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2-[4-(*o*-METHOXYPHENYL)PIPERAZIN-1-YLMETHYL]-1,3-DIOXOPERHYDROIMIDAZO[1,5-*a*]PYRIDINE AS A NEW SELECTIVE 5-HT_{1A} RECEPTOR LIGAND

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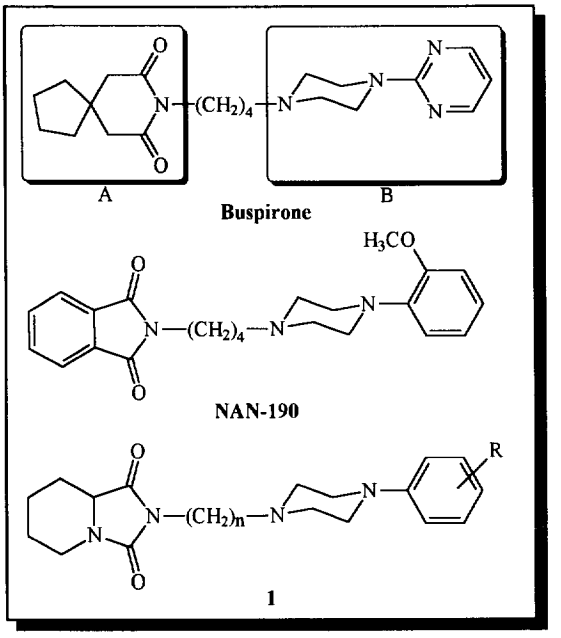
Abstract: A series of 2-[ω-(4-arylpiperazin-1-yl)alkyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine derivatives was prepared and evaluated for affinity at 5-HT_{1A} and α_1 receptors. The most promising analogue **1m** bound at 5-HT_{1A} sites with nanomolar affinity (K_i=31.7) and high selectivity over α_1, D_2 and 5-HT_{2A} receptors (K_i>1000, K_i>10 000, K_i>1000 nM, respectively). Preliminary studies showed that this agent is a presynaptic 5-HT_{1A} agonist, and it displayed activity in the face to face behavioural model.

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is involved in various physiological and pathophysiological processes.[1] It is generally accepted that receptors of the 5-HT_{1A} subtype are involved in psychiatric[2] disorders such as depression and anxiety. Buspirone, an arylpiperazine derivative with high affinity for 5-HT_{1A} receptor, was the first agent to be approved for clinical use.[3] However, this compound is not optimal in terms of selectivity and pharmacokinetic properties, and has a slow onset of action. Several structural changes have been made on the imide (A) and arylpiperazine (B) moieties of buspirone in order to increase the selectivity for the 5-HT_{1A} site. However, most of these compounds exhibit high level of undesired affinity for the α_1 adrenoceptor [e.g. NAN-190: K_i(5-HT_{1A})=0.6 nM, K_i(α_1)=0.8 nM], and attempts have been made to identify and eliminate the structural features that account for α_1-adrenergic binding.[4]

The influence of the arylpiperazine and the length of the spacer on 5-HT_{1A}/α_1 selectivity is clear, in contrast to the role of the cyclic imide. Some reported[4a,5] results have demonstrated that a lipophilic character in the imide portion is needed for high 5-HT_{1A} affinity, while another hypothesis[6] has suggested that steric factors play an important role.

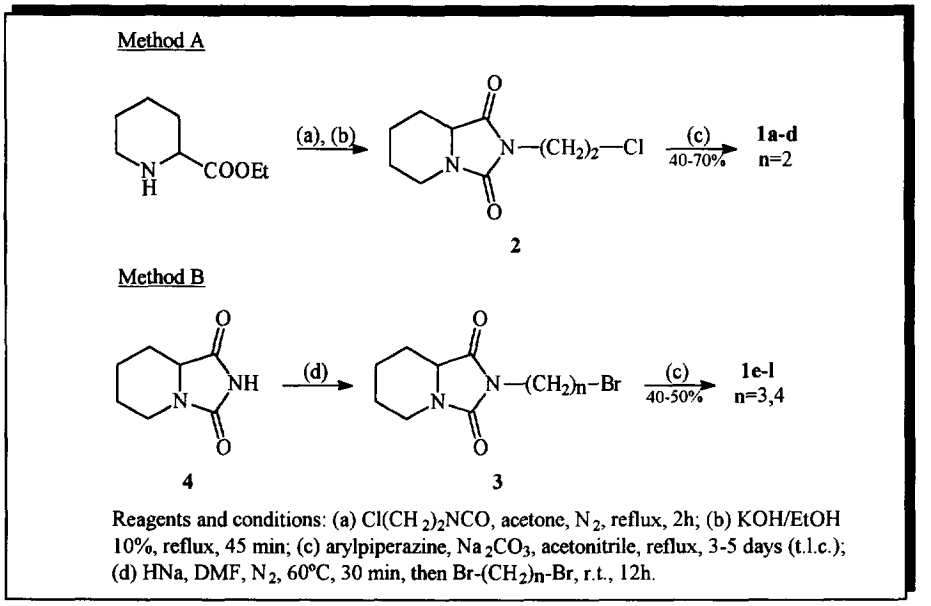
In the present communication, we have analyzed a new set of model arylpiperazines **1**, in which the imide moiety (part A) has been replaced by a bicyclohydantoin (V_W=77.04 $cm^3.mol^{-1}$) [preserving the steric requirements of the phtalimido (V_W=69.47) and the azaspirodione (V_W=89.72) moieties], in order to evaluate the influence of non-steric factors on the affinity and selectivity for 5-HT_{1A} sites. Herein we report the synthesis of **1** and the affinities for 5-HT_{1A} and α_1 receptors, obtained by radioligand binding studies.



Chemistry

The synthesis of **1a-l** is illustrated in Scheme 1. The desired compounds **1a-d** (n=2) (Method A) and **1e-l** (n=3,4) (Method B) were obtained by reaction of the intermediates **2,3** with the corresponding arylpiperazines in the presence of sodium carbonate and acetonitrile. The reaction of the ethyl pipecolinate with 2-chloroethyl isocyanate gave **2**; the key-intermediates **3a,b** (n=3,4) were prepared from **4**[7] by reaction with the appropriate dibromoalkane in the presence of HNa and N,N-dimethylformamide (DMF). Respective hydrochloride salts were prepared as samples for biological assays. All new compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopy and gave satisfactory combustion analyses (C,H,N).[8]

Scheme 1



Reagents and conditions: (a) $Cl(CH_2)_2NCO$, acetone, N_2, reflux, 2h; (b) KOH/EtOH 10%, reflux, 45 min; (c) arylpiperazine, Na_2CO_3, acetonitrile, reflux, 3-5 days (t.l.c.); (d) HNa, DMF, N_2, 60°C, 30 min, then Br-(CH_2)n-Br, r.t., 12h.

Results and Discussion

Final compounds **1a-l** were evaluated for *in vitro* activity on serotonin 5-HT_{1A} and adrenergic α_1 receptors by radioreceptor binding assays, using the following specific ligands and tissue sources: (a) serotonin 5-HT_{1A} receptors, [^{3}H]-8-OH-DPAT, rat cerebral cortex membranes;[9] (b) adrenergic α_1 receptors, [^{3}H]prazosin, rat cerebral cortex membranes.[10] The receptor binding affinities (K_i, nM) are shown in Table 1.

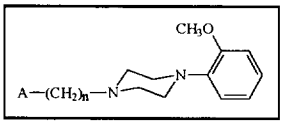
Table 1. Binding Data.

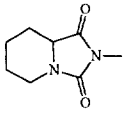
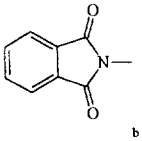
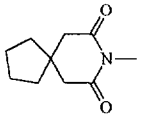
Compd	n	R	K_i ± SEM (nM)	
			5-HT_{1A} [^{3}H]-8-OH-DPAT	α_1 [^{3}H]prazosin
1a	2	H	>1000	>1000
1b	2	*o*-OCH_3	45.5 ± 4.6	131 ± 28
1c	2	*m*-Cl	128 ± 10	375 ± 16
1d	2	*m*-CF_3	65.8 ± 3.1	>1000
1e	3	H	154 ± 10	11.4 ± 0.9
1f	3	*o*-OCH_3	4.1 ± 0.6	9.9 ± 1.0
1g	3	*m*-Cl	53.6 ± 1.5	17.9 ± 1.1
1h	3	*m*-CF_3	5.7 ± 0.7	90.4 ± 5.1
1i	4	H	78.5 ± 6.8	18.6 ± 3.1
1j	4	*o*-OCH_3	8.8 ± 0.9	8.6 ± 1.0
1k	4	*m*-Cl	7.2 ± 0.6	12.1 ± 1.2
1l	4	*m*-CF_3	9.9 ± 0.9	72.4 ± 8.0

Most of the synthesized compounds demonstrated moderate to high affinity for the 5-HT_{1A} and α_1 receptor binding sites. An examination of the data of the phenylpiperazine part shows that, in agreement with the literature studies, analogs with a methoxy group at the *ortho* position displayed the highest affinity for 5-HT_{1A} and α_1 receptors. With respect to the influence of the alkyl chain length, in general, maximum affinity for 5-HT_{1A} as well as α_1 receptors is reached where n=3 or 4. Reduction of the hydrocarbon chain by two carbon atoms causes a decrease in affinity in both receptors.

We then examined the influence of the cyclic imide upon affinity at 5-HT_{1A} and α_1 sites. Comparing compounds **1b**, **1f** and **1j** (R=*o*-OCH_3) with the corresponding phtalimido[4b] and azaspirodione[11] analogs (Table 2), it is observed that affinity for 5-HT_{1A} and α_1 sites corresponds to the following order of potency: n=2 < n=4 < n=3 (5-HT_{1A}), n=2 < n=3 ≈ n=4 (α_1) for the bicyclohydantoin series; n=2 < n=3 < n=4 (5-HT_{1A} and α_1) for the phtalimido series; n=3 < n=2 ≈ n=4 (5-HT_{1A}) for the azaspirodione series.

Table 2. Affinities of ω-[4-(*o*-Methoxyphenyl)piperazin-1-yl]alkyl Derivatives at 5-HT_{1A} and α_1 Sites.



A	n = 2		n = 3		n = 4	
	5-HT_{1A}	α_1	5-HT_{1A}	α_1	5-HT_{1A}	α_1
 [a]	45.5	131	4.1	9.9	8.8	8.6
 [a]	990	130	20	33	0.6	0.8
 [b]	2.4	ND	80	ND	2.0	ND

[a] K_i, nM
[b] IC_{50}, nM

If one considers that the three classes of compounds interact with each receptor in the same way (due to similar steric properties), the length of the alkyl chain might exert the same type of influence upon the affinity. This is true

for α_1-adrenergic receptors, in which the affinity increases with increasing number of methylene units. However, this is not a general rule for 5-HT_{1A} receptors (only a logical gradation was found in the phtalimido series). These results suggest that a new derivative of **1** with n=1 (R=*o*-OCH_3) may show low α_1-adrenergic and significant 5-HT_{1A} serotoninergic receptors affinity. This analogue[12] (**1m**) binds at 5-HT_{1A} sites with nanomolar affinity (K_i=31.7) and is devoid of affinity at α_1-adrenergic receptors (K_i>1000 nM). Furthermore, **1m** is selective for 5-HT_{1A} sites over D_2[13] (K_i>10 000 nM) and 5-HT_{2A}[14] (K_i>1000 nM) sites (Table 3, buspirone and NAN-190 were used as reference compounds). Its activity in the hypothermia assay suggests that this agent is a presynaptic 5-HT_{1A} agonist and it also displayed activity in the face to face behavioural model.

Table 3. Binding Profile for **1m**, Buspirone and NAN-190.

Compd	K_i ± SEM (nM)			
	5-HT_{1A}	α_1	D_2	5-HT_{2A}
	[^{3}H]-8-OH-DPAT	[^{3}H]prazosin	[^{3}H]raclopride	[^{3}H]ketanserin
1m	31.7 ± 1.7	>1000	>10 000	>1000
buspirone	20.5 ± 2.3	367 ± 32	852 ± 70	482 ± 40
NAN-190[4b]	0.6	0.8	64	ND

Further pharmacological properties of **1m**, synthesis and biological evaluation of new derivatives of **1** (n=1) are currently in progress, and the results will be reported in due course.

Acknowledgment

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References and Notes

1. (a) Zifa, E.; Fillion, G. *Pharmacol. Rev.* **1992**, *44(3)*, 401. (b) Humphrey, P. P. A. 5-Hydroxytryptamine receptors and drug discovery. *Serotonin receptor subtypes: pharmacological significance and clinical implications*; Langer, S. Z.; Brunello, N.; Racagni, G.; Mendlewicz, J., Eds.; Karger: Basel, 1992; Vol 1, pp. 129-139. (c) Teitler, M. *Med. Chem. Res.* **1993**, *3*, 273. (d) Herndon, J. L.; Glennon, R. A. Serotonin receptors, agents and actions. *Drug design for neuroscience*; Kozikowski, A. P., Ed.; Raven Press, Ltd.: New York, 1993; pp. 167-212. (e) Saudou, F.; Hen, R. *Med. Chem. Res.* **1994**, *4*, 16.

2. (a) Fletcher, A.; Cliffe, I. A.; Dourish, C. T. *Trends Pharmacol. Sci.* **1993**, *14*, 441. (b) Hamon, M. *Trends Pharmacol. Sci.* **1994**, *15*, 36. (c) Blier, P.; Montigny, C. *Trends Pharmacol. Sci.* **1994**, *15*, 220.

3. (a) Taylor, D. P.; Moon, S. L. *Neuropeptides* **1991**, *19*, 15. (b) Levy, A. D.; van de Kar, L. D. *Life Sci.* **1992**, *51*, 83.

4. (a) Raghupathi, R. K.; Rydelek-Fitzgerald, L.; Teitler, M.; Glennon, R. A. *J. Med. Chem.* **1991**, *34*, 2633. (b) El-Bermawy, M.; Raghupathi, R.; Ingher, S. P.; Teitler, M.; Maayani, S.; Glennon, R. A. *Med. Chem. Res.* **1992**, *2*, 88.

5. (a) Abou-Gharbia, M.; Patel, U. R.; Webb, M. B.; Moyer, J. A.; Andree, T. H.; Muth, E. A. *J. Med. Chem.* **1988**, *31*, 1382. (b) van Steen, B. J.; van Wijngaarden, I.; Tulp, M. Th. M.; Soudijn, W. *J. Med. Chem.* **1993**, *36*, 2751.

6. van Steen, B. J.; van Wijngaarden, I.; Tulp, M. Th. M.; Soudijn, W. *J. Med. Chem.* **1994**, *37*, 2761.

7. (a) Freed, M. E.; Day, A. R. *J. Org. Chem.* **1960**, *25*, 2108. (b) Winterfeld, K.; Schüler, H. *Arch. Pharmaz.* **1960**, *293*, 203.

8. Melting point (°C) and formula, **1a**: 193-195, $C_{19}H_{26}N_4O_2.2HCl.H_2O$; **1b**: 178-180, $C_{20}H_{28}N_4O_3.2HCl.H_2O$; **1c**: 224-226, $C_{19}H_{25}ClN_4O_2.HCl$; **1d**: 208-210, $C_{20}H_{25}F_3N_4O_2.HCl$; **1e**: 213-215, $C_{20}H_{28}N_4O_2.2HCl.H_2O$; **1f**: 208-210, $C_{21}H_{30}N_4O_3.2HCl.3H_2O$; **1g**: 173-175, $C_{20}H_{27}ClN_4O_2.2HCl$; **1h**: 206-208, $C_{21}H_{27}F_3N_4O_2.2HCl.4H_2O$; **1i**: 198-200, $C_{21}H_{30}N_4O_2.2HCl.H_2O$; **1j**: 199-201, $C_{22}H_{32}N_4O_3.2HCl.H_2O$; **1k**: 190-192, $C_{21}H_{29}ClN_4O_2.2HCl$; **1l**: 140-142, $C_{22}H_{29}F_3N_4O_2.2HCl.1/2H_2O$.

9. Clark, R. D.; Weinhardt, K. K.; Berger, J.; Fisher, L. E.; Brown, C. M.; MacKinnon, A. C.; Kilpatrick, A. T.; Spedding, M. *J. Med. Chem.* **1990**, *33*, 633.

10. Ambrosio, E.; Montero, M. T.; Fernández, I.; Azuara, C.; Orensanz, L. M. *Neurosci. Lett.* **1984**, *49*, 193.

11. Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Smith, J. D.; Ismaiel, A. M.; Titeler, M.; Lyon, R. A. *J. Med. Chem.* **1989**, *32*, 1921.

12. Compound **1m** was prepared by Mannich reaction of 1,3-dioxoperhydroimidazo[1,5-*a*]pyridine **4** with formaldehyde and (*o*-methoxyphenyl)piperazine in 78% yield. **1m** was purified as its hydrochloride salt: mp 160-162°C. Anal. Calcd. for $C_{19}H_{26}N_4O_3.2HCl.H_2O$: C, 50.80; H, 6.68; N, 12.47. Found: C, 50.49; H, 6.70; N, 12.12.

13. Köhler, C.; Hall, H.; Ögren, S. O.; Gawell, L. *Biochem. Pharmacol.* **1985**, *34*, 2251.

14. Titeler, M.; Lyon, R. A.; Davis, K. H.; Glennon, R. A. *Biochem. Pharmacol.* **1987**, *36*, 3265.

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