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New 1-Aryl-4-(biarylmethylene)piperazines as Potential Atypical Antipsychotics Sharing Dopamine D_2-Receptor and Serotonin 5-HT_{1A}-Receptor Affinities

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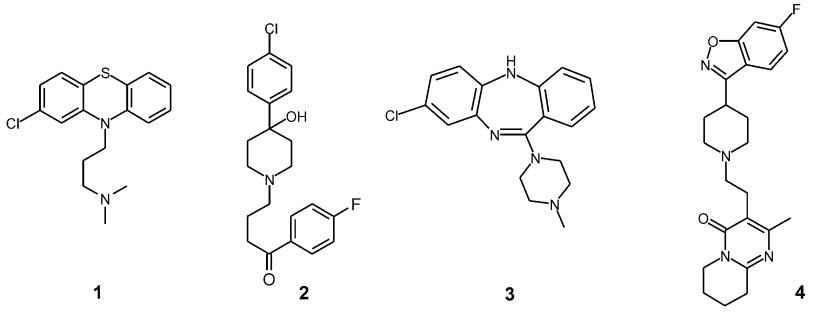
Abstract—This paper describes the syntheses of several 1-aryl-4-(biarylmethylene)piperazines and the results of the determination of their affinity for D_2 and 5-HT_{1A} receptors. A selection of these compounds was evaluated in vivo, resulting in the identification of a drug candidate which is being clinically evaluated as a potential atypical antipsychotic with reduced extrapyrimidal side effects.

Schizophrenia is a disease of which the etiology is unknown. The disease is characterized by the so-called positive and negative symptoms. Positive symptoms include hallucinations and paranoia. The most characteristic negative symptoms are social withdrawal and flattening of the personality. On top of that both cognitive as well as depressive symptoms may occur. After the serendipitous discovery of chlorpromazine **1** decades ago, several compounds, most commonly referred to as 'neuroleptics', have been developed which showed antipsychotic activity in the clinic. Of those, haloperidol **2** is the best known example. These compounds predominantly alleviate the positive symptoms by attenuating the dopaminergic neurotransmission system in the mesolimbic area of the brain. Therapy with these types of compounds is frequently accompanied by extrapyramidal side effects (EPS) resulting from a blockade of dopaminergic activity within the motor areas of the brain. Thus, about 20% of the treated patients suffer from EPS, of which Parkinson like symptoms are most common. Other side effects of these 'typical' neuroleptics include tardive dyskinesia and hyperprolactinemea. There is a strong need for compounds which induce less side effects and, equally important, also treat the other than positive symptoms of schizophrenia. An example of a successful attempt to reduce EPS and obtain broader efficacy in treating schizophrenia is clozapine **3**, a dopamine antagonist with modest potency. Clozapine shows affinity for several receptors, especially for serotonin receptor subtypes, which may account for the beneficial effect against negative symptoms.[1,2] For this reason, clozapine is termed an 'atypical' neuroleptic. Combining dopaminergic and serotonergic actitivity may be the way to develop atypical antipsychotics,[3] a rather recent example being risperidone **4**, which is known for binding to the dopamine D_2 and serotonin



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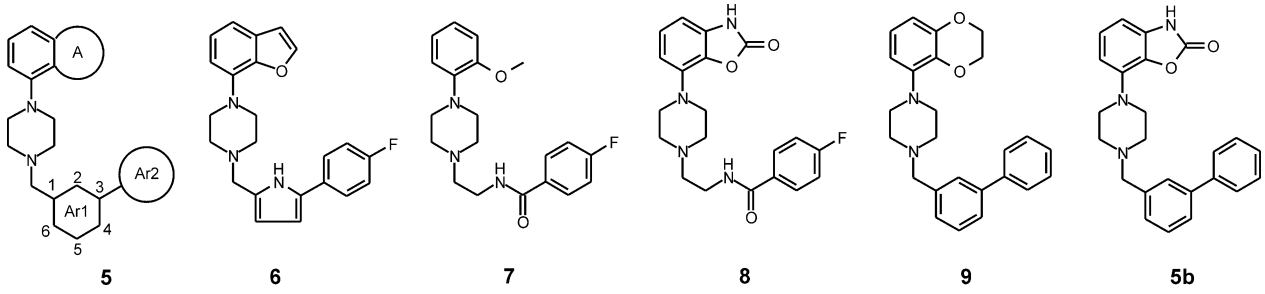
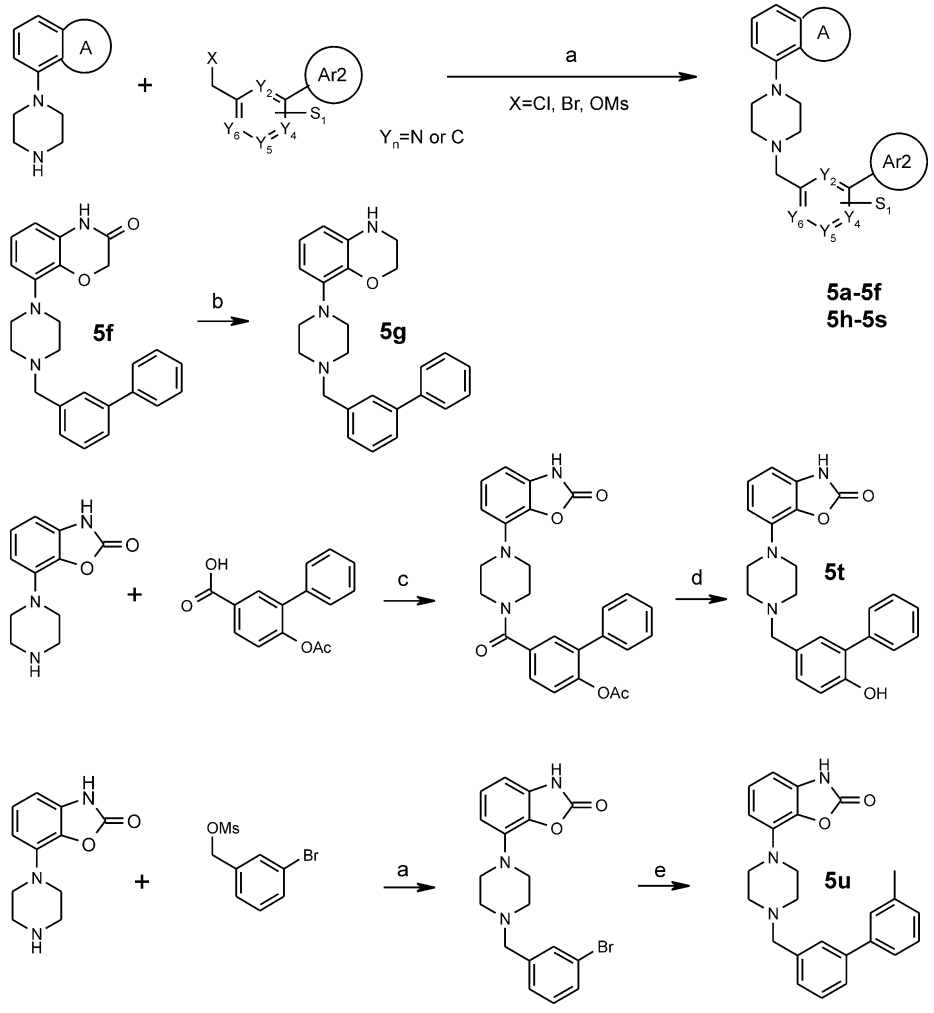
5-HT_{2A} receptors. This report focuses on compounds of type **5** which share affinity for dopamine D_2 as well as serotonin 5-HT_{1A} receptors.

The rationale behind the combination D_2 and 5-HT_{1A} is based on several preclinical data, supporting the hypothesis that selective 5-HT_{1A} receptor agonists are capable of antagonizing neuroleptic-induced EPS in animal models; for example, 8-hydroxy-2-(di-*n*-propylamino) tetralin [8-(OH)-DPAT] is capable of antagonizing haloperidol induced catalepsy in rats, attenuates the neuroleptic induced dystonia in nonhuman primates,[4] and reduces the forelimb retraction time in the paw test.[5]

In a previous study, we described phenylpyrroles like **6**,[6,7] which can be considered to be conformationally restricted derivatives of the known D_2 antagonist benzamides like **7**[6] and **8**;[16] **6** retains a high affinity for the D_2 receptor (K_i 0.42 nM). Later on, **6** turned out to be a very potent ligand on the serotonin 5-HT_{1A} receptor as well (K_i 1.5 nM). To elaborate on this structural class, we investigated the importance of the pyrrole NH





Scheme 1. Reagents and conditions.[8,9] (a) Et(*i*-Pr)$_2$N, KI, CH_3CN, reflux; (b) $LiAlH_4$, THF, reflux; (c) acid + DCC/HOBT, THF, 0 °C, piperazine; (d) $NaBH_3OAc$, dimethylethyleneglycol, 80 °C; (e) 3-Me-phenylboronic acid, Na_2CO_3/H_2O, $(PPh_3)_4Pd$, toluene, 85 °C.

moiety of **6** by testing its biphenyl analogue compound **9**. Surprisingly, **9** displayed K_i's of 1.7 and 0.91 nM for the D_2 receptor and 5-HT_{1A} receptor, respectively. In conclusion, the pyrrole NH moiety is apparently not essential for binding on the two receptors. Combining **8** and **9** resulted in the design of molecule **5b** which not only showed high affinities for the D_2 and 5-HT_{1A} receptors (2.2 nM and 9.3 nM, respectively), but favourable pharmacokinetic properties as well. To further explore this molecule **5b**, an additional 20 compounds were synthesized and evaluated for their pharmacological properties.

Chemistry

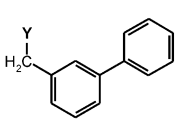
The synthesis of compounds **5** is depicted in Scheme 1.

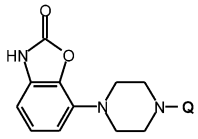
Most of the compounds **5** were prepared by reacting an arylpiperazine and a biarylmethyl chloride, bromide or mesylate in the presence of Et(*i*-Pr)$_2$N and KI in acetonitrile at reflux temperature. Yields of **5** ranged from approximately 45 to 95%. Compound **5g** was prepared from **5f** in 58% yield by reacting the latter with $LiAlH_4$ in refluxing THF. **5t** was prepared by reacting in THF the biaryl carboxylic acid and DCC/HOBT at 0 °C in THF and subsequent addition of the aryl piperazine, yielding the corresponding piperazinamide which could be reduced with $NaBH_3OAc$ in dimethylethyleneglycol to obtain **5t** in 41%. **5u** was prepared by reacting the phenyl piperazine and *O*-mesyl-3-bromobenzylalcohol yielding the corresponding *N*-(3-bromobenzyl) piperazine, the latter being cross coupled (Suzuki) to 3-methyl-phenylboronic acid to afford the desired **5u**. Most of compounds **5** were converted into their mono- or di-HCl salts by treatment with HCl/EtOH. The details of the syntheses are described in the corresponding patents.[8,9] In Table 1 the compounds **5** are depicted.

Results and Discussion

The affinities of compounds (**5**) for dopamine D_2 and the serotonin 5-HT_{1A} receptors were measured using

Table 1.





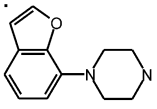
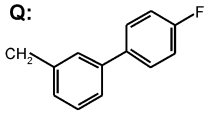
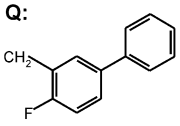
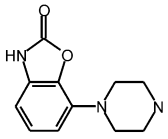
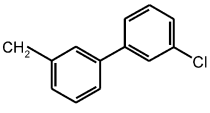
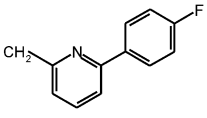
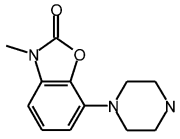
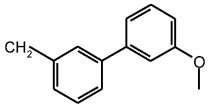
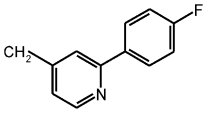
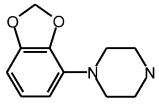
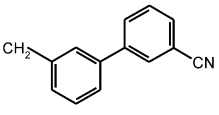
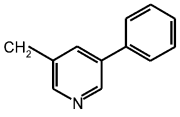
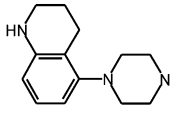
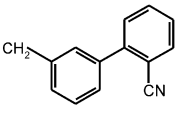
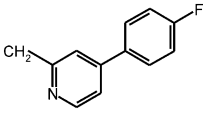
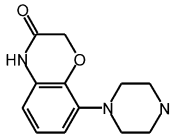
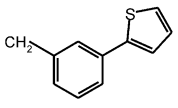
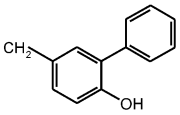
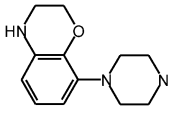
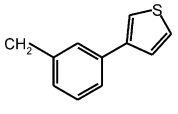
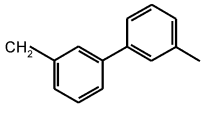
Y:	Compound	Q:	Compound	Q:	Compound
	**5a**		**5h**		**5o**
	**5b**		**5i**		**5p**
	**5c**		**5j**		**5q**
	**5d**		**5k**		**5r**
	**5e**		**5l**		**5s**
	**5f**		**5m**		**5t**
	**5g**		**5n**		**5u**

Table 2. Affinities for D_2 and 5-HT_{1A} receptors (K_i, nM)

Compounds	x HCl	D_2 (nM)[10]	5-HT_{1A} (nM)[11]
2	0	1.4	2800
3	0	69	270
4	0	3.1[15]	253[15]
6	0	0.42	1.5
7	1	5.0	1.0
8	0	4.6	7.9
9	2	1.7	0.91
5a	2	8.1	38
5b	1	2.2	9.3
5c	1	10	130
5d	1	10	15
5e	2	4.0	85
5f	0	1.0	49
5g	1	0.93	26
5h	1	8.1	14
5i	1	18	42
5j	2	10	21
5k	1	6.0	23
5l	1	2.0	32
5m	1	2.2	32
5n	0	1.3	17
5o	1	12	41
5p	0	3.0	200
5q	0	2.9	21
5r	0	1.8	7.8
5s	2	0.47	16
5t	1	0.41	7.6
5u	1	9.3	35

K_i values are based on three assays, each using 4–6 concentrations in triplicate.

[^{3}H]-spiperone[10] and [^{3}H]-8-OH-DPAT, respectively.[11] In Table 2, affinities of **5** for both receptors are given expressed as K_i (calculated from at least three independent experiments). In the first series (i.e., **5a**, **5c**–**5g**) the heterocyclic ring A was varied. In comparison to **5b** no improvement on D_2- and 5-HT_{1A}-receptor affinity was established in the case of only oxygen containing heterocyclic rings (**5a**, **5d**). *N*-Methylation (**5c**) turned out to be detrimental for the 5-HT_{1A} affinity, indicating that the N–H function appears to be essential. Enlargement of the heterocyclic ring of **5b** by only one CH_2 (**5f**), resulted in an increased affinity for the D_2 receptor, but in a decreased affinity for the 5HT_{1A} receptor. Similar effects are encountered for **5g** in which the carbonyl function of the amide moiety in **5f** is reduced to CH_2. Compound **5e**, which is structurally related to **5g**, shows a smaller potency for the 5-HT_{1A} receptor, whilst the D_2 affinity is acceptable. In conclusion, the benzoxazolinone moiety as presented in **5b** is superior for achieving high potency on both receptors.

In the second series (i.e., **5h**–**5u**), the biphenylmethylene part of **5b** was varied by introducing substituents and other aromatic rings. In compounds **5h**–**5l** and **5u**, effects of simple substituents on Ar2 were studied. A F-atom at the 4′-position slightly decreased both affinities **5h**; substitution at the 3′-position by groups differing in electronegativity like Cl, MeO, CN and Me (**5i**, **5j**, **5k** and **5u**, respectively) again gave no improvement in receptor affinities with regard to **5b**. Substitution at the 2′-position with the CN group **5l** resulted in a somewhat higher potency on the D_2 receptor, but unfortunately the 5-HT_{1A} receptor affinity decreased. Compounds having thienyl- instead of phenyl groups for Ar2 (**5m**, **5n**) showed high affinities on the D_2 receptor, and somewhat lower affinities on the 5-HT_{1A} receptor compared to **5b**.

Table 3. In vivo test results (ED_{50}, mg/kg)

Compounds	Climbing behaviour (mg/kg) po	CAR (mg/kg)		LLR (mg/kg) po
		ip	po	
2	0.2		0.3	
3	22		32	
4	0.1		1	
5b	0.1		0.8	10
5n	0.2	>20		>30
5r	0.1		0.4	3
5s	0.1		<10	>30
5t	7	20		>30

ED_{50} values are based on at least three dose levels.

In compounds **5o** and **5t**, effects of simple substituents on Ar1 were studied. Introduction of a F-atom at the 6-position (**5o**) lowered both affinities; a hydroxy substituent at the 4-position (**5t**) showed higher affinities, especially at the D_2 receptor. Compounds having a pyridyl instead of phenyl group for Ar1 (**5p**–**5s**), showed interesting features; all four showed comparable or higher affinities for the D_2 receptor and, in addition, **5r** also displayed a comparable affinity towards the 5-HT_{1A} receptor.

The most interesting compounds were assayed in models relevant for antipsychotic activity: inhibition of the apomorphine-induced climbing behavior in mice[12] and the suppression of the conditioned avoidance response in rats.[13] To assay the 5-HT_{1A} agonistic component in vivo, the compounds were tested for occurrence of so-called lower lip retraction (LLR).[14] The results are given in Table 3. Compound **5n** is potently active in antagonizing apomorphine-induced climbing behavior in mice, but no activity could be measured in the rat (CAR and LLR). Compounds **5b** and **5r** show promising results in all models with ED_{50} values in the D_2 antagonist related models below 1 mg/kg and in the LLR model between 1 and 10 mg/kg after oral administration. Compounds **5s** and **5t** showed no 5-HT_{1A} related activity (po) in the rat models. On the basis of broad preclinical profiling, **5b** was selected for further clinical development. More pharmacological details are expected to be published soon.

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