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Modulations of the amide function of the preferential dopamine D_3 agonist (*R,R*)-S32504: Improvements of affinity and selectivity for D_3 versus D_2 receptors

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ABSTRACT

Starting with the preferential dopamine (DA) D_3 agonist S32504, we prepared two series of derivatives of the general formula **I-A** and **I-B**, in an effort to improve both potency and selectivity. For the first set of derivatives, where the primary amide function of S32504 was replaced by either secondary and tertiary amide or ester, acid, nitrile and ketone, no improvement was obtained. Conversely, when the primary amide function was integrated in a lactam ring, an enhancement of affinity and selectivity was attained for the five-membered ring lactam but also for its five-membered ring lactone analogue.

Dopaminergic mechanisms are broadly involved in the control of diverse physiological functions and their perturbation is implicated in the etiology of debilitating central nervous system disorders like schizophrenia, depression and Parkinson's disease (PD). Consequently, dopaminergic ligands are of considerable interest as therapeutic agents and elucidation of the functional roles of the five individual classes of DA receptor (D_1–D_5) is of great importance.[1]

Since its discovery by Sokoloff and Schwartz[2] in the early 1990s, dopamine D_3 receptors, which display a pattern of ligand recognition and intracellular coupling similar but subtly different to closely-related D_2 receptors, have attracted much attention.[3–5] D_3 receptors share the importance of D_2 receptors in the control of mood, cognition, emotion, reward and motor function but, interestingly, their role is distinct. For example, D_3 but not D_2 receptor antagonists improve cognition and reduce relapse of drugs of abuse, while blockade of D_2 receptors is the core mechanism for controlling positive symptoms of schizophrenia.[6,7]

The respective significance of D_3 versus D_2 receptor stimulation to the control of symptoms in PD remains unclear, but preferential D_3 versus D_2 receptor agonists like ropinirole and pramipexole (Fig. 1), and the partial D_3 (and D_2) receptor agonist piribedil[8] are widely used as antiparkinson agents.[9,10] Of particular significance, beneficial D_3 receptor-mediated neuroprotective effects on dopaminergic neurones have been documented in cellular models, in rodents and in man.[11,12]

In our continuing effort to identify ligands interacting preferentially with D_3 receptors, we have already characterized S14297(**1**)[13–15] and a series of tetracyclic analogues[16] of S14297 as potent hD_3 antagonists.[17] More recently we discovered S32504 (***R,R***)-**2** which behaves as D_3 receptor agonist[18] (Fig. 2) and displays robust antiparkinsonian, neuroprotective and antidepressive activity in vivo in comparison to other agents such as ropinirole.[19,20]

In order to further increase the potency of S32504 and propose improved treatments of dopaminergic-related diseases (and more particularly PD) we decided to extensively modulate its amide function. To this end we elected to prepare compounds of general formula **I-A** and **I-B** (Fig. 2) to explore the influence of both minor modulations (amide bioisosteres, **I-A**) and more important transformations (rigidified analogues, **I-B**) of this functional group, upon potency at hD_3 receptors and selectivity versus hD_2 receptors.

Compounds of general formula **I-A** were prepared from triflate **3**[21] (Scheme 1). By action of zinc cyanide in presence of a catalytic amount of palladium tetrakis triphenylphosphine in DMF,[22] **3** was transformed in **4** in moderate yield (36%), which was further modified in (±)S32504 ((±)**2**) by treatment with potassium hydroxide in ethanol at reflux (80% yield). Ester **5** was obtained from **2**, in 65% yield, by action of 1,1-dimethoxy *N,N*-dimethylformamide (DMF–DMA) and then submitting the derivative obtained to sodium

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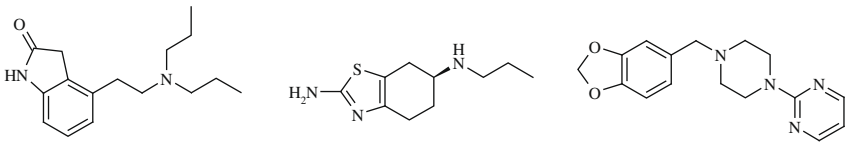


Figure 1. Structure of the preferential D_3 versus D_2 receptor agonists, ropinirole and pramipexole, and of the non-ergot D_3/D_2 partial agonist, piribedil.

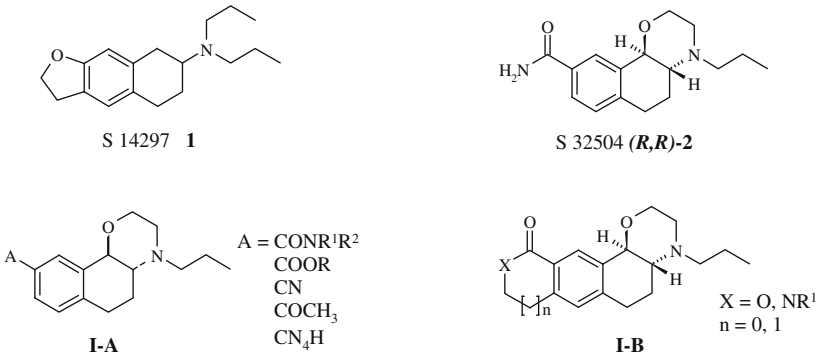


Figure 2. Structure of preferential antagonists and agonists at hD_3 versus hD_2 receptors.

methylate according to Anelli et al.[23] and Ono et al.[24] Finally, acid derivative **6** was obtained by basic hydrolysis of **5** using sodium hydroxide.

Excess butylvinyl ether in presence of 3 mol % of 1,3-bis(diphenylphosphino)propane (Dppp) and 2.5 mol % of palladium acetate allowed the transformation of triflate **3** in methyl ketone **7**, in 66% yield, according to Cabri et al.[25] Tetrazole **8** was prepared in 60% yield by a 1,3-dipolar cycloaddition of the cyano derivative **4** with trimethyltin azide in toluene followed by treatment with HCl gas, according to Duncia et al.[26] Finally, action of gaseous hydrochloric acid in ethanol on this same cyano derivative led to ethyl ester **9**.

From an analysis of the data reported in Table 1, it can be seen that the amide function present in **2** is the upmost functionality for affinity at D_3 receptors and selectivity versus D_2 receptors. Cyanide as in **4** and acetyl as in **7**, although conferring some selectivity, did not allowed for an improvement in affinity at D_3 receptors but led to derivatives of comparable potency than the reference compound ropinirole. Others functions examined, such as esters in **5** and **9**, carboxylic acid in **6** and tetrazole in **8**, were detrimental for affinity since these compounds are almost devoid of activity. Compound **2**, the most potent and selective of this first set of compounds was resolved by chiral HPLC.[27] (+)**2**[28] retained the affinity of the racemate and was two fold more selective, whereas (−)**2** was practically devoid of activity.

Next, we decided to examine the role of nitrogen substituants on the amide function and to this end synthetized amides **10–14** by coupling the corresponding amines with **6**, in the presence of TBTU (*O*-(benzotriazol-1-yl) *N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate) and $(Et)_3N$ as depicted in Scheme 2 (yields 38–56%). Mono substitutions as in **10**, **12**, **13**, **14** or di-substitution as in **11** dramatically decreased affinity for hD_3 receptors while having little impact on hD_2 affinities.

At this point and before further modifications of the amide part of S32504 it was deemed worthwhile to determine the absolute configuration of asymmetric carbons at ring junctions, since we did not envisaged to change this part of the molecule. For this purpose, we performed X-ray analysis on the methanesulfonate salt of the eutomer (+)**2**, which revealed a *R*,*R* configuration.[29] Consequently subsequent modulations were undertaken only on the corresponding *R*,*R* isomer (see Fig. 3).

On the structure of **2**, both position 8 and 10 of the hexahydro-2*H*-naphtho[1,2-*b*] [1,4] oxazine backbone were available for anchoring an extra cycle incorporating the amide function. Considering the X-ray structure of S32504 we decided to attach this fourth ring in position 8. The resulting rigidified or tetracyclic analogues **I-B** (**15–20**) of (*R*,*R*)-S32504 were prepared from (***R***,***R***)-**6**.

The lactam derivative **15** was synthetized as depicted in Scheme 3. To prepare the cyano derivative **22**, we first synthetized the *N*,*N*-diethylamide derivative **21** (76% yield using the same experimental conditions as for the preparation of **10**–**14**) to be able to perform an ortho directed lithiation at temperature below −70 °C, followed by

Table 1
Affinities of compounds **2**–**14** (**I-A**) at hD_3 and hD_2 dopamine receptors as determined by displacement of [^{3}H]-spiperone

	Affinity (pK_i)[a]		Selectivity[b]
	hD_3	hD_{2L}	$K_i(hD_2)/K_i(hD_3)$
(±)**2**	7.71 ± 0.06	6.12 ± 0.09	40
(+)(***R***,***R***)**2**	7.83 ± 0.15	5.92 ± 0.10	80
(−)(***S***,***S***)**2**	5.61 ± 0.04	<5	
4	7.40 ± 0.05	6.10 ± 0.18	20
5	<5	<6	
6	5.48 ± 0.12	<5	
7	7.02 ± 0.01	5.51 ± 0.11	32
8	<5	<5	
9	5.58 ± 0.13	N.T.	
10	<5	5.10 ± 0.08	
11	<5	5.73 ± 0.06	
12	<5	5.34 ± 0.01	
13	<5	5.47 ± 0.07	
14	5.56 ± 0.12	<5	
Ropinirole	7.44 ± 0.06	6.16 ± 0.06	20

[a] pK_i values are derived from at least two independent determinations each performed in duplicate. Experiments were undertaken on membranes of CHO cells stably transfected with cloned hD_3 or hD_2 receptors (hD_{2L}, long isoform). [^{3}H]-spiperone was used as the radioligand.

[b] Selectivity is expressed by the ratio of K_i (nM) values at hD_2 versus hD_3 receptors.

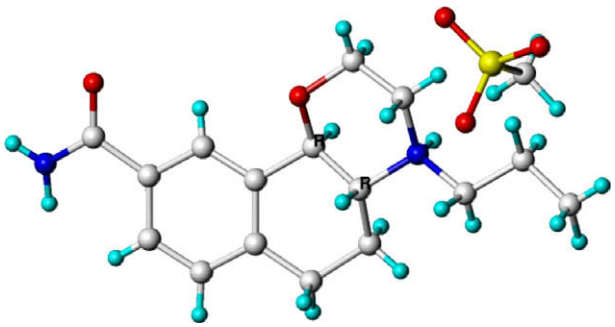


Figure 3. X-ray structure of the methanesulfonate salt of (+)**2**.

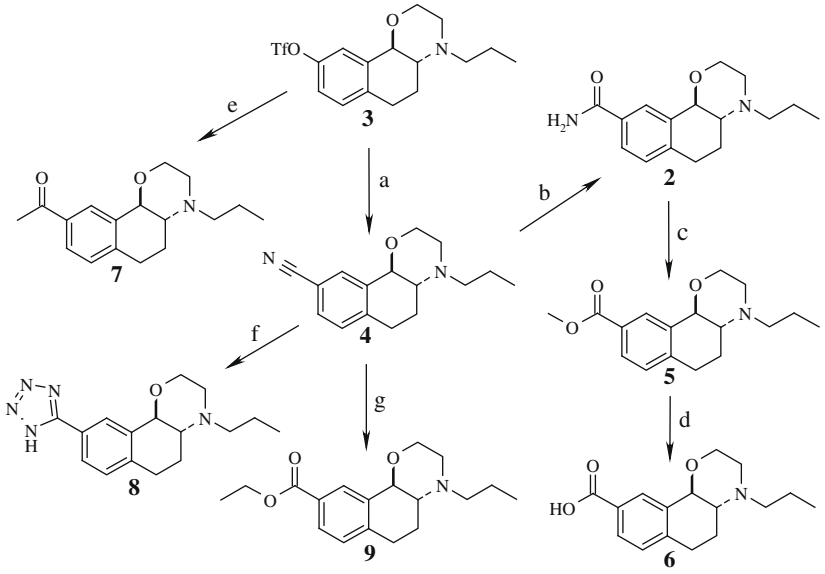
an electrophilic cyanation using phenylcyanate (PhOCN), as described by Sato.[30] Probably due to steric hindrance we were fortunate to isolate only **22** in 78% yield and without any evidence of cyanation in position 10. Then, **22** was submitted to a catalytic hydrogenation and **23**, which was isolated in 31% yield, was cyclized to yield compound **15** in presence of *t*-BuLi at −78 °C (99% yield).[31]

Lactone **16** and lactam **17** were prepared as depicted in Scheme 4 following a synthetic pathway similar to the one used for preparation of **15**. Intermediate **21** was lithiated, as previously, by *sec*-butyllithium in presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and the resulting lithoamide, treated by DMF in THF, led to **24**. Here again and despite a comparatively modest yield (47%) we only isolated the desired ortho isomer. Reduction with sodium borohydride afforded alcohol **25** and cyclization to compound **16** was achieved via treatment at reflux with HCl 6N. The overall yield for the two last steps was 12%.[32] Subsequently, reaction of **16** with methylamine at 120 °C led to **17** with a yield of 25%.

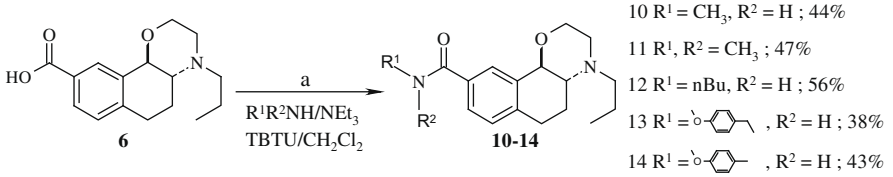
Lactone **18** and lactam **19** were prepared as depicted in Scheme 5 starting from amide **21**. The six-membered ring lactone **18** was obtained like the five-membered ring lactone **16** but using the lithio protected 2-bromoethanol as the electrophile instead of DMF. The overall yield for these two steps was only 10% but without any evidence of the other potential regioisomer. From alcohol **25**, lactam **19** was obtained through the sequence: chloride **27** (yield 75%), nitrile **28** (yield 96%), amine **29** (yield 30%), and lactam (yield 49%).[33]

Unfortunately, *N*,*N*-diethylamide **21** was not suitable for preparation of lactam **20**, which was synthetized according to Scheme 6, adapted from Fisher et al.[34] We anticipated that Weinreb's amide, easily obtained in 2 steps from **6** and with a yield of 61%, could serve as the ideal group for: (1) ortho directed metalation leading to **32** after reaction with methyl iodide, which (2) underwent regiospecific dilithiation on nitrogen and methyl and (3) in presence of DMF, allowed for the preparation of the N-protected methoxy lactam **33**, via a cyclization under mildly acidic conditions with an acceptable yield of 25% for the three steps. Finally deprotection was achieved with a moderate yield (31%) by use of titanium trichloride in ethanol at reflux.

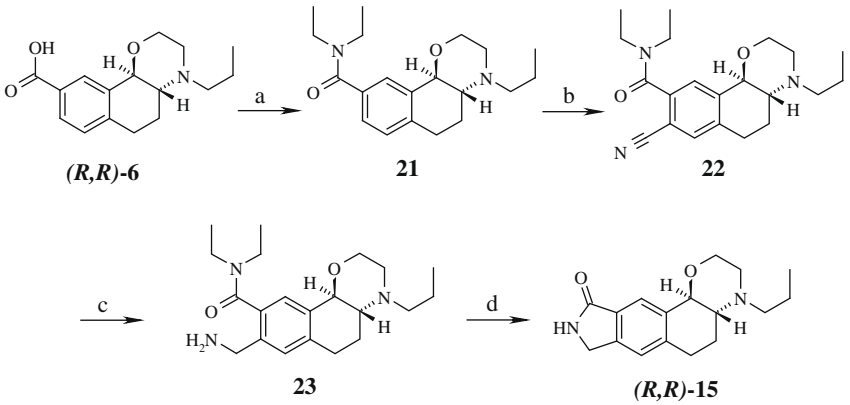
Several conclusions can be drawn from the affinities and selectivity's obtained with this second set of derivatives (Table 2). For rigidified derivatives, affinities at hD_3 and selectivity's versus hD_2 sites were markedly increased in comparison to derivatives presented in Table 1. Compound (***R***,***R***)-**15** shows the highest hD_3 receptor affinity amongst all compounds prepared in this study,



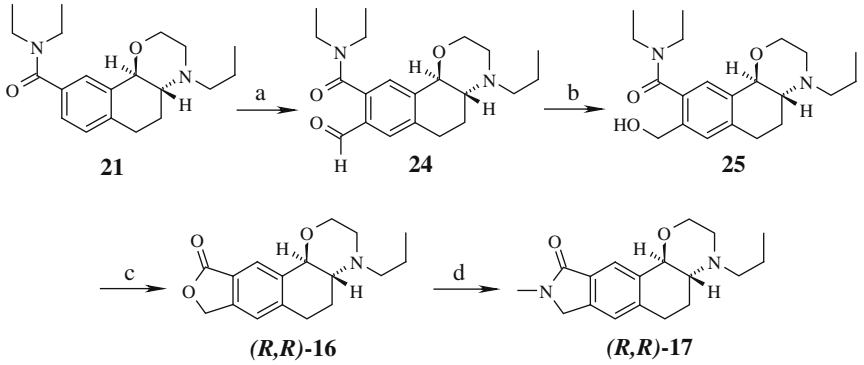
Scheme 1. Structure and preparation of compounds **2**–**9**. Reagents: (a) $Zn(CN)_2$, $Pd[P(Ph)_3]_4$, DMF, 36%; (b) KOH, EtOH, reflux, 80%; (c) (i) DMF–DMA, MeOH, (ii) MeONa, MeOH, THF, 65%; (d) NaOH, MeOH, reflux, 80%; (e) butylvinyl ether, NEt_3, Dppp, $Pd(OAc)_2$, DMF, HCl, heat 80 °C, 66%; (f) Me_3SnN_3, toluene, reflux, 60%; (g) EtOH, HClg, phosphate buffer, 85%.



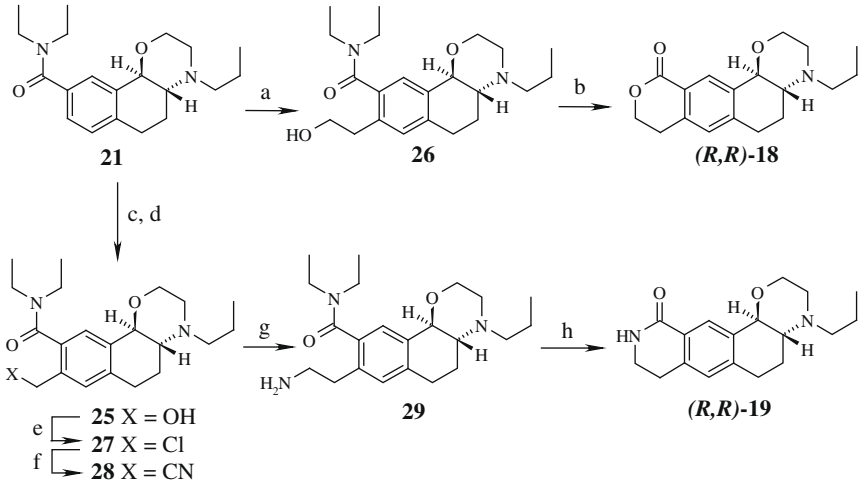
Scheme 2. Preparation of compounds (**10**–**14**).



Scheme 3. Preparation of compound **15**. Reagents: (a) $NH(Et)_2$, NEt_3, TBTU, CH_2Cl_2, 76%; (b) (i) *s*-BuLi, TMEDA, THF, (ii) PhOCN, 78%; (c) H_2, Raney Ni, MeOH, 31%; (d) *t*BuLi, THF, 99%.

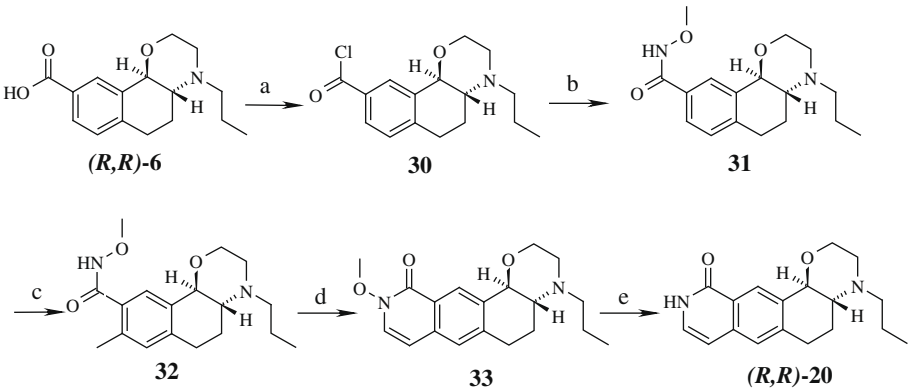


Scheme 4. Preparation of compounds **16** and **17**. Reagents: (a) (i) *s*-BuLi, TMEDA, THF, (ii) DMF, 47%; (b) $NaBH_4$, MeOH, 34%; (c) HCl 6 N, reflux, 35%; (d) $MeNH_2$, 120 °C, 25%.



Scheme 5. Preparation of compounds **18** and **19**. Reagents: (a) (i) *s*-BuLi, TMEDA, THF, (ii) LiOEtBr, 17%; (b) HCl 6 N, reflux, 57%; (c) (i) *s*-BuLi, TMEDA, THF, (ii) DMF, 47%; (d) $NaBH_4$, MeOH, 34%; (e) $SOCl_2$, 75%; (f) $(Bu)_4N^+NC^-$ (TBACN), THF, 96%; (g) H_2, Raney Ni, MeOH, 30%;, (h) *t*-BuLi, THF, −78 °C, 49%.

and the amelioration of selectivity in comparison to (***R***,***R***)-**2** was 2.5-fold. Moreover, the optical opposite (***S***,***S***)-**15** manifested only weak affinity at hD_3 receptors. Surprisingly, the second best affinity at hD_3 receptors and the most pronounced selectivity was revealed by the five-membered ring lactone (***R***,***R***)-**16**, which can be viewed as a rigidified analogue of the inactive ester **5** and acid **6**. In addition, the six-membered ring lactone **18** also interacted with hD_3 receptors, though displaying a modest pK_i of 6.9. On the other hand, the size of the extracycle seems to play a critical role for selectivity since the six-membered lactam **19** displayed 10-fold lower selectivity than the five-membered derivate (***R***,***R***)-**15**, a characteristic shared by lactone **18** which presented a selectivity twenty times inferior to lactone **16** due to a decrease of hD_3 affinity without modification of affinity at hD_2 sites. Affinity also seems dependent on the size of the cycle, since the six-membered derivatives **18** and **19** were about 10 times less potent than their five-membered analogues (***R***,***R***)-**15** and **16**. A further point to be raised is that the presence of a double bond in the six-membered cycle in-



Scheme 6. Preparation of compound **20**. Reagents and conditions: (a) $SOCl_2$, DMF, toluene, 97%; (b) $MeONH_2$, K_2CO_3, AcOEt, H_2O, 63%; (c) (i) *s*-BuLi, TMEDA, THF, (ii) CH_3I; (d) (i) *s*-BuLi, DMF, THF, (ii) HCl, THF, 25% on two steps; (e) $TiCl_3$, EtOH, reflux, 31%.

Table 2
Affinities of compounds **15**–**20** (**I**-**B**) at hD_3 and hD_2 dopamine receptors as determined by displacement of [^{3}H]-spiperone

	Affinity (pK_i)[a]		Selectivity[b]
	hD_3	hD_{2L}	$K_i(hD_2)/K_i(hD_3)$
(***R***,***R***)-**15**	8.38 ± 0.07	6.08 ± 0.18	199
(***S***,***S***)-**15**	6.05 ± 0.30	6.30 ± 0.07	0.5
(***R***,***R***)-**16**	8.12 ± 0.09	5.69 ± 0.19	250
(***R***,***R***)-**17**	5.66 ± 0.02	<5	—
(***R***,***R***)-**18**	6.92 ± 0.03	5.83 ± 0.04	12.5
(***R***,***R***)-**19**	7.42 ± 0.03	6.11 ± 0.08	20
(***R***,***R***)-**20**	7.72 ± 0.05	5.92 ± 0.01	63
(***R***,***R***)-**2**	7.83 ± 0.15	5.92 ± 0.10	80
Ropinirole	7.44 ± 0.06	6.16 ± 0.06	20

[a,b] See Table 1.

Table 3
Activation of hD_3 receptors by **2**, **15**, **16**, **19** as determined by an antibody capture/scintillation proximity assay of [^{35}S]GTPγS binding to $G\alpha_{i3}$

	(***R***,***R***)-**2**	(***R***,***R***)-**15**	(***R***,***R***)-**16**	(***R***,***R***)-**19**
pEC_{50}[a]	8.64 ± 0.07	8.85 ± 0.04	8.64 ± 0.02	8.33 ± 0.17
E_{max}	68% ± 2	74.2% ± 0.32	74% ± 5.00	34% ± 2.70

[a] pEC_{50}, −log(effective concentration$_{50}$).

creased affinity at hD_3 sites and, accordingly, selectivity (compare **20** and **19**). Finally, as for compounds **10–14**, substitution on the nitrogen atom of the lactam ring was deleterious for activity since 17, the *N*-methyl derivative of (***R***,***R***)-**15**, is devoid of activity.

Subsequently, it was necessary to verify the efficacy of the most potent and selective derivatives (***R***,***R***)-**15**, **16** and **19**. Indeed, the adjunction of the extra ring may in theory have transformed agonist into antagonist activity. For this purpose, we assessed the ability of these three compounds to stimulate hD_3 receptors. Table 3 shows their potency and maximal efficacies for activation of hD_3 receptors expressed relative to those of dopamine-induced facilitation of [^{35}S]GTPγS binding to $G\alpha_{i3}$, a G-protein isoform preferentially recruited by hD_3 and hD_2 receptors.[19,35]

The five-membered ring lactam (***R***,***R***)-**15** and lactone (***R***,***R***)-**16** are comparable in potency and maximal efficacy to the agonist (***R***,***R***)-**2**, but the six-membered ring lactam (***R***,***R***)-**19**, albeit as potent as (***R***,***R***)-**2**, is much less efficacious suggesting that the size of the extra ring plays an important role in determining ligand efficacy.

Replacement of the amide function of S32504 by an ester, acid, tetrazole or cyano function improved neither affinity at D_3 receptors nor selectivity versus D_2 receptors, while mono or disubstituted amide derivatives were devoid of activity. On the other hand, transformation of this primary amide function in lactam (***R***,***R***)-**15** or lactone (***R***,***R***)-**16** improved both potency and selectivity, providing that the additional ring was five-membered one. A five-membered ring is also requisite for maximal efficacy since the six-membered lactam (***R***,***R***)-**19** was less active. Since (***R***,***R***)-**15** behaved as a potent D_3 agonist in vitro with marked selectivity towards D_2 receptors ([^{35}S]GTPγS, pEC_{50} = 6.57 ± 0.2, E_{max} = 54%), further testing in animal models of Parkinson and depression are currently under progress and results will be reported in due course.

Acknowledgments

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21. Triflate **3** was prepared from compound **25** of Ref. 16. **25** was first reduced by $LiAlH_4$ and then transformed in triflate by using triflic anhydride.
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28. Characterization of (***R***,***R***)-**2**: mp 198–199 °C, $[\alpha]_D^{20}$ +65.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6) (δ ppm): 0.90 (t, 3H), 1.60–1.35 (m, 3H), 2.40–2.00 (m, 4H), 2.98–2.70 (m, 4H), 3.78 (m, 1H), 4.00 (dd, 1H), 4.20 (d, 1H), 7.14 (d, 1H), 7.15 (s, 1H), 7.66 (dd, 1H), 7.90 (s, 1H), 7.94 (s, 1H).
29. Crystallographic data for the structure in this Letter have been deposited in the Cambridge Crystallographic Data Centre for small molecules as supplementary publication number CCDC 713653. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.
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31. Characterization of (***R***,***R***)-**15**·**HCl**: mp 287–291 °C, $[\alpha]_D^{20}$ +52.4 (*c* 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) (δ ppm): 0.92 (t, 3H), 1.53 (m, 2H), 1.64 (m, 1H), 2.29 (m, 3H), 2.46 (td, 1H), 2.82 (m, 1H), 2.89 (d, 1H), 3.00 (m, 2H), 3.95 (td, 1H), 4.09 (m, 1H), 4.35 (d, 1H), 4.38 (m, 2H), 6.68 (m, 1H), 7.16 (s, 1H), 8.09 (s, 1H).
32. Characterization of (***R***,***R***)-**16**·**HCl**: mp 268–271 °C. ^{1}H NMR (300 MHz, DMSO-d_6) (δ ppm): 0.95 (t, 3H), 1.75 (sext, 2H), 2.10 (m, 1H), 2.55 (m, 1H), 3.15–2.95 (m, 3H), 3.45–3.15 (m, 3H), 3.60 (m, 1H), 4.25 (m, 2H), 5.10 (d, 1H), 5.40 (s, 2H), 7.50 (s, 1H), 7.80 (s, 1H), 11.90 (m, 1H).
33. Characterization of (***R***,***R***)-**19**·**HCl**: mp 263–265 °C. ^{1}H NMR (300 MHz, DMSO-d_6) (δ ppm): 1.00 (t, 3H), 1.75 (m, 2H), 2.00 (m, 1H), 2.50 (m, 2H), 2.85 (m, 2H), 3.00 (m, 3H), 3.4–3.15 (m, 5H), 3.60 (m, 1H), 4.25 (m, 2H), 5.00 (d, 1H), 7.10 (s, 1H), 7.75 (s, 1H), 7.90 (s, 1H).
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35. The activation of $G\alpha i_3$ subunit by hD_3 receptors in CHO cells was quantified using the classical [^{35}S]GTPγS binding assay coupled to an antibody capture/scintillation proximity assay (SPA) in 96-well plates (PerkinElmer Life Sciences). Membranes from CHO cells expressing hD_3 receptors were incubated with increasing concentration of each compound for 30 min before addition of a mouse monoclonal antibody specifically recognizing the $G\alpha i_3$ subunits recruited by D_3 receptors. After 1 h of incubation, the activation of $G\alpha i_3$ proteins was detected by adding scintillation beads, coated with anti-mouse secondary antibodies, which emitted light when stimulated by the [^{35}S]GTPγS bound.