5-HT_{1B} Receptor Antagonist Properties of Novel Arylpiperazide Derivatives of 1-Naphthylpiperazine

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A new series of arylpiperazide derivatives of 1-naphthylpiperazine of general formula **4** has been prepared and evaluated as 5-HT_{1B} antagonists. Binding experiments at cloned human 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors show that these derivatives are potent and selective ligands for 5-$HT_{1B/1D}$ subtypes with increased binding selectivity versus the 5-HT_{1A} receptor when compared to 1-naphthylpiperazine (1-NP). Studies of inhibition of the forskolin-stimulated cAMP formation mediated by the human 5-HT_{1B} receptor demonstrate that the nature of the arylpiperazide substituent modulates the intrinsic activity of these 1-NP derivatives. Among them, 2-[[8-(4-methylpiperazin-1-yl)naphthalen-2-yl]oxy]-1-(4-*o*-tolylpiperazin-1-yl)ethanone (**4a**) was identified as a potent neutral 5-HT_{1B} antagonist able to antagonize the inhibition of 5-HT release induced by 5-CT (5-carbamoyltryptamine) in guinea pig hypothalamus slices. Moreover, **4a** was found to potently antagonize the hypothermia induced by a selective 5-$HT_{1B/1D}$ agonist *in vivo* in the guinea pig following oral administration (ED_{50} = 0.13 mg/kg).

Introduction

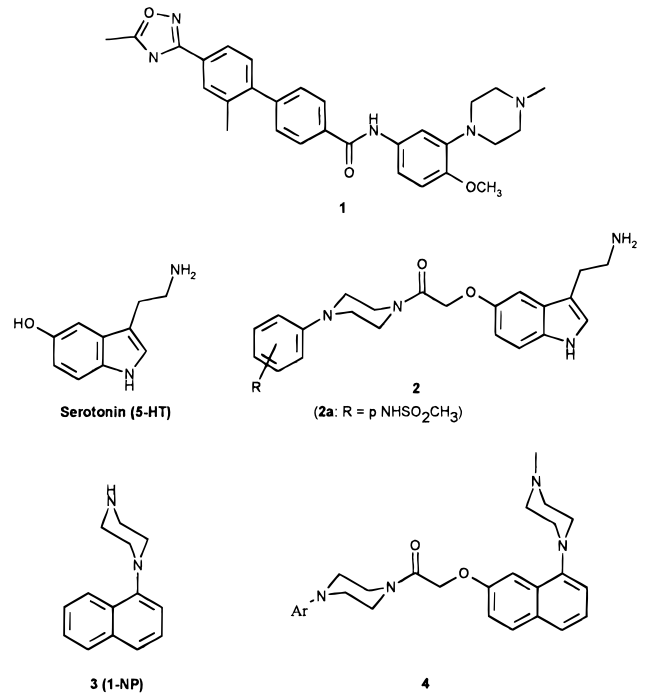
Serotonergic disturbance in depressive illness is now well established,[1] and several lines of evidence connect 5-$HT_{1B/1D}$ receptor function with the pathophysiology of depression.[2−4]

The blockade of terminal 5-HT_{1B} receptors by selective antagonists has recently been proposed[4−6] as a new approach toward the design of potentially efficient and/or fast-acting antidepressant drugs since acute 5-HT_{1B} autoreceptor blockade would in theory immediately elevate terminal 5-HT release.

A major step in the process of functional characterization of 5-$HT_{1B/1D}$ receptors has been the discovery of GR-127935 (**1**), *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)-phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-carboxamide (Chart 1), reported as the first example of selective 5-$HT_{1B/1D}$ antagonist.[7] More recent investigations at the level of human cloned receptors have shown that **1** acts as a weak but full agonist at 5-HT_{1D} sites and as a partial agonist at 5-HT_{1B} sites.[7,8] Thus, the identification of potent, selective, and silent 5-HT_{1B} antagonists still remains a fascinating goal to reach especially in order to evaluate the potential of such compounds as antidepressants.

During our investigations toward the design and identification of selective 5-$HT_{1B/1D}$ ligands, we have found that the 5-*O*-substitution of serotonin with arylpiperazide moieties through a carboxymethyl linker was a very efficient method to design potent, selective, and efficacious 5-$HT_{1B/1D}$ agonists.[9−11] This chemical modification of serotonin (which binds to at least 14 different receptor subtypes) into compounds of general formula **2** is a very efficient way to design selective 5-$HT_{1B/1D}$ agonists. This observation suggests that 5-$HT_{1B/1D}$ receptor subtypes possess a deep binding pocket in the binding domain recognizing the substituent attached in the 5-*O*-position of the serotonin residue. In particular, this region of bulk tolerance seems to differentiate between 5-$HT_{1B/1D}$ and 5-HT_{1A} receptor subtypes.[12]

Chart 1



A molecular dissection of 5-$HT_{1B/1D}$ agonists of formula **2** suggests that the tryptamine portion of such molecules is responsible for the intrinsic agonist activity of the molecule (analogous with serotonin), while the arylpiperazide part is mainly responsible for the binding selectivity (especially 5-$HT_{1B/1D}$ versus 5-HT_{1A} receptor subtypes) and may hopefully also contribute to improve *in vivo* pharmacological properties as, for example, metabolic stability, duration of action, bioavailability, and biodistribution. Starting from that hypothesis, it may be assumed that the replacement of the tryptamine

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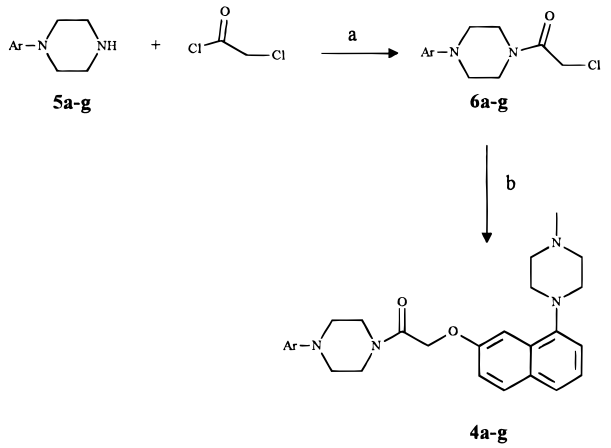
Scheme 1[a]



[a] $CaCO_3$, methyl ethyl ketone, >83%; (b) 7-hydroxy-1-(4-methylpiperazin-1-yl)naphthalene (**7**), K_2CO_3, KI, methyl ethyl ketone, reflux or Cs_2CO_3, DMF, rt, 35−72%.

residue found in compound **2** by a nonselective 5-$HT_{1B/1D}$ antagonist (for example, 1-naphthylpiperazine, **3**) should result in the identification of more potent and selective 5-$HT_{1B/1D}$ antagonists, provided that the linkage between the arylpiperazide moiety and the naphthylpiperazine residue will fit with the above-mentioned region of bulk tolerance.

As a part of our program directed toward the design, synthesis, and pharmacological characterization of new, potent, selective 5-HT_{1B} antagonists as potential new drugs for depression, we have prepared a series of 7-substituted derivatives of 1-naphthylpiperazine (1-NP) of general formula **4**.

Results

Chemistry. Compounds **4a**−**g** were prepared by alkylation of 7-hydroxy-1-naphthylpiperazine (**7**) with the appropriate (chloromethyl)piperazide **6a**−**g** (Scheme 1). This step was performed either in refluxing methyl ethyl ketone with potassium carbonate and catalytic potassium iodide or in dimethylformamide in the presence of cesium carbonate excess. The (chloromethyl)-piperazides **6a**−**g** were obtained by reaction of the corresponding arylpiperazine with chloroacetyl chloride in the presence of calcium carbonate in methyl ethyl ketone at 0 °C.

All compounds were purified by flash chromatography on silica gel and were used as free base or as fumarate salt for biological evaluation.

Biological Data. Receptor binding affinities (K_i) of compounds **4a**−**g**, 1-NP, 7-methoxy-1-NP, and **1** were measured at recombinant h5-HT_{1A} (in HeLa cells), h5-HT_{1B}, and h5-HT_{1D} (both in Cos-7 cells) receptors as previously described.[13,14] Agonist activity of these compounds (EC_{50} values) at h5-HT_{1B} receptors has been evaluated by measuring the inhibition of forskolin-stimulated cAMP formation mediated by h5-HT_{1B} receptors expressed in CHO-K_1 cells as previously reported[15] (E_{max} is expressed as the percentage of maximal inhibition obtained with 1 μM 5-HT). Antagonist potency was evaluated by measuring the extent of the antagonism of each compound tested at 1 μM against the agonist-induced inhibitory effect of 10 nM 5-CT (5-carbamoyltryptamine). Results are summarized in Table 1. Binding results show that the substitution of 1-NP in position 7 by arylpiperazide residues, as in compounds **4a**−**g,** improves the affinity for 5-HT_{1B} and 5-HT_{1D} human cloned receptors (when compared with 1-NP itself). Perhaps more importantly this substitution improves selectivity versus h5-HT_{1A} receptor subtypes (when compared with both 1-NP and 7-methoxy-1-NP). Thus, from a binding point of view, it is clear that the arylpiperazide derivatives of 1-NP (**4a**−**g**) do not differentiate between h5-HT_{1B} and h5-HT_{1D} receptors but recognize both of them with very high affinities (with the exception of **4g**, all compounds have K_i values in the subnanomolar range). The 5-$HT_{1B/1D}$ versus 5-HT_{1A} receptor selectivity observed with these compounds represents a major difference from that of 1-NP or 7-MeO-1-NP and offers a binding profile much closer to that of **1**, although chemical structures differ considerably. The 5-$HT_{1B/1D}$ versus 5-HT_{1A} receptor selectivity observed with compounds of general formula **4** is very informative from a structure−activity relationship point of view since *N*-4′-substituted derivatives of 1-(7-methoxynaphthyl)piperazine are known to be particularly potent agonists at 5-HT_{1A} receptors as reported earlier,[16,17] for example, with S 14506 and S 14671.

Analysis of the functional data (based on the 5-HT_{1B}-mediated inhibition of forskolin-stimulated cAMP formation) reveals major differences within the new series of arylpiperazide derivatives of 1-NP. Although compounds **4b**,**e**−**g** show non-negligible agonist activity together with some antagonist properties (antagonism of 5-CT-induced cyclase inhibition), the three other compounds (**4a,c,d)** appear as potent antagonists with no detectable intrinsic activity. These compounds can therefore be classified, in this particular model, as 5-HT_{1B} silent antagonists and, in that respect, can be compared to 1-NP, 7-MeO-1-NP, or **1**. The two most interesting compounds (**4a,d**) were studied in more detail in the cyclase model leading to calculated K_B values of 4.2 and 1.3 nM, respectively. Data reported in Table 1 show that, contrary to binding affinity, the intrinsic activity of compounds of general formula **4** at h5-HT_{1B} receptors clearly depends on the nature of the substitution of the aryl moiety of the arylpiperazide part of the molecule. This observation indicates that the naphthylpiperazine portion of these molecules is not sufficient to account for their antagonist properties or, maybe, that the mode of interaction of the naphthylpiperazine pharmacophore with the 5-HT_{1B} receptor is modulated by the nature of the arylpiperazide substituent.

The expression of h5-HT_{1B} receptors in rat C6-glial cells (but not in CHO-K_1 cells as shown in Table 1) has recently been reported[18] as a useful tool to measure with high sensitivity the differences in intrinsic activities of 5-HT_{1B} receptor ligands. Therefore, this model is particularly useful to discriminate between neutral antagonists and partial agonists showing intrinsic activity. For example, it was previously shown[18] that 1-NP, which appears as a neutral antagonist at 5-HT_{1B} receptors in CHO-K_1 cells, is clearly characterized as a partial agonist at h5-HT_{1B} receptors in C6-glial cells (EC_{50} = 65 nM). Contrary to 1-NP, compound **4a** did not show intrinsic activity in that particular model and could demonstrate potent antagonist activity ($K_B = 3 \times 10^{-8}$ M); compound **4d** also appeared to be a potent antagonist ($K_B = 4 \times 10^{-8}$ M) but showed some intrinsic

Table 1. Receptor Binding Affinities for h5-5HT$_{1A}$, h5-5HT$_{1B}$, and h5-5HT$_{1D}$ Receptors and 5-HT$_{1B}$-Mediated cAMP Formation[a]

		K_i (nM)		h5-HT$_{1B}$			
compd	aryl	h5-HT$_{1A}$	h5-HT$_{1D}$	K_i (nM)	EC_{50} (nM)	E_{max} (%)	antagonism (%)
4a	*o*-tolyl	49.5	0.69	0.30	>1000	<10	80
4b	*o*-cyanophenyl	12.3	0.51	0.38	P, 28	48	56
4c	1-naphthyl	114	0.88	0.43	>1000	<10	57
4d	*o*-xylyl	22.7	0.55	0.20	>1000	<10	87
4e	2,3-dimethoxyphenyl	13.4	0.62	0.44	P, 30	69	47
4f	benzodioxan-5-yl	14.1	0.45	0.43	P, 25	58	45
4g	mesitylene	117	1.9	1.4	P, 25	26	46
1-naphthylpiperazine		9.2	6.2	10.1	>1000	<10	96
7-methoxy-1-naphthylpiperazine		2.8	0.7	2	>1000	<10	95
1		71.7	0.74	0.14	>1000	16	102

[a] P: partial inhibition. E_{max} is the percentage of maximal inhibition of forskolin-stimulated cAMP formation obtained with 1 μM 5-HT. Antagonism of compound was tested at 1 μM against the agonist-mediated effect of 10 nM 5-CT. Values are given as the mean value of two or three experiments, each performed in duplicate, typically with individual values within ±10−20% of the mean.

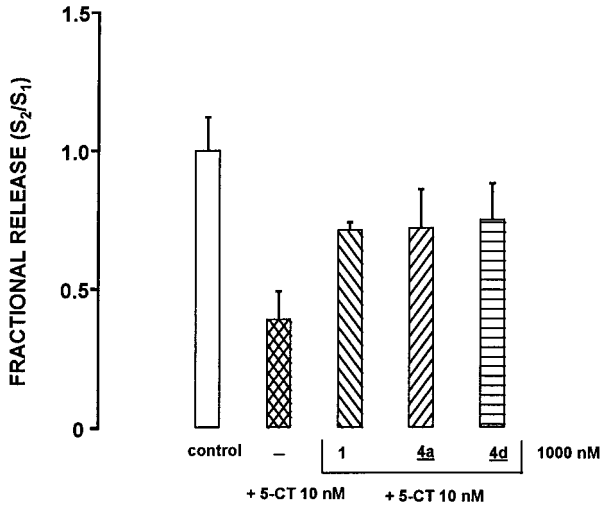


Figure 1. Antagonism by 1 μM **1** (GR-127935), **4a**, or **4d** of the inhibition by 5-CT (10 nM) of the electrically evoked release of [^{3}H]-5-HT from superfused slices of guinea pig hypothalamus. Ordinate: fraction of the total tissue radioactivity released by a 2-min period of electrical stimulation (5 Hz), expressed as the ratio S_2/S_1 obtained between the second period of stimulation in the presence of the drug (S_2) and the first control period (S_1), carried out within the same experiment. Each bar represents the mean value of at least five experiments.

activity when tested at 1 μM. A similar observation was made in the same system for compound **1**. Interestingly enough, compound **4a** did not show relevant binding affinity (IC_{50} > 100 nM) at 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, adrenergic (α_1, α_2, β_1, and β_2), dopaminergic (D_2), histaminergic (H_1 and H_2), muscarinic (M), or opioid receptors.[19]

As pointed out in the Introduction, the antidepressant potential of 5-HT$_{1B}$ antagonists is based on the observation that the activation of terminal 5-HT$_{1B}$ autoreceptors induces an inhibition of 5-HT release. It has previously been reported[20] that nonselective 5-HT$_{1B}$ antagonists like 1-NP or methiothepin are able to antagonize the inhibitory effect of 5-CT on the electrical field-stimulated release of preloaded [^{3}H]-5-HT from superfused slices of guinea pig brain regions (substantia nigra or hypothalamus). The arylpiperazide derivatives of 1-naphthylpiperazine (**4a,d**), as well as reference compound **1** included for comparative purposes, were evaluated in this procedure.[20] The results summarized in Figure 1 show that both 7-*O*-substituted naphthylpiperazine derivatives **4a,d** are able to antagonize the inhibition of [^{3}H]-5-HT release induced by 5-CT to a very similar extent in comparison to **1**. These results demonstrate that the newly reported 5-HT$_{1B}$ antagonists **4a,d** act as 5-HT terminal autoreceptor antagonists *in vitro* and therefore have the potential to control 5-HT neurotransmission.

Among the different methods available to evaluate 5-HT$_{1B/1D}$ antagonists *in vivo*, the reversal of hypothermia induced by a 5-HT$_{1B/1D}$ agonist in the guinea pig is particularly attractive since this model provides a means of demonstrating *in vivo* a central activity of 5-HT$_{1B}$ antagonists as well as their duration of effect and bioavailability. Compound **1** has been studied in this model by two different groups using either GR-46611[21] or SKF-99101H[22] as agonist tools to induce hypothermia. We have recently observed that such a 5-HT$_{1B}$-mediated hypothermia in guinea pig could also have been induced by arylpiperazide derivatives of serotonin which have recently been reported as particularly potent and selective 5-HT$_{1B/1D}$ agonists.[10] Among them, compound **2a** (Chart 1) was chosen as a tool for studying antagonists, according to the method previously reported for GR-46611.[21] The hypothermia induced by **2a** (10 mg/kg, ip) was dose-dependently blocked by **1** (ED_{50} = 0.31 mg/kg, ip) and the 7-substituted naphthylpiperazine derivative **4a** (ED_{50} = 0.17 mg/kg, ip) but not by derivative **4d**. Compound **4a** was also active in the hypothermia model following oral administration (ED_{50} = 0.13 mg/kg), suggesting a good bioavailability for that particular derivative. The discrepancies observed between the naphthylpiperazine derivatives **4a,d** in the hypothermia model are rather surprising especially in view of their close structural analogies. The differences in intrinsic activity between these two compounds as observed at the human cloned receptor level in rat C6-glial cells may, at least in part, explain these results, but other parameters may also be important (for example, access to the central nervous system since the hypothermia model is reported to involve central 5-HT$_{1B}$ receptors).

Conclusions

The substitution of 1-NP in position 7 by arylpiperazide moieties emerges as a new approach in the design of potent and selective 5-HT$_{1B/1D}$ ligands which discriminate between h5-HT$_{1B/1D}$ and h5-HT$_{1A}$ receptor subtypes. This observation parallels the previously reported binding data concerning 5-*O*-substituted derivatives of serotonin which also bind preferentially to 5-HT$_{1B/1D}$ receptor subtypes. However, both types of compounds (**2** and **4**, see Chart 1) differ from each other

in regard to intrinsic activity, since the previously reported 5-*O*-substituted arylpiperazide derivatives of serotonin are potent full agonists at human cloned 5-HT_{1B} receptors while the arylpiperazide derivatives of naphthylpiperazine (**4**) are either partial agonists or antagonists. The results reported in Table 1 clearly show that the increase in binding selectivity (5-$HT_{1B/1D}$ versus 5-HT_{1A}) is true for all reported examples (compounds **4a**−**g**), while the nature of the substituents on the arylpiperazide moiety plays a significant role in their intrinsic activity since only two compounds emerge as silent antagonists. Among them, the *o*-tolylpiperazide derivative **4a** appears as a very promising new 5-HT_{1B} antagonist which is able to antagonize the inhibition of [^{3}H]-5-HT release induced by 5-CT in superfused slices of guinea pig hypothalamus and can antagonize the hypothermia induced by **2a** (a potent and selective 5-$HT_{1B/1D}$ agonist) *in vivo* in the guinea pig following oral administration.

Experimental Section

Chemistry. Melting points were recorded on a Electrothermal 9200 apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Brüker AC200 (200 MHz) instrument. IR spectra were obtained on a Nicolet FT510P instrument. Mass spectra were recorded on a Nermag R10-10B spectrometer. Purification by chromatography refers to flash chromatography on silica gel (0.04−0.063 mm; supplied by S.D.S.) with the indicated eluant applied at a pressure of 0.5 atm. Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Fisons EA 1108/CHN instrument; analyses indicated by the symbols of the elements or functions are within ±0.4% of theoretical values. All reactions were conducted under nitrogen atmosphere. 1-Naphthylpiperazine **(5c**), (2,3-dimethoxyphenyl)piperazine (**5e**), 1-(benzodioxan-5-yl)piperazine (**5f),** and chloropiperazides **6a**−**g** were prepared according to literature procedures.[23−25]

Preparation of Aryl- and Naphthylpiperazines. They were all prepared following procedures described for naphthylpiperazine[23] from corresponding anilines.

Mesitylenepiperazine (5g): yield 55%; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 2.29 (s, 6H), 3.01 (m, 8H), 3.33 (bs, 1H), 6.81 (s, 2H).

7-Hydroxy-1-(4-methylpiperazin-1-yl)naphthalene (7): yield 48%; ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 2.58 (m, 4H), 2.96 (m, 4H), 6.98−7.72 (m, 6H), 9.66 (s, 1H).

Preparation of Naphthylpiperazides 4a−g. Method A: 2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-(4-*o*-tolylpiperazin-1-yl)ethanone (4a). A mixture of naphthylpiperazine **7** (615 mg, 2.54 mmol), chloropiperazide **6a** (770 mg, 3.05 mmol), and potassium iodide (42 mg, 0.25 mmol) in methyl ethyl ketone (60 mL) was heated to reflux for 4 h. The mixture was then diluted with water and extracted with ethyl acetate (3×). The organic layers were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated. The crude extract was chromatographed (CH_2Cl_2/MeOH/NH_4OH, 90/9/1) to give compound **4a** (81%). The fumarate salt was prepared by treatment of **4a** dissolved in dichloromethane with an adequate amount of fumaric acid followed by precipitation with Et_2O: ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 2.47 (s, 3H), 2.89 (m, 8H), 3.07 (m, 4H), 3.64 (m, 4H), 5.05 (s, 2H), 6.61 (s, 3H), 6.94−7.85 (m, 10H); $C_{28}H_{34}N_4O_2 \cdot 1.6C_4H_4O_4$ (C, H, N); mp 184 °C.

Method B: 2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-[(2,3-dimethoxyphenyl)piperazin-1-yl]ethanone (4e). A mixture of naphthylpiperazine **7** (360 mg, 1.5 mmol), chloropiperazide **6e** (540 mg, 1.8 mmol), and cesium carbonate (1.4 g, 4.5 mmol) in dimethylformamide (20 mL) was stirred at room temperature for 12 h. It was then diluted with water and extracted with ethyl acetate (4×). The organic layers were washed with sodium chloride-saturated solution (3×), dried over magnesium sulfate, filtered, and concentrated. The crude was chromatographed (CH_2Cl_2/MeOH/NH_4OH, 90/9/1) to give compound **4e** (50%): ^{1}H NMR ($CDCl_3$) (fumarate salt prepared as described above) δ 2.44 (s, 3H), 2.77 (m, 4H), 3.13 (m, 8H), 3.82 (m, 10H), 4.87 (s, 2H), 6.49 (d, 1H), 6.63 (d, 1H), 6.92−7.33 (m, 4H), 7.49 (d, 1H), 7.57 (d, 1H), 7.74 (d, 1H); $C_{29}H_{36}N_4O_4 \cdot 0.22H_2O$ (C, H, N); mp 181 °C.

2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-[4-(*o*-cyanophenyl)piperazin-1-yl]ethanone (4b): method A, yield 50%; ^{1}H NMR (DMSO-d_6) (free base) δ 2.43 (s, 3H), 2.74 (m, 4H), 3.19 (m, 8H), 3.85 (m, 4H), 4.88 (s, 2H), 6.93−7.77 (m, 10H); $C_{28}H_{31}N_5O_2$ (C, H, N); mp 200 °C.

2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-(4-naphthalen-1-ylpiperazin-1-yl)ethanone (4c): method A, yield 51%; ^{1}H NMR (DMSO-d_6) (fumarate salt) δ 2.36 (s, 3H), 2.76 (m, 4H), 3.10 (m, 8H), 3.81 (m, 4H), 5.06 (s, 2H), 6.57 (s, 2H), 7.06−8.19 (m, 13H); $C_{31}H_{34}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$ (C, H, N); mp 118 °C (amorphous solid).

2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-(4-*o*-xylylpiperazin-1-yl)ethanone (4d): method A, yield 67%; ^{1}H NMR (DMSO-d_6) (fumarate salt) δ 2.18 (s, 3H), 2.21 (s, 3H), 2.40 (s, 3H), 2.80 (m, 8H), 3.03 (m, 4H), 3.69 (m, 4H), 5.05 (s, 2H), 6.59 (s, 3H), 6.83−7.32 (m, 7H), 7.53 (d, 1H), 7.81 (d, 1H); $C_{29}H_{36}N_4O_2 \cdot 1.5C_4H_4O_4$ (C, H, N); mp 178 °C.

2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-[4-(benzodioxan-5-yl)piperazin-1-yl]ethanone (4f): method B, yield 62%; ^{1}H NMR (DMSO-d_6) (fumarate salt) δ 2.33 (s, 3H), 2.72 (m, 4H), 3.00 (m, 8H), 3.34 (m, 4H), 4.20 (m, 4H), 5.01 (s, 2H), 6.42−6.85 (m, 5.8H), 7.04−7.29 (m, 4H), 7.51 (d, 1H), 7.79 (d, 1H); $C_{29}H_{34}N_4O_4 \cdot 1.4C_4H_4O_4 \cdot 0.25H_2O$ (C, H, N); mp 206−207 °C.

2-[[1-(4-Methylpiperazin-1-yl)naphthalen-7-yl]oxy]-1-(4-mesitylenepiperazin-1-yl)ethanone (4g): method B, yield 35%; ^{1}H NMR (DMSO-d_6) (fumarate salt) δ 2.16 (s, 3H), 2.19 (s, 6H), 2.40 (s, 3H), 2.75 (m, 4H), 3.03 (m, 8H), 3.57 (m, 4H), 5.04 (s, 2H), 6.59 (s, 2H), 6.78 (s, 2H), 7.07−7.34 (m, 4H), 7.54 (d, 1H), 8.04 (d, 1H); $C_{30}H_{38}N_4O_2 \cdot C_4H_4O_4 \cdot 0.85H_2O$ (C, H, N); mp 106 °C (amorphous solid).

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