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SAR of Novel Biarylmethylamine Dopamine D_4 Receptor Ligands

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Abstract: SAR for a novel series of dopamine D_4 receptor ligands is shown. Very selective, highly potent compounds like 1-(2-pyrimidinyl)-4-(3-(3-thienyl)-benzyl)-piperazine (**5f**) and 2-(4-(1-fluorenylmethyl)-1-piperazinyl)-pyrimidine (**8c**) were obtained.

With a prevalence of 1% schizophrenia is a very severe psychiatric disease. The affected individuals experience hallucinations, delusions, disorganized thoughts and behavior, resulting in a major impairment of their normal social and economic function. Classical antipsychotics such as haloperidol are effective in treating schizophrenic patients. However, they cause severe side effects such as extrapyramidal symptoms and tardive dyskinesia. These side effects are mainly attributed to a blockade of dopamine receptors in the striatum. Recently, the D_4 receptor was cloned.[1] Its distribution throughout the brain differs from that of the D_2 receptor. Thus, the D_4 receptor is localized primarily in areas other than the striatum, such as the frontal cortex. Furthermore the D_4 receptor seems to be upregulated in schizophrenic brains although this is still under debate.[2] Together with the fact that the atypical antipsychotic clozapine expresses a certain selectivity towards the D_4 receptor over the D_2 receptor this has caused a lot of interest in this particular research area and some selective ligands were found.[3]

We screened our in-house compound collection and identified a biarylmethylamine (**3a**) as a ligand for the D_4 receptor with nanomolar affinity. Here we report structure activity relationships for this class of compounds.

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At first, we investigated the influence of the nature of the arylpiperazine on the affinity towards dopamine receptors. Chemistry was carried out in a straightforward manner by reacting biarylmethyl chloride **1a** with arylpiperazines **2** to give biarylmethylamines **3** (Scheme 1). Yields were generally in the 30 to 70% range.

A wide variety of arylpiperazines **2** were reacted. Selected examples are shown in Table 1. Unfortunately, none of the variations resulted in improvement of affinity and selectivity towards the D_4 receptor.[4]

It is interesting to note, however, that by changing the biarylmethyl chloride from **1a** to **1b** the 5-HT_{1A} affinity could be decreased with little effect on the affinities towards the dopamine receptors (compare **3a** and **3g**).

Scheme 1

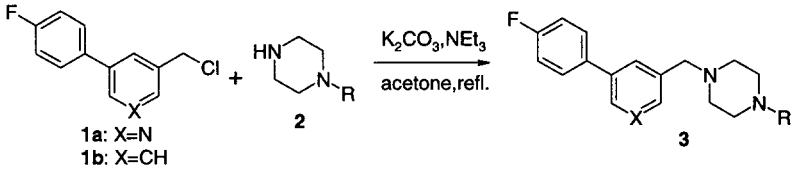
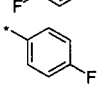


Table 1. Variation of the arylpiperazine substituent. IC_{50} values are given in nM.

Cpd.	X	R	D_2	D_3	D_4	5-HT_{1A}
3a	N		120	150	7,9	100
3b	N		450	480	25	400
3c	N		60	300	7	10
3d	N		25	8	3,7	20
3e	N		70	200	8	400
3f	N		23	33	6	70
3g	CH		49	59	2,7	700

Then a series of compounds **5a-f** was prepared by coupling reactions on bromide **4**. Suzuki coupling reactions were performed with the commercially available boronic acids. In other cases we used the appropriate arylzinc bromides in the presence of a Pd(II) catalyst (Scheme 2).[5] Arylzinc bromides were generated *in situ* from either Grignard reagents or aryl lithium compounds. The aryl lithium compounds were obtained by either halogen

metal exchange or by ortho metallation. Yields of final products ranged from 30% (not optimized) to 95% based on **4**.[6]

Scheme 2

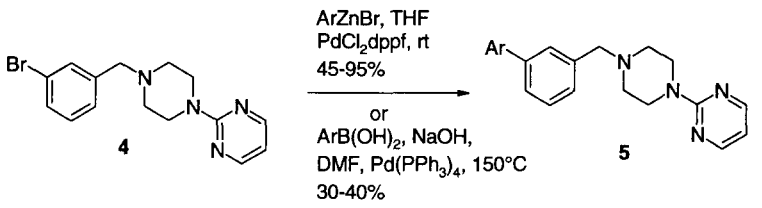
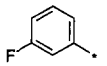
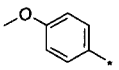
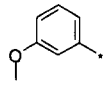
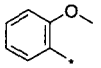


Table 2. Variation of the biaryl moiety. IC_{50} values are given in nM.

Cpd.	R	D_2	D_3	D_4	5-HT_{1A}
5a		81	200	4,9	300
5b		250	320	8	900
5c		50	72	57	2000
5d		490	1100	17	700
5e		360	710	16	300
5f		300	200	3,6	600

In Table 2 it is shown that moving the fluorine substituent from the *para* position (**3g**) to the *meta* (**5a**) or *ortho* position (**5b**) increased selectivity towards the D_4 receptor. In the case of the methoxy substituent the same trend was also found although affinities were slightly lower (**5c-5e**). By introducing 3-thiophene in the position of the terminal aromatic moiety (**5f**) a compound with high affinity and high selectivity towards the D_4 receptor was found.[7]

Conformationally restricted biaryl moieties were introduced by the reaction of 4-chloromethyl-dibenzothiophene(**6a**), 4-chloromethyldibenzofuran (**6b**) or chloromethyl-9*H*-fluorenes (**6c-6f**) with 2-piperazin-1-yl-pyrimidine (**7**) to give products **8a-f** (Scheme 3). Compounds **6a** and **6b** were obtained by orthometallation of dibenzothiophene and dibenzofurane, respectively, followed by reaction with formaldehyde[8] and conversion of

the resulting alcohol into the corresponding chloride. The chloromethylfluorenes (**6c-6f**) were obtained by reduction of the corresponding carboxylic acids or aldehydes and reaction of the resulting alcohols with thionylchloride.

Scheme 3

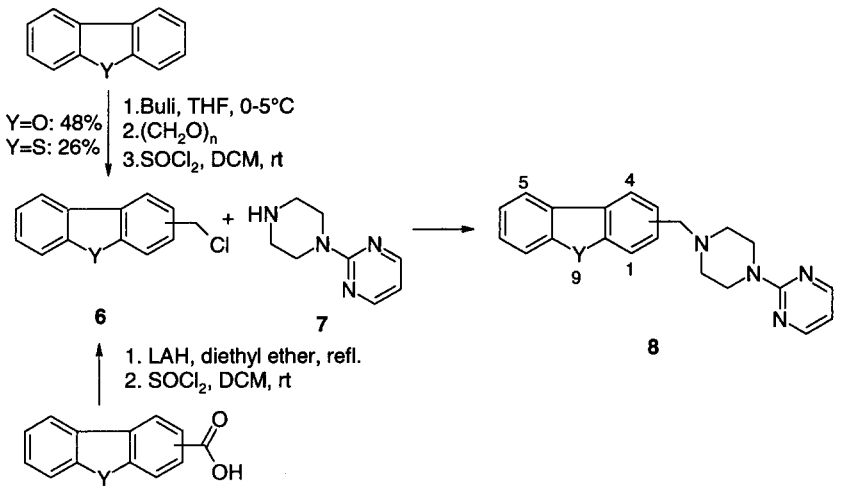
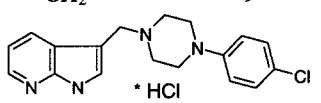
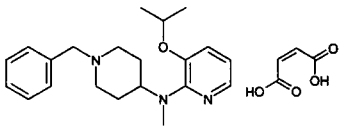


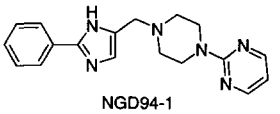
Table 3. Introduction of conformationally restricted biaryls. Affinities are given in either IC_{50} values (nM) or percent inhibition of control at 100nM concentration.

Cpd.	Y	position of attachment.	D_2	D_3	D_4	5-HT_{1A}
8a	S	1[a]	97%	101%	87%	>100
8b	O	1[a]	94%	91%	290	>100
8c	CH_2	1	9800	5600	20	>10000
8d	CH_2	2	89%	91%	87%	>100
8e	CH_2	4	2300	4000	4800	>100
8f	CH_2	9	100%	95%	99%	>100
L-745,870			360	80	1,5	>1000
U101 958			620	5500	5,8	>1000

a) numbering does not conform with IUPAC standards.

Neither the dibenzothiophene **8a** nor the dibenzofurane **8b** displayed affinity towards any of the dopamine receptors. Surprisingly, however, compound **8c** was found to be a very selective D_4 ligand although its potency was not high.[9] The position of the methylamine on the fluorene was found to be crucial as shown by the low affinties of **8d-8f** as compared to **8c**.

In summary, starting from the lead compound **3a**, we developed D_4 ligands with selectivity and potency which are at least comparable to the reference compounds **L-745,870** and **U101 958**. Compounds **5f** and **8c**[10] were found inactive ex vivo for dopamine turnover and *in vivo* in animal models indicative for antipsychotic activity.[11] Reports on the effects of selective D_4 antagonists are rare. So far only **YM-43611** shows an effect in the inhibition of climbing behavior in mice.[12] **NGD94-1** did not affect apomorphine induced stereotyped behavior in rats nor did it induce catalepsy.[13] Likewise, **L-745,870** and **U101 958** had no effects on dopamine turnover or in common animal models.[14] A substantial antipsychotic effect in animal models has not yet been proven and the early clinical experience with D_4 selective drugs -if published at all- is disappointing so far.[15]



NGD94-1

References and Notes

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4. General biochemical methods: Cloned human dopamine receptors, expressed in either A9L cells (D_2) or CHO cells (D_3 and $D_{4.2}$) were used to test the affinity of the compounds to dopamine receptors. ^{3}H-Spiperone, specific radioactivity 3.6 TBq/mmol, was used as ligand at a final concentration of about 0.15 nM; assays were run in 50 mM Tris buffer, pH=7.5. To test the 5-HT_{1A} affinity rat hippocampus

membranes (0.2 mg protein/tube) were incubated with 0.5 nM ^{3}H-8-OH-DPAT in a total volume of 0.5 ml at 25 °C for 30 min. Nonspecific binding was determined in the presence of 1 μM 8-OH-DPAT.

5. Overview: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

6. A typical experiment is described for the synthesis of **5a**: To a solution of 1.8g (7.6 mmol) of dried $ZnBr_2$ in 10 ml of THF was added a solution of 3-fluorophenylmagnesiumbromide in 5ml of THF (prepared from 0.83 ml of 3-fluorobromobenzene and 200mg (7.6 mmol) of magnesium turnings) at -20°C. After cooling to -50°C with stirring were added 11.2 mg (15.2 μmol) of $PdCl_2$dppf and 500 mg of **4**. Cooling was removed and the mixture was stirred at room temperature for 2h after which **4** could not be detected anymore by T.L.C.. The mixture was acidified with 1M HCl and extracted with ethyl acetate. The aqueous layer was then brought to basic pH by addition of 40% NaOH and extracted twice with ethyl acetate. The organic layers of the last two extractions were dried with $MgSO_4$, evaporated and the residue was purified by column chromatography (cyclohexane/diethylether 1:1). 500mg (94%) of **5a** were obtained. For biochemical testing compounds were precipitated as maleates or hydrochlorides.
Purities of compounds **3**, **5** and **8** were assessed by combustion analysis of the corresponding maleates or hydrochlorides and by T.L.C. or RP-HPLC of the free bases.

7. **5f** (maleate) m.p.: 208°C; EI-MS: 336 (M^+); ^{1}H-NMR (250 MHz, [D_4]DMSO) δ: 3.65-4.25 (m, 8H), 6.10 (s, 2H), 6.72 (t, 2H), 7.30-7.60 (m, 5H), 8.40 (d, 2H). Spectra of all compounds **3**, **5** and **8** were in accordance with the assigned structures.

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9. **8c** (maleate) m.p.: 218°C; EI-MS: 342 (M^+); ^{1}H-NMR (250 MHz, [D_4]DMSO) δ: 2.60-4.40 (m, 8H), 4,05 (s, 2H), 6.10 (s, 2H), 6.73 (t, 1H), 7.30-7.70 (m, 5H), 7.77-8.00 (m, 2H), 8.39 (d, 2H).

10. Affinites to 5-$HT_{1B/D}$, 5-HT_{2A}, 5-HT_{2C}, D_1, H_1, α_1 receptors were greater than 1000 nM for **5f** and **8c**.

11. **5f** and **8c** were tested in apomorphine induced climbing in mice (*s.c.*) and apomorphine induced stereotypies in rats (*s.c.*). Compounds **5f** and **8c** had halflifes of 0.7h and 0.4h, respectively, after *i.v.* administration in rats. Brain plasma ratios were 2-5, thus, indicating good blood brain barrier penetration properties.

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