Serotonin Receptor Affinity of Cathinone and Related Analogues

Richard A. Glennon* and Stephen M. Liebowitz

Department of Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298. Received June 22, 1981

A series of cathinone (α-aminopropiophenone) analogues was examined using the isolated rat fundus preparation. (S)-(-)-Cathinone possesses twice the serotonin receptor affinity of (+)-cathinone and four times the affinity of racemicamphetamine. Several derivatives of cathinone were found to either possess a lower affinity than the parent compound or did not interact with the receptors in a competitive manner. Several novel analogues, 1-(aminomethyl)-3,4-dihydronaphthalene hydrochloride (5), 4-(aminomethyl)-3-chromene hydrochloride (4b), as well as its 6-methoxy derivative, 4a, interact with serotonin receptors but in a fashion which is, most likely, dissimilar to the interaction of the substituted cathinone analogues.

In an effort to map the serotonin (5-hydroxytryptamine, 5-HT) receptors of the rat fundus, we have determined the receptor affinities of derivatives of several classes of compounds. The 5-HT receptor affinities of phenalkylamines, for example, vary depending upon the presence and location of substituent groups. Cathinone (α-aminopropiophenone, 1) and cathine (1-phenyl-2-aminopropanol or norpseudoephedrine, 2), isomers of which are naturally occurring psychoactive constituents of the shrub Catha edulis,4 possess a phenylisopropylamine backbone and offer a new series of compounds for evaluation.

In a preliminary investigation, it was found that racemic 1 possesses twice the 5-HT receptor affinity of racemic phenylisopropylamine (amphetamine) and that 2 acts in such a manner as to preclude determination of valid affinity data (pA2 values).3 Furthermore, the presence of a 2-methoxy substituent decreases affinity severalfold, and it was suggested that this substituent might sterically interfere with a side-chain conformation that is optimal for receptor binding.

How might cathinone and its derivatives interact with 5-HT receptors? Lysergic acid diethylamide (LSD) contains within its tetracyclic framework both an indole-alkylamine and a phenalkylamine component; these may represent the conformations in which the latter two classes of compounds interact with 5-HT receptors.5 The Csp2 position of LSD and the benzylc carbon atom of 1 are both sp2-hybridized. This sp2-hybridized atom may play a role in receptor affinity.

The aims of the present study are (a) to obtain the 5-HT receptor affinities of several additional cathinone analogues, in order to explore their SAR and to determine if similarities exist with the SAR of the phenalkylamines, and (b) to prepare several novel compounds which possess the sp2-hybridized carbon atom common to LSD and cathinone but which are somewhat more conformationally re-


Chemistry. Compound 3 was conveniently prepared by dehydration of (+)-1-(aminomethyl)-1-hydroxy-1,2,3,4-tetrahydronaphthalene hydrochloride (5).6 The tetrahydro derivative of 3 (i.e., 6) could be obtained by catalytic reduction of 5 or by hydrogenolysis of 5 using 10% Pd/C and HClO4 (Scheme I).

The synthesis of the chroman and chromene analogues is shown in Scheme II. Conceptually, the chromanols 13a and 13b can be dehydrated, in a manner similar to that employed for the preparation of 3, to afford 4a and 4b. Acylation of 4-methoxyphenol (7) with 3-chloropropionyl chloride yields 8, which upon heating with freshly sublimed AICl3 undergoes Fries rearrangement to 9. Compound 9 was not isolated but was treated with dilute base to afford 10 (after acidification). Although 12a might be prepared by methylation of 10, the yields of 10, from 7, were unacceptably low. Alternatively, alkylation of 7 with sodium chloropropionate, followed by cyclization of the resultant product by heating with PPA, gave 12a in an overall yield of about 60%. Compounds 12a and 12b were allowed to react with Me3SiCN, and the resultant products were reduced with LiAlH4 to give 13a and 13b, respectively.

Heating a methanolic solution of 13a (13b) in the presence of HCl effected dehydration to 4a (4b) in low yield. Under these conditions, exocyclic dehydration is apparently a competing reaction, and workup of the reaction results in isolation of varying amounts of NH4Cl. If the dehydration is performed at room temperature, 14a (14b) is isolated in 70% yield. Using ethanol as solvent, 13b yields 88% of 14c. Compound 14a (14c) was dissolved...
in glacial HOAc to which HCl had been previously added; heating this solution at reflux for 1–2 h gave 4a (4b) in 50% yield. Catalytic reduction of 4a gave the desired methoxy derivative 15. In another effort to prepare 4b and as a model reaction for the preparation of 15, the unsaturated nitrile 16 was prepared from 12b. Attempts to reduce 16 with a variety of reducing agents resulted in the formation of complex mixtures from which 4b could be identified (GC/MS) but not isolated.

Results and Discussion

While certain of the compounds interact with the 5-HT receptors in a competitive manner, as determined by the slopes of their Schild plots (Table I), some (i.e., 1b, 5, 6, 17, 20, and 21) do not. As a consequence, valid pA₂ values could not be obtained for the latter group of compounds. Racemic cathinone (1) possesses twice the affinity of (±)-amphetamine (25); (−)-cathinone (1a) possesses twice the affinity of 1, while its enantiomer, (+)-cathinone (1b), does not interact with the 5-HT receptors in a competitive manner. 4-Methoxylation of 1 (i.e., 18) has little effect on affinity, whereas demethylation of this methoxy group, to give 19, halves affinity. The 2,4-dimethoxy derivative 22 has one-fifth the affinity of 1; the 2-methoxy derivative 17 and the 4-halogenated compounds 20 and 21 result in a noncompetitive interaction. Removal of the α-methyl group of 1, to give 26 and reduction of the carbonyl group of 26 to the hydroxy derivative 27 also result in a non-competitive receptor interaction. Interestingly, when the carbonyl group of 26 is replaced by an amino group, the resultant compound, 28 does interact competitively, although it possesses a rather low affinity (pA₂ = 4.90).

The affinity of the dihydroanthalene analogue 3 (pA₂ = 5.81) is similar to that of (−)-cathinone (1a) and twice that of (±)-cathinone (1). Inclusion of an oxygen atom in the ring of 3 results in the chromene 4b (pA₂ = 4.94). Methoxylation of the latter compound para to the oxygen atom (i.e., 4a) results in a 15-fold increase in affinity; this is similar to the 10- to 20-fold increase in affinity observed for para-methoxylation of the corresponding methoxyphenalkylamines. The tetrahydronaphthalene 6 and the hydroxy intermediate 5 do not interact with the 5-HT receptors in a competitive manner. The same is true of the hydroxy (e.g., 13a) and alkoxy (14a,b) analogues in the chroman series; however, the reduced derivative of 4a (i.e., 15), unlike the reduced derivative of 3, interacts with the receptors in a competitive manner and possesses approximately half the affinity of 4a.

With respect to SAR, very few similarities exist between the cathinone analogues and the phenalkylamines (whose SAR has been previously reported); different modes of receptor interaction may be involved. Whereas the R₁ isomers of substituted phenalkylamines usually constitute the eutomer series with respect to 5-HT receptor affinity, (S)-(−)-cathinone possesses twice the affinity of its racemate. Furthermore, removal of the α-methyl group of phenylisopropylamines has no effect on affinity (e.g., compare 24 and 25), whereas removal of the α-methyl group of 1, to give 26, results in a noncompetitive interaction. The increase in affinity of 3 over that of phenethyamine (24; pA₂ = 5.26) might be due (a) to conformational re-
Serotonin Receptor Affinity of Cathinone and Analogues

Table I. Serotonin Receptor Affinity Data for Cathinone and Related Analogues

<table>
<thead>
<tr>
<th>no.</th>
<th>R</th>
<th>R'</th>
<th>X</th>
<th>pA₁,d</th>
<th>slope⁶</th>
<th>N&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>1</td>
<td>(-)-H</td>
<td>Me</td>
<td>=O</td>
<td>5.55 ± 0.29&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>5 (23)</td>
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<tr>
<td>1a</td>
<td>(-)-H</td>
<td>Me</td>
<td>=O</td>
<td>5.86 ± 0.14</td>
<td>1.08 ± 0.30</td>
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</tr>
<tr>
<td>1b</td>
<td>(-)-H</td>
<td>Me</td>
<td>=O</td>
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<td>17</td>
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<td>=O</td>
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<td>18</td>
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<td>=O</td>
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<td>0.90 ± 0.15</td>
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<td>=O</td>
<td>e</td>
<td>0.64&lt;sup&gt;f&lt;/sup&gt;</td>
<td>6 (27)</td>
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<tr>
<td>21</td>
<td>(-)-4-F</td>
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<td>=O</td>
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</tr>
<tr>
<td>22</td>
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<td>Me</td>
<td>=O</td>
<td>4.95 ± 0.09</td>
<td>0.81 ± 0.10</td>
<td>3 (15)</td>
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<td>23</td>
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<td>=O</td>
<td>6.14 ± 0.18</td>
<td>0.77 ± 0.28&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
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<td>H</td>
<td>5.26&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>25</td>
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<td>Me</td>
<td>H</td>
<td>e</td>
<td>0.53 ± 0.09</td>
<td>4 (20)</td>
</tr>
<tr>
<td>26</td>
<td>H</td>
<td>H</td>
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<td>e</td>
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<tr>
<td>27</td>
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<td>H</td>
<td>OH</td>
<td>e</td>
<td>0.63 ± 0.02</td>
<td>4 (20)</td>
</tr>
<tr>
<td>28</td>
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<td>H</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.90 ± 0.40</td>
<td>0.86 ± 0.21</td>
<td>5 (22)</td>
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<tr>
<td>29a</td>
<td>(2-aminotetralin)</td>
<td></td>
<td></td>
<td>5.61</td>
<td></td>
<td></td>
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<tr>
<td>29b</td>
<td></td>
<td></td>
<td></td>
<td>6.04 ± 0.13</td>
<td>1.07 ± 0.21</td>
<td>5 (22)</td>
</tr>
<tr>
<td>3</td>
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<td></td>
<td>5.81 ± 0.23</td>
<td>0.92 ± 0.14</td>
<td>8 (39)</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td></td>
<td></td>
<td>6.12 ± 0.34</td>
<td>0.86 ± 0.27</td>
<td>6 (28)</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td></td>
<td></td>
<td>4.94 ± 0.32</td>
<td>0.82 ± 0.23</td>
<td>4 (20)</td>
</tr>
<tr>
<td>5</td>
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<td></td>
<td></td>
<td>e</td>
<td>0.56 ± 0.18</td>
<td>3 (14)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>e</td>
<td>0.67 ± 0.21</td>
<td>5 (20)</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>5.94 ± 0.12</td>
<td>1.10 ± 0.02</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

* pA₁ value followed by standard deviation. Compounds 13a, 14a, and 14b were examined in duplicate determinations; Schild plot slopes ranged from -0.54 to -0.89. Compound 13b had no effect on the dose-response curve to 5-HT, at doses of up to 10 μM in one determination and 30 μM in a second determination. Negative slope of the Schild plot followed by standard deviation. Number of pA₁ determinations followed by total number of dose-response curves (in parentheses).

An example of a relatively rigid phenalkylamine, possesses twice the affinity of 24, while 29b, an analogue of 1, possesses three times the affinity of 1, conformational considerations may play a role in the higher affinity of 3 as compared with 24. On the other hand, reduction of the C₁-C₂ double bond of 3, to give 6, results in a noncompetitive interaction. Therefore, the double bond, through an electronic effect or through a conformational effect, also appears to play a role in the interaction of 3 with 5-HT receptors.

The cyclic compounds 3 and 4 appear to behave more like the phenethylamines than like the cathinone derivatives, in that their interaction with 5-HT receptors is competitive even though they lack an α-methyl group. However, because of the lower affinity of 4b as compared with 3 and because of the differences observed for the reduced analogues 6 and 15, the mode of interaction even within this series of cyclic derivatives may be dissimilar.

Figure 1. Structure of 3 (Y = CH₃; X = H), 4a (Y = O; X = OMe), and 4b (Y = O; X = H) superimposed over a molecule of (a) LSD or (b) tryptamine.

At this time, there are insufficient data to support the suggestion that 1, 3, and 4 might mimic a partial structure of LSD as shown in Figure 1a; an alternative interaction for 1 and/or 4 is also possible (Figure 1b). Additional studies on derivatives of 3 and 4 are necessary to resolve this problem; nevertheless, the sp<sup>2</sup>-hybridized atoms of 1 (position of 3 and 4 position of 4) appear to play a role in the 5-HT receptor interactions of these compounds.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were obtained on a Perkin-Elmer R-24 spectrometer, and chemical shifts are reported relative to tetramethylsilane (DSS, where D₂O was used as solvent). Infrared and mass spectra were determined using a Perkin-Elmer 257 spectrophotometer and a Finnigan 4000 series GC/MS, respectively. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, and values are within 0.4% of theoretical.

1-(Aminomethyl)-3,4-dihydronaphthalene Hydrochloride (3). Dry HCl gas was bubbled into a solution of 5 (4.5 g, 25.4 mmol) in absolute EtOH (100 mL) at 0 °C for 5 min. The solution
was shaken in an atmosphere of H2 at 50 psig overnight. The powder: mp 217-220 °C; NMR (D2O) to near dryness under reduced pressure.

Et2O (30 mL); the hydrochloride salt was obtained by bubbling HC1 gas through the ether solution to yield 82 mg (18%) of and evaporated to dryness. The solid residue was dissolved in NaHCO3 (15 mL) was added, and the mixture was extracted with H2O (100 mL). When cool, H2O (50 mL) was added; the mixture was extracted with CH2C12 (40 mL) at a rate to allow gentle reflux. The mixture was heated to 75 °C (oil bath) to evaporate the CH2C12; the temperature was slowly increased to 170 °C (2 h), and heating at this temperature was continued for another 1.5 h. The mixture was chilled to 0 °C, and H2O (150 mL) was slowly added; this was followed by the addition of concentrated HCl. The product was neutralized with Et2O and collected by filtration. Recrystallization from 2-propanol gave 16 mg (9%) of as small white needles, mp 129-131 °C (lit.9 mp 134-135 °C).

Method B. Dry HCl gas was bubbled into a solution of (8. g, 3.06 mmol) in glacial HOAc at 5 °C for 1 min, and the solution was then heated at reflux for 1 h. The solvent was removed under reduced pressure; the residual product was triturated with Et2O and collected by filtration. The crude off-white product was dissolved in hot absolute EtOH (10 mL) treated with charcoal, and precipitated by the addition of 10% HCl, and extracted with Et2O (3 mL) was introduced to a solution of 4-Methoxyphenol (35 g, 282 mmol) in 20% aqueous KOH (100 mL) in CH2C12 (25 mL). The benzene was removed in vacuo and the process was repeated twice to yield a crude yellowish precipitate. The precipitate was stirred with Et2O (25 mL overnight and collected by filtration. Recrystallization from 2-propanol gave 16 mg (8%) of the free base.

Method C. A solution of 5% dry HCl gas was bubbled into a solution of 4-chromanone (7.5 g, 35.7 mmol) in CH2C12 (40 mL) at a rate to allow gentle reflux. The solution was heated on a steam bath for 2 h and cooled to 0 °C, and Na2SO4.10H2O was added. The solution was filtered and the filtrate was extracted with 10% aqueous KOH (20 mL). Benzene (50 mL) was added at room temperature and the mixture was allowed to stir overnight (16 h). The mixture was filtered and the filtrate was extracted with 10% aqueous KOH (20 mL) and NaHCO3 (23.6 g, 282 mmol) in H2O (100 mL). The solution was heated on a steam bath for 3 h, acidified to pH 5 by the addition of 10% HCl, and extracted with Et2O (3 x 100 mL). The combined etheral solutions were extracted with 10% NaHCO3 (4 x 100 mL), and the aqueous extract was recrystallized to pH 5 by the addition of 10% HCl to yield a white precipitate. The precipitate was dissolved in CH2C12 (100 mL). The aqueous extract was extracted twice with CH2C12 (100 mL). The combined CH2C12 solutions were dried (Na2SO4) and evaporated to dryness under reduced pressure to afford crude 11. Recrystallization from benzene gave 7.1 g (75 %, based on recovered 4-methoxyphenol) of 11 as white crystals, mp 65-75 °C (oil bath) for 1 h. The warm red solution was slowly poured onto iced (50 g) and was stirred for 20 min. The resultant precipitate was collected by filtration and washed seven times with 10% NaHCO3 and then H2O. Distillation [Kugelrohr, 65-75 °C (0.14 mm)] yielded 5.2 g (82% of 12a as a white solid, mp 47-48 °C (lit.11 mp 47-50 °C).

(±)-4-(Aminomethyl)-6-methoxy-4-chromanol Hydrochloride (13b). Trime-thylisilyl cyanide (10 mL) was introduced via syringe to a flask containing 6-methoxycromanone (12a; 5.1 g, 28.7 mmol) and ZnCl2 (100 mg) under an atmosphere of N2. The solution was stirred at 50 °C (oil bath) for 5 h and cooled to room temperature, and dry THF (100 mL) was added. This solution was dropwise to a stirred suspension of LiAlH4 (2.28 g, 60 mmol) in dry THF (50 mL) at 0 °C. The mixture was heated at reflux for 2 h and cooled to 0 °C, and NaHCO3-10H2O was added in small portions until the evolution of H2 ceased. The precipitated material was removed by filtration and was washed with warm THF (30 mL). The combined THF solutions were dried (Na2SO4) and evaporated to dryness to give 5.4 g (90%) of the amine as a white solid: mp 105-107 °C; NMR (CDCl3) 4.05 s, 3 H, OH, CH2; 2.95 s (2 H, CH2N); 2.75 s (3 H, ArH); 4.2 s (2 H, OCH2); 6.75-7.0 (3 H, ArH); mass spectrum, m/e (relative intensity) 209 (8), 137 (100). The hydrochloride salt was prepared and recrystallized from an absolute EtOH-Et2O mixture, mp 157-158 °C. Anal. (C11H13NO3.HCl) C, H, N.

4-(Aminomethyl)-3,4-tetrahydro-2H-naphthalen-1-one Hydrochloride (14b). Compound 13b was prepared in 75% yield from 4-chromanol in the same manner employed for the preparation of 13a. The hydrochloride salt was recrystallized from a methanol–Et2O mixture: mp 172-174 °C; NMR (Me2SO-d6) 2.1 (2 H, 3°, CH2S); 4.1 (t, 2 H, OCH2); 6.1 (br signal, 1 H, OH); 6.6-7.2 (3 H, ArH).
Peptide Sweeteners. 5. Side-Chain Homologues Relating Zwitterionic and Trifluoroacetylated Amino Acid Anilide and Dipeptide Sweeteners

Masao Kawai,1 Rolf Nyfeier, Judd M. Berman, and Murray Goodman*

Department of Chemistry, B-014, University of California, San Diego, La Jolla, California 92039. Received September 8, 1981

Side-chain homologues of sweet trifluoroacetyl-L-α-aspartyl-p-cyanomalide have been synthesized and tasted. Removal of the trifluoroacetyl group only changes the potency of sweet taste, not the taste property. These results have been compared with the structure–taste relationships of dipptide sweeteners. An informative discontinuity of taste effects was found to exist with novel aminomalonyl dipeptide derivatives. The results are explained on topochemical grounds.

An extremely wide variety of structural features are found in sweet tasting compounds. Attempts to determine general characteristics from the great diversity of the structures of sweet compounds have been made, and molecular theories of sweet taste have been proposed.1,3

Recently, the relationship between structure and taste has been quantitatively analyzed by correlating the potency of sweet taste of L-aspartyl dipeptide analogues to steric, electronic, and hydrophobic parameters.4 Derivatives

References

(1) Visiting research chemist from Mitsubishi-Kasei Institute of Life Sciences, Machida-shi, Tokyo 194, Japan.


(3) L. B. Kier, J. Pharm. Sci. 61, 1384 (1972).