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α_1-Adrenoceptor Antagonists. 5. Pyridazinone-arylpiperazines. Probing the Influence on Affinity and Selectivity of Both *ortho*-Alkoxy Groups at the Arylpiperazine Moiety and Cyclic Substituents at the Pyridazinone Nucleus†

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Abstract—Our previous work on pyridazinone–arylpiperazine derivatives suggested some structural features that a compound should have to show high affinity and good selectivity for α_1 adrenoceptors (AR) with respect to α_2-AR. Accordingly, two classes of new alkoxyphenylpiperazinylheptylpyridazinones were designed and synthesized to evaluate the effect of the alkoxy substituent on affinity and selectivity. As expected, affinity increased with larger alkoxy groups. Affinity values are all comparable with that of the reference compound (prazosin), with the exception of compound **1c** found 4.5-fold more active than prazosin.

In recent years, the search for new selective α_1-AR antagonists has intensified, mainly due to their importance in the treatment of hypertension[2–4] and benign prostatic hyperplasia.[5–7] In this context, goal of our research was to discovery and develop novel adrenoceptor antagonists characterized by high affinity for α_1-AR and, possibly, selectivity toward α_1 receptor with respect to α_2-AR.

Building on the results from our previous work,[1] new compounds that have an *ortho*-substituted phenylpiperazinylheptyl pyridazinone moiety as a common chemical scaffold, which allows for variations to be introduced on the terminal moiety linked to the pyridazinone nucleus and on the size of the *ortho* alkoxy substituent, were designed and prepared for study.

It was recently reported by us[1] that a gradual increase in affinity may be obtained by lengthening from two up to seven carbon atoms the polymethylene spacer between the pyridazinone and arylpiperazine moieties of piperazinylalkylpyridazinone derivatives. Moreover, placing a methoxy group at the *ortho* position of the phenylpiperazine moiety, in conjunction with a seven carbon atom spacer, led to the best α_1 affinity profile. On the other hand, α_2/α_1 selectivity is mainly dependent on the terminal molecular fragment directly linked to the pyridazinone ring. In fact, although **2a** showed high affinity toward α_1-AR (1.4 nM) without any appreciable selectivity, **1a** exhibited an affinity of 1.9 nM and an interesting α_2/α_1 ratio of 274.

These findings led us to conclude that the ortho position is a crucial key for improving the α_1-AR antagonist properties in terms of affinity and selectivity, which are also strictly dependent on the polymethylene chain length and on the terminal cyclic fragment.[1,8]

Based on these considerations, compounds **1a** and **2a** (Table 1 and Scheme 1) were in turn used as a template to design the remaining compounds **1b**,**c** and **2b–e**. As a consequence, a heptyl spacer was maintained in the piperazine-pyridazinone system, and alkoxy moieties

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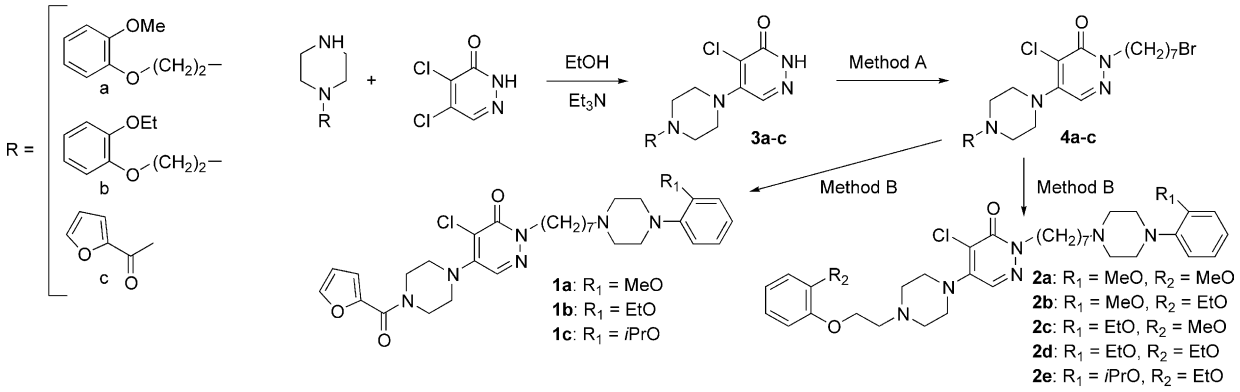

Scheme 1.

larger than a methoxy group were substituted at the ortho position of the phenyl ring, in agreement with a pharmacophore model for α_1-AR antagonists[1] suggesting that hydrophobic groups larger than a methoxy substituent can be accommodated by a hydrophobic pocket where the substituted phenyl ring bound to the piperazine lies. Moreover, to probe the influence of the terminal cyclic substituent on α_1-AR affinity and selectivity, a furoylpiperazine or a phenoxyethylpiperazine moiety was placed at the 5-position of the pyridazinone nucleus.

Compounds **1b**,**c** and **2b–e** were synthesized as outlined in Scheme 1. A mixture comprised of 4,5-dichloropyridazin-3(2*H*)-one and the appropriate 1-substituted piperazine was refluxed in ethanol and Et_3N for 15 h to afford intermediates **3a–c** that were in turn transformed into **4a–c** by treating with 1,7-dibromoheptane in acetone and potassium carbonate (method A). Compounds **1b**,**c** were obtained from **4c** with 1-(2-ethoxyphenyl)piperazine or 1-(2-isopropoxyphenyl)piperazine, respectively,[9,10] in isoamyl alcohol and sodium carbonate (method B). Following method B, compound **2c** was prepared from **4a** with 1-(2-ethoxyphenyl)piperazine. Similarly, compounds **2b**,**d**,**e** were obtained starting from **4b** with 1-(2-methoxyphenyl)piperazine, 1-(2-ethoxyphenyl) piperazine, and 1-(2-isopropoxyphenyl)-piperazine, respectively. Chemical and physical data of compounds **1a–c** and **2b–e** are reported in Table 1.[11]

The pharmacological profile of the new compounds was evaluated by radioligand binding assays (ability to displace [^{3}H]prazosin, [^{3}H]rauwolscine, and [^{3}H]8-OH-DPAT from α_1-AR, α_2-AR, and 5-HT_{1A}, respectively) on rat cerebral cortex. Moreover, in order to determine the intrinsic activity of **1c** and **2e** (the furoyl and phenoxyethyl derivatives found to have the best affinity profile toward α_1-AR), competitive binding studies were performed in the presence and in the absence of 1 mM GTP using the radiolabeled antagonist prazosin. The GTP shift values of the selected compounds (0.8 for **1c**, 1.7 for **2e**, and 1.2 for the reference compound prazosin) are indicative of an antagonist profile as prazosin.

All the newly synthesized compounds were found to have a subnanomolar affinity (data listed in Table 2) toward α_1-AR that is comparable to the affinity of prazosin. As expected, replacing the ortho methoxy substituent on the phenylpiperazine moiety of **1a** with larger alkoxy groups, enhanced affinity. In fact, while compound **1b** showed an improvement of about 4-fold in affinity with respect to the methoxy counterpart, affinity of **1c** was more than 40-fold higher than affinity of **1a**. Interestingly, compound **1c**, bearing the isopropoxy substituent, showed an affinity about 4.5-fold higher than the reference compound prazosin. Analogous considerations could be made for compounds **2**. In fact, **2c**

Table 1. Chemical and physical data of compounds **1** and **2**

Compd	R_1	R_2	Formula	Mp (°C)	Yield (%)
1a[a]	MeO		$C_{31}H_{41}ClN_6O_4$	128–130[b]	70
1b	EtO		$C_{32}H_{43}ClN_6O_4$	150–155[c]	40
1c	*i*PrO		$C_{33}H_{45}ClN_6O_4$	125–129[d]	30
2a[a]	MeO	MeO	$C_{35}H_{49}ClN_6O_4$	125–128[d]	75
2b	MeO	EtO	$C_{36}H_{51}ClN_6O_4$	65–70[c]	40
2c	EtO	MeO	$C_{36}H_{51}ClN_6O_4$	71–73[d]	45
2d	EtO	EtO	$C_{37}H_{53}ClN_6O_4$	50–55[e]	60
2e	*i*PrO	EtO	$C_{38}H_{55}ClN_6O_4$	61–66[b]	40

[a]Compounds described elsewhere by our research group.[1]
[b]As dihydrochloride.
[c]As trihydrochloride dihydrate.
[d]As trihydrochloride.
[e]As trihydrochloride monohydrate.

Table 2. α_1 And α_2-adrenoceptor binding affinities of compounds **1–2**

Compd	R_1	R_2	K_i, nM[a]			
			α_1-AR	α_2-AR	α_2/α_1	5-HT_{1A}
1a[b]	MeO		1.9±0.1	520.1±4.2	274	ND[c]
1b	EtO		0.50±0.02	4.0±0.2	8	ND[c]
1c	*i*PrO		0.052±0.007	0.56±0.19	11	0.80±0.23
2a[b]	MeO	MeO	1.4±0.1	4.6±0.5	3	ND[c]
2b	MeO	EtO	0.55±0.10	1.6±0.1	3	0.16±0.06
2c	EtO	MeO	0.58±0.15	8.2±0.3	14	ND[c]
2d	EtO	EtO	0.43±0.08	2.0±0.2	5	0.22
2e	*i*PrO	EtO	0.26±0.07	3.2±0.1	12	0.82±0.18
P[d]			0.24±0.05			
R[d]				4.0±0.3		
D[d]						2.0±0.2

[a]Values are means ± standard deviation of three binding experiments, calculated according to the equation $K_i = IC_{50}/(1 + [\text{radioligand}]/K_d)$.[12]
[b]Compounds reported elsewhere by our research group.[1] Compounds **1b**,**c** and **2b–e** have been submitted to an Italian patent.[13]
[c]ND: not determined.
[d]**P**, **R**, and **D** represent prazosin, rauwolscine, and 8-OH-DPAT, respectively.

is about 2-fold more active with respect to the corresponding methoxy counterpart **2a**. Finally, compounds **2b** and **2d**,**e**, bearing an ethoxy substituent on the phenyl ring opposite to the phenylpiperazine moiety, also showed improved affinity with respect to **2a** and comparable with that of **2c**. As expected, compound **2e**, with the largest R_1 substituent, was characterized by the best α_1-AR affinity profile among compounds **2**. Structure–activity relationships (SARs) of such compounds, in addition to validate the pivotal role of the alkoxy substituent in influencing affinity toward α_1-AR, suggested that variation on the size of the terminal aryl substituent attached to the pyridazinone nucleus affects affinity toward α_1-AR, in agreement with previous findings reported by our group.[1,8]

Regarding the α_2-AR affinity profile, compounds **1** showed a trend similar to that found for α_1 affinity. In fact, higher affinity was associated with bulkier alkoxy substituent at the *ortho* position of the arylpiperazine system. However, the opposite trend was found for compounds **2**. For example, **2a** showed an affinity (4.6 nM) of about 2-fold higher than the corresponding ethoxy derivative **2c** (8.2 nM). Similarly, a decrease in α_2 affinity was observed by replacing the methoxy substituent of **2b** (1.6 nM) with an ethoxy (**2d**, 2.0 nM) or isopropoxy group (**2e**, 3.2 nM).

It is interesting to note that **1a** was the sole compound characterized by a good α_2/α_1 selectivity profile. In fact, none of the reported compounds showed significant selectivity for α_1-AR with respect to α_2-AR, the highest α_2/α_1 ratio being 14 in compound **2c**. This last finding suggested that the bulkiness of the alkoxy group, while positively affects the affinity toward both α_1 and α_2-AR, leads in any case to α_2/α_1 unselective compounds. As an example, the enhanced α_1 and α_2-AR affinity of **1b** and **1c** with respect to **1a**, produces compounds with very low selectivity (8 and 11 for **1b** and **1c**, respectively).

Similarly, all compounds evaluated for their affinity toward 5-HT_{1A} exhibited values in the subnanomolar range without 5-HT_{1A}/α_1 selectivity, 15 being the most interesting 5-HT_{1A}/α_1 ratio found for compound **1c**.

In conclusion, based on suggestions derived from our previous work in the field of α_1-AR antagonists, a number of novel arylpiperazine-pyridazinone-containing compounds were designed, synthesized and evaluated for their biological properties. As a result, each of them was found to have a high affinity for α_1-AR. Moreover, the hypothesis that an *ortho* substituent larger than a methoxy group (up to a isopropoxy moiety) may significantly improve affinity toward α_1-AR in the arylpiperazine series, was confirmed by SAR studies. On the other hand, replacement of the methoxy group with ethoxy or even larger substituents differently affected α_2 affinity in the furoyl and phenoxyethyl series of compounds, in any case leading to molecules without appreciable selectivity with respect to α_2-AR and 5-HT_{1A}. Moreover, taking into account the excellent affinity data of all the new compounds prepared, a seven-carbon atom chain appeared to be the optimal spacer to bring both the pyridazinone and the piperazine ring at the right distance to interact with the receptor.

Additional studies are ongoing to further evaluate the influence of the terminal molecular portions on α_1-AR affinity and selectivity and will be reported in due time.

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References and Notes

1. Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. *J. Med. Chem.* **2001**, *44*, 2118.
2. 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.
3. Chern, J.-W.; Tao, P.-L.; Yen, M.-H.; Lu, G.-Y.; Shiau, C.-Y.; Lai, Y.-J.; Chien, S.-L.; Chan, C.-H. *J. Med. Chem.* **1993**, *36*, 2196.
4. Chern, J.-W.; Tao, P.-L.; Wang, K.-C.; Gutcait, A.; Liu, S.-W.; Yen, M.-H.; Chien, S.-L.; Rong, J.-K. *J. Med. Chem.* **1998**, *41*, 3128.
5. Bock, M. G.; Patane, M. A. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic: New York, 2000; Vol. 35, p 221.
6. Forray, C.; Noble, S. A. *Exp. Opin. Invest. Drugs* **1999**, *8*, 2073.
7. Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. *J. Med. Chem.* **1997**, *40*, 1293.
8. 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.
9. Martin, G. E.; Elgin, R. J., Jr.; Mathiasen, J. R.; Davis, C. B.; Kesslick, J. M.; Baldy, W. J.; Shank, R. P.; DiStefano, D. L.; Fedde, C. L.; Scott, M. K. *J. Med. Chem.* **1989**, *32*, 1052.
10. Reitz, A. B.; Baxter, E. W.; Codd, E. E.; Davis, C. B.; Jordan, A. D.; Maryanoff, B. E.; Maryanoff, C. A.; McDonnell, M. E.; Powell, E. T.; Renzi, M. J.; Schott, M. R.; Scott, M. K.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1998**, *41*, 1997.
11. C, H, N analysis of the new compounds gave results within $\pm 0.4\%$ of theoretical values. ^{1}H NMR spectra are consistent with the assigned structures of compounds **1b**,**c** and **2b–e**.
12. Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
13. Betti, L.; Botta, M.; Floridi, M.; Giannaccini, G.; Manetti, F.; Strappaghetti G. Italian Patent RM2002A000362, July 5, 2002.