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Studies towards the identification of a new generation of atypical antipsychotic agents

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Abstract—A rational structure–activity relationship study around compound (**1**) is reported. The lead optimisation programme led to the identification of sulfonamide (**25**), a molecule combining dopamine D_2/D_3 receptor antagonism with serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 receptor antagonism for an effective treatment of schizophrenia. Compound (**25**) was shown to possess the required in vivo activity with no EPS liability.

Schizophrenia is a severe psychiatric disorder affecting approximately 1.5% of the world population.[1] Diagnostic features of schizophrenia include positive symptoms (auditory hallucinations, disorganised thoughts and delusions), negative symptoms (social withdrawal, lack of motivation) and cognitive dysfunction (disorganised thinking, memory impairments).[2] One of the consequences of this debilitating illness is the high rate of suicide in patients affected by the disease.[3]

The pathophysiology of this complex and uniquely human disorder is believed to be associated with dopaminergic hyperactivity in the mesolimbic system of the brain.[4] Both first generation, typical antipsychotics (e.g., Haloperidol)[2,4,5] and newer atypical antipsychotics (e.g., Olanzapine and Aripiprazole)[6,7] modulate dopaminergic hyperactivity either by post-synaptic dopamine D_2 receptor antagonism[1] and/or partial agonism[8] at pre-synaptic dopamine D_2 receptors. Unfortunately, negative symptoms and cognitive impairment are not fully addressed by these two classes of drugs. Additionally, their broad receptor interaction profiles (affinities at up to 15 different neurotransmitter receptors)[9] may be responsible for side-effects, including sedation, hypotension, weight gain, movement disorders and seizures.[1,2]

An analysis of the receptor interaction profile of marketed antipsychotics[10,11] led to the identification of five key receptors for selective antagonism, D_3, D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 (Table 1) that should provide effective treatment of the disease alongside a reduced side-effect liability. Thus, dopamine D_2/D_3 receptor antagonism[12] is important for treatment of positive symptoms of schizophrenia; 5-HT_{2A} receptor antagonism is believed to contribute to an atypical antipsychotic profile;[13] 5-HT_{2C} receptor blockade has been reported to counteract dopamine D_2-mediated extra-pyramidal side-effects (EPS)[14] and may also confer anxiolytic/antidepressant properties;[15] 5-HT_6 receptor antagonism may address cognitive deficits.[16] Equally important for the identification of a superior antipsychotic drug is the exclusion of

Keywords: Dopamine; Serotonin; Antagonist; Sulfonamide; Benzazepine; Atypical; Antipsychotic; Schizophrenia.
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Table 1. Target profile

Receptor	pK_i	Beneficial effect from receptor antagonism
D_3	>8	Antipsychotic activity (treatment of positive and negative symptoms)
D_2	7–8[a]	
5-HT_{2A}	>8	Contributes to antipsychotic activity and atypicality
5-HT_{2C}	>8	Counteracts D_2-mediated extrapyramidal side-effect (EPS) Anxiolytic effect Antidepressant effect
5-HT_6	>8	Addresses cognitive deficits

[a] A slightly lower target affinity at the D_2 receptor was chosen in order to minimize the risk of D_2-mediated side-effects that occur at high levels of receptor occupancy.[17]

receptor interactions that may lead to unwanted side-effects and consequently impaired efficacy via reduced compliance.

In 2001 we embarked on a research programme at GlaxoSmithKline to discover novel chemical entities with the above profile (Table 1). Cross screening identified molecule (**1**) in Figure 1, a lead compound with many of the desired affinities, and with a structure which was particularly suitable for high-throughput array chemistry.

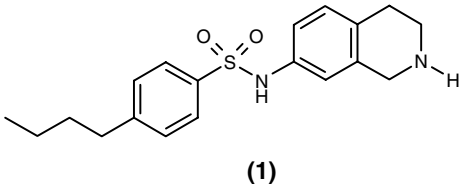
The main focus of our SAR study was to bring affinities of (**1**) to target levels at our panel of five key receptors (Table 1) and to identify compounds for further progression.

Examination of lead molecule (**1**) led us to focus on three main areas for structural manipulation: the aryl substituent (Ar), substitution (X) in the core benzene ring and the ring size in the right-hand side of molecule (**5**). The general synthetic process is highlighted in Scheme 1: sulfonamides (**5**) were synthesised by coupling sulfonyl chlorides (**2**) with the anilines (**3**) to afford intermediates (**4**) that were deprotected to yield target molecules (**5a**; R = H); sulfonamides (**5b**; R = methyl) were prepared by reductive alkylation of the basic nitrogen using formaldehyde and sodium triacetoxyborohydride.[18]

The first step in our lead optimisation programme aimed to examine the effect of the benzofused ring size and the alkylation effect of the basic nitrogen. Thus, three different ring systems were explored: the five (isoindoline), the six (tetrahydroisoquinoline) and the seven (benzazepine) membered rings as shown in Table 2.

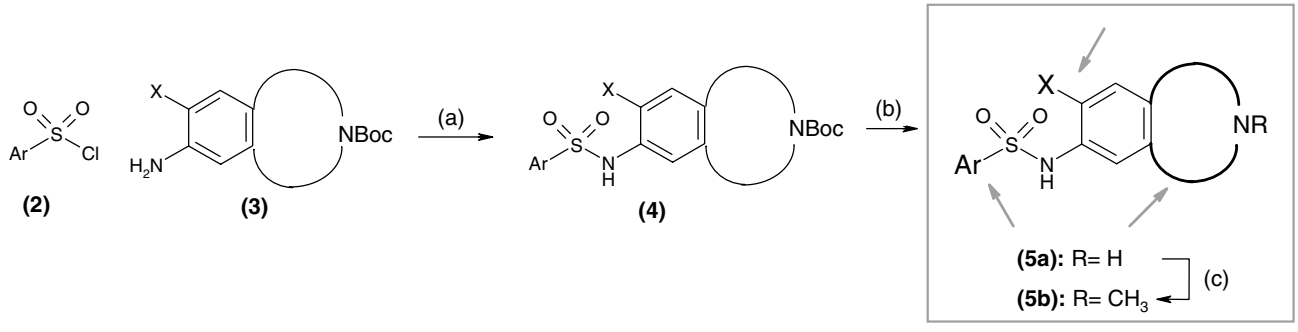
Primary receptor binding screening was based upon inhibition of radioligand binding to recombinant human dopamine D_3, D_2, receptors[19] and serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptors,[20] which provided the pK_i values reported in the tables.

An analysis of the three ring systems in (**6**), (**8**) and (**10**) reported in Table 2 indicates that the benzazepine (**10**) possesses the best overall receptor binding profile for both dopamine and serotonin receptors. Methylation of the basic nitrogen had a marked beneficial effect for five- and seven-membered ring systems only: in particular from compounds (**10**) to (**11**), the receptor binding profile was improved for dopamine D_2, D_3, and for serotonin 5-HT_{2A} and 5-HT_{2C} with a slight increase in 5-HT_6 affinity. Other substituents on the benzazepine nitrogen (e.g., ethyl, isopropyl and benzyl) did not bring dopamine and/or serotonin receptor affinities up to the desired target levels. Overall, compound (**11**) was the



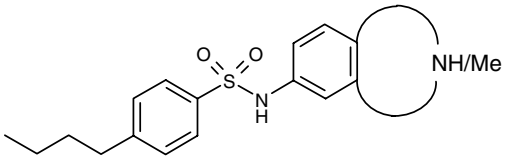
pKi: D_3 = 8.0
D_2 = 6.0
5-HT_{2A} = 7.9
5-HT_{2C} = 7.5
5-HT_6 = 7.6

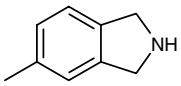
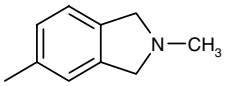
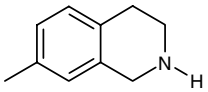
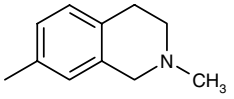
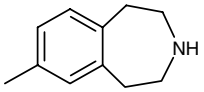
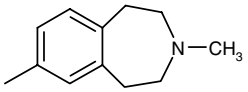
Figure 1. Lead molecule sulfonamide (**1**).



Scheme 1. General synthetic scheme and reaction conditions (a,b)[18] for the preparation of sulfonamide type (**5**). The arrows point out the areas involved in the SAR exploration.

Table 2. Effect of ring size and nitrogen alkylation in the right-hand side of the molecule



Compound	Ring system	pK_i[a]				
		D_3	D_2	5-HT_{2A}	5-HT_{2C}	5-HT_6
(**6**)		7.4 ± 0.08	6.1 ± 0.13	nd[b]	nd[b]	7.3 ± 0.05
(**7**)		7.7 ± 0.04	6.7 ± 0.02	8.3 ± 0.03	8.0 ± 0.03	8.3 ± 0.01
(**8**)		7.9 ± 0.04	6.1 ± 0.09	7.9 ± 0.02	7.5 ± 0.03	7.6 ± 0.1
(**9**)		7.6 ± 0.04	6.4 ± 0.06	nd[b]	nd[b]	nd[b]
(**10**)		7.8 ± 0.00	6.8 ± 0.01	7.8 ± 0.03	7.3 ± 0.03	8.7 ± 0.07
(**11**)		8.7 ± 0.05	7.5 ± 0.14	8.3 ± 0.10	8.0 ± 0.07	8.9 ± 0.03

[a] pK_i values represent means of at least three determinations for each compound reported in the table.
[b] Not determined.

best molecule in this series displaying the required target profile (Table 1) at all five key receptors.

Although possessing the desired in vitro profile, lead compound (**11**) showed high blood clearance (81 mL/min/kg) and major P450 liabilities (see Table 5) presumably due to metabolism taking place at the extended alkyl chain. In order to obviate this problem, the *n*-butyl group was replaced with a range of aryl substituents (Table 3) to endeavour to improve PK properties while maintaining the desired receptor profile.

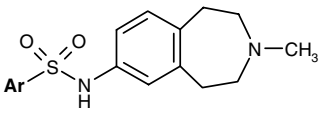
Encouragingly, replacement of the butyl side chain with the 4-chlorophenyl substituent in (**12**) retains many of the desired activities, although the 5-HT_{2A} receptor affinity is considerably reduced. Compound (**13**) has a broadly similar profile. Substitution of the outer ring with the more polar cyano group in (**14**) reduced affinity at all five receptors. Substitution of the inner benzene ring with a methyl group, in (**15**), gave a slight increase for dopamine D_2 and serotonin 5-HT_{2C} receptors but it did not have any effect on 5-HT_{2A}. When the inner ring was replaced with a five-membered ring in (**16**) changing the geometry of the molecule, only 5-HT_6 receptor binding held up. Heterocycles replacing the outer benzene ring in (**17**) and (**18**) led to a drop in potency across the whole set of receptors.

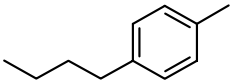
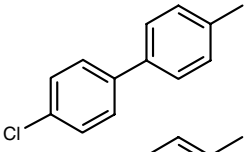
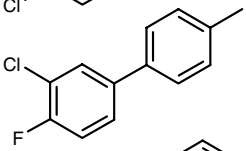
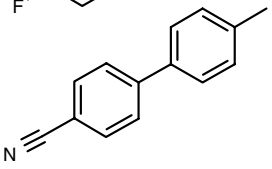
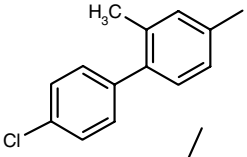
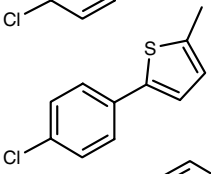
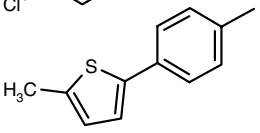
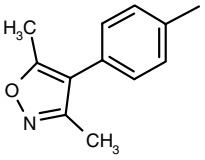
Further SAR exploration focussed on substitution at 8-position of the benzazepine aromatic ring to endeavour to further improve the in vitro profile of molecule (**12**).

The methyl group at the 8-position in (**19**, Table 4) improved both dopamine and 5-HT_{2A} receptor binding, but was detrimental for 5-HT_{2C} and 5-HT_6 receptor affinities. Increasing the bulk of the eight-substituent by the isopropyl group (**20**) lowered D_3 and D_2 receptor affinities, with a slight increase for 5-HT_{2C} receptor. Bulky halogens at the 8-position in (**21**) and (**22**) enhanced dopamine D_3 profile but were detrimental for 5-HT_6 receptor affinity. Interestingly, the chloro analogue (**22**) was beneficial for 5-HT_{2A} receptor affinity and had a slightly better overall profile compared to the bromo analogue (**21**).

Of major importance were alkoxy substituted derivatives (**23**) and (**24**) which displayed a significant increase in D_2, D_3 and 5-HT_{2A} receptor affinities. Unfortunately, the D_2 receptor affinity for these two compounds had extended outside our target range (Table 1). However, the best overall receptor binding

Table 3. Left-hand side modifications



Compound	Ar	pK_i[a]				
		D_3	D_2	5-HT_{2A}	5-HT_{2C}	5-HT_6
(**11**)		8.7 ± 0.05	7.5 ± 0.14	8.3 ± 0.10	7.9 ± 0.07	8.9 ± 0.03
(**12**)		7.8 ± 0.15	6.8 ± 0.11	6.7± 0.07	7.7 ± 0.03	8.3 ± 0.05
(**13**)		8.4 ± 0.07	7.3 ± 0.09	7.3 ± 0.05	7.5 ± 0.04	8.1 ± 0.05
(**14**)		7.8 ± 0.13	6.3 ± 0.10	6.1 ± 0.14	7.0 ± 0.1	7.6 ± 0.04
(**15**)		8.2 ± 0.05	7.5 ± 002	6.9 ± 0.04	7.3 ± 0.05	8.3 ± 0.08
(**16**)		7.4 ± 0.04	6.4 ± 0.06	nd[b]	6.9 ± 0.04	8.4 ± 0.13
(**17**)		7.6 ± 0.07	6.5 ± 0.08	7.3 ± 0.02	7.9 ± 0.09	8.2 ± 0.05
(**18**)		7.8 ± 0.03	7.0 ± 0.03	5.9 ± 0.03	6.4 ± 0.10	8.0 ± 0.13

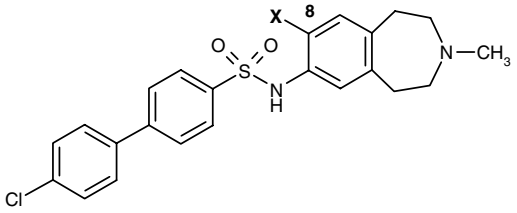
profile was achieved with the 8-dimethylamino derivative (**25**) which possessed excellent affinities at all targeted receptors.

Table 5 compares the P450 profile of the three main molecules discussed thus far: replacement of the *n*-butyl chain, in (**11**) with 4-chlorobenzene in (**12**), contributed to improve the P450 profile of the target molecule. In particular, sulfonamide (**25**) was devoid of major P450 interactions.

As compound (**25**) fulfilled all our in vitro criteria, it was progressed for further evaluation into DMPK. Encouragingly, this molecule showed a moderate blood clearance of 39 mL/min/kg, good oral bioavailability and half-life ($F = 69\%$, $t_{1/2} = 1.8$ h) and good CNS penetration (brain/blood = 3.4:1).

The synthesis[21,22] of sulfonamide (**25**) is reported in Scheme 2. Thus, 8-hydroxybenzazepine (**26**) was nitrated and reacted with triflic-chloride to afford triflate intermediate (**28**). Buchwald chemistry with dimethylamine followed by catalytic hydrogenation afforded compound (**29**). Coupling with the appropriate sulfonyl chloride and reductive alkylation with formaldehyde afforded the target material (**25**).

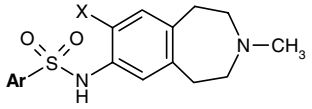
Table 4. Eight-position modifications

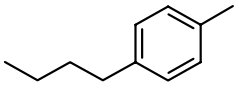
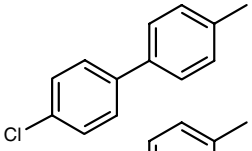
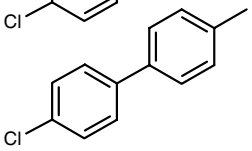


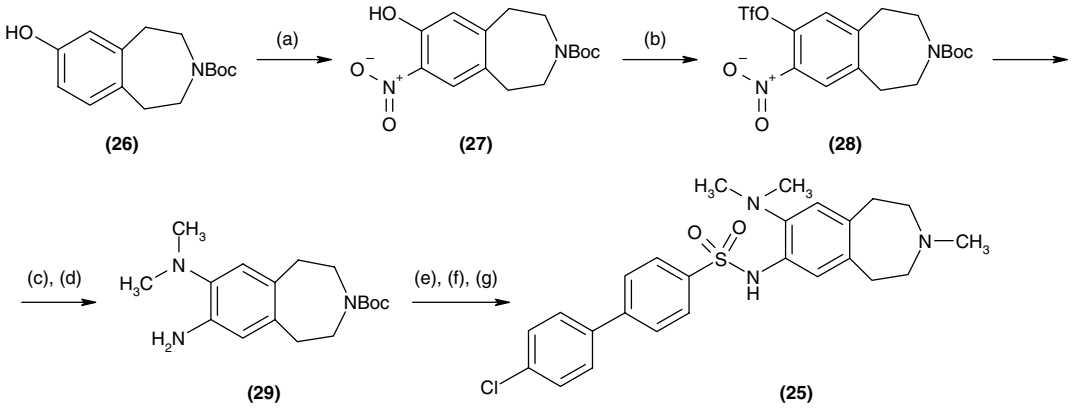
Compound	X	pK_i[a]				
		D_3	D_2	5-HT_{2A}	5-HT_{2C}	5-HT_6
(**12**)	H	8.0 ± 0.15	7.0 ± 0.11	6.7 ± 0.07	7.7 ± 0.03	8.3 ± 0.05
(**19**)	Me	8.8 ± 0.04	7.8 ± 0.04	7.7 ± 0.15	7.1 ± 0.04	7.8 ± 0.04
(**20**)	*i*-Pr	8.4 ± 0.05	7.0 ± 0.02	8.3 ± 0.11	7.8 ± 0.04	7.9 ± 0.10
(**21**)	Br	8.3 ± 0.12	7.2 ± 0.02	nd[b]	6.9 ± 0.07	7.3 ± 0.01
(**22**)	Cl	8.6 ± 0.01	7.4 ± 0.01	7.5 ± 0.06	7.4 ± 0.02	7.3 ± 0.02
(**23**)	MeO	9.1 ± 0.00	8.4 ± 0.00	7.6 ± 0.00	7.4 ± 0.01	8.0 ± 0.05
(**24**)	*i*-PrO	9.1 ± 0.03	8.2 ± 0.02	7.8 ± 0.03	7.4 ± 0.01	7.5 ± 0.09
(**25**)	NMe_2	8.5 ± 0.02	7.3 ± 0.04	8.8 ± 0.06	8.3 ± 0.02	8.1 ± 0.05

[a] pK_i values represent means of at least three determinations for each compound reported in the table.
[b] Not determined.

Table 5. Affinities (IC_{50}, μM) at cytochrome P450 isoforms



Compound	Ar	X	2C19	2C9	2D6	3A4	3A4	1A2
(**11**)		H	0.5	47	1.6	12	24	23
(**12**)		H	16	45	1.5	58	40	25
(**25**)		NMe_2	25	17	19	7.5	5.7	51



Scheme 2. Synthesis and reaction conditions (a–g)[21] for the preparation of target molecule (**25**).

In our functional assay compound (**25**) did not show any agonist activity[23] at the five key receptors; sulfonamide (**25**) was, therefore, progressed for evaluation in our in vivo pharmacodynamic model (reversal of amphetamine-induced hyperactivity in the rat),[24] where it was shown to be active with an ED_{50} of 20.6 mg/kg following oral dosing. Moreover, compound (**25**) did not show any propensity to induce catalepsy (a rat model of dopamine D_2-mediated EPS)[14] in rats at up to 100 mg/kg p.o.

In summary, we have identified a panel of five key receptors whose blockade we believe will deliver a superior antipsychotic effect. A rational SAR study around the early lead compound (**1**) led us to identify the sulfonamide (**25**), a molecule with the desired profile across dopaminergic and serotoninergic receptors and with a good DMPK profile. Furthermore, target molecule (**25**) showed in vivo activity at 20.6 mg/kg po and no EPS liability at up to 100 mg/kg po thus providing a substantial Therapeutic Index.

Further studies in this area will be the subject of a further publication.

Acknowledgment

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