

# Communications

## Identification of substituted pyrazole constrained arylpiperazines as selective ligands for serotonin 5HT<sub>1a</sub> and 5HT<sub>2a</sub> receptors<sup>†</sup>

Kamalkishor P. Landge, Jee Hee Kim, Woo-Kyu Park,<sup>‡</sup> Jae Yang Gong,<sup>‡</sup> Hun Yeong Koh,<sup>\*</sup> and Hee-Yoon Lee<sup>§,\*</sup>

Department of Chemistry, Inha University, Nam-gu, Incheon 402-751, Korea

<sup>‡</sup>Pharmaceutical Screening Research Team, Korea Research Institute of Chemical Technology, Daejeon 305-343, Korea

<sup>§</sup>Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea

\*E-mail: leehy@kaist.ac.kr

Received January 18, 2011, Accepted February 7, 2011

**Key Words :** Dopamine receptors, Serotonin receptors, Arylpiperazine, Pyrazole, Reductive amination

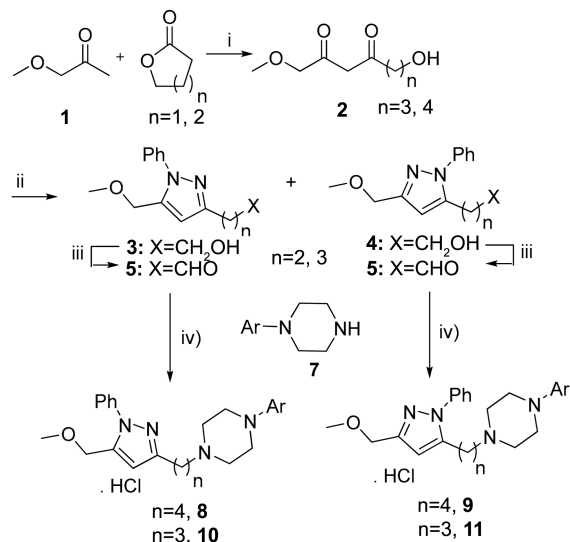
Neurotransmitters, dopamine and serotonin play important roles in the development of neurological and psychiatric disorders such as schizophrenia<sup>1</sup> and depression.<sup>2</sup> Extensive efforts have been made to explore potent and selective ligands of subtype dopamine D<sub>3</sub><sup>3</sup> or D<sub>4</sub><sup>4</sup> receptor for the discovery of antipsychotic drugs.<sup>5</sup>

In continuation of search for selective ligands for various GPCRs, we have recently reported<sup>6</sup> the design and synthesis of arylpiperazine derivative libraries with isoxazole rings for antagonist of dopamine and serotonin receptors. We envisaged that attaching aryl group to one of the nitrogen atoms of the pyrazole ring with proper alkyl linker between pyrazole and piperazine rings would provide a well defined constraint to the spatial orientation of aryl groups and the biogenic nitrogen. With this envision in mind, we designed and synthesized a focused library of aryl piperazine derivatives of phenyl substituted pyrazole ring with methoxymethyl substituent (Scheme 1). Herein we wish to report preparation of a series of arylpiperazine derivatives of pyrazole, and identification of compounds that show high selectivity for subtype serotonin receptors 5HT<sub>1a</sub> and 5HT<sub>2a</sub> as well as D<sub>3</sub> and 5HT<sub>7</sub>.

The pyrazolyl arylpiperazines **8-11** were synthesized from methoxyacetone **1** as shown in the Scheme 1.<sup>7</sup>

Table 1 shows the binding data of the compounds with interesting selectivity profile mainly for 5HT<sub>1a</sub> and 5HT<sub>2a</sub> receptors and somewhat for D<sub>3</sub>, D<sub>4</sub> and 5HT<sub>7</sub> receptors.<sup>8</sup> While the *anti*-isomer with phenylpiperazine, **8a** shows good selectivity for 5HT<sub>1a</sub> *syn*-isomer **9a** shows selectivity for 5HT<sub>2a</sub>. When phenyl group of the piperazine ring of the *anti*-isomer **8a** was substituted at the *ortho*-position, the binding affinity for 5HT<sub>1a</sub> improved regardless of the electronic nature of the substituent (**8b** and **8h**). The electron donating substituent shows binding activity for D<sub>3</sub> and 5HT<sub>7</sub> (**8h**), while electron withdrawing substituent shows good

selectivity only for 5HT<sub>1a</sub> (**8b**). When the chain length between piperazine ring and pyrazole was shortened from four to three, binding activity for 5HT<sub>1a</sub> has decreased by ten folds (**10h**). When the substituent was introduced at the *meta*-position, similar increase in binding activity for 5HT<sub>1a</sub> was observed along with improvement in the binding activity for 5HT<sub>7</sub> (**8c**). Replacing phenyl ring with 2-pyridyl ring (**8e**) showed the similar effect to the compound with electron withdrawing *ortho*-substituent (**8b**). When both *ortho*- and *meta*-positions were substituted no synergistic or additive effect was observed. Instead, there showed improvement



7	<b>7a</b>	<b>7b</b>	<b>7c</b>	<b>7d</b>	<b>7e</b>
Ar	Ph	2-F-Ph	3-CF <sub>3</sub> -Ph	2,3-diMe-Ph	2-Pyr.
7	<b>7f</b>	<b>7g</b>	<b>7h</b>	<b>7i</b>	<b>7j</b>
Ar	(4-F-Ph) <sub>2</sub> CH	3,4-diMe-Ph	2-MeO-Ph	4-F-Ph	4-Cl-Ph

**Scheme 1.** Reagents and reaction conditions: i) NaOMe/PhH, rt overnight. 40%, 60%. ii) PhNHNH<sub>2</sub>/MeOH, rt 4 hr. 52%, 60%. iii) PCC-SiO<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>, 5-12 h, 45%, 75%. iv) NaBH(OAc)<sub>3</sub>; HCl, 85%-95%.

<sup>†</sup>This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

**Table 1.** Binding affinities (IC<sub>50</sub>) of selective compounds to several subtype receptors.

	Binding Affinity : IC <sub>50</sub> (nM)							
	D <sub>4</sub>	D <sub>3</sub>	D <sub>2</sub>	5HT <sub>1a</sub>	5HT <sub>2a</sub>	5HT <sub>2c</sub>	5HT <sub>6</sub>	5HT <sub>7</sub>
<b>8a</b>	508	454	7735	10	213	1272	7164	168
<b>9a</b>	1605	652	3200	124	48	358	>10000	128
<b>8b</b>	647	160	1868	3.2	302	960	>10000	133
<b>9b</b>	879	328	3710	28	126	896	>10000	133
<b>8c</b>	403	252	1168	3.1	97	231	1299	42
<b>9c</b>	1026	531	1056	20	131	422	3558	27
<b>8d</b>	407	85	837	5.7	35	156	1881	32
<b>9d</b>	396	156	707	20	38	249	4359	17
<b>8e</b>	1851	3739	>10000	3.3	1425	6176	>10000	474
<b>9e</b>	2530	2835	>10000	67	404	2674	>10000	284
<b>8f</b>	911	177	2189	161	26	343	775	406
<b>9f</b>	681	92	902	785	47	1304	1426	424
<b>8g</b>	35	420	6862	64	34	160	1022	141
<b>9g</b>	129	1061	5548	240	24	240	3603	221
<b>8h</b>	527	83	1143	1.4	3093	1462	>10000	50
<b>9h</b>	225	235	1531	18	2010	1637	>10000	24
<b>8i</b>	403	1510	>10000	91	101	689	5881	432
<b>9i</b>	681	2065	>10000	371	20	246	8911	184
<b>8j</b>	45	1105	>10000	33	83	2023	3384	317
<b>9j</b>	259	1787	>10000	127	68	1283	6329	178
<b>8k</b>	257	1686	>10000	242	17	164	2055	174
<b>9k</b>	293	1222	9850	157	12	157	1606	142
<b>10d</b>	1284	688	>10000	4.1	111	425	4366	84
<b>11d</b>	1651	289	5727	23	53	370	3848	80
<b>10j</b>	576	4398	>10000	90	35	1201	5222	203
<b>11j</b>	538	3071	>10000	606	26	940	3825	206
<b>10h</b>	267	481	>10000	20	3364	1883	>10000	69
<b>11h</b>	729	797	2440	21	2785	2916	>10000	76
<b>10f</b>	4999	801	3274	2193	250	1266	2935	755
<b>11f</b>	3594	43	2496	1175	163	977	970	357
<b>10i</b>	3248	3979	>10000	35	67	1186	8875	66
<b>11i</b>	1742	6245	>10000	1006	78	777	7090	98
<b>10c</b>	1805	1246	>10000	3.8	195	372	4955	56
<b>11c</b>	2346	1270	9027	19	104	437	3248	42
<b>Clozapine</b>	94.4	531	248	695	9.0	12.5	9.8	74.6
<b>Olanzapine</b>	98.4	175	200	9313	7.4	17.1	11.6	598

in the binding activities for D<sub>3</sub>, 5HT<sub>2a</sub> and 5HT<sub>7</sub> (**8d** and **10d**). These substitution patterns also override the selectivity for 5HT<sub>2a</sub> of the *syn*-isomer **9a**, **9b**, **9c**, **9d**, **9e**, **9h**, **11d** and **11j**. This is a good indication that the *ortho*-substituted

phenyl piperazine ring system would have strong preference toward 5HT<sub>1a</sub> while selectivity for few other sub-types becomes worse. When the *para*-position of the phenyl ring was substituted, binding activity for 5HT<sub>1a</sub> became weak while the activity for 5HT<sub>2a</sub> was improved in both the *syn* and *anti* isomers (**8i**, **8j**, **10j**, **10i**, **9i**, **9j**, **11j** and **11i**) regardless of the chain length. When both the *meta*- and *para*-positions had substituents, selectivity for 5HT<sub>2a</sub> improved with better selectivity for chain length of three (**8g**, **10g**, **9g** and **11g**). When the phenyl ring was replaced by diphenylmethyl group, both the *syn* and *anti*-isomers showed the selectivity for 5HT<sub>2a</sub> with chain length of four (**8f** and **9f**). Based on these results, we could draw a pharmacophore map for 5HT<sub>1a</sub> or 5HT<sub>2a</sub> selective ligands of pyrazole constraint. It is noteworthy that the selectivity of the mono-substituted compounds is neither synergistic nor additive.

In summary, from a small focused library of 3-(methoxymethyl) phenyl piperazine compounds that was constructed through solution phase combinatorial synthesis, a series of compounds with selective binding to 5HT<sub>1a</sub> or 5HT<sub>2a</sub> and compounds with selective binding to sets of two receptors 5HT<sub>1a</sub>-5HT<sub>2a</sub> and 5HT<sub>1a</sub>-5HT<sub>7</sub> were identified.

**Acknowledgments.** The research was supported by the Ministry of Knowledge and Economy and the Converging Research Center Program through the Ministry of Education, Science and Technology (2010K001201).

## References

- (a) Roger, B. N.; Schmidt, C. J. *Ann. Rev. Med. Chem.* **2006**, *41*, 3-21. (b) Rowley, M.; Bristow, L. J.; Hutson, P. H. *J. Med. Chem.* **2001**, *44*, 477. (c) Davis, K. L.; Kahn, R. S.; Ko, G.; Davidson, M. *Am. J. Psychiatry* **1991**, *148*, 1474-1486.
- Averand, D. A. *Ann. Rev. Med. Chem.* **2006**, *41*, 23-38.
- Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. *Nature* **1990**, *347*, 146-151.
- Van Tol, H. M.; Bunzow, J. R.; Guan, H. C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. *Nature* **1991**, *350*, 610-614.
- Zhang, A.; Kan, Y.; Li, F. *Expert Opin. Thera. Pat.* **2006**, *16*, 587-630.
- (a) Cha, M. Y.; Choi, B. C.; Kang, K. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Koh, H. Y.; Lee, H. Y.; Jung, D. Y.; Kong, J. Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1327-1330. (b) Youn, H. S.; Lee, E. J.; Lee, J. E.; Park, W.-K.; Baek, D. J.; Cho, Y. S.; Koh, H. Y.; Choo, H.; Pae, A. N. *Bull. Korean Chem. Soc.* **2009**, *30*, 1873-1876.
- Kang, K. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Chung, B. Y.; Lee, J. E.; Jung, S. H.; Koh, H. Y.; Lee, H. Y. *Tetrahedron Lett.* **2001**, *42*, 1057-1060.
- The binding activity was determined by measuring the ability of receptors to displace radioligand [<sup>3</sup>H]spiperone for D<sub>2</sub>, D<sub>3</sub> and [<sup>3</sup>H]YM-09151-2 for D<sub>4</sub> from the cloned human dopamine receptors D<sub>2</sub>Long, D<sub>3</sub> and D<sub>4.2</sub> which were stably expressed in CHO cells. For serotonin receptors, compounds were evaluated against human recombinant 5HT<sub>1a</sub>, 5HT<sub>2a</sub>, 5HT<sub>2c</sub>, 5HT<sub>6</sub> and 5HT<sub>7</sub> receptors stably expressed by CHO-K1 cell lines through [<sup>3</sup>H]8-OH-DPAT, [<sup>3</sup>H]Ketanserin, [<sup>3</sup>H]Mesulergine and [<sup>3</sup>H]LSD binding assay, respectively.