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.73 (4′-$CH_2$), 31.82 ($COCH_2$), 50.55, 53.06, 54.71 (1′,3′,α-$CH_2N$), 55.25 ($OCH_3$), 105.55 (5-C), 113.90 (*m*-Ph), 125.91, 126.46, 126.56, 128.72 (5′,6′,7′,8′-Ar), 127.19 (*o*-Ph), 133.29, 133.88 (9′,10′-Ar), 149.45 (4-C), 157.45 (2-C), 159.37 (*p*-Ph), 170.13 (CO). Anal. calcd for $C_{22}H_{23}N_3O_2S$: C 67.15, H 5.89, N 10.68, S 8.15. Found: C 66.90, H 5.85, N 10.65, S 8.10.

#### 4.1.8. *N-(1,3-Benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1H)-yl]ethanamide (**6a**)*

*Procedure* A. Yield 47%, light yellow powder, m.p. 132–134 °C. IR, $\nu$ cm$^{-1}$: 1702 (C=O), 1530 (N–H), 1267 (C–N). $^1$H NMR, $\delta$ ppm: 2.9–3.0 (m, 4H, 3′,4′-$CH_2$), 3.47 (s, 2H, $COCH_2N$), 3.83 (s, 2H, 1′-$CH_2N$), 7.0–7.2 (m, 4H, ArH), 7.33 (t, $J$ = 8.5 Hz, 1H, 6-H), 7.43 (t, $J$ = 8.0 Hz, 1H, 5-H), 7.74 (d, $J$ = 8.1 Hz, 1H, 7-H), 7.81 (d, $J$ = 7.8 Hz, 1H, 4-H), 10.45 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.88 (4′-$CH_2$), 51.64, 56.10 (1′,3′-$CH_2N$), 60.85 ($COCH_2N$), 121.03, 121.38, 123.98, 126.22 (4,5,6,7-Ar), 126.02, 126.46, 126.77, 128.79 (5′,6′,7′,8′-Ar); 132.21, 133.18 (9′,10′-Ar), 148.45 (8,9-Ar); 157.06 (2-C), 169.25 (CO). Anal. calcd for $C_{18}H_{17}N_3OS$: C 66.85, H 5.30, N 12.99, S 9.91. Found: C 66.52, H 5.26, N 12.91, S 9.85.

#### 4.1.9. *N-(4-Chloro-1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1H)-yl]ethanamide (**6b**)*

*Procedure* C. Yield 63%, light beige powder, m.p. 124–126 °C. IR, $\nu$ cm$^{-1}$: 1686 (C=O), 1536 (N–H), 1216 (C–N). $^1$H NMR, $\delta$ ppm: 2.9–3.0 (m, 4H, 3′,4′-$CH_2$), 3.47 (s, 2H, $COCH_2N$), 3.80 (s, 2H, 1′-$CH_2N$), 7.0–7.2 (m, 4H, ArH), 7.24 (t, $J$ = 8.0 Hz, 1H, 6-H), 7.45 (d, $J$ = 8.0 Hz, 1H, 5-H), 7.71 (d, $J$ = 8.5 Hz, 1H, 7-H), 10.6 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.57 (4′-$CH_2$), 51.36, 56.08 (1′,3′-$CH_2N$), 60.91 ($COCH_2N$), 119.93, 124.48 (4,5,6,7-Ar), 125.99, 126.42, 126.70, 128.77 (5′,6′,7′,8′-Ar), 133.10, 133.61 (9′,10′-Ar), 145.58 (8,9-Ar), 157.97 (2-C), 169.74 (CO). Anal. calcd for $C_{18}H_{16}N_3ClOS$: C 60.41, H 4.51, N 11.74, S 8.96. Found: C 60.55, H 5.52, N 11.67, S 8.89.

#### 4.1.10. *N-(1,3-Benzothiazol-2-yl)-3-[3,4-dihydroisoquinolin-2(1H)-yl]propanamide (**6c**)*

*Procedure* C. Yield 63%, light beige powder, m.p. 123–125 °C. IR, $\nu$ cm$^{-1}$: 1686 (C=O), 1536 (N–H), 1216 (C–N). $^1$H NMR, $\delta$ ppm: 2.75 (t, $J$ = 5.7 Hz, 2H, $COCH_2$), 2.97 (m, 4H, 3′,4′-$CH_2$), 3.08 (t, $J$ = 5.7 Hz, 2H, $CH_2N$), 3.87 (s, 2H, 1′-$CH_2N$), 7.1–7.2 (m, 4H, ArH), 7.24 (t, $J$ = 9.0 Hz, 1H, 6-H), 7.37 (t, $J$ = 9.0 Hz, 1H, 5-H), 7.71 (d, $J$ = 9.1 Hz, 1H, 7-H), 7.77 (d, $J$ = 8.6 Hz, 1H, 4-H), 10.5 (bs, 1H, NHCO). $^{13}$C NMR, $\delta$ ppm: 28.43 (4′-$CH_2$); 31.90 ($COCH_2$), 50.34, 52.78, 54.77 (1′,3′,α-$CH_2N$), 121.00, 121.19, 123.57, 125.89, 126.04, 126.57, 126.61, 128.81, 132.32, 133.01, 133.82, 148.72, 157.45 (2-C), 170.75 (CO). GC–MS, *m*/*z* (%): 205 ($M^+$–tetrahydroisoquinoline, 9), 177 ($M^+$–tetrahydroisoquinoline–$CH_2CH_2$, 9), 150 ($M^+$–tetrahydroisoquinoline–$CH_2CH_2CO$, 100). LC–MS, *m*/*z* (%): 338 ($M^+ + 1$, 100). Anal. calcd for $C_{19}H_{19}N_3OS$: C 67.63, H 5.68, N 12.45, S 9.50. Found: C 66.64, H 5.73, N 12.12, S 9.32.

### 4.2. Biological activity assays

#### 4.2.1. *In vivo psychotropic activity assays*

The neurotropic activity of the synthesized compounds was studied in ICR female mice of 6 weeks old weighing 19–26 g in winter season. The animals, bred in our laboratory, were housed under standard conditions (cage size 43 × 27 × 15 cm). Our studies were in accordance with recognized guidelines on animal experimentation. The room temperature was maintained within the limits of 22 ± 2 °C, relative humidity of 55 ± 15%, air ventilation of 15–20 air volume change/h and 12 h (7:00–19:00) light/dark cycle. The litter was from "Basic micro" (The Netherlands) and food from "Lactamin" (Sweden). Food pellets and water were available *ad libitum* during maintenance.

The aqueous suspensions of tested compounds, prepared with the addition of two drops of Twin 80, were administered intraperitoneally 30 min before carrying out the experiment. The same volume of the sodium chloride isotonic solution was injected into the control animals. Comparative assessment of the action of the substance being investigated at a dose of 5 mg kg$^{-1}$ was carried out on groups of 6 animals on indicators of hexenal narcosis, phenamine hyperactivity and corazole spasm.

The action of the substances on the central nervous system was assessed by its effect on: a) the body temperature, (the criterion for the test was a lowering of the temperature by 3 °C and more); b) antispasmodic activity on spasms caused by the intravenous titration with 1% corazole solution at a rate of 0.01 ml/s; c) duration of the hexenal anaesthesia (0.4% hexenal solution at 70 mg kg$^{-1}$, intravenously) and ethanol narcosis (4 g kg$^{-1}$, intraperitoneally); d) locomotor activity and body temperature, measuring the rectal temperature with an electric thermometer, on joined action of amphetamine (0.4% amphetamine solution at 10 mg kg$^{-1}$, subcutaneously). The experimental data were processed statistically. The mean values of $ED_{50}$ for 12–25 observations were determined by the express method given in Ref. [60]. For assessing the mean duration of anaesthetic effect of hexenal, phenamine hyperactivity and degree of hypothermia, protective action in the corasole spasm test, the arithmetical mean values and their standard deviations (M ± m) in comparison with the appropriate control data were calculated. Assessment of the significance of the differences between the mean values was carried out on the basis of the Student criterion. Differences were regarded as significant at a level of probability $P \leq 0.5$.

#### 4.2.2. *In vivo anti-inflammatory activity assays*

The experiment was carried out according to the carrageenin-induced mouse paw oedema inhibition assay [26,55]. Oedema was induced in the right hind paw of AKR or A mice (20–30 g months old) by the intradermal injection of 0.05 ml of 2% carrageenin in water. Both sexes were used. Females pregnant were excluded. Each group consisted of 10 animals. The animals, bred in our laboratory, were housed under standard conditions and received a diet of commercial food pellets and water *ad libitum* during maintenance, but they were entirely fasted during the experiment period. Our studies were in accordance with recognized guidelines on animal experimentation. The tested compounds, 0.2 mmol kg$^{-1}$ body weight, were diluted (HCl salt) or suspended in water with few drops of Tween 80 and ground in a mortar before use and were administered intraperitoneally simultaneously with the carrageenin injection. The mice were euthanized 3.5 h after carrageenin injection. The difference between the weight of the injected and uninjected paws was calculated for each animal. The change in paw weight was compared with that in control animals (treated with water) and expressed as percent inhibition of the oedema, CPE values % (Table 3). Indomethacin, at 0.1 mmol kg$^{-1}$ (57.2%) was used as a reference compound. Assessment of the significance of the differences between the mean values was carried out on the basis of the Student criterion. Differences were regarded as significant at a level of probability $P \leq 0.5$.

#### 4.2.3. *In vitro antimicrobial activity assays*

For the determination of antimicrobial activity several reference microbial strains, received from the Microbial Strain Collection of Latvia (MSCL), Riga, Latvia, were used: *S. aureus* MSCL 334 (*SA*), *B. cereus* MSCL 330 (*BC*), *P. mirabilis* MSCL 590 (*PM*), *E. coli* MSCL 332 (*EC*), *P. aeruginosa* MSCL 331 (*PA*) and *C. albicans* MSCL 378 (*CA*) and

*A. niger* MSCL 324 (*AN*). All bacteria were cultivated on Plate count agar (Sanofi Diagnostics Pasteur, France) at 37 °C for 24 h. *C. albicans* was cultivated on Difco™ Malt extract agar (Becton, Dickinson and Company, UK) at 37 °C for 48 h. Antimicrobial activity was determined by agar well diffusion method [57]. The agar diffusion test was performed on Mueller–Hinton (Carl Roth GmbH + Co. KG, Germany) agar for bacteria and Malt extract agar for yeast. Suspensions of 18–24 h microbial cultures of turbidity $A_{540} = 0.16 \pm 0.20$ were used and uniformly spread on the Petri plates. Aliquots of 70 μl of each test-sample solution in dimethylsulfoxide, corresponding solvent and reference antimicrobial drugs solutions were added to 6.0 μm diameter agar wells. Gentamicin (KRKA, Slovenia) and fluconazole (Diflucan, Pfizer Ltd., UK), 10 mg $ml^{-1}$ and 5 mg $ml^{-1}$, were used as reference antibiotics. The antimicrobial activity was taken on the basis of diameter of zone of inhibition. After incubation at 37 °C for 24 h for bacteria and 48 h for yeast under aerobic conditions, the diameter of the clear zone (no growth) around the well in the bacterial lawn was measured. The inhibition zone diameter was measured in millimetres (mm). The tests were performed in duplicate. The final results were expressed as the arithmetic average. The observed zones of growth inhibition are presented in Table 4.

#### 4.2.4. *In vitro antitumour activity assays*

Monolayer tumour cell lines HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and normal mouse fibroblasts (NIH 3T3) were cultivated for 72 h in DMEM (Dulbecco's modified Eagle's medium) standard medium (Sigma) without an indicator and antibiotics [61]. Tumour cell lines were taken from the European Collection of Cell Culture (ECACC). After the ampoule was thawed not more than four passages were performed. The control cells and cells with tested substances in the range of $2–5 \times 10^4$ cells $ml^{-1}$ concentration (depending on line nature) were placed on a separate 96 wells plates. The volume of each plate was 200 μl. Solutions containing test compounds were diluted and added in wells to give the final concentrations of 50, 25, 12.5 and 6.25 μg/ml. Control cells were treated in the same manner only in the absence of test compounds. The plates were incubated for 72 h, 37 °C, 5% $CO_2$. The number of survived cells was determined using tris(4-dimethylaminophenyl)methyl chloride (crystal violet: CV) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) coloration which was assayed by multiscan spectrophotometer. The quantity of alive cells on the control plate was taken in calculations for 100% [59,61]. The $LC_{50}$ was calculated using Graph Pad Prism® 3.0 program, $r < 0.05$. Concentration of NO was determined according to procedure described in Fast et al. [59].

### 4.3. *X-ray crystallographic analysis*

Intensity data for compound **6a** (CCDC 907303; CCDC ID: AI631510) were collected at 293 K on a Nonius KappaCCD diffractometer for a colourless crystals using Mo-radiation (wavelength is 0.71073 Å). The main crystallographic and structure refinement data are given in Table 6. Programs used: SIR-97, SHELXL97 [62,63].

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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.2013.10.008.

## References

[1] K. Taori, V.J. Paul, H. Luesch, Structure and activity of largazole, a potent antiproliferative agent from the Floridian marine cyanobacterium Symploca sp, J. Am. Chem. Soc. 130 (2008) 1806–1807.
[2] F. Sasse, H. Steinmetz, G. Hofle, H. Reichenbach, Archazolids, new cytotoxic macrolactones from *Archangium gephyra* (myxobacteria), production, isolation, physico-chemical and biological properties, J. Antibiot. 56 (2003) 520–525.
[3] S. Kehraus, G.M. Koenig, A.D. Wright, Leucamide A: a new cytotoxic heptapeptide from the Australian sponge Leucetta microraphis, J. Org. Chem. 67 (2002) 4989–4992.
[4] K. Gerth, N. Bedorf, G. Hofle, H. Irschik, H. Reichenbach, Antifungal and cytotoxic compounds from *Sorangium cellulosum* (Myxobacteria) – production, physico-chemical and biological properties, J. Antibiot. 49 (1996) 560–563.
[5] B. Holla, K. Malini, B. Rao, B. Sarojini, N. Kumari, Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents, Eur. J. Med. Chem. 38 (2003) 313–318.
[6] R.G. Kalkhambkar, G.M. Kulkarni, G. Shivkumar, R. Nagendra Rao, Synthesis of novel triheterocyclic thiazoles as anti-inflammatory and analgesic agents, Eur. J. Med. Chem. 42 (2007) 1272–1276.
[7] P.K. Sharma, S.N. Sawnhney, A. Gupta, G.B. Sing, S. Bani, Synthesis and anti-inflammatory activity of some 3-(2-thiazolyl)-1,2-benzisothiazoles, Indian J. Chem. 37B (1998) 376–381.
[8] S. Bondock, W. Fadaly, M.A. Metwally, Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety, Eur. J. Med. Chem. 45 (2010) 3692–3701.
[9] P. Karegoudar, M.S. Karthikeyan, D.J. Prasad, M. Mahalinga, B.S. Holla, N.S. Kumari, Synthesis of some novel 2,4-disubstituted thiazoles as possible antimicrobial agents, Eur. J. Med. Chem. 43 (2008) 261–267.
[10] G. Turan-Zitouni, S. Demirayak, A. Özdemir, Z.A. Kaplancıklı, M.T. Yıldız, Synthesis of some 2-[(benzazole-2-yl)thioacetylamino]thiazole derivatives and their antimicrobial activity and toxicity, Eur. J. Med. Chem. 39 (2004) 267–272.
[11] B.K. Sarojini, B.G. Krishna, C.G. Darshanraj, B.R. Bharath, H. Manjunatha, Synthesis, characterization, in vitro and molecular docking studies of new 2,5-dichloro thienyl substituted thiazole derivatives for antimicrobial properties, Eur. J. Med. Chem. 45 (2010) 3490–3496.
[12] S.K. Bharti, G. Nath, R. Tilak, S.K. Singh, Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring, Eur. J. Med. Chem. 45 (2010) 651–660.
[13] A. Andreani, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, Synthesis and antitubercular activity of imidazo[2,1-*b*]thiazoles, Eur. J. Med. Chem. 36 (2001) 743–746.
[14] G.W.A. Milne (Ed.), Ashgate Handbook of Antineoplastic Agents, Gower Publishing Ltd, Hampshire, 2000.
[15] H. Liebig, H. Pfetzing, A. Grafe, Experimental results with purposely synthesized substances for antiviral chemotherapy. 2. Additional 2-amino-4-phenylthiazoles, tetrahydrobenzthiazoles, 4-phenylimidazoles, and 8-hydroxyquinolines, Arzneim. Forsch. 24 (1974) 887–892.
[16] G. Wells, T.D. Bradshaw, P. Diana, A. Seaton, D.-F. Shi, A.D. Westwell, M.F.G. Stevens, The synthesis and antitumour activity of benzothiazole substituted quinol derivatives, Bioorg. Med. Chem. Lett. 10 (2000) 513–515.
[17] Y. Kumar, R. Green, D.S. Wise, L.L. Wotring, L.B. Townsend, Synthesis of 2,4-disubstituted thiazoles and selenazoles as potential antifilarial and antitumour agents. 2-arylamido and 2-alkylamido derivatives of 2-amino-4-(isothiocyanatomethyl)thiazole and 2-amino-4-(isothiocyano-methyl)selenazole, J. Med. Chem. 36 (1993) 3849–3852.
[18] H.I. El-Subbagh, A.M. Al-Obaid, 2,4-Disubstituted thiazoles II. A novel class of antitumor agents, synthesis and biological evaluation, Eur. J. Med. Chem. 31 (1996) 1017–1021.
[19] A. Andreani, M. Granaiola, M. Guardigli, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, A. Roda, Synthesis and chemiluminescent high throughput screening for inhibition of acetylcholinesterase activity by imidazo[2,1-*b*]thiazole derivatives, Eur. J. Med. Chem. 40 (2005) 1331–1334.
[20] X.Y. Yu, J.M. Hill, G. Yu, W. Wang, A.F. Kluge, P. Wendler, P. Gallant, Synthesis and structure–activity relationship of a series of novel thiazoles as inhibitors of aminoacyl-tRNA synthetases, Bioorg. Med. Chem. Lett. 9 (1999) 375–380.
[21] K.D. Hargrave, F.K. Hess, J.T. Oliver, *N*-(4-Substituted-thiazolyl)oxamic acid derivatives, a new series of potent, orally active antiallergy agents, J. Med. Chem. 26 (1983) 1158–1163.
[22] J.C. Jean, L.D. Wise, B.W. Caprathe, H. Tecle, S. Bergmeier, C.C. Humblet, T.G. Heffner, L.T. Meltzer, T.A. Pugsley, 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: a novel class of compounds with central dopamine agonist properties, J. Med. Chem. 33 (1990) 311–317.
[23] N. Ergenc, G. Capan, N.S. Gunay, S. Ozkirimli, M. Gungor, S. Ozbey, E. Kendi, Synthesis and hypnotic activity of new 4-thiazolidinone and 2-thioxo-4,5-imidazolidinedione derivatives, Arch. Pharm. 332 (1999) 343–347.
[24] N. Siddiqui, M.F. Arshad, S.A. Khan, Synthesis of some new coumarin incorporated thiazolyl semicarbazones as anticonvulsants, Acta Pol. Pharm. 66 (2009) 161–167.
[25] A.M. Panico, A. Geronikaki, A. Mgonzo, V. Cardile, B. Gentile, I. Doytchinova, Aminothiazole derivatives with antidegenerative activity on cartilage, Bioorg. Med. Chem. 11 (2003) 2983–2989.

[26] A. Geronikaki, D. Hadjipavlou-Litina, A. Zablotskaya, I. Segal, Organosilicon containing thiazole derivatives as potential lipoxygenase inhibitors and anti-inflammatory agents, Bioinorg. Chem. Appl. (2007). ID 92145.
[27] A. Zablotskaya, I. Segal, S. Germane, I. Shestakova, I. Domracheva, A. Nesterova, A. Geronikaki, E. Lukevics, Silyl modification of biologically active compounds. 8. Trimethylsilyl ethers of hydroxyl containing thiazole derivatives, Chem. Heterocycl. Compd. 38 (2002) 859–866.
[28] K.W. Bentley, The Isoquinoline Alkaloids, Harwood Academic Publishers, Amsterdam, The Netherlands, 1998.
[29] J.D. Scott, R.M. Williams, Tetrahydroisoquinoline antitumor antibiotics, Chem. Rev. 102 (2002) 1668–1730.
[30] C. Marchand, S. Antony, K.W. Kohn, M. Cushman, A. Ioanoviciu, B.L. Staker, A.B. Burgin, L. Stewart, Y. Pommier, A novel norindenoisoquinoline structure reveals a common interfacial inhibitor paradigm for ternary trapping of the topoisomerase I-DNA covalent complex, Mol. Cancer Ther. 5 (2006) 287–295.
[31] Y. Mikami, K. Yokoyama, H. Tabeta, K. Nakagaki, T. Arai, Saframycin S, a new saframycin group antibiotic, J. Pharmacobiodyn. 4 (1981) 282–286.
[32] G.R. Pettit, V. Gaddamidi, D.L. Herald, S.B. Singh, G.M. Cragg, J.M. Schmidt, F.E. Boettner, M. Williams, Y. Sagawa, Antineoplastic agents, 120. Pancratium littorale, J. Nat. Prod. 49 (1986) 995–1002.
[33] E. Izbicka, R. Lawrence, E. Raymond, G. Eckhardt, G. Faircloth, J. Jimeno, G. Clark, D.D. Von Hoff, *In vitro* antitumor activity of the novel marine agent, Ecteinascidin-743 (ET-743, NSC-648766) against human tumors explanted from patients, Ann. Oncol. 9 (1998) 981–987.
[34] A. Kleemann, J. Engel, B. Kutscher, D. Reichert, Pharmaceutical Substances, fourth ed., Thieme, New York, 2001.
[35] T. Nagatsu, Isoquinoline neurotoxins in the brain and Parkinson's disease, Neurosci. Res. 29 (1997) 99–111.
[36] T. Yamakawa, S. Ohta, Isolation of 1-methyl-1,2,3,4-tetrahydroisoquinoline-synthesizing enzyme from rat brain: a possible Parkinson's disease-preventing enzyme, Biochim. Biophys. Res. Commun. 236 (1997) 676–681.
[37] H.R. Lin, M.K. Safo, D.J. Abraham, Identification of a series of tetrahydroisoquinoline derivatives as potential therapeutic agents for breast cancer, Bioorg. Med. Chem. Lett. 17 (2007) 2581–2589.
[38] U.R. Mach, A.E. Hackling, S. Perachon, S. Ferry, C.G. Wermuth, J.-C. Schwartz, P. Sokoloff, H. Stark, Development of novel 1,2,3,4-tetrahydroisoquinoline derivatives and closely related compounds as potent and selective dopamine D3 receptor ligands, Chem. Bio Chem. 5 (2004) 508–518.
[39] M.J. Mokrosz, A.J. Bojarski, B. Duszynska, E. Tatarczynska, A. Klodzinska, A. Deren-Wesolek, S. Charakchieva-Minol, E. Chojnacka-Wojcik, 1,2,3,4-Tetrahydroisoquinoline derivatives: a new class of 5-$HT_{1A}$ receptor ligands, Bioorg. Med. Chem. 7 (1999) 287–295.
[40] J. Lee, J. Lee, T. Szabo, A.F. Gonzalez, J.D. Welter, P.M. Blumberg, *N*-(3-Acyloxy-2-benzylpropyl)-*N*′-dihydroxytetrahydrobenzazepine and tetrahydroisoquinoline thiourea analogues as vanilloid receptor ligands, Bioorg. Med. Chem. 9 (2001) 1713–1720.
[41] T.K. Sasikumar, L. Qiang, W.-L. Wu, D.A. Burnett, W.J. Greenlee, K. O'Neill, B.E. Hawes, M. van Heek, M. Graziano, Tetrahydroisoquinolines as MCH-R1 antagonists, Bioorg. Med. Chem. Lett. 16 (2006) 4917–4921.
[42] Anticonvulsants, SmithKline Beecham Pharmaceuticals, UK, 2000.
[43] I. Segal, A. Zablotskaya, E. Lukevics, Lipid type organosilicon derivatives of 8-hydroxyquinoline and *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydro(sila, iso)quinolines, Chem. Heterocycl. Compd. 41 (2005) 613–624.
[44] A. Zablotskaya, I. Segal, S. Belykov, E. Lukevics, Synthesis, physico-chemical and biological evaluation of *N*-(trialkoxysilylalkyl)tetrahydro(iso, silaiso) quinoline derivatives, Appl. Organomet. Chem. 20 (2006) 149–154.
[45] C.M. Tarby, R.F. Kaltenbach III, T. Huynh, A. Pudzianowski, H. Shen, M. Ortega-Nanos, S. Sheriff, J.A. Newitt, P.A. McDonnell, N. Burford, C.R. Fairchild, W. Vaccaro, Z. Chen, R.M. Borzilleri, J. Naglich, L.J. Lombardo, M. Gottardis, G.L. Trainor, D.L. Roussell, Inhibitors of human mitotic kinesin Eg5: characterization of the 4-phenyl-tetrahydroisoquinoline lead series, Bioorg. Med. Chem. Lett. 16 (2006) 2095–2100.
[46] C. Jiang, Q. You, F. Liu, W. Wu, Q. Guo, J. Chern, L. Yang, M. Chen, Design, synthesis and evaluation of tetrahydroisoquinolines as new kinesin spindle protein inhibitors, Chem. Pharm. Bull. 57 (2009) 567–571.
[47] A. Zablotskaya, I. Segal, E. Lukevics, S. Belyakov, H. Spies, Tetrahydroquinoline and tetrahydroisoquinoline mixed ligand rhenium complexes with the SNS/S donor atom set, Appl. Organomet. Chem. 21 (2007) 288–293.
[48] H. Malonne, G. Atassi, DNA topoisomerase targeting drugs: mechanisms of action and perspectives, Anticancer Drugs 8 (1997) 811–822.
[49] A. Kleemann, J. Engel, B. Kutscher, D. Reichert, Pharmaceutical Substances, Thieme, Stuttgart, New York, 2009.
[50] D.A. Erlanson, W. Jahnke (Eds.), Fragment-based Approaches in Drug Discovery, Wiley-VCH, Weinheim, 2006.
[51] R.B. Silverman, The Organic Chemistry of Drug Design and Drug Action, Elsevier Academic Press, Amsterdam, 2004, pp. 525–526.
[52] G.J. Peters, C.I. Van der Wilt, C.J.A. Van Moorsel, J.R. Kroep, A.M. Bergman, S.P. Ackland, Basis for effective combination cancer chemotherapy with antimetabolites, Pharmacol. Ther. 87 (2000) 227–253.
[53] J.B. Bremner, J.I. Ambrus, S. Samosorn, Dual action-based approaches to antibacterial agents, Curr. Med. Chem. 14 (2007) 1459–1477.
[54] A. Geronikaki, G. Theophilidis, Synthesis of 2-(aminoacetylamino)thiazole derivatives and comparison of their local anaesthetic activity by the method of action potential, Eur. J. Med. Chem. 27 (1992) 1–9.
[55] C.A. Winter, G.A. Risley, G.W. Nuss, Carrageenin-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs, Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.
[56] BioByte Corporation, C-QSAR database 201 West 4th Str., Suite 204, Claremont, California 91711, USA.
[57] A. Wanger, Disk diffusion test and gradient methodologies, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press, Boca Raton, London, New York, 2007, pp. 53–73.
[58] A. Zablotskaya, I. Segal, Yu. Popelis, E. Lukevics, Shipra Baluja, I. Shestakova, I. Domracheva, Silyl modification of biologically active compounds. 12. Silyl group as true incentive to antitumour and antibacterial action of choline and colamine analogues, Appl. Organomet. Chem. 20 (2006) 721–728.
[59] D.J. Fast, R.C. Lynch, R.W. Leu, Nitric oxide production by tumor targets in response to TNF: paradoxical correlation with susceptibility to TNF-mediated cytotoxicity without direct involvement in the cytotoxic mechanism, J. Leukoc. Biol. 52 (1992) 255–261.
[60] S.K. Germane, O.E. Eberlinjsh, A.N. Kozhuhov, Scientific and Methodological Aspects of Biological Study of Novel Drugs, Zinatne, Riga, 1987, pp. 86–99.
[61] P.J. Freshney, Culture of Animal Cells (A Manual of Basic Technique), Wiley-Liss, New York, 1994, p. 296.
[62] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M.C. Burla, G. Polidori, M. Camalli, SIRPOW.92 – a program for automatic solution of crystal structures by direct methods optimized for powder data, J. Appl. Crystallogr. 27 (1994) 435–436.
[63] G.M. Sheldrick, SHELXL97. Program for the Refinement of Crystal Structures, University of Gottingen, Germany, 1997.