Opioid Binding and in Vitro Profiles of a Series of 4-Hydroxy-3-methoxyindolomorphinans. Transformation of a δ-Selective Ligand into a High Affinity κ-Selective Ligand by Introduction of a 5,14-Substituted Bridge

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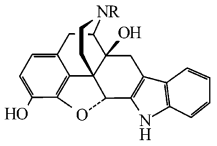
In investigation of the effects of 14-substitution in the indolomorphinan series of δ-selective opioid ligands, 5,14-bridged indolomorphinans (**4**) were prepared from the equivalent dihydrothebainone acid-catalyzed rearrangement products of the dihydrothevinols. Though the new ligands generally had low affinity for opioid receptors and no δ-selectivity, **4b** had high κ-affinity and substantial selectivity which was also seen in the precursor morphinanone (**3b**). This indicates that the methylbenzylidene-substituted bridge in these compounds is a dominant κ-opioid receptor binding motif.

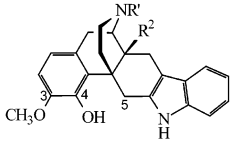
Introduction

Since the discovery of multiple opioid receptors[1,2] most of the interest of medicinal chemists in the field has been in δ and κ types. This was originally driven by the possibility that δ and κ agonism might provide analgesics as effective as the μ agonists, e.g., morphine and fentanyl, but lacking the limiting unwanted effects of respiratory depression, constipation, tolerance, and dependence. But selective δ and κ agonists have been shown to have other therapeutic possibilities. δ-Agonists stimulate respiration[3] and appear to have antidiarrheal effects without affecting GI motility;[4] they also have immunostimulating properties.[5] κ-Opioid agonists have been therapeutic targets for the treatment of pain and hyperalgesia and for psychostimulant abuse, particularly relating to cocaine,[6−8] though undesirable effects (sedation, dysphoria, diuresis) limit their application.[9−12]

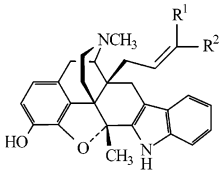
The first selective non-peptide δ-selective ligand was the antagonist naltrindole (NTI, **1a**);[13] its 17-methyl congener oxymorphindole (OMI, **1b**) is a selective δ-partial agonist.[13] Related 4-hydroxy-3-methoxyindolomorphinans (**2b**, **2d**) and the equivalent 14-deoxy analogues (**2a**, **2c**) had very much lower δ-receptor affinity than OMI and NTI but **2c** had an order of magnitude higher selectivity than NTI for δ over both μ and κ.[14] Our particular interest has been to explore the effect of variation of the 14-substituent in the 17-methylindolomorphinan structure on δ-affinity, efficacy and selectivity in the search for new δ-agonists. We here report the synthesis and evaluation in opioid receptor binding and in vitro functional assays of a series of 5,14-bridged analogues (**4**) of 4-hydroxy-3-methoxyindolomorphinan (**2a**). None of the new ligands showed significant δ-selectivity, but one (**4b**) had subnanomolar affinity for κ and substantial selectivity over δ and μ.



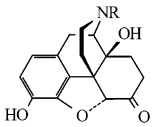
1
a: R = $CH_2c\text{-}C_3H_5$; NTI
b: R = Me; OMI



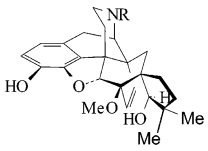
2
a: $R^1 = CH_3$, $R^2 = H$
b: $R^1 = CH_3$, $R^2 = OH$
c: $R^1 = CH_2c\text{-}C_3H_5$, $R^2 = H$
d: $R^1 = CH_2c\text{-}C_3H_5$, $R^2 = OH$



5
a: $R^1 = H$, $R^2 = C_6H_5$
b: $R^1 = R^2 = CH_3$



6a: $R = CH_2c\text{-}C_3H_5$
6b: $R = CH_3$



9

Chemistry. The 5,14-bridged dihydrothebainone precursors (**3a**, **3b**, **3d**) were prepared from the acid-catalyzed rearrangement of dihydronepenthol (**7a**)[15] and dihydrothevinols (**7b**, **7d**).[16,17] **3c** was prepared by similar rearrangement from 6,14-endoethano-7-ethylidenetetrahydrothebaine (Scheme 1).[18] The Fischer indolization of the dihydrothebainones to give the indolomorphinans (**4**) was performed in a sealed tube with phenylhydrazine in ethanol with methanesulfonic acid as catalyst.

Results and Discussion

The opioid binding assays were conducted in recombinant human opioid receptors (HOR) transfected into chinese hamster ovary (CHO) cells in which the displaced radioligands were [^{3}H]Cl-DPDPE (δ), [^{3}H]U69593 (κ), and [^{3}H]DAMGO (μ).[19] The 5,14-bridged indolomorphinans (**4**) generally showed moderate affinity for HOR without substantial selectivity for any individual type (Table 1). The exception was the methyl dihydroflavonepenthone derivative (**4b**) that had high κ affinity

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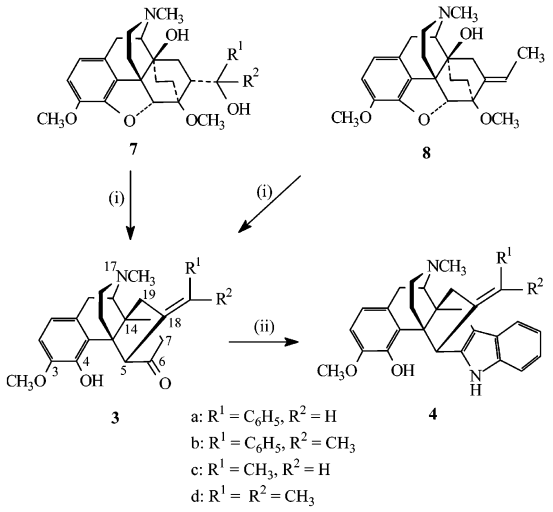
Scheme 1[a]



[a](i) H^+, heat; (ii) $C_6H_5NHNH_2$, EtOH, MsOH.

Table 1. Binding of Indolomorphinan (**4**) and Precursor Ketones (**3**) to Recombinant HOR Transfected into CHO Cells

	K_i (nM)				
structure	δ	κ	μ	κ/δ	μ/δ
4a	15.9 ± 6.6	34.6 ± 4.1	6.3 ± 1.1	2.2	0.4
4b	23.2 ± 8.7	0.61 ± 0.22	13.4 ± 4.7	0.03	0.6
4c	82.5 ± 1.3	239 ± 88	122 ± 29	2.9	1.5
4d	103 ± 17	28.4 ± 2.6	330 ± 38	0.3	3.2
3a	5.50 ± 1.3	0.2 ± 0.02	0.43 ± 0.02	0.04	0.08
3b[a]	5.66 ± 0.24	0.14 ± 0.10	4.54 ± 0.23	0.02	0.8
5a[b]	12.5 ± 2.5	94.2 ± 0.49	43.8 ± 1.6	7.5	3.5
5b[b]	51.4 ± 2.7	440 ± 119	254 ± 4.9	8.6	4.9
1a NTI	0.2 ± 0.05	10.1 ± 0.65	6.3 ± 2.3	50.5	31.5
6a NTX	10.8 ± 3.0	0.4 ± 0.1	0.2 ± 0	0.04	0.02

[a] Data from ref 17. [b] Data from ref 20.

(K_i = 0.62 nM) with substantially lower δ affinity (K_i = 23.2 nM) and μ affinity (K_i = 13.4 nM). The equivalent ligand lacking methyl substitution in the unsaturated bridge (**4a**) had similar affinity to **4b** for δ and μ but nearly 60-fold lower κ-affinity. The etheno- and isopropeno-substituted bridge derivatives (**4c**, **4d**) had lower affinity for HOR than **4a** and **4b** with μ providing the greatest difference (~20-fold). The κ-affinity of **4d** was eight times greater than that of **4c**, a similar though lesser effect than between **4b** and **4a**.

Comparison of the HOR binding profiles of **4a** and **4b** with the precursor flavonepenthones **3a** and **3b** (Table 1) shows that affinity of the indolomorphinans is lower. This difference is modest for **4b** but for **4a** it is substantial at μ (15-fold) and dramatic (173-fold) at κ. The very high κ-affinity of **4b** and its selectivity over δ and μ follows the profile of the precursor ketone (**3b**) that was also shown to have unexpectedly high κ affinity and selectivity.[17] Dihydroflavonepenthone (**3a**) had high κ-affinity similar to **3b**, but this was not retained in the indolomorphinan (**4a**). This difference suggests that there is a specific κ-receptor interaction involving the bridge methyl group (R^2) in **4b** that is not present in **4a**. There was a similar though less pronounced difference in κ-affinity between **4d** and **4c** presumably for the same reason. The small loss of δ-affinity on conversion of ketones **3a** and **3b** into indolomorphinans (**4a**, **4b**) is in contrast to the >1000-fold increase in δ-affinity in the conversion of naltrexone (**6a**) to naltrindole (**1a**).[13] This shows that the 5,14-bridge, particularly in **4b**, has a greater effect on opioid binding than the indole ring.

The effect of the 5,14-bridge can be gauged by comparison of the data for **4a**−**d** with the published data for **2a**,[14] though the receptor preparations involved were different (recombinant CHO cells for **4**, rat brain membranes for **2a**). For **2a**, δ-affinity (K_i 94 nM) was in the range of **4c** and **4d** but significantly lower than that of **4a** and **4b**, whereas it had little or no κ or μ affinity and substantial δ selectivity. This shows that the bridge in the new indolomorphinans does not inhibit δ-binding though it enhances κ- and μ-binding and thus destroys δ-selectivity. Data are also available for the 5,14-substituted, 4,5-epoxyindolomorphinans (**5a**, **5b**)[20] for comparison with **4a** and **4d**, respectively. This shows that δ-binding affinity is not substantially affected by formation of the cyclopentane ring in **4a**, **4d** but it enhances μ-affinity (in **4a**) and κ-affinity (in **4d**).

Functional activity for the indolomorphinans at the individual HOR was determined by stimulation of [^{35}S]-GTPγS binding.[19,21] The new 4-hydroxy-3-methoxy analogues (**4**) had only moderate or low potency agonist activity in these assays (Table 2), considerably lower than would have been expected from their binding affinities, and none of the new ligands displayed functional selectivity for any particular HOR. However for **4b**, the difference in κ agonist potency (EC_{50} 82 nM) and κ binding (K_i = 0.61 nM), i.e., 135-fold is not very different from that for the standard κ agonist U69,593 which had K_i = 0.3 nM and EC_{50} 26 nM.[19] **4a** and **4b** were full, or nearly full, agonists for δ, κ, and μ receptors; the efficacy of **4b** for δ and μ receptors was exceptional, being 68% and 44% higher than the respective standards (DPDPE δ; DAMGO μ). The potency of **4a** for δ and μ was higher than for κ whereas **4b** was more potent for κ, though with very little selectivity over μ and δ in contrast to its κ-binding selectivity. Both **4c** and **4d** which lack phenyl groups in the 5,14-bridge were δ-antagonists and very low potency κ and μ partial agonists. Thus the efficacy of **4a** and **4b** for HOR was very much higher than that of **4c** and **4d**. The difference for δ was particularly striking between full agonist (**4a**, **4b**) and antagonist (**4c**, **4d**).

Summary and Conclusions

The 5,14-bridge in indolomorphinans (**4**) has very little effect on affinity for δ-opioid receptors but markedly increases μ and κ affinity, resulting in total loss of δ-selectivity. **4b**, in which the methene linkage to the bridge is disubstituted, has subnanomolar κ-affinity and significant selectivity for κ over δ and μ; this effect is also shown to a smaller extent by **4d**. Comparison of the indolomorphinans (**4a**, **4b**) with the precursor ketones (**3a**, **3b**) shows that the bridge has a greater influence on HOR binding profile than the indole ring which would normally enhance binding to δ. Interestingly, comparison of the structures of **4a** and **4b** with that of the spiro orvinol analogue **9** indicates that the pendant methyl group (R^2) of **4a** occupies the same region of space as the spiro cyclopentane ring in **9**. This ring has previously been proposed to occupy a lipophilic site on the κ-receptor that is important for κ-agonist binding in the orvinol and related series.[22−24]

Table 2. Stimulation of [^{35}S]GTPγS Binding of Indolomorphinan (**4**) and Precursor Ketones (**3**) in Recombinant HOR Transfected into CHO Cells

	δ		κ		μ	
structure	EC_{50} (nM)	% stim[a]	EC_{50} (nM)	% stim[b]	EC_{50} (nM)	% stim[c]
4a	42.6 ± 15	87 ± 1	323 ± 3.2	83 ± 3	44.7 ± 13	110 ± 0.2
4b	368 ± 62	168 ± 5	82.4 ± 14	97 ± 9	139 ± 2.9	144 ± 8
4c	221 ± 22[d]		2210 ± 307	36 ± 2	1644 ± 388	41 ± 4
4d	211 ± 26[d]		866 ± 286	44 ± 8	1016 ± 218	52 ± 5
3a	4.19 ± 2.2	80 ± 2	17.5 ± 7.2	85 ± 10	6.7 ± 2.3	123 ± 27
3b	72.3 ± 33	108 ± 8	3.38 ± 0.38	116 ± 19	15.2 ± 3.6	108 ± 5
5a[e]	21.8 ± 5.3	79 ± 3	2046 ± 60	60 ± 10	804 ± 41	85 ± 3
5b[e]	90.1 ± 30	43 ± 4	945 ± 191	31 ± 7	1201 ± 92	72 ± 4
1a NTI	0.11 ± 0.005[d]		4.95 ± 0.32[f]		4.26 ± 0.3[g]	
6a NTX	5.44 ± 0.75[d]		1.86 ± 0.16[f]		0.59 ± 0.04[g]	

[a] DPDPE = 100. [b] U69,593 = 100. [c] DAMGO = 100. [d] K_e (nM) vs DPDPE. [e] Data from ref 20. [f] K_e (nM) vs U69593. [g] K_e (nM) vs DAMGO.

Experimental Section

Chemistry. Melting points were recorded on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. ^{1}H NMR were recorded on a JEOL Lambda 300 MHz instrument, and ^{13}C NMR spectra were carried out on the same machine at 75 MHz. Chemical shifts are measured in parts per million using TMS as a standard. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Coupling constants are measured in hertz. IR spectra were recorded on a Perkin-Elmer 881 Instrument. Both high and low resolution mass spectra were obtained from a V.G. Autospec instrument equipped with a Fisons autosampler, using electron impact ionization at 70 eV. Microanalysis was performed with a Perkin-Elmer 240C analyzer.

4-Hydroxy-3-methoxy-17-methyl-18-*E*-benzylidene-5,-14-ethanomorphinan-6-one (3a). A mixture of **7a** (0.30 g, 0.67 mmol) with concentrated HCl (10 mL) was heated on a steam bath for 2 h. Cooling, dilution with water (20 mL), basification (NH_4OH), and extraction with EtOAc to yield **3a** as a white solid (0.25 g, 88%), which was purified by flash chromatography (MeOH: CH_2Cl_2, 5:95). R_f 0.59 (CH_2Cl_2/CH_3-OH 95:5). IR (film) ν_{max}/cm^{-1} 3533 (s, C-4 hydroxyl), 1707 (s, C-6 carbonyl) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, NC*H*$_3$), 2.57 (d, *J* 18.5, 1H, 19-H), 3.12 (d, *J* 18.5, 1H, 10-H$_\beta$), 3.81 (s, 3H, OC*H*$_3$), 4.18 (s, 1H, 5-H), 5.85 (s, 1H, 4-OH), 6.53 (s, 1H, 20-H), 6.63 (s, 2H, 1-H, 2-H), 7.35 (m, 5H, 20-Ph). ^{13}C NMR ($CDCl_3$): δ 24.0, 31.8, 32.5, 34.5, 35.7, 43.3, 45.3, 45.5, 46.5, 55.8, 58.2, 69.4, 108.7, 118.0, 124.5, 125.3, 126.5, 128.3, 128.4, 132.5, 137.7, 138.0, 143.1, 144.8, 209.3. EIMS *m*/*z* (relative intensity) 415 (100%, M$^+$). HRMS ($C_{27}H_{29}NO_3$) calc. 415.2150 found 415.2147. Anal. ($C_{27}H_{30}NO_3Cl$·1.5H_2O) C, H, N.

General Procedure for the Synthesis of the Indolomorphinans 4. The method adopted for the synthesis of 4-hydroxy-3-methoxy-17-methyl-18-isopropylidene-[6,7:2′,3′]-indolomorphinan (**4d**) is described: A solution of thebainone **3d** (0.74 g: 2.0 mmol),[16] phenylhydrazine hydrochloride (0.57 g: 4.0 mmol), and methanesulfonic acid (0.5 mL) in ethanol (10 mL) was heated to reflux in a sealed tube under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered to remove excess phenyl hydrazine, and the filter cake was washed with ethanol (3 × 1 mL). The filtrate was basified (NH_4OH, water) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were washed with water and brine and then dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was subjected to purification by flash chromatography (CH_2Cl_2/CH_3OH, 1% NH_4OH 30:1) to give 0.39 g (44%) indolomorphinan **4d** as a solid. R_f 0.54 (CH_2Cl_2/CH_3OH, 1% NH_4OH 10:1). Mp (oxalate) > 200 °C. IR (film): ν_{max}/cm^{-1}: 3534, 3474, 3527, 3475, 3413. ^{1}H NMR ($CDCl_3$, selected signals): δ 1.54 (s, 3H), 1.81 (s, 3H), 2.39 (s, 3H, NC*H*$_3$), 3.69 (s, 3H, OC*H*$_3$), 4.47 (s, 1H), 5.49 (s, 1H), 6.47 (d, *J* 8.3, 1H), 6.56 (d, *J* 8.3, 1H), 6.90−7.02 (m, 2H), 7.20−7.24 (m, 2H), 7.74 (s, 1H, indole-N*H*). ^{13}C NMR ($CDCl_3$): δ 20.80, 20.95, 24.52, 32.43, 33.38, 36.02, 43.55, 45.19, 45.46, 46.40, 47.80, 55.50, 58.98, 105.00, 107.99, 110.60, 117.36, 117.99, 118.60, 119.62, 120.08, 126.83, 128.10, 131.44, 135.44, 139.49, 140.80, 142.33, 143.80. EIMS *m*/*z* (relative intensity) 440 (100%, M$^+$). HRMS ($C_{29}H_{32}N_2O_2$) calc. 440.2464 found 440.2460. Anal. ($C_{29}H_{32}N_2O_2$·$(COOH)_2$·C_2H_5OH) C, H, N.

4-Hydroxy-3-methoxy-17-methyl-18-*E*-benzylidene-[6,7:2′,3′]-indolomorphinan (4a) from 3a:[15] Yield: 58%. R_f 0.55 (CH_2Cl_2/CH_3OH 95:5). Mp (hydrochloride): >250 °C. IR ($CHCl_3$): ν_{max}/cm^{-1}: 3534, 3474. ^{1}H NMR ($CDCl_3$, selected signals): δ 2.37 (s, 3H, NC*H*$_3$), 2.90 (d, *J* 16.7, 1H, 10-H$_\alpha$), 2.94 (dd, *J* 17.0, 1.4, 1H, 19-H), 3.00 (*J* 6.4, 1H, 9-H$_\alpha$), 3.17 (d, *J* 16.7, 1H, 10-H$_\beta$), 3.70 (s, 3H, OC*H*$_3$), 3.76 (dd, *J* 17.0, 1.8, 1H, 19-H), 4.37 (s, 1H, 5-H), 5.50 (s, 1H, 4-OH), 6.34 (s, 1H, 20-H), 6.50 (d, *J* 8.3, 1H, 1-H), 6.60 (d, *J* 8.3, 1H, 2-H), 6.97−7.31 (m, 9H, indole-, 20Ph-*H*), 7.83 (1H, s, indole-N*H*). ^{13}C NMR ($CDCl_3$): δ 24.49, 32.53, 33.35, 36.91, 43.52, 44.35, 46.10, 46.61, 54.70, 55.49, 58.82, 105.11, 108.13, 110.74, 117.50, 118.11, 118.71, 120.01, 120.04, 125.59, 126.40, 127.98, 128.00, 128.10, 131.39, 135.86, 138.30, 138.38, 142.30, 143.82, 150.08. EIMS *m*/*z* (relative intensity) 488 (100%, M$^+$). HRMS ($C_{33}H_{32}N_2O_2$) calc. 488.2464 found 488.2456. Anal. ($C_{33}H_{32}N_2O_2$·$(COOH)_2$·2H_2O) C, H, N.

4-Hydroxy-3-methoxy-17-methyl-18-(1*E*-methylbenzylidene-[6,7:2′,3′] indolomorphinan (4b) from 3b:[17] Yield: 48%. R_f 0.56 (ethyl acetate/hexane 6:4). Mp (hydrochloride): >250 °C. IR ($CHCl_3$): ν_{max}/cm^{-1}: 3533. ^{1}H NMR ($CDCl_3$): δ 1.51 (m, 1H), 2.06 (d, *J* 16.5, 1H), 2.09−2.16 (m, 1H), 2.19 ("s", 3H), 2.30 (s, 3H), 2.35−2.44 (m, 2H), 2.83−3.02 (m, 3H), 3.11 (d, *J* 17.9, 1H), 3.42 (d, *J* 16.5, 1H), 3.68 (s, 3H, OC*H*$_3$), 4.67 (s, 1H), 5.53 (s, 1H), 6.48 (d, *J* 8.4, 1H., 1-H), 6.56 (d, *J* 8.4, 1H, 2-H), 6.94−7.04 (m, 2H), 7.10−7.29 (m, 7H), 7.82 (s, 1H, indole-N*H*). ^{13}C NMR ($CDCl_3$): δ 21.28, 24.44, 32.67, 33.34, 36.73, 43.54, 45.28, 45.52, 46.30, 48.80, 55.59, 58.68, 105.73, 108.06, 110.66, 117.54, 118.06, 118.64, 119.79, 125.49, 125.76, 126.67, 127.90, 128.16, 131.63, 135.63, 138.76, 142.35, 143.72, 143.8, 144.29. EIMS *m*/*z* (relative intensity) 502 (100%, M$^+$). HRMS ($C_{34}H_{34}N_2O_2$) calc. 502.2620 found 502.2620. Anal. ($C_{34}H_{34}N_2O_2$·$(COOH)_2$·H_2O) C, H, N.

4-Hydroxy-3-methoxy-17-methyl-18-(*E*)-ethylidene-[6,7:2′,3′]-indolomorphinan (4c). A sample of ethylidene compound **8**[18] (0.69 g, 1.8 mmol) in 5 mL of concentrated hydrochloric acid was heated to reflux for 4 h. After this time, all the volatiles were removed in vacuo, the residue was redissolved in 10 mL of ethanol, and 0.51 g (3.6 mmol) phenylhydrazine hydrochloride and 0.4 mL of methanesulfonic acid were added. The reaction mixture was then heated to reflux in a sealed tube under an atmosphere of nitrogen for 24 h and worked up as described in the general procedure. Fractional crystallization of the oxalate of **4c** gave 0.13 g (14%) as a dark brown solid. Mp (oxalate) >200 °C. R_f 0.36. IR (film): ν_{max}/cm^{-1}: 3404. ^{1}H NMR ($CDCl_3$): δ 1.48 (d, *J* 6.8, 3H), 1.96 (d, *J* 16.6, 1H), 2.08−2.14 (m, 2H), 2.38 (s, 3H, NC*H*$_3$), 2.41−2.45 (m, 3H), 2.88 (dd, *J* 15.4, 1.71, 1H), 2.96−3.04 (m, 2H), 3.15 (m, 1H), 3.34 (d, *J* 16.1, 1H), 3.63 (s, 3H), 4.16 (s, 1H), 5.30 (m, 1H), 5.51 (s, br., 1H), 6.46 (d, *J* 8.3, 1H), 6.57 (d, *J* 8.3, 1H), 6.92−7.01 (m, 2H), 7.19−7.23 (m, 2H), 7.81 (s, br., 1H). ^{13}C NMR ($CDCl_3$): δ 14.37, 24.46, 32.47, 33.37, 34.20, 43.60, 45.07, 45.36, 46.29, 52.18, 55.51, 58.95, 104.74, 107.99, 110.67, 113.53, 117.44, 117.99, 118.63, 119.75, 126.80, 128.16, 131.57, 135.68, 139.50, 142.32, 143.78, 147.92. EIMS *m*/*z* (relative

intensity) 426 (100%, M^+). HRMS ($C_{28}H_{30}N_2O_2$) calc. 426.2307 found 426.2320. Anal. ($C_{28}H_{30}N_2O_2 \cdot (COOH)_2 \cdot H_2O$) C, H, N.

Pharmacology. Pharmacological assays were performed following the procedures given in refs 19 and 21. EC_{50} and % stimulation values (±SEM) represent data from two experiments, each carried out in triplicate. K_e values (±SEM) represent data from five or six experiments.

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