Pergamon

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Bioorganic & Medicinal Chemistry Letters 13 (2003) 1591–1595

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Design, Synthesis, and Activity of Novel *cis*- and *trans*-3,6-Disubstituted Pyran Biomimetics of 3,6-Disubstituted Piperidine as Potential Ligands for the Dopamine Transporter

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Received 4 November 2002; accepted 16 December 2002

Abstract—In our effort to develop novel molecules for the dopamine transporter, we converted our previously designed dopamine transporter specific 3,6-disubstituted piperidine template into corresponding pyran derivatives. *cis*-Pyran derivative **7b**, like their piperidine counterparts, exhibited greater activity for the dopamine transporter compared to the *trans*-isomer. Further molecular modifications of the *cis* derivative led to the development of potent analogues which indicated successful bioisosteric replacement of the piperidine ring by a pyran moiety in these 3,6-disubstituted derivatives.

Cocaine is a potent drug of abuse which poses a great burden to our society due to its impact on the economy, crime and spread of HIV.[1] Extensive studies have been conducted so far to understand the mechanism of action of cocaine which might eventually lead to development of a much needed medication for cocaine dependence. Cocaine binds to all three monoamine transporter systems in the brain but its central reinforcing action is thought to be derived mainly from binding to the dopamine transporter (DAT).[2,3] This does not rule out the involvement of nondopaminergic systems in cocaine reward pathways (Fig. 1).[4]

Many efforts have been directed so far to develop molecules targeting DAT. These have resulted in the generation of a database with many molecules exhibiting high selectivity and potency for the DAT. Two comprehensive review articles have been published so far which describe this work in detail.[5,6] Our effort to develop molecules targeting DAT started with piperidine analogues of GBR 12909. Our structure–activity relationship study led to development of many potent and highly selective molecules for the DAT and some of them exhibited interesting in vivo properties.[7–9] In our recent effort to design structurally constrained molecule of flexible piperidine analogues of GBR derivatives, we converted one of our lead piperidine analogues into structurally constrained 3,6-disubstituted piperidine derivatives (Fig. 2). Our study demonstrated that the *cis*-structure in this novel template exhibited preferential interaction with the DAT compared to the *trans*-structure.[10] Our initial study was later followed by a more extensive structure–activity study that produced potent optically active 3,6-disubstituted compounds, thus, confirming the specificity of this novel template for the DAT.[11] In our current study, we wanted to extend these findings by replacing the piperidine ring by a pyran moiety.

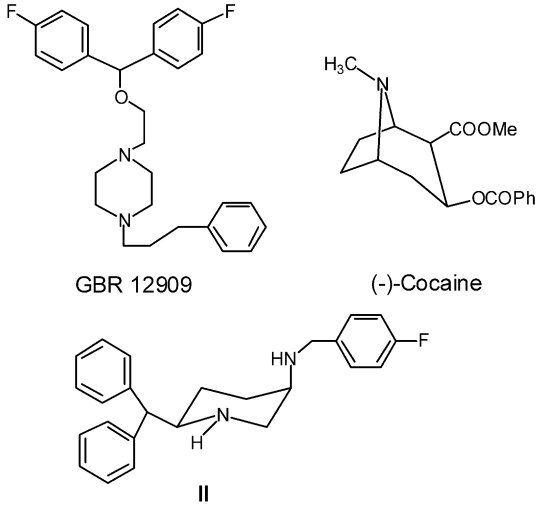

Figure 1. Structure of dopamine transporter blockers.

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doi:10.1016/S0960-894X(03)00169-0

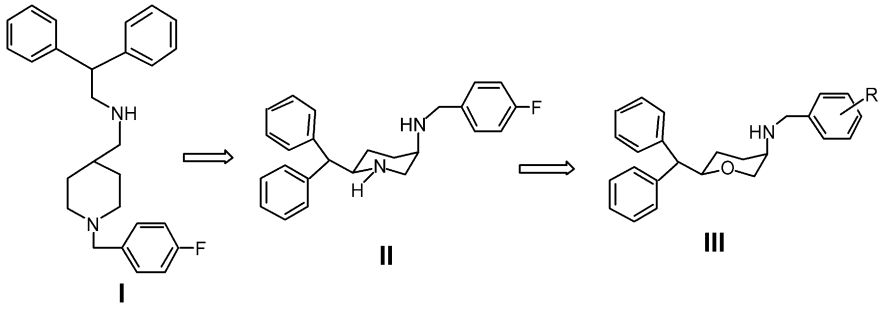


Figure 2. Structural transformation of **I** into more conformationally constrained molecule.

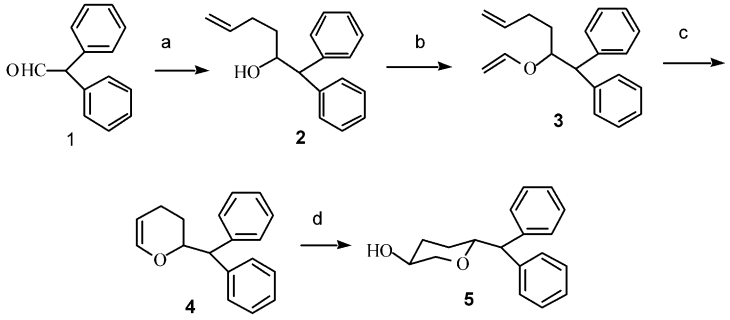
Transformation of certain DAT-selective 3-aryltropane analogues into oxy-3-aryltropane derivative was carried out earlier and was shown to have minimal influence on activity for the DAT compared to its parent bioisosteric N-analogues.[12] On the other hand, benztropine molecules that underwent such transformation to oxy-benztropine analogues, lost their potency completely for the DAT.[13] These results are interesting since both oxy-3-aryltropane and oxy-benztropine analogues contain constrained pyran moiety albeit oxy-3-aryltropane analogues contain additional substitutions; yet they exhibited different pharmacological properties. The results also point to the N-atom in benzopyran as a critical requirement for binding to the DAT whereas the N-atom in 3-aryltropane analogues may be not so critical, reflecting a possible involvement of different binding modes between these two series of compounds. Hence, a structurally constrained pyran moiety requires more molecular specificity for exhibiting activity at DAT compared to a structurally constrained piperidine motif. In our study, we decided to explore this specificity further by converting our newly developed 3,6-disubstituted piperidine template into corresponding pyran analogues. Several changes may occur in molecular interaction with the receptor with such modification. Conceivably, the mode of interaction between DAT and pyran derivatives may differs from their bioisosteric piperidine counterparts. Moreover, CNS-active pyran derivatives are relatively rare and it will be interesting to examine how pyran derivatives behave in in vivo experiments compared to their piperidine counterparts.

The synthesis of our target compounds is shown in Schemes 1–3.

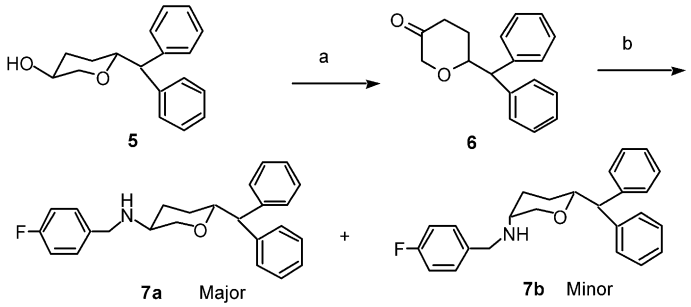
Scheme 1 delineates the preparation of the key intermediate **5**. Diphenylacetaldehyde **1** reacted with a Grignard reagent, prepared in situ by reacting magnesium with 4-bromo-1-butene, to furnish 1,1-diphenyl-hex-5-en-2-ol **2** in 91% yield.[14] Vinyllation of compound **2** with ethyl vinyl ether in presence of mercury trifluoroacetate produced 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene **3** in 66% yield.[15] Ring closing metathesis of **3** with Grubb's catalyst in refluxing benzene afforded cyclic olefin **4** in 92.6% yield.[16] Hydroboration of **4** with 9-BBN in THF, followed by oxidation with NaOH and H_2O_2, regioselectively produced hydroxylated compound **5**. The compound *trans*-6-benzhydryl-tetrahydropyran-3-ol **5** was obtained in major amount (93.5% yield).

As described in Scheme 2, compound **5** was subjected to Swern oxidation condition, which produced the keto product **6**, 6-benzhydryl-dihydro-pyran-3-one, in 91% yield. This was followed by reductive amination[10] with 4-fluoro-benzylamine to produce the target compound **7a**, *trans*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-fluoro-benzyl)-amine, as a major product in 50% yield.

Scheme 3 shows the synthesis of *cis*-target compounds. Compound **5** was converted into amine **10**, *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-amine, by three steps in overall 85% yield. Thus, mesylation with methanesulfonyl chloride and triethylamine in dichloromethane produced **8** which on displacement with sodium azide in DMF produced azide **9**. Catalytic hydrogenation in presence of 10% Pd/C as a catalyst in methanol yielded amine **10** in good yield. Reductive amination of compound **10** with various aldehydes furnished target *cis* compounds **7b–e** in good yield.



Scheme 1. (a) 4-Bromo-1-butene, Mg, Et_2O; (b) ethyl vinyl ether, $Hg(OCOCF_3)_2$; (c) Grubb's catalyst, benzene; (d) 9-BBN/THF NaOH, H_2O_2.



Scheme 2. (a) DMSO, oxalyl chloride, Et_3N; (b) 4-fluorobenzylamine, AcOH, $ClCH_2CH_2Cl/NaCNBH_3$ MeOH.

The assignment of the structures of target compounds was determined by 1-D and 2-D NMR (300 MHz) experiments.[17,18] The assumption that the diphenylmethyl moiety would assume the equatorial position was confirmed by the NMR data.

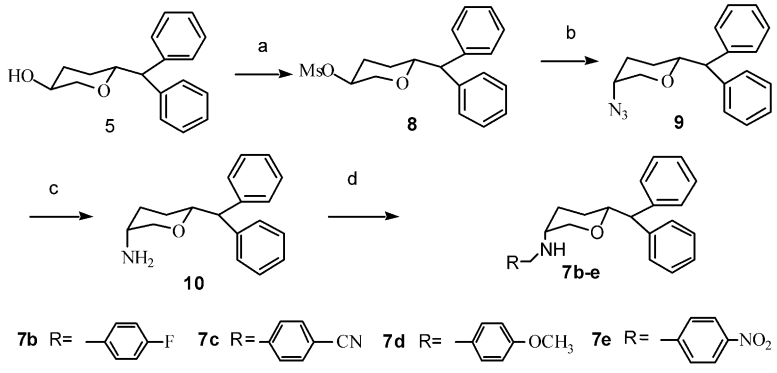
In the *trans* compound **7a** (Table 1), the signal attributed to H-6, δ 3.99, is a doublet of triplets ($^3J = 2.1$ and 9 Hz) where $^3J_{5ax,6} = {}^3J_{6,CH(Ph)2}$. The large coupling constant between H-6 and H-5ax is consistent with H-6's axial orientation. The triplet of triplets signal at δ 2.68 ($^3J = 4.2$ Hz and 10.5 Hz) attributed to H-3 is 39 Hz broad composed of $\Sigma\left({}^3J_{2ax,3} + {}^3J_{3,4ax} + {}^3J_{2eq,3} + {}^3J_{3,4eq}\right)$. The axial orientation of H-3 can be confirmed by having two smalls $^3J_{ax,eq}$ and two large $^3J_{ax,ax}$ coupling. This orientation also can be confirmed by the signal at δ 3.11 ppm attributed to H-2ax which appears as triplet ($^2J_{2ax,2eq}$ and $^3J_{2ax,3}$) with $^2J = {}^3J = 10.5$ Hz.

In the *cis* compound **7b** (Table 1), the signal from H-6, δ 4.08, appears as doublet of triplet with $^3J = 2.4$ Hz and 9 Hz, same as in the *trans* compound. The multiplet signal at δ 2.64 with width of 12 Hz, attributed to H-3. This small Σ^3J is consistent with H-3 equatorial orientation, which has same vicinal coupling from adjacent four protons ($^3J_{2ax,3} + {}^3J_{2eq,3} + {}^3J_{4ax,3} + {}^3J_{4eq,3}$). This equatorial orientation also can be confirmed by the signals from H-2, two doublet of doublets with $^3J = 1.8$ Hz and $^2J = 11.4$ Hz. the large coupling is from the geminal coupling of the two protons in C-2, the small one is from vicinal coupling with H-3.

In addition, the axial orientation of H-6 was also confirmed by the nuclear Overhauser experiment. Irradiation of H-2ax resulted in an enhancement of H-6 and H-2eq signal. Therefore, diphenylmethyl moiety must be equatorially oriented in order to have this interaction.

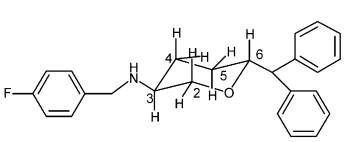
Our earlier SAR results delineated certain differences between flexible and constrained piperidine analogues which reflected different requirement of molecular determinants for their activity for DAT. One of our goals in this endeavor is to gain an understanding of bioactive conformations of molecules through this molecular rigidification. As a part of extension of our studies from piperidine derivatives, in this current study, we wanted to examine biological properties of corresponding bioisosteric pyran derivatives.

Following our synthesis, novel molecules were characterized for their potency in binding to the monoamine transporter systems by monitoring inhibition of binding of [^{3}H]WIN 35, 428 to DAT, [^{3}H]citalopram to SERT, and [^{3}H]nisoxetine to NET in rat brain tissue (Table 2). The current *trans*- and *cis*-derivatives, **7a** and **7b** correspond to our initial 3,6-disubstituted piperidine derivatives. The objective was to test whether the same *cis* isomeric preference for the DAT exhibited by the piperidine version is also maintained in these pyran derivatives. Binding results confirmed this outcome by showing higher activity in the expected *cis*-compound **7b** albeit less potent than the corresponding piperidine version **II**. Interestingly, a difference in activity was found for their interaction with the NET as the *cis*-pyran derivative **7b** was 4-fold more active at the NET compared to the piperidine version **II**.

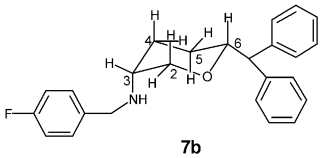


Scheme 3. (a) Ch_3SO_2Cl, Et_3N/CH_2Cl_2; (b) NaN_3/DMF; (c) H_2/Pd/C, MeOH; (d) aldehyde, AcOH, $ClCH_2CH_2Cl/NaCNBH_3$, MeOH.

Table 1. Selected NMR data of **7a** and **7b**



7a



7b

Compd	Chemical shift	Multiplicity	Coupling constants
7a	H_{2ax}, 3.11	t	$J_{2ax,2eq} = J_{2ax,3eq} = 10.5$ Hz
	H_{3ax}, 2.68	tt	$J_{2eq,3ax} = J_{4eq,3ax} = 4.2$ Hz $J_{2ax,3ax} = J_{4ax,3ax} = 10.5$ Hz
	H_{6ax}, 3.99	dt	$J_{5eq,6ax} = 2.1$ Hz $J_{CH(Ph)2,6ax} = J_{5ax,6ax} = 9$ Hz
7b	H_{2ax}, 3.57	dd	$J_{2ax,3eq} = 1.8$ Hz, $J_{2eq,2ax} = 11.4$ Hz
	H_{3eq}, 2.64	m	Peak width = 12 Hz
	H_{6ax},4.08	dt	$J_{5eq,6ax} = 2.4$ Hz $J_{CH(Ph)2,6ax} = J_{5ax,6ax} = 9$ Hz

Table 2. Affinity of drugs at the dopamine, serotonin and norepinephrine transporters in rat striatum and in inhibition of dopamine (DA) reuptake

Compd	DAT binding, IC_{50} (nM), [^{3}H]WIN 35, 428[a]	SERT binding, IC_{50} (nM), [^{3}H]citalopram[a]	NET binding, IC_{50} (nM), [^{3}H]nisoxetine[a]	DAT uptake, IC_{50} (nM), [^{3}H]DA[a]
Cocaine	266±37	737±160	3530±554	
GBR 12909	10.6±1.9	132±0	496±22	6.63±0.43
I	19.7±1.4	137±46	1110±120	49.6±7.2
(±)-**II**	32.5±12.6	2220±590	1020±72	45.7±5.1
(±)-**7a**	313±71	8410±163	12,700±3,180	
(±)-**7b**	163±29	1860±22	232±46	156±36
(±)-**7c**	52.6±5.9	863±52	1580±89	58.6±13.2
(±)-**7d**	84.0±6.5	1180±269	1550±682	59.5±11.6
(±)-**7e**	38.3±3.9	738±164	968±98	102±7

Results are average ±SEM of three independent experiments assayed in triplicate
[a]The DAT was labeled with [^{3}H]WIN 35,428, the SERT with [^{3}H]citalopram and the NET with [^{3}H] nisoxetine (see ref 8 for details).

Effects of both electron withdrawing and electron donating substituents were tried on the phenyl ring of the *N*-benzyl group. Thus, the electron donating methoxy substituent in compound **7d** made it more potent at DAT than **7b** (Table 2). On the other hand, the strong electron withdrawing substituents cyano and nitro in compounds **7c** and **7e** resulted in the development of greater potencies in these compound. In this regard, the racemic cyano compound **7c** was about one and half time less potent at DAT than the corresponding piperidine version analogue. Affinity of these compounds for the SERT and NET were weak demonstrating their preferential interactions with the DAT.

Evaluation of inhibition of dopamine uptake activity was carried out with the new derivatives. No differential activity was observed between binding and uptake potency except in compound **7e**. Compound **7e** was almost three times more potent in inhibiting binding than in inhibiting uptake.

In conclusion, we have synthesized novel 3,6-di-substituted-pyran derivatives, which showed preferential affinity for the DAT. The synthesis of these compounds was carried out with a key intermediate step, which involved ring formation via a ring closing metathesis process by using Grubb's catalyst to generate the key intermediate **5**. Stereochemistry of the target products **7b–e** was controlled by selective displacement of a good leaving group in compound **8**. Our current results indicate that bioisosteric replacement of the N-atom by an oxygen atom did not interfere with activity at the DAT, although it is not known at this time whether the two groups of compounds bind in an identical manner. We are currently expanding our initial findings with expanded SAR studies to explore this aspect in greater detail. In addition, our future in vivo studies with these compounds will tell whether 3,6-pyran derivatives, despite the fact that their binding activities at DAT are similar to those of the corresponding piperidine analogues, exert differential behavioral activities.

Acknowledgements

This work was supported by the National Institute on Drug Abuse, Grant No. DA 12449 (AKD). We thank Mrs. Janet L. Berfield and Li Juan Wang for performing the binding and uptake assays.

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17. Racemic **7a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18–1.44 (m, 2H, H-5), 1.55 (m, 1H, H-4), 1.75 (bm, NH), 2.02 (m, 1H, H-4), 2.68 (tt, $J=4.2$ Hz, 10.5 Hz, 1H, H-3), 3.11 (t, $J=10.8$ Hz, 1H, H-2ax), 3.76 (s, 2H, (F)–Ph–CH_2), 3.86 (d, $J=9$ Hz, 1H, Ph_2CH), 3.99 (dt, $J=3$ Hz, 8.7 Hz, 1H, H-6), 4.06 (m, 1H, H-2eq), 6.9–7.38 (m, 14H, aromatic–CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 29.93, 31.46, 50.81, 53.37, 57.78, 73.00, 79.42, 126.50, 126.73, 128.56, 128.65, 128.80, 129.77, 129.88. Free base was converted into oxalate $C_{27}H_{28}NO_5F$ $0.65H_2O$. Anal. theory C 67.96H 6.19 N 2.94, found C 67.93H 6.02 N 3.02.
18. Racemic **7b** ^{1}H NMR (300 MHz, $CDCl_3$) 1.33 (m, 1H, H-5), 1.46–1.72 (m, 2H, H-5, H-4), 1.94 (m, 1H, H-4), 2.03 (bm, 1H, NH), 2.64 (m, 1H, H-$_{3eq}$), 3.57 (dd, $J=1.8$ Hz, 11.4 Hz, 1H, H-2ax), 3.75 (m, 2H, (F)Ph–CH_2), 3.95–4.14 (m, 3H, H-6, H-2eq, Ph_2CH), 4.08 (dt, $J=2.4$ Hz 9 Hz, 1H, H_{69x}), 6.9–7.38 (m, 14H, aromatic–CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 21.50, 29.95, 32.00, 55.72, 65.62, 76.05, 101.50, 126.88, 127.09, 128.60, 128.68, 128.90, 128.97, 141.36, 141.62. Free base was converted into oxalate $C_{27}H_{28}NO_5F$. Anal. theory C 69.66H 6.06 N 3.01, found C 69.60H 6.09 N 2.97.