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Synthesis and SAR of highly potent and selective dopamine D_3-receptor antagonists: 1*H*-Pyrimidin-2-one derivatives

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Abstract—The synthesis and SAR of novel highly potent and selective dopamine D_3-receptor antagonists based on a 1*H*-pyrimidin-2-one scaffold are described. **A-690344** antagonized PD 128907-induced huddling deficits in rat (ED_{50} 6.1 mg/kg po), a social interaction paradigm.

Drug therapy of schizophrenia has traditionally involved the use of neuroleptics which pharmacologically act as antagonists at the dopamine D_2 receptor. This has been an important basis for the 'dopamine hypothesis' of schizophrenia. However, medical treatment of dopamine related disorders is often limited by side effects as a consequence of binding to various dopamine or other related monoamine receptors. Due to its localization, the dopamine D_3 receptor subtype might be a target for the development of antipsychotics, with a reduced risk of side effects.[1] This hypothesis is supported by data reported for two selective D_3 antagonists: A-437203 (also known as BSF-201640[2]) and SB-277011[3] (Chart 1) which exhibit efficacy in a variety of preclinical models predictive of antipsychotic activity without inducing catalepsy or raising plasma prolactin levels.

A program in our laboratories aimed at exploring further the potential of the pyrimidyl-piperazine core (Q, Chart 1) of A-437203. Here, we present the synthesis and SAR of novel D_3 antagonists based on a 1*H*-pyrimidin-2-one moiety. Its structural similarity with the 3*H*-pyrimidin-4-one pharmacophore of A-437203 has prompted us to evaluate the possibility of using 1*H*-pyrimidin-2-ones for the design of D_3-antagonists (Chart 1).

As numerous substituted uracils are commercially available, a convenient two-step route[4] was devised (Scheme 1): alkylation[5] of the pyrimidin-2-one on N^1 to introduce the spacer followed by nucleophilic substitution and introduction of the piperazine-pyrimidine moiety (Q).[6]

The non commercially available substituted uracils were readily accessible using published procedures[7–9] or modifications[4] of them (Scheme 2). 4-Alkyl (compound **2a**) and 4-cycloalkyl (compounds **2b**–**d**) substituted 1*H*-pyrimidin-2-ones were prepared from the corresponding β-keto acetals[4,10] **1a**–**d** by reaction[4,7] with urea. 4-Ph derivative **3** was prepared from 2,4-dichloro-pyrimidine by selective Suzuki coupling[8,11] and subsequent hydrolysis[9,11] of the remaining chloride. Introduction of a cyclic amine (azetidine, piperidine) in position 4 (**6a** and **b**) proceeded via thio-derivative[4,12] **5** in good yields (40–55%): the original procedure[13] (described in a sealed tube) was adapted to microwave conditions.[4] The N^3-substituted derivatives (**8a** and **b**) were obtained by methylation[4] of the halogenated precursors **7a** and **b** using iodomethane in the presence of KOH.

Keywords: Dopamine D_3 receptor antagonists; Atypical antipsychotics; 1*H*-Pyrimidin-2-ones.
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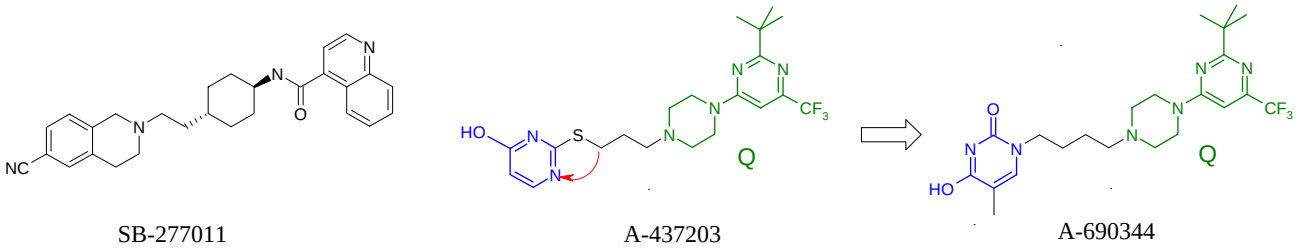
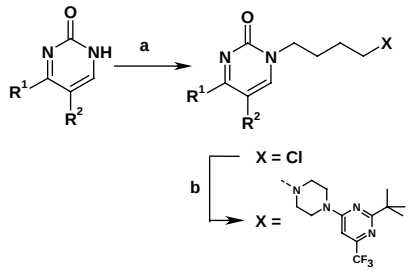
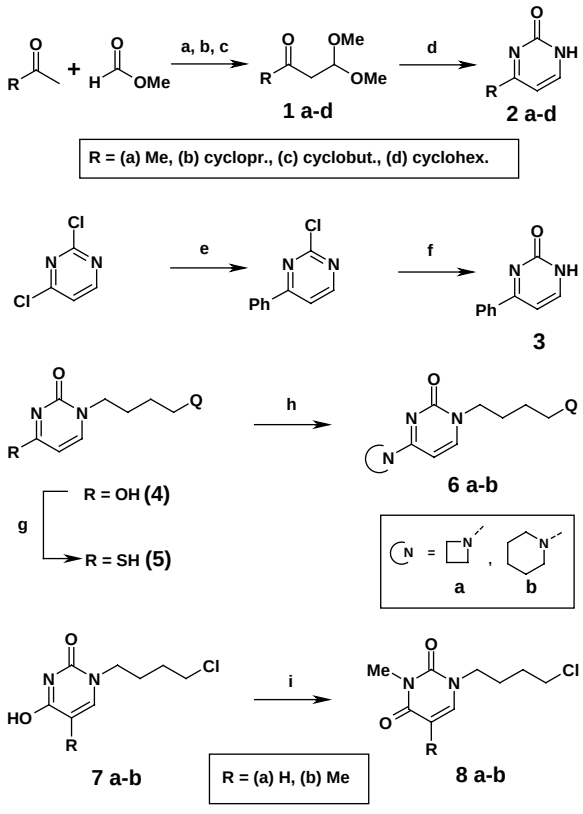


Chart 1. Reference compounds—from **A-437203** to **A-690344**.



Scheme 1. Reagents and conditions: (a) K_2CO_3, 1-bromo-4-chlorobutane, DMF, 12 h, rt; (b) 2-*tert*-butyl-4-piperazin-1-yl-6-(trifluoromethyl)pyrimidine,[6] Et_3N, DMF, 24 h, 110 °C.



Scheme 2. Reagents and conditions: (a) NaOMe, DEE, 3 h, rt; (b) H_2SO_4, MeOH, 12 h, rt; (c) aq KOH (pH 8); (d) Urea, HCl, EtOH, 2 h, reflux; (e) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, $PhCH_3$, MeOH, 3 h, rt, 70%; (f) concd HCl, 1 h, 100 °C, quant.; (g) 1/2 P_2S_5, dioxane, 1 h, reflux, quant.; (h) **NH**, EtOH, 1 h, 60 °C, μW Milestone Ethos 1600, 55% (azetidine), 41% (piperidine); (i) MeI, 5 equiv KOH, DMSO, 5 h, rt, 58% (R=H); quant. (R=Me).

Receptor affinities for the compounds described have been determined in binding assays[4] using human cloned dopamine D_3 and D_2 receptors. Compounds with a $K_i \leqslant 10$ nmol/l and a D_3 versus D_2 selectivity of >50-fold were analyzed in vitro for their functional properties with a hD_3-GTPγS binding assay:[14] all compounds tested displayed antagonistic activities ($E_{max} < 10\%$).

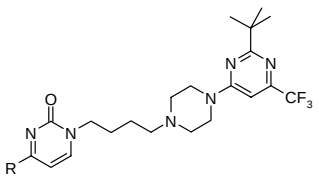
In the course of our studies[15] to explore further the potential of the pyrimidyl-piperazine core (Q, Chart 1) of A-437203, a novel series of potent and selective D_3 antagonists based on a 1*H*-pyrimidin-2-one scaffold was identified. Unexpectedly, although the C-linkage of the side chain was shifted to a N-linkage when the 3*H*-pyrimidin-4-one moiety of A-437203 was replaced by a 1*H*-pyrimidin-2-one moiety (Chart 1), comparable D_3-affinity and selectivity versus D_2 could be achieved (A-437203 and **4**, Table 1).

Molecular modelling: A model for the D_3 dopamine receptor has been developed internally, based on the three-dimensional models of the D_1 and D_2 dopamine receptors,[16] by changing the residues that are different between the human sequences of the receptors. Therefore, comparative modeling of a ligand in two different receptor models (in our case D_3 and D_2) might give a clue for the observed selectivity as a result from the different interactions of the ligand with the amino acids in the binding site of each receptor model.

As exemplified with **A-690344** (Fig. 1), modeling suggested a strong interaction of the carbonyl group in position 2 of the 1*H*-pyrimidin-2-one moiety with a threonine residue (Thr 368 on TM7) present in the D_3 model. In the corresponding D_2 model, this threonine is replaced by a phenylalanine residue (Phe 411) which cannot exert any H-bond donor interaction.[17] The D_2 and D_3 receptor models thus support the high affinity for the D_3 receptor and the high selectivity versus the D_2 receptor of **A-690344**, both resulting from the interaction of the carbonyl group in position 2: favorable with Thr 368 in the D_3 model, bad with Phe 411 in the D_2 model.

4-Substitution: In analogy with former data,[1,15] a five single bond spacer length was recognized as optimal for both high D_3 affinity and high selectivity versus D_2 (data not shown). However, based on the comparison

Table 1. Variation of 4-substituent



Compound	R	K_i (nM)		Sel. versus D_2[b]
		D_3[a]	D_2[a]	
9	H	12.9	447	35
4	OH	1.9	196	104
10	OEt	7.4	290	39
11	Me	4.4	307	71
12	*t*-Bu	2.6	216	82
13		3.7	155	41
14		7.4	273	37
15		4.8	302	63
16	Ph	1.4	168	122
6a		4.4	82.1	19
6b		3.4	89.4	26
A-437203		2.9	351	120

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] K_i D_2/K_i D_3.

with the nonsubstituted derivative **9**, a 4-substituent was required for low nanomolar D_3-affinity and high selectivity versus D_2 (Table 1). Pyrimidin-2,4-dione **4** was among the best representatives in terms of D_3-affinity and selectivity versus D_2 (above 100-fold). H-bond donor group like OH seemed to be beneficial regarding selectivity versus D_2 when one compares **4** with OEt-derivative **10**.

Surprisingly, lipophilic alkyl groups (compounds **11**, **12**) were shown to be also well tolerated: the more sterically demanding *t*-Bu group (compound **12**) exhibited both high D_3 affinity and selectivity versus D_2. The 4-cycloalkyl analogs **13**–**15** and the 4-Ph analog **16** confirmed that sterically more demanding groups were advantageous in terms of selectivity versus D_2, whereas D_3-affinity was hardly affected. Cyclic amino groups in position 4 (**6a** and **b**) are not tolerated with respect to selectivity versus D_2: a 3-fold improvement of D_2-binding was observed for comparable D_3-affinity (**14** and **6a**, **15** and **6b**).

5-Substitution: Although a 5-substituent in the pyrimidin-2,4-dione series is not a prerequisite for high D_3 affinity and selectivity versus D_2 (compound **4**), highly diverse residues are well tolerated in position 5 (Table 2: D_3-affinity of 5 nM or lower, selectivity vs D_2 90-fold or more). The highest selectivity was obtained with R = Me (**A-690344**, sel. vs D_2 246-fold). Increase of steric bulk in this position (R = Et, **17**) reduced the selectivity versus D_2 (89-fold). Interestingly, variation of the 5-substituent influences dramatically the physico-chemical properties of the molecule as reflected in the calculated polar surface areas[18] (**21**, 110 $Å^2$ compared to 87 $Å^2$ for **18**). Position 5 is thus the place of choice for fine-tuning—for example, to adjust the pharmacokinetic properties.

N^3-Methylation: N^3-Methylation decreased D_3-affinity (K_i > 10 nM, 6- to 8-fold higher than for the nonmethylated compounds) as well as D_2-affinity (Table 3, **22** and **23** compared to **4** (Table 1) and **A-690344** (Table 2)). The selectivity versus D_2 remains thus high to moderate. An unsubstituted NH is therefore required for good affinity and selectivity. However, it is not clear whether this effect is due to additional steric hinderance introduced by the *N*-methyl group, or to the removal of a hydrogen bond donor, either the N^3H itself or eventually the tautomeric OH-forms in position 2 and 4, their formation being blocked by the N-methylation.

A-690344 was further characterized and displayed a selectivity higher than a 100-fold versus the whole panel of targets in a broad CEREP profile.[19] Moreover, **A-690344** showed in vitro metabolic stability in liver microsomes of rat and human (>97% recovery),[20] oral bioavailability, and brain penetration, and was characterized by moderate permeability in the Caco-2 model (P_{app} 1.94×10^{-6} cm/s).[21]

In vivo efficacy was evaluated in a rat social interaction paradigm. Naturally occurring social interaction in rats (huddling) can be disrupted by a D_3 preferring agonist, such as PD 128907.[22] Antipsychotics have been shown to reverse the effect of PD 128907 (at least partially).[23] **A-690344** antagonized PD 128907-induced huddling deficits in rat (ED_{50} 6.1 mg/kg po). Deficits in huddling might represent one component of deficient social behavior and thus constitute an animal model for negative symptoms of schizophrenia.[23]

In conclusion, the combination of diversely substituted 1*H*-pyrimidin-2-ones with the disubstituted pyrimidine–piperazine moiety of A-437203 has yielded a family

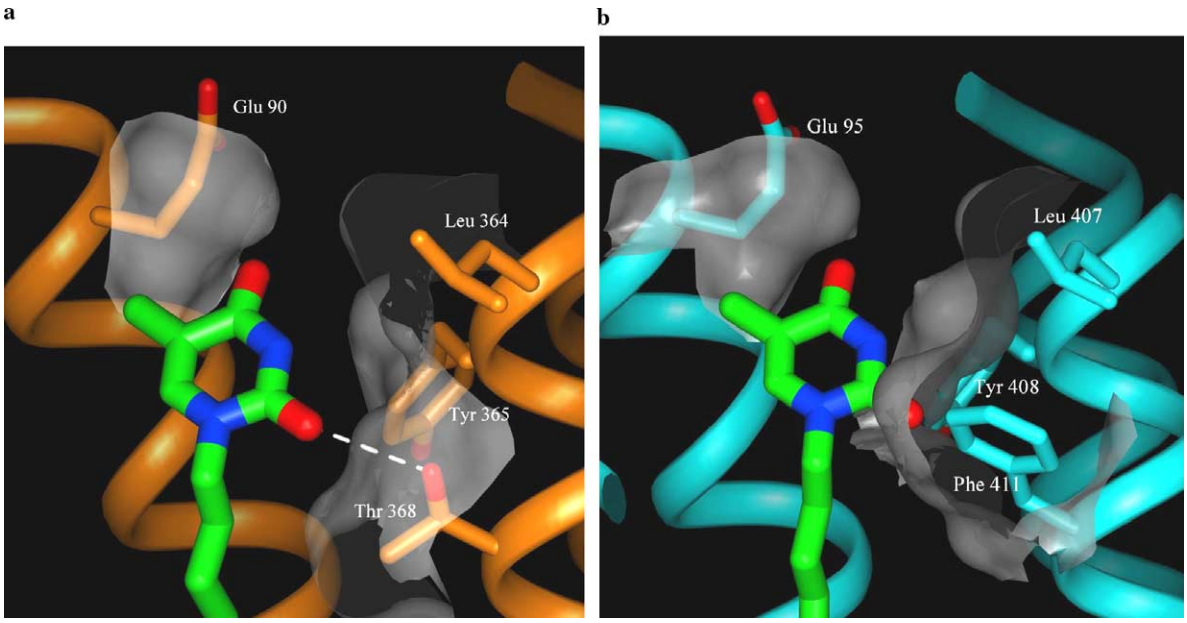
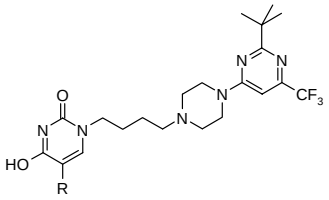


Figure 1. (a) **A-690344** (in stick presentation) in the D_3 model. Interactions with the 1*H*-pyrimidin-2-one moiety.[17] The semitransparent white surface represents the molecular surface of the protein and the dashed line the interaction with Thr 368. (b) **A-690344** (in stick presentation) in the D_2 model. Interactions with the 1*H*-pyrimidin-2-one moiety.[17] The semitransparent white surface represents the molecular surface of the protein. The ligand cannot bind in this orientation due to bad steric contacts with Phe 411.

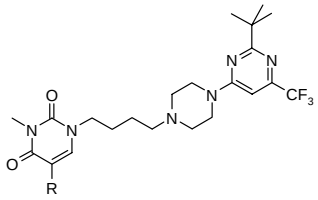
Table 2. Variation of 5-substituent



Compound	R	K_i (nM)		Sel. versus D_2[b]
		D_3[a]	D_2[a]	
4	H	1.9	196	104
A-690344	CH_3	1.3	320	246
17	C_2H_5	1.7	148	89
18	F	3.0	602	201
19	Cl	2.3	220	97
20	CF_3	5.4	646	119
21	CN	4.8	473	99

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] K_i D_2/K_i D_3.

Table 3. Effect of N^3-methylation



Compound	R	K_i (nM)		Sel. versus D_2[b]
		D_3[a]	D_2[a]	
22	H	11.8	610	52
23	CH_3	10.4	356	34

[a] Values are means of 2–3 experiments. Standard deviation of max 30% of the mean.
[b] K_i D_2/K_i D_3.

of highly potent and very selective D_3-antagonists. Potency and selectivity versus D_2 are supported by our molecular model. Two critical positions of the 1*H*-pyrimidin-2-one scaffold were identified: position 4 was shown to play an important role for the discrimination of the related D_3 and D_2 receptors, whereas position 5 was recognized as the place of choice to modify the physico-chemical properties of the molecule. In vivo efficacy was shown for **A-690344** after po administration.

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