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Discovery of cariprazine (RGH-188): A novel antipsychotic acting on dopamine D_3/D_2 receptors

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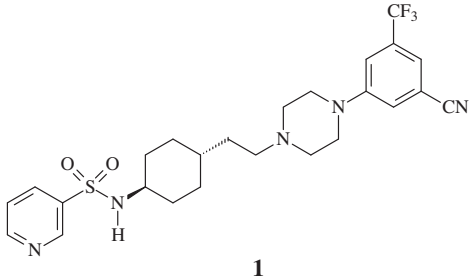
ABSTRACT

Medicinal chemistry optimization of an impurity isolated during the scale-up synthesis of a pyridylsulfonamide type dopamine D_3/D_2 compound (**1**) led to a series of new piperazine derivatives having affinity to both dopamine D_3 and D_2 receptors. Several members of this group showed excellent pharmacokinetic and pharmacodynamic properties as demonstrated by outstanding activities in different antipsychotic tests. The most promising representative, **2m** (cariprazine) had good absorption, excellent brain penetration and advantageous safety profile. Based on its successful clinical development we are looking forward to the NDA filing of cariprazine in 2012.

The overwhelming majority of the clinically used antipsychotics seems to exert their activity via interaction with dopamine D_2 receptors. Most of the typical and atypical antipsychotics, however, show affinities toward several other receptor types as well. These secondary interactions may contribute to the overall efficacy and safety of these drugs. One of the receptors the modulation of which could significantly influence the therapeutic value of the drug may be the dopamine D_3 receptor. Our plan aiming the development of a new antipsychotic was based on two hypotheses, beside the conviction that dopamine D_2 affinity was indispensable. On one hand the dopamine D_3 antagonism/partial agonism may exert cognitive enhancement and diminished liability for catalepsy. On the other hand compounds should show higher affinity to the D_3 than the D_2 receptors because of the different expression levels of the two receptors in the adequate brain areas.

We have recently reported on a 3-pyridylsulfonamide derivative (**1**) as a high-affinity dopamine D_3/D_2 receptor ligand with significant antipsychotic efficacy coupled with beneficial cognitive and extrapyramidal side effect (EPS) profile.[1–3]



1

rD_3-K_i: 0.4 nM; rD_2-K_i: 24 nM;
r%F: 55; brain t_{max}: 1 hour, C_{max}: 921 ng/ml
apomorphine climbing in mice ED_{50}: 22 mg/kg (p.o.);
catalepsy in rats: MED: > 200 mg/kg (p.o.)

During the resynthesis of compound **1** (Scheme 1) a persistent impurity was detected, and subsequently isolated and tested. It turned out that during the deprotection (in ethyl acetate) of the precursor (4-{2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazine-1-yl]-ethyl}-cyclo-hexyl)-carbamic acid *tert*-butyl ester and the subsequent sulfonylation of deprotected amine with pyridine-3-sulfonyl chloride, a small amount of compound **2a** was formed besides the main product **1**. Interestingly, **2a** showed superior properties when investigated in our early phase screening

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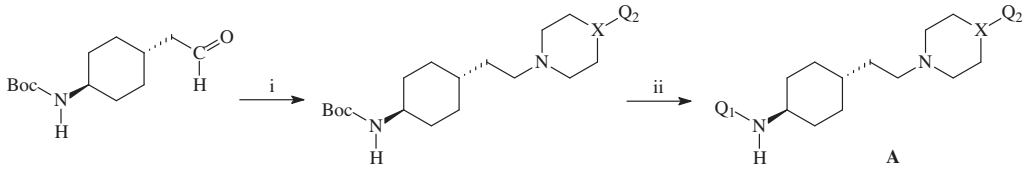
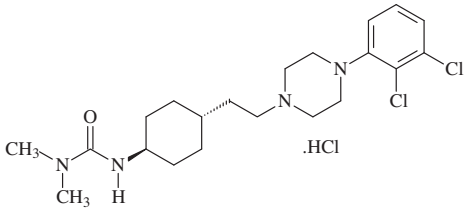


Scheme 1. Reagents and conditions: (i) cyclic amine/$NaBH(OAc)_3/CH_2Cl_2$; (ii) (1) HCl/EtOAc, (2) in most cases Q_1Cl or $Q_1OQ_1/TEA/CH_2Cl_2$.

cascade. Although, it had somewhat lower affinity to the dopamine D_3 and D_2 receptors **2a** was about 10 times more active in vivo than compound **1** (Table 1). This observation was rather surprising, since it contradicts to the consensus of the relevant literature indicating that an aromatic or heteroaromatic carboxamide moiety is an essential structural element of the dopamine D_3 receptor pharmacophore.[4,5] Since the formation of **2a** was only observed in those cases when the deprotection was performed with HCl-containing ethyl acetate it is reasonable to assume that the small amount of acetic acid, which could always be present in the raw product isolated from the reaction, transformed some pyridine-3-sulfonyl chloride to pyridine-3-sulfonyl acetate, a reactive acetylating agent that competed with the unchanged pyridine-3-sulfonyl chloride for the nucleophile.[6]

In order to explore the influence of small amide-like functionalities at the cyclohexyl side of the molecule a series of analogues was prepared and tested (Scheme 1).[7,8] In the design of these amidocyclohexyl-amines (general formula **A**) we utilized our earlier structure–activity relationship (SAR) experience as far as the amine part was concerned.[1] This basic moiety was either piperazine (homopiperazine) or piperidine. Substituents Q_2 were selected from substituted phenyl or benzyl in case of piperazines and substituted phenyl, benzyl, and phenoxy in case of piperidines. The amide part of **A** was decorated with alkylsulfonyl, substituted acyl, alkoxycarbonyl, carbamoyl and N-mono- or N,N-disubstituted carbamoyl groups. A selection of the most active derivatives, their affinities to rat dopamine D_3 and D_2 receptors and activities in the apomorphine induced climbing test in mice are shown in Table 1.[9–11] In general, these compounds had high affinity to D_3 receptors, with low nanomolar or subnanomolar IC_{50} values and somewhat lower affinities to the D_2 receptors. The most active derivatives (in vitro and in vivo) contained 2,3-dichlorophenyl-piperazine moiety. Taking into account many other features (like off-target activity, metabolic stability, interactions with CYP enzymes, permeability and in vivo activity in several behavioral pharmacological models, part of which has already been published[14,15]) of the synthesized compounds the most promising member of this group proved to be **2m**.

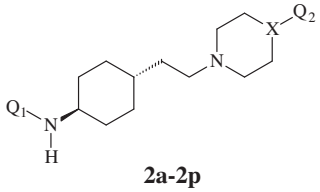


2m (cariprazine)

rD_3-K_i: 0.71 nM; rD_2-K_i: 9.3 nM;
hD_3-K_i: 0.09 nM; hD_{2L}-K_i: 5.7 nM; hD_{2S}-K_i: 0.81 nM
r%F: 52; brain t_{max}: 0.5-1 hour, C_{max}: 91 ng/ml
apomorphine climbing in mice ED_{50}: 0.27 mg/kg p.o.);
catalepsy in rats: MED: > 85 mg/kg (p.o.)

In order to determine whether the 2,3-dichlorophenyl-piperazine derivative **2m** was the most suitable for preclinical development 'chloro-scan' was performed, and a series of analogues having no chlorine, one chlorine or two chlorine atoms in different positions of the phenyl ring was prepared and tested (Table 2). Besides the affinities to dopamine D_2 and D_3 receptors the affinities to α-1 adrenoceptors were measured in order to determine the

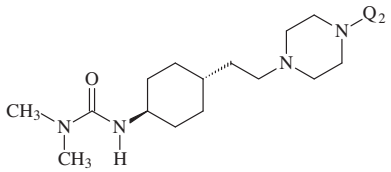
Table 1
Selected compounds (**2a–2p**): affinities to rat dopamine D_2 and D_3 receptors and activities in the apomorphine-induced climbing test in mice



2a-2p

Code	Q_1	*X*	Q_2	rD_3-IC_{50} (nM)	rD_2-IC_{50} (nM)	Apo-ED_{50} (mg/kg)
2a	MeCO	N	3-CN-5-CF_3-Ph	1.9	143	1.54
2b	$MeSO_2$	N	3-CN-5-CF_3-Ph	0.9	135	8.2
2c	MeCO	N	3-CF_3-Ph	1.9	39	0.7
2d	$MeSO_2$	N	3-CF_3-Ph	4.8	66	4.34
2e	MeCO	CH	3-CF_3-Bn	3.3	64	2.2
2f	MeCO	CH	3-CF_3-PhO	5.3	85	1.8
2g	$MeSO_2$	N	3-CF_3-Bn	11	158	1.34
2h	EtOCO	N	3-CF_3-Bn	5.1	25	5.37
2i	CF_3CO	N	2,3-Di-Cl-Ph	0.41	5.9	4.32
2j	MeCO	N	2,3-Di-Cl-Ph	0.29	2.3	0.17
2k	$MeSO_2$	N	2,3-Di-Cl-Ph	0.48	5.4	0.91
2l	EtCO	N	2,3-Di-Cl-Ph	0.26	7.1	0.21
2m	Me_2NCO	N	2,3-Di-Cl-Ph	1.6	16	0.27
2n	EtNHCO	N	2,3-Di-Cl-Ph	0.34	16.9	0.38
2o	Et_2NCO	N	2,3-Di-Cl-Ph	0.62	42.9	0.71
2p	H_2NCO	N	2,3-Di-Cl-Ph	0.32	29	0.87

Table 2
Close analogues of **2m** (**3a**–**3h**): affinities to rat dopamine D_2, D_3 and α-1 receptors.



2m, 3a-3h

Code	Q_2	rD_3-K_i[a] (nM)	rD_2-K_i[a] (nM)	D_2/D_3 Ratio	$r\alpha$-1-K_i[a] (nM)	α-1/D_3 Ratio
2m	2,3-Di-Cl-Ph	0.71	9.3	13.1	214	301
3a	Ph	15.9	94.0	5.9	204	12.8
3b	2-Cl-Ph	1.6	19.8	12.3	45.9	28.7
3c	3-Cl-Ph	4.95	53.4	10.8	72.9	14.7
3d	4-Cl-Ph	13.1	392	29.9	106.4	8.1
3e	2,4-Di-Cl-Ph	5.40	106	19.6	156	28.9
3f	2,5-Di-Cl-Ph	0.66	8.20	12.4	34.9	52.8
3g	3,4-Di-Cl-Ph	3.3	110	33.3	29.6	8.9
3h	3,5-Di-Cl-Ph	0.44	20.2	45.9	667	1516

[a] Shown are the mean K_i values from two to four independent experiments with at least six concentrations in duplicates.

hypotensive liability of the analogues.[12] Comparing affinities measured on rat dopamine D_2, D_3 receptors and α-1 adrenoceptors of **2m** to those of compounds **3a**–**3h** showed that most of the derivatives had lower affinity to the dopamine receptors than **2m**. One of the two exceptions (**3f**) had higher affinity to the α-1 receptors while the other (**3h**), which showed the most promising receptor profile, had lower metabolic stability (73% in rat and 58% in human liver microsomes) compared to that of **2m** (93% in rat and 96% in human microsomes).[13] These results indicated that among the close analogues **2m** had the most advantageous properties at this level. It should be noted that **2m** showed practically no affinity to other dopamine receptors (for rD_1, hD_1, $hD_{4.2}$ and hD_5 $IC_{50} > 1000$ nM) and a set of other GPCRs and ion channels while its affinity to some serotonin receptors ($5HT_{1A}$, $5HT_{2A}$, $5HT_{2B}$ and $5HT_{2C}$ was comparable to that measured for D_3 and D_2 receptors.[14]

As part of the late phase screening cascade and subsequent preclinical development cariprazine (**2m**) was subjected to detailed neurochemical and in vivo pharmacological characterization. Cariprazine demonstrated antagonist-partial agonist properties depending on actual dopaminergic tone that suggests its unique dopamine system stabilizer character.[14] Pharmacokinetic studies in rat revealed that cariprazine has good absorption and excellent brain penetration. The apparent terminal half-life ($t_{1/2}$) in rats was 2 h following i.v. or p.o. administration. Brain concentrations of cariprazine were much higher than plasma levels, with brain to plasma AUC ratio of 7.6:1.[15] Its beneficial side effect and safety profile compared to several known antipsychotics have also been demonstrated in several studies.[15]

In conclusion, the medicinal chemistry optimization of an impurity isolated during the synthesis of compound **1** led to a series of new piperazine/piperidine derivatives having high affinity to both dopamine D_3 and D_2 receptors. The most promising representative of this family of compounds, **2m** (INN:cariprazine hydrochloride) showed good pharmacokinetic profile with excellent brain penetration, enhanced cognitive function and did not cause catalepsy. Based on the promising non-clinical efficacy and safety data the compound was selected for clinical development. The proof of concept and dose finding clinical studies revealed the efficacy and safety of cariprazine in patients with acute schizophrenia and mania.[16,17] The recently available top line results from pivotal clinical trials demonstrated the safety and efficacy of cariprazine in bipolar mania[18] and schizophrenia[19] indications. These positive results validate the NDA filing of cariprazine as a new atypical antipsychotic drug.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.03.104. These data include MOL files and InChiKeys of the most important compounds described in this article.

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10. D_2 binding assay: binding of [^{3}H]spiperone (0.7 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).
11. 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).
12. α-1 binding assay: binding of [^{3}H]-prazosin (0.5 nM) to rat cerebral cortical membranes was determined according to the method described in Greengrass,

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13. Metabolic stability was assessed in vitro using human and rat liver microsomes. Test compounds at 2.5 μM final initial concentration were incubated up to 20 min with human (XenoTech, USA) or rat (Richter, Hungary) liver microsomes. Kinetic analysis of test substance consumption was undertaken using linear regression (Graphpad Prism, 4.0). The plot of substrate consumption against time was linear. In vitro intrinsic clearance (CLint) and metabolic bioavailability (FM) were calculated using the basic concept of clearance prediction (**1**) according to the following equations: FM = (1−EH) × 100; EH = CLint/(CLint + HBF); CLint = V_{max}/KM or if [*S*] << KM CLint = *V*/*S*; EH = hepatic extraction ratio; HBF = hepatic blood flow; V_{max} = maximal rate of enzyme reaction; KM = affinity constant of a substrate; [*S*] = substrate concentration; V = actual rate of enzyme reaction under first order conditions (Rane, A. et.al. *J. Pharmacol. Exp. Ther.*, **1977**, *200*, 420–424).
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