Sci Pharm. 2008; 76: 415–438 doi:10.3797/scipharm.0804-20 
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# Synthesis, Pharmacophore Modeling, and Biological Evaluation of Novel 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-one Derivatives as 5-$HT_{2A}$ Receptor Antagonists

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## Abstract

Novel 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one derivatives linked through an ethylene bridge to various phenylpiperazine groups were prepared for evaluation as 5-$HT_{2A}$ receptor antagonists. The target compounds **11a–p** were prepared through the initial synthesis of the 2-chloroethyl intermediates **10a–d** which were then reacted with the appropriate phenylpiperazines. All compounds were tested for their antagonistic activity on 5-$HT_{2A}$ receptors using inhibition of 5-hydroxytryptophan(5-HTP)-induced head twitches in mice. Pharmacophore modeling study, based on a hypothetical pharmacophore template generated from a set of diverse known active ligands, revealed good fitting of the designed compounds to the generated hypothetical pharmacophore.

## Keywords

Arylpiperazines • 5-$HT_{2A}$ antagonists • Thiazolo[3,2-*a*]pyrimidines • Inhibition of 5-HTP induced head twitches.

## Introduction

Serotonin (5-hydroxytryptamine, 5-HT) has been recognized for more than 50 years as an effector on various smooth muscles and, subsequently, as an important neurotransmitter in the brain [1]. The serotonin receptors represent a diverse family

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of receptors that has been initially classified pharmacologically into multiple subtypes [2]. The advent of molecular cloning provided additional discrimination within the serotonin receptor family revealing the existence of seven subfamilies containing a total of fourteen distinct receptors based on primary sequence, pharmacology and signal transduction pathways [1]. Serotonin receptor dysfunction has been implicated in many neuropsychiatric disorders including anxiety, depression and schizophrenia [1]. Clinical use of therapeutics affecting serotonergic function is exemplified by selective serotonin reuptake inhibitors for depression [2], 5-$HT_{1A}$ partial agonists for anxiety and depression, 5-$HT_{1D}$ agonists for acute migraine [3], 5-$HT_{2A}$ and 5-$HT_{2C}$ antagonists for migraine prophylaxis, depression, schizophrenia [4, 5], 5-$HT_3$ antagonists for chemotherapy-induced emesis [6], and 5-$HT_4$ agonists for gastrointestinal disorders [7].

With particular emphasis on the 5-$HT_2$ receptor family, the three receptor subtypes, 5-$HT_{2A}$, 5-$HT_{2B}$ and 5-$HT_{2C}$, are G-protein coupled receptors (GPCRs) that couple through the $G_q$ and $G_{11}$ proteins eliciting their second messenger effects through increases in activity of phospholipase C (diacylglycerol pathway) and/or phospholipase A (arachidonic acid pathway). These subtypes share an overall amino acid homology of approximately 50%. 5-$HT_{2A}$ receptors are broadly distributed in the prefrontal, parietal, and somatosensory cortex, claustrum and in platelets [8]. The 5-$HT_{2A}$ receptor has been implicated as a therapeutic target for schizophrenia and depression. Representative 5-$HT_{2A}$ antagonists include ketanserin **1** [8], the prototype of a large group of structurally related derivatives such as risperidone **2** [9], and ritanserin **3** [10]. Other 5-$HT_{2A}$ antagonists, belonging to different chemical classes, include the spiro compound, spiperone **4**, the tricyclic derivative, clozapine **5**, the indole derivative, sertindole **6** [11], and the arylpiperazine derivative, aripiprazole **7** [12] (Chart 1).

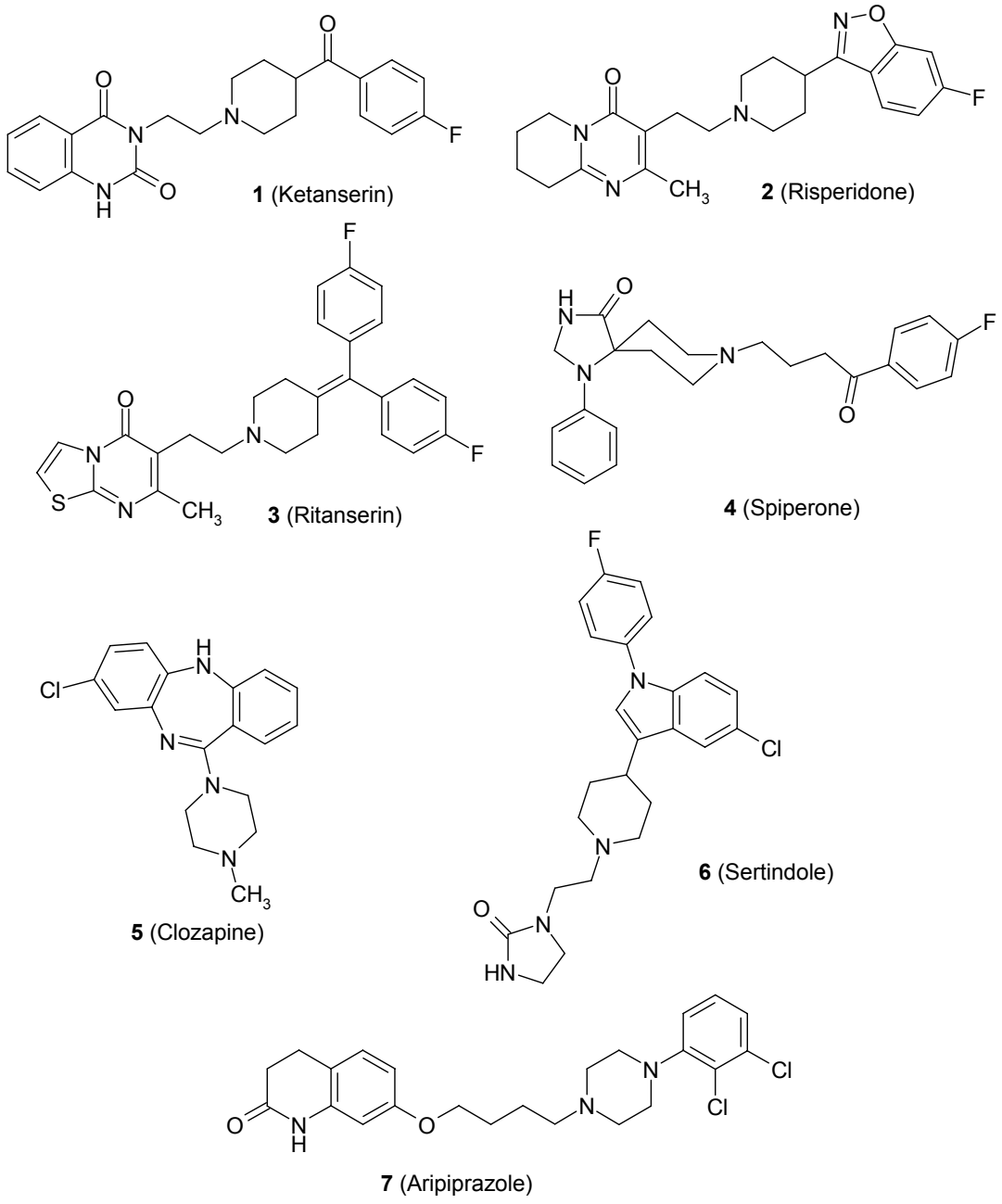



**Chart 1.**

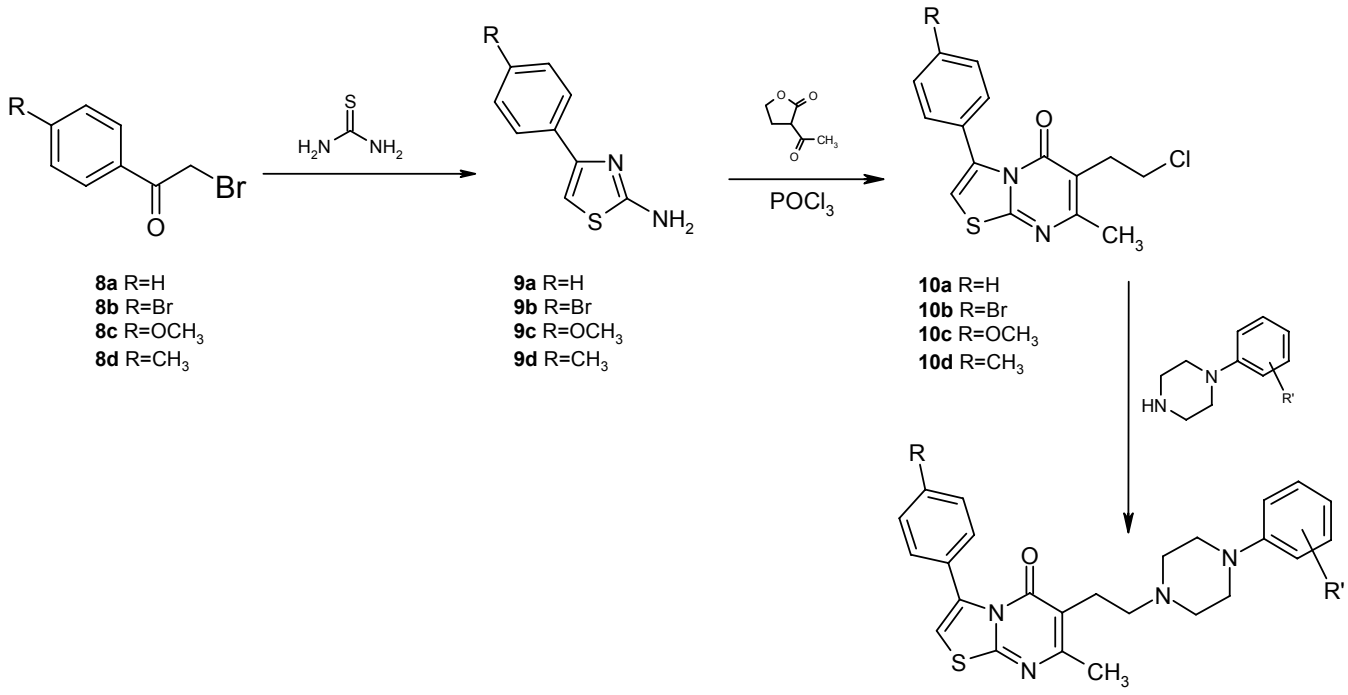
Experimental structure activity data for 5-$HT_{2A}$ antagonists suggest that two planar aromatic or heterocyclic ring systems separated by an aliphatic or alicyclic chain, containing basic protonatable nitrogen, seem to constitute a potent 5-$HT_{2A}$ ligand. Additional hydrophobic substituent in the heterocyclic ring, as demonstrated by the 4-fluorophenyl group in sertindole **6** and the chlorophenyl ring in clozapine **5**, enhances the antagonistic potency [11, 13].

Inspired by this knowledge, the newly synthesized compounds were designed as structural mimics of ketanserin **1** and its analogs **2** and **3**. The new compounds possessed an additional phenyl group on the thiazolopyrimidine nucleus, hoping to enhance the 5-$HT_{2A}$ antagonistic activity. Moreover, the piperidine ring in the lead compounds was replaced by the isosteric piperazine ring with the aromatic substitution directly attached to it as in risperidone. The two carbon spacer (the ethylene bridge) was retained to keep the distance between the heterocyclic nucleus and the protonatable nitrogen ($N^1$ of the piperazine ring) as supported by the modeling study.

## Results and Discussion

### *1. Chemistry*

The target compounds **11a–p** were prepared according to Scheme 1. The 2-aminothiazole derivatives **9a–d** were obtained through a cyclocondensation reaction of the corresponding *α*-bromoacetophenones **8a–d** [14] to thiourea according the reported procedures [15, 16]. Reaction of the appropriate 2-aminothiazole **9a–d**, and 2-acetylbutyrolactone in phosphorous oxychloride furnished the 2-chloroethyl intermediates **10a–d**. This was followed by alkylation of various phenylpiperazines with these intermediates in dry dimethylformamide in the presence of triethylamine under nitrogen atmosphere to give the final compounds **11a–p**.




**8a** R=H
**8b** R=Br
**8c** R=$OCH_3$
**8d** R=$CH_3$

**9a** R=H
**9b** R=Br
**9c** R=$OCH_3$
**9d** R=$CH_3$

**10a** R=H
**10b** R=Br
**10c** R=$OCH_3$
**10d** R=$CH_3$

| | | | | | |
|---|---|---|---|---|---|
| **11a** | R=H | R'=2-$OCH_3$ | **11i** | R=$OCH_3$ | R'=2-$OCH_3$ |
| **11b** | R=H | R'=4-Cl | **11j** | R=$OCH_3$ | R'=4-Cl |
| **11c** | R=H | R'=3-$CF_3$ | **11k** | R=$OCH_3$ | R'=3-$CF_3$ |
| **11d** | R=H | R'=H | **11l** | R=$OCH_3$ | R'=H |
| **11e** | R=Br | R'=2-$OCH_3$ | **11m** | R=$CH_3$ | R'=2-$OCH_3$ |
| **11f** | R=Br | R'=4-Cl | **11n** | R=$CH_3$ | R'=4-Cl |
| **11g** | R=Br | R'=3-$CF_3$ | **11o** | R=$CH_3$ | R'=3-$CF_3$ |
| **11h** | R=Br | R'=H | **11p** | R=$CH_3$ | R'=H |

**Sch. 1.**

## *2. Pharmacology*

The new compounds were evaluated, *in vivo*, for their 5-$HT_{2A}$ antagonistic activity by measuring their ability to inhibit the 5-HTP induced head twitches in mice [17, 18]. Risperidone was chosen as the standard drug. Risperidone was preferred over ritanserin as the standard drug, although the latter is more closely related to the tested compounds, because the former, unlike ritanserin, is widely marketed for clinical treatment of psychosis. The observed data were summarized in Tab. 1 which showed the response percent calculated as the percent of mice showing no head twitches to the total number of mice in each group. $ED_{50}$ for all compounds are shown in Tab. 2. The doses were calculated in mmol/kg and were administered

intraperitoneally (ip). From the obtained data (Tabs. 1,2 and Fig. 7), all compounds were found to exhibit 5-$HT_{2A}$ receptor antagonistic activity with no significant difference from the activity of risperidone, except for compounds **11n**, **11o**, and **11p**. Compounds **11i** and **11k** possess an activity profile identical to that of risperidone. The impact of the phenylpiperazine substituent (R') viz. 2-$OCH_3$, 4-Cl, 3-$CF_3$, and H, upon activity is not absolute. However, the substituent (R) on the phenyl ring at position 3 of the heterocyclic nucleus seems to play role in switching the activity; so that compounds with R=$CH_3$, especially compounds **11n**, **11o**, and **11p**, are significantly less active than other derivatives with R= H, Br, or $OCH_3$. On the other hand, the series of compounds with R=$OCH_3$ **11i–l** shows the highest activity among other series; especially compounds **11i** and **11k**. Slightly lower activity is exhibited by compounds with R=H **11a–d** and R=Br **11e–h** which have almost similar activity profiles.

### *3. Pharmacophore modeling*

A molecular modeling experiment was carried out to develop a hypothetical pharmacophore model for the 5-$HT_{2A}$ receptor aiming to study the fitting of the designed compounds to this pharmacophore. A ligand-based pharmacophore model was developed using a training set of ten 5-$HT_{2A}$ antagonists of diverse chemical structures including compounds **1–6** (Chart 1), in addition to, setoperone, chlorpromazine, cyproheptadine, and tefludazine [11]. Fig. 1 shows the alignment of the ten selected structures. The generated hypothetical pharmacophore (Fig. 2) shows seven overlapping points with similar chemical properties in the training set, **F1**: a hydrogen bond acceptor center; **F2**: an aromatic or hydrophobic center with two parallel places **F3** and **F5** for Pi orbital accommodation; **F4**: an aromatic center with a H-bond donor group; **F6**: a hydrophobic center; and **F7**: a second H-bond acceptor center.

Fitting of the designed compounds **11a–d** to the pharmacophore revealed the presence of the appropriate chemical groups superimposed on the pharmacophoric elements (Figs. 3–6). The phenylpiperazine tail represents the aromatic ring with its

Pi orbitals properly oriented to fit to **F2**, **F3** and **F5**. Also, $N^1$ of the piperazine ring is a H-bond acceptor corresponding to **F1**. The ethylene spacer is the hydrophobic group fitting to **F6**; it is worth mentioned that this 2 carbon spacer was perfect in adjusting the distance between other groups in the molecule. The thiazolo-pyrimidine ring is a suitable aromatic group for **F4** with the nitrogen atom, at position 8, as a H-bond acceptor group for **F7**. Finally, it is interesting to note that, according to the created model, the phenyl group at position 3 is not part of the pharmacophore. Therefore, it will not be required to study the fitting of the rest of the compounds **11e-p** since variations in the substituents on the 3-phenyl group will not affect the fitting results.

In conclusion, it could be assumed that the presence of the phenyl ring on the heterocyclic nucleus, although seeming not essential for activity as suggested by the molecular modeling study, yet the activity of the new compounds is in great part dependent on it. The role of the 3-phenyl group is unclear but it can be assumed that it fits into an accessory site of the receptor. Pharmacological data, supported by the modeling study, showed that the phenylpiperazine moiety is a suitable bioisostere of the arylpiperidine group present in ketanserin **1** and its analogs. In addition, the ethylene bridge is the proper spacer that keeps other groups in the molecule in the perfect position.

**Tab. 1.** Response % of the tested compounds (mmol/Kg) towards inhibition of 5-HTP induced head twitches

| Compound | Response%[a] of the tested animals towards dose mmol/kg | | | Compound | Response%[a] of the tested animals towards dose mmol/kg | | |
|---|---|---|---|---|---|---|---|
| | 12.2 | 24.4 | 48.8 | | 12.2 | 24.4 | 48.8 |
| **Risperidone** | 66.67% | 100% | 100% | **11i** | 66.67% | 100% | 100% |
| **11a** | 0% | 50% | 83.33% | **11j** | 50% | 83.33% | 100% |
| **11b** | 50% | 66.67% | 100% | **11k** | 66.67% | 100% | 100% |
| **11c** | 33.33% | 83.33% | 100% | **11l** | 33.33% | 83.33% | 100% |
| **11d** | 16.67% | 100% | 100% | **11m** | 0% | 50% | 83.33% |
| **11e** | 16.67% | 83.33% | 100% | **11n** | 0% | 16.67% | 50% |
| **11f** | 0% | 83.33% | 100% | **11o** | 16.67% | 33.33% | 83.33% |
| **11g** | 16.67% | 100% | 100% | **11p** | 0% | 33.33% | 66.67% |
| **11h** | 33.33% | 100% | 100% | | | | |

[a] Response % of the tested animals showing no head twitches to the total number of mice in each group.

**Tab. 2.** Potency ($ED_{50}$) of the tested compounds in inhibition of 5-HTP induced head twitches.

| Compound | $ED_{50}$ (mmol/kg) | Compound | $ED_{50}$ (mmol/kg) |
|---|---|---|---|
| **Risperidone** | 3.58 | **11i** | 3.58 |
| **11a** | 29.43 | **11j** | 7.53 |
| **11b** | 9.78 | **11k** | 3.58 |
| **11c** | 10.27 | **11l** | 10.27 |
| **11d** | 10.7 | **11m** | 29.43 |
| **11e** | 13.24 | **11n** | 79.08[a] |
| **11f** | 16.45 | **11o** | 30.53[a] |
| **11g** | 10.7 | **11p** | 45.95[a] |
| **11h** | 8.11 | | |

[a] Significantly different from risperidone at $p < 0.05$.

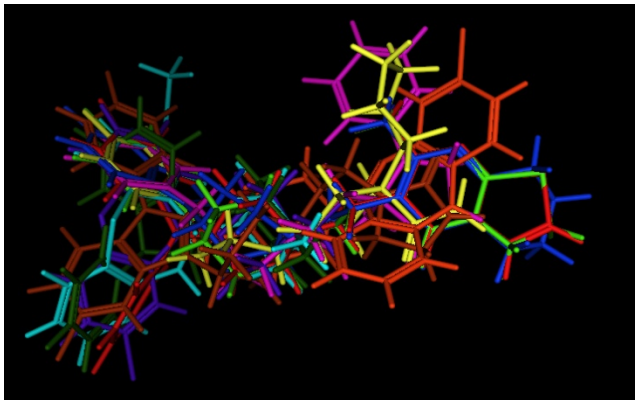


**Fig. 1.** Alignment of a training set of ten 5-$HT_{2A}$ antagonists.

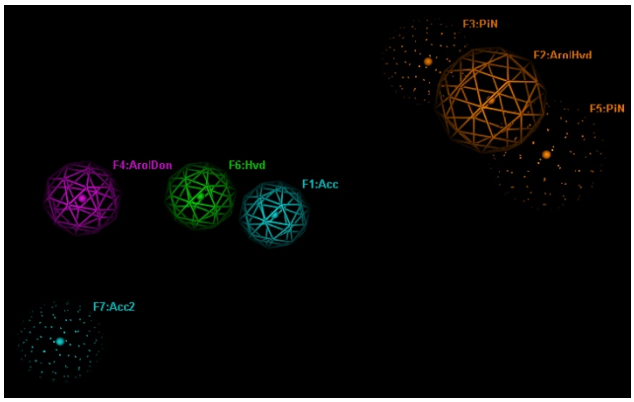



**Fig. 2.** The hypothetical pharmacophore developed for the 5-$HT_{2A}$ receptor**.**

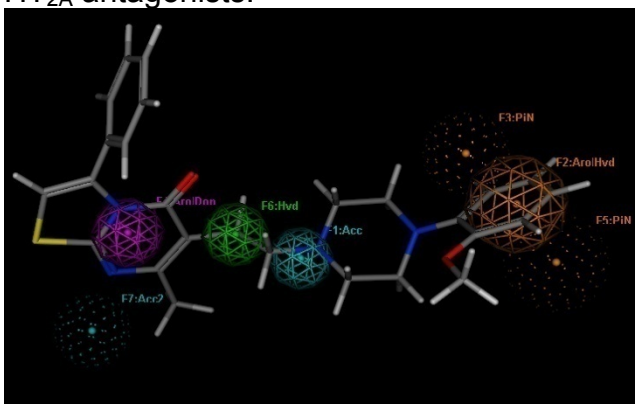



**Fig. 3.** Superimposition of the energy-minimized structure of compound **11a** on the hypothetical 5-$HT_{2A}$ receptor pharmacophore.

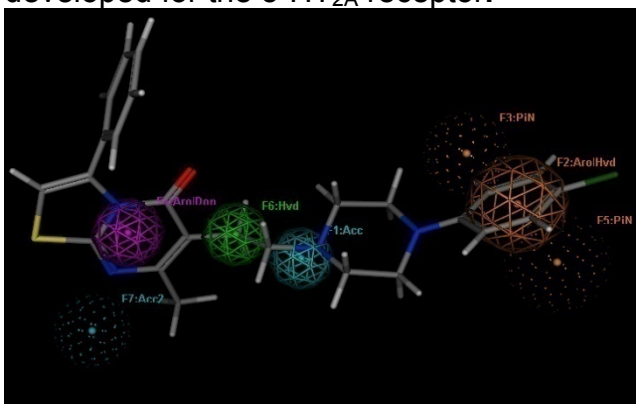



**Fig. 4.** Superimposition of the energy-minimized structure of compound **11b** on the hypothetical 5-$HT_{2A}$ receptor pharmacophore.

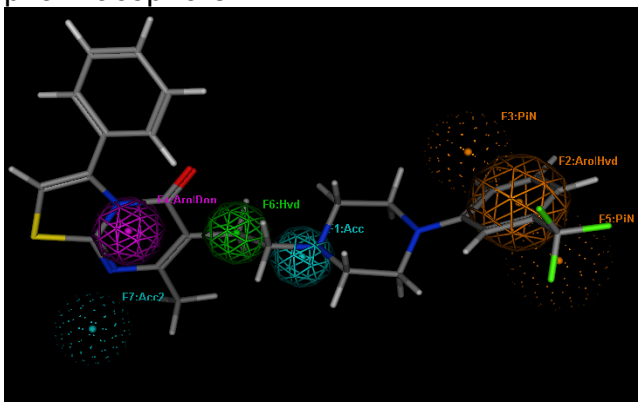



**Fig. 5.** Superimposition of the energy-minimized structure compound **11c** on the hypothetical 5-$HT_{2A}$ receptor pharmacophore.

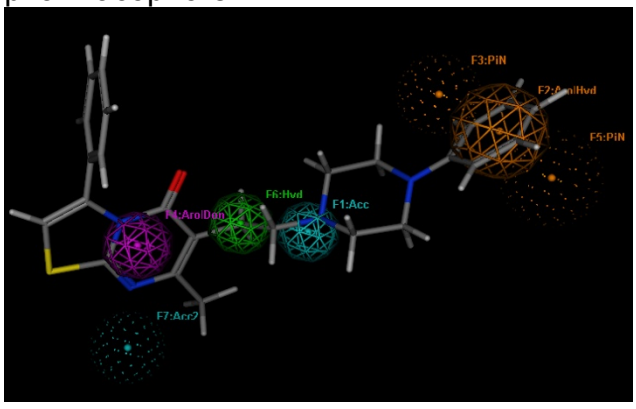



**Fig. 6.** Superimposition of the energy-minimized structure of compound **11d** on the hypothetical 5-$HT_{2A}$ receptor pharmacophore.

F1: Hydrogen bond acceptor center; F2: Aromatic or hydrophobic center; F3and F5: Aromatic or Pi orbital place at the receptor site; F4: Aromatic center carrying a H-bond donor; F6: Hydrophobic center; F7: H-bond acceptor place at the receptor site.

## Experimental

### *1. Chemistry*

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Dimethylformamide (DMF) was dried over molecular sieve 4Å. TLC was monitored on FLUKA silica gel TLC aluminium cards (0.2mm thickness) with fluorescent indicator 254 nm using chloroform:methanol (9:1) as eluent. Melting points were performed on Stuart SMP3 version 5 digital melting point apparatus and were uncorrected. Elemental microanalyses were performed at the microanalytical center, Faculty of Science, Cairo University. NMR spectra were recorded on 200 MHz $^{1}$H NMR Varian Gemini 200, and 300 MHz $^{1}$H and 75.45 MHz $^{13}$C NMR Varian mercury 300BB. Chemical shift values (δ) were given in ppm. Mass spectra were performed on Fennigan MAT, SSQ 7000 mass spectrophotometer at 70eV. IR spectra were recorded on Bruker FT-IR spectrophotometer as potassium bromide disc. Compounds **8a–d** [14], and **9a** [15], and **9b–d** [16] were prepared according to the published procedures.

### *1.1. General procedure for the preparation of 6-(2-chloroethyl)-7-methyl-3-(un)substituted- phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 10a–d:*

A mixture of **9a–d** (6 mmol) and 2-acetylbutyrolactone (0.65 ml, 6 mmol) in phosphorous oxychloride (15 ml) was heated under reflux for 2h. Excess phosphorous oxychloride was distilled under reduced pressure. The residue was triturated with ice-water and the suspension was neutralized with 2M ammonium hydroxide solution. The crude product was filtered, dried and crystallized from DMF-ethanol.

#### *1.1.1. 6-(2-Chloroethyl)-7-methyl-3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10a):*

Yield 43%; mp. 120-122$^{o}$. $^{1}$H-NMR (200 MHz, $CDCl_3$) δ 2.49 (s, 3H, -$CH_3$), 3.04 (t, 2H, J= 6.6 Hz, -$\underline{CH_2}CH_2Cl$), 3.68 (t, 2H, J= 6.6 Hz, -$CH_2\underline{CH_2}Cl$), 6.55-7.68

(m, 6H, aromatic H). MS m/z (%): $M^+$ 304 (12.08), $[M+2]^+$ 306 (4.78), 176 (100). Analysis calculated for $C_{15}H_{13}ClN_2OS$ (304.80): C, 59.11; H, 4.30; N, 9.19. Found: C, 59.26; H, 4.19; N, 9.33.

### *1.1.2. 3-(4-Bromophenyl)-6-(2-chloroethyl)-7-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (10b):*

Yield 38%; mp. 176-179°. $^1$H-NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H, -$CH_3$), 2.77 (t, 2H, J= 6 Hz, -$\underline{CH_2}CH_2Cl$), 3.66 (t, 2H, J= 6 Hz, -$CH_2\underline{CH_2}Cl$), 6.67-7.67 (m, 5H, aromatic H). MS m/z (%): $M^+$ 384.15 (0.36). Analysis calculated for $C_{15}H_{12}BrClN_2OS$ (383.53): C, 46.98; H, 3.15; N, 7.30. Found: C, 46.40; H, 3.50; N, 6.98.

### *1.1.3. 6-(2-Chloroethyl)-3-(4-methoxyphenyl)-7-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one (10c):*

Yield 52%; mp. 152-155°. $^1$H-NMR (200 MHz, DMSO-$d_6$) δ 2.49 (s, 3H, -$CH_3$), 2.89 (t, 2H, J= 8 Hz, -$\underline{CH_2}CH_2Cl$), 3.66 (t, 2H, J= 8 Hz, -$CH_2\underline{CH_2}Cl$), 3.80 (s, 3H, -$OCH_3$), 6.9-7.35 (m, 5H, aromatic H). MS m/z (%): $M^+$ 334 (13.48), $[M+2]^+$ 336 (5.39), 149 (100). Analysis calculated for $C_{16}H_{15}ClN_2O_2S$ (334.83): C, 57.40; H, 4.52; N, 8.37. Found: C, 57.17; H, 4.48; N, 8.06.

### *1.1.4. 6-(2-Chloroethyl)-7-methyl-3-(4-methylphenyl)-5*H*-thiazolo[3,2-a]pyrimidin-5-one (10d):*

Yield 48%; mp.196-200°. $^1$H-NMR (200 MHz, $CDCl_3$) δ 2.41 (s, 3H, -$CH_3$ tolyl), 2.47 (s, 3H, -$CH_3$), 3.008 (t, 2H, J= 6.4 Hz, -$\underline{CH_2}CH_2Cl$), 3.69 (t, 2H, J= 6.4 Hz, -$CH_2\underline{CH_2}Cl$), 6.66-7.31 (m, 5H, aromatic H). MS m/z (%): $M^+$ 318 (36.54), $[M+2]^+$ 320 (12.03), 269 (100). Analysis calculated for $C_{16}H_{15}ClN_2OS.2H_2O$ (354.86): C, 54.16; H, 5.39; N, 7.89. Found: C, 54.04; H, 5.40; N, 8.21.

### *1.2. General procedure for the preparation of 7-methyl-3-(un)substitutedphenyl-6-{2-[4-((un)substitutedphenyl)piperazin-1-yl]ethyl}-5*H*-thiazolo[3,2-a]pyrimidin-5-ones 11a–p:*

A solution of compound **10a–d** (2 mmol), the appropriate phenylpiperazine (2.1 mmol), and triethylamine (5 ml) in dry DMF (10 ml) was heated in a boiling water bath under nitrogen atmosphere for 10h. The solvent was removed under vacuum, and the residue was triturated with ice-water. The crude product was filtered, dried, and crystallized from the appropriate solvent.

### *1.2.1. 6-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-7-methyl-3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (11a):*

Yield 33%; mp. 116-118$^{o}$ (isopropanol). $^{1}$H-NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H, -$CH_3$), 2.65 (t, 2H, J= 6 Hz, $\underline{CH_2}CH_2N$-), 2.79 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 3.11 (t, 2H, J= 6 Hz, -$CH_2\underline{CH_2}$N-), 3.25 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.844 (s, 3H, -$OCH_3$), 6.65-7.91 (m, 10H, aromatic H). MS m/z (%): $M^+$ 460.75 (1.23), 335 (100). Analysis calculated for $C_{26}H_{28}N_4O_2S$ (460.60): C, 67.80; H, 6.13; N, 12.16. Found: C, 67.30; H, 6.30; N, 12.46.

### *1.2.2. 6-{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}-7-methyl-3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (11b):*

Yield 42%; mp. 170-171$^{o}$ (isopropanol). $^{1}$H-NMR (300 MHz, DMSO-$d_6$) δ 2.34 (s, 3H, -$CH_3$), 2.64 (t, 2H, J= 7.2 Hz, $\underline{CH_2}CH_2N$-), 3.06 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 3.13 (t, 2H, J= 7.2 Hz, -$CH_2\underline{CH_2}$N-), 3.48 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.95-8.06 (m, 10H, aromatic H). $^{13}$C-NMR (75.45 MHz, $CDCl_3$) δ 21.39 ($CH_3$), 23.08 ($\underline{CH_2}CH_2N$), 49.14 ($(CH_2)_2N^4$ piperazinyl), 52.40 ($CH_2\underline{CH_2}N$), 56.08 ($(CH_2)_2N^1$ piperazinyl), 101.42, 110.88, 114.25, 116.62, 117.60, 120.70 , 122.99, 126.99, 127.08, 128.50, 129.09 (aromatic C), 137.12 (aromatic C-1 of phenylpiperazine), 149.82 (C-7 of thiazolopyrimidine ring), 160.76 (C=O), 168.13 (-S-C(N)=N- of thiazolopyrimidine ring). MS m/z (%): $M^+$ 464 (3.99). IR, $Cm^{-1}$: 3058 (aromatic CH), 2920 (aliphatic CH), 1660 (CO). Analysis calculated for $C_{25}H_{25}ClN_4OS$ (465.02): C, 64.57; H, 5.42; N, 12.05. Found: C, 64.51; H, 5.88; N, 12.02.

### *1.2.3. 7-Methyl-3-phenyl-6-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11c):**

Yield 37%; mp. 139-142$^{o}$ (ethanol-water). $^{1}$H-NMR (200 MHz, DMSO-$d_6$) δ 2.36 (s, 3H, -$CH_3$), 2.65 (t, 2H, J= 7 Hz, $\underline{CH_2}CH_2N$-), 2.95 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 3.11 (t, 2H, J= 7 Hz, -$CH_2\underline{CH_2}$N-), 3.41 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.99-7.93 (m, 10H, aromatic). IR, $Cm^{-1}$: 3057 (aromatic CH), 2925 (aliphatic CH), 1663 (CO). MS m/z (%): $M^+$ 498.5 (4.95), 176 (100). Analysis calculated for $C_{26}H_{25}F_3N_4OS$ (498.57): C, 62.64; H, 5.05; N, 11.24. Found: C, 63.12; H, 5.25; N, 11.55.

### *1.2.4. 7-Methyl-3-phenyl-6-[2-(4-phenylpiperazin-1-yl)ethyl]-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11d):**

Yield 37%; mp. 152-154$^{o}$ (ethanol). $^{1}$H-NMR (200 MHz, DMSO-$d_6$) δ 2.36 (s, 3H, -$CH_3$), 2.66 (t, 2H, J= 6.6 Hz, $\underline{CH_2}CH_2N$-), 2.99 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 3.15 (t, 2H, J= 6.6 Hz, -$CH_2\underline{CH_2}$N-), 3.44 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.95-8.01 (m, 11H, aromatic H). MS m/z (%): $M^+$ 430.25 (2.92), 207 (100). Analysis calculated for $C_{25}H_{26}N_4OS.2H_2O$ (466.61): C, 64.35; H, 6.48; N, 12.01. Found: C, 64.70; H, 6.90; N, 12.46.

### *1.2.5. 3-(4-Bromophenyl)-6-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-7-methyl-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11e):**

Yield 35%; mp. 132-3$^{o}$ (isopropanol). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, -$CH_3$), 2.54 (t, 2H, J= 8 Hz, $\underline{CH_2}CH_2N$-), 2.74 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 3.01(t, 2H, J= 8 Hz, -$CH_2\underline{CH_2}$N-), 3.10 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.85 (s, 3H, -$OCH_3$), 6.66-7.66 (m, 9H, aromatic H). $^{13}$C-NMR (75.45 MHz, $CDCl_3$) δ 21.82 ($CH_3$), 23.34 ($\underline{CH_2}CH_2N$), 50.52 ($(CH_2)_2N^4$ piperazinyl), 53.23 ($CH_2\underline{CH_2}N$), 55.33 ($(CH_2)_2N^1$ piperazinyl), 56.60 ($OCH_3$), 103.21, 109.89, 111.28, 115.37, 118.17, 120.96, 121.51, 123.32, 127.51, 130.67, 131.60 (aromatic C), 137.37 (aromatic C-1 of phenylpiperazine), 152.24 (C-7 of thiazolopyrimidine ring), 160.10 (C=O), 167.31 (-S-C(N)=N- of thiazolopyrimidine ring). MS m/z (%): $M^+$ 538.25 (0.82), $[M+2]^+$

540.25 (0.79), 205 (100). Analysis calculated for $C_{26}H_{27}BrN_4O_2S$. $1.5H_2O$ (566.52): C, 55.12; H, 5.16; N, 9.89. Found: C, 55.30; H, 5.10; N, 10.22.

### *1.2.6. 3-(4-Bromophenyl)-6-{2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl}-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (11f):*

Yield 43%; mp. 182-185° (isopropanol). $^1$H-NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H, $-CH_3$), 2.55 (t, 2H, J= 8 Hz, $\underline{CH_2}CH_2N$-), 2.66 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.74 (t, 2H, J= 8 Hz, $-CH_2\underline{CH_2}N$-), 3.13 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.67-7.66 (m, 9H, aromatic H). IR, $Cm^{-1}$: 3058 (aromatic CH), 2916 (aliphatic CH), 1650 (CO). Analysis calculated for $C_{25}H_{24}BrClN_4OS$ (543.92): C, 55.21; H, 4.45; N, 10.30. Found: C, 55.05; H, 4.60; N, 10.20.

### *1.2.7. 3-(4-Bromophenyl)-7-methyl-6-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (11g):*

Yield 32%; mp. 158-160° (ethanol-water). $^1$H-NMR (200 MHz, DMSO-$d_6$) δ 2.46 (s, 3H, $-CH_3$), 2.53 (t, 2H, J= 8 Hz, $\underline{CH_2}CH_2N$-), 2.68 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.74 (t, 2H, J= 8 Hz, $-CH_2\underline{CH_2}N$-), 3.17 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.69-7.70 (m, 9H, aromatic H). MS m/z (%): $M^+$ 577.40 (0.25), 243 (100). Analysis calculated for $C_{26}H_{24}BrF_3N_4OS$ (577.47): C, 54.08; H, 4.19; N, 9.70. Found: C, 54.04; H, 4.39; N, 9.57.

### *1.2.8. 3-(4-Bromophenyl)-7-methyl-6-[2-(4-phenylpiperazin-1-yl)ethyl]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (11h):*

Yield 46%; mp. 167-170° (isopropanol). $^1$H-NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H, $-CH_3$), 2.53 (t, 2H, J= 8 Hz, $\underline{CH_2}CH_2N$-), 2.74 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.83 (t, 2H, J= 8 Hz, $CH_2\underline{CH_2}N$-), 3.23 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.66-7.66 (m, 10H, aromatic H). IR, $Cm^{-1}$: 3060 (aromatic CH), 2920 (aliphatic CH), 1651 (CO). Analysis calculated for $C_{25}H_{25}BrN_4OS$ (509.47): C, 58.94; H, 4.95; N, 11.00. Found: C, 59.26; H, 5.19; N, 10.77.

### *1.2.9. 3-(4-Methoxyphenyl)-6-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-7-methyl-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11i):**

Yield 54%; mp.180-182$^{o}$ (methanol). $^{1}$H-NMR (200 MHz, DMSO-$d_6$) δ 2.37 (s, 3H, -$CH_3$), 2.52 (t, 2H, J= 6.6 Hz, $\underline{CH_2}CH_2N$), 2.60 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.96 (t, 2H, J= 6.6 Hz, $CH_2\underline{CH_2}N$-), 3.36 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.78 ( s, 6H, 2 -$OCH_3$ groups), 6.83-7.76 (m, 9H, aromatic H). IR, Cm$^{-1}$: 3055 (aromatic CH), 2920 (aliphatic CH), 1663 (CO). Analysis calculated for $C_{27}H_{30}N_4O_3S$ (490.63): C, 66.10; H, 6.16; N, 11.42. Found: C, 66.36; H, 6.63; N, 11.60.

### *1.2.10. 6-{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}-3-(4-methoxyphenyl)-7-methyl-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11j):**

Yield 57%; mp. 147-150$^{o}$ (methanol). $^{1}$H-NMR (200 MHz, DMSO-$d_6$) δ 2.35 (s, 3H, -$CH_3$), 2.51 (t, 2H, J= 6 Hz, $\underline{CH_2}CH_2N$), 2.58 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.94 (t, 2H, J= 6 Hz, $CH_2\underline{CH_2}N$-), 3.10 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.78 (s, 3H, -$OCH_3$), 6.81-7.73 (m, 9H, aromatic H). Analysis calculated for $C_{26}H_{27}ClN_4O_2S$ (495.05): C, 63.08; H, 5.50; N, 11.32. Found: C, 63.40; H, 4.88; N, 11.26.

### *1.2.11. 3-(4-Methoxyphenyl)-7-methyl-6-(2-{4-[3-(trifluoromethyl)phenyl]-piperazin-1-yl}ethyl)-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11k):**

Yield 42%; mp. 171-174$^{o}$ (ethanol-water). $^{1}$H-NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H, $CH_3$), 2.57 (t, 2H, J= 7.4 Hz, $\underline{CH_2}CH_2N$), 2.77 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.88 (t, 2H, J= 7.4 Hz, $CH_2\underline{CH_2}N$-), 3.35 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.81 (s, 3H, -$OCH_3$), 6.56-7.71 (m, 9H, aromatic H). MS m/z (%): $M^+$ 528.2 (0.62), 243 (100). IR, Cm$^{-1}$: 3057 (aromatic CH), 2922 (aliphatic CH), 1652 (CO). Analysis calculated for $C_{27}H_{27}F_3N_4O_2S$ (528.60): C, 61.36; H, 5.15; N, 10.60. Found: C, 61.44; H, 5.19; N, 10.35.

### *1.2.12. 3-(4-Methoxyphenyl)-7-methyl-6-[2-(4-phenylpiperazin-1-yl)ethyl]-5***H***-thiazolo[3,2-a]pyrimidin-5-one (11l):**

Yield 49%; mp. 168-170$^{o}$ (ethanol). $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H, -$CH_3$), 2.52 (t, 2H, J= 7 Hz, $\underline{CH_2}CH_2N$), 2.67 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.75 (t,

2H, J= 7 Hz, $CH_2$ $\underline{CH_2}$N-), 3.19 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.82 (s, 3H, -$OCH_3$), 6.56-7.71 (m, 10H, aromatic H). $^{13}$C-NMR (75.45 MHz, $CDCl_3$) δ 21.80 ($CH_3$), 23.50 ($\underline{CH_2}CH_2N$), 49.05 ($(CH_2)_2N^4$ piperazinyl), 53.07 ($CH_2\underline{CH_2}N$), 55.26 ($(CH_2)_2N^1$ piperazinyl), 56.62 ($OCH_3$), 100.94, 108.38, 112.96, 113.91, 115.92, 119.50, 124.27, 127.23, 129.02, 130.46 (aromatic C), 138.59 (aromatic C-1 of phenylpiperazine), 151.06 (C-7 of thiazolopyrimidine ring), 159.04 (aromatic C-4 of methoxyphenyl ring), 160.25 (C=O), 167.12 (-S-C(N)=N- of thiazolopyrimidine ring). MS m/z (%): $M^+$ 460.25 (1.82), 175 (100). Analysis calculated for $C_{26}H_{28}N_4O_2S$ (460.60): C, 67.80; H, 6.13; N, 12.16. Found: C, 67.46; H, 6.10; N, 12.8.

### *1.2.13. 6-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-7-methyl-3-(4-methylphenyl)-5*H*-thiazolo[3,2-a]pyrimidin-5-one (11m):*

Yield 42%; mp. 165-166° (isopropanol). $^1$H-NMR (200 MHz, DMSO-$d_6$) δ 2.32 (s, 3H, -$CH_3$ tolyl), 2.34 (s, 3H, -$CH_3$), 2.56 (t, 2H, J= 6.6 Hz, $\underline{CH_2}CH_2N$), 2.76 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.92 (t, 2H, J= 6.6 Hz, $CH_2\underline{CH_2}N$-), 3.35 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 3.79 (s, 3H, -$OCH_3$), 6.88-7.81 (m, 9H, aromatic H). MS m/z (%): $M^+$ 474.15 (1.08), 205 (100). Analysis calculated for $C_{27}H_{30}N_4O_2S$ (474.63): C, 68.33; H, 6.37; N, 11.80. Found: C, 68.51; H, 5.96; N, 11.21.

### *1.2.14. 6-{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}-7-methyl-3-(4-methylphenyl)-5*H*-thiazolo[3,2-a]pyrimidin-5-one (11n):*

Yield 46%; mp. 130-133° (methanol). $^1$H-NMR (200 MHz, DMSO-$d_6$) δ 2.31 (s, 3H, -$CH_3$ tolyl), 2.36 (s, 3H, -$CH_3$), 2.52 (t, 2H, J= 6.6 Hz, $\underline{CH_2}CH_2N$), 2.78 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.91 (t, 2H, J= 6.6 Hz, $CH_2\underline{CH_2}N$-), 3.35 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.93-7.71 (m, 9H, aromatic H). Analysis calculated for $C_{26}H_{27}ClN_4OS$ (479.05): C, 65.19; H, 5.68; N, 11.70. Found: C, 65.30; H, 5.30; N, 11.46.

### *1.2.15. 7-Methyl-3-(4-methylphenyl)-6-(2-{4-[3-(trifluoromethyl)phenyl]-piperazin-1-yl}ethyl)-5*H*-thiazolo[3,2-a]pyrimidin-5-one (11o):*

Yield 35%; mp. 123-126° (ethanol-water). $^1$H-NMR (200 MHz, DMSO-$d_6$) δ 2.32 (s, 3H, -$CH_3$ tolyl), 2.34 (s, 3H, -$CH_3$), 2.53 (t, 2H, J= 7 Hz, $\underline{CH_2}CH_2N$), 2.81 (br

s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.89 (t, 2H, J= 7 Hz, $CH_2\underline{CH_2}N$-), 3.38 (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.99-7.83 (m, 9H, aromatic H). MS m/z (%): $M^+$ 512.15 (2.84), 243 (100). IR, $Cm^{-1}$: 3060 (aromatic CH), 2919 (aliphatic CH), 1661 (CO). Analysis calculated for $C_{27}H_{27}F_3N_4OS$ (512.60): C, 63.27; H, 5.31; N, 10.93. Found: C, 63.30; H, 5.40; N, 10.66.

### *1.2.16. 7-Methyl-3-(4-methylphenyl)-6-[2-(4-phenylpiperazin-1-yl)ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one (11p):*

Yield 41%; mp. 155-157° (isopropanol). $^1$H-NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3H, $-CH_3$ tolyl), 2.44 (s, 3H, $-CH_3$), 2.50 (t, 2H, J= 7 Hz, $\underline{CH_2}CH_2N$), 2.76 (br s, 4H, $(CH_2)_2N^1$ piperazinyl), 2.89 (t, 2H, J= 7 Hz, $CH_2\underline{CH_2}N$-), 3.23 (br s, 4H, (br s, 4H, $(CH_2)_2N^4$ piperazinyl), 6.65-7.71(m, 10 H, aromatic H). MS m/z (%): $M^+$ 444.15 (3.17), 175 (100). IR, $Cm^{-1}$: 3059 (aromatic CH), 2918 (aliphatic CH), 1657 (CO). Analysis calculated for $C_{26}H_{28}N_4OS$ (444.60): C, 70.24; H, 6.35; N, 12.60. Found: C, 70.52; H, 6.38; N, 12.85.

### *2. Pharmacological screening*

*Inhibition of 5-HTP induced head twitches in mice.*

The antagonism of 5-$HT_{2A}$ receptors was determined *in vivo* by inhibition of 5-HTP induced head twitches in mice [18]. The animals were divided into seventeen groups each of six male mice (18–22g) to test compounds **11a–p** and risperidone as the standard drug (Tab. 1). The animals received 75mg/kg pargyline HCl as a solution in water intraperitoneally (ip). Thirty minutes later, they were treated with the test drug ip in a dose of 24.4 mmol/kg as a suspension in saline and Tween 80. Thirty minutes after the test drug, the animals were injected ip with 10mg/kg DL-5-HTP as a suspension in saline and Tween 80. An additional group of six mice was used as a control group which was injected with water-Tween 80 as a vehicle. An animal was considered to give positive response if it does not show head twitches 20 min. after 5-HTP injection. According to the observed response%, the experiment was repeated similarly using a lower and a higher dose of the drug

(12.2 and 48.8 mmol/kg). Inhibition of head twitches after treatment with the drug was observed relative to a control group of six mice treated with pargyline and 5-HTP only.

Using the inhibition of 5-HTP induced head twitches in mice, the effects of the treatment with the new compounds on the dose-response% were graphically illustrated in comparison with that of risperidone (Fig. 7).

The potencies ($ED_{50}$) of the tested compounds (Tab. 2), and statistical t-test for comparison between the potencies of the tested compounds and risperidone were performed by Prism 3 software.

### *3. Pharmacophore modeling study*

All molecular modeling calculations were performed using "Molecular Operating Environment (MOE) version 2007.09", Chemical Computing Group Inc., running on "Windows XP" operating system installed on an Intel Pentium IV PC with a 2.8 MHz processor and 512 RAM.

#### *General methodology:*

*1-Alignment of the training set compounds:*

The training set compounds, consisting of ten known 5-$HT_{2A}$ antagonists of diverse chemical structure, were built using the builder interface of the MOE software. The compounds were aligned using the flexible alignment tool of the program adjusting the energy cut off to 10 kcal/mol and root mean square deviation (RMSD) tolerance to 0.5. The stochastic conformation search option was used as the method of alignment (Fig. 1).

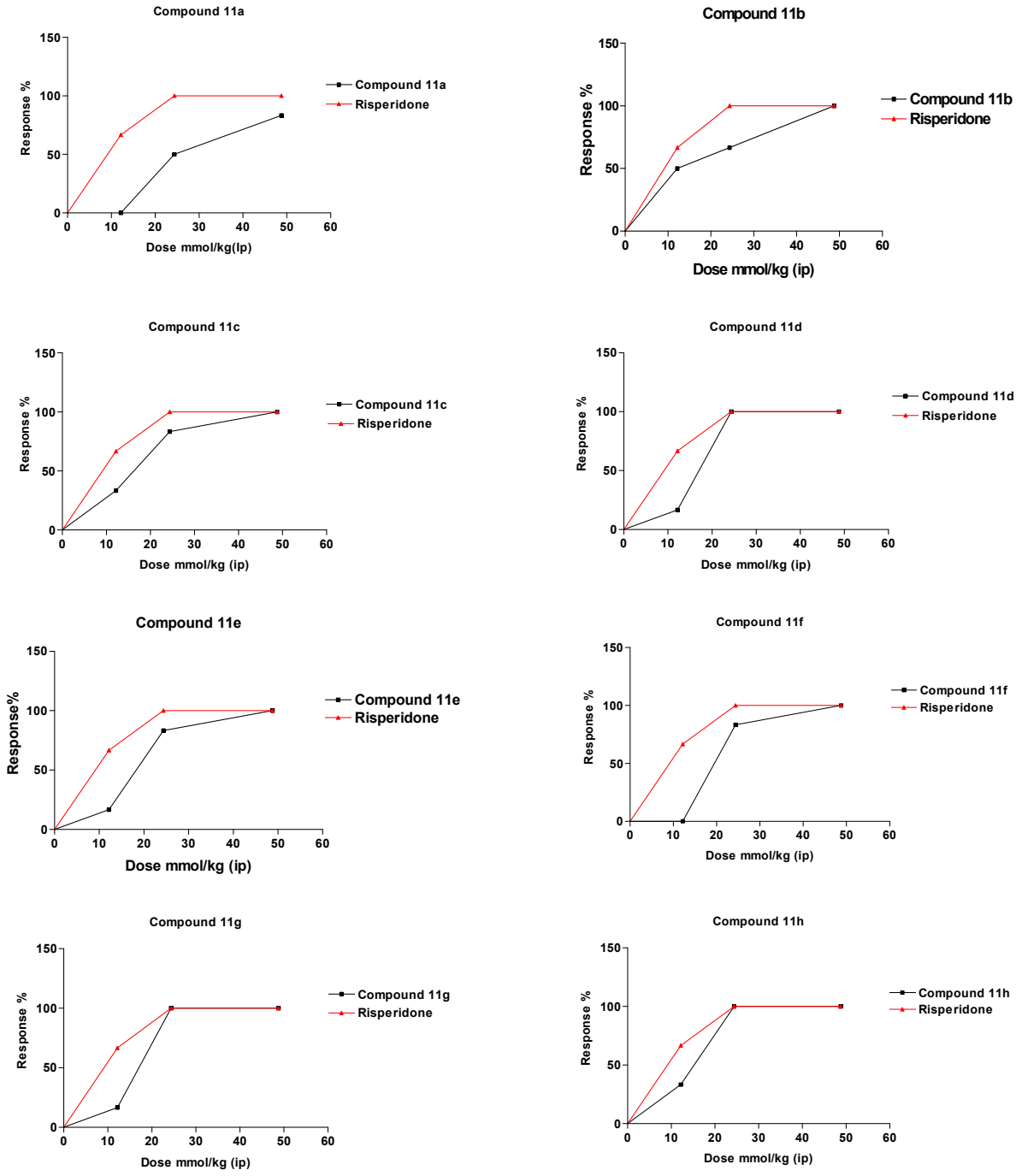



**Fig. 7.** Dose-response% curves showing pharmacological activity of the tested compounds in inhibition of 5-HTP induced head twitches in relation to risperidone.

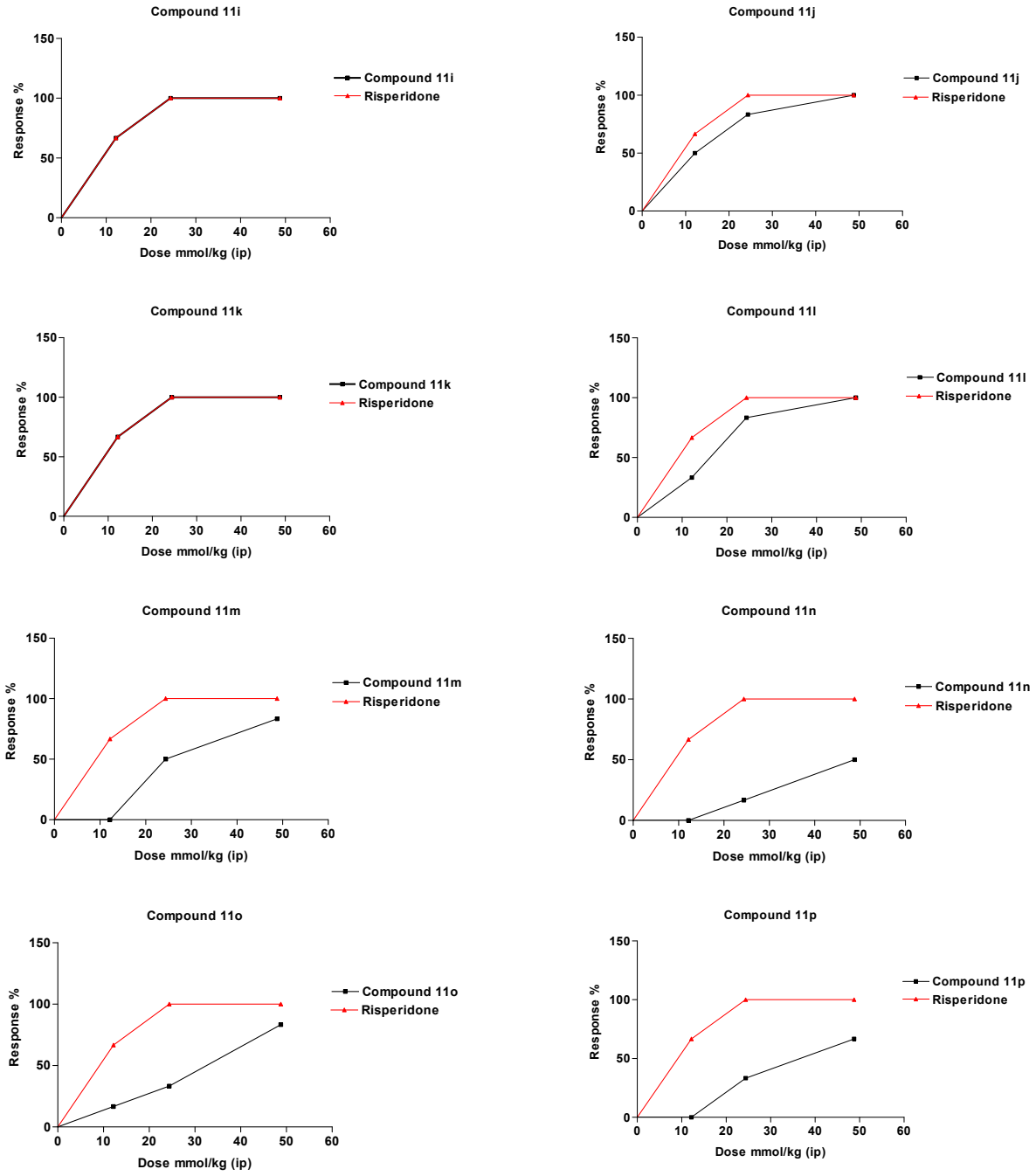

Compound 11i
Response %
Dose mmol/kg (ip)
Compound 11i
Risperidone
Compound 11j
Response %
Dose mmol/kg (ip)
Compound 11j
Risperidone
Compound 11k
Response %
Dose mmol/kg (ip)
Compound 11k
Risperidone
Compound 11l
Response %
Dose mmol/kg (ip)
Compound 11l
Risperidone
Compound 11m
Response %
Dose mmol/kg (ip)
Compound 11m
Risperidone
Compound 11n
Response %
Dose mmol/kg (ip)
Compound 11n
Risperidone
Compound 11o
Response %
Dose mmol/kg (ip)
Compound 11o
Risperidone
Compound 11p
Response %
Dose mmol/kg (ip)
Compound 11p
Risperidone

**Fig. 7.** (Cont.).

*2-Target compounds optimization:*

Conformational analyses of the built molecules were performed in a two-step procedure. First, the target compounds were subjected to energy minimization tool using the included MOPAC 7.0. The geometry of the compounds was optimized with the semiemperical PM3 Hamiltonian using Restricted Hartree-Fock (RHF) and RMS gradient of 0.05 Kcal/mol. Then, the produced model was subjected to the 'Systematic Conformational Search' of the MOE. All items were set as default with RMS gradient of 0.01 Kcal/mol and RMS distance of 0.1 Å. The obtained data were then saved as MBD file to be used in the pharmacophore fitting calculations.

*3-Pharmacophore Building:*

A pharmacophore model was created using the 'Pharmacophore Query Editor'. The aligned training set compounds were used as the template for building the model. The settings of the software parameters were adjusted to:

'Unified' as the scheme of annotation

'Consensus method' for model building

Tolerance was set to 1.2 Å and the threshold was set to 50%.

The produced model was saved as *.ph file for testing compound-pharmacophore fitting and further calculations (Fig. 2).

*4-Fitting of the target compounds on the built model:*

Using the generated pharmacophore model and the saved conformations of each molecule; the fitting of the target compounds **11a–d** into the model was tested (Figs. 3-6). The root mean square deviation value for each conformer was calculated and the one having the lowest RMSD value was taken for further visual and energy inspection.

## Acknowledgement

I am grateful to Dr. Rania Khalef AbdelKader, research assistant in the Pharmacology laboratory, Theodore Bilharz Institute, Giza, Egypt, for her kind help

and advice in the pharmacological screening. Also, I acknowledge Dr. Mohammed Kamal Abdel-Hamid, assistant lecturer in Pharmaceutical Chemistry Department, Faculty of Pharmacy, Assiut University, Assiut, Egypt, for performing the modeling study.

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*Received April 19th, 2008*
*Accepted (after revision) August 5th, 2008*
*Available online at www.scipharm.at August 9th, 2008*