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Communications

Identification of substituted pyrazole constrained arylpiperazines as selective ligands for serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors†

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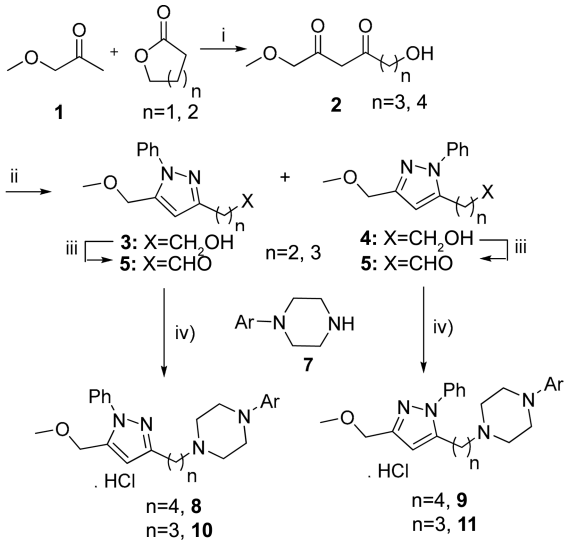
Neurotransmitters, dopamine and serotonin play important roles in the development of neurological and psychiatric disorders such as schizophrenia[1]and depression.[2] Extensive efforts have been made to explore potent and selective ligands of subtype dopamine D_3[3] or D_4[4] receptor for the discovery of antipsychotic drugs.[5]

In continuation of search for selective ligands for various GPCRs, we have recently reported[6] 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 receptor s $5HT_{1a}$ and $5HT_{2a}$ as well as D_3 and $5HT_7$.

The pyrazolyl arylpiperazines **8-11** were synthesized from methoxyacetone **1** as shown in the Scheme 1.[7]

Table 1 shows the binding data of the compounds with interesting selectivity profile mainly for $5HT_{1a}$ and $5HT_{2a}$ receptors and somewhat for D_3 , D_4 and $5HT_7$ receptors.[8] While the *anti*-isomer with phenylpiperazine, **8a** shows good selectivity for $5HT_{1a}$ *syn*-isomer **9a** shows selectivity for $5HT_{2a}$. When phenyl group of the piperazine ring of the *anti*-isomer **8a** was substituted at the *ortho*-position, the binding affinity for $5HT_{1a}$ improved regardless of the electronic nature of the substituent (**8b** and **8h**). The electron donating substituent shows binding activity for D_3 and $5HT_7$ (**8h**), while electron withdrawing substituent shows good selectivity only for $5HT_{1a}$ (**8b**). When the chain length between piperazine ring and pyrazole was shortened from four to three, binding activity for $5HT_{1a}$ has decreased by ten folds (**10h**). When the substituent was introduced at the *meta*-position, similar increase in binding activity for $5HT_{1a}$ was observed along with improvement in the binding activity for $5HT_7$ (**8c**). Replacing phenyl ring with 2-pyridyl ring (**8e**) showed the similar effect to the compound with electron withdrawing *ortho*-substitutent (**8b**). When both *ortho*- and *meta*-positions were substituted no synergistic or additive effect was observed. Instead, there showed improvement



7	**7a**	**7b**	**7c**	**7d**	**7e**
Ar	Ph	2-F-Ph	3-CF_3-Ph	2,3-diMe-Ph	2-Pyr.
7	**7f**	**7g**	**7h**	**7i**	**7j**
Ar	$(4\text{-F-Ph})_2CH$	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) $PhNHNH_2$/MeOH, rt 4 hr. 52%, 60%. iii) PCC-SiO_2/CH_2Cl_2, 5-12 h, 45%, 75%. iv) $NaBH(OAc)_3$; HCl, 85%-95%.

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

Table 1. Binding affinities (IC_{50}) of selective compounds to several subtype receptors.

	Binding Affinity : IC50(nM)							
	D_4	D_3	D_2	$5HT_{1a}$	$5HT_{2a}$	$5HT_{2c}$	$5HT_6$	$5HT_7$
8a	508	454	7735	10	213	1272	7164	168
9a	1605	652	3200	124	48	358	>10000	128
8b	647	160	1868	3.2	302	960	>10000	133
9b	879	328	3710	28	126	896	>10000	133
8c	403	252	1168	3.1	97	231	1299	42
9c	1026	531	1056	20	131	422	3558	27
8d	407	85	837	5.7	35	156	1881	32
9d	396	156	707	20	38	249	4359	17
8e	1851	3739	>10000	3.3	1425	6176	>10000	474
9e	2530	2835	>10000	67	404	2674	>10000	284
8f	911	177	2189	161	26	343	775	406
9f	681	92	902	785	47	1304	1426	424
8g	35	420	6862	64	34	160	1022	141
9g	129	1061	5548	240	24	240	3603	221
8h	527	83	1143	1.4	3093	1462	>10000	50
9h	225	235	1531	18	2010	1637	>10000	24
8i	403	1510	>10000	91	101	689	5881	432
9i	681	2065	>10000	371	20	246	8911	184
8j	45	1105	>10000	33	83	2023	3384	317
9j	259	1787	>10000	127	68	1283	6329	178
8k	257	1686	>10000	242	17	164	2055	174
9k	293	1222	9850	157	12	157	1606	142
10d	1284	688	>10000	4.1	111	425	4366	84
11d	1651	289	5727	23	53	370	3848	80
10j	576	4398	>10000	90	35	1201	5222	203
11j	538	3071	>10000	606	26	940	3825	206
10h	267	481	>10000	20	3364	1883	>10000	69
11h	729	797	2440	21	2785	2916	>10000	76
10f	4999	801	3274	2193	250	1266	2935	755
11f	3594	43	2496	1175	163	977	970	357
10i	3248	3979	>10000	35	67	1186	8875	66
11i	1742	6245	>10000	1006	78	777	7090	98
10c	1805	1246	>10000	3.8	195	372	4955	56
11c	2346	1270	9027	19	104	437	3248	42
Clozapine	94.4	531	248	695	9.0	12.5	9.8	74.6
Olanzapine	98.4	175	200	9313	7.4	17.1	11.6	598

in the binding activities for D_3, $5HT_{2a}$ and $5HT_7$ (**8d** and **10d**). These substitution patterns also override the selectivity for $5HT_{2a}$ 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 $5HT_{1a}$ while selectivity for few other sub-types becomes worse. When the *para*-position of the phenyl ring was substituted, binding activity for $5HT_{1a}$ became weak while the activity for $5HT_{2a}$ 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 $5HT_{2a}$ 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 $5HT_{2a}$ with chain length of four (**8f** and **9f**). Based on these results, we could draw a pharmacophore map for $5HT_{1a}$ or $5HT_{2a}$ 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 $5HT_{1a}$ or $5HT_{2a}$ and compounds with selective binding to sets of two receptors $5HT_{1a}$-$5HT_{2a}$ and $5HT_{1a}$-$5HT_7$ were identified.

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8. The binding activity was determined by measuring the ability of receptors to displace radioligand [^{3}H]spiperone for D_2, D_3 and [^{3}H]YM-09151-2 for D_4 from the cloned human dopamine receptors D_2Long, D_3 and $D_{4.2}$ which were stably expressed in CHO cells. For serotonin receptors, compounds were evaluated against human recombinant $5HT_{1a}$, $5HT_{2a}$, $5HT_{2C}$, $5HT_6$ and $5HT_7$ receptors stably expressed by CHO-K1 cell lines through [^{3}H]8-OH-DPAT, [^{3}H]Ketanserin, [^{3}H]Mesulergine and [^{3}H]LSD binding assay, respectively.