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Potent dihydroquinolinone dopamine D_2 partial agonist/serotonin reuptake inhibitors for the treatment of schizophrenia

Yinfa Yan [a,*], Ping Zhou [a], David P. Rotella [a,*], Rolf Feenstra [b], Chris G. Kruse [b], Jan-Hendrik Reinders [b], Martina van der Neut [b], Margaret Lai [c], Jean Zhang [c], Dianne M. Kowal [c], Tikva Carrick [c], Karen L. Marquis [c], Mark H. Pausch [c], Albert J. Robichaud [a]

[a] Chemical Sciences, Wyeth Research, CN 8000 Princeton, NJ 08543, United States
[b] Solvay Pharmaceuticals Research Laboratories, C.J. van Houtenlaan 36, 1381 CP, Weesp, The Netherlands
[c] Discovery Neuroscience, Wyeth Research, CN 8000 Princeton, NJ 08543, United States

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ABSTRACT

A dihydroquinolinone moiety was found to be a potent serotonin reuptake inhibitor pharmacophore when combined with certain amines. This fragment was coupled with selected D_2 ligands to prepare a series of dual acting compounds with attractive in vitro profiles as dopamine D_2 partial agonists and serotonin reuptake inhibitors. Structure–activity studies revealed that the linker plays a key role in contributing to D_2 affinity, function, and SRI activity.

Based on the hypothesis that the efficacy of antipsychotic agents can be expanded by combining a dopamine D_2 partial agonist with serotonin reuptake inhibition (SRI),[1–3] we reported a series of tetrahydrocarbazole-based dual acting compounds that showed antipsychotic-like activity in animal models (see structures **1** and **2** in Fig. 1).[4] The receptor binding profile of these molecules indicated less than a 10-fold separation between affinity at the primary targets (SRI and D_2) and potentially undesirable receptors such as α1.[5,6] In an attempt to address this deficiency and better understand the complex structure–activity relationships that determine primary target selectivity, we now report the results obtained with additional SRI and D_2 building blocks.

The design hypothesis for compounds described in this report is embodied in a compound template (see Fig. 2) which includes a D_2 ligand, an SRI moiety, and a linker. Selection of the dihydroquinolinone moiety as the SRI pharmacophore was based in part on the observation that aripiprazole, **3** (Fig. 2) an approved agent for the treatment of schizophrenia displays weak SRI activity (K_i 1080 nM using a citalopram binding assay similar to that used in this work).[7,8] The choice of D_2 pharmacophores was guided by dopamine D_2 moieties known in the literature.[9,10] The two building blocks can be efficiently linked via alkyl- and piperidine-based linkers.

The synthesis of the final targets is outlined in Schemes 1–5. The oxygen linked compounds were prepared as outlined in Scheme 1.[11]

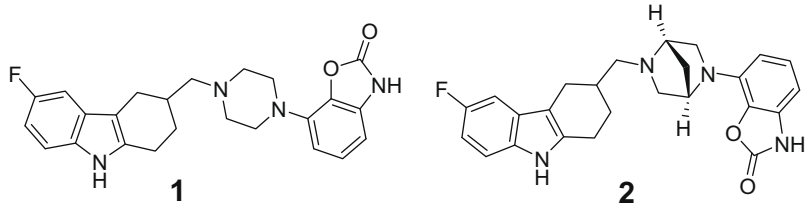

Figure 1. D_2/SRI partial agonists.

* Corresponding authors. Tel.: +1 215 801 0191.
E-mail address: drotella@comcast.net (D.P. Rotella).

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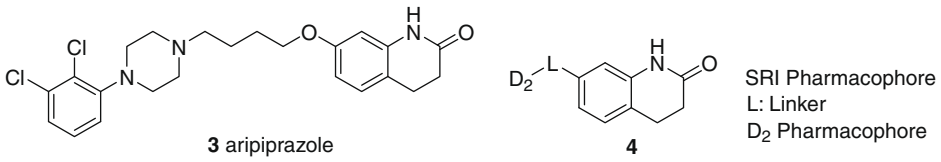
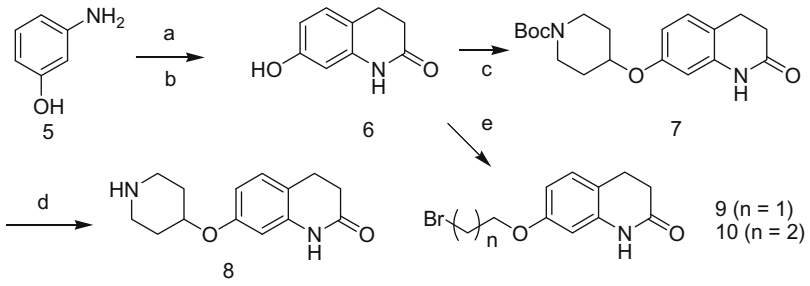
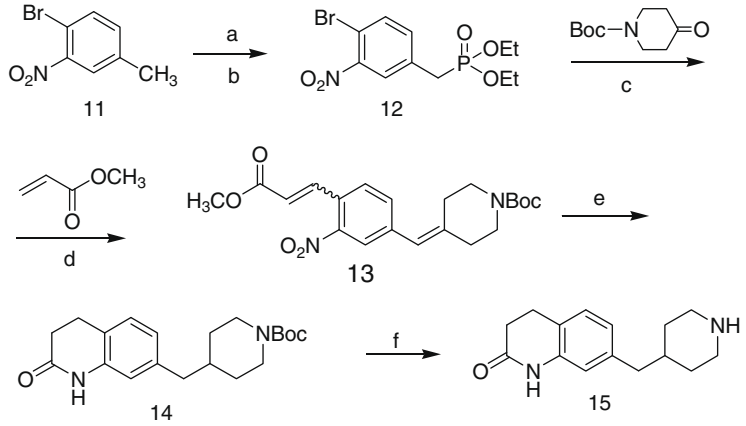


Figure 2. D_2/SRI design approach.

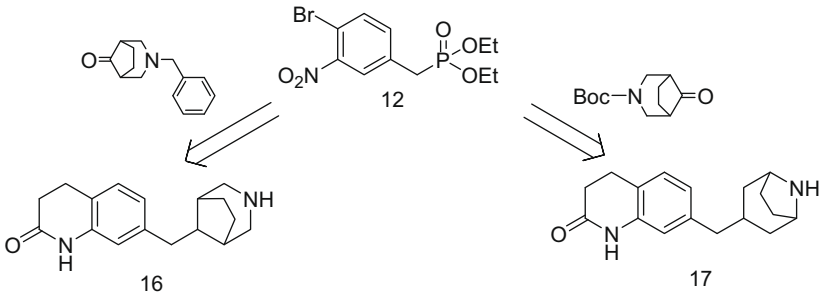


Scheme 1. Synthesis of dihydroquinolinone analogs **I**. Reagents and conditions: (a) $ClCH_2CH_2COCl$, $NaHCO_3$/MeOH/H_2O/rt, 24 h; (b) $AlCl_3$ neat/200 °C; (c) *t*-butyl 4-(2-nitrophenylsulfonyloxy)piperidine-1-carboxylate, Et_3N/CH_2Cl_2; (d) HCl/ether; (e) $Br(CH_2)_nBr$, Cs_2CO_3/acetone/DMF reflux.

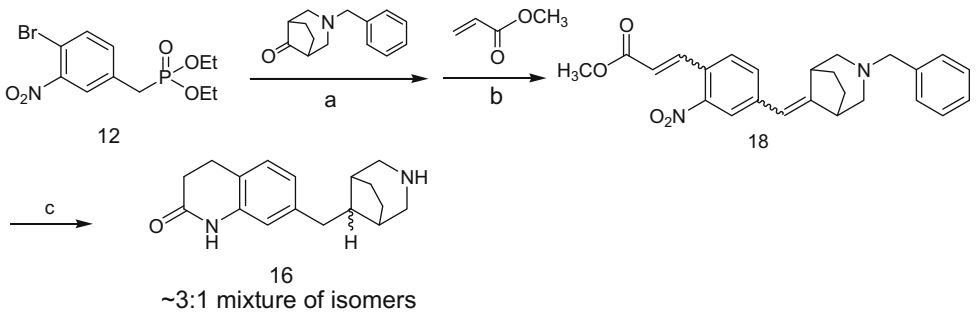


Scheme 2. Synthesis of dihydroquinolinone analogs **II**. Reagents and conditions : (a) NBS and AIBN/CCl_4 reflux 24 h; (b) $(POEt)_3$ 160 °C, 3 h; (c) NaH/DMSO rt; (d) $Pd(OAc)_2$, di-isopropyl ethyl amine/DMF; (e) Pd/C, H_2/MeOH 6 h; (f) HCl/ether.

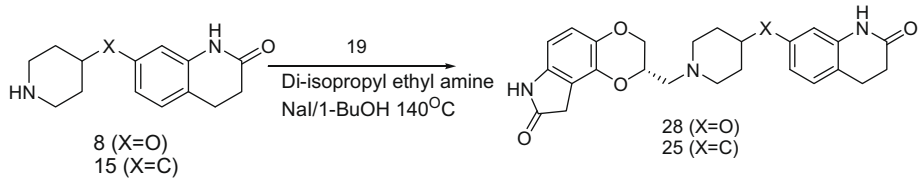
Acylation of 3-aminophenol with 3-chloropropanoyl chloride afforded the desired product which was cyclized under Friedel–Crafts conditions to give lactam **6**, followed by alkylation and acidic deprotection to give compound **8**. Alkylation of **6** with 1,2-dibromoethane or 1,3-dibromopropane affords intermediates **9** and **10**, respectively. Scheme 2 shows the synthesis of piperidinylmethyl 3,4-dihydroquinolinone **15**.[11] Bromination of 3-nitro-4-bromotoluene **11** with NBS affords 2-bromo-4-(bromomethyl)-1-nitrobenzene, which was converted to phosphonate **12**. Wittig–Horner reaction of **12** yielded the corresponding olefin intermediate, followed by Heck coupling with methyl acrylate, catalytic hydrogenation, and deprotection furnished **15**. The piperidinylmethyl 3,4-dihydroquinolinone **15** was coupled with various D_2 moieties to yield the desired products by either direct alkylation (halide) or reductive amination (ketones or aldehydes). Several intermediates were prepared by similar chemistry utilizing different ketones (Scheme 3).



Scheme 3. Synthesis of dihydroquinolinone analogs **III**.



Scheme 4. Synthesis of bridged compounds. Reagents and conditions: (a) NaH/DMSO, 0 °C–rt; (b) $Pd(OAc)_2$, di-isopropyl ethyl amine/DMF; (c) Pd/C, H 50 psi/MeOH 6 h.



Scheme 5. Synthesis of target compounds.

In the case of [3.2.1]azabicyclo fragment **16** (Scheme 3), NMR analysis showed that this intermediate was obtained as a 3:1 mixture of *exo*- and *endo* isomers. These two isomers were separated by preparative HPLC, and NOE experiments were essential to determine relative stereochemistry on the azacycle. In the major *exo* isomer derived from **16**, the axial proton on the cyclohexane ring displayed NOE interactions with protons in the ethyl bridge. These interactions were not observed in the *endo* isomer where the methylene hydrogens in the axial position showed NOE effects with protons in the bridge. Similar interactions were observed in the separate isomers derived from **17**. The D_2 building blocks used (**19**–**21**) are listed in Figure 3. The synthesis of these compounds was carried out as previously described in the literature.[12,13]

Coupling the amino-SRI and D_2 fragments was carried out optimally in refluxing 1-butanol (Scheme 5) in the presence of di-isopropyl ethyl amine and an iodide source to afford products in 40–78% yield. It was observed that improved yields were obtained by conversion of the amine hydrochloride to the corresponding free base by stirring a methanol solution in the presence of a basic ion exchange resin (Amberlyst A-26(OH) ion exchange resin).

Target compounds were screened for binding at the human serotonin reuptake site in a [^{3}H]citalopram displacement assay.[4] D_2 receptor binding was measured using [^{3}H]spiperone as the ligand.[4] Compounds with K_i values less than 50 nM at both receptors were evaluated in an in vitro D_2 functional assay that measured changes in intracellular cAMP levels.[4] Agonist activity was defined as a ratio (α-value) relative to the full agonist quinpirole (α-value = 1). Preferred compounds exhibited α-values between 0.2 and 0.5 in the in vitro D_2 functional assay.

Dopamine D_2 and SRI binding data for each linker series are shown in Tables 1–3. Table 1 shows results with alkyl linkers attached via oxygen to the lactam SRI fragment**.** These compounds consistently show good D_2 affinity, and less potent SRI affinity.

Conformational restriction of the alkyl amino linker provides piperidinyl derivatives **25–30** as shown in Table 2. This series examined the effect of substituting carbon for oxygen at the point of attachment to the SRI pharmacophore. In general, these piperidine derivatives showed improved SRI affinity compared to alkoxy-linked analogs **22**–**24**. When oxygen and carbon linked compounds are compared, using the same D_2 ligands, some carbon analogs provide more potent SRI affinity (cf. **25** vs **28–30**) with similar D_2 affinity. However, this is not a general property, as oxygen analogs **29–30** furnish derivatives with comparable SRI affinity to methylene-connected compounds **27** and **28**. This observation is similar to that observed earlier in that there appears to be a complex and not completely predictable structure–activity relationship in this series of dual acting compounds.[4]

When the piperidine was rigidified with a bicyclic system (8-(B1) or 3-(B2) azabicyclo[3.2.1]octane), the SRI binding affinity was improved up to 10-fold (**31**–**33**) over piperidine linked compounds (**26**–**30**). In this set of analogs, it is noteworthy that linkers influence SRI binding more than D_2 binding and the effect on D_2 binding is somewhat variable. The data reported in Table 3 was obtained using the mixtures of *exo* and *endo* isomers described above. Interestingly, the separated *exo* and *endo* isomers derived from **31**–**34** showed comparable SRI and D_2 affinity. Two of these bicyclic linker compounds (**32** and **33**) displayed the desired dopamine D_2 partial agonist activity between 0.2 and 0.4. 8-Aza analog **31** showed full antagonist activity in this screen (α <0.1), while 3-aza derivative **34** functioned as a full agonist (α = 0.85). In this limited set of derivatives, there is no clear structure–activity trend in D_2 functional activity.

Compounds containing sulfonamide D_2 moieties (**29**, **30**, **33** and **34**) display substantially improved α1 receptor selectivity compared to the benzodioxolanyl or phenyloxazolone D_2 building blocks.[4] It is widely held that antagonist activity at this receptor

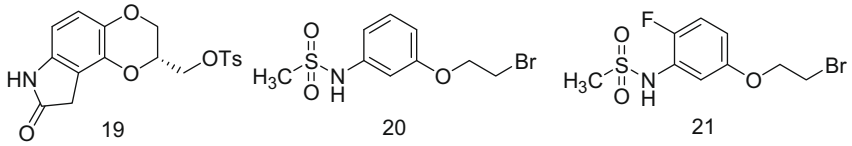
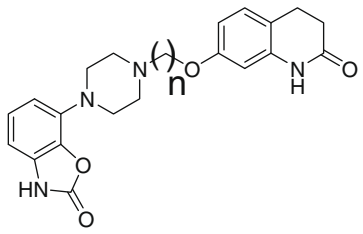


Figure 3. Structures of D_2 building blocks.

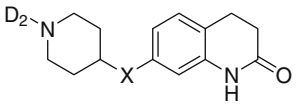
Table 1
Alkoxy-linked analogs



Compd	*n*	SRI binding (K_i, nM)	D_2 binding (K_i, nM)
22	2	538	8.6
23	3	93	8.6
24	4	94	8.3

Standards: D_2-haloperidol K_i 3 nM, SRI escitalopram K_i 1 nM. All K_i values represent averages of at least three independent experiments.

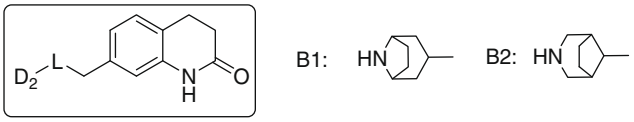
Table 2
Oxy-/methylene-linked 4-piperidine analogs



Compd	D_2	X	SRI (K_i, nM)	D_2 (K_i, nM)	D_2 func. (α-value)	α1 (K_i, nM)
25	19	C	1.9	8	0.38	2
26	20	C	19	9	<0.1	NT
27	21	C	20	19	<0.1	NT
28	19	O	20	2.5	0.41	2
29	20	O	22	18	0.21	91
30	21	O	30	9	<0.1	354

All K_i values represent averages of at least three independent experiments. α-Values represent average of at least two independent experiments.

Table 3
Bridged piperidine analogs



Compd	D_2	L	SRI (K_i, nM)	D_2 (K_i, nM)	D_2 fn. (α-value)	α1 (K_i, nM)
31	19	B1	0.26	16	<0.1	8
32	19	B2	1.5	6.3	0.4	46
33	20	B2	1.7	11	0.25	>3300
34	21	B2	5	7	0.85	1100

All K_i values represent averages of at least three independent experiments. α-Values represent average of at least two independent experiments.

could induce sedation, and may lead to cardiovascular issues.[5,6] Compounds **33** (α1 K_i >3300 nM) and **34** (α1 K_i 1100 nM) were especially noteworthy in this regard, with substantial separation between the primary targets and α1 affinity. Interestingly the functional activity of these two compounds differs substantially, as **33** shows D_2 partial agonist activity in cells, while **34** is essentially a full agonist. Compound **33** has a superior receptor profile compared to tetrahydrocarbazoles **1** and **2** and is a candidate for more detailed in vivo studies, in animal models of antipsychotic and serotonin reuptake inhibition. Compared with the tetrahydrocarbazole compounds **1** and **2**,[4] selected compounds reported here showed improved α1 selectivity (**33** and **34**) and comparable dopamine D_2 partial agonist activity, with potent SRI affinity.

In summary, in combination with cyclic linkers, the dihydroquinolinone pharmacophore has been shown to display potent SRI activity and furnished compounds with good D_2 receptor affinity using a variety of D_2 pharmacophores. The tetrahydrocarbazole analogs described in the first paper in this series showed variable D_2 affinity.[4] Using selected cyclic amine linkers, the dihydroquinolinone SRI moiety can furnish potent, dual acting compounds with attractive in vitro profiles and dopamine D_2 partial agonist activity. A rigid piperidine linker, in the form of a [3.2.1] azabicyclo ring system, provides derivatives with superior SRI affinity compared to alkoxy or simple piperidine linkers. Among the two regioisomeric azabicycles studied in this work, the 8-azabicyclo isomer was superior to the 3-isomer in terms of SRI and D_2 affinity. Several compounds in this group furnished dopamine D_2 partial agonist activity in the desired range. Sulfonamide-based D_2 moieties provided improved α1 receptor selectivity, compared to benzodioxolanyl and phenyloxazolone derivatives. Compound **33** is a candidate for more detailed in vivo studies to more fully assess its potential as a dual acting antipsychotic agent.

Acknowledgement

This manuscript is dedicated to our colleague Jan-Hendrik Reinders who passed away on February 4, 2008.

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