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Multitarget 1,4-Dioxane Compounds Combining Favorable D_2-like and 5-HT_{1A} Receptor Interactions with Potential for the Treatment of Parkinson's Disease or Schizophrenia

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Abstract

The effect of methoxy and hydroxy substitutions in different positions of the phenoxy moiety of the *N*-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)-2-phenoxyethan-1-amine scaffold on the affinity/activity for D_2-like, 5-HT_{1A} and α_1-adrenoceptor subtypes was evaluated. Multitarget compounds with suitable combinations of dopaminergic and serotoninergic profiles were discovered. In particular, the 2-methoxy derivative **3** showed a multitarget combination of 5-HT_{1A}/D_4 agonism and D_2/D_3/5-HT_{2A} antagonism, which may be a favorable profile for the treatment of schizophrenia. Interestingly, the 3-hydroxy derivative **8** behaved as a partial agonist at D_2 and as a potent full agonist at D_3 and D_4 subtypes. In addition to its potent 5-HT_{1A} receptor agonism, such a dopaminergic profile makes **8** a potential multitarget compound for the treatment of Parkinson's

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Author Contributions

F.D.B., D.A., M.G., G.G., A.P., L.C., S.F. and W.Q. designed the novel compounds and planned the procedures for their synthesis. F.D.B. and D.A. developed the chemical synthesis and characterized the novel compounds. They wrote the relative chemical experimental parts of the manuscript. A.C. performed binding experiments at 5-HT_{1A} receptors and α_1-AR subtypes. A.B., T.M.K. and A.H.N. performed binding experiments at dopamine D_2, D_3 and D_4 receptors, provided functional assays through the NIDA Addiction Treatment Discovery Program contract with Oregon Health & Science University and discussed the biological data. G.G. and W.Q. drafted the main text of the manuscript. All authors critically discussed and approved the final version of the manuscript.

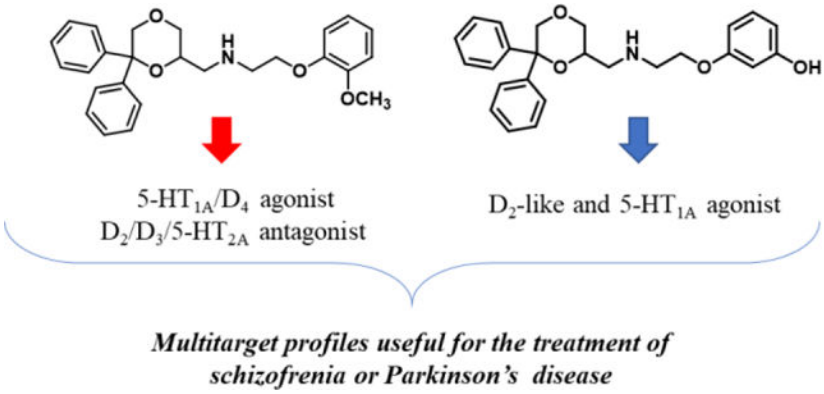
ASSOCIATED CONTENT

Supporting Information. Figures S1–S3, representing the bar graph versions of Tables 1 and 2.

The authors declare no competing financial interest.

disease (PD). Indeed, the activation of 5-HT_{1A} receptors might be helpful in reducing dyskinetic side effects associated with dopaminergic stimulation.

Graphical Abstract



Keywords

serotonin receptors; dopamine receptors; 1,4-dioxane derivatives; multitarget agents; Parkinson's disease; schizophrenia

The multitarget or "magic shotgun" approach to drug discovery has been raised with an increasing interest and awareness within the medicinal chemistry community, owing to its advantages in the treatment of complex diseases.[1] Although in some cases combined therapies are used, multitarget drugs may offer clear advantages, including more predictive pharmacokinetics, better patient compliance, and reduced risk of drug interactions.[2,3]

Several neurotransmitter pathways are functionally altered in complex diseases, such as psychiatric and neurodegenerative disorders.[4] Among them, central dopamine (DA) and serotonin (5-HT) receptor systems play crucial roles in regulating psycho-emotional, cognitive and motor functions in the central nervous system (CNS). In the DA receptor system, D_2-like receptors, comprising D_2, D_3, and D_4 subtypes, are involved in several pathological conditions in the CNS and thus are considered attractive drug targets.[5] In particular, full or partial D_2 and D_3 receptor agonists are widely used in Parkinson's disease (PD) therapy, whereas D_2/D_3 receptor antagonists or partial agonists proved to be efficacious in the treatment of schizophrenia. Noteworthy, different DA disorders might be treated with D_2/D_3 partial agonists with different levels of intrinsic activity. In particular, D_2/D_3 partial agonists endowed with higher intrinsic activity are efficacious in case of DA activity deficiency (e.g. PD), while for "DA hyperactivation" diseases (e.g. schizophrenia) lower intrinsic activity D_2/D_3 partial agonists are preferred.[5–8]

Moreover, D_4 receptor agonists may be useful in reversing cognitive deficits in schizophrenia.[9] Early reports indicated that D_4 antagonists might be potential therapeutic agents for attenuating L-DOPA-induced dyskinesias.[10] Additional data also highlight the therapeutic benefit of molecules targeting the 5-HT_{1A} receptor in treating schizophrenia and PD.[11]

The multitarget approach, combining DA and 5-HT receptor systems, revealed improved results in the treatment of polyfactorial pathologies such as PD and schizophrenia.[12,13] In particular, the combination of 5-HT_{1A} receptor agonism, D_2/D_3 antagonism and 5-HT_{2A} antagonism has been reported to be beneficial in the treatment of schizophrenia.[14,15] 5-HT_{1A} receptor agonists may also behave as adjuvants in ameliorating the induction of dyskinesia in L-DOPA-treated PD patients.[16,17] SLV-308 (pardoprunox), a multitarget agent in which a full 5-HT_{1A} receptor agonism is associated with a partial D_2/D_3 receptor agonism (Figure 1), reached phase III clinical trials for the treatment of PD. Compared with other dopaminergic agents, SLV-308 has lower propensity to elicit side effects like dyskinesia.[18] Therefore, ligands endowed with such a multitarget profile might be effective in PD pharmacotherapy.

WB-4101 (**1**, Figure 2), a well-known α_1-adrenoceptor (α_1-AR) antagonist, has been the starting point of numerous SAR studies previously reported by us. This compound also shows good affinity for 5-HT_{1A} receptors ($pK_i = 8.61$) and moderate affinity for D_2-like receptors ($pK_i = 6.91$).[19] This compound includes two phenoxyethylamine fragments, which might play a role in determining its affinity for DA receptors. In fact, this fragment is part of the chemical structures of several ligands endowed with DA receptor affinity.[20–22] Extensive structure-activity relationship (SAR) studies described for adrenergic and serotoninergic receptors demonstrated that the replacement of the 1,4-benzodioxane nucleus of **1** with the 6,6-diphenyl-1,4-dioxane scaffold, affording compound **2**, significantly decreased the affinity for α_1-AR subtypes, while maintaining high affinity for 5-HT_{1A} receptor (Table 1).[23] The removal of one or both of the *ortho* methoxy groups of **2** led to compounds **3** and **4**, respectively, which behaved as potent 5-HT_{1A} receptor and α_1-AR ligands with high selectivity for α_{1d} over α_{1a} and α_{1b} subtypes.[23] Recently, compound **3** and its 2-hydroxy and 2-(methoxymethoxy) analogues **5** and **6** (Figure 2), all endowed with nanomolar 5-HT_{1A} receptor affinity, were evaluated at D_2-like receptor subtypes. Among them, **5** and especially **3** displayed good affinity for all the D_2-like receptor subtypes (Table 1).[24]

Altogether, the results obtained so far have demonstrated that small changes of the substituents on the phenoxy terminal of this class of compounds differentially affect the affinity profiles at D_2-like, 5-HT_{1A} and α_1-AR subtypes. On the basis of this observation and encouraged by the interesting 5-HT_{1A}/D_2-like receptor affinity profiles of the 2-methoxy and the 2-hydroxy derivatives **3** and **5**, respectively, the aim of the present study was to obtain novel multitarget analogues with improved D_2-like receptor affinity, high affinity for 5-HT_{1A}, and low affinity for α_1-AR subtypes. As mentioned above, this multitarget affinity profile might be favorable in schizophrenia or PD pharmacotherapy, depending on the combination of functional potencies and efficacies.

To pursue this aim, the effect of the substituent in different positions of the phenoxy terminal was explored by moving the methoxy or hydroxy groups of the known compounds **3** and **5**, respectively, from *ortho* to *meta* and *para* positions, affording the novel compounds **7**-**10** (Figure 2). Moreover, the high 5-HT_{1A} receptor affinity and selectivity over α_1-AR shown by the previously reported 2,6-dimethoxy derivative **2** prompted us to evaluate this compound for its affinity at D_2-like receptor subtypes and to investigate the effect of di-

substitution in different positions on the phenoxy moiety, by studying the novel compounds **11**-**13** (Figure 2).

The novel compounds **7**-**13** were tested at human D_2, D_3, D_4, 5-HT_{1A} receptors and α_1-AR subtypes, in radioligand competition binding assays. The previously reported compound **4** was also tested for its affinity at D_2-like receptor subtypes, to evaluate the effect of removal of substituents in the phenoxy moiety. Finally, the pharmacological profile of the most interesting compounds **3** and **8** was further assessed in binding assays at other selected targets and in *in vitro* functional assays at receptors in which they showed the highest affinities.

RESULTS AND DISCUSSION

The novel compounds were prepared following the procedure described in Scheme 1. The suitable amines **14–20**, commercially available or prepared according to previously reported procedures,[25–27] were reacted with the iodo derivative **21**[23] or the tosyl derivative **22**[28] in 2-methoxyethanol, to give the final compounds **7**, **9**, **11**-**13**, and the intermediates **23** and **24**. The 3- and 4-hydroxy derivatives **8** and **10**, respectively, were prepared by cleavage of the benzyl group of **23** and **24** with 4% formic acid in methanol in the presence of 10% palladium on activated charcoal as a catalyst.

The pharmacological profiles of **7–13** were evaluated by radioligand competition binding assays using the radioligands [^{3}H]*N*-methylspiperone to label hD_2, hD_3 or hD_4 receptors stably expressed in HEK293 cells, [^{3}H]Prazosin to label cloned human α_1-ARs expressed in CHO cells and [^{3}H]8-OH-DPAT to label cloned human 5-HT_{1A} receptors expressed in HeLa cells, according to previously reported procedures.[29–32] The previously reported compounds **2** and **4** were also evaluated at hD_2, hD_3, and hD_4 subtypes. The affinity values, expressed as pK_i, were calculated according to the Cheng–Prusoff equation[33] and are reported in Table 1 together with those of **3**, **5**, and **6**, included for useful comparison. For the most interesting compounds **3** and **8** the affinity values, expressed as pK_i, were also determined by receptor binding assays at other targets, using [^{3}H]SCH23390 to label human D_1 receptors stably expressed in mouse fibroblast cells, and I^{125}DOI to label human 5-HT_{2A} and 5-HT_{2C} receptors stably expressed in HEK cells (data were obtained through the NIDA Addiction Treatment Discovery Program contract with Oregon Health & Science University).

From an analysis of the data reported in Table 1 it can be observed that all the novel compounds **7**-**13** show low affinity for α_1-AR subtypes (all pK_i values ≤ 7.01). The unsubstituted compound **4** binds D_2-like receptor subtypes and shows a modest preference for the D_3 subtype (D_3/D_4 = 13.4, D_3/D_2 = 4.6). Concerning the methoxy-substituted derivatives, the shifting of the methoxy group of **3** from the 2- to 3-position of the phenoxy terminal, affording compound **7**, causes a significant decrease in the affinity for all the studied targets with the exception of 5-HT_{1A} receptor (pK_i = 8.91). Therefore, unlike the lead **3**, its isomer **7** proved to be highly selective for the 5-HT_{1A} receptor over α_1-AR and D_2-like subtypes. Instead, the presence of the methoxy substituent in the 4-position (compound **9**) is detrimental for the affinity for all studied receptors. The insertion of a second methoxy group in the 6-position of the phenoxy moiety of **3** (compound **2**) reduced

the affinities for D_2, D_3 and D_4 receptors. Therefore, this compound proved to be highly selective for the 5-HT_{1A} receptor not only over α_1-ARs,[23] but also over the D_2-like receptor subtypes. All the other di-substituted derivatives (**11**-**13**) show decreased affinities for all the targets compared to the mono-methoxy lead **3**.

Concerning the hydroxy-substituted compounds, analogously to what was observed for the methoxy derivatives, no favorable effect on the affinities for all the studied targets was observed when the hydroxy group is in the *para* position (compound **10**), leading us to hypothesize that the steric bulk in this position is detrimental for the interaction with such receptor systems. Compared to the 2-hydroxy derivative **5**, the 3-hydroxy isomer **8** maintains high affinity for the 5-HT_{1A} receptor and low affinity for α_1-ARs. Interestingly, compound **8** also shows significantly increased affinities for D_2, D_3, and D_4 receptors.

Overall, among the mono-substituted derivatives, the methoxy in 2-position favors a good 5-HT_{1A}/D_2-like affinity profile combination, but also confers to compound **3** high affinity for α_{1d}-AR. A more optimally balanced 5-HT_{1A}/D_2-like multitarget profile is seen with the 3-hydroxy derivative **8**, which also binds all the α_1-AR subtypes with very low affinity (all pK_i values ≤ 6.56).

Due to their interesting multitarget 5-HT_{1A}/D_2-like affinity profiles, compounds **3** and **8** were also evaluated by binding assays at other selected targets (D_1, 5-HT_{2A}, and 5-HT_{2C} receptors - data were obtained through the NIDA Addiction Treatment Discovery Program contract with Oregon Health & Science University). The results reveal that compound **8** shows affinity values for all the studied targets (pK_i: D_1 = 6.91, 5-HT_{2A} = 5.85, 5-HT_{2C} = 5.01) lower than those of compound **3** (pK_i: D_1 = 7.64, 5-HT_{2A} = 7.28, 5-HT_{2C} = 5.74) and has, therefore, the best multitarget 5-HT_{1A}/D_2-like selectivity profile within this series of compounds.

Compounds **3** and **8** were also evaluated in *in vitro* functional assays at all receptors for which they had pK_i values > 6. The results, reported in Table 2, show that derivative **3** behaves as an antagonist with very low potency at the D_1 receptor and with higher potencies at D_2 and D_3 subtypes. On the contrary, it is a potent full agonist at the D_4 receptor. Concerning the serotoninergic system, its previously reported high 5-HT_{1A} agonist potency[23] is associated with a weak antagonism at the 5-HT_{2A} subtype. Considering that the combination of 5-HT_{1A} receptor agonism, D_2/D_3 antagonism and 5-HT_{2A} antagonism has been reported to be beneficial in the treatment of schizophrenia,[14,15] and that D_4 receptor stimulation might improve cognitive impairment associated with schizophrenia,[9] the multitarget pharmacological profile of **3** might be advantageous in the treatment of such a disorder.

The 3-hydroxy derivative **8** behaves as a very weak antagonist at D_1, as a partial agonist at D_2 and as a potent full agonist at D_3 and D_4 subtypes. Moreover, it shows a potent 5-HT_{1A} receptor agonism, that might be helpful in reducing dyskinetic side effects associated with dopaminergic stimulation. The multitarget profile of **8** makes this compound a potential therapeutic agent for the treatment of PD.

In conclusion, we investigated how methoxy and hydroxy groups in different positions on the phenoxy moiety of **4** may afford multitarget compounds with suitable combinations of dopaminergic and serotoninergic affinity/activity profiles.

The 2-methoxy derivative **3** and the 3-hydroxy derivative **8**, endowed with good affinity for D_2-like and 5-HT_{1A} receptors, emerged as the most interesting compounds in the series. The multitarget combination of 5-HT_{1A}/D_4 agonism and D_2/D_3/5-HT_{2A} antagonism makes **3** a good starting point to develop new pharmacological tools potentially useful in the treatment of schizophrenia. Due to its simultaneous agonist potency at D_2-like subtypes and the 5-HT_{1A} receptor, derivative **8** might be useful in PD therapy. Indeed, the activation of 5-HT_{1A} receptors might be helpful in reducing dyskinetic side effects associated with dopaminergic stimulation. Looking to the future, evaluation of **3** and **8** in schizophrenia or PD animal models would shed light on their therapeutic potential.

Methods

Chemistry

General: Melting points were taken in glass capillary tubes on a Büchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian Mercury AS400 instruments, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), or m (multiplet). IR spectral data (not shown because of the lack of unusual features) were obtained for all compounds reported and are consistent with the assigned structures. The microanalyses were recorded on FLASH 2000 instrument (ThermoFisher Scientific). The elemental composition of the compounds agreed to within ± 0.4% of the calculated value. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040–0.063 mm, Merck) by flash chromatography. Compounds were named following IUPAC rules as applied by ChemBioDraw Ultra (version 11.0) software for systematically naming organic chemicals.

N-((6,6-Diphenyl-1,4-dioxan-2-yl)methyl)-2-(3-methoxyphenoxy)ethanamine (7).: A solution of **14** (Aldrich, 1.61 g, 10.5 mmol) and **21**[23] (1.33 g, 3.5 mmol) in 2-methoxyethanol (20 mL) was heated to reflux for 5 h. Removal of the solvent under reduced pressure gave a residue, which was dissolved in water. The aqueous solution was basified with NaOH and extracted with $CHCl_3$. Removal of dried solvents gave a residue, which was purified by column chromatography, eluting with cyclohexane/ethyl acetate 1:1, to give **7** as an oil: 26% yield. The free base was transformed into the hydrochloride salt, which was recrystallized from 2-PrOH: mp 63–68 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.59 (br s, 1H, exchangeable with D_2O), 8.85 (br s, 1H, exchangeable with D_2O), 7.58–7.09 (m, 11H), 6.47 (m, 3H), 4.58 (d, 1H), 4.35 (m, 2H), 4.01 (m, 1H), 3.80 (m, 1H), 3.68 (s, 3H), 3.65–3.08 (m, 6H). Anal. calcd for $C_{26}H_{29}NO_4 \cdot HCl \cdot H_2O$: C, 65.88%, H, 6.80%, N, 2.96%. Found: C, 65.85%, H, 6.62%, N, 2.90%.

3-(2-(((6,6-Diphenyl-1,4-dioxan-2-yl)methyl)amino)ethoxy)phenol (8).: A solution of **23** (1.22 g, 2.47 mmol) in 4.4% HCOOH/MeOH (35 mL) was added dropwise to a mixture of 10% Pd/C (1.80 g) in 4.4% HCOOH/MeOH (70 mL). The mixture was stirred overnight at

room temperature under nitrogen atmosphere. After the catalyst was filtered off over Celite and washed with MeOH, the solvent was evaporated and the residue was dissolved in 3 M HCl solution in MeOH and stirred for 30 min. After evaporation of the solvent, the residue was recrystallized from 2-PrOH: 91% yield; mp 165–167 °C. ^{1}H-NMR (400 MHz, DMSO) δ: 9.58 (br s, 2H, exchangeable with D_2O), 9.22 (br s, 1H, exchangeable with D_2O), 7.58 (d, 2H), 7.40–7.01 (m, 9H), 6.40 (m, 3H), 4.84 (d, 1H), 4.37 (m, 1H), 4.22 (m, 2H), 3.99–3.72 (m, 5H), 3.17 (m, 1H), 2.83 (dd, 1H). Anal. calcd for $C_{25}H_{27}NO_4 \cdot HCl \cdot 2H_2O$: C, 62.82%, H, 6.75%, N, 2.93%. Found: C, 62.69%, H, 6.81%, N, 2.88%.

4.1.4. N-((6,6-Diphenyl-1,4-dioxan-2-yl)methyl)-2-(4-methoxyphenoxy)ethanamine (9).: This compound was prepared starting from **16** (Aldrich) and **22**[28] following the procedure described for **7**. An oil was obtained: 28% yield. The free base was transformed into the hydrochloride salt, which was recrystallized from 2-PrOH: mp 156–158 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.93 (br s, 2H, exchangeable with D_2O), 7.50 (d, 2H), 7.28 (m, 8H), 6.78 (dd, 4H), 4.58 (d, 1H), 4.32 (m, 2H), 4.01 (m, 1H), 3.80 (dd, 1H), 3.72 (s, 3H), 3.60 (d, 1H), 3.45 (dd, 1H), 3.35 (m, 2H), 3.19 (m, 2H). Anal. calcd for $C_{26}H_{29}NO_4 \cdot HCl$: C, 68.49%, H, 6.63%, N, 3.07%. Found: C, 68.57%, H, 6.50%, N, 3.00%.

4-(2-((6,6-Diphenyl-1,4-dioxan-2-yl)methylamino)ethyl)phenol (10).: This compound was prepared starting from **24** following the procedure described for **8**. The residue was recrystallized from 2-PrOH: 27% yield; mp 192–194 °C. ^{1}H-NMR (400 MHz, DMSO) δ: 9.10 (br s, 2H, exchangeable with D_2O), 9.02 (br s, 1H, exchangeable with D_2O), 7.59 (d, 2H), 7.42–7.18 (m, 8H), 6.84 (d, 2H), 6.68 (d, 2H), 4.83 (d, 1H), 4.19 (m, 2H), 3.90 (m, 1H), 3.78 (dd, 1H), 3.52–3.22 (m, 4H), 3.17 (m, 2H). Anal. calcd for $C_{25}H_{27}NO_4 \cdot HCl \cdot 2H_2O$: C, 62.82%, H, 6.75%, N, 2.93%. Found: C, 62.99%, H, 6.80%, N, 2.98%.

2-(2,3-Dimethoxyphenoxy)-N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (11).: This compound was prepared starting from **18**[25] and **22**[28] following the procedure described for **7**. An oil was obtained: 33% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, 2H), 7.41–7.19 (m, 8H), 6.99 (t, 1H), 6.62 (dd, 2H), 4.63 (d, 1H), 4.17 (m, 2H); 3.93–3.73 (m, 8H), 3.66–3.50 (m, 2H), 3.14–2.72 (m, 4H), 1.85 (br s, 1H, exchangeable with D_2O). Anal. calcd for $C_{26}H_{29}NO_4 \cdot HCl$: C, 68.49%, H, 6.63%, N, 3.07%. Found: C, 68.57%, H, 6.50%, N, 3.00%. The free base was transformed into the oxalate salt, which was recrystallized from 2-PrOH: mp 179–181 °C, Anal. calcd for $C_{27}H_{31}NO_5 \cdot H_2C_2O_4$: C, 64.55%, H, 6.16%, N, 2.60%. Found: C, 64.50%, H, 6.29%, N, 2.72%.

2-(3,4-Dimethoxyphenoxy)-N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (12).: This compound was prepared starting from **19**[25] and **21**[23] following the procedure described for **7**. An oil was obtained: 76% yield. The free base was transformed into the hydrochloride salt, which was recrystallized from 2-PrOH: mp 75–80 °C. ^{1}H-NMR (400 MHz, DMSO) δ: 9.35 (br s, 1H, exchangeable with D_2O), 8.26 (br s, 1H, exchangeable with D_2O), 7.55 (d, 1H), 7.41–7-14 (t, 9H), 6.84 (d, 1H), 6.60 (s, 1H), 6.49 (dd, 1H), 4.84 (d, 1H), 4.39 (m, 2H), 3.91 (m, 1H), 3.81 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.53–3.05 (m,

6H). Anal. calcd for $C_{27}H_{31}NO_5$·HCl: C, 66.73%, H, 6.64%, N, 2.88%. Found: C, 66.87%, H, 6.51%, N, 2.78%.

2-(Benzo[d][1,3]dioxol-5-yloxy)-N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (13).: This compound was prepared starting from **20** (Aldrich) and **21**[23] following the procedure described for **7**. An oil was obtained: 72% yield. The free base was transformed into the hydrochloride salt, which was recrystallized from 2-PrOH: mp 142–146 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, 1H), 7.41–7-14 (m, 9H), 6.70 (d, 1H), 6.52 (s, 1H), 6.35 (dd, 1H), 5.90 (s, 2H), 4.61 (d, 1H), 4.02 (m, 2H), 3.82 (m, 1H), 3.78 (m, 1H), 3.52 (m, 2H), 3.05–2.82 (m, 3H), 2.72 (dd, 1H), 2.48 (br s, 1H, exchangeable with D_2O). Anal. calcd for $C_{26}H_{27}NO_5$·HCl: C, 66.45%, H, 6.01%, N, 2.98%. Found: C, 66.33%, H, 5.90%, N, 2.92%.

2-(3-(Benzyloxy)phenoxy)-N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (23).: This compound was prepared starting from **15**[26] and **22**[28] following the procedure described for **7**. An oil was obtained: 57% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.55 (d, 2H), 7.47–7.15 (m, 14H), 6.58 (m, 3H), 5.02 (s, 1H), 4.62 (d, 1H), 4.05 (m, 2H), 3.83 (m, 1H), 3.79 (m, 1H), 3.58 (m, 2H), 2.90 (m, 3H), 2.72 (dd, 1H), 2.27 (br s, 1H, exchangeable with D_2O).

2-(4-(Benzyloxy)phenoxy)-N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (24).: This compound was prepared starting from **17**[27] and **22**[28] following the procedure described for **7**. An oil was obtained: 54% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, 2H), 7.38 (m, 13H), 6.89 (m, 4H), 5.03 (s, 2H), 4.61 (d, 1H), 4.07 (m, 2H), 3.84 (m, 1H), 3.80 (dd, 1H), 3.52 (m, 2H), 2.98 (m, 3H), 2.73 (dd, 1H), 2.07 (br s, 1H, exchangeable with D_2O).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATION USED

PD	Parkinson’s disease
DA	dopamine
5-HT	serotonin
CNS	central nervous system
α_1-AR	α_1-adrenoceptor
SAR	structure-activity relationship

ppm	part per million
TMS	tetramethylsilane

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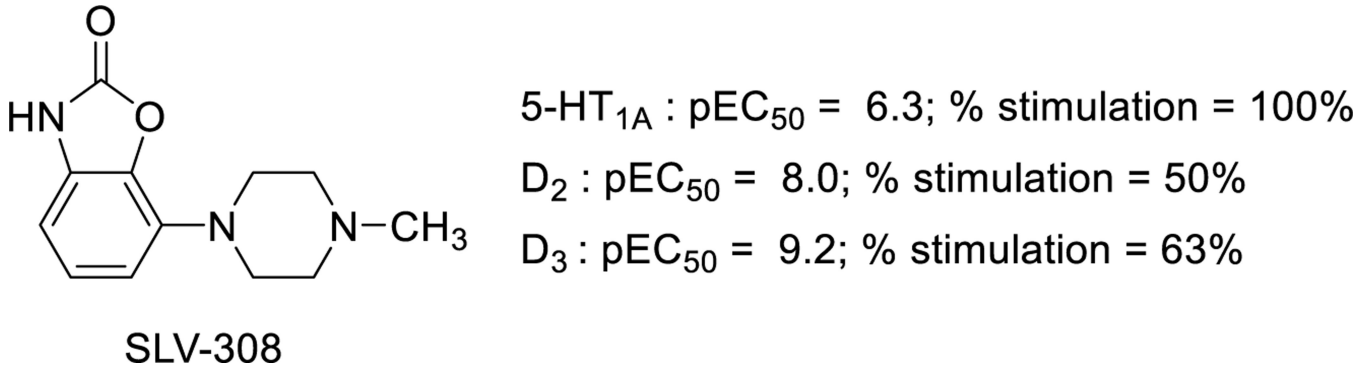


Figure 1.
Chemical structure and biological profile of SLV-308 (pardoprunox).[18]

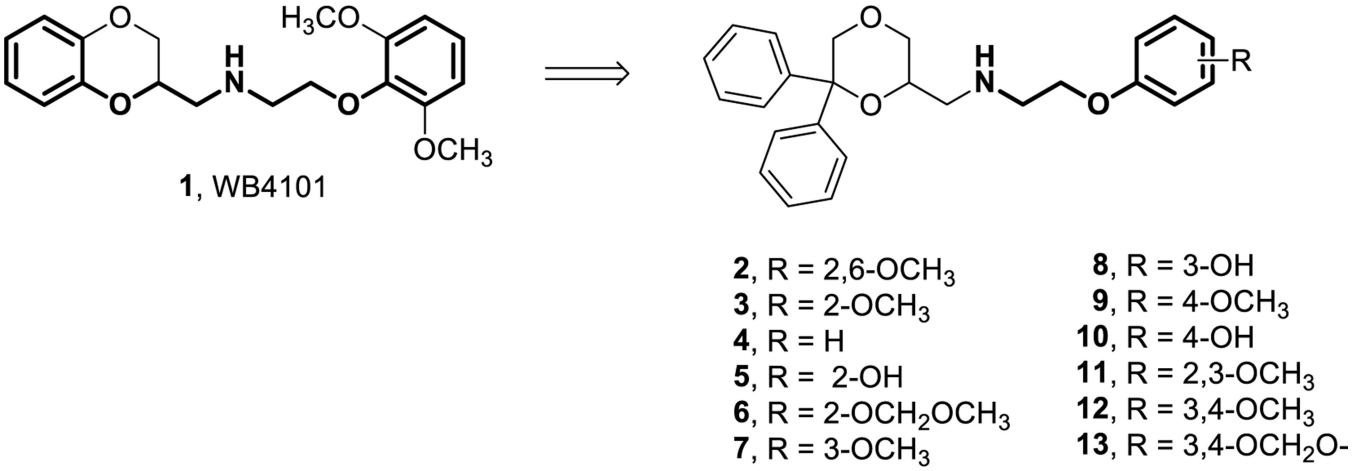
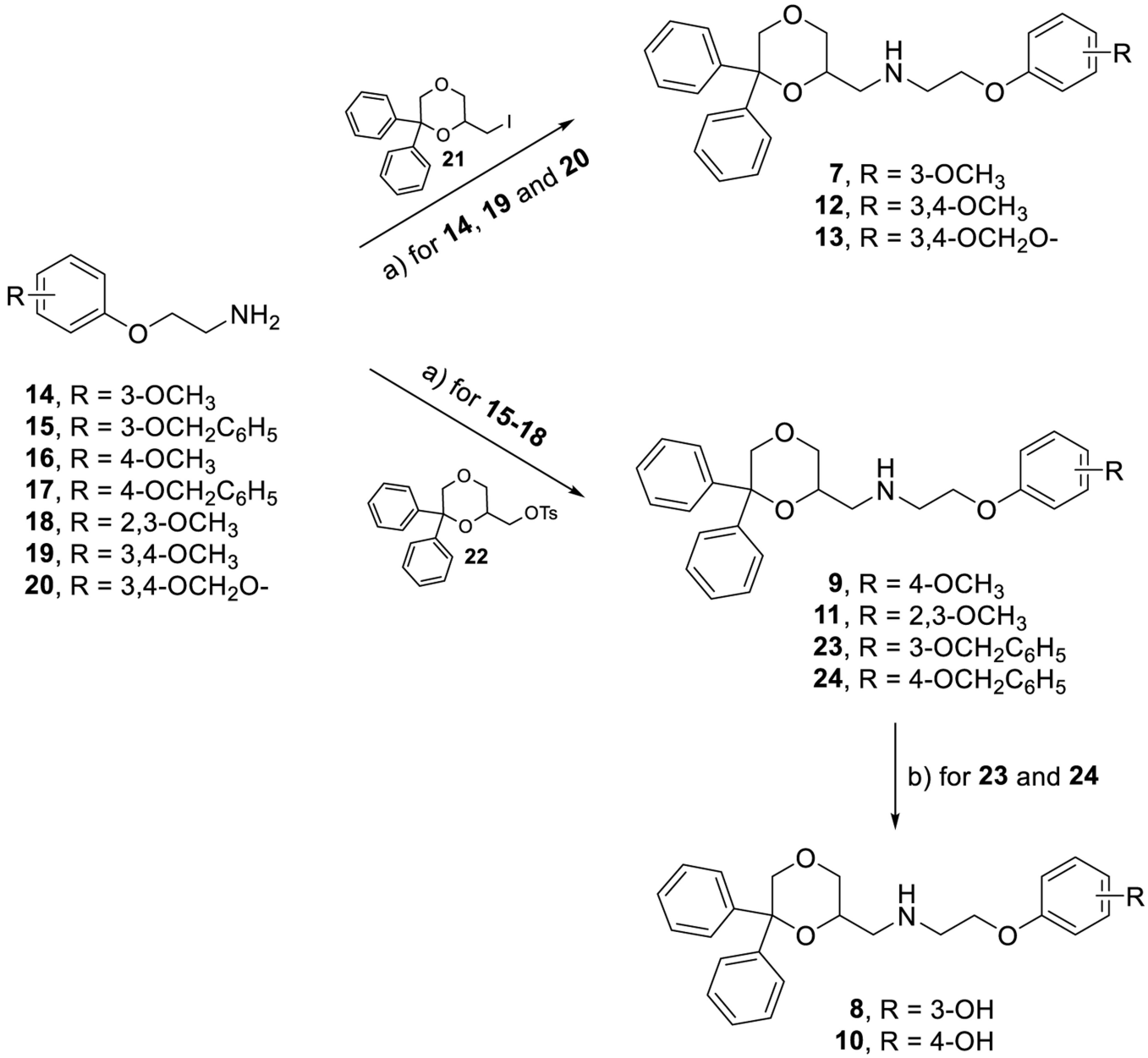


Figure 2.
Chemical structures of compounds **1–13**. The phenoxyethylamine fragments are in bold.

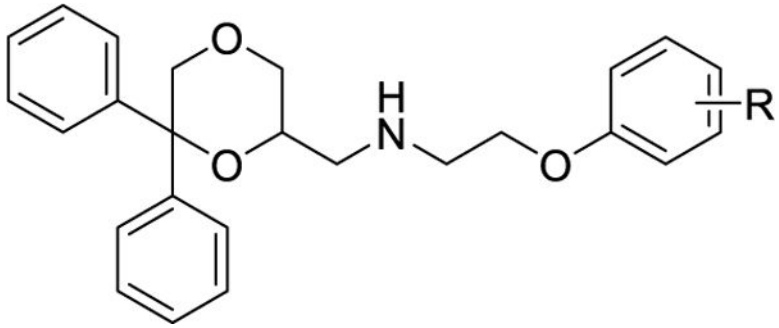


Scheme 1 –.

a) $CH_3OCH_2CH_2OH$, reflux, 5 h; b) HCOOH/MeOH, Pd/C, 24 h.

Table 1.

Affinity constants (pK_i) of **2-13**for human recombinant D_2, D_3 and D_4 receptors, α_{1a}-, α_{1b}-, α_{1d}-AR subtypes, and 5-HT_{1A} receptor[a]



compd	R	pK_i, human cloned receptor						
		D_2	D_3	D_4	α_1a	α_1b	α_1d	5-HT_{1A}
2	2,6-OCH_3	6.33	6.34	5.77	6.47[b]	6.49[b]	7.18[b]	8.85[b]
3	2-OCH_3	7.91[c]	7.88[c]	8.08[c]	7.56[b]	7.25[b]	8.94[b]	9.18[b]
4	H	7.26	7.92	6.80[c]	6.77[b]	6.92[b]	8.44[b]	9.23[b]
5	2-OH	7.81[c]	7.47[c]	7.44[c]	6.71[c]	6.43[c]	7.11[c]	9.16[c]
6	2-OCH_2OCH_3	6.98[c]	7.18[c]	7.29[c]	6.55[c]	6.54[c]	7.10[c]	9.20[c]
7	3-OCH_3	6.88	7.37	6.45	6.41	<6	6.98	8.91
8	3-OH	8.50	8.86	7.98	<6	<6	6.56	8.94
9	4-OCH_3	5.85	6.41	6.45	<6	<6	<6	7.17
10	4-OH	6.70	7.37	6.49	6.56	<6	7.01	7.59
11	2,3-OCH_3	6.69	6.79	6.87	ND[b]	ND[b]	ND[b]	ND[b]
12	3,4-OCH_3	<5	6.10	5.84	<6	<6	<6	7.71
13	3,4-OCH_2O-	6.70	6.99	6.79	6.32	<6	6.81	8.04

[a]Affinity values are reported as pK_i = -logK_i. Equilibrium dissociation constants (K_i) were derived from IC_{50} values using the Cheng-Prusoff equation.[33] Each experiment was performed in triplicate. K_i values were from three experiments, which agreed within ± 20%.

[b]Taken from reference 23.

[c]Taken from reference 24.

[d]ND = not determined.

Table 2.

Potency Values (Expressed as pEC_{50}[a] or pIC_{50}[a]) and Efficacy Values (Expressed as % stimulation[b] or % inhibition[c]) of Compounds **3**and **8**at Dopamine D_1-D_4, 5-HT_{1A}, and 5-HT_{2A} receptors.

Receptor	Functional profile of 3		Functional profile of 8	
	pEC_{50} (pIC_{50})	**% stimulation[b] (% inhibition)[c]**	**pEC_{50} (pIC_{50})**	**% stimulation[b] (% inhibition)[c]**
D_1 cAMP assay	(5.90 ± 0.04)	(91.3)	(5.49 ± 0.10)	(78)
D_2 mitogenesis assay	(7.60 ± 0.10)	(95.0)	7.49 ± 0.11	65.8
D_3 mitogenesis assay	(6.72 ± 0.07)	(88.0)	8.99 ± 0.09	101.7
D_4 adenylate cyclase	8.84 ± 0.12	89.6	8.80 ± 0.07	96.2
5-HT_{1A} [^{35}S]GTPγS binding	9.40 ± 0.13[d]	81.5[d]	8.28 ± 0.15	86.4
5-HT_{2A} IP-1 formation	(5.85 ± 0.06)	(96.5)	ND[e]	ND[e]

[a] Each experiment was performed in triplicate. pEC_{50} or pIC_{50} values were from three experiments and data are presented as means ± SEM.

[b] % Stimulation was determined in comparison to standard agonists SKF-38393 (D_1), quinpirole (D_2, D_3, D_4), serotonin (5-HT_{1A}, 5-HT_{2A}).

[c] % Inhibition was determined in comparison to standard antagonists SCH 23390 (D_1), (+)-butaclamol (D_2, D_3), NGB 2904 (D_3) and haloperidol (D_4), WAY 100,635 (5-HT_{1A}), Ketanserin (5-HT_{2A}). Data were obtained through the NIDA Addiction Treatment Discovery Program contract with Oregon Health & Science University.

[d] Taken from reference 23.

[e] ND = not determined.