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Multitarget 1,4-Dioxane Compounds Combining Favorable D\textsubscript{2}-like and 5-HT\textsubscript{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-phenoxethan-1-amine scaffold on the affinity/activity for D\textsubscript{2}-like, 5-HT\textsubscript{1A} and \(\alpha\textsubscript{1}\)-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\textsubscript{1A}/D\textsubscript{4} agonism and D\textsubscript{2}/D\textsubscript{3}/5-HT\textsubscript{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\textsubscript{2} and as a potent full agonist at D\textsubscript{3} and D\textsubscript{4} subtypes. In addition to its potent 5-HT\textsubscript{1A} receptor agonism, such a dopaminergic profile makes 8 a potential multitarget compound for the treatment of Parkinson’s disease.
Indeed, the activation of 5-HT<sub>1A</sub> receptors might be helpful in reducing dyskinetic side effects associated with dopaminergic stimulation.

**Graphical Abstract**

![Graphical Abstract](image)

**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. A. 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.

Several neurotransmitter pathways are functionally altered in complex diseases, such as psychiatric and neurodegenerative disorders. 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<sub>2</sub>-like receptors, comprising D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> subtypes, are involved in several pathological conditions in the CNS and thus are considered attractive drug targets. In particular, full or partial D<sub>2</sub> and D<sub>3</sub> receptor agonists are widely used in Parkinson’s disease (PD) therapy, whereas D<sub>2</sub>/D<sub>3</sub> receptor antagonists or partial agonists proved to be efficacious in the treatment of schizophrenia. Noteworthy, different DA disorders might be treated with D<sub>2</sub>/D<sub>3</sub> partial agonists with different levels of intrinsic activity. In particular, D<sub>2</sub>/D<sub>3</sub> 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<sub>2</sub>/D<sub>3</sub> partial agonists are preferred.

Moreover, D<sub>4</sub> receptor agonists may be useful in reversing cognitive deficits in schizophrenia. Early reports indicated that D<sub>4</sub> antagonists might be potential therapeutic agents for attenuating L-DOPA-induced dyskinesias. Additional data also highlight the therapeutic benefit of molecules targeting the 5-HT<sub>1A</sub> receptor in treating schizophrenia and PD.
The multitarget approach, combining DA and 5-HT receptor systems, revealed improved results in the treatment of polyfactorial pathologies such as PD and schizophrenia. In particular, the combination of 5-HT1A receptor agonism, D2/D3 antagonism and 5-HT2A antagonism has been reported to be beneficial in the treatment of schizophrenia. 5-HT1A receptor agonists may also behave as adjuvants in ameliorating the induction of dyskinesia in L-DOPA-treated PD patients.

SLV-308 (pardoprunox), a multitarget agent in which a full 5-HT1A receptor agonism is associated with a partial D2/D3 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. Therefore, ligands endowed with such a multitarget profile might be effective in PD pharmacotherapy.

WB-4101 (1, Figure 2), a well-known α1-adrenoceptor (α1-AR) antagonist, has been the starting point of numerous SAR studies previously reported by us. This compound also shows good affinity for 5-HT1A receptors (pKᵢ = 8.61) and moderate affinity for D2-like receptors (pKᵢ = 6.91). This compound includes two phenoxethylamine 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.

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 α1-AR subtypes, while maintaining high affinity for 5-HT1A receptor (Table 1). 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-HT1A receptor and α1-AR ligands with high selectivity for α1d over α1a and α1b subtypes. Recently, compound 3 and its 2-hydroxy and 2-(methoxymethoxy) analogues 5 and 6 (Figure 2), all endowed with nanomolar 5-HT1A receptor affinity, were evaluated at D2-like receptor subtypes. Among them, 5 and especially 3 displayed good affinity for all the D2-like receptor subtypes (Table 1).

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 D2-like, 5-HT1A and α1-AR subtypes. On the basis of this observation and encouraged by the interesting 5-HT1A/D2-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 D2-like receptor affinity, high affinity for 5-HT1A, and low affinity for α1-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-HT1A receptor affinity and selectivity over α1-AR shown by the previously reported 2,6-dimethoxy derivative 2 prompted us to evaluate this compound for its affinity at D2-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 D₂, D₃, D₄, 5-HT₁₅ receptors and α₁-AR subtypes, in radioligand competition binding assays. The previously reported compound 4 was also tested for its affinity at D₂-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 or the tosyl derivative 22 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 [³H]N-methylspiperone to label hD₂, hD₃ or hD₄ receptors stably expressed in HEK293 cells, [³H]Prazosin to label cloned human α₁-ARs expressed in CHO cells and [³H]8-OH-DPAT to label cloned human 5-HT₁₅ receptors expressed in HeLa cells, according to previously reported procedures. 29–32 The previously reported compounds 2 and 4 were also evaluated at hD₂, hD₃, and hD₄ subtypes. The affinity values, expressed as pKᵢ, 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 pKᵢ, were also determined by receptor binding assays at other targets, using [³H]SCH23390 to label human D₁ receptors stably expressed in mouse fibroblast cells, and [¹²⁵]DOI to label human 5-HT₂A and 5-HT₂C 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 α₁-AR subtypes (all pKᵢ values ≤ 7.01). The unsubstituted compound 4 binds D₂-like receptor subtypes and shows a modest preference for the D₃ subtype (D₃/D₄ = 13.4, D₃/D₂ = 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-HT₁₅ receptor (pKᵢ = 8.91). Therefore, unlike the lead 3, its isomer 7 proved to be highly selective for the 5-HT₁₅ receptor over α₁-AR and D₂-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

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the affinities for D₂, D₃ and D₄ receptors. Therefore, this compound proved to be highly selective for the 5-HT₁₅ receptor not only over α₁-ARs but also over the D₂-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-HT₁₅ receptor and low affinity for α₁-ARs. Interestingly, compound 8 also shows significantly increased affinities for D₂, D₃, and D₄ receptors.

Overall, among the mono-substituted derivatives, the methoxy in 2-position favors a good 5-HT₁₅/D₂-like affinity profile combination, but also confers to compound 3 high affinity for α₁₅-AR. A more optimally balanced 5-HT₁₅/D₂-like multitarget profile is seen with the 3-hydroxy derivative 8, which also binds all the α₁-AR subtypes with very low affinity (all pKᵢ values ≤ 6.56).

Due to their interesting multitarget 5-HT₁₅/D₂-like affinity profiles, compounds 3 and 8 were also evaluated by binding assays at other selected targets (D₁, 5-HT₂A, and 5-HT₂C 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 (pKᵢ: D₁ = 6.91, 5-HT₂A = 5.85, 5-HT₂C = 5.01) lower than those of compound 3 (pKᵢ: D₁ = 7.64, 5-HT₂A = 7.28, 5-HT₂C = 5.74) and has, therefore, the best multitarget 5-HT₁₅/D₂-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 pKᵢ values > 6. The results, reported in Table 2, show that derivative 3 behaves as an antagonist with very low potency at the D₁ receptor and with higher potencies at D₂ and D₃ subtypes. On the contrary, it is a potent full agonist at the D₄ receptor. Concerning the serotoninergic system, its previously reported high 5-HT₁₅ agonist potency is associated with a weak antagonism at the 5-HT₂A subtype. Considering that the combination of 5-HT₁₅ receptor agonism, D₂/D₃ antagonism and 5-HT₂A antagonism has been reported to be beneficial in the treatment of schizophrenia, and that D₄ receptor stimulation might improve cognitive impairment associated with schizophrenia, 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 D₁, as a partial agonist at D₂ and as a potent full agonist at D₃ and D₄ subtypes. Moreover, it shows a potent 5-HT₁₅ 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 serotonergic affinity/activity profiles.

The 2-methoxy derivative 3 and the 3-hydroxy derivative 8, endowed with good affinity for D₂-like and 5-HT₁A receptors, emerged as the most interesting compounds in the series. The multitarget combination of 5-HT₁A/D₄ agonism and D₂/D₃/5-HT₂A 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 D₂-like subtypes and the 5-HT₁A receptor, derivative 8 might be useful in PD therapy. Indeed, the activation of 5-HT₁A 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 (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 CHCl₃. 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. ¹H-NMR (400 MHz, CDCl₃) δ: 10.59 (br s, 1H, exchangeable with D₂O), 8.85 (br s, 1H, exchangeable with D₂O), 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 C₂₆H₂₉NO₄·HCl·H₂O: 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) \(\delta\): 9.58 (br s, 2H, exchangeable with D\(_2\)O), 9.22 (br s, 1H, exchangeable with D\(_2\)O), 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\(_4\)·HCl·2H\(_2\)O: 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\(_3\)) \(\delta\): 8.93 (br s, 2H, exchangeable with D\(_2\)O), 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). Anal. calcd for C\(_{26}\)H\(_{29}\)NO\(_4\)·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) \(\delta\): 9.10 (br s, 2H, exchangeable with D\(_2\)O), 9.02 (br s, 1H, exchangeable with D\(_2\)O), 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), 3.35 (m, 2H). Anal. calcd for C\(_{25}\)H\(_{27}\)NO\(_4\)·HCl·2H\(_2\)O: 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\(_3\)) \(\delta\): 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\(_2\)O). Anal. calcd for C\(_{26}\)H\(_{31}\)NO\(_5\)·H\(_2\)C\(_2\)O\(_4\): 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) \(\delta\): 9.35 (br s, 1H, exchangeable with D\(_2\)O), 8.26 (br s, 1H, exchangeable with D\(_2\)O), 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 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\(_3\)) \(\delta\): 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\(_2\)O). 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 and 22 following the procedure described for 7. An oil was obtained: 57% yield. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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\(_2\)O).

2-(4-(Benzyloxy)phenoxy)-N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (24): This compound was prepared starting from 17 and 22 following the procedure described for 7. An oil was obtained: 54% yield. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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\(_2\)O).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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ABBREVIATION USED

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
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<tr>
<td>5-HT</td>
<td>serotonin</td>
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<td>CNS</td>
<td>central nervous system</td>
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<td>α(_1)-AR</td>
<td>α(_1)-adrenoceptor</td>
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<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
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</table>

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References


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Figure 1.
Chemical structure and biological profile of SLV-308 (pardoprunox).\textsuperscript{18}

5-\textit{HT}_{1A} : pEC\textsubscript{50} = 6.3; \% stimulation = 100%
D\textsubscript{2} : pEC\textsubscript{50} = 8.0; \% stimulation = 50%
D\textsubscript{3} : pEC\textsubscript{50} = 9.2; \% stimulation = 63%
Figure 2.
Chemical structures of compounds 1–13. The phenoxyethyamine fragments are in bold.
Scheme 1

a) CH$_3$OCH$_2$CH$_2$OH, reflux, 5 h; b) HCOOH/MeOH, Pd/C, 24 h.
Table 1.
Affinity constants (pKᵢ) of 2-13 for human recombinant D₂, D₃ and D₄ receptors, α₁a⁻, α₁b⁻, α₁d⁻-AR subtypes, and 5-HT₁A receptor

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<th>compd</th>
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<td>3-OH</td>
<td>8.50</td>
</tr>
<tr>
<td>9</td>
<td>4-OCH₃</td>
<td>5.85</td>
</tr>
<tr>
<td>10</td>
<td>4-OH</td>
<td>6.70</td>
</tr>
<tr>
<td>11</td>
<td>2,3-OCH₃</td>
<td>6.69</td>
</tr>
<tr>
<td>12</td>
<td>3,4-OCH₃</td>
<td>&lt;5</td>
</tr>
<tr>
<td>13</td>
<td>3,4-OCH₂O⁻</td>
<td>6.70</td>
</tr>
</tbody>
</table>

ₐAffinity values are reported as pKᵢ = -logKᵢ. Equilibrium dissociation constants (Kᵢ) were derived from IC₅₀ values using the Cheng-Prusoff equation. ₐ₃₃ Each experiment was performed in triplicate. Kᵢ values were from three experiments, which agreed within ± 20%.

₇bTaken from reference 23.

₇cTaken from reference 24.

₇dND = not determined.
Table 2.

Potency Values (Expressed as pEC$_{50}$ or pIC$_{50}$) and Efficacy Values (Expressed as % stimulation or % inhibition) of Compounds 3 and 8 at Dopamine D$_1$-D$_4$, 5-HT$_{1A}$, and 5-HT$_{2A}$ receptors.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Functional profile of 3</th>
<th>Functional profile of 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pEC$<em>{50}$ (pIC$</em>{50}$)</td>
<td>% stimulation $^b$ (% inhibition)$^c$</td>
</tr>
<tr>
<td>D$_1$ cAMP assay</td>
<td>(5.90 ± 0.04)</td>
<td>(91.3)</td>
</tr>
<tr>
<td>D$_2$ mitogenesis assay</td>
<td>(7.60 ± 0.10)</td>
<td>(95.0)</td>
</tr>
<tr>
<td>D$_3$ mitogenesis assay</td>
<td>(6.72 ± 0.07)</td>
<td>(88.0)</td>
</tr>
<tr>
<td>D$_4$ adenylate cyclase</td>
<td>8.84 ± 0.12</td>
<td>89.6</td>
</tr>
<tr>
<td>5-HT$_{1A}$ [35S]GTP$\gamma$S binding</td>
<td>9.40 ± 0.13$^d$</td>
<td>81.5$^d$</td>
</tr>
<tr>
<td>5-HT$_{2A}$ IP-1 formation</td>
<td>(5.85 ± 0.06)</td>
<td>(96.5)</td>
</tr>
</tbody>
</table>

$a$ 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.