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Novel sulfonamides having dual dopamine D2 and D3 receptor affinity show in vivo antipsychotic efficacy with beneficial cognitive and EPS profile

Éva Ágai-Csongor,* Katalin Nógrádi, János Galambos, István Vágó, Attila Bielik, Ildikó Magdó, Györgyi Ignácz-Szendrei, György Miklós Keserű, István Greiner, István Laszlovszky, Éva Schmidt, Béla Kiss, Katalin Sághy, Judit Laszy, István Gyertyán, Mária Zájer-Balázs, Larisza Gémesi and György Domány

Gedeon Richter Ltd, Budapest, 10. PO Box 27, H-1475, Hungary

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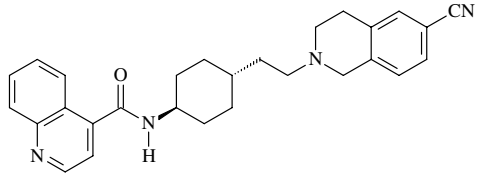
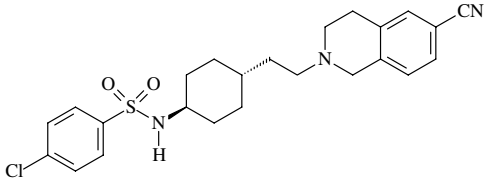
Abstract—A novel series of arylsulfonamides was prepared either by automated parallel or by traditional solution-phase synthesis. Several members of this compound library were identified as high-affinity dopamine D3 and D2 receptor ligands. The most interesting representative, compound **2**, showed potent antipsychotic behaviour coupled with a beneficial cognitive and EPS profile.

An increasing body of clinical evidence supports the notion that multiple ligands may be more efficacious than strictly selective agents, particularly in the treatment of CNS disorders.[1] We decided to utilize this approach in our antipsychotic research. Our quest was based on three interrelated hypotheses: (1) that dopamine D2 antagonism is required for antipsychotic activity; (2) that dopamine D3 antagonism may carry favourable effects such as cognitive enhancement and lack of catalepsy; and (3) in order to achieve a simultaneous in vivo manifestation of D2 and D3 antagonism compounds should have a higher affinity to D3 than to D2 receptors.



SB-277011
rD3-Ki: 8.25 nM; rD2-Ki: 4667 nM; r%F: 63

Surveying the literature for drug-like and potent dopamine D3 receptor ligands we identified **SB-277011**[2] as a promising starting point and an analogue (**1**) prepared by us was subsequently chosen as a lead compound (affinities to rat dopamine D3 and D2 receptors as well as the rat bioavailability were measured in our laboratories).[3–5]



1
rD3-Ki: 1.68 nM; rD2-Ki: 1166 nM; r%F: 80

After having prepared a few dozen analogues by traditional solution-phase synthesis (as depicted in Scheme 1) 32 representatives were evaluated in a 3D-QSAR study using CoMFA based on their affinities to D3 receptors (see Supporting Information). The underlying principle for the selection was that the affinity values should cover as wide a range as possible. All computations were performed using Sybyl 6.8 molecular modeling software (Tripos Inc.).[6] The

Keywords: Arylsulfonamides; Dopamine D3 and D2 ligands; Antipsychotic; Cognition enhancer.
* Corresponding author. Tel.: +36 1 431 5112; fax: +36 1 432 6002; e-mail: e.csongor@richter.hu

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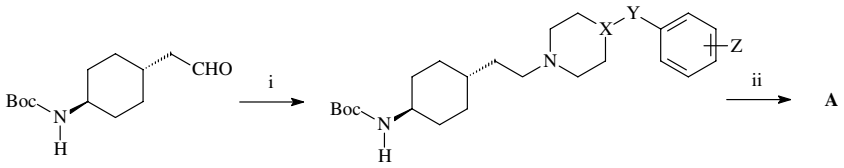


Scheme 1. Reagents: (i) cyclic amine/$NaBH(OAc)_3/CH_2Cl_2$; (ii) 1—HCl/EtOAc; 2—$QSO_2Cl/TEA/CH_2Cl_2$.

molecules were superimposed based on a pharmacophore model built with the help of DISCO technique (see Fig. 1). The predictivity of the model (shown in Fig. 2) gave us the confidence to use this model for predicting the D3 affinity for a 1288 membered virtual library with the general formula **A**. This library was created based on 28 aryl- and heteroarylsulfonylchlorides and 46 cyclic secondary amines like 4-aryl- and 4-benzylpiperazines, 4-aryl-, 4-benzyl-, 4-aryloxy- and 4-arylaminopiperidines.

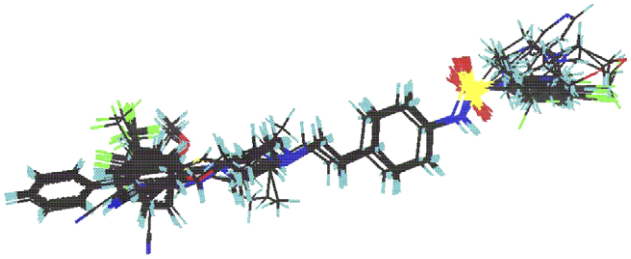


Figure 1. Superposition of the structures of the training set.

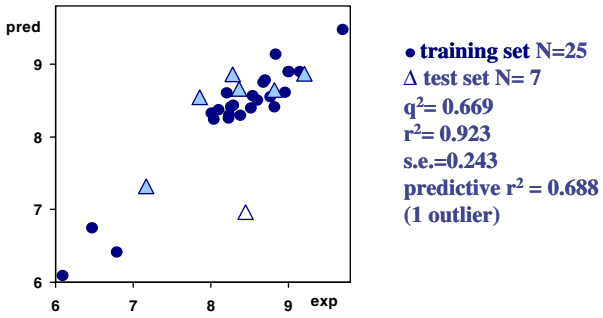
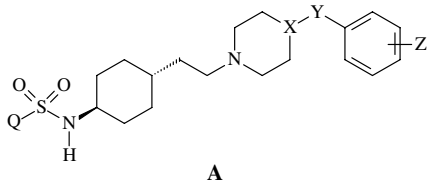


Figure 2. CoMFA of a series of sulfonamides. Predicted vs experimental D3 affinity ($-\log IC_{50}$) of training and test set molecules.

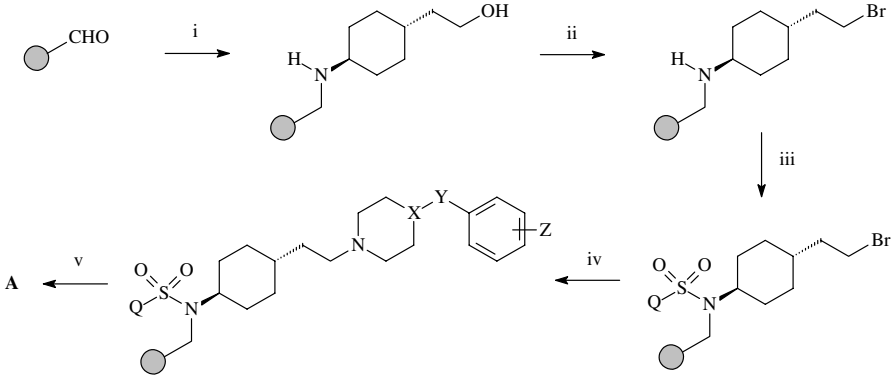


A

After CoMFA focussing and reactivity filtering a 288 membered focussed compound library was prepared by automated solid-phase parallel synthesis (Scheme 2).[7]

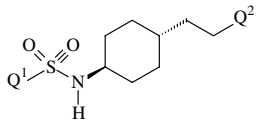
Of these compounds, 107 showed displacement higher than 70% at the 5 nM screening concentration on rat dopamine D3 receptor binding. From these derivatives 45 had K_i values between 1 and 5 nM while 41 had K_i values lower than 1 nM. All compounds having high affinity to D3 receptors ($K_i < 10$ nM) were subsequently tested in dopamine D2 binding experiments. A selection of compounds having high affinity to D3 and somewhat lower affinity to D2 receptors is shown in Table 1. The presented data indicate that a relatively high variety of substituents is tolerated at both termini of the molecules.

Several key compounds were selected for PK studies and those with higher than 20% oral bioavailability in rats were tested for in vivo antipsychotic activity (inhibition of the apomorphine-induced climbing behaviour in mice[8] and conditioned avoidance response in rats[9]). From these studies compound **2**[10]



Scheme 2. Reagents: (i) *trans*-4-aminocyclohexylethanol/$NaBH(OAc)_3/CH_2Cl_2$/AcOH; (ii) PPh_3/Br_2/imidazole/CH_2Cl_2; (iii) QSO_2Cl/TEA/THF; (iv) cyclic amine/KI/DMF; (v) TFA/CH_2Cl_2.

Table 1. Representatives of the 288 membered compound library



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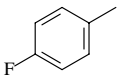
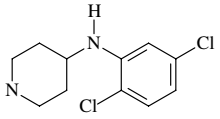
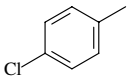
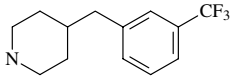
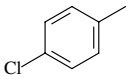
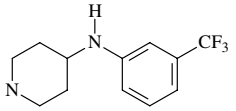
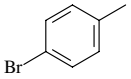
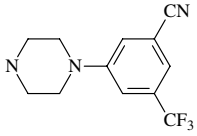
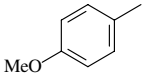
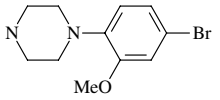
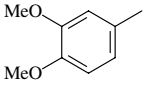
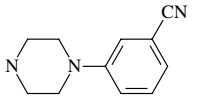
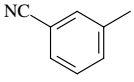
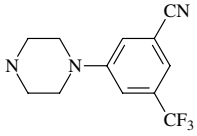
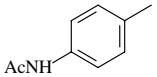
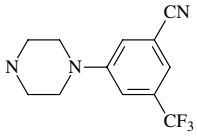
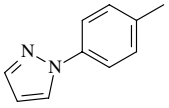
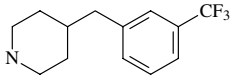
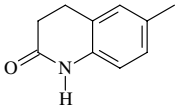
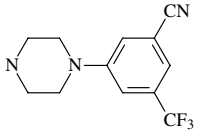
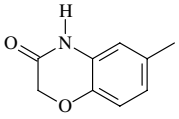
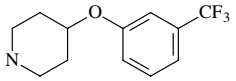
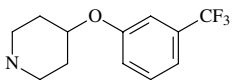
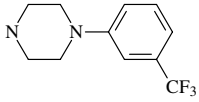
2a			2.0	9
2b			3.8	41
2c			3.0	16
2d			3.3	26
2e			0.5	28
2f			0.7	57
2g			5.8	23
2h			0.9	39
2i			0.5	4.3
2j			0.7	30
2k			1.0	5.3
2l			2.8	66
2m			0.3	29

Table 1 (*continued*)

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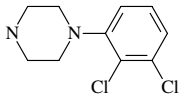
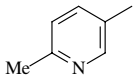
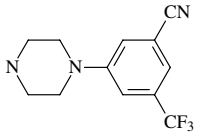
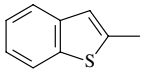
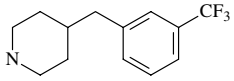
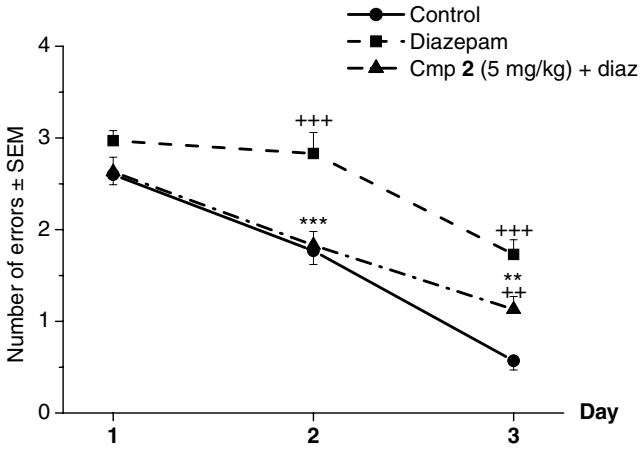
2n			0.2	4
2o			4.2	39
2p			2.6	91

was identified as the most promising candidate. This compound was tested against 55 diverse molecular targets in vitro (including adrenergic, glutamatergic, serotonergic, histaminergic and cholinergic receptors) and found to have a clean profile: it displayed high affinity to D3 and moderate affinity to D2 dopamine receptors only. In functional experiments (e.g. [^{35}S]GTPγS binding using membrane preparations from CHO cells expressing either human D3 or D2 receptors) **2** showed antagonist activity. In vivo its antipsychotic activity is comparable to those of known antipsychotics (Table 2). Extended evaluation indicated that **2** had little propensity to induce catalepsy[11] and that it had a beneficial effect on learning performance as measured in a water-labyrinth experiment (Fig. 3).[12]

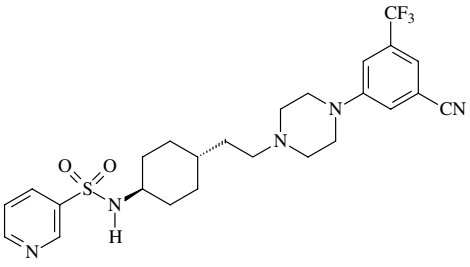
Table 2. Inhibition of CAR by compound **2** compared to the effect of known antipsychotics

Compound	CAR ED_{50}, mg/kg po
Compound **2**	11.6
Olanzapine	3.9
Aripiprazole	17.9



+++ and ++: p<0.001 and p<0.01, respectively, vs. control
*** and **: <0.001 and p<0.01, respectively, vs. diazepam treated
ANOVA, followed by post-hoc Duncan-test

Figure 3. Cognition enhancing effect of compound **2** at 5 mg/kg po dose against diazepam in the water-labyrinth test.



2
rD3-K_i: 0.4 nM; rD2-K_i: 24 nM;
r%F: 55; brain t_{max}: 1 hour, C_{max}: 921 ng/ml
apomorphine ind. climbing ED_{50}: 22 mg/kg (p.o.);
inhib. of CAR ED_{50}: 11.6 mg/kg (p.o.)
catalepsy in rats: MED: > 200 mg/kg (p.o.)

In summary, we have identified a new class of potent dopamine D3/D2 ligands. The most interesting representative of this series, compound **2**, had good bioavailability in rats and showed antipsychotic activity in two in vivo models. We speculate that because of its favourable dopamine D3 and D2 affinities it did not cause catalepsy at pharmacologically active doses, and elicited significant cognition improvement in rats having diazepam-induced memory impairment.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.08.015.

References and notes

1. Gray, J. A.; Roth, B. L. *Drug Discov. Today: Ther. Strateg.* **2006**, *3*, 413.
2. Branch, C. L.; Johnson, C. N.; Stemp, G. PCT Int. Appl. WO 1998/050364, 1998; *Chem. Abstr.* **1999**, *130*, 3775.
3. D3 binding assay was carried out on rat recombinant D3 receptors expressed in Sf9 cells using [^{3}H]spiperone (1.0 nM) as ligand and haloperidol (10 μM) for determination of non-specific binding. The assay was performed according to RBI assay protocol for D3 receptor (Cat. No. D-181).
4. *D2 binding assay:* Binding of [^{3}H]spiperone (0.5 nM) to rat striatal membranes was determined according to the

method described in Creese et al. *Eur. J. Pharm.* **1979**, 60, 55–66. The non-specific binding was determined in the presence of (+)-butaclamole (1 μM).

5. Pharmacokinetic studies were carried out on male rats following intravenous and oral administration of the compounds at dose levels of 5 and 10 mg/kg, respectively. The drug concentration in plasma and brain samples was analysed by an HPLC–UV method. Absolute oral bioavailability, plasma clearance, volume of distribution, elimination half-life and brain to plasma AUC ratio were calculated.
6. Sybyl 6.8, Tripos Inc., 2001, 1699 South Hanley Road, St. Louis, Missouri, 63144, USA.
7. The purity of compounds prepared by automated parallel synthesis was determined by HPLC–MS analysis and was higher than 85%. Selected representatives of this series and those compounds that were prepared by traditional solution-phase synthesis underwent structure elucidation. The IR, ^{1}H NMR, ^{13}C NMR and MS spectra were consistent with the assigned structures. Moreover, the purity of the samples was checked by HPLC (two eluent systems) and HRMS analysis.
8. *Apomorphine-induced climbing:* One hour after the oral administration of the vehicle or doses of the test compound, male CD1 mice were placed for habituation into cylindrical cages with walls of vertical metal bars. At the end of the 10 min adaptation period 1.5 mg/kg apomorphine HCl was administered subcutaneously to the animals and they were replaced into the cages. The measurement of climbing behaviour started 10 min after the apomorphine treatment and lasted for 16 min. Every minute the climbing behaviour was scored from 0 (four paws on the floor) to 2 (four paws grasping the bars).
9. *Conditioned avoidance response (CAR):* Male Wistar rats weighing 180–200 g at the beginning of conditioning were trained to perform two-way active avoidance responses in a computer controlled six-channel shuttle box apparatus. Daily sessions consisted of 48 cycles with 10 s intersignal interval, 10 s intermittent light + tone as conditioned stimuli and 5 s electric foot shock (0.6 mA) as unconditioned stimulus. Drug treatments were carried out with animals showing a stable, at least 75% avoidance performance. The test compounds were administered orally, 1 h before testing. Learning performance on the previous day served as the control level.
10. Galambos, J.; Nógrádi, K.; Ágai-Csongor, É.; Keserű, Gy. M.; Vágó, I.; Domány, Gy.; Kiss, B.; Gyertyán, I.; Laszlovszky, I.; Laszy, J. PCT Int. Appl. WO 2003/029233, 2003; *Chem. Abstr.* **2003**, *138*, 287701.
11. *Catalepsy test:* Thirty minutes after the treatment with the different compounds male Wistar rats weighing 200–220 g ($n = 10$/group) were placed in extraordinary position: placing both forepaws of the rat on a 10 cm high podium. Cut-off time for correction of body posture was 30 s. The frequency of cataleptic animals was also determined at 1, 2, 3, 4 and 5 h after the treatment.
12. *Water-labyrinth test:* The learning process of rats was assessed in a 3-choice point water-labyrinth system. The number of directional turning errors was recorded in three daily trials for three experimental days. Male Wistar rats weighing 180–200 g ($n = 10$/groups) were treated orally with vehicle or the test compounds 1 h before each daily session. Diazepam (5 mg/kg ip) as amnestic agent was injected 30 min prior to the first daily trial. Data were analysed by three-way repeated measures ANOVA followed by post hoc Duncan test.