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Application of thin-layer chromatographic data in quantitative structure–activity relationship assay of thiazole and benzothiazole derivatives with H_1-antihistamine activity. II

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Abstract

Quantitative structure–activity relationship (QSAR) analysis of H_1-antihistamine activity was carried out and chromatographic data of 2-[2-(phenylamino)thiazol-4-yl]ethanamine, 2-(2-benzyl-4-thiazolyl)ethanamine, 2-(2-benzhydrylthiazol-4-yl)ethylamine derivative, and 2-(1-piperazinyl- and 2-(hexahydro-1*H*-1,4-diazepin-1-yl)benzothiazole derivatives were obtained. Normal-phase (NP) TLC plates (silica gel $60F_{254}$), impregnated with solutions of selected amino acid mixtures (L-Asp, L-Asn, L-Thr and L-Lys) were used in two developing solvents as human histamine H_1-receptor (hH1R) antagonistic interaction models. The lipophilicity data of the examined compounds were obtained and used in the QSAR assay. Using regression analysis, relationships between chromatographic and biological activity data were found. The correlations obtained in the present experiment with NP-TLC are more significant that those obtained in the experiment with RP2 TLC, because of the optimal fitting of the chromatographic system conditions to the lipophilicity of solutes. All proposed chromatographic models should facilitate pre-selection of the new drug candidates. The correlations of calculated $pA_2(H_1)$ values of the tested compounds predicted by the use of the best equations versus their $pA_2(H_1)$ obtained from the biological tests were significant (R^2=0.91–0.94).

Keywords: Structure–activity relationships; Lipophilicity; Regression analysis; Planar chromatography; Thiazole; Benzothiazoles; Histamine; Organosulfur compounds

1. Introduction

Information necessary for developing new antihistamine H_1-receptor drugs is often obtained from investigation of other potent agonists or antagonists, using the structure–activity relationship, pharmacophoric models, selectivity, in vitro characterisation and their putative interaction with the helical transmembrane (TM) domains of the human histamine H_1-receptor (hH1R) [1–3]. Binding site models, proposed in the literature, of H_1-receptor for H_1-histaminergic and H_1-antihistamine drugs were described in detail in part I of this paper [4]. It has been suggested that the key binding residues are amino acids: Asp107 within the third transmembrane residue of the H_1-receptor, and Thr194, Asn198 and

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Lys191 within the fifth transmembrane residue of H_1-receptor.

The application of RP2 TLC chromatographic data in quantitative structure–activity relationship (QSAR) assay has been described in part I of this paper [4]. Chromatographic models of interactions of the thiazole and benzothiazole derivatives with human histamine H_1-receptor (hH1R) were proposed. These models consisted of the application of RP2 TLC silanised pre-coated plates (silica gel RP2 $60F_{254}$), impregnated with solutions of amino acids important for H_1-agonist and H_1-antagonist interaction, to hH1R in two developing solvents. Significant correlation between H_1-activity and chromatographic data was found in experiments with all proposed models with plates impregnated with simple amino acids and their mixtures containing Asp, Asn, Thr and Lys. The best multivariate relationships useful for predicting the pharmacological activity of thiazole and benzothiazole drug candidates were obtained under the conditions of the experiment with RP2 TLC plates using the developing solvent acetonitrile–methanol–buffer (40:40:20, v/v). The lipophilicity data of the examined compounds ($\log P$) were obtained and used in the QSAR assay. On the basis of the described results [4], we can say that the $\log P$ parameter is a crucial indicator of the H_1-antihistamine effect of the thiazole derivatives. An increase of the $\log P$ value favours higher biological activity of the tested compounds. Numerous significant multivariate relationships of the H_1-antihistamine effect involve the $\log P$ values of solutes. The univariate relationships calculated as the correlation coefficients between $pA_2(H_1)$ and $\log P$ values were: $r=0.79$ for the whole group of compounds **1**–**18** (thiazole and benzothiazole derivatives $n=18$) and 0.91 for thiazole derivatives **1**–**12** ($n=12$). Optimal fitting of the chromatographic system conditions to the lipophilic properties of the examined compounds should facilitate obtaining the desired effect in the experiment.

We analysed the relationship between the behaviour of the examined compounds in a chromatographic control environment (C) (without amino acids) and their $\log P$ values.

Analysis of data from chromatographic studies (RP2 $60F_{254}$ plates) and physicochemical parameter calculations led to the conclusion that there is no correlation between $\log P$ values of compounds **1**–**18** and their $R_{M(C)}$ chromatographic data. The calculated correlation coefficients (R) in developing solvents acetonitrile–methanol–buffer (40:40:20, v/v) (DS_A) and acetonitrile–methanol–methylene chloride–buffer (60:10:10:20, v/v) (DS_B) were 0.40 and 0.37, respectively. This result may indicate that the use of the other chromatographic system could be better for this experiment. On the basis of these facts we attempted to find a better chromatographic system. In the next study we investigated the role of the interaction between the examined thiazole and benzothiazole derivatives with L-Asp, L-Asn, L-Thr and L-Lys in chromatographic environment with normal-phase (NP) TLC plates using the same developing solvents DS_A and DS_B. The results of this study are described in the present paper.

The analysis of chromatographic data proposed in this paper aims at finding a better analytical model of H_1-antihistamine activity of the thiazole and benzothiazole derivatives group. The approach should facilitate the pre-selection of drug candidates, at the same time reducing costs and the use of laboratory animals.

2. Experimental

2.1. Examined compounds

Both in the present and previous study [4] the same compounds **1**–**18** were examined. The synthesis method, analytical data and biological activity of the 2-[2-(phenylamino)thiazol-4-yl]ethanamines (compounds **1** and **2**), 2-(2-benzyl-4-thiazolyl)-ethanamines (compounds **3**–**6**), 2-(2-benzhydrylthiazol-4-yl)ethylamine derivatives (compounds **7**–**12**), and 2-(1-piperazinyl- and 2-(hexahydro-1*H*-1,4-diazepin-1-yl)benzothiazole derivatives (compounds **13**–**18**) have been described in previous papers [5–7]. The thiazole and benzothiazole derivatives in pharmacological assays showed antagonistic and partial agonistic activity on H_1-receptor. Some compounds showed antagonistic activity both on the H_1- and H_3-receptor (the structures, H_1- and H_3-antihistamine activity and lipophilicity of compounds **1**–**18** are shown in Fig. 1 and Table 1 of Ref. [4]).

2.2. Chromatography

In this new experiment silica gel $60F_{254}$ NP-TLC plates and the developing solvents (used in the last experiment [4]) DS_A and DS_B were used because an insignificant correlation was found between lipophilicity parameter $\log P$ and behaviour of the examined compounds in chromatographic control environment (C) (without amino acids) with RP2 $60F_{254}$ plates [4]. Analysis of data from chromatographic assay with NP-TLC plates and physicochemical parameter calculations led to the conclusion that there was a correlation between the $\log P$ values of compounds **1**–**18** and their $R_{M(C)}$ chromatographic data. The calculated correlation coefficients (R) in developing solvents DS_A and DS_B were 0.61 and 0.72, respectively. This result may indicate that this chromatographic system should be used for this experiment, especially under the chromatographic conditions with DS_B developing solvent.

For the chromatographic evaluation of commercially available compounds, 20×20 cm NP-TLC plates (silica gel $60F_{254}$; Merck, Darmstadt, Germany) were used. The solutes were applied to the plate as described in part I [4]. Under these chromatographic condition, the amino acids used for the impregnation of plates (L-Asp, L-Asn, L-Thr, L-Lys) are quite motionless (R_f-solutes>R_f-amino acids).

As new chromatographic models of H_1-interaction with solutes, the impregnated silica gel NP-TLC plates were used. The plates were impregnated with solutions of amino acids important for this interaction with ligands. Based on the previous experiment (part I), solutions of simple amino acids: L-Asp (S1), L-Asn (S2), L-Thr (S3), L-Lys (S4) and their mixtures: L-Asn+L-Thr (S5), L-Asn+L-Lys (S6), L-Asp+L-Asn+L-Thr (S7) were used for making chromatographic models of H_1-receptor interaction. Models S1–7 and the control plates were prepared as in part I [4]. Running time amounted to 22±2 min (in the experiment with developing solvent DS_B) and 33±2 min (in the experiment with developing solvent DS_A) in which time the front reached 12 cm from the lower edge of the plate.

R_M values were calculated according to Bate-Smith and Westall [8]: $R_M = \log(1/R_f - 1)$.

$R_{M(S1-S7)}$ values indicate interaction of models S1–7 on test compounds, and $R_{M(C)}$ values represent the behaviour of compounds in the chromatographic control environment (C). All chromatographic data are shown in Tables 1 and 2.

2.3. QSAR analysis

QSAR analysis of H_1-antihistamine activity was carried out and chromatographic data of compounds **1**–**18** was obtained. The correlation between biological activity data pA_2 and the behaviour of the examined compounds in chromatographic environment (S1–S7) (Tables 1 and 2) was investigated by linear and multivariate regression analysis. The regression analysis was carried out using the STATISTICA 5.1 program. The use of more than one variable in a multivariate equation was justified by an inter-correlation study. The following descriptors derived from chromatographic data were used as data representing the interaction of test compounds with the environment of proposed models (the independent variables): $R_{M(S1-7)}$ (S1–S7); $R_{M(C)} - R_{M(S1-7)}$ (C−S1–7); $R_{M(S1-7)}/R_{M(C)}$ (S1–7/C), and we used pA_2 values as data representing the H_1- and H_3-activity (dependent variable). Additionally, the $\log P$ values of solutes were applied as independent variables in the regression analysis.

3. Results and discussion

The relationship between the behaviour of the examined thiazole and benzothiazole derivatives in biochromatographic environments S1–7 (proposed as the analytical models of H_1-antihistamine activity) and their biological activity was investigated according to the previous experiment [4]. The chromatographic data obtained in the present experiments are collected in Tables 1 and 2.

Analysis of the data from pharmacological and chromatographic studies led to the conclusion that there was no correlation between the H_1-antihistamine activities of compounds **1**–**18** and their C-chromatographic data (in the chromatographic control environment without amino acids). The calculated correlation coefficients (R) in developing solutes DS_A and DS_B were 0.33 and 0.43, respectively. This result may indicate that other significant rela-

Table 1
R_M values for the experiment with NP-TLC plates and DS_A developing solvent

Compound[a]	NP-TLC R_M (DS_A)							
	$R_{M(C)}$ (C)[b]	$R_{M(S1)}$ (S1)[c]	$R_{M(S2)}$ (S2)	$R_{M(S3)}$ (S3)	$R_{M(S4)}$ (S4)	$R_{M(S5)}$ (S5)	$R_{M(S6)}$ (S6)	$R_{M(S7)}$ (S7)
1	0.052	0.028	0.476	0.599	−0.185	0.337	−0.185	−0.048
2	0.009	0.003	0.432	0.586	−0.213	0.264	−0.259	−0.058
3	0.087	0.050	0.488	0.631	−0.149	0.283	−0.122	−0.022
4	0.078	0.056	0.478	0.630	−0.158	0.283	−0.131	−0.036
5	0.070	0.060	0.483	0.631	−0.167	0.278	−0.158	−0.034
6	0.070	0.067	0.489	0.619	−0.158	0.301	−0.122	−0.027
7	−0.052	−0.047	0.384	0.508	−0.259	0.163	−0.308	−0.149
8	−0.525	−0.587	−0.499	−0.491	−0.259	−0.509	−0.466	−0.597
9	−0.070	−0.047	0.368	0.528	−0.259	0.154	−0.317	−0.153
10	−0.070	−0.027	0.368	0.521	−0.259	0.152	−0.308	−0.131
11	−0.061	−0.032	0.363	0.533	−0.269	0.166	−0.327	−0.143
12	0.194	0.162	0.541	0.647	−0.009	0.336	0.026	0.012
13	0.477	0.393	0.684	0.732	0.264	0.590	0.298	0.267
14	0.269	0.240	0.517	0.560	0.061	0.361	0.096	0.141
15	0.158	0.294	0.092	0.127	−0.087	0.021	−0.017	0.193
16	−0.269	−0.038	−0.272	−0.231	−0.562	−0.339	−0.477	−0.167
17	−0.575	−0.240	−0.610	−0.587	−0.771	−0.679	−0.771	−0.359
18	−0.575	−0.271	−0.630	−0.609	−0.753	−0.690	−0.771	−0.385

[a] Compounds are numbered as in part I [4].
[b] $R_{M(C)}$, retention parameter of the compounds in chromatographic control environment.
[c] $R_{M(S1–7)}$, retention parameters of the compounds in the chromatographic environments of models S1–S7.

Table 2
R_M values for the experiment with NP-TLC and DS_B developing solvent

Compound[a]	NP-TLC R_M (DS_B)							
	$R_{M(C)}$ (C)[b]	$R_{M(S1)}$ (S1)[c]	$R_{M(S2)}$ (S2)	$R_{M(S3)}$ (S3)	$R_{M(S4)}$ (S4)	$R_{M(S5)}$ (S5)	$R_{M(S6)}$ (S6)	$R_{M(S7)}$ (S7)
1	0.231	0.293	0.341	0.378	0.105	0.232	0.122	0.233
2	0.194	0.233	0.295	0.224	0.083	0.155	0.070	0.157
3	0.250	0.280	0.387	0.235	0.140	0.198	0.158	0.217
4	0.231	0.249	0.355	0.191	0.122	0.153	0.114	0.134
5	0.213	0.236	0.330	0.167	0.105	0.147	0.105	0.157
6	0.250	0.295	0.372	0.345	0.140	0.243	0.149	0.154
7	0.114	0.151	0.131	0.057	0.078	0.075	0.035	0.085
8	−0.176	−0.149	−0.116	−0.085	0.061	−0.038	−0.114	−0.080
9	0.087	0.154	0.128	0.043	0.070	0.070	0.017	0.078
10	0.105	0.158	0.146	0.043	0.078	0.069	0.026	0.076
11	0.070	0.135	0.107	0.043	0.070	0.065	0.009	0.050
12	0.176	0.163	0.134	0.085	0.087	0.058	0.043	0.043
13	0.454	0.519	0.593	0.527	0.278	0.466	0.347	0.007
14	0.347	0.467	0.463	0.391	0.185	0.389	0.259	0.247
15	0.176	0.462	0.111	0.080	0.009	0.094	0.070	0.223
16	−0.087	0.050	−0.122	−0.094	−0.288	−0.050	−0.105	0.007
17	−0.194	−0.040	−0.339	−0.296	−0.562	−0.308	−0.443	−0.030
18	−0.432	−0.100	−0.434	−0.425	−0.562	−0.420	−0.537	−0.075

[a] Compounds are numbered as in part I [4].
[b] $R_{M(C)}$, retention parameter of the compounds in chromatographic control environment.
[c] $R_{M(S1–7)}$, retention parameters of the compounds in the chromatographic environment of models S1–S7.

tionships, mentioned below (Table 3), depend upon the specific biochromatographic environment.

A distinct relationship between $pA_2(H_1)$ values, log P values and the interaction data of the examined compounds with models S1–7 can be observed.

Under the conditions of the experiment with DS_A, good univariate relationships of the H_1-antihistamine effect involve interactions of solutes with environments of the models S2–S7 (in the case of analysis for $n=18$ and $n=12$) (Table 3). These univariate relationships explain ~55% of the total variance obtained by use of descriptors S2–7/C (equations not shown). Models S2–7 describe the interaction of compounds with Asp107, Asn198, Thr194 and Lys191 (in TM3 and TM5 of hH1R). In analysing the whole group of compounds, significant multivariate relationships of the H_1-antihistamine effect involving log P values of solutes, explaining 85–91% of the variance, were obtained from models S1–7 (some of which are shown in Table 3). The best multivariate equations may be useful in predicting the pharmacological activity of thiazole and benzothiazole drug candidates (Eq. (3) in Table 4). The correlation of calculated $pA_2(H_1)$ values of the tested compounds predicted by Eq. (3) versus their $pA_2(H_1)$ values obtained from the biological tests was significant ($R^2=0.91$).

The equations below describe a possible interaction between the H_1-ligands and all proposed amino acids residues in TM3 and TM5 of hH1R. The correlations obtained in the present experiment with NP-TLC and DS_A are more significant that those

Table 3
The relationships between $pA_2(H_1)$ values and descriptors obtained in the experiment with DS_A and DS_B developing solvent

Equation	Independent variables in equation $pA_2=$	R[a]	F[b]	S[c]	$P<$[d]	n[e]
Developing solvent DS_A						
(1)	$a+b\log P+c$ S6/C $+d$ S4	0.94	34.098	0.29350	0.00000	18
(2)	$a+b\log P+c$ S7/C $+d$ S6	0.94	34.722	0.29117	0.00000	18
(3)	$a+b\log P+c$ S7/C $+d$ S4	0.95	47.040	0.25413	0.00000	18
(4)	$a+b\log P-c$ S5/C $+d$ (C − S1)	0.94	36.078	0.28629	0.00000	18
(5)	$a+b\log P-c$ S5/C $+d$ S4	0.94	36.373	0.28525	0.00000	18
(6)	$a+b\log P-c$ S3/C $+d$ (C − S1)	0.94	35.488	0.28838	0.00000	18
(7)	$a+b\log P-c$ S3/C $+d$ S4	0.94	37.249	0.28226	0.00000	18
(8)	$a+b\log P-c$ S2/C $+d$ S4	0.94	37.798	0.28043	0.00000	18
(9)	$a+b\log P-c$ S2/C $+d$ (C − S1)	0.94	36.087	0.28625	0.00000	18
(10)	$a+b\log P+c$ S6/C	0.97	62.930	0.25047	0.00001	12
(11)	$a+b\log P+c$ S4/C	0.97	63.829	0.24881	0.00000	12
(12)	$a+b\log P+c$ S7/C	0.97	71.693	0.23562	0.00000	12
(13)	$a+b\log P-c$ S5/C	0.97	64.801	0.24706	0.00000	12
(14)	$a+b\log P-c$ S3/C	0.97	65.525	0.24578	0.00000	12
(15)	$a+b\log P-c$ S2/C	0.97	66.543	0.24402	0.00000	12
Developing solvent DS_B						
(16)	$a+b\log P-c$ S4/C $+d$ S5	0.92	25.098	0.33495	0.00001	18
(17)	$a+b\log P-c$ (C − S4) $+d$ S7	0.93	28.057	0.31954	0.00000	18
(18)	$a+b\log P-c$ (C − S4) $+d$ S1	0.92	26.395	0.32789	0.00001	18
(19)	$a-b$ S7 $+c$ S4/C	0.91	21.953	0.39989	0.00035	12
(20)	$a-b$ S5	0.91	46.089	0.38838	0.00005	12
(21)	$a-b$ S5 $+c$ S4/C	0.95	43.431	0.29708	0.00002	12
(22)	$a+b$ S1/C $-c$ S5/C	0.94	36.495	0.32123	0.00005	12
(23)	$a-b$ S3 $+c$ (C − S2)	0.93	29.549	0.35247	0.00011	12

[a] Correlation coefficient.
[b] Value of the F-test of significance.
[c] Standard error of estimate.
[d] Significance level of the equation.
[e] Number of compounds used to derive the regression equation.

Table 4
The observed and predicted $pA_2(H_1)$ values of the examined compounds **1**–**18** (under the conditions of experiment with NP-TLC DS_A and DS_B)

Compound	Obtained pA_2	Predicted pA_2					
		Eq. (3)	Eq. (12)	Eq. (13)	Eq. (14)	Eq. (15)	Eq. (21)
1	4.440	4.530	4.484	4.484	4.516	4.509	4.174
2	4.000	3.829	3.996	3.968	3.970	3.968	4.538
3	4.530	4.624	4.487	4.502	4.489	4.491	4.455
4	4.820	4.776	4.695	4.741	4.726	4.729	4.780
5	4.650	4.917	4.857	4.907	4.887	4.888	4.875
6	4.140	4.370	4.227	4.207	4.208	4.207	4.033
7	5.880	5.866	5.920	5.808	5.822	5.833	5.870
8	6.150	5.686	5.775	5.759	5.751	5.751	6.180
9	6.380	6.040	6.152	6.120	6.130	6.129	5.989
10	5.990	5.785	5.876	5.868	5.879	5.881	5.979
11	5.870	6.189	6.340	6.317	6.325	6.320	6.244
12	5.980	6.099	6.021	6.150	6.127	6.124	5.712
13	5.700	5.923	–	–	–	–	–
14	5.820	5.457	–	–	–	–	–
15	5.600	5.604	–	–	–	–	–
16	5.990	6.232	–	–	–	–	–
17	6.080	6.123	–	–	–	–	–
18	5.770	5.741	–	–	–	–	–

obtained in the experiment with RP2 TLC and DS_A [4]:

$$pA_2 = 0.04(\pm0.01)S6/C + 1.11(\pm0.35)S4 + 0.57(\pm0.08)\log P + 4.23(\pm0.19) \quad (1)$$

$$pA_2 = 1.16(\pm0.34)S4 + 0.16(\pm0.03)S7/C + 0.54(\pm0.07)\log P + 4.16(\pm0.17) \quad (3)$$

$$pA_2 = 2.51(\pm0.81)C - S1 - 0.04(\pm0.01)S5/C + 0.59(\pm0.09)\log P + 4.07(\pm0.23) \quad (4)$$

$$pA_2 = 1.06(\pm0.33)S4 - 0.02(\pm0.00)S3/C + 0.56(\pm0.08)\log P + 4.31(\pm0.19) \quad (7)$$

$$pA_2 = 1.05(\pm0.23)S4 - 0.2(\pm0.01)S2/C + 0.56(\pm0.08)\log P + 4.32(\pm0.19) \quad (8)$$

After excluding compounds **13**–**18** from the calculations (under the conditions of experiment with DS_A), possessing both H_1- and H_3-antihistamine activity [7], we can conclude that the $pA_2(H_1)$ effect correlates better with the behaviour of the examined compounds in the proposed chromatographic environment. Significant bivariate relationships of the H_1-antihistamine effect involve interactions of solutes with the environments of models S2–7 and log *P* values of the solutes (some of which are shown in Eqs. (10)–(15) in Table 3) and explain 93–94% of variance. These relationships describe a possible interaction between the H_1-ligands and amino acids residues in TM3 and TM5 of hH1R: Asp107, Lys191, Thr194 and Asn198. They can be expressed by the following equations:

$$pA_2(H_1) = 0.13(\pm0.03)S7/C + 0.62(\pm0.08)\log P + 3.81(\pm0.20) \quad (12)$$

$$pA_2(H_1) = -0.03(\pm0.01)S5/C + 0.66(\pm0.08)\log P + 3.85(\pm0.22) \quad (13)$$

$$pA_2(H_1) = -0.02(\pm0.00)S3/C + 0.65(\pm0.08)\log P + 3.85(\pm0.21) \quad (14)$$

$$pA_2(H_1) = -\ 0.02(\pm 0.00)S2/C + 0.65(\pm 0.08)\log P + 3.86(\pm 0.21) \quad (15)$$

It is clearly seen that Eqs. (10)–(15) (Table 3) may have predictive value for the design of new H_1-antihistamine drugs (Table 4 and Fig. 1). The correlations of calculated $pA_2(H_1)$ values of the tested compounds predicted by the use of the above mentioned equations versus their $pA_2(H_1)$ values obtained from the biological tests was significant ($R^2 = 0.93$–0.94).

Under the conditions of experiment with DS_B there was no correlation between the H_1-antihistamine effects of the whole group of compounds **1**–**18** and their behaviour in the environment of the particular chromatographic models. Good multivariate relationships were obtained after including the log P parameter in the calculation (Table 3). The best relationships involve interactions of the examined thiazole and benzothiazole derivatives with models S1, S4 and S7, which represent the whole group of amino acids used:

$$pA_2 = 3.52(\pm 0.92)S7 - 3.52(\pm 0.79)C - S4 + 0.87(\pm 0.11)\log P + 2.84(\pm 0.40) \quad (17)$$

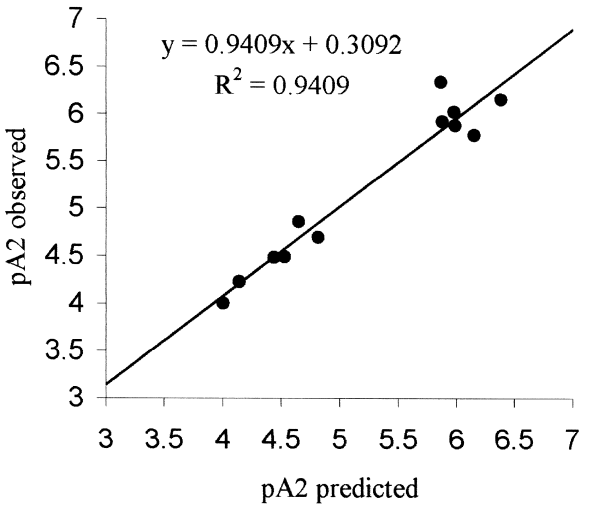

Fig. 1. Correlation of calculated $pA_2(H_1)$ values of the tested compounds predicted by Eq. (12) versus their $pA_2(H_1)$ values observed in the biological tests.

$$pA_2 = 2.28(\pm 0.63)S1 - 3.30(\pm 0.79)C - S4 + 0.79(\pm 0.10)\log P + 3.14(\pm 0.35) \quad (18)$$

In the group of compounds without H_3-antihistamine activity (**1–12**) there were some good univariate relationships. They involve the interactions of solutes with the environments of the models S3, S5, S6, S7 (as $R_{M(S)}$ parameters) and explain 62–82% of the variance (Eq. (20) in Table 3). Significant bivariate relationships (Eqs. (19), (21)–(23) in Table 3) describe an interaction which is possible between the H_1-ligands and amino acid residues in TM3 and TM5 of hH1R: Asp107, Lys191, Thr194 and Asn198. The best of these relationships can be expressed by the following equations:

$$pA_2(H_1) = 0.81(\pm 0.28)S4/C - 8.80(\pm 0.95)S5 + 5.69(\pm 0.18) \quad (21)$$

$$pA_2(H_1) = 2.60(\pm 0.37)S1/C - 3.99(\pm 0.50)S5/C + 4.76(\pm 0.40) \quad (22)$$

$$pA_2(H_1) = 6.39(\pm 2.50)C - S2 - 3.95(\pm 1.03)S3 + 6.27(\pm 0.17) \quad (23)$$

The correlation of calculated the $pA_2(H_1)$ values of the tested compounds predicted by Eq. (21) versus their $pA_2(H_1)$ values obtained from the biological tests was significant ($R^2 = 0.91$). The predictive role of the equation is shown in Table 4.

We conclude that the DS_B developing solvent is better for this small group of compounds than the DS_A. The $pA_2(H_1)$ effect correlates better with the behaviour of the examined compounds in the particular chromatographic environment of the models. However, multivariate relationships are less strong than those calculated in the experiment with DS_A. In this case, we were not able to use the important parameter log P in the multivariate equations because of its strong inter-correlation with other independent variables. This limitation explains the obtained results.

4. Conclusion

It is evident in QSAR assay that the best correla-

tions obtained in regression analysis for thiazole and benzothiazole derivatives (**1–18**) with H_1-antihistamine activity ($pA_2(H_1)$) indicate interaction with the proposed biochromatographic models S1–7 using NP-TLC silica gel plates and DS_A and DS_B developing solvents. We can also see that the log *P* values of the particular compounds are very important for this kind of activity. After changing the chromatographic environment we obtained a better relationship between $R_{M(C)}$ and the log *P* values of the examined compounds. Optimal fitting of the chromatographic system conditions to the lipophilic properties of solutes resulted in the desired effects. The results of experiment with silica gel NP-TLC $60F_{254}$ plates are better than those obtained in previous experiment with silica gel RP2 TLC $60F_{254}$ silanised pre-coated plates [4]. Some of the calculated equations can be applied to predict the pharmacological activity of new drug candidates: this should facilitate their preselection, at the same time reducing cost and the use of laboratory animals.

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