Heteroatom Chemistry
Volume 21, Number 4, 2010

Structure–Activity Relationship of *s*-Triazoles and Thiadiazoles as Analgesics

Agata Siwek,[1] Monika Wujec,[1] Tomasz Plech,[1] Edyta Kuśmierz,[1] Ewa Jagiełło-Wójtowicz,[2] and Anna Chodkowska[2]

[1]*Department of Organic Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin, Poland*

[2]*Department of Toxicology, Faculty of Pharmacy, Medical University, Chodzki 8, 20-093 Lublin, Poland*

Received 11 October 2009; revised 31 March 2010

ABSTRACT: *The influence of* s*-triazoles (***6–9***) and thiadiazoles (***10–11***) on the central nervous system of mice in some behavioral tests was investigated. It was found that compounds (***10***) and (***11***) are the possible candidates for further development as analgesic agents. The correlation between the molecular descriptors and analgesic potential has been studied by using the pattern recognition methods: principal component analysis (PCA) and hierarchical cluster analysis (HCA). Our results, however, showed that the relationship between molecular descriptors and analgesic activity of* s*-triazoles and thiadiazoles cannot be easily explained on the basis of PCA and HCA.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:256–264, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20605

INTRODUCTION

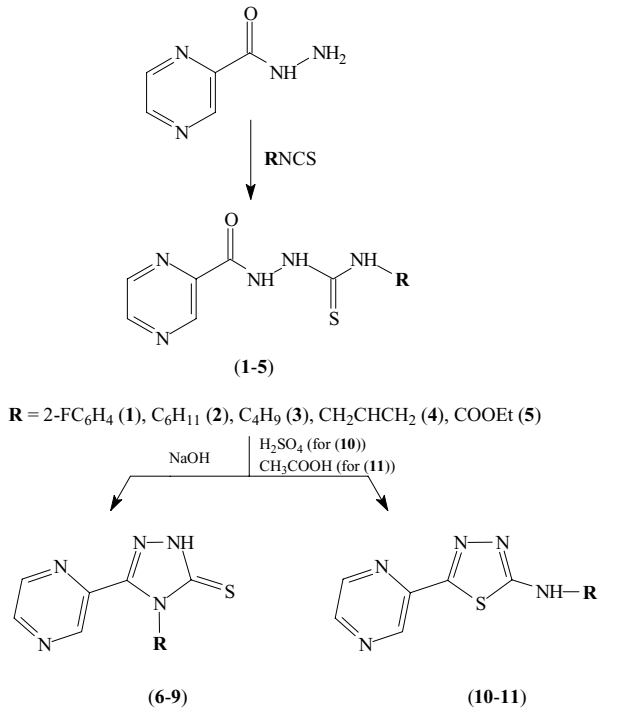
Many compounds bearing an azole ring in their structure have an extensive spectrum of pharmacological activities. Therefore, *s*-triazoles and thiadiazoles have been synthesized in our laboratory for a long time and their anticonvulsant, antidepressant, and analgesic potentials have been investigated [1–3]. Previous studies [2,3] have shown a strong analgesic activity of *s*-triazoles, having furane or thiophene moiety. Furthermore, some of tested compounds possessed anticonvulsant, antidepressive, and antiserotoninergic properties. In addition, the promising results for azole-like compounds as potent anti-inflammatory and analgesic agents were described and discussed in several publications [4–9]. Promoted by these observations, we herein present preliminary evaluation of pharmacological properties of four *s*-triazoles with pyrazine moiety and, for comparison, two pyrazine-thiadiazoles. Although most of the titled compounds are known, their activities on central nervous system (CNS) have not yet been reported.

Nowadays, structure–activity relationship (SAR) studies have been proven to be helpful in the understanding of the influence of molecular properties on the biological activity presented by several kinds of compounds [10]. To this end, a large number of various molecular descriptors have been proposed for establishing the SAR and a number of program packages have been developed for the calculations of these descriptors [11]. However, the practice showed that the number of molecular descriptors accessible for the calculation can be significantly greater than the number of compounds in the teaching set. Such a relation between the number of descriptors and that of compounds in the teaching set makes highly probable the appearance of accidental correlations and classification rules, which describe well the learning set as such but are incapable of predicting the

Correspondence to: Agata Siwek; e-mail: agata.siwek@am.lublin.pl.
© 2010 Wiley Periodicals, Inc.

activity of new compound. In addition, molecular descriptors used in the search for SARs—especially descriptors belonging to the same type (such as topological indices of molecular connectivity of various orders)—were frequently rather strongly correlated, which led to additional difficulties. One possible approach to eliminating the aforesaid problems consists of using so-called principal components (PCs) [12]. Principal component analysis (PCA) is one of the most popular chemometric method used to study interdependencies between molecular descriptors, to eliminate the correlation between the variables, and to reduce dimensionality of the data [13].

Thus, with the aim to correlate some molecular descriptors of *s*-triazoles and thiadiazoles and their biological analgesic activity, PCA has been employed. To test the results obtained on the basis of PCA method, another statistical analysis has been performed. Because, in such cases, it is good practice to apply a method leaning on a completely different algorithm, the hierarchical cluster analysis (HCA) has been used. This technique consists of grouping samples into respective clusters according to their similarities and differences. The results of a clustering method are generally reported in a plot (so-called dendrogram), where the ordinate is the similarity between groups and the abscissa has no specific meaning, but is used only to separate the clusters [14].



SCHEME 1 Synthesis of 1-(pyrazin-2-ylcarbonyl)-4-substituted thiosemicarbazides (**1–5**), 4-substituted-5-(pyrazin-2-yl)-s-triazole-3-thiones (**6–9**), and 2-aminosubstituted-5-(pyrazin-2-yl)-1,3,4-thiadiazoles (**10**) and (**11**).

RESULTS AND DISCUSSION

Chemistry

The synthesis of the titled compounds (**6–11**) based on a common procedure in this structural class [15–18] is depicted in Scheme 1. In short, pyrazine-2-carboxylic acid hydrazide was reacted with isothiocyanates. Cyclization of the formed thiosemicarbazides (**1–5**) to the *s*-triazoles (**6–9**) occurred in the presence of aqueous sodium hydroxide solution. The thiadiazoles (**10**) and (**11**) were prepared by treatment of (**2**) and (**5**) with sulfuric acid or glacial acetic acid, respectively.

The structures of known compounds (**2–4**) and (**6–10**) were confirmed by the results of elemental analysis, melting points, and spectroscopic data compared to literature values [19–23]. The characterization and spectral data of original compounds (**1**), (**5**), and (**11**) are presented later. The ^{1}H NMR spectra of (**6–9**) show a sharp singlet at 14.21–14.58 ppm typical for the proton linked to N1, indicating the presence the thione tautomer [24].

Pharmacological Evaluation

Preliminary behavioral study showed that none of the tested compounds (**6–11**) was found to show neurotoxic activity because in the dose of 0.1 LD_{50} they did not affect the motor coordination of mice in the "chimney test." Interestingly, of the six examined compounds, the most active compounds were thiadiazoles (**10**) and (**11**). Compounds (**10**) and (**11**) in the doses 0.025, 0.05, and 0.1 of LD_{50} showed strong analgesic activity in the "writhing syndrome" test. Among tested *s*-triazoles, only (**6**) and (**7**) in the doses 0.05 and 0.1 of LD_{50} displayed the analgesic effect. In addition, compound (**7**) in the doses 0.05 and 0.1 of LD_{50} showed antiserotoninergic activity in the "head twitches" test as well as antiepileptic action in the "pentetrazole-induced convulsions" test. In the remaining tests, the title compounds did not produce any significant activity on the CNS of mice. Compounds (**6**) and (**9**) showed depressive activity in mice; they significantly prolonged the thiopental sleeping time in the "thiopental-induced sleep" test. Compound (**11**) increased the tonic pentetrazole-induced seizures as well as mortality of mice in the

"pentetrazole-induced convulsions" test. Compound (**8**) was pharmacologically inactive.

PCA and HCA of Variables

With the aim to correlate some structural parameters of *s*-triazoles and thiadiazoles and their analgesic potential, we employed the chemometric methods PCA and HCA. For this evaluation, we included title compounds (**6–11**) as well as compounds (**12–28**) reported in the literature as having different degrees of analgesic activities [1–3,25–27] (Fig. 1).

Among 16 variables tested, the most important descriptors found in our PCA analysis were Vol, R, M_W, $\Delta E_{\text{LUMO-HOMO}}$, E_T, A (grid), E_{LUMO}, PA, and μ. The calculated values of these nine variables are presented in Table 1. It has been assumed that the power must exceed the value of 0.900 (see Table 2). The selected parameters were subjected to the proper classification analysis.

The PCA results presented in Table 3 reveal that the first four PCs explain 97.24% of the variance. Because the first two PCs explain a great percentage of the variance (79.23%), further presentation of the results will be shown on the basis of the aforesaid two dimensions. In two generated dimensions (PC1 vs. PC2), two clusters of compounds comprising active, moderately active, and inactive *s*-triazoles and thiadiazoles have observed (see Fig. 2 and Table 4). The loading values for the nine selected structural descriptors have been described as well (see Fig. 3 and Table 5). According to the values displayed in Table 5, PC1 and PC2 are expressed through the following equations:

$$\begin{aligned}\text{PC1} = {} & -0.968\,[M_w] - 0.717\,[E_{\text{LUMO}}] \\ & - 0.688\,[\Delta E_{\text{LUMO-HOMO}}] - 0.977\,[\text{Vol}] \\ & + 0.957\,[E_T] + 0.330\,[\mu] - 0.958\,[A_{\text{grid}}] \\ & - 0.984\,[R] + 0.301\,[\text{PA}] \\ \text{PC2} = {} & -0.102\,[M_w] + 0.565\,[E_{\text{LUMO}}] \\ & + 0.030\,[\Delta E_{\text{LUMO-HOMO}}] - 0.100\,[\text{Vol}] \\ & + 0.187\,[E_T] + 0.470\,[\mu] - 0.151\,[A_{\text{grid}}] \\ & + 0.012\,[R] - 0.794\,[\text{PA}]\end{aligned}$$

Based on the above-mentioned analysis, it may be inferred that the first cluster of compounds (on the left-hand side of the Fig. 2) shows higher values of such structural descriptors as: E_{LUMO}, R, M_w, $\Delta E_{\text{LUMO-HOMO}}$, Vol, and A (grid). The other cluster (on the right-hand side of the Fig. 2) shows higher values for E_T and μ. Distinguished two clusters, however, include both active and inactive molecules. The HCA results were similar to the PCA ones as shown in Fig. 4. The point representing the compound (**11**), which has the highest negative score on PC2, does not group with either cluster. It is proper to note that this compound is characterized by the highest value of the PA parameter.

To save time, money, and research animals, it is crucial to develop efficient means of predicting biological effects of untested compounds. One way to accomplish the estimation of the pharmacological profile of novel molecules is to construct mathematical models, the so-called quantitative structure–activity relationship (QSAR) models. The useful tools in deriving multivariate QSARs are chemometric methods such as PCA and HCA. Successful applications of the use of PCA and HCA for the recognition of lipophilicity, steric, and electronic properties as major determinants of analgesic activity of cannabinoid compounds were described by Arroio et al. [10] With this aim in mind, we employed the same procedure to obtain the relationship between the molecular descriptors and the analgesic activity of *s*-triazoles and thiadiazoles. Our results, however, revealed that the pattern recognition methods PCA and HCA are far from being universally applicable for screening new *s*-trazioles and thiadiazoles as analgesic agents.

In conclusion, although we have found that compounds (**10**) and (**11**) are a possible candidates for further development as analgesic agents, our results cannot be easily explain on the basis of PCA and HCA methods.

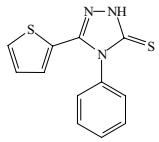
EXPERIMENTAL

Chemistry

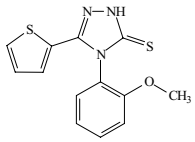
Melting points were determined on a Fischer–Johns block and are uncorrected. Elemental analyses were determined by an AMZ-CHX elemental analyzer and are within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Bruker Avance (300 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane as an internal standard. Analytical thin layer chromatography (TLC) was performed with Merck $60F_{254}$ silica gel plates and visualized by UV irradiation (254 nm). All of the chemicals used in the syntheses were purchased from Sigma-Aldrich and Lancaster and were used as such.

*Synthesis of 1-(Pyrazin-2-ylcarbonyl)-4-Substituted Thiosemicarbazides (**1–5**)*

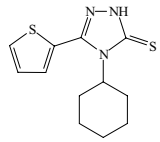
The mixture of pyrazin-2-carboxylic acid hydrazide (0.01 mol) and isothiocyanate (0.01 mol) was heated



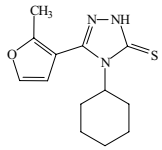
12
Moderately active



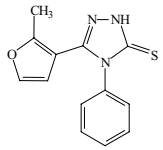
13
Moderately active



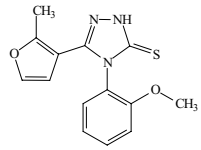
14
Moderately active



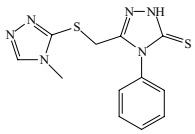
15
Moderately active



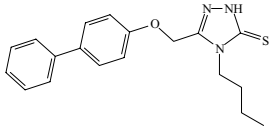
16
Moderately active



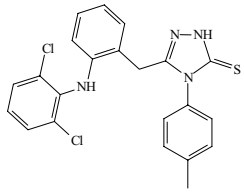
17
Moderately active



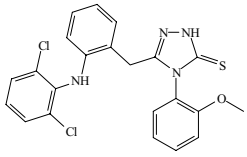
18
Moderately active



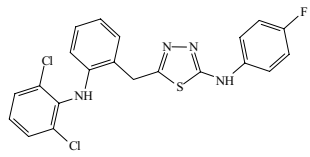
19
Active



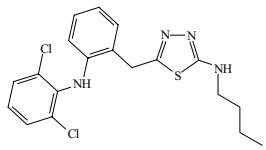
20
Moderately active



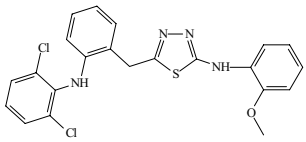
21
Moderately active



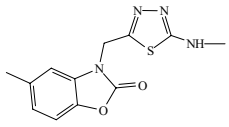
22
Moderately active



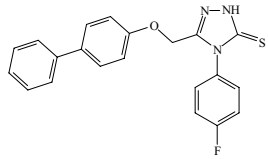
23
Moderately active



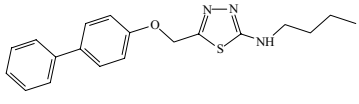
24
Moderately active



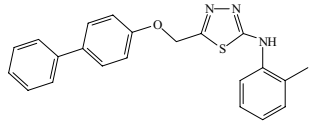
25
Moderately active



26
Active



27
Inactive



28
Inactive

FIGURE 1 Chemical structures of *s*-triazoles and thiadiazoles studied.

TABLE 1 Calculated Values for the Nine More Important Descriptors used in PCA and HCA Analyses

Compound	*Vol*	*R*	M_w	$\Delta E_{LUMO\text{-}HOMO}$	E_T	*A (grid)*	E_{LUMO}	*PA*	μ
6	729.77	72.56	273.29	7.76	−77407.51	449.36	−1.07	59.40	4.66
7	749.71	72.75	261.35	7.58	−68485.75	454.97	−1.03	59.40	4.58
8	698.89	65.61	235.31	7.39	−61938.86	428.01	−1.20	59.40	4.42
9	634.13	60.90	219.26	7.46	−57684.12	400.24	−1.17	59.40	4.45
10	759.02	71.02	261.34	7.76	−68512.61	468.44	−1.14	63.60	4.97
11	702.68	61.05	251.26	7.84	−72505.53	454.05	−1.46	89.90	2.56
12	687.67	78.56	259.34	7.54	−61469.89	422.45	−0.96	33.62	4.27
13	748.16	85.02	289.37	7.29	−72426.91	450.14	−0.84	42.85	3.21
14	728.90	78.97	265.39	7.72	−63427.50	441.09	−0.70	33.62	4.78
15	714.32	76.63	257.31	8.16	−69907.78	434.23	−0.20	46.76	4.54
16	722.89	76.84	275.30	7.80	−67939.70	439.49	−0.68	55.99	4.15
17	752.17	77.04	263.36	7.60	−78789.12	448.55	−0.76	46.76	5.12
18	825.02	86.90	304.39	7.81	−76721.80	499.64	−0.72	64.34	8.99
19	999.15	109.51	339.46	8.29	−88895.44	582.16	−0.29	42.85	4.25
20	1125.78	136.82	441.38	8.20	−111398.80	629.29	−0.33	45.64	3.89
21	1133.89	138.91	457.38	8.20	−118776.00	626.60	−0.32	54.88	2.83
22	1115.55	131.12	445.34	7.90	−118699.00	646.85	−0.83	49.84	3.68
23	1099.55	119.99	407.36	7.82	−103172.20	634.92	−0.40	49.84	3.20
24	1169.59	137.37	457.38	7.94	−118806.57	661.59	−0.59	59.07	4.33
25	768.99	76.44	276.31	8.16	−77533.14	477.01	−0.83	72.96	3.76
26	1020.81	120.45	377.44	8.33	−104362.94	596.59	−0.52	42.85	3.77
27	1037.91	107.77	339.46	8.00	−88916.70	625.51	−0.62	47.04	3.54
28	1081.96	123.06	373.47	7.82	−97109.77	642.34	−0.82	47.04	2.62

in an oil bath at 80°C and progress of reaction was monitored by TLC. After 12 h, the reaction was completed and crude reaction mixture was washed with diethyl ether and crystallized from ethanol.

*4-(2-Fluorophenyl)-1-(pyrazin-2-yl-carbonyl)-thiosemicarbazide (**1**).* Yield 94%; mp 193–195°C; ^{1}H NMR (DMSO-d_6): δ 7.15–7.32 (m, 4H, ArH), 8.77–8.78 (dd, 1H, ArH), 8.90–8.91 (d, 1H, ArH), 9.21–9.22 (d, 1H, ArH), 9.55, 9.97, 10.99 (3s, 3H, 3NH, D_2O exchangeable); IR (KBr) cm^{-1}: 3316, 3249, 3063, 3007, 1690, 1671, 1627, 1600, 1489, 1460, 1244, 755; anal. Calcd $C_{12}H_{10}FN_5OS$: C 49.48, H 3.46, N 24.04, found: C 49.52, H 3.20, N 24.44.

*4-Ethoxycarbonyl-(pyrazin-2-ylcarbonyl)-thiosemicarbazide (**5**).* Yield 81%; mp 239–241°C; ^{1}H NMR (DMSO-d_6): δ 1.24–1.29 (t, 3H, CH_3), 4.19–4.26 (q, 2H, CH_2), 8.80–8.81 (dd, 1H, ArH), 8.94–8.95 (d, 1H, ArH), 9.21–9.22 (d, 1H, ArH), 11.20, 11.35, 11.68 (3s, 3H, 3NH, D_2O exchangeable); IR (KBr) cm^{-1}: 3295, 2966, 2915, 1725, 1683, 1575, 1458, 1395, 1285; anal. Calcd. for $C_9H_{11}N_5O_3S$: C 40.14, H 4.12, N 26.01, found: C 39.75, H 3.69, N 25.72.

TABLE 2 Variable Importance

Variable	*Power*	*Importance*
Vol	0.974	1
R	0.972	2
M_w	0.971	3
$\Delta E_{LUMO\text{-}HOMO}$	0.958	4
E_T	0.955	5
A (grid)	0.945	6
E_{LUMO}	0.925	7
PA	0.911	8
μ	0.906	9
Non	0.871	10
E_{HOMO}	0.822	11
A	0.822	12
HE	0.744	13
N_{rotb}	0.742	14
NOHNH	0.722	15
log *P*	0.560	16

*Synthesis of 5-(Pyrazin-2-yl)-4-Substituted-s-triazole-3-thiones (**6–9**)*

A solution of (**1–4**) (0.01 mol) in 2% sodium hydroxide solution (30 mL) was heated under reflux for

TABLE 3 Ratio of Variance Explained by the PC's

Principal Component	*Variance Explained (%)*	*Total Variance Explained (%)*
PC1	65.34	65.34
PC2	13.89	79.23
PC3	10.37	89.60
PC4	7.64	97.24

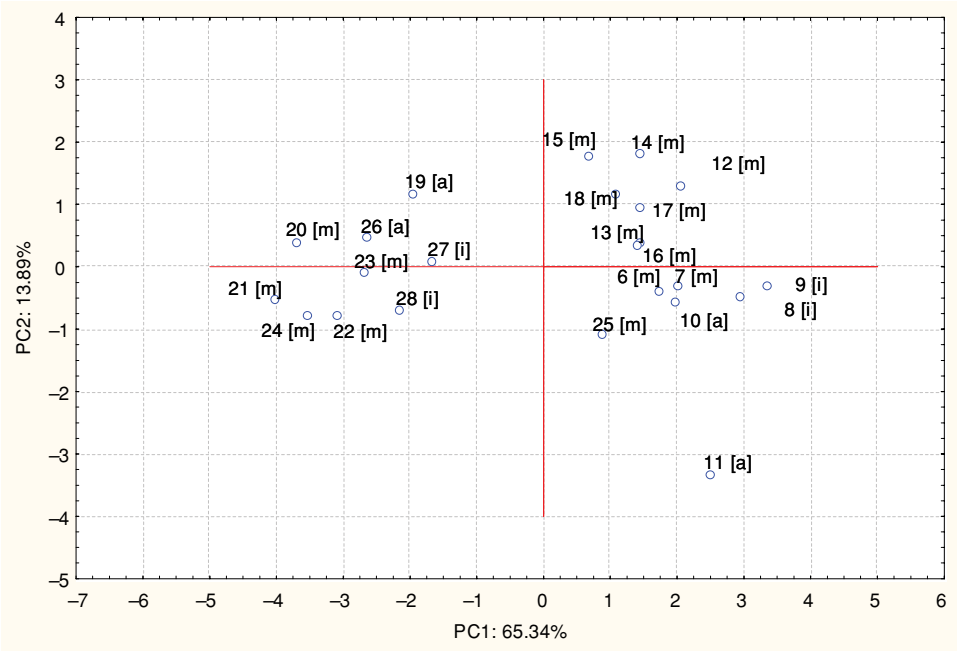


FIGURE 2 PC1 vs. PC2 score plot. Activity signature: [a]-active, [m]-moderately active, [i]-inactive.

2 h. After cooling, the mixture was neutralized with 11% hydrochloric acid solution. The resulting precipitates were collected by filtration and crystallized from ethanol.

TABLE 4 Score Values for PC1 and PC2

Compound	*PC1*	*PC2*
6	1.748	−0.406
7	2.047	−0.317
8	2.964	−0.502
9	3.369	−0.315
10	2.000	−0.602
11	2.517	−3.342
12	2.071	1.277
13	1.469	0.374
14	1.471	1.791
15	0.704	1.751
16	1.439	0.316
17	1.463	0.911
18	1.113	1.145
19	−1.955	1.153
20	−3.697	0.380
21	−3.993	−0.555
22	−3.066	−0.810
23	−2.671	−0.121
24	−3.499	−0.803
25	0.898	−1.125
26	−2.612	0.444
27	−1.653	0.066
28	−2.129	−0.710

*Synthesis of 2-Arylamino-5-(pyrazin-2-yl)-1,3,4-thiadiazoles (**10**) and (**11**)*

*Procedure for (**10**)*: The thiosemicarbazide (**2**) (0.01 mol) was dissolved in concentrated H_2SO_4 (10 mL). The solution was kept at room temperature for 2 h and then poured into crushed ice to precipitate a crude solid. The product was then filtered, dried, and crystallized from ethanol.

*Procedure for (**11**)*: The thiosemicarbazide (**5**) (0.01 mol) was dissolved in glacial acetic acid (10 mL), and the reaction mixture was refluxed for 9 h. Then it was kept at room temperature to complete precipitation of the product, which was filtered, dried, and crystallized from ethanol.

*2-Ethoxycarbonylamino-5-(pyrazin-2-yl)-1,3,4-thiadiazole (**11**)*. Yield 52%; mp 266–268°C; ^{1}H NMR (DMSO-d_6): δ 1.28–1.32 (t, 3H, CH_3), 4.25–4.32 (q, 2H, CH_2), 8.75–8.78 (m, 2H, ArH), 9.37–9.38 (m, 1H, ArH), 12.48 (s, 1H, NH, D_2O exchangeable); IR (KBr) cm^{-1}: 3428, 2991, 2896, 1447, 1723, 1563; anal. Calcd. for $C_9H_9N_5O_2S$: C 43.02, H 3.61, N 27.87, found: C 42.64, H 3.95, N 28.10.

Pharmacology

The experiments were carried out on male Albino Swiss mice (20–25 g). The animals were housed in colony cages with free access to tap water and food (standard laboratory pellets, Bacutil, Motycz,

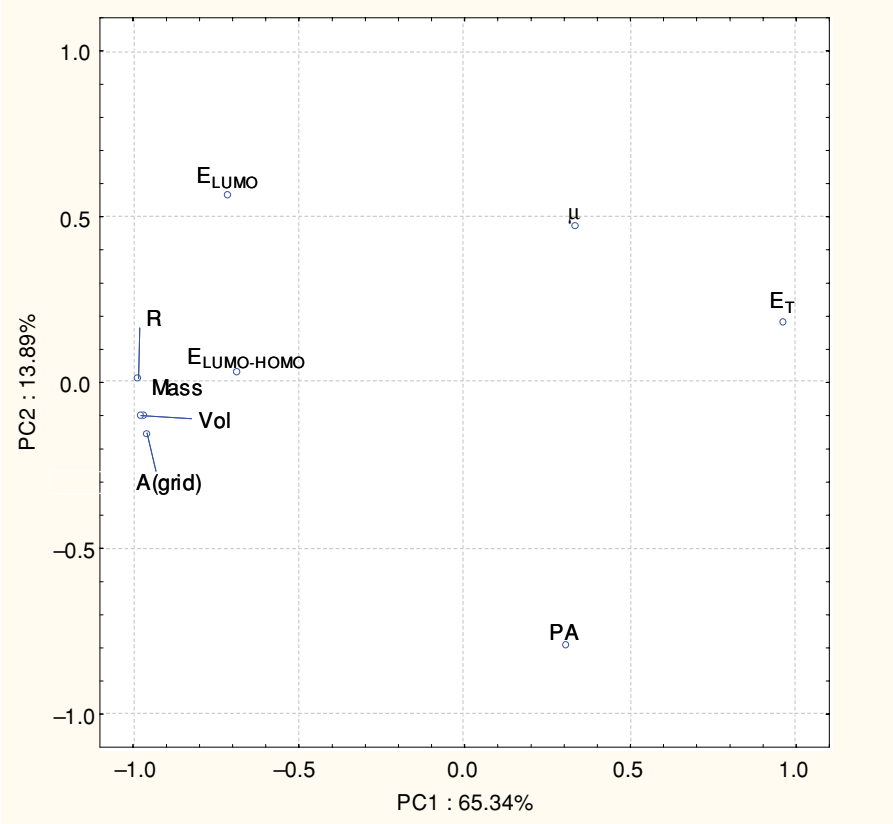


FIGURE 3 Loading vectors for the nine selected descriptors (details are given in the text).

Poland) and maintained in the 12/12 h light–dark cycle (light on from 7 a.m. to 7 p.m.). Experimental and control groups consisting of 10 animals. The experiments were performed between 8 a.m. and 3 p.m. The investigated compounds were administrated intraperitoneally (ip) in doses of 25, 50, and 100 mg/kg (equivalent to 0.025, 0.05, and 0.1 of their LD_{50}) as suspensions in a 1% Tween 80 in the contrast volume 10 mL/kg. Control animals received the equivalent volume of solvent. The rectal body temperature was measured with a thermometer (Ellab, Copenhagen, Denmark) before the administration of compounds in the dose of 0.1 of their LD_{50} and 15, 30, 45, 60, 90, and 120 min afterwards. The screening of CNS activity in mice was performed in a series of tests described below. Mean values were obtained with uncertainties evaluated using the Student's *t*-test or the exact Fischer test.

TABLE 5 Loading Values for the Selected Descriptors

Variable	*PC1*	*PC2*
M_W	−0.968	−0.102
E_{LUMO}	−0.717	0.565
$\Delta E_{LUMO\text{-}HOMO}$	−0.688	0.030
Vol	−0.977	−0.100
E_T	0.957	0.187
μ	0.330	0.470
A (grid)	−0.958	−0.151
R	−0.984	0.012
PA	0.301	−0.794

Motor impairment was quantified with the "chimney test" [28]; 30 min after the administration of the investigated compounds, mice had to climb up backwards in a plastic tube (3-cm inner diameter, 25-cm length). Mice unable to perform the task within 60 s were considered to display motor impairment. Motor impairment was quantified as the percentage of animals that failed to complete the test.

Anxiolytic activity was assessed by the "four plate" test in mice according to Aron et al. [29]; 30 min after the injection. The number of punished crossings was counted for 1 min.

Antidepressive properties were assessed by the "forced swimming" test according to Porsolt et al. [30]; 30 min after the administration of the tested compound mice were individually placed and forced to swim in a glass cylinder (27 × 16 cm) containing

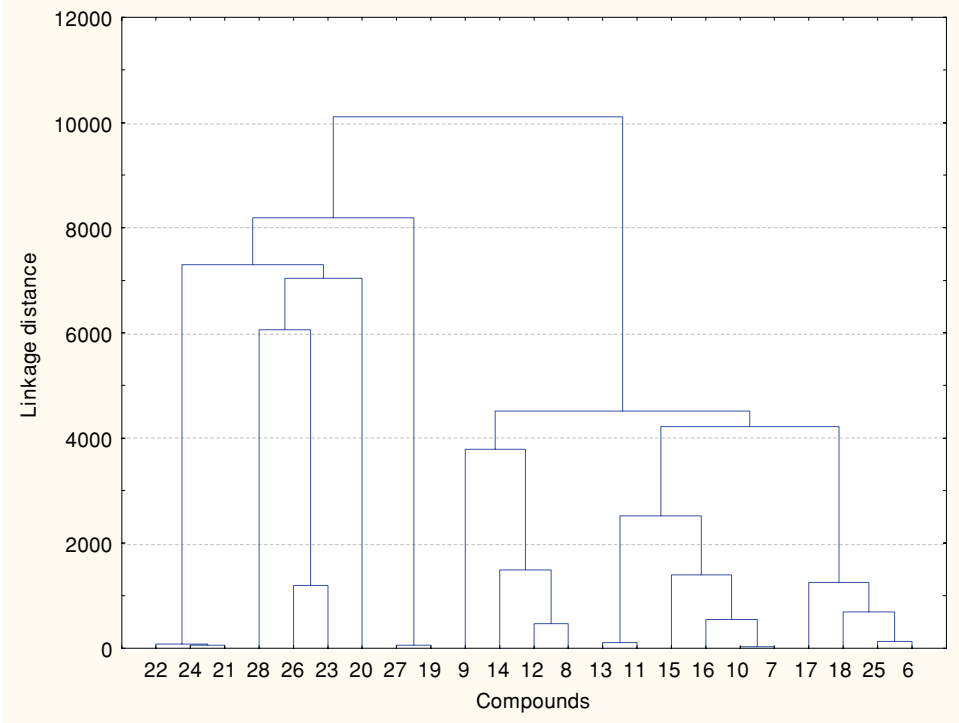


FIGURE 4 Dendrogram obtained for the investigated *s*-triazoles and thiadiazoles.

15 mL of water (25°C). A mouse was considered immobile when it floated in the water, in an upright position, and made only small movements to keep its head above water. The total immobility time of mice was measured during the last 4 min of the 6-min test.

Thiopentanal-induced sleep. Thiopental (60 mg/kg ip) was given 30 min after the administration of compounds in doses varying from 0.025 to 0.1 of their LD_{50}. The sleeping time of mice (from disappearance to return of the righting reflex) was measured.

Pain reactivity was measured by the "writhing syndrome" test [31]. The test was performed by the ip injection of a 0.6% solution of acetic acid 30 min after the administration of compounds in doses varying from 0.0031 to 0.1 of their LD_{50}. The number of writhing episodes was counted for 30 min after the injection of acetic acid.

Pentetrazole-induced seizures [32]. Pentetrazol (115 mg/kg sc) was administered 30 min after the injection of investigated compounds in the doses of 0.05 or 0.1 of their LD_{50}. The mice were placed singly in plexiglass cages (25 × 15 × 10 cm) and were observed for 30 min. The clonic and tonic seizures, as well as mortality, were recorded in this period.

L-5-Hydroxytryptophan-induced head-twitches. Head-twitches responses were measured according to Corne et al. [33]; L-5-hydroxytryptophan, L-5HTP, (190 mg/kg ip) was administered 30 min after the investigated compound. The number of head twitch episodes was observed during 60 min after the L-5HTP administration.

Computational Methods

The following molecular descriptors: mass (M_w), logarithm of the partition coefficient (log *P*), energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), energy of the gap HOMO–LUMO ($\Delta E_{LUMO\text{-}HOMO}$), hydration energy (HE), volume (Vol), hydrogen bond donor/acceptor (*nOHNH*/*nON*), total energy (E_T), dipole moment (μ), polarizability (α), rotatable bonds (*nrotb*), surface area (*A*), refractivity (*R*), and polar surface area (PA) were calculated using AM1 as implemented in HyperChem [34] or were obtained with the Interactive Polar Surface Area Calculator [35].

In a first step, the molecular geometries of *s*-triazoles and thiadiazoles were fully optimized in the gas phase to gradients of 0.01 kcal/(mol Å) and afterwards the molecular descriptors were performed. Next, to select the most characteristic

structural parameters for a set of *s*-triazoles and thiadiazoles, PCA and HCA methodologies have been performed. Investigated compounds were divided into three groups (active, inactive, and moderately active) according to their pain inhibition percentage (% PIP). All statistical analyses were done by using Statistica 8.0 package for Windows [36].

REFERENCES

[1] Siwek, A.; Wujec, M.; Dobosz, M.; Jagiełło-Wójtowicz, E.; Kleinrok, A.; Chodkowska, A.; Paneth, P. Phosphorus Sulfur Silicon Relat Elem 2008, 183, 2669–2677.

[2] Siwek, A.; Wujec, M.; Dobosz, M.; Jagiełło-Wójtowicz, E.; Chodkowska, A.; Kleinrok, A.; Paneth, P. Cent Eur J Chem 2008, 6, 47–53.

[3] Maliszewska-Guz, A.; Wujec, M.; Pitucha, M.; Chodkowska, A.; Jagiełło-Wójtowicz, E.; Mazur, L.; Kozioł, A. E. Coll Czech Chem Commun 2005, 70, 51–62.

[4] Rimoli, M. G.; Avallone, L.; de Caprariis, P.; Luraschi, E.; Abignente, E.; Filippelli, W.; Bernino, L.; Rossi, F. Eur J Med Chem 1997, 32, 195–203.

[5] Abdel-Latif, N. A.; Nermien, M.; Sabry, N. M.; Mohamed, A. M.; Abdulla, M. M. Monatsh Chem 2007, 138, 715–721.

[6] Simsek, R.; Chang-Fong, J.; Lee, M.; Dukat, M.; Martin, B. R.; Glennon, R. A. Bioorg Med Chem Lett 2003, 13, 2917–2920.

[7] Tewari, A. K.; Mishra, A. Bioorg Med Chem 2001, 9, 715–718.

[8] Sondhi, S. M.; Singh, N.; Johar, M.; Kumar, A. Bioorg Med Chem 2005, 13, 6158–6166.

[9] Sondhi, S. M.; Jain, S.; Dinodia, M.; Shukla, R.; Raghubir, R. Bioorg Med Chem 2007, 15, 3334–3344.

[10] Arroio, A.; Honório, K. M.; da Silva, A. B. F. J Mol Struct (Theochem) 2004, 709, 223–229.

[11] Ekins, S.; Mestres, J.; Testa, B. Br J Pharmacol 2007, 152, 9–20.

[12] Kabankin, A. S.; Gabrielyan, L. I. J Pharm Chem 2006, 40, 307–311.

[13] Johnson, R. A.; Wichern, D. W.; Applied Multivariate Statistical Analysis; Prentice-Hall: Englewood Cliffs, NJ, 1982.

[14] Forina, M.; Armanino, C.; Raggio, V. Anal Chim Acta 2002, 454, 13–19.

[15] Ezabadi, I. R.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Soković, M.; Glamočilijad, J.; Ćirić, A. Bioorg Med Chem 2008, 16, 1150–1161.

[16] Kus, C.; Ayhan-Kılcıgil, G.; Özbey, S.; Kaynak, F. B.; Kaya, M.; Çobanc, T.; Can-Ekec, B. Bioorg Med Chem 2008, 16, 4294–4303.

[17] Önkol, T.; Doğruer, D. S.; Uzun, L.; Adak, S. Özkan, S.; Şahin, M. F. J Enzyme Inhib Med Chem 2008, 23, 277–284.

[18] Shams, H. Z.; Mohareb, R. M.; Helal, M. H.; Mahmoud, A. E. Phosphorus Sulfur Silicon Relat Elem 2007, 182, 237–263.

[19] Rui, R.; Liren, J.; Xiuqin, W.; Yuchu, H.; Chunying, W.; Yanjun, W. Zhongguo Yaoke Daxue Xuebao 1991, 22, 233–235.

[20] Pancechowska-Ksepko, D.; Foks, H.; Janowiec, M.; Zwolska-Kwiek, Z. Acta Polon Pharm 1988, 45, 193–200.

[21] Segura-Cabrera, A.; Rodriguez-Perez, M. A. Bioorg Med Chem Lett 2008, 18, 3152–3157.

[22] Maoli, X.; Xinghan, L. Yaoxue Xuebao 1985, 20, 100–104.

[23] Vergne, F.; Andrianjara, Ch.; Ducrot, P. Eur Pat Appl 2002, EP 1193261 A1 20020403.

[24] Siwek, A.; Wujec, M.; Wawrzycka-Gorczyca, I.; Dobosz, M.; Paneth, P. Heteroatom Chem 2008, 19, 337–344.

[25] Kumar, H.; Javed, S. A.; Khan, S. A.; Amir, M. Eur J Med Chem 2008, 43, 2688–2698.

[26] Amir, M.; Shikha, K. Eur J Med Chem 2004, 39, 535–545.

[27] Salgın-Gökşen, U.; Gökhan-Kelekçi, N.; Göktaş, O.; Köysal, Y.; Kılıç, E.; Işık, S.; Aktay, G.; Özalp, M. Bioorg Med Chem 2007, 15, 5738–5751.

[28] Boissier, J. R.; Tardy, J.; Diverres, J. C. Med Exp 1960, 3, 81–84.

[29] Aron, C.; Simon, P.; Larousse, C.; Boissier, J. R. Neuropharmacology 1971, 10, 459–469.

[30] Porsolt, R. D.; Bertin, A.; Deniel, M.; Jalfre, M. Arch Int Pharmacodyn Thér 1977, 229, 327–336.

[31] Koster, R.; Anderson M.; DeBeer E. J. Fed Proc 1959, 18, 412–415.

[32] Löscher, W.; Hönack, D.; Fassbender, C. P.; Nolting, B. Epilepsy Res 1991, 8, 171–89.

[33] Corne, S. J.; Pickering, R. W.; Warner, B. T. Br J Pharmacol Chemother 1963, 20, 106–120.

[34] HyperChem 8.0.3, HyperCube Gainsville, FL, 2007.

[35] http://www.molinspiration.com/cgi-bin/properties

[36] StatSoft, Inc. (2007). STATISTICA (data analysis software system), version 8.0. www.statsoft.com.