Computer Aided Predicting the Biological Activity Spectra and Experimental Testing of New Thiazole Derivatives

Athina Geronikaki[1], Vladimir Poroikov[2]*, Dimitra Hadjipavlou-Litina[1], Dmitrii Filimonov[2], Alexei Lagunin[2] and Remi Mgonzo[1]

[1]Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki 54006, Greece; [2]Institute of Biomedical Chemistry RAMS, Pogodinskaya Str., 10, Moscow, 119832, Russia

Abstract

Computer aided prediction of biological activity spectra has been carried out for 50 new thiazolyl and benzothiazolyl derivatives. Predicted activity spectra for different compounds from the set include 1–8 activities with estimated probability to be found more than 50%, which cover both possible therapeutic and adverse/side effects. Experimental data coincide with the prediction for 25 of 39 compounds tested as NSAIDs (64.1%); for 4 of 6 compounds tested as local anaesthetics (66.7%); for 1 compound tested as antioxidants (100%). The concordance that describes the overall percentage of correct predictions equals to 65.2% that is sufficient to use this approach for optimization of biological testing. In particular, the compounds from studied data set will be further tested according to the additional predicted activities. Description of the current version of computer system PASS and feasibility for free testing is available via Internet on http://www.ibmh.msk.su/PASS.

1 Introduction

Thiazolyl group is of great importance in biological systems. It has been found that the alkyl/aryl-aminoacetyl derivatives of 2-amino-4-phenylthiazolyl [1], 2-amino-benzothiazolyl [2, 3], 2-amino (substituted) benzothiazolyl [4–6], 2-phenyl-amino-4-phenyl-thiazolyl [7, 8], 2-amino-4-methyl-thiazolyl [9] and in general 2-(N-substituted or N, N-disubstituted) acetamido derivatives [10–14] have significant local anaesthetic activity. Antiinflammatory, analgesic, antipyretic activities for some thiazolyl and benzoisothiazolyl derivatives are also known [15, 16]. All these are just a part of variety of the biological activities found in different thiazolyl and benzothiazolyl derivatives. It is obvious that known pharmacological actions of tested thiazolyl derivatives do not represent the comprehensive biological activity spectra of the compounds. The screens for these compounds have been chosen on the basis of certain researchers' purposes. Therefore, there is no any thiazolyl derivative that has been tested in the battery of all available tests. Moreover, there were no means earlier for rational selecting the screens associated to the activity of this chemical series. The majority of existed approaches to the computer aided drug discovery operate with a single kind of biological activity [17]. They are used in finding and optimizing the new leads for this activity, but they cannot estimate the general pharmacological properties of a compound. However, recently a computer approach for predicting general activity spectrum for a compound on the basis of its structural formula has been developed [18–20]. Computer system PASS (Prediction of Activity Spectrum for Substance) provides the means to estimate which activities are expected for the majority of compounds from the data set (typical activities), and which can be suggested only for a few compounds within the series (minor activities).

PASS 4.30 predicts the probabilities of presence/absence for 114 biological actions simultaneously (main and side pharmacological effects, mechanisms, specific toxicity) on the basis of the compound's structural formula [21–23],

* To receive all correspondence

Key words: Thiazoles, benzothiazoles, biological activity spectra prediction, computer system PASS, structure–activity relationships, NSAID, local anaestetics, antioxidants.

Abbreviations: AO, antioxidant; GABA, γ-amino-butyric acid; LA, local anaesthetics; MAO, monoaminoxidase; NSAIDs, non-steroid antiinflammatory drugs; PASS, Prediction of Activity Spectrum for Substance; SAR, structure–activity relationships.

  0931-8771/99/0510-0016 $17.50+.50/0

which represent its biological activity spectrum. The biological activity spectrum of a compound reflects every activity that the compound might have despite the difference in essential conditions of experimental testing. If the difference in species, sex, age, dose, route, etc. is neglected, the biological activity can be identified only qualitatively. Thus, 'biological activity spectrum' is defined as the 'intrinsic' property of the compound depending only on its structure and physico-chemical characteristics.

The mean accuracy of biological activity prediction with PASS is 70–80% both in leave-one-out cross validation and in prediction for independent test sets of about 5000 compounds diverse in both structure and activity [18–20]. PASS prediction accuracy exceeds more than 3 times the expert's guess-work [21]. In blind prediction for 100 new drug-candidates from the PharmaProjects database it is more than random guess-work by a factor 46 [22]. Special experiment on the PASS application in high throughput screening for independent diverse test set shows that the economic viability may be about 500–800% [23]. It is shown that used in PASS original algorithm of structure-activity relationships' analysis provides highly robust results of prediction [24]. Meanwhile, the reliability of predictions relates to the researcher's purpose. The ultimate decision on how many and which structures should be selected for testing (and in which screens) depends on the estimated probabilities for a compound to be active (Pa) and inactive (Pi), experimental facilities and the researcher's aspiration concerning the extent of innovation in the result (see the example for 3-piperidine-N-[4-(4-methoxyphenyl)thiazolyl-2]-propionamide given below). Using PASS new leads with antiulcer [18, 25], antitumor [18] and antiamnestic [26] activities have been already found. New mechanism of action for some compounds with known effect are discovered too [27].

In this paper we describe the computer aided prediction of biological activity spectra and biological testing of some predicted activities (antiinflammatory activity in vivo, local anaesthetic and antioxidant activity in vitro) for 50 new thiazolyl derivatives.

2 Materials and Methods

2.1 Chemistry

Fifty new designed and prepared thiazolyl and benzothiazolyl derivatives are considered in this study. All amino-ketone thiazolyl derivatives were synthesized using the modified Mannich reaction [28] and were reported in our previous papers [29–31]. Aminoacetamido- and propionamido- thiazolyl derivatives as well as thiazolyl and benzothiazolyl Schiff bases were synthesized according to our previous publications [32, 33]. The structures of all synthesized compounds are shown in Table 1.

2.2 Pharmacological Testing

Compounds as hydrochloride salts in water were tested to assess antiinflammatory, [34] antioxidant [35] and local anaesthetic activities [36].

Carrageenin-Induced mice paw edema bioassay. Antiinflammatory activity of the compounds was evaluated in vivo on the mice carrageenin-induced hind paw edema test by the procedure described earlier [31, 35, 37–39]. The tested compounds were compared to Indomethacin, used as a reference drug, which activity equals to $48.0 \pm 2.1\%$ in this assay.

Interaction with the stable radical 1,1-Diphenyl-2-picrylhydrazyl (DPPH) [35]. The compounds (0.1 mM) in absolute ethanol were added to a solution of DPPH (0.1 mM) in ethanol. The absorbance at 517 nm was measured after 20 min. The interaction expressed their reducing activity and indicates their ability to scavenge free radicals. The activity of reference drug Acetylsalicylic acid equals to $80.5 \pm 2.1\%$.

Local anaesthetic activity was studied according to the procedure described in [36]. Tested compounds were compared to Procaine used as a reference drug which activity equals to $64.0 \pm 2.0\%$.

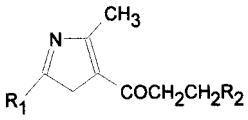
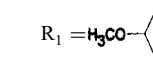
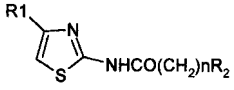
2.3 Biological Activity Spectra Prediction

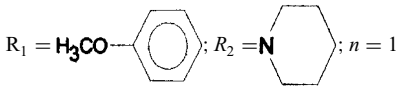
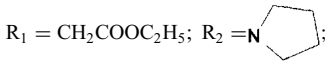
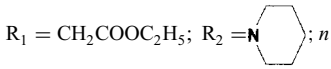
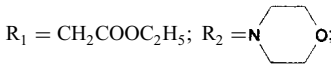
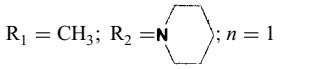
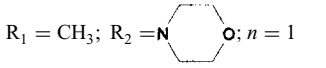
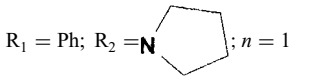
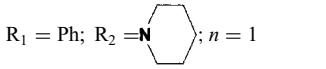
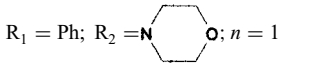
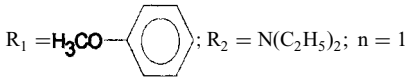
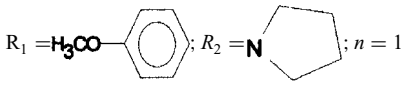
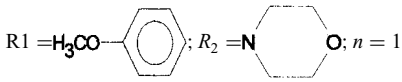
All calculations were performed using PASS version 4.30 in IBM PC 486/100 MHz. The method of predicting many kinds of biological activity simultaneously is described in details earlier [20]. Description of current version of computer system PASS and feasibility for its free testing are available via Internet on: http://www.ibmh.msk.su/PASS/.

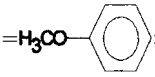
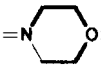
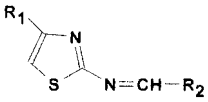
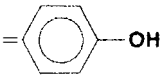
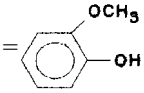
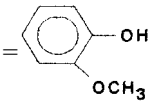
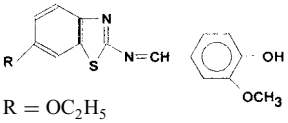
In PASS 4.30 Substructure Superposition Fragment Notation codes (SSFN), initially introduced by Avidon *et al*. [42] and later modified by Leibov [43], are used as the chemical descriptors. Biological activity is considered qualitatively (yes/no). Total list of 114 activities predicted by PASS 4.30 is given in [20]. Below we describe the peculiarities of the mathematical approach applied in this study.

Designations: n is the total number of compounds in the training set (in PASS 4.30 $n = 9314$); n_i is the number of compounds from the training set that have SSFN code (structural descriptor) i ($i = 1, \ldots, 5574$); n_k is the number of compounds from the training set that have activity k

Table 1. Structures and predicted* activities for thiazole derivaties under study

No	Structure	Predicted Activity Spectra	Pa, %*	Pi, %*
				
1	$R_1 = NH_2; R_2 = N(CH_3)_2$	GABAergic stimulator	68	13
		Analeptic	59	7
		Cardiovascular analeptic	56	8
		Respiratory analeptic	52	10
2	$R_1 = NHCH_3; R_2 = N(C_2H_5)_2$	Analeptic	59	7
		Cardiovascular analeptic	55	8
		GABAergic stimulator	57	21
3	$R_1 = NHC_2H_5$; $R_2 =$ 	Psychostimulant	58	6
		GABAergic stimulator	61	18
4	$R_1 = NHC_3H_7$; $R_2 =$ 	GABAergic stimulator	69	11
		Analeptic	53	11
5	$R_1 =$ Ph; $R_2 =$ 	H1-histamine blocker	46	8
6	$R_1 = C_6H_4CH_3$; $R_2 = N(C_2H_5)_2$	Psychostimulant	44	12
7	$R_1 = NH_2$; $R_2 = N(C_2H_5)_2$	GABAergic stimulator	63	16
		Interferon inducer	53	9
		Analeptic	54	10
8	$R_1 = NH_2$; $R_2 =$ 	GABAergic stimulator	60	19
9	$R_1 = H_3CHN$; $R_2 =$ 	Analeptic	53	11
		GABAergic stimulator	54	23
10	$R_1 = C_2H_5HN$; $R_2 = N(C_2H_5)_2$	Psychostimulant	52	8
		Cardiovascular analeptic	51	9
		Analeptic	52	12
11	$R_1 = C_2H_5HN$; $R_2 =$ 	Psychostimulant	47	10
12	$R_1 = C_2H_5HN$; $R_2 =$ 	Psychostimulant	52	8
13	$R_1 = NHC_3H_7$; $R_2 = N(C_2H_5)_2$	Analeptic	56	9
		Cardiovascular analeptic	55	8
		GABAergic stimulator	62	17
14	$R_1 = C_6H_5$; $R_2 = N(C_2H_5)_2$	Psychostimulant	48	10
15	$R_1 =$  ; $R_2 = N(C_2H_5)_2$	NSAID	44	9
				
16	$R_1 = H$; $R_2 = N(CH_3)_2$; $n = 1$	GABAergic stimulator	86	2
		Respiratory analeptic	80	2
		Analeptic	72	3
		Antibacterial	55	6
		Carcinogenic	52	12
17	$R_1 = CH_3$; $R_2 = N(C_2H_5)_2$; $n = 1$	GABAergic stimulator	85	3
		Antibacterial	61	4
		Analeptic	55	10
		Respiratory analeptic	51	11
18	$R_1 =$ Ph; $R_2 =$  ; $n = 1$	GABAergic stimulator	67	13
		Antiviral	53	9

No	Structure	Predicted Activity Spectra	Pa, %*	Pi, %*
19	$R_1 = Ph;\ R_2 = (C_2H_5)_2;\ n = 1$	Analeptic	57	8
		Respiratory analeptic	56	8
		Antiviral	51	11
		GABAergic stimulator	54	23
20		NSAID	61	3
		MAO inhibitor reversible	55	8
		Analeptic	53	12
		GABAergic stimulator	59	19
		Respiratory analeptic	51	11
		Abortion inducer	50	12
21	$R_1 = CH_2COOC_2H_5;\ R_2 = N(CH_3)_2;\ n = 1$	GABAergic stimulator	75	7
		NSAID	56	4
		Non-morphine analgesic	53	4
22	$R_1 = CH_2COOC_2H_5;\ R_2 = N(C_2H_5)_2;\ n = 1$	GABAergic stimulator	72	9
		NSAID	53	5
23		GABAergic stimulator	82	4
		NSAID	53	5
		Carcinogenic	52	13
24		GABAergic stimulator	78	6
		NSAID	53	5
		Non-morphine analgesic	50	5
25		GABAergic stimulator	69	12
		NSAID	52	52
		Carcinogenic	50	14
26		GABAergic stimulator	90	1
		Antibacterial	50	7
		Analeptic	51	13
27		GABAergic stimulator	81	4
28	$R_1 = Ph;\ R_2 = N(CH_3)_2;\ n = 1$	Analeptic	57	8
		Respiratory analeptic	56	8
		Antiviral	51	11
29	$R_1 = Ph;\ R_2 = N(C_2H_5)_2;\ n = 1$	MAO inhibitor reversible	59	6
		Antiviral	54	9
		Analeptic	52	12
30		GABAergic stimulator	67	13
		Antiviral	53	9
31		GABAergic stimulator	58	20
32		MAO inhibitor reversible	51	10
33		MAO inhibitor reversible	63	5
		NSAID	61	3
		Analeptic	55	10
		Respiratory analeptic	51	11
34		NSAID	61	3
		GABAergic stimulator	66	14
		MAO inhibitor reversible	57	7
		Analeptic	53	12
		Respiratory analeptic	50	12
35		NSAID	60	3
		MAO inhibitor reversible	57	7
36	$R_1 = H;\ R_2 = N(CH_3)_2;\ n = 2$	Respiratory analeptic	76	2
		Analeptic	70	3
		GABAergic stimulator	70	11
		Cardiovascular analeptic	63	5

No	Structure	Predicted Activity Spectra	Pa, %*	Pi, %*
37	$R_1 = CH_3$; $R_2 = N(CH_3)_2$; n = 2	GABAergic stimulator	73	8
		Cardiovascular analeptic	62	5
		Mutagenic	52	7
		Analeptic	53	12
		Antiviral	50	11
38	R_1 = Ph; R_2 =  ; $n = 2$	NSAID	68	2
		Antiviral	56	8
		Analgesic agent	50	7
39	R_1 =  ; R_2 =  ; $n = 2$	NSAID	74	1
		Analgesic agent	60	4
		Non-morphine analgesic	56	3
		Abortion inducer	55	8
		MAO inhibitor reversible	51	9
		Analeptic	51	13
40	R_1 = Ph; R_2 =  ; $n = 2$	NSAID	66	2
		Analgesic agent	50	7
41	$R_1 = CH_2COOC_2H_5$; $R_2 = N(CH_3)_2$; n = 2	NSAID	72	1
		Non-morphine analgesic	67	2
		GABAergic stimulator	64	1
		Analgesic agent	50	7
		Immunomodulator	50	10
42	$R_1 = CH_2COOC_2H_5$; $R_2 = N(C_2H_5)_2$; n = 2	NSAID	70	1
		Non-morphine analgesic	64	2
		GABAergic stimulator	59	19
		Immunomodulator	50	10
43	$R_1 = CH_2COOC_2H_5$; R_2 =  ; $n = 2$	NSAID	70	1
		GABAergic stimulator	74	8
		Non-morphine analgesic	63	3
		Immunomodulator	54	7
44	$R_1 = CH_2COOC_2H_5$; R_2 =  ; $n = 2$	NSAID	70	2
		Non-morphine analgesic	65	2
		GABAergic stimulator	67	13
		Analgesic agent	51	6
45	$R_1 = CH_2COOC_2H_5$; R_2 =  ; $n = 2$	NSAID	68	2
		Non-morphine analgesic	60	3
		Immunomodulator	50	9
		GABAergic stimulator	56	21
46	R_1 = H; R_2 = 	Antimycobacterial	58	5
		Carcinogenic	52	13
47	$R_1 = CH_3$; R_2 = 	Antimycobacterial	55	6
48	R_1 = Ph; R_2 = 	MAO inhibitor reversible	69	3
		Antimycobacterial	67	3
				
49	$R = OC_2H_5$	MAO inhibitor reversible	63	5
		Nucleotide metabolism regulator	52	12
50	R = F	MAO inhibitor reversible	48	11

*Only activities with $P_a > 50\%$ or the activity with the highest value of P_a–P_i are shown.

($k = 1, \ldots, 114$); n_{ik} is the number of compounds from the training set that have both SSFN code i and activity k.

The following function of integer argument L ($L = 1, 2, 3, \ldots$) is defined:

$$B(0) = 0, B(L) = B(L-1) + 1/L.$$

For each descriptor and every activity we calculate the values:

$$b_{ik} = B(n_{ik}) + B(n - n_i - n_k + n_{ik}) - B(n_i - n_{ik}) - B(n_k - n_{ik}).$$

We calculate the average value of b_{ik} for a new compound that is under prediction taking into account all various descriptors included in this structure:

$$s_k = \Sigma_i b_{ik}/m,$$

where m is the number of particular descriptors contained by the structure.

The correlation coefficients are calculated between all 114 activities taking into account each of 9314 compounds of the training set. For each activity six other associated activities having the highest values of correlation coefficients' modules are identified. For each activity under consideration we use the indicator variable $w_{jkk'} = 1$ if activity k is associated with activity k'; and 0 if activity k is not associated with activity k'. Intermediate estimates of t_k are calculated as:

$$t_k = a_k + \Sigma_j x_{jk} \Sigma_{k'} w_{jkk'} s_{k'},$$

where a_k, x_{jk} are the regression coefficients, and the estimates of probability P_k:

$$P_k = 1/(1 + \exp(-t_k)).$$

The regression coefficients a_k, x_{jk} are calculated by minimizing the sum:

$$\Sigma_{\text{active}} \exp(-t_{kq}/2) + \Sigma_{\text{inactive}} \exp(t_{kq}/2),$$

where q is the number of compounds in the training set.

The values t_{kq} are calculated by leave-one-out procedure:

$$b_{ik} = B(n_{ik} - 1) + B(n - n_i - n_k + n_{ik}) - B(n_i - n_{ik}) - B(n_k - n_{ik})$$

for active compounds;

$$b_{ik} = B(n_{ik}) + B(n - n_i - n_k + n_{ik}) - B(n_i - n_{ik} - 1) - B(n_k - n_{ik})$$

for inactive compounds.

Table 2. List of the most typical and the most minor activities predicted for the series of thiazole derivatives

Activity	Percentage of the Sample	Compound's No
GABAergic stimulator	80.0	26, 16, 17, 23, 27, 24, 21, 43, 37, 22, 36, 4, 25, 1, 44, 18, 30, 34, 41, 7, 13, 3, 8, 42, 20, 31, 2, 45, 9, 19, 28, 12, 33, 38, 35, 29, 39, 32, 10, 11
Analeptic	74.0	16, 36, 2, 1, 19, 28, 13, 33, 17, 7, 9, 4, 34, 20, 37, 10, 29, 39, 26, 3, 12, 35, 18, 30, 31, 8, 38, 11, 27, 15, 48, 32, 40, 14, 47, 6, 5
Respiratory analeptic	68.0	16, 36, 19, 28, 1, 33, 20, 17, 34, 2, 26, 39, 37, 29, 35, 31, 18, 30, 9, 13, 27, 7, 4, 38, 32, 10, 48, 12, 3, 40, 8, 15, 11, 47
NSAID	68.0	39, 41, 42, 43, 44, 45, 38, 40, 33, 34, 20, 35, 21, 22, 23, 24, 25, 19, 28, 29, 18, 30, 31, 32, 15, 48, 36, 37, 6, 5, 14, 50, 49, 47
Antibacterial	56.0	17, 16, 26, 37, 27, 14, 6, 36, 13, 7, 1, 18, 30, 29, 19, 28, 5, 2, 46, 3, 4, 10, 15, 8, 47, 31, 38, 32
Analgesic agent	54.0	39, 44, 40, 38, 41, 45, 43, 20, 42, 35, 34, 33, 31, 48, 24, 19, 28, 21, 32, 25, 36, 18, 30, 23, 22, 29, 49
Non-morphine analgesic	54.0	41, 44, 42, 43, 45, 39, 21, 24, 22, 38, 23, 40, 25, 20, 33, 34, 35, 19, 28, 31, 48, 29, 18, 30, 32, 49, 36
Antiviral	52.0	38, 29, 18, 30, 19, 28, 37, 40, 31, 17, 32, 36, 48, 46, 16, 26, 14, 27, 49, 6, 47, 7, 33, 13, 34, 5
Carcinogenic	52.0	16, 46, 23, 25, 27, 21, 18, 30, 24, 43, 32, 22, 45, 19, 28, 41, 26, 17, 36, 31, 44, 38, 42, 29, 40, 48
5HT-receptors blocker	46.0	37, 5, 26, 27, 36, 14, 6, 17, 11, 8, 12, 9, 1, 4, 10, 7, 16, 2, 3, 13, 40, 15, 32
Beta-1,2 adrenergic stimulator	2.0	49
Antitussive	2.0	5
Imipramin-like antidepressant	2.0	9
Vasopressor	2.0	3
Hypoglycemic	2.0	26
Thyroid hormone antagonist	2.0	46
Antimalarial	2.0	33

By using the leave-one-out procedure for each compound and every predicted activity we calculate the estimates P_{kq}. On the basis of these estimates we calculate the estimates for distribution functions of P_{kq} for inactive compounds F_{0k}

and active compounds F_{1k}. These functions are calculated by the following procedure:

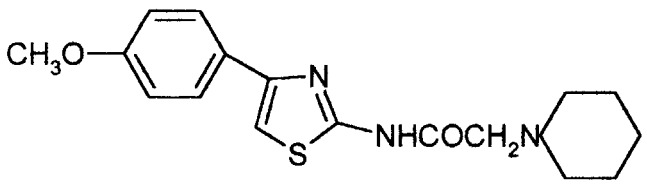
1. P_q values are sorted in ascending order.
2. $F(z) = \mathrm{Arg}\{\Sigma\, qP_qF^{q-1}(1-F)^{n-q}(n-1)!/(q-1)(n-1)! = z\}$

The result of prediction is represented as the estimates of probability to be active P_a, $P_a = F_1(P)$, and probability to be inactive P_i, $P_i = 1 - F_0(P)$. The values P_a and P_i for the compound under prediction are considered as the measures of membership to the active and inactive compounds subsets respectively. As P_a and P_i values are estimated independently, $P_a + P_i \neq 1$.

3 Results and Discussion

Structures of 50 compounds from the set and their biological activity spectra included the activities with the highest predicted probabilties are presented in Table 1. Summarized results on the most typical and the most minor activities that are predicted for compounds from the series are given in Table 2. The compounds, for which a particular activity is predicted ($P_a > P_i$), are placed in the descending order of the difference ($P_a - P_i$). For example, the differences of possibilities to be or not to be a GABAergic stimulator for various compounds are: $90 - 1 = 89\%$ (no. 26), $86 - 2 = 84\%$ (no. 16), $85 - 3 = 82\%$ (no. 17), ..., $39 - 34 = 5\%$ (no. 11). The percentage of the sample given in Table 2 shows which fraction of compounds from the total set is predicted to have the particular activity. Activities with the highest values of this percentage can be considered as typical for the studied chemical series. The probability to find such activity in experimental testing is more in compounds from this series. In the case of low percentage, the appropriate activity might be found only in an individual derivatives of this series (minor activity). On the basis of data from Table 2 one can conclude that many compounds within the series are expected to have as typical the following activities: GABAergic stimulator, analeptic, respiratory analeptic, NSAID, antibacterial, antiviral, analgesic, a.o. Vasopressor, coronary vasodilator, hypertensive, uricosuric, thyroid hormone antagonist, antimalarial, etc. are the minor activities within the series.

The example of predicted activity spectrum for 3-piperidine-N-[4-(4-methoxyphenyl)thiazolyl-2]-propionamide (comp. no. 20 in Table 1) is given below.



Total no. of Descriptors: 14, new Descriptors: 0.

Predicted Activities	P_a, %	P_i, %
NSAID	61	3
MAO inhibitor reversible	55	8
Analeptic	53	12
GABAergic stimulator	59	19
Respiratory analeptic	51	11
Abortion inducer	50	12
Analgesic agent	46	9
Non-morphine analgesic	42	6
MAO inhibitor	41	10
Antimycobacterial	36	13
Antihypertensive	42	22
Dopaminergic stimulator	31	16
Spasmogenic	34	21
Narcotic or narcotic's antagonist	21	14
Adrenergic stimulator	18	15

Predicted activity is considered as significant for the compound, if $P_a > P_i$. The reliability of prediction is high when $P_a > 70\%$. However, the tested compound may turn out to be an analogue of well-known drug from the training set. Both the reliability of prediction and compound's similarity to the known drugs are less, if $P_a = 50$–70%. They are much less if $P_a < 50\%$. However, the less is the calculated probability for the activity, the more is chance to discover a new chemical entity (the compound from chemical series for which this activity was never found).

Based on the results of prediction, 3-piperidine-N-[4-(4-methoxyphenyl)thiazolyl-2]-propionamide have to be tested as NSAID, MAO inhibitor, analeptic, GABAergic stimulator, etc. (typical activities within the series). Some minor activities are also predicted, like: adrenergic stimulator, narcotic or narcotic's antagonist, spasmogenic, etc. These activities might be tested in case of particular interest of a researcher.

To evaluate the applicability of the approach to the thiazole derivatives, the results of prediction are compared to experimental data for some compounds from the set, studied as non-steroid antiinflammatory (39 compounds); local anaethetics (6 compounds); antioxidants (1 compound) tests. These data are given in Table 3. The compound is considered as active if its activity is no less than the activity of the appropriate reference drug taking into account the experimental errors. For example, if NSAID activity determined for comp. no. 14 is $91.7 \pm 7.7\%$ and that of Indomethacine is $100.0 \pm 4.8\%$, the compound no. 14 is considered as active. Predicted activity is considered as significant if its estimated $P_a > P_i$. Coincidence of experiment and prediction is designated respectively by '+/+' (active/active) or '−/−' (inactive/inactive), contradiction between the experiment and prediction is designated by '−/+' (inactive/active) or '+/−' (active/inactive). Experiment coincides with the prediction

Table 3. Comparison of predicted and experimental data for some synthesized and tested compounds

No	Activity	Experimental data, %	Pa, %	Pi, %	Coincidence (Exp./Pred.)
3	LA[a)]	84.4 ± 10.0	11	42	−/−
4	NSAID[b)]	123.3 ± 1.7	16	44	+/−
	LA	103.4 ± 9.0	14	35	+/−
7	NSAID	100.0 ± 2.1	23	31	+/−
8	NSAID	62.5 ± 1.0	24	29	−/−
9	NSAID	50.0 ± 2.5	21	34	−/−
10	NSAID	106.3 ± 6.9	18	41	+/−
11	NSAID	83.3 ± 2.1	19	38	−/−
12	NSAID	116.7 ± 1.9	17	41	+/−
13	NSAID	89.6 ± 2.3	16	44	−/−
	LA	53.9 ± 4.7	17	29	−/−
14	NSAID	91.7 ± 7.7	37	14	+/+
15	NSAID	68.8 ± 1.5	44	9	+/+
16	NSAID	97.5 ± 4.2	9	60	+/−
17	NSAID	89.6 ± 3.8	14	48	−/−
	LA	98.8 ± 8.3	22	20	+/+
18	LA	125.5 ± 5.2	29	13	+/+
19	NSAID	97.9 ± 3.8	49	6	+/+
20	NSAID	111.1 ± 3.8	61	3	+/+
21	NSAID	93.5 ± 6.5	56	4	+/+
22	NSAID	112.5 ± 2.1	53	5	+/+
23	NSAID	74.0 ± 1.9	53	5	−/+
24	NSAID	126.0 ± 4.6	53	5	+/+
25	NSAID	103.5 ± 5.4	52	5	+/+
26	NSAID	70.2 ± 3.8	14	49	−/−
27	NSAID	66.9 ± 4.0	16	44	−/−
28	NSAID	114.4 ± 6.9	49	6	+/+
29	NSAID	97.9 ± 3.4	47	8	+/+
30	NSAID	102.5 ± 3.1	46	8	+/+
	LA	53.9 ± 12.5	29	13	−/+
31	NSAID	84.2 ± 5.2	46	8	−/+
32	NSAID	167.3 ± 2.7	46	8	+/+
34	NSAID	114.2 ± 2.5	61	3	+/+
35	NSAID	125.0 ± 3.3	60	3	+/+
39	NSAID	82.5 ± 3.3	74	1	−/+
40	NSAID	167.3 ± 2.7	66	2	+/+
41	NSAID	108.5 ± 4.0	72	2	+/+
42	NSAID	135.2 ± 2.7	70	1	+/+
43	NSAID	72.9 ± 5.0	70	1	−/+
44	NSAID	88.3 ± 2.1	70	2	−/+
45	NSAID	122.1 ± 2.3	68	2	+/+
46	NSAID	123.3 ± 11.5	18	40	+/−
47	NSAID	74.2 ± 5.2	28	23	−/+
49	NSAID	149.6 ± 6.9	30	19	+/+
50	NSAID	81.3 ± 4.6	35	16	−/+
	AO[c)]	24.5 ± 2.7	17	19	−/−

a) Relative activity to Procaine (100.0 ± 3.1%) in percentage;
b) Relative activity to Indomethacine (100.0 ± 4.8%) in percentage;
c) Relative activity to Acetylcalicylic acid (100.0 ± 2.6%) in percentage.

for 25 of 39 compounds tested as NSAIDs (64.1%); for 4 of 6 compounds tested as local anaesthetics (66.7%); for 1 compound tested as antioxidant (100%). Concordance that describes the overall percentage of correct predictions ('+/+' and '−/−') equals to 30/46 (65.2%. It is less than 80% average accuracy obtained in cross-validation [20], but taking into account that the probability of random guessing any activity for a compound is $(1/114) < 1\%$, the average accuracy of prediction seems to be sufficient. The values of first kind (+/−) and second kind (−/+) errors are close, 15.2% and 19.6% respectively. Therefore, PASS could be used for arranging both further pharmacological study of compounds from this set and testing of new thiazolyl derivatives. The results presented in this paper confirm the previous experience [18–27] that computer system PASS can be effectively used to optimize the synthesis and biological testing of lead compounds from different chemical series.

References

[1] Srivastava, P.N. and Rai, S.K., Some derivatives of 2-aminothiazole as potential local anaesthetic. *Eur. J. Med. Chem.–Chimica Therapeutica*. *15*, 274 (1980).

[2] Bhargava, P.N. and Nair, M.G.R., Synthesis of new local anaesthetics. *J. Indian Chem. Soc. 34*, 42–44 (1957).

[3] Bhargava, P.N. and Singh, P.R., Synthesis of new local anaesthetics II. *J. Indian Chem. Soc*. *37*, 241–243 (1960).

[4] Bhargava, P.N. and Baliga, B.T., Studies on 2-aminobenzothiazoles. *J. Indian Chem. Soc*. *35*, 807–810 (1958).

[5] Bhargava, P.N. and Jose, K.A., Synthesis of new local anaesthetics III. *J. Indian Chem. Soc*. *37*, 314–316 (1960).

[6] Srivastava, P.N. and Srivastava, P.K., Synthesis of some local anaesthetics. *J. Med. Chem*. *13*, 304–305 (1970).

[7] King, L.C. and Dodson, P.M., The reaction of ketones with Halogens and Thiourea. *J. Amer. Chem. Soc*. *67*, 2242–2243 (1945).

[8] King, L.C. and Dodson, P.M., The reaction of acetophenone with Thiourea and Oxidizing agents. *J.Amer. Chem. Soc*. *68*, 871 (1945).

[9] Geronikaki, A. and Theophilidis, G., Synthesis of 2-(aminoacetylamino)thiazole derivatives and comparison of their local anaesthetic activity by method of action potential. *Eur. J. Med. Chem*. *27,* 709–716 (1992).

[10] Srivastava, P.K., Sharma, R.D., Upadhyaya, J.S., Synthesis and potential local anaesthetic activity of some 2-substituted benzothiazoles. *Indian J. Pharmacy*. *39*, 56–58 (1977).

[11] Srivastava, P.K., Sharma, R.D., Rai, S.K., Search for new local anaesthetic agents. III Synthesis of 2-alkyl-arylaminoacetylamino-4-phenylthiazoles. *Acta Chim*. *94*, 229–232 (1977).

[12] Srivastava, P.K., Rai, S.K., Yadav, G.C., Synthesis and potential local anaesthetic activity of some derivatives of substituted 2-aminobenzothiazoles III. *Curr. Sci*. *48*, 711 (1979).

[13] Lakhan, R. and Rai, B.J., Local anaesthetics IV. Synthesis and activity of 2-(N-substituted or N,N-disubstituted aminoacetamido)-4 or 4,5-substituted thiazoles. *Il Farmaco*. *41*, 788–783 (1986).

[14] Vicini, P., Amoretti, L., Chiavarini, M., Impicciatore, M., Synthesis and local anaesthetic activity of alkyl aminoacyl derivatives of 3-amino-1,2-benzoisothiazoles. *Il Farmaco*. *45*, 933–944 (1990).

[15] Klose, N., Niedbolla, K., Schwartz, K., Bottcher, I., 4,5-Bis (4-methoxyphenyl)-2-arylthio-azole mit antiphlogischer wirkung. *Arch. Pharm*. *316*, 941–951 (1983).

[16] Satsangi, R.K., Zaidi, S.M., Misra, V.S., 1-(4-Substituted-thiazol-2-yl) hydantoins as antiinflammatory and CNS-active agents. *Pharmazie*. *38*, 341–342 (1983).

[17] Wermuth, C., Ed., The Practice of Medicinal Chemistry. Acad. Press, London a.o., 968 pp., (1996).

[18] Poroikov, V.V., Computer aided prediction in new drug research and development. *Sc.D. in Pharmacology Thesis (Rus)*. Staraya Kupavna (Moscow Region): Natl. Res. Center for Biologically Active Compounds, 348 pp.(1995) .

[19] Filimonov, D.A., Poroikov, V.V., Karaicheva, E.I. et. al., Computer-aided prediction of biological activity spectra of chemical substances on the basis of their structural formulae: computerized system PASS. *Experimental and Clinical Pharmacology (Rus)*. *58*, 56–62 (1995).

[20] Filimonov, D.A. and Poroikov, V.V., PASS: Computerized prediction of biological activity spectra for chemical substances. In: *Bioactive Compound Design: Possibilities for Industrial Use*, BIOS Scientific Publishers, Oxford, 47–56 (1996).

[21] Poroikov, V.V, Filimonov, D.A., Boudunova, A.P., Comparison of the results of prediction of the spectra of biological activity of chemical compounds by experts and the PASS system. *Automatic Documentation and Mathematical Linguistics*. Allerton Press, Inc. *27*, 40–43 (1993).

[22] Charlish, P., Russian computer program to cut screening costs? *Pharma Rrojects Magazine*. 1, No 11, 2–3 (1996).

[23] Poroikov, V.V, Filimonov, D.A., Boudouna, A.P., Computer assisted prediction of biological activity spectra: estimating the effectivity of use in high throughput screening. In: *Abstr.: XIV International Symposium on Medicinal Chemistry*, Maastricht (The Netherlands). P-3.05 (1996).

[24] Filimonov, D.A. and Poroikov, V.V., Robust prediction of many biological activities. In: *Abstr. 11th European Symposium on Quantitative Structure–Activity Relationships: Computer-Assisted Lead Finding and Optimization*, Lausanne (Switzerland). P-59A (1996).

[25] Trapkov, V.A., Boudunova, A.P. Burova, O.A., Filimonov, D.A., Poroikov, V.V., Discovery of new antiulcer agents by computer aided prediction of biological activity. *Problems in Medical Chemistry* (Moscow). *43*, 41–57 (1997).

[26] Filimonov, D.A., Poroikov, V.V., Boudunova, A.P, Rudnitskih, A.V., Burov, Y.V., Computerized prediction of antiamnestic activity for chemical compounds: PASS possibilities extending. In: *Abstr. SCI Conference "Design of Bioactive Compounds"*, Potsdam (Germany). 26 (1995).

[27] Poroikov, V.V., Boudunova, A.P., Shamshin, V.P., Suhanova, S.A., Trapkov, A.A., Burov, Yu.V., Revealing of new mechanism for barbiturates activity potentiation on the basis of computer aided prediction of biological activity spectra. *Bull. Natl. Res. Center for Biologically Active Compounds* (Rus). No 1, 39–45 (1994).

[28] Gall, M. and Kamdaw, B.V., Synthesis of aminoalkyl-substituted imidazo[1,2]- and imidazo[1,5]-benzodiazepines. *J. Org. Chem*. *46*, 1575. (1981).

[29] Geronikaki, A., Sotiropoulou, E., Kourounakis, P., Synthesis of some thiazole derivatives with prospective local anaesthetic activity. *Pharmazie*. *44*, 349 (1989).

[30] Geronikaki, A., Sotiropoulou, E., Kourounakis, P.N., Synthesis and mass spectra of some thiazole aminoketones with prospective local anaesthetic activity. *Pharmazie*. *47*, 298–300 (1992).

[31] Mgonzo, R., Geronikaki, A., Kourounakis, P., Synthesis and antiinflammatory activity of some new thiazole derivatives. *Pharmazie*. *50*, 505–506 (1995).

[32] Geronikaki, A. and Hadjipavlou-Litina, D., Novel thiazole and benzothiazole derivatives designed as possible lipoxygenase inhibitors. In: *Abstracts of XIV International Symposium on Medicinal Chemistry*, Maastricht (The Netherlands), P-5.21 (1996).

[33] Geronikaki, A., Synthesis and studies of some thiazole Schiff bases. *Farmatsija*. *40*, 17–22 (1990).

[34] Shen, T.Y., In: *Burger's Medicinal Chemistry, Non steroidal antiinflammatory Agents*, Ed. by Wolff, N.E., J. Willey and Sons, Chapter *62*, 1217–1219 (1980).

[35] Geronikaki, A. and Hadjipavlou-Litina, D., In vitro studies of some 2,4-disubstituted thiazolyl-aminoketones with antiinflammatory activity. Correlation with lipophilicity and structural characteristics. *Arz. Forsh./Drug Res*. *46* (II), 1134–1137 (1996).

[36] Mgonzo, R., Geronikaki, A., Theophilidis, G., Synthesis of new thiazole derivatives and comparative study of their local anaesthetic activity using the evoked action potential in the sciatic nerve. *Res. Commun. in Pharmacol. and Toxicol*. *1* Nos. 2 & 3, 137–148 (1996).

[37] Geronikaki, A. and Hadjipavlou-Litina, D., Lipophilicity and biological studies of some 2-(aminoacetylamino)thiazole derivatives with antiinflammatory activity. *Pharmazie*. *48*, 948–949 (1993).

[38] Hadjipavlou-Litina, D., Geronikaki, A., Sotiropoulou, E., Antiinflammatory activity of aminoketone derivatives of 2,4-disubstituted thiazoles. *Res. Commun.Chem. Path. and Pharmacol*. *79*, 355–362 (1993).

[39] Hadjipavlou-Litina, D.J. and Geronikaki, A.A., Effect of 2,4-disubstituted thiazol-5-yl aminoketones on carrageenin induced inflammation. Biological evaluation and a structure-activity approach. *Res. Commun.in Molecular Pathol and Pharmacol*. *96*, 307–318 (1997).

[40] Avidon, V.V., Pomerantsev, I.A., Rozenblit, A.B., Golender, V.E., Structure-activity relationship oriented languages for chemical structure representation. *J. Chem. Inform. Comput. Sci*. *22*, 207–214 (1982).

[41] Leibov, A.E., Automatic coding of chemical structures in SSFN codes. In: *The Achievements of Science and Technology. Ser. Informatics*. (Rus). M.: VINITI. *15*, 141–158 (1991).

Received on: March 30, 1998; accepted on October 26, 1998