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Synthesis and SAR of highly potent and selective dopamine D_3-receptor antagonists: Quinolin(di)one and benzazepin(di)one derivatives

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Abstract—The synthesis and SAR of novel and selective dopamine D_3-receptor antagonists based on a 3,4-dihydro-1*H*-quinolin-2-one, a 1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one, 1*H*-quinoline-2,4-dione or a 3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-dione scaffold are discussed. **A-706149** (2.15 mg/kg, po) antagonizes PD 128907-induced huddling deficits in rat, a social interaction paradigm.
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Despite the introduction of atypical neuroleptics, which are much less likely to cause extra-pyramidal side effects or hyperprolactinemia than the conventional typical antipsychotics,[1] there is still a strong need for compounds which induce fewer side effects and, equally importantly, also address the negative symptoms and cognitive deficits of schizophrenia more efficiently.

Due to its localization and pharmacology, the dopamine D_3-receptor subtype might play a role in the pathophysiology of CNS disorders such as schizophrenia and might represent a novel target for drugs to treat this disorder.[1] Efficacy in a variety of models predictive of antipsychotic activity without induction of catalepsy or increase of plasma prolactin levels has been reported for A-437203 (also known as BSF-201640[2a,b]) and SB-277011,[2c,d] two selective D_3 antagonists (Chart 1). A selective D_3 antagonist may thus address both the positive and negative symptoms of the disease and might not produce the side effects associated with current standard therapies (e.g., olanzapine).

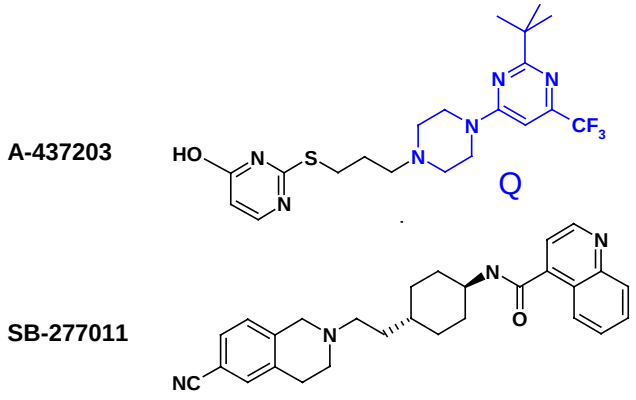

Chart 1. Reported dopamine D_3 receptor antagonists.

In the course of our studies 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 benzolactam scaffold[3] was identified.

The starting benzolactams are either commercially available, their synthesis described in the literature[4] or readily accessible using published procedures or modifications thereof.[5] Depending on the length of the spacer unit, two synthetic routes were devised starting

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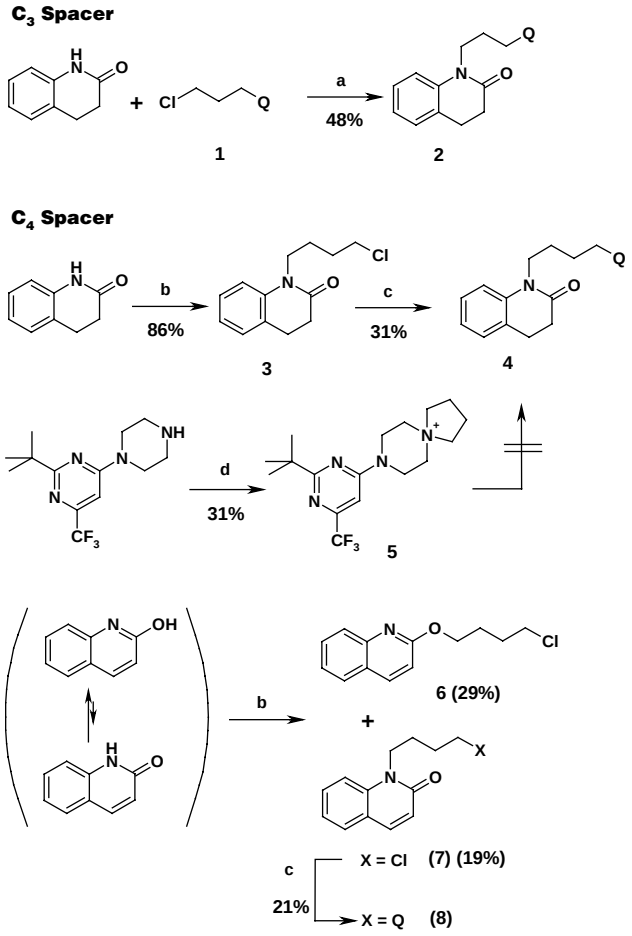
from 3,4-dihydro-1*H*-quinolin-2-one, as exemplified in Scheme 1. In the case of a propyl (C_3) spacer, chloride **1**[6] was reacted with the benzolactam after deprotonation with NaH. To introduce the butyl (C_4) spacer, reaction of 3,4-dihydro-1*H*-quinolin-2-one with 1-bromo-4-chloro-butane was preferred,[3a] followed by coupling of halide **3** with QH.[6] The spiro-fused quaternary salt **5**, formed when dihalide was first reacted with QH,[6] was unreactive in our hands.[1,7] When 1*H*-quinolin-2-one was the substrate, the O-alkylated derivative **6**—resulting from the aromatized tautomeric quinolin-2-ol—was isolated as main compound (**7**:**6** 40:60, total yield 48%; chlorides **6** and **7** were separated by column chromatography).[5] Compounds derived from 1*H*-quinoline-2,4-dione and 3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-diones were prepared following the same sequence. However, the yield for the desired alkylation was lower (ca. 40%) due to side reactions induced by the presence of the enol tautomeric form of the carbonyl group in position 5.

Receptor affinities for the compounds described have been determined in binding assays[5] using human cloned dopamine D_3 and D_2 receptors. Compounds with a $K_i \leqslant 10$ nM and a D_3 versus D_2 selectivity of >50-fold were further analyzed in vitro for their functional properties with a hD_3-GTPγ S binding assay:[8] all compounds tested displayed antagonistic activities ($E_{max} < 10\%$).



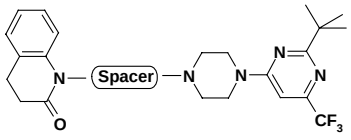
Scheme 1. Reagents and conditions: (a) NaH, DMF, 12 h, rt; (b) 1-bromo-4-chloro-butane, NaH, DMF, 12 h, RT; (c) QH,[6] Et_3N, DMF, 12–20 h, 100 °C; (d) 1-bromo-4-chloro-butane, Et_3N, DMF, 12–20 h, 100 °C.

Our data demonstrate (Table 1) a clear preference for a butyl spacer (compound **4**) versus propyl and pentyl spacers (compounds **2** and **9**, respectively). Therefore, in the following variations a separation of four atoms was chosen. An unsaturation (compound **10**) was well tolerated, whereas an additional methyl group in the α or γ position of the linker next to the piperazine was detrimental in both the unsaturated and saturated cases (compounds **11** to **13**, 6- to 19-fold loss of D_3 affinity).

Table 2 depicts the binding data collected when varying the 3,4-dihydro-1*H*-quinolin-2-one scaffold. Introduction in position 4 of oxygen (compound **14**) or of an unsaturation (1*H*-quinolin-2-one **8**) slightly disfavored the D_3 affinity as compared to 3,4-dihydro-1*H*-quinolin-2-one derivative **4**. Isomerism of the lactam (compound **15**) led to large loss of D_3 affinity.

Ring enlargement to the 1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one derivative **17** (Table 3) led to a decrease in D_3 affinity and thus a loss of selectivity versus D_2 (for comparable D_2 affinity). Although introduction of a sulfur atom into position 5 (compound **18**) had no significant effect on both affinity and selectivity, the 1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one series is marked by the amazing effect of a carbonyl group in position 5 (**A-706149**) which dramatically improved both the D_3 affinity (0.8 nM) and selectivity versus D_2 (296-fold). This effect could not be transferred to the 3,4-dihydro-1*H*-quinolin-2-one series (see 1*H*-quinoline-2,4-dione **16**, Table 2) and could not be 'mimicked' by introduction of a methoxy or hydroxy group into the neighboring position 6 (compounds **19**, **20**). The presence of an H-bond donor in position 6 seemed however to be beneficial for the D_3 binding (compared to compound **17**). Substitution of the fused benzo ring within this series appeared to be

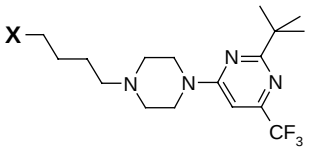
Table 1. Variation of the spacer unit

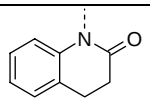
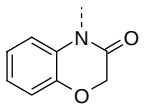
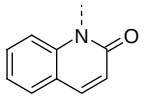
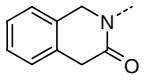
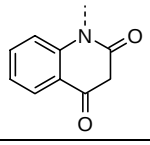


Compound	Spacer	D_3[a] K_i (nM)	D_2[a] K_i (nM)	Sel. vs D_2[b]
2	$-(CH_2)_3-$	93.8		
4	$-(CH_2)_4-$	3.4	126	37
9	$-(CH_2)_5-$	4054		
10		9.2	254	28
11		58.9	669	11
12		64.9	261	4
13		22.4	289	13

[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.

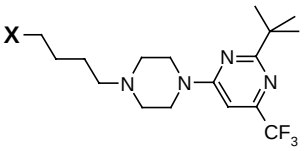
Table 2. Variation of the quinolinone core

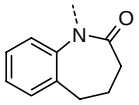
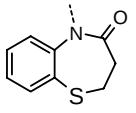
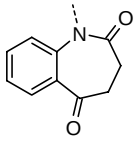
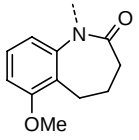
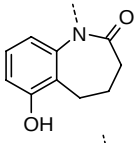
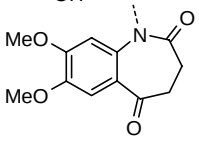
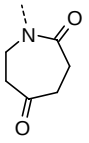


Compound	X	D_3[a] K_i (nM)	D_2[a] K_i (nM)	Sel. vs D_2[b]
4[c]		3.4	126	37
14[c]		12.1	354	29
8[c]		11.2	151	14
15[4a]		293		
16[4b]		39.6	142	4

Benzolactams prepared according to literature Refs. [4a,4b].
[a,b]Refer to Table 1.
[c] Benzolactam is commercially available.

Table 3. Variation and/or substitution of the benzazepinone core



Compdound	X	D_3[a] K_i (nM)	D_2[a] K_i (nM)	Sel. vs D_2[b]
17[4c]		16.8	118	7
18[4d]		9.6	83	9
A-706149[4e]		0.8	246	296
19[4f]		10.1	243	24
20[4f]		2.5	93	38
21[4g]		4.5	467	104
22[4h]		3.9	65	17

Benzolactams prepared according to literature Ref. [4c–4h].
[a,b]Refer to Table 1.

well tolerated in terms of D_3 affinity and selectivity versus D_2 (compound **21**). Interestingly, the monocyclic azepane-2,5-dione **22** maintained nanomolar D_3 binding but suffered from a loss of selectivity versus D_2.

A model for the D_3 dopamine receptor has been developed based on the three-dimensional models of the D_1 and D_2 dopamine receptors.[9] It supports some of the SAR observed. **A-706149** is characterized by subnanomolar affinity for the D_3 receptor as well as very high selectivity versus the D_2 receptor: this can be rationalized by the following observations (Figs. 1A and B):

- the methylene groups of the lactam ring show a favorable interaction with the side chain of Leu 364 on TM7;
- furthermore, an additional interaction between the carbonyl in position 2 and Thr 368 on TM7 (in the D_3 model) seems to be beneficial for the binding to the D_3 receptor. In the D_2 model, Thr 368 is replaced by a Phe 411 which cannot exert any H-bond donor interaction and thus lead to a lower affinity for the D_2 receptor (K_i D_2/K_i D_3);
- finally, the fused phenyl ring of the 1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one scaffold fits very well in a pocket formed by Val 107, Val 86 and the methylene groups of glutamate 90.

The model also contributes to a better understanding of the different affinities/selectivities observed for **16** (K_i D_3 39.6 nM, 4-fold selectivity versus D_2) and **A-706149** (K_i D_3 0.8 nM, 296-fold selectivity versus D_2). The interaction of the carbonyl in position 2 with Thr 368 (D_3 model) described above is also present in the case of **16** (not shown). However, the 1*H*-quinoline-2,4-dione residue can rotate along the axis formed by the nitrogen of the quinolindione and the carbon of the butyl spacer. This new conformation (Fig. 2) permits a favorable perpendicular interaction (edge to face) between the 2 phenyl rings of the quinolindione scaffold and the Phe 411 (in the D_2 model), and may thus be responsible for the lower observed selectivity versus D_2. This rotation is less favorable in the case of **A-706149** for two reasons: it would lead to a high energy conformation (in the D_2 model) and the carbonyl in position 2 would no longer fit into the receptor pocket. Both assumptions may explain the higher observed selectivity versus D_2.

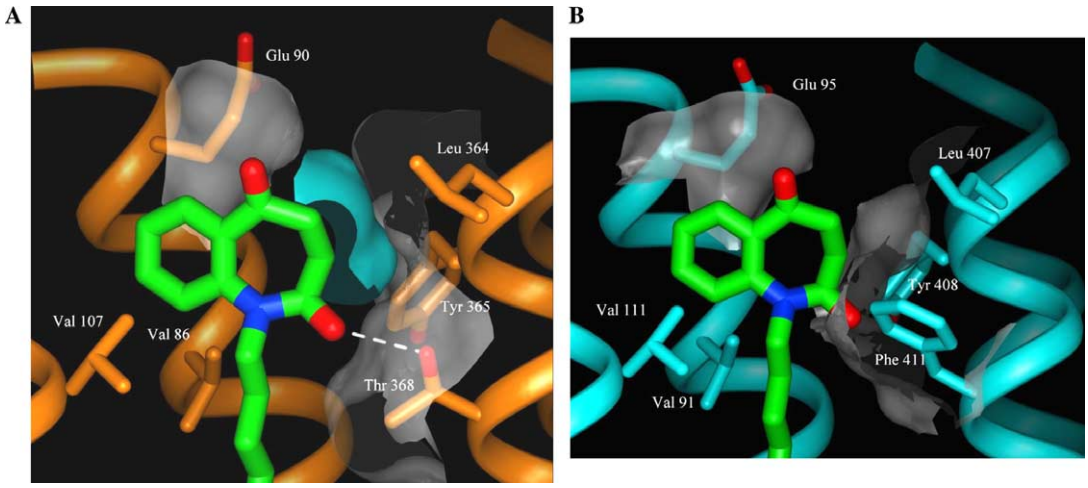


Figure 1. (A) **A-706149** (in stick presentation) in the D_3 model (interactions with the benzazepindione moiety); the semitransparent white surface represents the molecular surface of the protein and the dashed line the interaction with Thr 368; the light blue surface represents the interactions between the side chain of Leu 364 and the methylene groups of the lactam ring. (B) **A-706149** (in stick presentation) in the D_2 model (interactions with the benzazepindione moiety); 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.

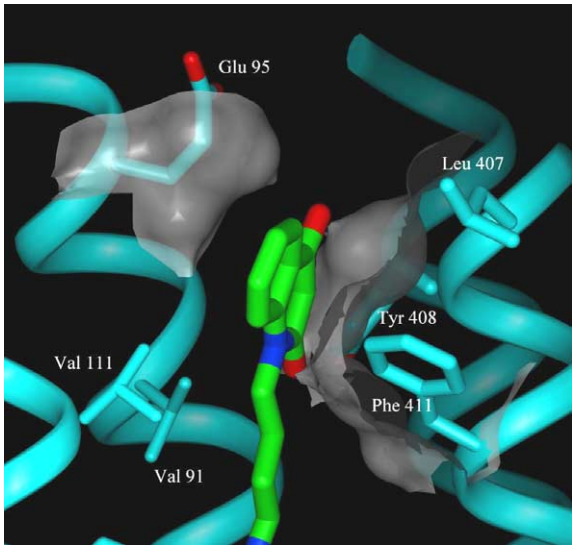


Figure 2. Compound **16** (in stick presentation) in the D_2 model (interactions with the quinolindione moiety); the semitransparent white surface represents the molecular surface of the protein. Favorable ligand–receptor edge to face interaction.

A further favorable interaction may contribute to the better affinity of **16** for the D_2 receptor. The thermodynamically favored enol form of the carbonyl in position 4[10] facilitates an additional interaction with a glutamic acid residue present in both receptors (Glu 90 of D_3 and Glu 95 of D_2, Figs. 1A and B) and may be responsible for the low differentiation of the two receptors. This is not true for **A-706149** (no stabilizing aromatization being possible) in which the carbonyl form is favored and thus cannot interact with the glutamic acid.

The reduced selectivity of compound **22** compared to that of **A-706149** is also supported by this model. Both compounds interact with Thr 368 of the D_3 receptor (see above). However, **22** cannot make the additional interactions with the hydrophobic pocket described for the benzo ring of **A-706149**: therefore, **22** is ca. 5-fold less potent at the D_3 receptor. In the D_2 receptor model, Thr 368 is now a Phe (Phe 411), therefore the hydrogen-bonding interaction cannot occur and the ligand will have to adjust. The monocyclic **22** (and not **A-706149**) can find a good alternative conformation with the C6 and C7 methylenes occupying a hydrophobic pocket formed by Val 91, Val 92, Tyr 408, and Phe 411. Therefore, the selectivity of **A-706149** is much larger than for **22** due to its better D_3 affinity and a larger loss in D_2 affinity (Fig. 3).

A-706149 was further characterized and exhibited high selectivity versus dopamine D_4 and serotonin 5-HT_{1A} (>100-fold) and IC_{50} values of >10 μM[11] for CNS relevant receptors such as adenosine, adrenergic, central benzodiazepine, dopamine D_1, D_5, GABA, muscarine, and 5-HT, for a series of peptide receptors including cholecystokinin and opiate receptors as well as neurotransmitter transporters. Moreover, **A-706149** showed in vitro metabolic stability in liver microsomes of rat, dog, and human (>97% recovery),[12] but was characterized by moderate permeability in the Caco-2 model (P_{app} 3.3×10^{-7} cm/s)[13] and suboptimal pharmacokinetic profile ($F < 10\%$).

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.[14a] Antipsychotics have been shown to reverse the effect of PD 128907 (at least partially).[14b] After disruption, **A-706149** was able to restitute huddling up to 37% after p.o. administration (2.15 mg/kg). PD 128907 induced deficits in huddling might represent one component of deficient social behavior and thus constitute an animal model for negative symptoms of schizophrenia.[14b]

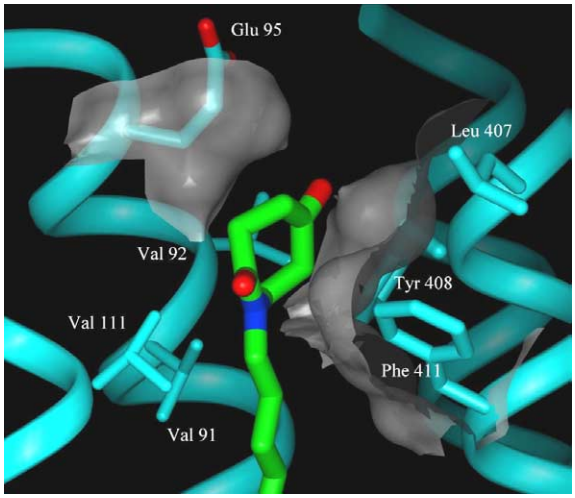


Figure 3. Compound **22** (in stick presentation) in the D_2 model (interactions with the azepane-2,5-dione moiety; the semitransparent white surface represents the molecular surface of the protein. Favorable hydrophobic pocket formed by Val 91, Val 92, Tyr 408, and Phe 411).

In summary, novel potent and selective dopamine D_3 receptor antagonists have been synthesized. We have shown the dramatic beneficial effect of the introduction of a carbonyl functionality into position 5 of a 1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one scaffold on both D_3 affinity and selectivity versus D_2. This effect is supported by our molecular model. In vivo efficacy was shown for **A-706149**. However, due to its low oral bioavailability, **A-706149** is clearly not a viable drug candidate. Efforts to improve DMPK properties are ongoing. Compounds with improved profile may prove beneficial in the treatment of psychiatric disorders such as schizophrenia.

Acknowledgments

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