Bioorganic & Medicinal Chemistry Letters 18 (2008) 5140–5145

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological affinity of new imidazo- and indol-arylpiperazine derivatives: Further validation of a pharmacophore model for α_1-adrenoceptor antagonists

Giovannella Strappaghetti [a,*], Luciano Mastrini [a], Antonio Lucacchini [b], Gino Giannaccini [b], Laura Betti [b], Laura Fabbrini [b]

[a] Dipartimento di Chimica e Tecnologia del Farmaco, Università degli Studi di Perugia, via del Liceo 1, 06123 Perugia, Italy
[b] Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università degli Studi di Pisa, via Bonanno 6, 56126 Pisa, Italy

ARTICLE INFO

Article history:
Received 13 May 2008
Revised 18 July 2008
Accepted 19 July 2008
Available online 24 July 2008

Keywords:
α_1-AR affinity
α_2-AR affinity
5-HT_{1A} affinity
Serotonin reuptake inhibitors (SSRI)
6-(Imidazol-1-yl)-pyridazin-3(*2H*)-one
6-(Indol-1-yl)-pyridazin-3(*2H*)-one
fragment
Arylpiperazines
Structure–activity relationships (SARs)

ABSTRACT

In the continuing search for selective α_1-adrenoceptor (AR) antagonists, new alkoxyarylpiperazinylalkylpyridazinone derivatives were designed and synthesized. The new compounds were tested for their affinity toward α_1-AR, α_2-AR and 5-HT_{1A} receptors.

The ability of these compounds to inhibit the serotonin transporters (SERT) was also determined. The pharmacological data confirm that increasing the size of the *ortho* alkoxy substituent on the phenyl ring of the arylpiperazine moiety afforded compounds with enhanced affinity toward the α_1-AR. The isopropoxy group, the largest group evaluated, led the best α_1-AR affinity profile. In contrast, the compounds which have an amide group within of the *o*-alkoxy-phenylpiperazine fragment showed low affinity toward the receptors studied.

Similar results were obtained when the amide group was present in the linker of the junction between the two major constituents of the molecule.

α_1-Adrenergic receptors (α_1-ARs) belong to the seven transmembrane-domain receptor super family and play a primary role in the regulation of several physiological processes, particularly in the cardiovascular system. To date, three different α_1-AR subtypes, namely, $\alpha_{1A} - \alpha_{1B}$-, and α_{1D}-AR, have been cloned and characterized.[1,2]

In the last years, α_1-adrenoceptors (α_1-AR) have been the subject of intense research, in part because receptor-binding studies and molecular biology have opened up new aspects of understanding, but also because of the potential for finding new drugs that could act in pathophysiological processes where α_1-AR are involved, such as benign prostatic hyperplasia (BPH) or hypertension.[3–6]

In this context, the goal of our research was to discover and develop novel α_1-AR antagonists characterized by a high affinity for α_1-AR and possibly, selectivity toward the α_1-ARs receptor with respect to α_2-AR or 5-HT_{1A} receptors.

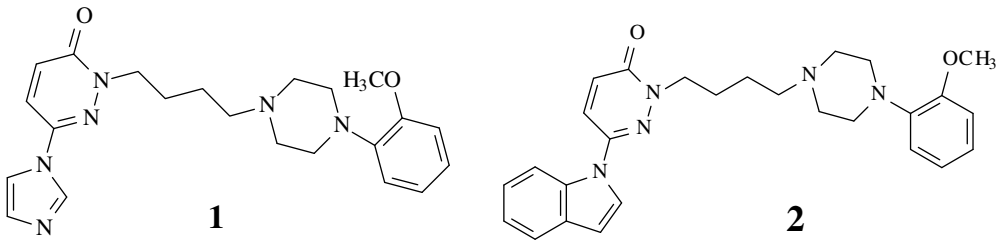
The arylpiperazines are one of the most studied classes of molecules with affinity at the α_1-AR. In fact, a large amount of work has been done and reported, describing synthetic procedures, biological evaluation at the α_1-AR and the corresponding subtypes, and structure-activity relationships (SARs).[7]

We previously reported the synthesis and pharmacological data of several classes of arylpiperazines, in which an alkoxyarylpiperazinylalkylpyridazinone moiety is present as a common chemical scaffold.[8–15] Based on these results, Botta et al.,[8,9,11] described the construction and validation of a three-dimensional pharmacophore model of α_1–AR antagonists sharing a phenylpiperazinyl alkyl scaffold as a common structural feature and bearing a wide variety of heterocyclic moieties at the edge of the alkyl spacer. The pharmacophoric model[8,9,11] that suggests the three-dimensional structural properties for an ideal α_1–AR antagonist includes:

(1) A positively ionizable group, corresponding to the more basic nitrogen atom of the aryl piperazine ring. (2) An *ortho*- or *meta*-substituted phenyl ring, both of which constitute the arylpiperazine system and satisfy three of the five features of the pharmacophoric hypothesis. (3) A polar group (corresponding to the pyridazinone ring) that provides a hydrogen bond acceptor feature, filling one of the portions of the pharmacophore that is required at the edge of the molecule opposite the arylpiperazine moiety. (4) A hydrophobic moiety, corresponding to the terminal molecular por-

* Corresponding author. Tel.: +39 075 5855136; fax: +39 075 5855161.
E-mail address: noemi@unipg.it (G. Strappaghetti).

0960-894X/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2008.07.084



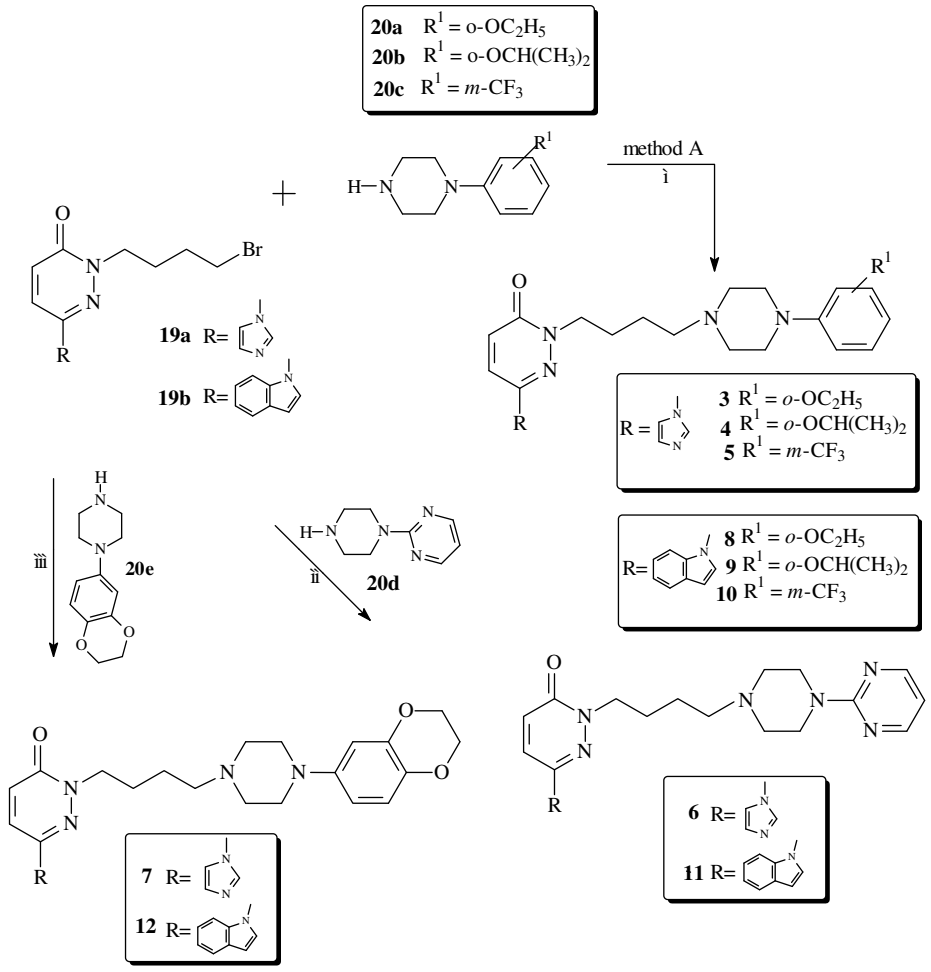
1 **2**

tions directly linked to the pyridazinone ring, was hypothesized to fit one of the five features of the model. The pharmacophoric model also suggests that the hydrophobic region accommodating the substituted phenyl can contain constituents that are larger than a methoxy group. Moreover, affinity and selectivity depend on the length of the polymethylene chain that connects the pyridazinone and arylpiperazine moieties. A four carbon-atom spacer is optimal for α_1-AR affinity, and a heterocyclic fragment linked to the pyridazinone ring is required at the terminal molecular portion for best α_1-AR affinity.

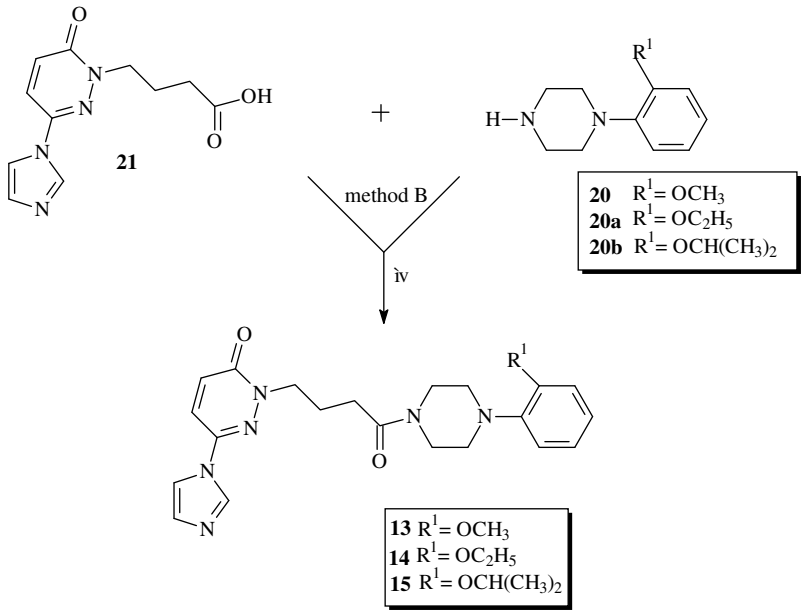
Based on these considerations, and taking into account our previous experience in this field, compounds **1**[9] and **2**[9] were used as a template to design compounds **3**, **4**, **8** and **9**.

A spacer of four carbon atoms was maintained in the piperazine-pyridazinone system, and alkoxy moieties, larger than a methoxy group, were substituted at the *ortho* position of the phenyl ring. This was in agreement with the pharmacophoric model generated for α_1-AR antagonists that suggested that hydrophobic groups larger than a methoxy substituent can be accommodated by a hydrophobic pocket, [8,9,11]where the substituted phenyl ring that is bound to the piperazine lies. For the same objective, an *ortho*-alkoxyphenylpiperazine group was replaced by *meta*-CF_3-phenyl-piperazine group (compounds **5** and **10**), to pyrimidinpiperazine, or a 1-(2,3-dihydro-1,4-benzodioxin-6-yl)piperazine group (compounds **6**, **7**, **11**, and **12**).

To confirm the importance of the positively ionizable group, which corresponds to the more basic nitrogen atom of the piperazine ring, compounds **13**, **14**, and **15** were synthesized, in which an amide group was linked to the arylpiperazine fragment. To further investigate if four carbon-atom spacer was indeed optimal for α_1-



Scheme 1. Reagents and conditions: (i) acetonitrile, dry potassium carbonate, **20a**, **20b**, **20c,** reflux; (ii) **20d** acetonitrile, dry potassium carbonate, reflux; (iii) butan-2-one, dry potassium carbonate, reflux.



Scheme 2. Reagents and conditions: (iv) (CDI), CH_2Cl_2, room temperature.

AR selectivity, compounds **16**, **17**, and **18**, were synthesized, in which an amide group was present into linker of junction of the two major constituents of the molecule.

The synthetic pathways to compounds **3–12** are shown in Scheme 1.

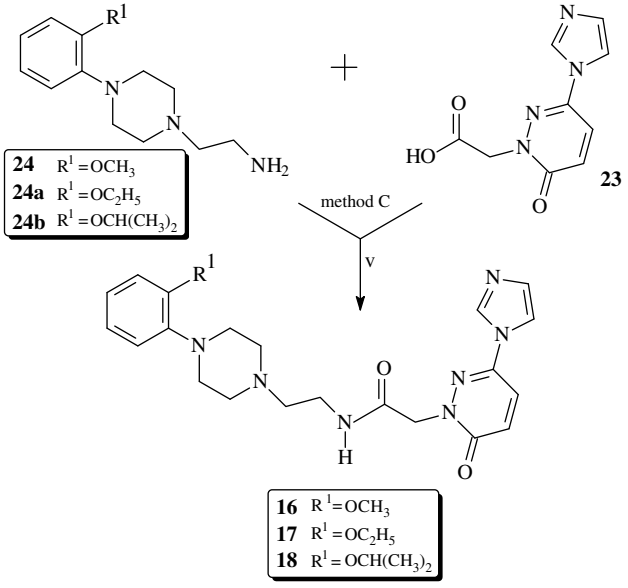
Alkylation of 2-(4-bromobutyl)-6-(imidazol-1-yl)pyridazin-3(*2H*)-one (**19a**), or 2-(4-bromobutyl)-6-(indol-1-yl)pyridazin-3(2*H*)-one (**19b**), synthesized following the previously described method,[9] with 1-(2-ethoxyphenyl)piperazine (**20a**), 1-(2-isopropoxyphenyl)piperazine[16] (**20b**) or with 1-[3-(trifluoromethyl) phenyl]piperazine (**20c**), respectively, in acetonitrile in the presence of dry potassium carbonate, at reflux, afforded the corresponding compounds **3–5** and **8–10**. Using the same procedure, compounds **6** and **11** were made by alkylation starting from **19a** or **19b** with pyrimidin-piperazine (**20d**); compounds **7** and **12** were made by alkylation of compounds **19a** or **19b** with 1-(2,3-dihydro-1,4-benzodioxin-6-yl)piperazine (**20e**) in butan-2-one and dry potassium carbonate.

The synthesis of compounds **13, 14**, and **15** is illustrated in Scheme 2.

The 4-(3-(imidazol-1-yl)-6-oxopyridazin-1(6*H*)-yl)butanoic acid (**21**) was treated with 1-(2-methoxyphenyl)piperazine (**20**), with 1-(2-ethoxyphenyl)piperazine (**20a**) or with 1-(2-isopropoxyphenyl)piperazine[16] (**20b**), respectively, in CH_2Cl_2 in the presence of 1-(1*H*-imidazol-1-yl-carbonyl)-1*H*-imidazole (CDI) under stirring overnight at room temperature. After evaporation to dryness, the mixture was purified by column chromatography eluting with (CH_2Cl_2/EtOH) to afford the corresponding amides **13–15** as an oil, in 55–80% overall yield.

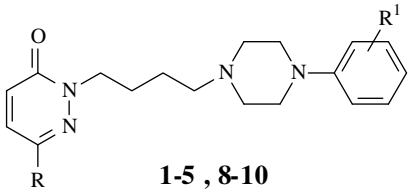
Acid **21** was obtained by starting with the condensation of 6-(imidazol-1-yl)pyridazin-3(2*H*)-one[9] with ethyl 4-bromobutanoate in acetone/dry potassium carbonate at reflux for 3 h, the corresponding ester, after purification by column chromatography on silica gel, eluting with CH_2Cl_2/EtOH (96:4), was treated with 5% hydrochloric acid at reflux for 3 h, after which time, the crystalline acid was precipitated in a quantitative yield (compound **21**).

Compounds **16**, **17**, and **18** (Scheme 3), containing an amide group in the linker of the junction of the two major constituents of the molecule, were prepared by treating the [3-(imidazol-1-yl)-6-oxopyridazin-1(6*H*)-yl]acetic acid (**23**) with 2-[4-(2-alkoxyphenyl)piperazin-1-yl]ethanamine **24**, **24a**, and **24b**, respectively, in the presence of 1-(3-dimethylaminopropyl)*N*-ethylcarbodimidine hydrochloridre (EDCI), 4-dimethylaminopyridine (DMAP), and 1-hydroxybenzotriazol-hydrate (HOBt), in dichloromethane stirred at room temperature under nitrogen atmosphere overnight. The compounds were purified by column chromatography on silica gel eluting with CH_2Cl_2/EtOH. The [3-(imidazol-1-yl)-6-oxo-pyridazin-1(6*H*)-yl]acetic acid (**23**) was prepared by alkylation of the 6-imidazoil-pyridazinone[9] with ethyl bromoacetate in the presence of sodium dissolved in dry ethanol. The mixture was refluxed under stirring for 15 h. After purification by chromatography on silica gel, the ethyl[3-(imidazol-1-yl)-6-oxopyridazin-1(6*H*)-yl]acetate was treated with 5% hydrochloric acid for 2 h at reflux, after which time, the crystalline acid precipitated in a quantitative yield (compound **23**).

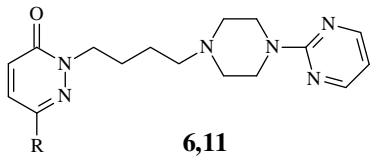


Scheme 3. Reagents and conditions: (v) EDCI, DMAP, HOBt, CH_2Cl_2, room temperature.

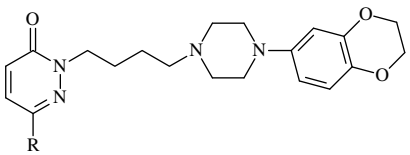
Table 1
α_1-AR, α_2-AR, 5-HT_{1A} serotoninergic receptors and SERT binding affinities of compounds **3**–**12** and comparison with compounds **1** and **2**



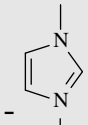
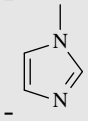
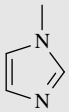
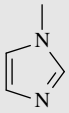
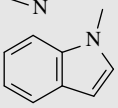
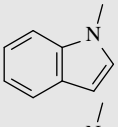
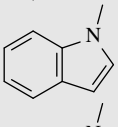
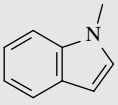
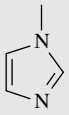
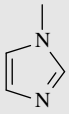
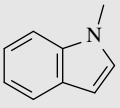
1-5 , 8-10



6,11



7, 12

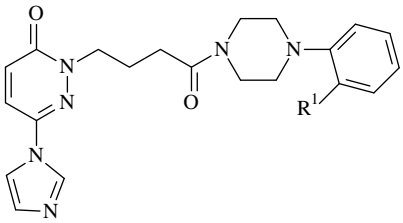
Compound	R	R^1	K_i[a] (nM)					
			α_1-AR	α_2-AR	5-HT_{1A}	SERT	Ratio α_2/α_1	Ratio 5-HT_{1A}/α_1
1[b]		*o*-OCH_3	47.5 ± 6.3	393.0 ± 31.8	nd[c]	nd[c]	8.3	nd[c]
3		*o*-OC_2H_5	0.8 ± 0.4	147.0 ± 12.0	14.0 ± 5.3	15%(10μM) > 10000	163.3	15.5
4		*o*-$OCH(CH_3)_2$	0.4 ± 0.1	44.0 ± 4.7	6.8 ± 1.1	10%(10μM) > 10000	110.0	17.0
5		*m*-CF_3	118.0 ± 14	656.0 ± 170	13.0 ± 7	230.0 ± 20	5.6	9.1
2[b]		*o*-OCH_3	0.9 ± 0.1	20.0 ± 4.9	253.0 ± 24.5	nd[c]	22.2	281.0
8		*o*-OC_2H_5	1.1 ± 0.1	70.12 ± 10	27.7 ± 0.5	639.0 ± 120	62.6	24.7
9		*o*-$OCH(CH_3)_2$	1.7 ± 0.3	20.1 ± 3.3	22.8 ± 3.4	1040.0 ± 281	12.0	13.6
10		*m*-CF_3	60.0 ± 10	462.0 ± 240	62.0 ± 12	109.0 ± 8.0	7.7	1.03
6		—	710 ± 200	1550 ± 70	890.0 ± 260	5%(10μM) > 10000	2.2	1.25
11		—	19.0 ± 9.0	725.0 ± 1.4	210.0 ± 70	25%(10μM) > 10000	38.1	11.1
7		—	251.0 ± 80	996.0 ± 50	937.0 ± 270	26%(10μM) > 10000	3.9	3.73
12		—	14.0 ± 6.0	476.0 ± 100	627.0 ± 64	177 ± 8.0	34.0	44.8
[^{3}H]prazosin			0.24 ± 0.05					
[^{3}H]rauwolscine				4.0 ± 0.3				
[^{3}H]8-OH-DPAT					2.0 ± 0.2			
[^{3}H]paroxetine						0.08 ± 0.2		

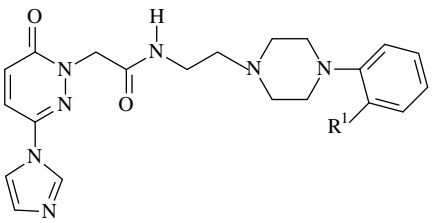
[a] The K_i values are means ± SD of separate assays, each performed in triplicate. Inhibition constants (K_i) were calculated according to the equation of Cheng and Prusoff:[18] $K_i = IC_{50}/1+(L/K_d)$, where [L] is the ligand concentration and K_d its dissociation constant. K_d of [^{3}H]prazosin binding to rat cortex membranes was 0.24 nM (α_1), K_d of [^{3}H]rauwolscine binding to rat cortex membranes was 4 nM (α_2), K_d of [^{3}H]8-OH-DPAT binding to rat cortex membranes was 2.0 nM (5-HT_{1A}), and K_d of [^{3}H]paroxetine binding to human platelet membranes was 0.08 ± 0.2 nM (SERT).

[b] Compounds reported elsewhere by our research group.[9]

[c] nd: not determined.

Table 2
α_1-AR, α_2-AR, 5-HT_{1A} serotoninergic receptors and SERT binding affinities of compounds **13–18**





Compound	R^1	K_i[a] (nM)					
		α_1-AR	α_2-AR	5-HT_{1A}	SERT	Ratio α_2/α_1	Ratio 5-HT_{1A}/α_1
13	$-OCH_3$	2190 ± 964	1895 ± 400	318 ± 79	3%(10μM) >10000	0.86	0.14
14	$-OC_2H_5$	492 ± 241	1757 ± 273	2250 ± 582	11%(10μM) >10000	3.57	4.57
15	$-OCH(CH_3)_2$	897 ± 342	1343 ± 327	1556 ± 158	2%(10μM) >10000	1.49	1.73
16	$-OCH_3$	688 ± 137	2968 ± 493	2067 ± 318	3464 ± 164	4.3	3.0
17	–OEt	234 ± 22	3136 ± 327	1150 ± 230	5977 ± 178	13.4	4.9
18	–O*i*Pr	220 ± 44	1956 ± 191	1911 ± 382	>10000	8.89	8.7
[^{3}H]prazosin		0.24 ± 0.05					
[^{3}H]rauwolscine			4.0 ± 0.3				
[^{3}H]8-OH-DPAT				2.0 ± 0.2			
[^{3}H]paroxetine					0.08 ± 0.2		

[a] Each value is the mean ± SE for data of three different experiments conducted in triplicate. Expressed as K_i, see Refs. 18–20.

Table 3
Chemical and physical data of compounds **3–18**

Compound	Formula	Mp (°C)	Yield (%)
3	$C_{26}H_{34}Cl_2N_4O_2$	182–188	80
4	$C_{27}H_{36}Cl_2N_4O_2$	169–174	75
5	$C_{22}H_{26}Cl_2F_3N_6O$	164–168	42
6	$C_{19}H_{27}Cl_2N_8O$	257–260	60
7	$C_{23}H_{30}Cl_2N_6O_3$	246–249	30
8	$C_{28}H_{35}Cl_2N_5O_2$	149–153	85
9	$C_{29}H_{37}Cl_2N_5O_2$	140–145	70
10	$C_{27}H_{30}\ Cl_2F_3N_5O$	200–205	35
11	$C_{24}H_{29}Cl_2N_7O$	225–230	49
12	$C_{28}H_{33}Cl_2N_5O_3$	181–185	39
13	$C_{22}H_{28}Cl_2N_6O_3$	Hygroscopic	70
14	$C_{23}H_{30}Cl_2N_6O_3$	Hygroscopic	64
15	$C_{24}H_{32}Cl_2N_6O_3$	Hygroscopic	56
16	$C_{22}H_{29}Cl_2N_7O_3$	182–196	57
17	$C_{23}H_{31}Cl_2N_7O_3$	178–184	25
18	$C_{24}H_{33}Cl_2N_4O_3$	104–108	27

Compounds as hydrochlorides, prepared by bubbling dry HCl into the dry ethanol or diethyl ether solution of the compound.

The corresponding ethanamines **24, 24a**, and **24b** were prepared from 1-phenylpiperazines **20**, **20a**, and **20b** with *N*-(2-bromoethyl)phthalimide, in the presence of dry potassium carbonate and acetonitrile, under stirring at reflux for 12 h. After purification by column chromatography on silica gel eluting with CH_2Cl_2/EtOH, the corresponding phthalimidoethyl derivatives were treated with hydrazine hydrate in absolute ethanol at reflux for 3 h.

Synthesized compounds were characterized by ^{1}H NMR, mass spectra, and elemental analysis, and the analytical data were consistent with the proposed structures.[17] The chemical and physical data for these compounds are reported in Table 3.

The pharmacological profiles of these compounds (reported in Tables 1 and 2) were evaluated for their affinities toward α_1–AR, α_2-AR, and 5-HT_{1A} serotoninergic receptors by determining the ability of each compound to displace [^{3}H]prazosin, [^{3}H]rauwolscine, and [^{3}H]8-OH-DPAT, respectively, from specific binding sites on rat cerebral cortex.[18,19]

Moreover, the ability of these compounds to inhibit a serotonin reuptake in human platelet membranes was determined using [^{3}H]paroxetine as a reference substance.[20]

The pharmacological data expressed in K_i and reported in Table 1 clearly confirm that as the size of the *ortho* alkoxy substituent on the phenyl ring of the arylpiperazine moiety increases the affinity toward α_1-AR also increases (compounds **3** and **4**). In fact, the largest group tested, the isopropoxy group (compound **4**), gave the best α_1-AR affinity profile (K_i = 0.4 nM). The affinity value was over 100-fold greater than that of the compound in which a methoxy group was present, (compound **1**), with K_i = 47.5 nM. This pharmacological profile was inverted when the imidazole group was replaced by indole group (compounds **8** and **9**). The affinity toward α_1–AR decreases when the *ortho*-alkoxyphenylpiperazine group was replaced by pyrimidin-piperazine fragment, (compounds **6** and **11**) or when this moiety was replaced by a 1-(2,3-dihydro-1,4-benzodioxin-6-yl)piperazine group (compounds **7** and **12**). A similar reduction in affinity was observed when a *meta* trifluoromethyl group in the piperazine fragment was present (compounds **5** and **10**).

The α_2-AR affinity profile of these compounds showed a trend similar to that found for α_1-AR affinity. In fact, higher affinity was associated with a bulkier alkoxy constituent at the *ortho* position of the arylpiperazine system, while the affinity decreased when the *ortho*-alkoxyarylpiperazine system was replaced by a 1-(2,3-dihydro-1,4-benzodioxin-6-yl)piperazine or a pyrimidin-piperazine or when a *meta*-trifluoromethyl group was present in the arylpiperazine moiety.

A similar pharmacological profile was obtained with the 5-HT_{1A} receptor. In fact compound **4**, with an isopropoxy group present, showed an interesting affinity for 5-HT_{1A} receptor with a K_i value of 6.8 nM. A significant decrease in affinity for the 5-HT_{1A} receptor was observed when the arylpiperazine moiety was replaced by pyrimidin-piperazine or a 1-(2,3-dihydro-1,4-benzodioxin-6-yl)piperazine fragment. The low affinity of these compounds for the SERT suggests that no uptake inhibition is expected with these derivatives.

It is interesting to note that for compounds **5** and **10**, the affinity toward 5-HT_{2A} was evaluated using [^{3}H]ketanserine as reference substance. The binding assay was performed in triplicate, with 0.5 nM [^{3}H]ketanserine (K_d = 0.48 ± 0.2) in the absence or presence of unlabelled 10 μM spipern.[21] The pharmacological data showed that compound **10** having an indole moiety at the 6-position of the pyridazinone group had an interesting affinity toward 5-HT_{2A}

with a value data of K_i = 83.0 ± 19 nM, while the affinity decreased (K_i = 166.0 ± 52) when this group was replaced by an imidazole fragment (compound **5**).

The pharmacological data reported in Table 2 clearly confirm that the presence of the amide group linked to the arylpiperazine fragment leads to a marked drop in affinity toward all the receptors studied (compounds **13, 14**, and **15**). Similar results were obtained when this group is present along the length of the alkyl chain that is used as a spacer between the phenylpiperazine and the terminal moiety (compounds **16, 17**, and **18**).

In conclusion, these pharmacological data confirm further on the pharmacophoric model for α_1-antagonist, in fact

(a) An increase in the bulkiness of the alkoxy group at the *ortho*-position of the phenyl ring attached to the piperazine fragment leads to an enhanced affinity toward α_1–AR, the isopropoxy group and a linker of four carbon atoms had the highest affinity of the compounds tested. (b) It was confirmed that a *meta*-substitution or the presence of the pyrimidin-piperazine, or 1-(2,3-dihydro-1,4-benzodioxin-6-yl)piperazine fragment, leads to a marked drop in affinity toward α_1–AR. (c) The presence of an amide in the alkyl chain that is used as a spacer between the phenylpiperazine and the terminal moiety leads to a marked drop in affinity toward α_1–AR. (d) Finally it is confirmed that the presence of an amide group linked to the arylpiperazine fragment showed low affinity toward all the receptors studied, confirming the importance of the positively ionizable group, corresponding to the more basic nitrogen atom of the piperazine ring.

References and notes

1. Ford, A. P. D. W.; Williams, T. J.; Blue, D. R.; Clarke, D. E. **1994**, *15*, 167.
2. Hieble, J. P.; Bylund, D. B.; Clarke, D. E.; Eikenberg, D. C.; Langer, S. Z.; Lefklowitz, R. J.; Minneman, K. P.; Ruffolo, R. R. *Pharmacol. Rev.* **1995**, *47*, 267.
3. Lepor, H. *J. Androl.* **1991**, *12*, 389.
4. Caine, M. *Urol. Clin. North. Am.* **1990**, *17*, 641.
5. Russell, R. K.; Press, J. B.; Rampulla, R. A.; McNally, J. J.; Falotico, R.; Keiser, J. A.; Bright, D. A.; Tobia, A. *J. Med. Chem.* **1988**, *31*, 1786.
6. (a) Gifford, R. W., Jr. *Cleveland Clinic J. Med.* **1993**, *60*, 273; (b) Kasztreiner, E.; Matyus, P.; Rabloczky, G.; Jaszlits, L. *Drugs Future* **1989**, *14*, 622.
7. Manetti, F.; Corelli, F.; Strappaghetti, G.; Botta, M. *Curr. Med. Chem.* **2002**, *9*, 1303.
8. (a) Corsano, S.; Strappaghetti, G.; Barbaro, R.; Giannaccini, G.; Betti, L.; Lucaccchini, A. *Bioorg. Med. Chem.* **1999**, *7*, 933; (b) Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. *J. Med. Chem.* **2001**, *44*, 2118.
9. Betti, L.; Botta, M.; Corelli, F.; Floridi, M.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Tafi, A.; Corsano, S. *J. Med. Chem.* **2002**, *45*, 3603.
10. Betti, L.; Botta, M.; Corelli, F.; Floridi, M.; Fossa, P.; Giannaccini, G.; Manetti, F.; Strappaghetti, G.; Corsano, S. *Bioog. Med. Chem. Lett.* **2002**, *12*, 437.
11. (a) Cinone, N.; Carrieri, A.; Strappaghetti, G.; Corsano, S.; Barbaro, R.; Carotti, A. *Bioorg. Med. Chem.* **1999**, *7*, 2615; (b) Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. *Bioog. Med. Chem.* **2002**, *10*, 361.
12. Betti, L.; Floridi, M.; Giannaccini, G.; Manetti, F.; Strappaghetti, G.; Tafi, A.; Botta, M. *Bioog. Med. Chem. Lett.* **2003**, *13*, 171.
13. Betti, L.; Corelli, F.; Floridi, M.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Botta, M. *J. Med. Chem.* **2003**, *46*, 3555.
14. Betti, L.; Floridi, M.; Giannaccini, G.; Manetti, F.; Paparelli, C.; Strappaghetti, G.; Botta, M. *Bioorg. Med. Chem.* **2004**, *12*, 1527.
15. (a) Betti, L.; Zanelli, M.; Giannaccini, G.; Manetti, F.; Schenone, S.; Strappaghetti, G. *Bioog. Med. Chem.* **2006**, *14*, 2828; (b) Strappaghetti, G.; Brodi, C.; Giannaccini, G.; Betti, L. *Bioog. Med. Chem. Lett.* **2006**, *16*, 2575.
16. Martin, G. E.; Elgin, R. J.; Mathiasen, J. R.; Davis, C. B.; Kesslick, J. M.; Baldy, W. J.; Shank, R. P.; Di Stefano, D. L.; Fedde, C. L.; Scott, M. K. *J. Med. Chem.* **1989**, *32*, 1052.
17. C, H, and N analysis of these compounds gave results within ±0.4% of theoretical values. ^{1}H NMR mass spectra are consistent with the assigned structures of compounds **3**–**18**.
18. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
19. Lowry, O. H.; Rosenbrough, N. J.; Farr, A. L.; Randall, R. J. *J. Biol. Chem.* **1951**, *19*, 3265.
20. Marazziti, D.; Rossi, A.; Gemignani, A.; Giannaccini, G.; Pfanner, C.; Milanfranchi, A.; Presta, S.; Lucacchini, A.; Cassano, G. B. *Neuropsychobiology* **1996**, *34*, 184.
21. Leysen, J. E.; Niemergeers, C. J.; Van Neuten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301.