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Anticonvulsant Effects of New Morphinan Derivatives

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Abstract—We synthesized a series of compounds that are modified in positions 3 and 17 of the morphinan ring system, with the intention of developing ideal anticonvulsant agents. We examined the effects of these compounds on kainic acid (KA)-induced seizures, and on locomotor patterns in rats. We found that compounds **5**, **6**, and **8** exhibit novel anticonvulsant effects, with negligible psychotropic effects.

Introduction

Dextromethorphan (3-methoxy-17-methylmorphinan, DM) is a non-narcotic morphinan derivative that has been widely used as an antitussive for almost 40 years. It has recently attracted attention because of its anticonvulsant and neuroprotective properties.[1–5] The encouraging experimental results led to a number of clinical trials in neurological disorders, including epilepsy.[6] However, case reports of toxicity in children[7] and of psychotomimetic reactions[8–17] associated with high-dose DM ingestion are likely attributable to this metabolite, as is the reported abuse potential in adolescent youths.[11,18] We have demonstrated that DM itself produces psychotropic behavioral patterns,[12,14] and that DM can potentiate cocaine's behavioral effects in rodents.[12,14,15] Moreover, we have described how chronic DM administration perturbs cellular immune responses, and that this is similar to the immunosuppressive effects caused by phencyclidine.[19]

In this study, we synthesized a series of compounds that are modified in positions 3 and 17 of the morphinan ring system, with the intention of developing compounds that could retain the anticonvulsant/neuroprotective activities with negligible psychotropic effects. We then evaluated these compounds as anticonvulsant agents. Since the syndromes characterized by systemic kainic acid (KA) administration are very similar to temporal lobe epilepsy in humans,[20] we used this neurotoxin for our study.

Chemistry

The synthesis of new morphinan derivatives was carried out as follows (Scheme 1). Dextrorphan (DX, **2**) was obtained in quantitative yield via *O*-demethylation of DM (**1**) HBr with 47% HBr. DM·HBr was converted to the free base by extraction with aqueous NH_4OH. Potassium carbonate and 1-chloroethyl chloroformate were added to a solution of the crystalline free base (**1**) in 1,2-dichloroethane at 0 °C, and then refluxed for 6 h under a nitrogen atmosphere to give 3-methoxymorphinan (**3**). **3** was treated with 47% HBr to yield 3-hydroxymorphinan (**4**) in 70% yield. **2** reacted with allyl bromide or bromomethylcyclopropane in the presence of sodium hydride to produce 3-allyloxy-17-methylmorphinan (**5**) and 3-cyclopropylmethoxy-17-methylmorphinan (**6**) in 98 and 94% yield, respectively.

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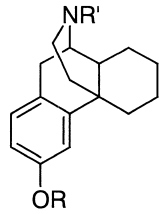
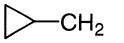
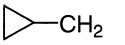
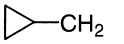


entry	R	R'		entry	R	R'	
1	CH_3	CH_3	**1**(DM)	6		CH_3	**6**
2	H	CH_3	**2**(DX)	7	CH_3	CH_2=CH-CH_2	**7**
3	CH_3	H	**3**	8	CH_2=CH-CH_2	H	**8**
4	H	H	**4**	9	CH_2=CH-CH_2		**9**
5	CH_2=CH-CH_2	CH_3	**5**	10		CH_2=CH-CH_2	**10**

Scheme 1.

3-Allyloxy-17-methylmorphinan was treated with 1-chloroethyl chloroformate to give 3-allyloxymorphinan (**8**). The other morphinan derivatives (**7**, **9**, and **10**) were prepared using a method similar to that described above.[21]

Results

The compounds synthesized were evaluated for their anticonvulsant (neuroprotective) activity against seizures induced by kainic acid. The locomotor patterns (circling behavior) characterized by psychotomimetic activity were examined.[9,12] The intensity of activator protein (AP)-1 DNA binding activity in the rat hippocampus was examined in order to confirm the anticonvulsant effects biochemically.[1,3]

To reduce side effects while retaining anticonvulsant effects, we prepared a series of 3- and 17-substituted morphinans that are structurally similar to DM (**1**), but are either not expected to be metabolized to DX (**2**, a major metabolite of **1**; **2** produces phencyclidine-like psychotomimetic effects) or expected to do so at a reduced rate as compared to **1**. The size effect and rate of hydrolysis of ether were considered.

The circling behavior mediated by the morphinans is shown in Table 1. Among the morphinans in our study, compound **2** caused the most significant increase in circling activity, comparable to that induced by phencyclidine. This enhanced activity was significantly reduced when position 3 was substituted with an allyloxy- or cyclopropylmethoxy-group (entry **5** or **6**). In particular, modifications of both the methoxy group at the 3-position and the methyl group at the 17-position more significantly attenuated the enhanced circling behavior induced by compounds **1** and **2** (entry **8**). Furthermore, compounds **5**, **6**, and **8** produced strong neuroprotective activity, as reflected by seizure score, AP-1 DNA binding activity, and mortality. The anticonvulsant/neuroprotective activity of compound **8** was the most pronounced (Table 2).

In contrast, the circling behavior induced by other metabolites (**3** and **4**) of DM was comparable to that induced by **1,** but not to that by **2** or phencyclidine. The cause of the phenomenon remains elusive. Although compound **2**-induced enhanced circling behavior and KA-induced increased mortality were both attenuated by treatment with compounds **3**, **4**, **7**, **9**, and **10**, the anticonvulsant activities mediated by compounds **3**, **4**, **7**, **9**, and **10** were less potent than those of compounds **5**, **6**, and **8**. An alkyl substituent at the 17-position did not significantly influence the anticonvulsant effects of 3-alkyl morphinans, as shown in Table 2 (refer to compounds **7**, **9**, and **10**). Thus, alkylation at position 3 or

Table 1. Circling behavior induced by the morphinans in the rats[a]

Compound	Dose (mg/kg, ip)	*N*	Circling behavior (absolute turn angular ±SE/3 min)
—	Saline	16	129±10
1 (DM)	20	12	192±21[b]
	40	12	265±21[c]
2 (DX)	20	12	310±19[d,f]
	40	12	384±16[d,f]
3	20	12	186±14[b,h]
	40	12	258±21[c,h]
4	20	12	194±13[b,h]
	40	12	262±18[c,h]
5	20	12	168±14[h]
	40	12	219±18[c,h]
6	20	12	160±12[h]
	40	12	202±19[b,h]
7	20	12	224±18[c,g]
	40	12	282±17[d,g]
8	20	12	152±12[h]
	40	12	184±10[b,e,h]
9	20	12	172±14[h]
	40	12	250±18[c,h]
10	20	12	175±16[h]
	40	12	242±22[c,h]
Phencyclidine	5	12	420±20[d]

[a]Circling behavior (marginal activity) was examined using an automated videotracking system[12] 30 min after injection of the drugs. *N* = numbers of animals.
[b]$p<0.05$ vs saline.
[c]$p<0.01$ vs saline.
[d]$p<0.001$ vs saline.
[e]$p<0.05$ vs corresponding dose of compound **1** (DM).
[f]$p<0.01$ vs corresponding dose of compound **1** (DM).
[g]$p<0.05$ vs corresponding dose of compound **2** (DX).
[h]$p<0.01$ vs corresponding dose of compound **2** (DX), (Williams–Wilcoxon multiple rank sum test).

Table 2. Anticonvulsant (neuroprotective) activity induced by the morphinans in the rats[a]

Compound	Dose (mg/kg, ip)	KA (10 mg/kg, ip)	Seizure score	Hippocampal AP-1 DNA binding activity (densitometric units)		Mortality (for 48 h)
				4 h	4 days	
—	—	− (saline)	0.0±0.0	1.4±0.2	1.8±0.1	0/14
—	—	+ (KA alone)	4.2±0.3[b]	28.1±2.2[b]	19.4±2.0[b]	10/19[b]
1 (DM)	20	+	2.2±0.3[d]	15.9±1.4[d]	11.0±0.9[c]	4/19[c]
	40	+	1.4±0.1[d,g]	12.0±1.1[d]	7.8±0.5[d,g]	2/19[e]
2 (DX)	20	+	2.8±0.2[c]	20.4±1.5[c]	14.9±0.9[c]	5/19
	40	+	1.8±0.1[d]	14.2±1.3[d]	10.8±0.5[d]	4/19[c]
3	20	+	2.4±0.3[c]	19.2±1.5[c]	14.0±0.8	4/19[c]
	40	+	2.0±0.2[d]	15.4±1.6[d]	11.0±0.9[c]	4/19[c]
4	20	+	2.5±0.4[c]	19.0±1.9[c]	13.8±0.9[c]	5/19
	40	+	2.1±0.2[d]	15.2±1.4[d]	9.9±0.6[d]	4/19[c]
5	20	+	1.9±0.3[d]	16.0±1.0[d]	10.2±1.0[d]	3/19[d]
	40	+	1.5±0.1[d]	12.1±1.4[d]	9.1±0.8[d]	3/19[d]
6	20	+	1.8±0.2[d,g]	15.5±1.2[d,g]	9.6±0.9[d,g]	3/19[d]
	40	+	1.3±0.1[d,g]	11.4±0.9[d]	8.2±0.9[d]	2/19[e]
7	20	+	2.9±0.3[c]	24.8±2.0	16.0±1.2	6/19
	40	+	2.2±0.2[d]	16.9±1.7[c]	11.2±0.8[c]	6/19
8	20	+	1.5±0.1[d,h,k,m]	12.3±1.2[d,g,k,m]	8.4±0.6[d,h,k,m]	11/19[f]
	40	+	1.0±0.1[e,h,i,k,m,o]	10.0±1.0[e,g,j,l]	5.3±0.7[e,h,i,k,l,n]	1/19[f]
9	20	+	2.8±0.2[c]	21.2±1.7	14.8±0.9	4/19[c]
	40	+	2.0±0.2[d]	17.0±1.9[c]	10.9±1.0[c]	4/19[c]
10	20	+	2.7±0.3[c]	22.4±2.4	15.2±1.6	5/19
	40	+	2.2±0.2[d]	17.3±1.8[c]	11.4±1.8[c]	4/19[c]

[a]Each value is the mean±SE of 15 animals (for seizure score) or four animals (for AP-1 DNA binding activity). KA = kainic acid. Under an automated videotracking system, seizure activity was scored for 4 h after KA injection.[3,22,23] AP-1 DNA binding activity was examined 4 h and 4 days after KA injection.[1,3] AP-1 DNA binding activity was calculated using a Williams–Wilcoxon multiple rank sum test. The statistical significance of the mortality was calculated using the *Chi-square test*.
[b]$p<0.001$ vs saline.
[c]$p<0.05$ vs KA alone.
[d]$p<0.01$ vs KA alone.
[e]$p<0.005$ vs KA alone.
[f]$p<0.001$ vs KA alone.
[g]$p<0.05$ vs corresponding dose of compound **2** (DX).
[h]$p<0.01$ vs corresponding dose of compound **2** (DX).
[i]$p<0.05$ vs corresponding dose of compound **1** (DM).
[j]$p<0.05$ vs corresponding dose of compound **9**.
[k]$p<0.01$ vs corresponding dose of compound **9**.
[l]$p<0.05$ vs corresponding dose of compound **10**.
[m]$p<0.01$ vs corresponding dose of compound **10**.
[n]$p<0.05$ vs corresponding dose of compound **5**.
[o]$p<0.01$ vs corresponding dose of compound **5**.

demethylation at position 17 might be required to retain the anticonvulsant/neuroprotective activity, although more evidence is required.

In conclusion, compounds **5**, **6**, and **8** are promising anticonvulsants that exhibit only weak phencyclidine-like psychotomimetic effects. Of these, compound **8** is the most efficacious anticonvulsant agent. However, their effects in response to various epileptic seizures remain to be further characterized, and their precise mechanisms remain to be determined.

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21. **3-Methoxymorphinan·HCl** (**3**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (d, J = 19.36 Hz, 2H), 7.22 (d, J = 8.34 Hz, 1H), 6.93 (d, 1H), 6.90 (dd, 1H), 3.83 (s, 3H), 3.70 (s, 1H), 3.19 (m, 1H), 3.11 (s, 1H), 3.07 (s, 1H), 2.52 (d, 2H), 2.03 (q, 1H), 1.88 (m, 1H), 1.70 (d, J = 12.13 Hz, 1H), 1.57 (t, 3H), 1.41 (td, 2H), 1.23 (t, 1H), 1.00 (qd, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.44, 138.98, 129.04, 126.33, 112.07, 110.84, 55.01, 49.87, 40.32, 37.84, 36.86, 36.18, 35.15, 27.15, 25.45, 25.06, 21.45. **4-Hydroxymorphinan·HBr** (**4**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.82 (s, 1H), 7.00 (d, J = 8.26 Hz, 1H), 6.71 (s, 1H), 6.64 (q, 1H), 3.65 (s, 1H), 3.07 (m, 2H), 2.90 (d, J = 18.9 Hz, 1H), 2.46 (d, J = 9.05 Hz, 1H), 2.30 (d, J = 13.45 Hz, 1H), 1.88 (d, J = 12.29, 1H), 1.73 (td, 1H), 1.55 (dd, 2H), 1.43 (d, J = 12.48 Hz, 2H), 1.31 (m, 2H), 1.08 (m, 1H), 0.91 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.43, 138.63, 128.93, 124.26, 113.97, 111.55, 50.15, 40.44, 38.81, 37.92, 37.14, 35.94, 35.19, 27.20, 25.44, 25.04, 21.44. **3-Allyloxy-17-methylmorphinan** (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.69 (q, J = 8.3 Hz, 1H), 6.05 (m, J = 5.2 Hz, 1H), 5.34 (q, 2H), 4.50 (d, J = 5.3 Hz, 2H), 2.96 (d, J = 18.1 Hz, 1H), 2.80 (m, 1H), 2.57 (q, J = 5.7 Hz, 1H), 2.38 (m, J = 5.7 Hz, 1H), 2.38 (m, 5H), 2.08 (m, 1H), 1.82 (q, 1H), 1.73 (m, 1H), 1.63 (d, 1H), 1.51 (d, 1H), 1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 140.7, 132.6, 129.0, 127.4, 116.5, 110.9, 110.5, 67.8, 57.0, 46.3, 44.4, 41.8, 41.1, 36.2, 35.7, 25.8, 25.6, 22.3, 21.2; IR (film) 2900, 1810, 1500, 1460, 1370, 1280, 1240, 1180, 1110, 1030, 920, 860 cm^{-1}. **3-Cyclopropylmethoxy-17-methylmorphinan** (**6**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.67 (q, 1H), 3.76 (d, J = 6.9 Hz, 2H), 2.97 (d, J = 18.1 Hz, 1H), 2.80 (m, 1H), 1.82 (t, 1H), 1.73 (m, 1H), 1.63 (d, 1H), 1.50 (d, 1H), 1.25 (m, 7H), 0.63 (m, 2H), 0.34 (q, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 142.0, 130.2, 128.8, 112.2, 111.6, 73.1, 58.4, 47.7, 45.8, 43.2, 42.5, 37.6, 37.0, 27.2, 27.0, 23.7, 22.7, 10.8, 3.6, 3.5; IR (film) 2900, 1800, 1500, 1450, 1280, 1240, 1150, 1100, 1020, 860, 800 cm^{-1}. **3-Methoxy-17-allylmorphinan** (**7**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.36 Hz, 1H), 6.80 (d, J = 2.61 Hz, 1H), 6.69 (q, J = 8.36 Hz, 1H), 5.94–5.85 (m, 1H), 5.22–5.11 (m, 2H), 3.78 (s, 3H), 3.24–3.11 (m, 2H), 2.92 (m, 2H), 2.62–2.52 (m, 2H), 2.34 (d, J = 12.57 Hz, 1H), 2.03 (td, 1H), 1.83 (q, J = 9.70 Hz, 1H), 1.74 (td, 1H), 1.63 (q, J = 2.52 Hz, 1H), 1.50 (t, J = 8.83 Hz, 1H), 1.49–1.27 (m, 5H), 1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.16, 141.78, 135.95, 129.74, 128.42, 117.36, 111.06, 110.62, 58.28, 55.81, 55.15, 45.45, 45.05, 41.81, 37.77, 36.59, 26.79, 26.54, 23.84, 22.21; IR (film) 2900, 1810, 1500, 1460, 1370, 1280, 1240, 1180, 1110, 1030, 920, 860 cm^{-1}. **3-Allyloxymorphinan** (**8**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 3.83 Hz, 1H), 6.82 (d, J = 3.14 Hz, 1H), 6.70 (m, 1H), 6.05 (m, 1H), 5.41 (d, J = 17.35, 1H), 5.27 (d, J = 10.35 Hz, 1H), 4.50 (q, 2H), 4.11 (q, J = 7.12 Hz, 1H), 3.14–2.95 (m, 2H), 2.79–2.57 (m, 3H), 2.39 (s, 1H), 2.28 (t, J = 9.54 Hz, 1H), 2.04 (s, 2H), 1.74 (q, J = 3.26 Hz, 1H), 1.65–1.49 (m, 3H), 1.41–1.30 (m, 5H), 1.25 (t, J = 7.07 Hz, 2H), 1.11–1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.22, 141.71, 133.63, 130.25, 128.50, 117.62, 112.06, 111.56, 68.87, 51.17, 45.99, 42.73, 39.23, 38.31, 37.03, 33.62, 26.89, 26.76, 22.14; IR (film) 3900, 3800, 3700, 3100, 2950, 2850, 2700, 2400, 2300, 1700, 1300, 1250 cm^{-1}. **3-Allyloxy-17-cyclopropylmethylmorphinan** (**9**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.36 Hz, 1H), 6.83 (d, J = 2.56 Hz, 1H), 6.68 (q, J = 8.40 Hz, 1H), 6.05 (m, 1H), 5.40 (q, J = 1.51 Hz, 1H), 5.28 (q, J = 1.29 Hz, 1H), 3.08 (s, 1H), 2.88 (d, J = 18.12 Hz, 1H), 2.70 (q, 1H), 2.57 (q, 1H), 2.48 (q, 1H), 2.31 (t, 2H), 2.00 (m, 1H), 1.86 (d, J = 12.69 Hz, 1H), 1.76 (m, 1H), 1.56 (m, 2H), 1.43–1.21 (m, 7H), 1.14 (m, 1H), 0.06 (m, 2H), 0.49 (m, 2H), 0.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.19, 141.96, 133.63, 130.16, 128.39, 117.62, 111.93, 111.50, 68.86, 60.00, 55.86, 45.80, 45.13, 41.93, 37.92, 36.69, 26.91, 26.64, 23.91, 22.29, 9.45, 4.09, 3.64; IR (film) 3944, 3757, 3691, 3054, 2987, 2932, 2685, 2521, 2410, 2305, 2254, 1422, 1254, 1155 cm^{-1}. **3-Cyclopropylmethoxy-17-allylmorphinan** (**10**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.33 Hz, 1H), 6.82 (d, J = 2.56 Hz, 1H), 6.67 (q, 1H), 5.88 (m, 1H), 5.18 (q, 1H), 5.11 (s, J = 10.18 Hz, 1H), 3.76 (d, J = 6.94 Hz, 2H), 3.15 (m, 2H), 3.91 (t, 2H), 2.55 (m, 2H), 2.35 (t, 1H), 2.03 (m, 2H), 1.81 (d, J = 12.61 Hz, 1H), 1.72 (td, 1H), 1.56 (m, 2H), 1.41–1.21 (m, 4H), 1.14 (m, 1H), 0.63 (m, 2H), 0.34 (q, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.57, 141.85, 136.26, 129.87, 128.34, 117.10, 111.87, 111.79, 72.70, 58.34, 55.81, 45.45, 45.22, 41.93, 37.82, 36.63, 26.83, 26.59, 23.87, 22.28, 10.36, 3.17, 3.12; IR (film) 3944, 3757, 3691, 3052, 2987, 2685, 2521, 2410, 2305, 1551, 1422, 1252, 1156, 909, 693 cm^{-1}.

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