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COMPUTER ANALYSIS OF THE STRUCTURE–ACTIVITY RELATIONSHIP FOR IMMUNOACTIVE THIAZOLO[3,2-*a*]BENZIMIDAZOLE DERIVATIVES

V. M. Dianov,[1, *] E. K. Alekhin,[1] L. A. Tyurina,[2, **] and E. L. Aleksandrova[1]

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Computer analysis of the structure–activity relationship and purposeful design of effective immunomodulators among thiazolo[3,2-*a*]benzimidazole derivatives was performed. A mathematical recognition model was formulated. Immunomodulating activity of condensed azoles was predicted (80 – 100% learning recognition). Potentially active structures were generated. Their activities were predicted. Theoretical and experimental results agreed. The tested thiazolo[3,2-*a*]benzimidazole derivatives exhibited the predicted activities.

Keywords: computer system SARD, structure–activity relationship, thiazolobenzimidazoles, immunomodulating activity.

Azole derivatives are of great interest as natural and synthetic immunomodulators [1]. The search for new highly efficacious and safe immunomodulators remains critical despite notable progress in the synthesis of condensed azoles, e.g., thiazolobenzimidazoles with immunomodulating properties [2 – 4].

Information technology is now being used more and more often in addition to traditional methods for targeted synthesis of compounds with certain properties. The information required to investigate the structure–immunomodulating-activity relationship and to discover new active compounds was obtained from various databases, literature searches, and our own experimental results. These input data were included in a computer database with a molecular diagram (connectivity matrix) of the chemical compound that enabled visualization of the molecular structural formula and its immunomodulating activity. The optimal model for recognizing β-lymphocyte activity was formulated using 15 series of full SARD calculations [5] with sliding sampling control and variation of controlling thresholds and criteria affecting the test set (TS) descriptors and recognition of learning compounds.

The total number of fragment descriptors in the working version was 743; initial, 76; aggregates consisting of two and three initial descriptors, 206 and 461, respectively; after reducing the thresholds, 28, 29, and 42. A reduced set of fragment descriptors was used to generate 15,320 structural logical descriptors (disjunctive and conjunctive). The formulated mathematical models were reliable. Active compounds were recognized from a learning set using two algorithms (geometry and voting) at 100 and 84%, respectively. Inactive com-

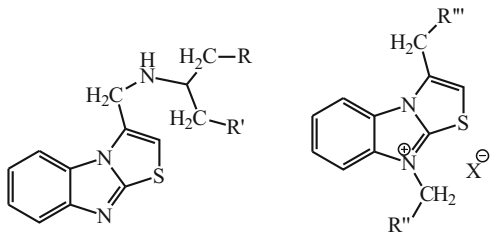


Fig. 1. Structures of compounds coinciding with the calculated standard.

[1] Bashkir State Medical University, Ufa, Bashkortostan, 450008 Russia.
[2] Scientific Research Technological Institute of Herbicides and Growth Regulators, Ufa, Bashkortostan, 450029 Russia.
[*] e-mail: dianov@inbox.ru.
[**] Deceased.

TABLE 1. TS Descriptors in Immunomodulating Activity Recognition Model

No.	Descriptor content	Information value
1	[CHap.-Cap.-(N=C)] \/* [CHap.-Cap.-N] /\ [CH_3-N-(C=C)]	0.715
2	[Cap.-Cap.-N] \/ [Cap.-(N=C)-NH] \/ [CH_3-N-(C=C)]	0.715
3	[Cap.-(N=C)-S] \/ [CHap.-Cap.-N] \/ [CH_3-N-(C=C)]	0.648
4	[CH-N-(N=C)] \/ [(N=C)-S-(C=C)] \/ [Cap.-(N=C)-NH]	0.638
5	[NH-(C=C)-(C=O)] \/ [Cap.-Cap.-(C=C)] \/ [CH_{2het}-N-(C=C)]	– 0.743
6	[Cap.-Cap.-(C=C)] \/ [CH-Cap.-CHap.] \/ [CH_{2het}-N-(C=C)]	– 0.743
7	[CH_3-N-CH_3] \/ [NH-(C=C)-(C=O)] \/ [CH_{2het}-N-(C=C)]	– 0.718
8	[CH-Cap.-CHap.] \/ [CHap.-Cap.-(C=C)] \/ [CH_{2het}-N-(C=C)]	– 0.693
9	[CH_2het-O-(C=O)] \/ [NH-(C=C)-(C=O)] \/ [CH_{2het}-N-(C=C)]	– 0.658
10	[Cap.-Cap.-NH] \/ [CH_3-N-CH_3] \/ [CH_{2het}-N-(N=C)]	– 0.601
11	CHap.-Cap.-NH] \/ [CH_3-N-CH_3] \/ [CH_{2het}-N-(N=C)]	– 0.601

\/, sign for disjunctive combination of fragments “or”.

pounds were recognized 92% by geometry and 91% by voting.

The results indicated that the recognition level for learning was adequate and that this rule could be used for subsequent prediction of immunomodulating properties of both simple and multicyclic azoles.

Recognition by various prediction models of compounds for T-cells was 80 – 92%, i.e., the models were reliable. The working version of the model included 22 descriptors. Recognition of compounds in class A (active) and B (inactive) by geometry was 94 and 82%; by voting, 88 and 82%. All TS descriptors were disjunctive.

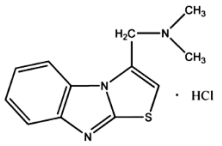
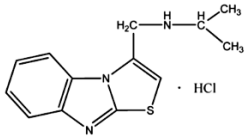
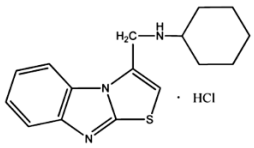
Recognition of learning compounds using the resulting mathematical model identified structures and established priorities of compounds, targeted chemical modification of which was most likely to afford compounds with the required activity. The distance to structures of active and inactive learning standards, distance to the hypothetically ideal structure giving a generalized active form; activity indices; and an expert evaluation of the synthetic steps were considered.

The distance was determined geometrically in TS descriptor space. Structures of this class were distributed among 11 ranks depending on the distance to the structural active standards (geometrically, in TS descriptor space) (Ta-

TABLE 2. Variable Structure Elements Selected Based on Game Theory Assessment

Change priority, number, code, and type of fragment				Maximum and minimum information value of fragment at each aggregation level (maximum and minimum)			
				second and third level of first reaction			maximum of maxima/minimum of minima regardless of level
6	1	7	Car<	0.105	0.239\0.036	0.239\– 0.130	0.239\– 0.130
9	2	5	CHar	0.047	0.121\0.036	0.376\0.036	0.376\0.036
10	3	7	Car<	0105	0.209\0.121	0.376\0.167	0.376\0.105
8	4	14	>N	– 0.211	0.209\– 0.388	0.376\– 0.130	0.376\– 0.388
6	5	15	Nar	0.036	0.036\0.036	0.239\– 0.130	0.239\– 0.130
5	6	16	NH	– 0.056	0.188\0.167	0.188\0.167	0.188\0.056
7	7	1	CH_3	– 0.018	0.239\0.167	0.239\0.167	0.239\– 0.018
1	8	3	CH_2	– 0.213	0.167\– 0.388	0.167\0.115	0.167\– 0.388
2	9	3	CH_2	– 0.213	0.167\0.115	0.167\0.115	0.167\– 0.213
3	10	26	OH	– 0.075	0.167\0.167	0.167\0.167	0.167\– 0.075
3	11	42	CH	– 0.018	– 0.075\– 0.075	0.167\0.167	0.167\– 0.075
4	12	116	cycle	0.167	0.167\0.167	0.167\0.167	0.167\0.167

TABLE 3. Acute Toxicity of Thiazolo[3,2-*a*]benzimidazole Derivatives After i.p. Injection

Compound	Acute toxicity (LD_{50}), mg/kg	
	mice[a]	rats[b]
 **I**	140.4 (126.6 – 155.6)	145.0
 **II**	266.0 (236.4 – 299.2)	250.0
 **III**	187.0 (174.0 – 201.0)	180.0
Levamisole	43.0 (39.3 – 47.1)	47.0

[a] Litchfield—Wilcoxon method; [b] van der Waerden method.

ble 1). Compounds with a condensed tricyclic system containing a six-membered carbocycle and two five-membered azole rings, i.e., imidazole and thiazole with one unsaturated C=C bond (structures A and B, Fig. 1), were closest to the hypothetical structural standard (practically coincided with it because the distance to the standard was zero).

The relative quantitative contributions of the structure elements to the immunomodulating activity were determined for each compound of the learning set (Table 2).

The priority for modifying the base structure fragments and constructing from them new potentially active compounds were determined based on the above estimates.

An analysis of fragments calculated for 25 active compounds substituted in the first, second, and third sites showed that the fragments with first priority for substitution were hydrogen bonded to a heteroatom (H-het), 38%; CH_3, 17%; CH_2 bonded to a heteroatom or Cl, 13%; aromatic CH and benzene ring, 8% each. The distribution for second priority was CH_2 in a heterocycle, CH-ar, C-ar, and N=C, 13% each; H-het, I, CH_3, two rings, and three rings; 8% each. Third priority was given to H-het, 17%; CH_3 and NH, 13% each; N^+, O, and C-ar atoms, 8% each. The other structure elements accounted for 2 – 4%.

Therefore, substituents bonded to a heteroatom and the heterocyclic system were most favorable for substitution. However, modification of the cyclic system itself was most interesting because new classes of compounds were produced.

An analysis of recognition, distances to the hypothetical standard, and the most probable structural elements for modification indicated that compounds with an aromatic six-membered ring in the cyclic system tended to be most likely to manifest activity.

Thus, a mathematical model for recognition and prediction of immunomodulating properties of condensed azoles (learning recognition 90 – 100%) was formulated as a result of the research. Potentially active structures were generated. Their activities were predicted.

Several compounds designed by the SARD system were synthesized by us and tested for the predicted activity. The experiment showed that, in general, the results agreed satisfactorily with the calculations. Most tested compounds exhibited the predicted activity. Synthesized **I-III** had comparatively low toxicities after i.p. injection to mice and rats (Table 3).

TABLE 4. Effect of Thiazolo[3,2-*a*]benzimidazole Derivatives on Transplantation Immunity

Compound	*n*	Dose, mg/kg	Median graft lifetime, d
I	9	14.0	6.6 ± 0.6
II	7	26.0	5.7 ± 0.3
III	9	9.0	8.3 ± 0.6 *
Control	17	–	6.2 ± 0.2

* Difference statistically significant vs. control for $p < 0.05$.

TABLE 5. Effect of Thiazolo[3,2-*a*]benzimidazole Derivatives on Development of Contact Hypersensitivity to DNFB

Compound	*n*	Dose, mg/kg	Reaction intensity, % vs. normal-immune control
With sensitization by an immunogenic (normal-immune) dose of DNFB			
I	5	7.0	24.6 ± 8.4[a]
II	5	13.0	30.2 ± 14.3[a]
III	5	4.5	39.0 ± 9.2[a]
With sensitization by a hyperimmune dose of DNFB			
I	8	7.0	37.5 ± 5.4[b]
II	10	13.0	40.0 ± 7.2[b]
III	9	4.5	23.3 ± 5.1
Normal-immune control	6	–	100.0 ± 9.0
Hyperimmune control	11	–	17.0 ± 5.2[a]

[a] Difference statistically significant vs. normal-immune control for $p < 0.05$;
[b] difference statistically significant vs. hyperimmune control for $p < 0.05$.

Compound **III** affected the survival of a skin allotransplant (Table 4) by increasing considerably its lifetime.

All tested compounds suppressed the development of contact hypersensitivity with sensitization of the animals by an immunogenic dose of 2,4-dinitrofluorobenzene (DNFB). However, compounds **I-III** prevented the development of tolerance with sensitization of the animals by a hyperimmune dose of DNFB, which is known to induce hapten-specific T-suppressors (Table 5).

EXPERIMENTAL PHARMACOLOGICAL PART

Acute toxicity (LD_{50}) of the studied compounds was determined by the Litchfield—Wilcoxon, and Miller and Tainter methods [6].

The effects of the thiazolobenzimidazoles on the survival of a skin allotransplant were studied using white laboratory mice of both sexes (16 – 18 g, C57BL/6, CBA, BALB/C). Allotransplantation of a skin graft used a histone-compatible donor (C57BL/6 mice) and recipient (CBA mice). Compounds were injected into the mice in equivalent doses of 10% of LD_{50} daily from the first to seventh day (day of the transplant was day "0") (Table 4).

Contact hypersensitivity to DNFB was assessed in BALB/C mice by the usual method [7] with sensitization of the animals after immunogenic (25 μL of 0.5% DNFB solution) and hyperimmunogenic doses of the antigen (150 μL of 0.5% DNFB solution). A resolving dose (20 μL of 0.2% DNFB solution) was injected into the dorsal side of the neck 4 d after sensitization. The result was assessed after 24 h from the increase of neck thickness. Compounds were injected i.p. at a dose of 5% of LD_{50} on the 4th d after immunization (Table 5).

REFERENCES

1. S. V. Sibiryak, Yu. V. Strokin, R. F. Sadykov, et al., *Khim.-farm. Zh.*, **24**(11), 19 – 24 (1990); *Pharm. Chem. J.*, **24**(11), 789 – 796 (1990).
2. R. L. Finichel, S. K. Dheer, N. H. Grant, et al., *J. Immunopharmacol.*, **5**(4), 333 – 340 (1983).
3. R. L. Finichel, H. L. Alturn, P. A. Schrech, et al., *J. Immunopharmacol.*, **2**(4), 491 – 508 (1980).
4. S. Gilman, R. Carlson, J. Chang, and A. Lewis, *Agents Actions*, **17**(1), 53 – 59 (1985).
5. L. A. Tyurina, O. V. Tyurina, and A. M. Kolbin, *Methods and Results of the Design and Prediction of Biologically Active Compounds* [in Russian], Gilem, Ufa (2007), pp. 25 – 30.
6. M. L. Belen'kii, *Elements of Quantitative Assessment of Pharmacological Effects* [in Russian], Medgiz, Leningrad (1963), pp. 81 – 106.
7. P. Phauphak, J. W. Moorhead, and H. N. Claman, *J. Immunol.*, **112**(1), 115 – 123 (1974).