5-[(3-Nitropyrid-2-yl)amino]indoles: Novel Serotonin Agonists with Selectivity for the 5-HT_{1D} Receptor. Variation of the C3 Substituent on the Indole Template Leads to Increased 5-HT_{1D} Receptor Selectivity

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The large family of serotonin (5-HT) receptors provides a plethora of medicinally important targets, and the neurotransmitter serotonin has been implicated in a wide variety of disease states ranging from depression and anxiety to migraine and sexual dysfunction.[1] The search for agents which can selectivity mimic or oppose the action of serotonin at a single receptor subtype, while leaving other 5-HT receptors unmolested, has become increasingly enticing with the almost continual discovery of novel receptor subtypes within the 5-HT family of receptors.[2]

There has already been success in this approach. Buspirone is a selective partial agonist at somatodendritic 5-HT_{1A} autoreceptors, and this drug has been shown to be effective as an anxiolytic for generalized anxiety disorders.[3] Even more recently, sumatriptan (Imigran), a 5-$HT_{1\text{-like}}$ agonist has been approved as a novel treatment for migraine headaches, and its selectivity for the 5-HT_{1D} receptor has been proposed as the source of its antimigraine activity.[4] The success of sumatriptan has initiated the search for other 5-HT_{1D} receptor selective agonists with the purpose of further elucidating the mechanism of action of these compounds in relation to their antimigraine activity.[5]

During the course of our studies in the area of conformationally restricted agonists of serotonin,[6] we became aware of the preference of the 5-HT_{1D} receptor for the presence of a C5-hydroxy versus a C5-alkoxy substituent.[7] Our efforts to optimize this preference led us to synthesize analogs with novel hydrogen bond donors located at C5 of the indole nucleus. Furthermore, our studies and the studies of others suggested the presence of a binding site within the 5-HT_{1D} receptor which favored aromatic and heteroaromatic substitution proximate to C5 of the indole nucleus.[5b] This line of reasoning led to the replacement of C5-OH in serotonin with a C5-[(3-nitropyridyl)amino] substituent which we found to impart reasonable selectivity to the tryptamine derivative (**10**, Table 1). In this paper we present a novel series of 5-[(3-nitropyrid-2-yl)amino]indoles (**5**, **8**, **10**, and **15**) which have different types of conformational restraint of the C3-aminoethyl functionality. The binding and functional selectivity varies within this series of 5-HT_{1D} agonists depending on the method of conformational constraint employed at C3 of the indole nucleus.

Chemistry.[8] The syntheses of all of the desired targets (**5**, **8**, **10**, and **15**, Scheme 1) were seen resulting from the appropriately C3-substituted 5-aminoindole derivatives. Accordingly, reaction of 5-amino-3-[2-(dimethylamino)ethyl]indole (**9**)[9] with 2-chloro-3-nitropyridine in refluxing ethanol in the presence of triethylamine afforded the desired functionalized tryptamine **10**[10] in good yield (Scheme 1a).

Previous chemistry employed in the synthesis of 3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]-5-methoxyindole (CP-108,509) utilized the condensation of CBZ-*d*-proline acid chloride and the magnesium salt of 5-methoxyindole to append the conformationally restricted C3-substituent with stereochemical integrity.[6g] We chose to use this same strategy in the synthesis of **5** and **8** (Scheme 1b,c). Protection of 5-aminoindole was required for this approach, and we chose to utilize simple benzyl groups for this purpose. Reaction of the magnesium salt of 5-(dibenzylamino)indole with the acid chloride of CBZ-*d*-proline afforded the 3-ketoindole derivative **2**. Complete reduction of the CBZ-to-*N*-methyl and keto-to-methylene was accomplished with a single application of excess lithium aluminum hydride and lithium borohydride in refluxing THF to afford the desired protected aminoindole derivative **3**. Catalytic hydrogenation removed the benzyl groups, and the resulting 5-aminoindole **4** was condensed with 2-chloro-3-nitropyridine as described above to afford the (*N*-methylpyrrolidin-2-yl)methyl analog **5**[11] of our tryptamine **10**.

In previous studies, a series of 3-(pyrrolidin-2-ylmethyl)indoles had shown a significant increase in potency in an animal model of inhibition of neurogenic inflammation (a potential pharmacological marker of antimigraine activity) depending on the degree of substitution on the pyrrolidine nitrogen.[6h,12] Therefore, in order to explore the pharmacological effect of substitution on the basic nitrogen in the pyrrolidine ring in **5**, a synthesis of the requisite 5-aminoindole derivative (**7**) was needed (Scheme 1c). The keto group in **2** was selectively reduced to methylene using lithium borohydride in refluxing THF to afford **6**. Use of catalytic hydrogenation removed both the CBZ and benzyl groups from **6**, affording the secondary amine (**7**). Differentiation of the reactivities of the two amino groups[13] in **7** was achieved using refluxing *acetic acid* as the reaction solvent and sodium acetate as the base in the addition/elimination reaction of **7** with 2-chloro-3-nitropyridine, affording a low yield of the desired secondary amine analog **8**.[14] Apparently, the acetic acid protonated the more basic amine in the pyrrolidine ring, thus greatly reducing its reactivity as a nucleophile, while the 5-amino group was relatively unaffected.

For the synthesis of the pyrrolidin-3-ylindole analog of **10**, we sought to take advantage of the Michael reaction between indoles (electron neutral and electron rich) and maleimide derivatives which formed 3-(indol-3-yl)succinimides (Scheme 1d).[6i] 5-Benzamidoindole (**11**) reacted smoothly with *N*-methylmaleimide in the desired manner to form the succinimide **12**. Reduction of the succinimide was effected via the addition of the succinimide **12** to a solution/mixture of LAH (excess) in THF, followed by heating. The resulting benzyl group in **13** was consequently removed by catalytic hydrogenation to afford our desired 5-aminoindole derivative **14**. Condensation of **14** with 2-chloro-3-nitropyridine was accomplished routinely in refluxing acetic acid with

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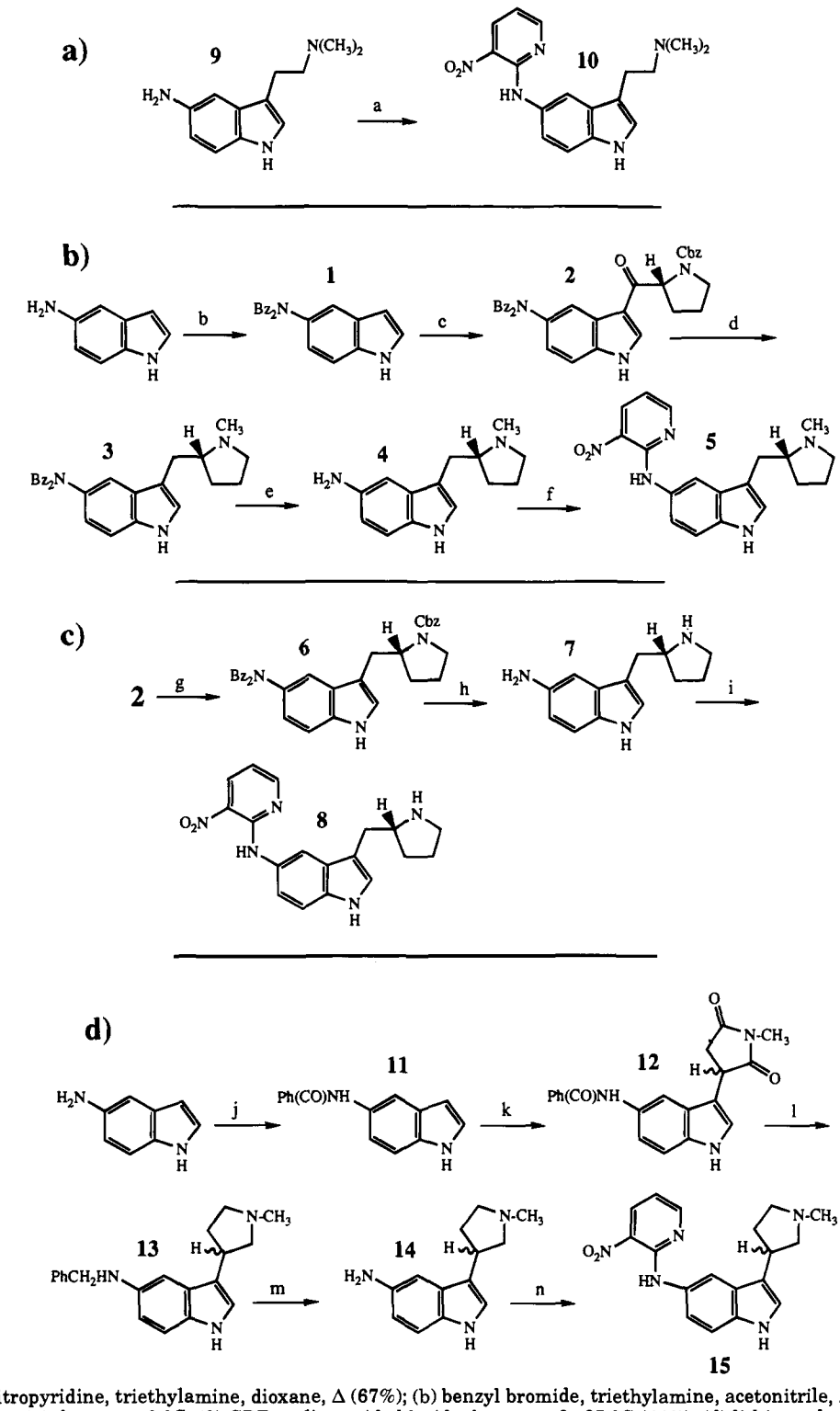
Scheme 1. Synthesis of 5-[(3-Nitropyrid-2-yl)amino]indoles[a]



[a] (a) 2-Chloro-3-nitropyridine, triethylamine, dioxane, Δ (67%); (b) benzyl bromide, triethylamine, acetonitrile, Δ (88%); (c) (1) EtMgBr (2 equiv), indole (2 equiv), benzene, 0 °C; (2) CBZ-proline acid chloride, benzene, 0–25 °C (44%); (d) lithium aluminum hydride/lithium borohydride, THF, Δ (89%); (e) palladium hydroxide on carbon, H_2, ethanol (99%); (f) 2-chloro-3-nitropyridine, triethylamine, acetonitrile, Δ (81%); (g) lithium borohydride, THF, Δ (70%); (h) palladium hydroxide on carbon, H_2, ethanol (100%); (i) 2-chloro-3-nitropyridine, sodium acetate, acetic acid, Δ (23%); (j) benzoyl chloride, triethylamine, THF (97%); (k) *N*-methylmaleimide, acetic acid, Δ (29%); (l) lithium aluminum hydride, THF, Δ (49%); (m) palladium hydroxide on carbon, H_2, ethanol (34%); (n) 2-chloro-3-nitropyridine, sodium acetate, acetic acid, Δ (44%).

sodium acetate as the HCl scavenger to yield the pyrrolidin-3-ylindole analog (**15**)[15] of **10**.

Pharmacology. Table 1 summarizes the 5-HT_1 receptor pharmacology of compounds **5** (CP-135,807), **8** (CP-123,803), **10** (CP-113,113), and **15** (CP-124,439) along with 5-HT and sumatriptan. Binding measurements were performed using previously published protocols.[16] The ability of the compounds to mimic agonist activity (i.e., inhibition of forskolin-stimulated adenylate cyclase) at 5-HT_{1A} and 5-HT_{1D} receptors was measured using methods described previously,[16] and compounds **5**, **8**, **10**, and **15** were all equally efficacious with 5-HT

Table 1. Pharmacology[a]

compound	binding (IC_{50} ± SEM, nM)			inhibition of adenylate cyclase (EC_{50} ± SEM, nM)		
	5-HT_{1A}	5-HT_{1D}	selectivity (1A/1D)	5-HT_{1A}	5-HT_{1D}	selectivity (1A/1D)
serotonin	5.2 ± 1.5	3.0 ± 0.3	2	10 ± 1	5.2 ± 0.9	2
sumatriptan	640 ± 180	61 ± 14	10	1300 ± 200	97 ± 27	13
10	73 ± 4	10 ± 2	7	170 ± 70	2.0 ± 1.4	85
5	33 ± 1	3.1 ± 0.8	11	47 ± 18	1.3 ± 0.8	36
8	120 ± 10	6.2 ± 0.6	19	220 ± 90	1.3 ± 0.7	170
15	320 ± 90	15 ± 2	21	885 ± 54	2.0 ± 0.7	440

[a] Values presented represent a minimum of three independent determinations and are arithmetric means.

at maximal doses at both the 5-HT_{1A} and 5-HT_{1D} receptors. Compounds **5**, **8**, **10**, and **15** and sumatriptan were tested at other non-5-HT_1 receptors (i.e., 5-HT_{2A}, 5-HT_{2C}) and found to be essentially inactive with binding affinity only demonstrated at micromolar concentrations (data not presented).

The replacement of the C5-[$CH_3NHSO_2CH_2$–] group in sumatriptan with the C5-[(3-nitropyrid-2-yl)amino] group led to tryptamine **10** which had a similar modest selectivity for the 5-HT_{1D} receptor. However, **10** was significantly more potent at 5-HT_1 receptors than sumatriptan both in binding and in its functional activity. While **10** was 3 times less potent than 5-HT in its binding affinity for the 5-HT_{1D} receptor, it was about twice as potent as 5-HT in its ability to inhibit adenylate cyclase.

Replacement of the (*N*,*N*-dimethylamino)ethyl portion of **10** with the conformationally restricted (*N*-methylpyrrolidin-2(*R*)-yl)methyl group led to compound **5**. It should be noted that only the *R*-enantiomer was synthesized in this study because previous studies had shown that 5-HT receptors showed significant stereogenic differentiation between 3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]indoles and their *S*-antipodes. In these particular studies, the *R*-enantiomer was favored over the *S*-enantiomer at all of the 5-HT receptors tested.[6g] Compound **5** was found to be more potent in its affinity for 5-HT_1 receptors than the corresponding tryptamine analog **10**, but **5** was slightly less selective as an agonist for the 5-HT_{1D} receptor than **10**. Examination of the secondary amine **8** (the normethyl analog of **5**) showed an equivalent binding affinity and functional potency at the 5-HT_{1D} receptor when compared to **5**. However, the secondary amine **8** showed improved binding and, especially, functional selectivity for the 5-HT_{1D} receptor when compared to the tertiary amines **10** and **5**.

Finally, replacement of the tryptamine side chain in **10** with a racemic 3-(*N*-methylpyrrolidin-3-yl) group led to **15**, which was not as potent in its binding affinity for the 5-HT_{1D} receptor as its 3-(pyrrolidin-2(*R*)-ylmethyl) counterparts (**5** and **8**). However, the binding and functional selectivity of **15** was found to be the best in the group of compounds studied. Since our previous studies[6g] suggest that a significant stereogenic differentiation exists within the binding site of 5-HT receptors, the separation of racemic **15** into its component antipodes has been studied extensively. Unfortunately, resolution of **15** has proved to be very difficult and has not yet been achieved. Accordingly, significant continued effort is presently being devoted toward the isolation of the individual enantiomers of the 3-(pyrrolidin-3-yl)indole (**15**).

Discussion. Examination of the data contained in Table 1 can be summarized as follows:

Rank order of binding potency at 5-HT_{1D} receptors: 5-HT ≈ **5** > **8** > **10** ≈ **15** ≫ sumatriptan.

Rank order of agonist potency at 5-HT_{1D} receptors: **5** ≈ **8** ≈ **10** ≈ **15** > 5-HT ≫ sumatriptan.

Rank order of binding selectivity: **15** > **8** > **5** ≈ sumatriptan > **10** > 5-HT.

Rank order of functional selectivity: **15** > **8** > **10** > **5** > sumatriptan > 5-HT.

The (3-nitropyrid-2-yl)amino substituent at C5 of the indoles in **5**, **8**, **10**, and **15** affords these serotonin analogs a degree of 5-HT_{1D} receptor selectivity versus the 5-HT_{1A} receptor. This is consistent with the available information thus far, which points to modification of the C5-OH of 5-HT as a major area of molecular design aimed at achieving 5-HT_{1D} receptor selectivity.[5b] However, examination of the binding and functional results of our series demonstrates that *modification of the C3 aminoethyl substituent of 5-HT offers an additional approach for designing and improving 5-HT_{1D} receptor-selective agonists*. Modification of the substituent at C3 in our series of 5-[(3-nitropyrid-2-yl)amino]-indoles affected primarily the affinity and potency of these compounds for the 5-HT_{1A} receptor. The clear choice in our series is the replacement of the 3-[2-(*N*,*N*-dimethylamino)ethyl] group in **10** with the racemic 3-(*N*-methylpyrrolidin-3-yl) group found in **15**, and its remarkable 5-HT_{1D} receptor selectivity resulted primarily from a loss of 5-HT_{1A} receptor activity as opposed to an increase in 5-HT_{1D} receptor activity.

We are presently examining the full pharmacology of **5**, **8**, **10**, and **15**, especially in relation to their activity in appropriate models predictive of antimigraine activity, and these results will be presented in due course in an appropriate forum. Furthermore, we are examining the effect of the replacement of the 3-[2-(*N*,*N*-dimethylamino)ethyl] group in other 5-HT_{1D} receptor selective tryptamines with the racemic 3-(*N*-methylpyrrolidin-3-yl) group. This course of study should lead to more selective pharmacological tools for use in the study of the 5-HT_{1D} receptor subtype.

Supplementary Material Available: Full experimental description of chemical syntheses and products and the pharmacological methods used in this paper (13 pages). Ordering information is given on any current masthead page.

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(7) Unpublished results of a study in our lab showed that 5-hydroxyindole serotonergics were more potent in their binding to the 5-HT_{1D} receptor when compared to the analogous 5-methoxyindole serotonergics.

(8) All new compounds reported herein have been fully characterized including IR, ^{1}H NMR, ^{13}C NMR, LRMS, and elemental analysis and/or HRMS.

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(10) The spectral and physical properties of **10** are as follows: red solid; mp 59.0–61.0 °C; IR (KBr) 3420–2780 (br), 1604, 1574, 1500, 1485, 1443 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.66 (br s, 1H), 8.51 (dd, J = 8.3 and 1.8 Hz, 1H), 8.41 (dd, J = 4.4 and 1.8 Hz, 1H), 7.76 (br s, 1H), 7.30–7.24 (m, 2H), 6.97 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 8.3 and 4.4 Hz, 1H), 2.97–2.91 (m, 2H), 2.70–2.63 (m, 2H), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.7, 151.5, 135.5, 134.5, 129.4, 128.2, 127.9, 122.8, 119.3, 114.4, 114.3, 113.0, 111.5, 60.3, 45.4, 23.7; LRMS (*m/z*, relative intensity) 325 (M^+, 100), 280 (23), 267 (33), 220 (55); HRMS calculated for $C_{17}H_{19}N_5O_2$ 325.1539, found 325.1533. Anal. Calcd for $C_{17}H_{19}N_5O_2 \cdot {}^1/_3H_2O$: C, 61.62; H, 5.98; N, 21.13. Found: C, 61.58; H, 5.65; N, 20.80.

(11) The spectral and physical properties of **5** are as follows: amorphous red foam; IR (KBr) 3192 (br), 1608, 1593, 1580, 1533, 1507, 1488, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.11 (br s, 1H), 8.52 (dd, J = 1.8 and 8.4 Hz, 1H), 8.43 (dd, J = 1.8 and 4.5 Hz, 1H), 8.33 (br s, 1H), 7.77 (d, J = 1.7 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.26 (dd, J = 2.0 and 8.6 Hz, 1H), 7.03 (d, J = 2.1 Hz, 1H), 6.74 (dd, J = 4.4 and 8.4 Hz, 1H), 3.21–3.12 (m, 2H), 2.68–2.58 (m, 1H), 2.54–2.46 (m, 1H), 2.47 (s, 3H), 2.28–2.18 (m, 1H), 1.89–1.73 (m, 2H), 1.73–1.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155.7, 151.5, 135.5, 134.3, 129.5, 128.2, 128.1, 123.1, 119.4, 114.3, 113.0, 111.4, 66.7, 57.5, 40.8, 31.5, 29.9, 21.9. FAB LRMS (*m/z*, relative intensity) 352 (MH^+, 100), 322 (70). Anal. Calcd for $C_{19}H_{21}N_5O_2 \cdot {}^1/_3H_2O$: C, 63.85; H, 6.11; N, 19.59. Found: C, 63.86; H, 5.86; N, 19.31. Attempts to measure the optical rotation for **5** were thwarted by the intense orange color of the compound in solution.

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(13) Under neutral conditions, competition between the two amino groups in **7** occurred. For example, reaction of **7** with $(BOC)_2O$ led to a complex reaction mixture of products. Therefore, it was decided to incorporate the (3-nitropyrid-2-yl) group in a single reaction which took advantage of the different basicities of the amines in **7**.

(14) The spectral and physical properties of **8** are as follows: amorphous red foam; IR ($CHCl_3$) 3361, 1605, 1575, 1481, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.05 (br s, 1H), 9.23 (br s, 1H), 8.49 (dd, J = 1.8 and 8.3 Hz, 1H), 8.39 (dd, J = 1.8 and 4.5 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.33–7.22 (m, 2H), 6.98 (s, 1H), 6.73 (dd, J = 4.5 and 8.3 Hz, 1H), 3.46–3.34 (m, 1H), 3.10–2.97 (m, 1H), 2.97–2.78 (m, 3H), 1.99–1.64 (m, 3H), 1.56–1.42 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.7, 151.5, 135.5, 134.5, 129.2, 128.1, 127.8, 123.8, 119.4, 114.3, 113.0, 111.6, 59.5, 45.7, 31.3, 30.6, 24.7; FAB LRMS (*m/z*, relative intensity) 338 (6, [MH^+]), 309 (12), 155 (49), 135 (38), 119 (100); HRMS calculated for $C_{18}H_{19}N_5O_2$ 337.1541, found 337.1537. Anal. Calcd for $C_{18}H_{19}N_5O_2 \cdot {}^2/_3C_2H_4O_2$ [acetic acid]: 61.53; H, 5.79; N, 18.56. Found: C, 61.57; H, 5.74; N, 18.82. Attempts to measure the optical rotation for **8** were thwarted by the intense orange color of the compound in solution.

(15) The spectral and physical properties of **15** are as follows: red solid; mp 55.0–57.0 °C; IR (KBr) 3310–2800 (br), 1612, 1580, 1540, 1510, 1480, 1466, 1445 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.05 (br s, NH), 9.15 (br m, NH), 8.59 (dd, J = 8.3 and 1.8 Hz, 1H), 8.41 (dd, J = 4.5 and 1.8 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.7 and 2.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.74 (dd, J = 8.3 and 4.5 Hz, 1H), 3.82–3.71 (m, 1H), 3.35 (dd, J = 10.2 and 8.0 Hz, 1H), 3.19–2.89 (m, 3H), 2.66 (s, 3H), 2.49–2.38 (m, 1H), 2.16–2.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.7, 151.5, 135.5, 135.0, 129.0, 128.1, 127.1, 121.7, 119.3, 119.2, 114.7, 113.0, 111.6, 62.8, 56.2, 42.4, 35.1, 32.1; LRMS (*m/z*, relative intensity) 337 (M^+, 100), 320 (41), 280 (35), 220 (82), 120 (47). Anal. Calcd for $C_{18}H_{19}N_5O_2 \cdot {}^1/_2C_4H_4O_2$ [ethyl acetate]: C, 62.98; H, 6.08; N, 18.36. Found: C, 62.71; H, 5.80; N, 18.51.

(16) Reference 6a and references cited therein. A more detailed description of receptor binding and functional studies is contained as supplementary material for this paper.