Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5749–5753

Two new phenylpiperazines with atypical antipsychotic potential

Mirko Tomić,[a,*] Djurdjica Ignjatović,[a] Gordana Tovilović,[a] Deana Andrić,[b] Goran Roglić[b] and Sladjana Kostić-Rajačić[c]

[a]*Department of Biochemistry, Institute for Biological Research, Bul. Despota Stefana 142, 11060 Belgrade, Serbia*
[b]*Faculty of Chemistry, 11000 Belgrade, Serbia*
[c]*Institute for Chemistry, Technology and Metallurgy, 11000 Belgrade, Serbia*

Received 14 June 2007; revised 22 August 2007; accepted 28 August 2007
Available online 31 August 2007

Abstract—Two new series of substituted arylpiperazines with heterocyclic 3-propoxy-benzimidazole or 3-propoxy-benzimidazole-2-thione groups were synthesized and their in vitro binding affinities for the D_2, 5-HT_{1A}, 5-HT_{2A}, and α_1-adrenergic receptors determined. Among them, only two compounds with phenyl aryl-constituent (8a and 9a) showed 5-HT_{2A}/D_2 pK_i binding ratios proposed for atypical neuroleptics. As to their behavioral screening on rodents, both compounds exhibited a non-cataleptic action in rats and antagonized D-amphetamine-induced hyperlocomotion in mice, suggesting their possible atypical antipsychotic potency.

Schizophrenia is an overwhelming mental illness for which there is currently no ideal therapy. Classical antipsychotic drugs, exhibiting the mechanism of the central dopamine (DA) D_2 receptors blockade in the limbic forebrain, are useful for the treatment of the positive symptoms, but failed to manage the negative symptoms of schizophrenia.[1] Moreover, antipsychotics with prominent DA D_2 antagonist potency were shown to cause tardive dyskinesia and extrapyramidal side effects (EPS) in humans, presumably by simultaneous blockade of striatal DA receptors.[1,2] Limited efficacy and undesirable side effects of typical antipsychotics have driven the development of improved ''atypical'' antipsychotic agents, like the prototype antipsychotic drug—clozapine, which are in general effective for both positive and negative symptoms of schizophrenia, more efficacious than classical antipsychotics in treatment-refractory patients, and have a low incidence of extrapyramidal side effects.[1,2] A number of current approaches for the development of superior antipsychotic agents involve the mechanisms based on the reduction of the DA neurotransmission with partial D_2 agonists or DA autoreceptor agonists, together with antagonism at the central serotonin 5-HT_{2A} and partial agonism at 5-HT_{1A} receptors.[1–4] The blockade of 5-HT_{2A} receptors has been implicated in both the enhanced efficacy against negative symptoms of schizophrenia and improved EPS profile of the atypical antipsychotics,[3] while the 5-HT_{1A} receptor agonists are believed to attenuate some D_2 receptor-mediated side effects.[4] Thus, new compounds may retain antipsychotic efficacy, while having reduced liability for severe movement disorders often developed upon acute and long-term treatments, and could potentially alleviate certain negative schizophrenia-associated symptoms.[1,2] Additionally, upon modulation of the central 5-HT neurotransmission, these compounds may also exhibit certain anxiolytic and/or antidepressant effects.[1,5]

During the last decade, we have formulated the strategy on drug design and synthesis of mixed DA-/5-HT-ergic heterocyclic arylpiperazines, with different specific structure of heteroaryl-group that mimics catechol moiety of the dopamine,[6,7] and may exhibit atypical neuroleptic potential. In previous papers, we have presented some of the most appealing compounds upon alteration of heterocyclic and aryl groups.[7] Here, we present some selected newly synthesized ligands containing benzimidazole or benzimidazole-2-thione linked by propyloxy bridge to four different arylpiperazines, already characterized by improved interaction with the D_2 receptors.[7] Aryl parts of the ligands were chosen in accordance to their best pharmacological profiles[6–8] and our intention was also to further evaluate the influence of the propyloxy linker of the new ligands (instead of ethyloxy linker

Keywords: Arylpiperazines; Dopamine receptors; Serotonin receptors; Atypical antipsychotics.
* Corresponding author. Tel.: +381 11 2078306; fax: +381 11 2761433; e-mail: mitomic@ibiss.bg.ac.yu

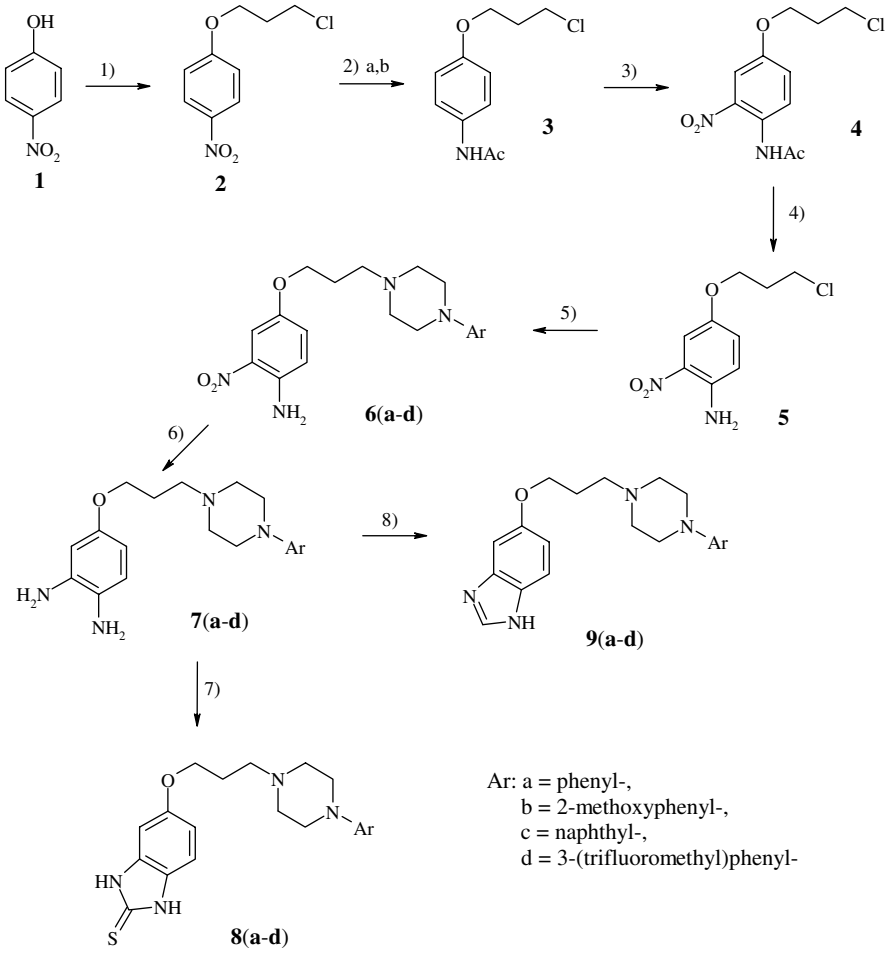
0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.08.066

found in our previously synthesized compounds) on the receptor binding profiles.

Synthetic pathways, similar to previously described procedure,[8] of the two sets of ligands, 5-[3-(4-arylpiperazin-1-yl)propoxy]-1,3-dihydro-2*H*-benzimidazole-2-thiones (**8a–d)** and 6-[3-(4-arylpipera-zin-1-yl)propoxy]-1*H*-benzimidazoles (**9a–d)**, submitted to pharmacological exploration in the present study, are shown in Scheme 1. Yield and chemical characterization of the compounds **8a–d** and **9a–d** are given under Notes.[9,10]

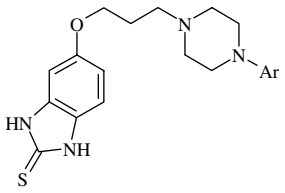
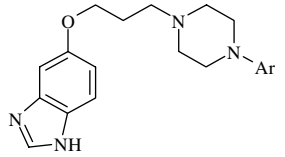
Eight new compounds (**8a–d**, **9a–d**) and clozapine were initially evaluated for cytotoxicity by MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide) colorimetric assay,[11] performed on the stable transfected CHO hD_2L cell line. Concentrations of the compounds killing 50% of the cells (EC_{50}) were estimated from the curves obtained with a series of ligand concentrations in culture media. The eight new ligands were also evaluated by in vitro assays for binding affinities at the specific DA (D_2), 5-HT (5-HT_{1A}, 5-HT_{2A}), and α_1-adrenergic receptors. These receptors were chosen concerning their anticipated role in the action of atypical antipsychotic drugs.[1–4] Specific binding affinities (pK_i, Table 1) of the new arylpiperazines and clozapine were determined by measuring the extent of displacement of ^{3}H-labeled specific ligands from rat striatal or cortical synaptosomes with a range of concentrations of selected compounds.[7,11] Based on their high pK_i's 5-HT_{2A}/D_2 receptor binding ratio, two of the compounds were selected to be assayed in simple animal behavioral models relevant to atypical antipsychotic activity. These compounds (**8a**, **9a**) were applied to rodents in 2–3 single doses (in the range 1–10 mg/kg bw; ip) and their possible cataleptic effects were evaluated in rats,[12] while their influence on spontaneous locomotion and amphetamine-induced hyperactivity was assessed in mice with an open-field test.[13]

The MTT assay revealed that all compounds had a low cytotoxic potential, mainly weaker than that of clozapine (EC_{50} = 56 μM). Compound **9c** expressed the highest cytotoxicity among the examined ligands (EC_{50} = 43 μM), while the EC_{50} values for the remaining ligands ranged from 139 to 859 μM. Binding affinities of arylpiperazines **8a–d**, **9a–d** for the D_2, 5-HT_{1A}, 5-HT_{2A}, and α_1–adrenergic receptors are listed in Table 1. The binding affinities of these new compounds appeared to be somewhat decreased for D_2 and 5-HT_{1A} receptors,



Scheme 1. Synthetic pathways of the new arylpiperazines. Reagents: (1) $Cl(CH_2)_3Br$, MEK, Na_2CO_3, 93%; (2) a—$SnCl_2$, $(CH_3)_2$ CHOH b—Ac_2O, $(CH_3)_2CHOH$, 94%; (3) Ac_2O, H_2SO_4/HNO_3, 68%; (4) 4 N HCl, 93%; (5) DMF, Na_2CO_3, arylpiperazine, 78–90%; (6) RaNi, N_2H_4; (7) CS_2, KOH; (8) 98% HCO_2H, 4 N HCl.

Table 1. Binding affinities of the new compounds and clozapine

Compound	Ar	pK_i				
		D_2	$5HT_{2A}$	$5HT_{1A}$	α_1	5-HT2A/D2
						
8a	Phe	7.38	8.69	6.03	7.53	1.18
8b	2-MeOPhe	8.77	7.72	6.75	8.71	0.88
8c	Naphthyl	7.02	6.72	6.26	6.37	0.96
8d	3-CF_3Phe	6.44	6.50	7.00	6.31	1.01
						
9a	Phe	7.12	7.86	6.19	7.58	1.10
9b	2-MeOPhe	8.06	7.10	7.82	8.23	0.88
9c	Naphthyl	7.38	7.29	7.22	7.20	0.99
9d	3-CF_3Phe	7.82	6.99	6.41	6.92	0.89
Clozapine		6.84	7.88	7.02	7.65	1.15

*Values are means of at least 3 experiments (SEM were less than 5%).

when compared to the previously synthesized arylpiperazines of the similar structure and with the ethyloxy linker.[7] SAR analysis of the present compounds demonstrated that 2-methoxyaryl substitutions improved binding affinity at D_2 and α_1 receptors, while reducing it at 5-HT_{2A} receptors, and this was more obvious for thiones. On the other hand, only phenylpiperazines shifted the preferred affinity of the ligands from D_2 toward 5-HT_{2A} receptors, where the pK_i's 5-HT_{2A}/D_2 ratios of **8a** and **9a** were 1.10 and 1.18, respectively, which is close to that of clozapine (1.15). Although Meltzer and collegues[3] suggested pK_i's 5-HT_{2A}/D_2 ratios over 1.14 as the criterion for a possible atypical neuroleptic action of new ligands, both the mentioned compounds were chosen here for behavioral screening of their atypical antipsychotic potency. In the first instance, it was noticed that neither of the two selected ligands provoked catalepsy in rats (0/5 animals following 1.0 or 10.0 mg/kg bw of **8a** or **9a**, observed after 30, 60, 90, or 180 min), the same as 1.0 mg/kg clozapine (0/5 animals at the same time points), while haloperidol induced catalepsy at 1.0 mg/kg (3/5 animals after 30 min and 5/5 after 60, 90, and 180 min). In addition, the individual effects of the compounds on the spontaneous mice locomotion and amphetamine-induced hyperlocomotion were estimated in an open-field test (Fig. 1).[13] One way ANOVA indicated a significant influence of the treatments on the two observed parameters: (a) activity time ($F_{13,70} = 7.76$, $p < 0.001$) and (b) the distance traveled by heads of animals ($F_{13,70} = 19.71$, $p < 0.001$). Post hoc analysis revealed non-significant variation ($p > 0.05$) of these parameters following two **8a** or **9a** doses (1.0 and 10 mg/kg ip) when compared to the basal activity of saline controls. However, apparent, although non-significant, decrements of both parameters were noticed after the lower **9a** dose, suggesting its attenuating action on locomotion at lower concentrations. While this is similar to the pattern of behavioral action of an antidepressant roxindole,[5] it might be suggested that **9a** could also express antidepressant effects. Since it is not the topic of the present initial behavioral screening, this possibility will be tested in the future, more advanced study. Nonetheless, it is noticeable in this survey that almost all treatments generated a significant decline of the amphetamine-induced hyperlocomotion in mice. Even though the doses of the ligands in this behavioral test were chosen according to in vitro binding data (Table 1), with the expectation that the active threshold dose should be between 1.0 and 10 mg/kg ip, it appeared that these compounds, especially **9a**, may calm down the hyperlocomotion even after the lowest dose applied (1.0 mg/kg). Compound **9a** seems to be a stronger blocking agent for amphetamine hyperactivity, but differently from **8a**, it did not show a clear dose response relation. This could not be partially explained by the interaction of **9a** with D_2 or 5-HT_{2A} receptors, since it expressed lower binding affinities for these receptors comparing to **8a** (Table 1). Both compounds showed similarly low affinity at the 5-HT_{1A} receptors, which should exclude any significant participation of this interaction in their behavioral action. While high affinity of neuroleptics at the α_1-adrenergic receptors was explained as partially beneficial for their antipsychotic action, but also undesirable at high extent, because of their contribution to the side effects,[14] it seems that moderate affinity of **8a** and **9a** at this receptor (pK_i ~7.5), that is almost equal to that of

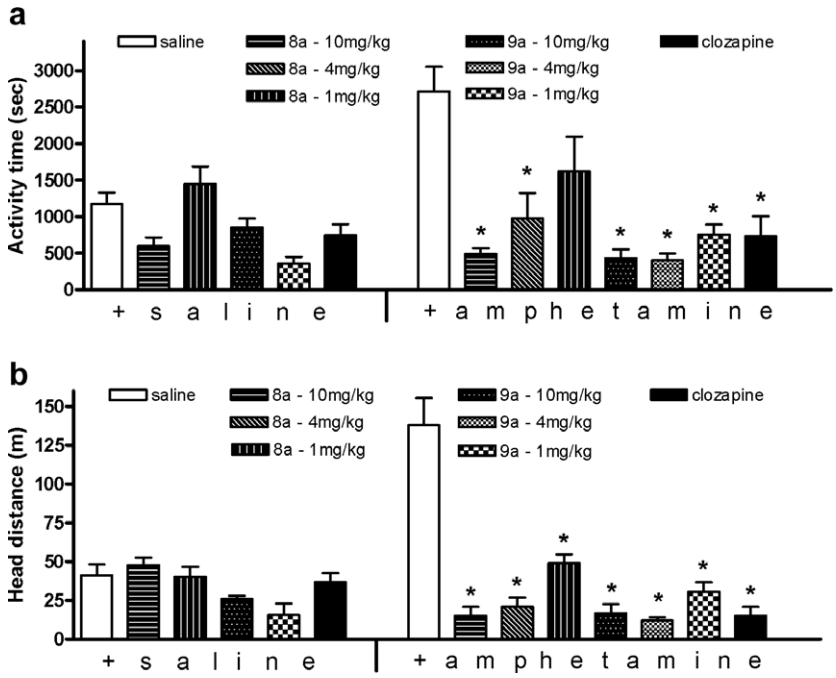


Figure 1. The effects of **8a**, **9a**, and clozapine (5 mg/kg) on spontaneous (+saline) and amphetamine-stimulated locomotor activity in mice. Animal locomotion was determined by (a) the cumulative time of activity and (b) total distance traveled by head of animals in an open field during 60-min registration period (for details see Ref. 13). $^{*}p < 0.001$ versus saline + amphetamine (3 mg/kg) control group, by Bonferroni's post ANOVA test.

clozapine (Table 1), could be at the reasonable level and optimal for their complete antipsychotic action. However, as it is well known that arylpiperazine template may show decent affinity for a number of receptors coupled to G protein, it cannot be excluded that significant interaction of our compounds with some other CNS receptors would participate in their total behavioral effects. These interactions with certain receptor classes (e.g. D_1, D_3, 5-HT_{2C}) would be elucidated soon.

The new compounds in this study show the most of structural similarities with aripiprazole, among official neuroleptics, but they did not share a comparable receptor binding profile according to the published pharmacological data of aripiprazole.[15] Aripiprazole displays a combination of much higher affinity for the D_2, 5-HT_{2A}, and especially 5-HT_{1A} receptors than any of our compounds. While it shows a partial agonism at D_2 and 5-HT_{1A} and antagonism at 5-HT_{2A} receptors,[15] the question arises whether the new arylpiperazines may exhibit the same functional activity. It was found that **8a** and **9a** may act as D_2 partial agonists by initial in vitro studies on hD_{2L} receptor-mediated inhibition of forskoline-stimulated cAMP accumulation in CHO cells (to be published). However, as postulated D_2 partial agonism of aripiprazole has been contradictorily replicated and it was proposed that this compound might function as a D_2 antagonist, agonist, or partial agonist depending on the precise complement of D_2 receptors and G-proteins in a particular cell,[16] this set of new arylpiperazines is also currently submitted to the more comprehensive assessment upon clarification of their exact functional activity.

In summary, we have described here the synthesis and binding affinity of new heterocyclic arylpiperazines, with benzimidazole and benzimidazole-2-thione linked to N-arylpiperazines by a propyloxy-bridge. Two of the compounds with phenyl constituent, that showed appropriate pK_i's 5-HT_{2A}/D_2 ratio suggested for atypical antipsychotics, have also expressed certain behavioral pattern of atypical antipsychotics in experimental rodents. Consequently, together with few other arylpiperazines already found to have atypical antipsychotic potency,[7] compounds **8a** and **9a** are subjected to a thorough preclinical profiling. More pharmacological details will be published in the near future.

Acknowledgment

This work was supported by the Ministry for Science, Technology and Environmental Protection of Serbia, Grants #143032 (authors 1–4) and #142009 (authors 5,6).

References and notes

1. (a) Taylor, D. M. *Schizophrenia in Focus*; Pharmaceutical Press: London, Chicago, 2006, Chapters 1–8, 14–16.; (b) Sramek, J. J.; Cutler, N. R.; Kurtz, N. M.; Murphy, M. F.; Carta, A. *Optimizing the Development of Antipsychotic Drugs*; Wiley: Chichester, 1997, Chapters 2,3.
2. (a) Tandon, R.; Jibson, M. D. *Psychoneuroendocrinology* **2003**, *28*, 9; (b) Miyamoto, S.; Duncan, G. E.; Marx, C. E.; Lieberman, J. A. *Mol. Psychiatry* **2005**, *10*, 79.
3. (a) Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *Psychopharmacol. Bull.* **1989**, *25*, 390; (b) Meltzer, H. Y.; Li, Z.;

Kaneda, Y.; Ichikawa, J. *Prog. Neuropsychopharmacol.* **2003**, *27*, 1159; (c) Meltzer, H. Y. *Curr. Op. Pharmacol.* **2004**, *4*, 53.
4. (a) Ichikawa, J.; Meltzer, H. Y. *Brain Res.* **2000**, *858*, 252; (b) Bantick, R. A.; Deakin, J. F.; Grasby, P. M. *J. Psychopharmacol.* **2001**, *15*, 37.
5. (a) Grunder, G.; Wetzel, H.; Hammes, E.; Benkert, O. *Psychopharmacology (Berl.)* **1993**, *111*, 123; (b) Maj, J.; Kolodziejczyk, K.; Rogóz, Z.; Skuza, G. *J. Neural. Transm.* **1996**, *103*, 627.
6. (a) Dukić, S.; Kostić-Rajačić, S.; Dragović, D.; Šoškić, V.; Joksimović, J. *J. Pharm. Pharmacol.* **1997**, *49*, 1036; (b) Kostić-Rajačić, S.; Šoškić, V.; Joksimović, J. *Arch. Pharm. (Weinheim)* **1998**, *331*, 22.
7. (a) Tomić, M.; Kundaković, M.; Butorović, B.; Vasilev, V.; Dragović, D.; Roglić, G.; Ignjatović, D.; Šoškić, V.; Kostić-Rajačić, S. *Pharmazie* **2003**, *58*, 677; (b) Tomić, M.; Kundaković, M.; Butorović, B.; Janać, B.; Andrić, D.; Roglić, G.; Ignjatović, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 42.
8. Šukalović, V.; Andrić, D.; Roglić, G.; Kostić-Rajačić, S.; Schrattenholz, A.; Šoškić, V. *Eur. J. Med. Chem.* **2005**, *40*, 481.
9. Compound (**8a**): Yield: 69%; mp 141 °C; 1H NMR (DMSO-d_6): δ 2.00 (t, 2H, J = 6 Hz), 2.85 (s, 6H), 3.24–3.39 (m, 4H), 4.02 (t, 2H, J = 6 Hz), 6.70–6.84 (m, 3H, ArH), 6.94–7.06 (m, 3H, ArH), 7.23 (t, 2H, J = 7.4 Hz, ArH), 12.41 (d, 2H, J = 8.2 Hz, NH). MS: *m/e* 163 (100), 369 (M+). $C_{20}H_{24}N_4OS$; (**8b**): Yield: 53%; mp 195 °C; 1H NMR (DMSO-d_6): δ 1.92 (s, 2H), 2.46–2.54 (m, 6H), 2.97 (s, 4H), 3.77 (s, 3H, OCH3), 4.00 (t, 2H, J = 6.4 Hz), 6.68–6.76 (m, 2H, ArH), 6.87–6.95 (m, 4H, ArH), 7.04 (d, 1H, J = 8.8 Hz, ArH), 12.40 (s, 2H, NH). MS: *m/e* 397 (100), 397 (M+). $C_{21}H_{26}N_4O_2S$; (**8c**): Yield: 61%; mp 221 °C; 1H NMR (d6DMSO): δ 2.13 (s, 2H), 2.50–2.53 (m, 6H), 3.22 (s, 4H), 4.07 (t, 2H, J = 6 Hz), 6.73–6.79 (m, 2H, ArH), 6.73 (s, 1H, ArH), 6.90 (d, 1H, J = 2.4 Hz, ArH), 7.10 (d, 1H, J = 6.8 Hz, ArH), 7.16 (d, 1H, J = 7 Hz, ArH), 7.41–7.66 (m, 4H, ArH), 7.89–7.94 (m, 1H, ArH), 8.11–8.16 (m, 1H, ArH), 12.45 (d, 2H, J = 10.2 Hz, NH). MS: *m/e* 242 (100), 419 (M+). $C_{24}H_{26}N_4OS$; (**8d**): Yield: 68%; mp 223 °C; 1H NMR (DMSO-d_6): δ 1.98 (s, 4H), 2.51–2.56 (m, 4H), 3.24 (s, 4H), 4.00 (t, 2H, J = 6 Hz), 6.69–6.76 (m, 2H, ArH), 7.02–7.09 (m, 2H, ArH), 7.17–7.24 (m, 2H, ArH), 7.42 (t, 1H, J = 8 Hz, ArH), 12.41 (d, 2H, J = 6.8 Hz, NH). MS: *m/e* 437 (100), 437 (M+). $C_{21}H_{23}F_3N_4OS$.
10. Compound (**9a**): Yield: 83%; mp 136 °C; 1H NMR: δ 2.04 (t, 2H, J = 7 Hz), 2.58–2.72 (m, 6H), 3.20–3.25 (m, 4H), 4.07 (t, 2H, J = 6.2 Hz), 6.82–6.96 (m, 3H, ArH), 7.11 (s, 1H, ArH), 7.23–7.31 (m, 2H, ArH), 7.53 (d, 1H, J = 8.4 Hz, ArH), 7.98 (s, 1H, CH). MS: *m/e* 221 (100), 337 (M+). C20H24N4O; (**9b**): Yield: 90%; oil; 1H NMR: δ 2.02 (t, 2H, J = 6.8 Hz), 2.59–2.70 (m, 6H), 3.12 (s, 4H), 3.85 (s, 3H, OCH3), 4.03 (t, 2H, J = 6.2 Hz), 6.84–7.12 (m, 6H, ArH), 7.53 (d, 1H, J = 7.4 Hz, ArH), 7.99 (s, 1H, CH). MS: *m/e* 251 (100), 367 (M+). $C_{21}H_{26}N_4O_2$; (**9c**): Yield: 78%; mp 241 °C; 1H NMR: δ 2.05 (t, 2H, J = 6.6 Hz), 2.65–2.78 (m, 6H), 3.15 (s, 4H), 4.05 (t, 2H, J = 6 Hz), 6.94 (d, 1H, J = 8.6 Hz, ArH), 7.04 (s, 1H, ArH), 7.09 (d, 1H, J = 3.6 Hz, ArH), 7.38–7.56 (m, 5H, ArH), 7.79–7.84 (m, 1H, ArH), 8.00 (s, 1H, CH). MS: *m/e* 387 (100), 387 (M+). $C_{24}H_{26}N_4O$; (**9d**): Yield: 88%; mp 187 °C; 1H NMR: δ 2.22–2.30 (m, 2H), 3.25–3.33 (m, 4H), 3.60 (s, 6H), 4.15 (t, 2H, J = 5.8 Hz), 6.87–6.91 (m, 1H, ArH), 7.16 (d, 2H, J = 6.2 Hz, ArH), 7.30 (d, 2H, J = 7.8 Hz, ArH), 7.44–7.55 (m, 2H, ArH), 8.32 (s, 1H, CH).). MS: *m/e* 405 (100), 405 (M+). $C_{21}H_{23}F_3N_4O$.
11. Vogel, G. H. In *Drug Discovery and Evaluation—Pharmacological Assays*; Vogel, G. H., Ed., 2nd ed.; Springer-Verlag: Berlin, Heidelberg, 2002; pp 500–543.
12. Test for catalepsy was done on adult Mill-Hill hooded rat males (bw 200–250 g). Catalepsy was scored by the horizontal bar test. Details are given in ref. [7b].
13. Open-field test. A total of 84 adult CPU mice males (30–40 g) were divided into 14 experimental groups (each consisting of 6 animals). Six groups were used to evaluate the effects of test compounds on spontaneous locomotor activity. Compounds **8a** and **9a** were originally dissolved in DMSO (final conc. up to 2%), diluted with saline, and ip injected (1.0 mg, or 10.0 mg in 2.0 ml per kg bw) 20 min before another injection of saline. The controls received first saline/DMSO and the comparison drug's group was primary treated with clozapine (5 mg/kg). Remaining eight groups of mice were employed to assess the effects of the first treatment on amphetamine-induced hyperactivity. They received (by the same schedule as above) either 1.0 mg, 4.0 mg, or 10.0 mg of **8a** or **9a**, saline/DMSO or clozapine (5 mg/kg), 20 min prior to D-AMPH sulphate (3.0 mg/kg). Each animal was positioned in the center of the plastic open-box ($40 \times 40 \times 30$ cm) immediately after the second injection and for the next 15 min they were allowed to adapt to the environment. The test room with the acoustic isolation was dimly illuminated (indirect 2×40 W light). During the following 60 min interval, locomotion was registered by a web-camera connected to PC and controlled by ANY-maze software (ANY-maze Video Tracking System 4.30, Stoelting Co., USA). The same program was also used to calculate two parameters chosen to illustrate total animal locomotion. (1) Time of activity (in seconds) was the sum of periods when animals moved in space. (2) Total head distance (in meters) demonstrated both the total locomotion in space and the head movements made in place, also representing a measure of some stereotype behaviors. Crude data was analyzed by GraphPad Prysm (4.00) using one-way ANOVA followed by Bonferroni's multiple group comparison test.
14. (a) Wadenberg, M. L.; Hertel, P.; Fernholm, R.; Hygge Blakeman, K.; Ahlenius, S.; Svensson, T. H. J. *Neural. Transm.* **2000**, *107*, 1229; (b) Svensson, T. H. *Progr. Neuropsychopharmacol. Biol. Psychiatry* **2003**, *27*, 1145.
15. (a) Shapiro, D. A.; Renock, S.; Arrington, E.; Chiodo, L. A.; Liu, L. X.; Sibley, D. R.; Roth, B. L.; Mailman, R. *Neuropsychopharmacology* **2003**, *28*, 1400; (b) DeLeon, A.; Patel, N. C.; Crismon, M. L. *Clin. Therapeutics* **2004**, *26*, 650.
16. Roth, B. L.; Sheffler, D. J.; Kroeze, W. K. *Nat. Rev. Drug Discovery* **2004**, *3*, 353.