Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 21, pp. 2527-2532, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00368-8

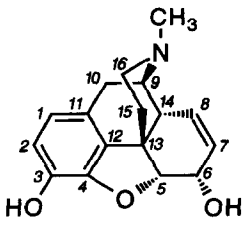
PALLADIUM-CATALYZED SYNTHESIS OF C3-SUBSTITUTED 3-DEOXYMORPHINES.

Martin H. Hedberg,[a] Anette M. Johansson,[a,*] Christopher J. Fowler,[b] Lars Terenius,[c] and Uli Hacksell.[a]

[a] Organic Pharmaceutical Chemistry, Uppsala Biomedical Centre, Uppsala University, Box 574, S-751 23 Uppsala, Sweden, [b] Astra Pain Control AB, Preclinical R&D, Novum Unit, S-141 57 Huddinge, Sweden, [c] Department of Drug Dependence Research, Karolinska Institute, S-171 76 Stockholm, Sweden.

Abstract: The facile synthesis of a series of C3-substituted analogues of 3-deoxymorphine (**2**) by use of palladium-catalyzed reactions is described. Although none of the new compounds were as potent as morphine at either κ-, μ- or δ-opioid receptors, the μ-receptor selectivity of the C3-furyl derivative **7** approached that of morphine.

Morphine is one of the most used and studied natural products. Numerous structure-activity studies have been undertaken to reveal structural factors of importance for its pharmacological effects.[1] The morphinan skeleton has been the subject of many modifications, especially around the cyclohexenol and piperidine ring moieties. For example, the 7,8-double bond has been saturated, the allylic alcohol has been replaced by different groups and the N-substituent has been substituted for a variety of groups. In addition, simplified analogs of morphine have been synthesized. These manipulations have resulted in compounds with varing activities at opiate receptors. The least studied moiety of morphine is the aromatic ring with the phenolic hydroxyl group,[2] which has generally been assumed to be of importance for the interaction of the compounds with the receptors.[1a,3] However, several derivatives, mainly prodrugs, have been synthesized in which the C3-hydroxyl group has been converted into ethers or esters. The C3-deoxy analog of morphine, 3-deoxymorphine (**2**), has been reported in a study in which the role and importance of the C3-hydroxyl group for agonist activity at the opiate receptor from rat brain homogenate was investigated.[3,4] In comparison to morphine, compound **2** was found to have lower affinity for the opiate receptor although the antinociceptive activity was retained. Two derivatives of morphine having methyl or phenyl substituents bound to the C3-position of the morphinane skeleton via a C-C bond were recently described.[5,6] However, the pharmacological activities of these two new derivatives were not reported.



In the present communication we describe a short, efficient and high-yielding synthetic protocol leading to stereochemically well-defined analogues of morphine containing various substituents in the C3-position. The novel compounds were evaluated for binding to opiate κ-, μ- and δ-receptors labelled with [^{3}H]U-69593, [^{3}H]DAMGO and [^{3}H]DPDPE, respectively, in guinea-pig brain membrane preparations. The new derivatives

had lower affinity for the opiate κ-, μ- and δ-receptors than morphine itself. The C3-furyl derivative **7**, however, was shown to be the most μ-selective compound, with a selectivity approaching that of morphine.

Synthesis.

The stereochemically pure analogs of morphine were readily prepared from the monotrifluoromethanesulfonate **1** by efficient palladium-catalyzed transformations (Scheme 1).[7] The key-intermediate **1** was obtained from morphine by treatment with triethylamine and *N*-phenyltrifluoromethanesulfonimide in dichloromethane.[5] Palladium-catalyzed coupling of **1** with (1-ethoxy)vinyltributyltin gave the 1-ethoxyvinyl derivative, which was converted to methylketone **4** by acid hydrolysis.[8,9] The C3-aryl substituted compounds **5-10** were synthesized by palladium-catalyzed couplings of the corresponding arylboronic acid with **1** (see below).[10] The arylboronic acids were prepared using standard conditions.[11] Compounds **2** and **3** were synthesized according to reported procedures.[5] The overall yields of the novel compounds from morphine are given in Table 1.

A typical experimental procedure for the palladium-catalyzed arylboronic acid coupling of **1** is given below: Aqueous 2M Na_2CO_3 (0.72 mL, 1.44 mmol) was added to a stirred solution of **1**[7] (200 mg, 0.480 mmol), 3-furylboronic acid[11] (80 mg, 0.72 mmol), $[PPh_3]_4Pd(0)$ (14 mg, 12 μmol) and LiCl (41 mg, 0.96 mmol) in 1,2-dimethoxyethane (DME, 3 mL) and EtOH (0.75 mL). After reflux at 95 °C under nitrogen for 4h the mixture was partitioned between $CHCl_3$ and 10% aqueous $NaHCO_3$. The combined organic extracts was dried (Na_2SO_4), filtered and concentrated. Purification by repeated column chromatography [SiO_2, $CHCl_3$/MeOH (19:1), CH_2Cl_2/MeOH (9:1) and neutral Al_2O_3, $CHCl_3$/MeOH (19:1)] followed by recrystallization from CH_2Cl_2/ether/pentane gave 144 mg (90%) of pure **7**.

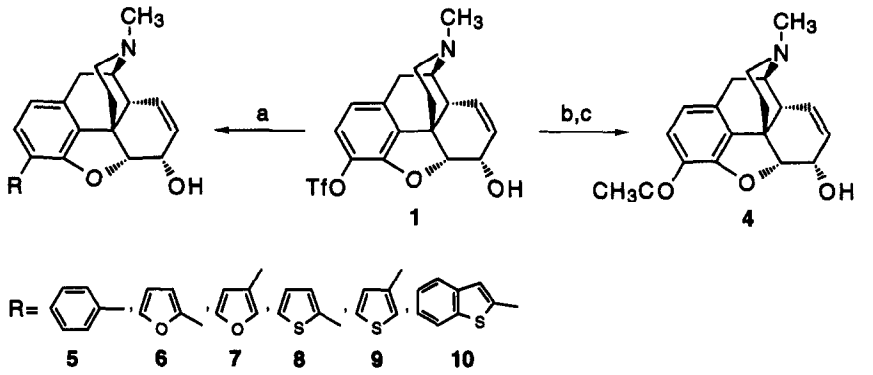
In vitro binding to opiate κ-, μ- and δ-receptors.

The abilities of the novel compounds to inhibit [^{3}H]U-69593, [^{3}H]DAMGO and [^{3}H]DPDPE binding to κ-, μ- and δ-receptors, respectively, in guinea-pig brain membranes *in vitro*, are given in Table II and inhibition curves of the novel compounds and morphine at μ-receptors labelled by [^{3}H]DAMGO are shown in Figure 1.

Materials. [^{3}H]U-69593 (5α,7α,8β)-(-)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxa-spiro[4.5]dec-8-yl]-(phenyl-^{3}H(n)benzenacetamide) (specific activity: 65 Ci/mmol) and [^{3}H]DAMGO ([^{3}H][D-Ala^2,N-Methyl Phe^2, glyol^5]-enkephalin) (specific activity: 59-60 Ci/mmol) were obtained from Amersham International plc, Amersham, U.K. [^{3}H]DPDPE ([^{3}H][D-Pen^2,D-Pen^5]-enkephalin) (specific activity: 33 Ci/mmol) was obtained from NEN (Du Pont Scandinavia AB, Biotechnology Systems Division, Stockholm, Sweden). Levallorphan tartrate was obtained from Roche and morphine hydrochloride from Apoteksbolaget, Stockholm, Sweden. The test compounds were dissolved in DMSO to a concentration of 10 mM and diluted to the appropriate concentrations with assay buffer.

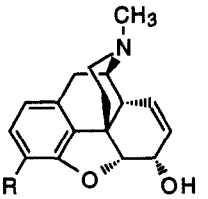
Preparation of membranes. Prefrozen cerebella (κ) or brains minus cerebella (μ and δ) from 300-400 g male Dunkin-Hartley guinea-pigs (HB Sahlins Försöksdjursfarm, Malmö, Sweden) were used (3-5 brains/preparation). Membranes were prepared essentially as described by Sharif *et al.*[12] Briefly, the tissue was homogenized in ice-cold 50 mM Tris buffer (1:20 (w/v), pH 7.4 containing 1 mM EDTA), using an Ultra-Turrax

Scheme 1



Reagents: a) $RB(OH)_2$, $Pd[PPh_3]_4$, LiCl, 2M Na_2CO_3, EtOH, DME; b) $CH_2=C(OC_2H_5)SnBu_3$, PPh_3, $PdCl_2(PPh_3)_2$, DMF, 2,6-di-*t*-butyl-4-methylphenol; c) THF, 1M HCl.

Table 1. Physical Data of some Novel Morphine Derivatives.[7]



Compd	R	reaction time (h)	yield (%)[a]	mp, (°C)	recrystn solvent[b]	$[\alpha]_D$[c,d]	Anal.
1	CF_3SO_2O	48	90	123-124	A	-78°	$C_{18}H_{18}F_3NO_4S$
2	H	18	82	228-229	B	-222°	$C_{17}H_{19}NO_2$
3	CH_3	6	68	181-183	B	-195°	$C_{18}H_{21}NO_2$
4	CH_3CO	3	50	176-178	C	-32°	$C_{19}H_{21}NO_3$
5	Phenyl	3	72	169-171	B	-49°	$C_{23}H_{23}NO_2$
6	2-Furyl	2	65	77-79	B	-40°	$C_{21}H_{21}NO_3$
7	3-Furyl	4	81	137-139	B	-49°	$C_{21}H_{21}NO_3$
8	2-Thienyl	2	89	121-123	B	-20°	$C_{21}H_{21}NO_2S$
9	3-Thienyl	4	53	139-141	B	-29°	$C_{21}H_{21}NO_2S$
10	2-Bensothienyl	4	79	177-178	B	+44°	$C_{25}H_{23}NO_2S$

[a] Overall yields of recrystallized compounds from natural morphine. [b] Recrystallization solvent: (A) Ether; (B) CH_2Cl_2/ether/pentane; (C) Ether/EtOAc. [c] (*c* 1.0, MeOH) [d] Room temperature.

Table 2. Potencies of Morphine and Ten Analogues at κ-, μ- and δ-Opioid Receptor Recognition Sites Labelled by [^{3}H]U-69593, [^{3}H]DAMGO and [^{3}H]DPDPE, respectively, in the Guinea-pig Cerebellum (κ) and Guinea-pig Brain minus Cerebellum (μ and δ).

		IC_{50} (nM)		
Compd	R	[^{3}H]U-69593(κ)	[^{3}H]DAMGO (μ)	[^{3}H]DPDPE (δ)
Morphine	HO	130	8.5	430
1	CF_3SO_2O	111000	6400	14% at 10 μM
2	H	11000	530	32% at 10 μM
3	CH_3	36000	4500	12% at 10 μM
4	CH_3CO	5100	640	7900
5	Phenyl	76000	43% at 10 μM	16% at 10 μM
6	2-Furyl	9500	2600	31% at 10 μM
7	3-Furyl	910	200	7400
8	2-Thienyl	25000	49% at 10 μM	17% at 10 μM
9	3-Thienyl	15000	3300	10% at 10 μM
10	2-Bensothienyl	126000	41% at 10 μM	14% at 10 μM

Values given are either the IC_{50} values (calculated from Hill slope replots of the mean (N=3-6) data over the % inhibition range of 10-90; in all cases the r^2 for the regression line >0.98) or the mean (N=3) inhibition at the highest concentration tested. In the κ-opioid receptor assay, the compounds were tested up to 300 μM [except **2**, **4** (100 μM); **7** (30 μM) and morphine (10 μM)] in 3-4 experiments. The 300 μM concentrations were dissolved in 3% DMSO. The ligands and concentrations used were. κ-receptors, 0.90±0.02 nM; μ-receptors, 0.86±0.02 nM [^{3}H]DAMGO; δ-receptors, 0.92±0.02 nM [^{3}H]DPDPE. If it is assumed that the interactions are competitive in nature, K_i values can be estimated from the IC_{50} values by division by 2.02 (κ)1.86 (μ) or 1.75 (δ).

(Ika-Werk). The homogenate was centrifuged in a Beckman J2-MC centrifuge at 48,000 *g* for 20 min. The pellet was resuspended in the same buffer and incubated for 30-45 min at 37 °C in order to degrade any endogenous ligands. The membranes were centrifuged at 48,000 *g* for 20 min, resuspended in 50 mM Tris buffer (pH 7.4 without EDTA) and recentrifuged. The final pellets were resuspended in 50 mM Tris buffer (200 mg wet weight/ml) and stored in aliquots at -85 °C until used for assay.

Receptor binding assays. The assay was undertaken using microtiter plates (U form). To each well was added test compounds (in 50 mM Tris buffer, pH 7.4), radioligand (in 50 mM Tris buffer, pH 7.4 + 0.8% bovine serum albumin [assay concentration 0.1%]) and membranes (5 mg wet weight/well, diluted in 50 mM Tris buffer, pH 7.4) in a final volume of 200 μl. The radioligand concentrations were chosen to be near the K_D values reported in the literature. The wells were incubated for 60 min at 22 °C, after which binding was rapidly terminated by vacuum filtration using a Brandel Cell Harvester (Brandel, Gaithersburg, USA). Separation of bound from free ligand was achieved by Whatman GF/B glass fibre filters that had been pre-soaked with 0.1% polyethyleneimine. After separation, the filters were washed with 50 mM Tris buffer, pH 7.4 + 0.1% bovine serum albumin for 10-12 sec at a constant flow rate, so that each well received a total of 10-15 ml wash buffer. The tritium contents of the filters were determined by liquid scintillation spectroscopy with quench correction

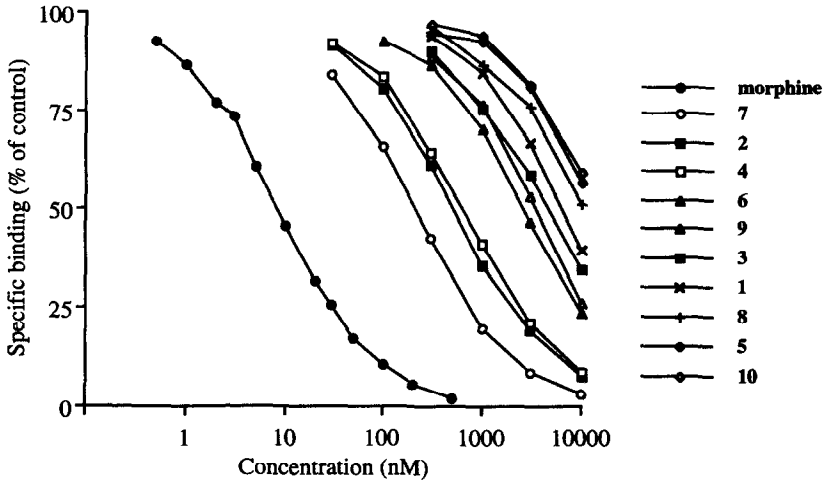


Figure 1. Effect of Morphine and Ten Analogues on the Specific Binding of [^{3}H]DAMGO to μ-opioid Receptor Recognition Sites in the Guinea-pig Brain Minus Cerebellum.
Data are means, N=3-4 (except for morphine, where N=3-6 [except at 500 nM, where N=2) of determinations in three membrane preparations. In no case did the S.E.M. exceed 5%. The ligand concentration was 0.86±0.02 nM, and the specific and non-specific d.p.m./assay were 1080±55 and 150±2, respectively.

using a Packard 1900 TR spectrometer. Non-specific binding ("NSB") was determined in wells containing 1 μM levallorphan.

Results. The affinity of morphine at κ-,[13] μ- and δ-opioid[14] receptors is essentially consistent with the literature. Both the absolute affinities and the selectivities for the μ-receptors varied considerably for the novel compounds. None of the compounds were as potent as morphine at either the κ-, μ- or the δ-opioid receptor. However, the μ-selectivity of the 3-furyl derivative **7** (κ/μ:4.6; δ/μ:37) approached that of morphine (κ/μ:15; δ/μ:51).

Conclusion.

The present data show that C3-substituted derivatives of 3-deoxymorphine can be synthesized by use of efficient palladium-catalyzed reactions. Despite the bulkiness of the C3-substituent, compound **7** shows significant affinity. However, introduction of different substituents in the C3-position of the morphinane skeleton inhibits the binding to opiate κ-, μ- and δ-receptors as compared to morphine. These results indicate that the C3-hydroxyl group of morphine is of importance for the molecular interaction of morphine with the opiate receptors.

Acknowledgment.

Financial support was obtained from the Swedish National Board for Industrial and Technical Development (NUTEK) and the Swedish Natural Science Research Council.

References and Notes.

1. a) Eddy, N.B.; May, E.L. *Science*, **1973**, *181*, 407-414 b) Hite, G. In "Principles of Medicinal Chemistry", W.D. Foye, Ed., Lea & Febiger, London, 1989, pp 239-275 c) Zimmerman, D.M.; Leander, J.D. *J. Med. Chem.* **1990**, *33*, 895-902 d) Evans, S.M.; Lenz, G.R.; Lessor, R.A. *Ann. Rep. Med. Chem.* **1990**, *25*, 11-20 e) Portoghese, P. *J. Med. Chem.* **1992**, *35*, 1927-1935.
2. Klein, P.; Nelson, W. *J. Med. Chem.* **1992**, *35*, 4589-4594.
3. Reden, J.; Reich, M.F.; Rice, K.C.; Jacobson, A.E.; Brossi, A.; Stready, R.A.; Klee, W.A. *J. Med. Chem.* **1979**, *22*, 256-259.
4. Brossi, A. *Heterocycles* **1978**, *11*, 521-545.
5. Hedberg, M.H.; Johansson, A.M.; Hacksell U. *J. Chem. Soc. Chem. Comm.* **1992**, 845-46.
6. Other derivatives have been reported but without experimental details.
7. The new compounds were analyzed for C, H and N, and the results were within 0.4% of theoretical values. ^{1}H and ^{13}C NMR-spectra were obtained at 270 MHz and 67.5 MHz, respectively, in $CDCl_3$. The assignment of chemical shifts and couplings constants were done in accordance with previously published data[15] and by using ^{1}H-^{1}H and ^{1}H-^{13}C correlation experiments. Selected data: **7**: ^{1}H NMR δ 1.93 (1 H, ddd, $J_{15eq,15ax}$=12.8 Hz, $J_{15eq,16ax}$=3.6 Hz, $J_{15eq,16eq}$=1.6 Hz, H-15eq), 2.13 (1 H, ddd, $J_{15ax,16ax}$=12.5 Hz, $J_{15ax,16eq}$=5.2 Hz, H-15ax), 2.36 (1 H, dd, $J_{10ax,9}$=6.1 Hz, $J_{10ax,10eq}$=19.1 Hz, H-10ax), 2.47 (1 H, ddd, H-16ax), 2.48 (3 H, s, N-CH_3), 2.65 (1 H, app dd, $J_{16ax,16eq}$=12.2 Hz, H-16eq), 2.71-2.78 (1 H, m, H-14), 3.10 (1 H, app d, H-10eq), 3.40 (1 H, dd, $J_{9,14}$=3.2 Hz, H-9), 4.18-4.24 (1 H, m, H-6), 4.97 (1 H, dd, $J_{5,6}$=6.6 Hz, $J_{5,7}$=1.1 Hz, H-5), 5.32 (1 H, ddd, $J_{7,8}$=10.0 Hz, $J_{8,14}$=2.1 Hz, $J_{8,6}$=3.2 Hz, H-8), 5.64-5.71 (1 H, m, H-7), 6.67 (1 H, app d, $J_{1,2}$=7.9 Hz, H-1), 6.77 (1 H, dd, $J_{4',5'}$=1.8 Hz, $J_{4',2'}$=0.7 Hz, H-4'), 7.20 (1 H, d, H-2), 7.46 (1 H, dd, $J_{5',2'}$=1.5 Hz, H-5'), 7.94 (1 H, app s, H-2'); ^{13}C NMR δ 21.0 (C-10), 35.7 (C-15), 40.7 (C-14), 42.3 (C-13), 43.0 (N-*C*H_3), 46.3 (C-16), 58.8 (C-9), 66.3 (C-6), 91.0 (C-5), 108.3 (C-4'), 112.0 (C-3), 119.6 (C-1), 121.3, 125.4 (C-2), 128.4 (C-8), 129.9, 133.4 (C-7), 140.3 (C-2'), 143.0 (C-5'), 155.2 (C-4); IR (CCl_4) 3560 cm^{-1} (ν OH). **4**: ^{1}H NMR δ 2.60 (3 H, s, -$COCH_3$); IR (film) 1670 cm^{-1} (ν C=O). **6**: ^{1}H NMR δ 6.49 (1 H, dd, $J_{4',3'}$=3.3 Hz, $J_{4',5'}$=1.7 Hz, H-4'), 6.77 (1 H, app d, H-3'), 7.44 (1 H, app d, H-5'); IR (film) 3550 cm^{-1} (ν OH). **8**: ^{1}H NMR δ 7.07 (1 H, dd, $J_{4',3'}$=3.6 Hz, $J_{4',5'}$=4.9 Hz, H-4'), 7.26 (1 H, dd, $J_{5',3'}$=1.0 Hz, H-5'), 7.51 (1 H, dd, H-3'); IR (film) 3550 cm^{-1} (ν OH). **9**: ^{1}H NMR δ 7.35 (1 H, dd, $J_{4',2'}$=3.0 Hz, $J_{4',5'}$=5.1 Hz, H-4'), 7.53 (1 H, dd, $J_{5',2'}$=1.2 Hz, H-5'), 7.73 (1 H, d, H-2'); IR (KBr) 3550 cm^{-1} (ν OH). **10**: ^{1}H NMR δ 7.25-7.33 (2 H, m, H-5', H-6'), 7.74-7.81 (3 H, m, H-3', H-4', H-7'); IR (CCl_4) 3560 cm^{-1} (ν OH).
8. a) Kwon, H.B.; McKee, B.M.; Stille, J.K. *J. Org. Chem.* **1990**, *55*, 3114-3118 b) Saá, J.M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1992**, *57*, 678-685.
9. Experimental details for preparation of **4**: (1-Ethoxyvinyl)tributyltin (446 mg, 1.20 mmol) and three crystals of 4-methyl-2,6-di-*tert*-butylphenol were added to a stirred solution of **1** (250 mg, 0.599 mmol), $(PPh_3)_2PdCl_2$ (50 mg, 0.072 mmol), PPh_3 (94 mg, 0.36 mmol) and LiCl (208 mg, 4.91 mmol) in dry DMF (5.5 mL). After stirring under nitrogen at 120 °C for 3h the volatiles were evaporated. THF (20 mL) and 1 M HCl (3 mL) were added and the mixture was stirred at rt for 10 min. The volatiles were evaporated and the residue was partitioned between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered and concentrated. Purification by column chromatography [SiO_2, $CHCl_3$/MeOH (19:1 and 9:1), and preparative TLC [SiO_2, $CHCl_3$/MeOH (4:1)] followed by recrystallization from ether-EtOAc gave 103 mg (55%) of pure **4**.
10. a) Huth, A.; Beetz, I.; and Schumann, I. *Tetrahedron*, **1989**, *45*, 6679-82 b) Fu, J.-m. and Snieckus, V. *Tetrahedron Lett.*, **1989**, *31*, 1665-68.
11. Phenylboronic acid was bought from Merck AG Darmstadt, Germany. All other boronic acids were prepared according to literature procedures: Thompson, W.J. and Gaudino, J. *J. Org. Chem.*, **1984**, *49*, 5237-43.
12. Sharif, N.A.; Durie, E.; Michel, A.D.; Whiting, R.L. *Brain Res.* **1990**, *510*, 108-114.
13. Lahti, R.A.; Mickelson, M.M.; McCall, J.M.; Von Voigtlander, P.F. *Eur. J. Pharmacol.* **1985**, *109*, 281-284.
14. Magnan, J.; Paterson, S.J.; Tavani, A.; Kosterlitz, H.W. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1982**, *319*, 197-205.
15. Neville, G.A.; Ekiel, I.; Smith, I.C.P. *Magn. Res. Chem.* **1987**, *25*, 31-35.

(*Received in Belgium* 20 *April* 1994; *accepted* 14 *September* 1994)