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Brief Article

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Discovery of Bishomo(hetero)arylpiperazines as Novel Multifunctional Ligands Targeting Dopamine D_3 and Serotonin 5-HT_{1A} and 5-HT_{2A} Receptors

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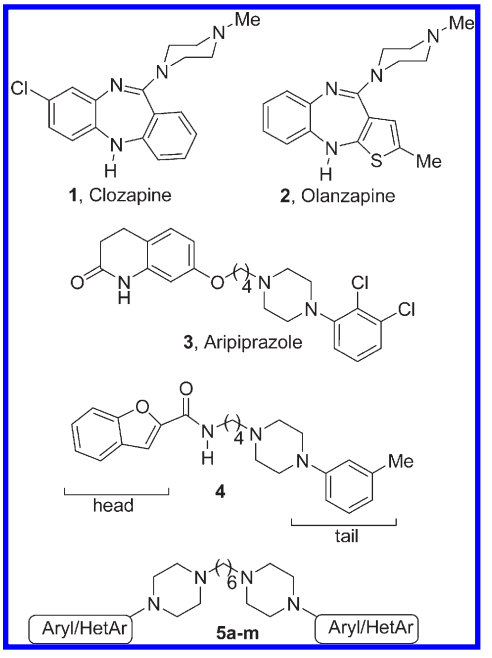
As a continuation of our efforts to develop innovative ligands for D_3, 5-HT_{1A}, and 5-HT_{2A} receptors with low propensity to block hERG channels, we propose a series bishetero(homo)arylpiperazines **5a**−**m** as novel and potent multifunctional ligands characterized by low occupancy at D_2 and 5-HT_{2C} receptors.

Introduction

Schizophrenia is a chronic mental disorder that globally affects ∼1% of the world population.[1] "Typical" antipsychotics (e.g., haloperidol), potent dopamine D_1 receptor (D_1R[a]) and D_2 receptor (D_2R) antagonists, are effective in the treatment of the positive symptoms of schizophrenia but fail to manage the negative symptoms and the cognitive impairment and induce side effects such as extrapyramidal symptoms (EPS) and hyperprolactinemia.[2] "Atypical" antipsychotics (e.g., clozapine (**1**) and olanzapine (**2**), Chart 1), characterized by a multireceptor affinity profile, are effective on therapy-resistant schizophrenic patients[3] although accompanied by a series of unwanted effects. Olanzapine may precipitate diabetes[4] and increase appetite,[5] and clozapine may induce agranulocytosis, while other antipsychotics (ziprasidone, risperidone, and quetiapine) may induce long QT syndrome (risk of malignant ventricular arrhythmia). Recently, aripiprazole (**3**, Chart 1), a potent D_2R ligand,[6,7] characterized by low risk of side effects, has been launched.[8]

The unmet clinical needs such as the treatment of refractory patients, poor treatment of negative symptoms, and cognitive dysfunction boosted us to exploit a novel paradigm[9−13] for developing innovative antipsychotics based on a unique multireceptor affinity profile.[14] Our pharmacological approach combines occupancy at dopamine D_3 receptor (D_3R), 5-HT_{2A} receptor (5-$HT_{2A}R$), and 5-HT_{1A} receptor (5-$HT_{1A}R$) with low affinity for D_2R (no liability of EPS at antipsychotic doses) and 5-HT_{2C} receptor (5-$HT_{2C}R$) (reducing the risk of obesity under chronic treatment). Our original design strategy[14] was based on the hypothesis that dopamine/serotonin competitive ligands, although characterized by different structural scaffolds, are able to interact with similar clusters of key receptor residues by adopting multiple binding modes.[9−14] We hypothesized that the flexible arylpiperazine skeleton could allow the proper orientation of the pharmacophoric moieties (i.e. the two aromatic rings, the protonated nitrogen, the H-bond donor/acceptor atom(s)) to settle into different dopamine/serotonin receptor sites. Structure−activity relationships (SARs) of the original arylpiperazines were associated (i) with the variation of the aromatic systems at the "head" and "tail" (Chart 1) of the structure, (ii) with the length of the methylene linker, and (iii) with

Chart 1. Reference and Title Compounds



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[a] Abbreviations: D_1R, dopamine D_1 receptor; D_2R, dopamine D_2 receptor; D_3R, dopamine D_3 receptor; EPS, extrapyramidal symptoms; 5-$HT_{2A}R$, serotonin 5-HT_{2A} receptor; 5-$HT_{1A}R$, serotonin 5-HT_{1A} receptor; 5-HT_{2C}, serotonin 5-HT_{2C} receptor; SARs, structure−activity relationships; hERG, human ether-a-go-go-related gene; PCP, phencyclidine; MAMP, methamphetamine; AUC, area under the curve; TEA, triethylamine.

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Table 1. Binding Affinities for D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} Receptors (K_i, nM)[a] and hERG Channels (K_i, μM)[b] of Compounds **5a**−**m** and Reference Antipsychotics

Compd	Aryl/HetAr	Aryl/HetAr	D_2[c]	D_3[c]	5-HT_{1A}[c]	5-HT_{2A}[c]	5-HT_{2C}[c]	hERG[c]
5a			>1000	1	3	31	>1000	8.0
5b			>1000	70	48	20	120	2.2
5c			>1000	27	8	28	303	2.4
5d			>1000	11	16	98	504	0.3
5e			>1000	159	16	45	>1000	>10
5f			>1000	34	30	39	>1000	13
5g			>1000	24	8	25	309	6.4
5h			>1000	20	19	10	182	3.8
5i			>1000	41	49	34	>1000	3.8
5j			>1000	44	2	10	150	8.7
5k			>1000	33	11	6	68	4.1
5l			NT[d]	NT[d]	NT[d]	NT[d]	NT[d]	0.9
5m			>1000	4	1	7	92	1.2
1			210	319	160	10	4.8	17
2			20	39	610	4.0	4.1	36
3			0.8	3.3	5.6	8.7	22	1.02
4			263	4.5	11.9	15.3	206	0.93

[a] Each value is the mean of three determinations, and all SD were within 10% of the mean. [b] Each value is the mean of two determinations, and all SD were within 10% of the mean. [c] Tests performed as in ref 14. [d] NT: not tested.

the replacement of the amide bond with an ether function.[14] According to our binding mode hypothesis, we rationalized SARs on the basis of dopamine/serotonin receptor homology by using 3D receptor models. This approach allowed us to identify the key structural elements responsible for achieving the fine balancing of activity and selectivity toward the receptors of interest and led to the identification of innovative atypical antipsychotics.[14] Furthermore, to improve the drugability of the novel antipsychotics, we directed our design strategy at limiting human ether-a-go-go-related gene (hERG) potassium channel inhibition by up to 1 μM, thus minimizing the risk of long QT syndrome and cardiac side effects.

In an effort to identify new scaffolds for the development of multifunctional ligands for the same panel of receptors, we applied the lessons learned from our previous studies and we developed novel bishomo(hetero)arylpiperazines as flexible ligands for specific occupancy of D_3R, 5-HT_{1A}R, and 5-HT_{2A}R. The bishomo(hetero)arylpiperazines **5a**−**m** (Chart 1 and Table 1) described herein demonstrated the predicted receptor affinity profile, being potent and selective for D_3R, 5-HT_{1A}R, and 5-HT_{2A}R (with low binding affinity for D_2R and 5-HT_{2C}R). Our design strategy also proved to be successful for reducing hERG occupancy. In fact, most compounds showed a low propensity to block hERG potassium channels.

Chemistry

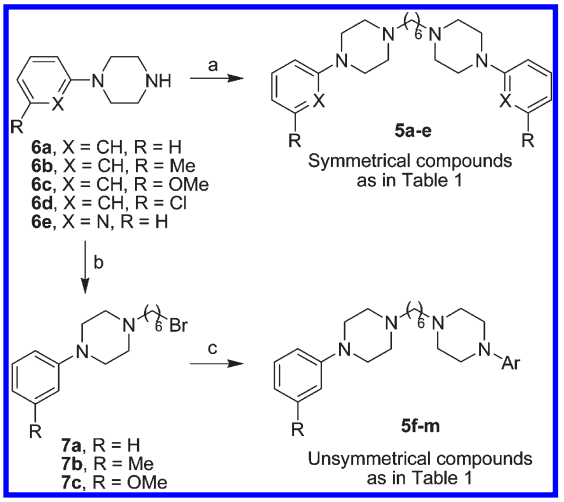
For the synthesis of the bishomoarylpiperazines **5a**−**e** (Scheme 1) 2 equiv of the correspondent arylpiperazines **6a**−**e** were reacted with 1,6-dibromohexane in the presence of a base. Unsymmetrical bisarylpiperazines **5f**−**m** were synthesized by a two-step synthesis. Bromo derivatives **7a**−**c** were at first synthesized using an excess of the 1,6-dibromohexane (2 equiv) in the presence of the appropriate arylpiperazine (**6a**−**c**). Bromo derivatives **7a**−**c** were then used as the alkylating agents of the appropriate arylpiperazine (**6b**,**d**,**e**, **10a**,**b**) to afford **5f**−**m**.

The noncommercially available arylpiperazines **10a**,**b** were synthesized (Scheme 2) starting form *N*-Boc-piperazine (**8**) that was N-substituted with the appropriate heteroaryl bromide following a standard palladium catalyzed protocol.[15,16] Deprotection of derivatives **9a**,**b** by trifluoroacetic acid afforded **10a**,**b** as trifluoroacetates.

Structure−Activity Relationships of Compounds 5a−m

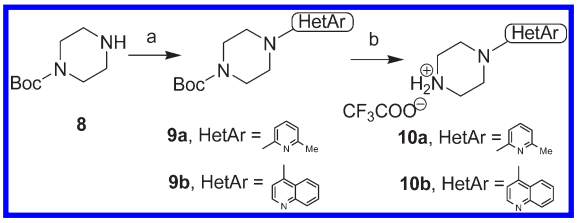
Compounds **5a**−**m** showed a receptor affinity profile similar to that of our original arylpiperazine series,[14] being, on average, more selective for the desired panel of receptors (i.e., D_3R, 5HT_{1A}R, 5HT_{2A}R; Table 1). These results

Scheme 1[a]



[a] Reagents and conditions: (a) 1,6-dibromohexane (0.5 equiv), TEA, MeCN, 12 h, room temp; (b) 1,6-dibromohexane (2.0 equiv), TEA, MeCN, 12 h, room temp; (c) arylpiperazine (**6b**,**d**,**e**, **10a**,**b**), TEA, MeCN, 12 h, room temp.

Scheme 2[a]



[a] Reagents and conditions: (a) 2-bromo-6-methylpyridine or 4-bromoquinoline, $Pd_2(dba)_3$, (±)-BINAP, NaO^{t}Bu, toluene, 90 min, 70 °C; (b) trifluoroacetic acid, dichloromethane, 1 h, room temp.

validated our design strategy and binding mode hypothesis. Indeed, our previous studies[14] indicated that an intramolecular H-bond between the carbonyl oxygen and the protonatable nitrogen of **4** (and its analogues) stabilized a conformation that could fit the dopamine/serotonin receptor pharmacophore. Molecular modeling calculations performed on the bishomo(hetero)arylpiperazine scaffold also indicated that **5a**−**m** (Table 1) tend to adopt a similar conformation (Figure 1; Figure 1 SI and Table 1 SI of the Supporting Information).

Indeed, conformational search results pointed out that most of the low energy conformers (i.e., $\Delta E_{GM} \leq 5$ kcal/mol) of **5a**−**m** presented an intramolecular H-bond between their protonated and unprotonated aliphatic nitrogens (Figure 1 SI, Table 1 SI). At physiological pH, apparent estimated pK_a values of the new compounds (Table 2 SI) predicted a 50:50 equilibrium between the mono- and the diprotonated forms (p$K_{a1} \approx 8.2$, p$K_{a2} \approx 7.4$, SD = ±0.40). In the case of **5i** and **5l**, this equilibrium involved the diprotonated and the triprotonated forms because the first protonation was estimated to occur on the 4-aminoquinoline moiety. However, taking into account the observed conformational behavior of **5a**−**m** and the presence an intramolecular H-bond that engages one aliphatic nitrogen lone pair, water protonation of both aliphatic nitrogens was disfavored. Taken together, our results indicated that at physiological pH, the monoprotonated (diprotonated for **5i** and **5l**) forms of **5a**−**m** tend to prevail because of the internal proton exchange between the two

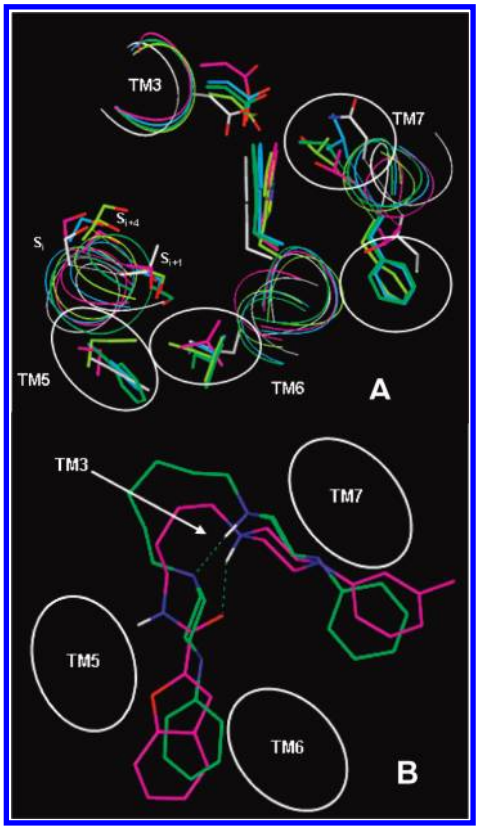


Figure 1. (A) Transversal view of serotonin and dopamine 3D receptor models. D_2R (yellow), D_3R (white), 5-$HT_{2A}R$ (cyan), and 5-$HT_{2C}R$ (green), and 5-$HT_{1A}R$ (magenta) are superimposed by Cα atoms. Key residues on TM3, TM5, TM6, and TM7 are displayed. Amino acids involved in subtype selectivity are highlighted by white circles. Ser residues on TM5 are labeled. (B) Transversal view of **5a** (green) and **4** (magenta), superimposed by fitting their pharmacophoric moieties (i.e., "head" ring centroid, protonated piperazine nitrogen hydrogen, H-bond donor group, "tail" ring centroid). The hypothesized interactions with TM3, TM5, TM6, and TM7 receptor helices are indicated.

(equally basic) aliphatic nitrogens. As a consequence, **5a**−**m** were predicted to adopt a conformation able to fulfill the dopamine/serotonin pharmacophore reproducing the binding mode of **4**[14] (Figure 1, Figure 1 SI, Table 1 SI), placing (i) the protonated N in contact with the Asp residue on TM3, (ii) the two aromatic rings on the aromatic pockets on TM6 and TM7 (or TM4), and (iii) the H-bond donor groups close to the donor/acceptor residues on TM5 and (in D_3R and 5$HT_{1A}R$) on TM7.[14] Accordingly, the bishomo(hetero)arylpiperazine scaffold was designed to support our hypothesis of multiple binding modes related to the pseudosymmetry of the receptor binding sites. Resulting affinity profiles of **5a**−**m** (Table 1) proved this hypothesis, with **5a** (bearing two unsubstituted phenyl groups) being one of the most potent and selective ligands of the series. In agreement with our previous SARs,[14] the low occupancy at D_2R and 5$HT_{2C}R$ (**5a**, Table 1) could be related to (i) the constraint due to the H-bond acceptor groups hypothesized to interact with TM5 in a bulky piperazine ring (Figure 1), (ii) the increased length of the alkyl chain, and (iii) the consequent optimal distance between the aromatic ring binding to the relevant aromatic pocket on TM6 and the protonated N binding to TM3 (Table 3 SI: Y−N2 distance). Because of the higher tolerance of D_3R, 5$HT_{1A}R$, and 5$HT_{2A}R$ to the mentioned structural modifications,[14] **5a** maintained the desired affinity profile on these receptors.

Since **5a** was found to be a weak hERG potassium channel ligand (hERG K_i = 8.0 μM, Table 1), this indicated[14] that hERG affinity was strongly influenced by the dipole of the phenyl ring at the "tail". In our original series we observed that a meta-substituent on the phenyl ring at the "tail" (Chart 1) of the arylpiperazine moiety, such as in **4**, led to an optimal balance in receptor affinity profile.[14] Consequently, different substituents at the meta position of the phenyl rings were investigated (**5b**−**d**,**h**,**j**−**m**, Table 1). Electron rich nitrogen containing aromatic rings (**5e**−**g**,**i**−**l**, Table 1) were also introduced to further reduce hERG channel interaction, according to the observation that electron-withdrawing atoms at the "tail" of arylpiperazines strongly increased hERG affinity.[14] The tight correlation between the electron density at the aromatic rings and hERG affinity was confirmed in the new series (**5d** > **5m** > **5b** and **5e**, **f** > **5a**; Table 1). Furthermore, comparing hERG occupancy in the subseries **5a**−**c** (**5b** ∼ **5c** > **5a**), **5f**,**g**,**i** (**5i** > **5g** > **5f**), and **5j**−**l** (**5l** > **5k** > **5j**), we observed that, besides electronic effects, hERG interaction was dependent on the steric hindrance at the meta position. With respect to receptor interaction, the methyl groups of **5b** reduced affinity for D_3R and 5-HT_{1A}R while increasing affinity for 5-HT_{2A}R and 5-HT_{2C}R (**5b** vs **5a**). Analogous to what occurred at the "tail" of our original arylpiperazines, the replacement of the methyl groups of **5b** with chlorine atoms (**5d**) improved potency at D_3R, worsening affinity for 5-HT_{2A}R. Introduction of methoxy groups (**5c**) was tolerated at the three receptors of interest, while the introduction of two 2-pyridine systems was detrimental for D_3R affinity (**5e**). Interestingly, in the heterodimer series (**5f**−**m**), the combination of the phenylpiperazine functionality with the 2-pyridinylpiperazine (**5f**), together with **5a**, provided the best affinity profile of the series. A bulky 6-methyl substituent at the pyridine (**5g**) provided a compound equally active at D_3R and 5-HT_{2A}R with respect to **5f** while increasing occupancy at 5-HT_{1A}R and 5-HT_{2C}R. Exploration of other combinations (**5h** and **5i**) did not improve the original profile of **5a** and **5f**. Introduction of a bicyclic system as in **5i** was well tolerated by the three receptors of interest, as well as the combination of the *m*-tolylpiperazine with different pyridinylpiperazines (**5k** and **5j**). Occupancy of $5HT_{2C}$R increased with the introduction of a methyl substituent on the phenyl and the pyridine ring (**5a** vs **5b**, **5f** vs **5g**, **5j** vs **5k**), and **5k** was the most potent compound of the series. As discussed above, when the *m*-tolylpiperazine was combined with the bulky 4-quinolylpiperazine (protonated at physiological pH, Table 2 SI), hERG affinity was highly increased (**5l**). When a *m*-methoxyphenylpiperazine was combined with a 3-chlorophenylpiperazine system (**5m**), an excellent ligand for D_3R, 5-HT_{1A}R, and 5-HT_{2A}R was obtained. These SARs proved that the bisheteroarylpiperazine represents a new scaffold for selective interaction with D_3R, 5-HT_{1A}R, and 5-HT_{2A}R. Except for **5d**, the other members of the series showed micromolar affinity for hERG potassium channels with **5f** that combines the desired binding profile to the lowest occupancy at hERG (Table 1).

The intriguing multireceptor affinity profile of **5a**,**e**−**h**,**k**,**j** prompted us to further explore the antipsychotic potential by means of standard animal models (Table 3 SI). In parallel to these studies preliminary pharmacokinetic parameters were also evaluated (Table 2 and Figure 2 SI).

Preliminary tests performed to evaluate the ability of our compounds to inhibit spontaneous exploratory locomotor activity indicated that, with the exception of **5j** (Table 3 SI), the compounds only reduced spontaneous exploratory locomotor activity in relatively high doses (between 10 and 30 mg/kg, sc). These data indicated a low potential for inducing sedation and extrapyramidal side effects consistent with low D_2R occupancy. When locomotor activity was increased by phencyclidine (PCP), all tested compounds produced a potentiation of PCP-induced locomotor activity at doses between 3 and 10 mg/kg (data not shown). The antipsychotic potential of the compounds was also assessed in mice rendered hyperactive by methamphetamine (MAMP) or MK801 pretreatment. **5a** caused a nonsignificant reduction in MAMP-induced hypermotility at 30 mg/kg, whereas **5g** and **5f** significantly reduced the MK801-induced hypermotility at 10 and 30 mg/kg, respectively. For **5g** this represents a dose that is 3 times lower than the doses able to reduce spontaneous locomotor activity, whereas for **5f**, it is a dose that is 3 times higher than that able to reduce exploratory lomotor activity. At the lower doses (1−0.3 mg/kg), **5k** and **5j** moderately increased MK801- and MAMP-induced hypermotility, respectively. Taken together, these preliminary data indicate that the new compounds, although possessing a valuable in vitro profile, fail to show an effect in animal models sensitive to antipsychotic treatment.

Table 2. Pharmacokinetic Results for Compounds **5a**,**e**−**h**,**k** and **4** after Administration of 3 mg/kg (ip) in Mouse

compd	AUC[a] (h·ng·mL^{-1})	T_{max} (h)	C_{max} (ng·mL^{-1})	$T_{1/2}$ (h)
5a	198	0.5	71	NA
5e	84	1.0	26	NA
5f[b]	58	1.0	50	NA
5g	362	0.3	121.3	2.5
5h	147	0.5	41	NA
5k	243	2.0	58	NA
4	128	0.5	155	NA

[a] Area under the curve. [b] Exposure was only observed for one animal.

In parallel we measured plasma concentration of **5a**,**e**−**h**,**k** after administration of 3 mg/kg (ip) in mice. Compound **4**, characterized by an amide moiety linked to an arylpiperazine system, was tested as a reference analogue. In Table 2 and in Figure 2 SI, **4** showed an AUC (0−6 h interval, h·ng·mL^{-1}) of 128 while all the other tested compounds showed an AUC between 58 and 362. T_{max} was higher for **5e**,**f**,**k**, while all the other tested compounds displayed a similar value compared to **4**. While C_{max} for **4** was 155 ng/mL, the values of the other analogues were 26−121 ng/mL. These data suggest that the new bisarylpiperazines do not possess an improved pharmacokinetic profile over **4**. By comparison of the plasma level profiles of **5g**,**h**,**k**, it emerges that after administration of 3 mg/kg ip in mice, the plasma concentration was higher for **5g** than for **5k** and **5h**, probably indicating a different metabolic stability of these analogues.

In summary, following our strategy for developing innovative antipsychotics we generated novel bisarylpiperazinehexanes for a specific interaction with D_3R, 5-HT_{1A}R, and 5-HT_{2A}R, minimizing occupancy at D_2R and 5-HT_{2C}R. Among the compounds synthesized the multireceptor affinity profile of **5a**,**f**,**j** was particularly intriguing.

Since the risk of drug-induced cardiac arrhythmia is recognized as a major hurdle in the successful development of new drugs, investigation of hERG channel blockade is a key step for the drug discovery process. We decided to include hERG channel interaction evaluation at the early stage of the design process. While **5d** and **5l** showed a submicromolar activity on

hERG, compounds **5a**,**f**,**g**,**j** showed low liability to block hERG channels. When tested in vivo to investigate their behavioral effects, the novel compounds did not show the expected antipsychotic potential. Compound **5g** was able to slightly reduce MK801-induced locomotor activity at 10 mg/kg, and in other cases, at the lowest doses tested, a potentiation of PCP-induced locomotor activity was observed. Although this novel series of compounds shows the desired affinity profile, the lack of antipsychotic potential in vivo might be explained assuming a different intrinsic activity with respect to **4** and analogues.[14] Furthermore, the different orientation of the H-bond donor/acceptor group(s), supposed to interact with the Ser/Thr residues on TM5, with respect to the aromatic ring, supposed to contact TM6 (such as in **5a** and **4**, Figure 1), might affect receptor activation, thus contributing to the results obtained when measuring in vivo antipsychotic efficacy.

Experimental Section

Standard Synthesis of Symmetrical Compounds 5a−e. To a solution of the appropriate 1-arylpiperazine (1.0 mmol) in dry acetonitrile (30.0 mL), 1,6-dibromohexane (0.5 mmol) and TEA (0.5 mmol) were added. The mixture was stirred at room temperature for 12 h. The crude was extracted with dichloromethane (3 × 20 mL), dried, and evaporated. The residue was purified by means of flash chromatography (10% methanol in chloroform) to give the pure compound.

Standard Synthesis of Unsymmetrical Compounds 5f−m. To a solution of the 1-(6-bromohexyl)arylpiperazine (1.0 mmol) in dry acetonitrile (30.0 mL), the appropriate 1-arylpiperazine (1.3 mmol) and TEA (1.3 mmol) were added. The mixture was stirred at room temperature for 12 h. The crude was extracted with dichloromethane (3 × 20 mL), dried, and evaporated. The residue was purified by means of flash chromatography (10% methanol in chloroform) to give the pure compound.

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Supporting Information Available: Tables 1−3 SI, Figures 1 SI and 2 SI, experimental procedures for intermediates and characterization of final compounds, experimental procedures for molecular modeling studies, in vivo tests, and pharmacokinetic studies and elemental analysis results for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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