

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

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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],

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

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 anti-amnesic [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 (anti-inflammatory 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 anti-inflammatory, [34] antioxidant [35] and local anaesthetic activities [36].

Carrageenin-Induced mice paw edema bioassay. Anti-inflammatory 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/>.








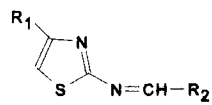
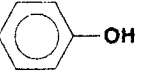
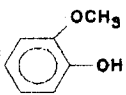
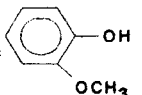
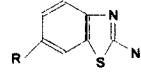
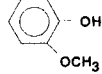
In PASS 4.30 Substructure Superposition Fragment Notation codes (SSFN), initially introduced by Avidon *et al.* [42] and later modified by Leibov [43], are used as the chemical descriptors. Biological activity is considered qualitatively (yes/no). Total list of 114 activities predicted by PASS 4.30 is 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 ($i = 1, \dots, 5574$); n_k is the number of compounds from the training set that have activity k

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

No	Structure	Predicted Activity Spectra	Pa, %*	Pi, %*
1	R ₁ = NH ₂ ; R ₂ = N(CH ₃) ₂	GABAergic stimulator Analeptic Cardiovascular analeptic Respiratory analeptic	68 59 56 52	13 7 8 10
2	R ₁ = NHCH ₃ ; R ₂ = N(C ₂ H ₅) ₂	Analeptic Cardiovascular analeptic GABAergic stimulator	59 55 57	7 8 21
3	R ₁ = NHC ₂ H ₅ ; R ₂ =	Psychostimulant GABAergic stimulator	58 61	6 18
4	R ₁ = NHC ₃ H ₇ ; R ₂ =	GABAergic stimulator Analeptic	69 53	11 11
5	R ₁ = Ph; R ₂ =	H1-histamine blocker	46	8
6	R ₁ = C ₆ H ₄ CH ₃ ; R ₂ = N(C ₂ H ₅) ₂	Psychostimulant	44	12
7	R ₁ = NH ₂ ; R ₂ = N(C ₂ H ₅) ₂	GABAergic stimulator Interferon inducer Analeptic	63 53 54	16 9 10
8	R ₁ = NH ₂ ; R ₂ =	GABAergic stimulator	60	19
9	R ₁ = H ₃ CHN; R ₂ =	Analeptic GABAergic stimulator	53 54	11 23
10	R ₁ = C ₂ H ₅ HN; R ₂ = N(C ₂ H ₅) ₂	Psychostimulant Cardiovascular analeptic Analeptic	52 51 52	8 9 12
11	R ₁ = C ₂ H ₅ HN; R ₂ =	Psychostimulant	47	10
12	R ₁ = C ₂ H ₅ HN; R ₂ =	Psychostimulant	52	8
13	R ₁ = NHC ₃ H ₇ ; R ₂ = N(C ₂ H ₅) ₂	Analeptic Cardiovascular analeptic GABAergic stimulator	56 55 62	9 8 17
14	R ₁ = C ₆ H ₅ ; R ₂ = N(C ₂ H ₅) ₂	Psychostimulant	48	10
15	R ₁ = ; R ₂ = N(C ₂ H ₅) ₂	NSAID	44	9
16	R ₁ = H; R ₂ = N(CH ₃) ₂ ; n = 1	GABAergic stimulator Respiratory analeptic Analeptic Antibacterial	86 80 72 55	2 2 3 6
17	R ₁ = CH ₃ ; R ₂ = N(C ₂ H ₅) ₂ ; n = 1	Carcinogenic GABAergic stimulator Antibacterial Analeptic Respiratory analeptic	52 85 61 55 51	12 3 4 10 11
18	R ₁ = Ph; R ₂ = ; n = 1	GABAergic stimulator Antiviral	67 53	13 9

No	Structure	Predicted Activity Spectra	Pa, %*	Pi, %*
19	$R_1 = \text{Ph}; R_2 = (\text{C}_2\text{H}_5)_2; n = 1$	Analeptic Respiratory analeptic Antiviral GABAergic stimulator	57 56 51 54	8 8 11 23
20	$R_1 = \text{H}_3\text{CO}$ -  ; $R_2 = \text{N}$ -  ; $n = 1$	NSAID MAO inhibitor reversible Analeptic GABAergic stimulator Respiratory analeptic Abortion inducer	61 55 53 59 51 50	3 8 12 19 11 12
21	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5; R_2 = \text{N}(\text{CH}_3)_2; n = 1$	GABAergic stimulator NSAID Non-morphine analgesic	75 56 53	7 4 4
22	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5; R_2 = \text{N}(\text{C}_2\text{H}_5)_2; n = 1$	GABAergic stimulator NSAID	72 53	9 5
23	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5; R_2 = \text{N}$ -  ; $n = 1$	GABAergic stimulator NSAID Carcinogenic	82 53 52	4 5 13
24	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5; R_2 = \text{N}$ -  ; $n = 1$	GABAergic stimulator NSAID Non-morphine analgesic	78 53 50	6 5 5
25	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5; R_2 = \text{N}$ -  - $\text{O}; n = 1$	GABAergic stimulator NSAID Carcinogenic	69 52 50	12 52 14
26	$R_1 = \text{CH}_3; R_2 = \text{N}$ -  ; $n = 1$	GABAergic stimulator Antibacterial Analeptic	90 50 51	1 7 13
27	$R_1 = \text{CH}_3; R_2 = \text{N}$ -  - $\text{O}; n = 1$	GABAergic stimulator	81	4
28	$R_1 = \text{Ph}; R_2 = \text{N}(\text{CH}_3)_2; n = 1$	Analeptic Respiratory analeptic Antiviral	57 56 51	8 8 11
29	$R_1 = \text{Ph}; R_2 = \text{N}(\text{C}_2\text{H}_5)_2; n = 1$	MAO inhibitor reversible Antiviral Analeptic	59 54 52	6 9 12
30	$R_1 = \text{Ph}; R_2 = \text{N}$ -  ; $n = 1$	GABAergic stimulator Antiviral	67 53	13 9
31	$R_1 = \text{Ph}; R_2 = \text{N}$ -  ; $n = 1$	GABAergic stimulator	58	20
32	$R_1 = \text{Ph}; R_2 = \text{N}$ -  - $\text{O}; n = 1$	MAO inhibitor reversible	51	10
33	$R_1 = \text{H}_3\text{CO}$ -  ; $R_2 = \text{N}(\text{C}_2\text{H}_5)_2; n = 1$	MAO inhibitor reversible NSAID Analeptic Respiratory analeptic	63 61 55 51	5 3 10 11
34	$R_1 = \text{H}_3\text{CO}$ -  ; $R_2 = \text{N}$ -  ; $n = 1$	NSAID GABAergic stimulator MAO inhibitor reversible Analeptic Respiratory analeptic	61 66 57 53 50	3 14 7 12 12
35	$R_1 = \text{H}_3\text{CO}$ -  ; $R_2 = \text{N}$ -  - $\text{O}; n = 1$	NSAID MAO inhibitor reversible	60 57	3 7
36	$R_1 = \text{H}; R_2 = \text{N}(\text{CH}_3)_2; n = 2$	Respiratory analeptic Analeptic GABAergic stimulator Cardiovascular analeptic	76 70 70 63	2 3 11 5

No	Structure	Predicted Activity Spectra	Pa, %*	Pi, %*
37	$R_1 = \text{CH}_3$; $R_2 = \text{N}(\text{CH}_3)_2$; $n = 2$	GABAergic stimulator Cardiovascular analeptic Mutagenic Analeptic Antiviral	73 62 52 53 50	8 5 7 12 11
38	$R_1 = \text{Ph}$; $R_2 = \text{N}$  ; $n = 2$	NSAID Antiviral Analgesic agent	68 56 50	2 8 7
39	$R_1 = \text{H}_3\text{CO}$  ; $R_2 = \text{N}$  ; $n = 2$	NSAID Analgesic agent Non-morphine analgesic Abortion inducer MAO inhibitor reversible Analeptic	74 60 56 55 51 51	1 4 3 8 9 13
40	$R_1 = \text{Ph}$; $R_2 = \text{N}$  ; $n = 2$	NSAID Analgesic agent	66 50	2 7
41	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5$; $R_2 = \text{N}(\text{CH}_3)_2$; $n = 2$	NSAID Non-morphine analgesic GABAergic stimulator Analgesic agent Immunomodulator	72 67 64 50 50	1 2 1 7 10
42	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5$; $R_2 = \text{N}(\text{C}_2\text{H}_5)_2$; $n = 2$	NSAID Non-morphine analgesic GABAergic stimulator Immunomodulator	70 64 59 50	1 2 19 10
43	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5$; $R_2 = \text{N}$  ; $n = 2$	NSAID GABAergic stimulator Non-morphine analgesic Immunomodulator	70 74 63 54	1 8 3 7
44	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5$; $R_2 = \text{N}$  ; $n = 2$	NSAID Non-morphine analgesic GABAergic stimulator Analgesic agent	70 65 67 51	2 2 13 6
45	$R_1 = \text{CH}_2\text{COOC}_2\text{H}_5$; $R_2 = \text{N}$  ; $n = 2$ 	NSAID Non-morphine analgesic Immunomodulator GABAergic stimulator	68 60 50 56	2 3 9 21
46	$R_1 = \text{H}$; $R_2 =$ 	Antimycobacterial Carcinogenic	58 52	5 13
47	$R_1 = \text{CH}_3$; $R_2 =$ 	Antimycobacterial	55	6
48	$R_1 = \text{Ph}$; $R_2 =$ 	MAO inhibitor reversible Antimycobacterial	69 67	3 3
49	$R = \text{OC}_2\text{H}_5$  	MAO inhibitor reversible Nucleotide metabolism regulator	63 52	5 12
50	$R = \text{F}$	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.

($k = 1, \dots, 114$); 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 ($L = 1, 2, 3, \dots$) 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:

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

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:

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

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:

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

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:

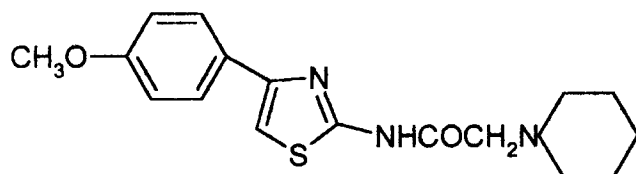
1. P_q values are sorted in ascending order.
2. $F(z) = \text{Arg}\{\sum q P_q F^{q-1} (1 - F)^{n-q} (n - 1)! / (q - 1)(n - 1)! = z\}$

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 probabilities 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 anaesthetics (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 Acetylsalicylic 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.

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