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Synthesis and NMR Characterization of a Novel Class of Thienomorphinans

Silvano Ronzoni,* Alberto Cerri, Giulio Dondio, Giovanni Fronza,[1] Paola Petrillo, Luca F. Raveglia, and Pier Andrea Gatti[2]

SmithKline Beecham S.p.A., Via Zambeletti, 20021 Baranzate, Milano, Italy

silvano_ronzoni@sbphrd.com

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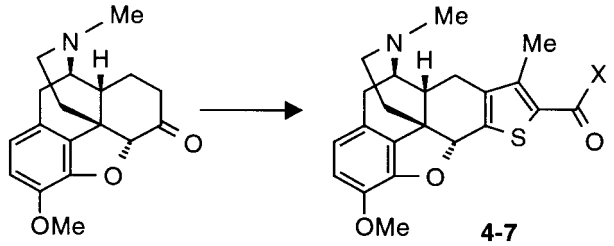
ABSTRACT



Synthesis of four novel thieno derivatives 4–7 featuring the codeine skeletal backbone is reported. Characterization by ^{1}H and ^{13}C NMR is also discussed, along with binding profile for opioid receptors.

The latex obtained by incision of the unripe seed capsule of the poppy plant (*Papaver somniferum*), known as opium, is the source of several alkaloids which are potent analgesic agents. Among these, morphine and codeine are the best known. These drugs exert their pharmacological action preferentially through the activation of the μ-opioid receptor and are associated with several unwanted side effects such as constipation and physical dependence. Chemical modifications of the skeleton of morphinan derivatives allow the biological activity to be shifted from the activation of the μ to that of the δ-opioid receptor, which is known to be involved in the modulation of pain but potentially not associated with the severe side effects exerted by the activation of μ-opioid receptors.[3] Recently, our group identified a novel class of potent and selective δ-opioid ligands, the pyrrolomorphinans of general formula **1** (see Figure 1), and reported their in vitro profile.[4]

As a part of our lead optimization process, we decided to study the role of the pyrrole ring of compounds of general

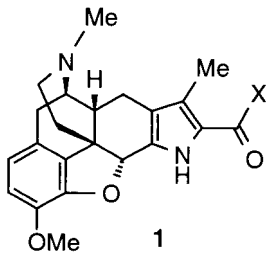


Figure 1. General formula of pyrrolomorphinans; X = OR, NR_1R_2.

formula **1**, and in the present paper, we describe the synthesis and chemical characterization of the novel thienomorphinan nuclei (**4**−**7**). The aim of the replacement of the pyrrole ring with the thiophene was 2-fold: (i) to verify the role of the pyrrole ring in the interaction with the δ-receptor (by changing its H-bond capability) and (ii) to increase the overall lipophilicity of this class of δ-ligands and, consequently, their ability to cross the blood−brain barrier (BBB).

Our strategy for the synthesis of the prototype thienomorphinan **4** started from 7-acetyldihydrocodeinone **2** (see Scheme 1), which was prepared according to the literature.[5]

(1) C.N.R. Centro di Studio delle Sostanze Organiche Naturali, Dipartimento di Chimica del Politecnico, Via Mancinelli 7, 20131 Milano, Italy.

(2) Present address: Bioindustria L.I.M. S.p.A., Via De Abbrosiis 2, Novi Ligure (Al), Italy.

(3) Rapaka, R. S.; Porreca, F. *Pharm. Res.* **1991**, *8*, 1.

(4) Ronzoni, S.; Artico, M.; Artino, A.; Gatti, P. A.; Graziani, D.; Parini, C.; Petrillo, P.; Dondio, G. *SAR Studies on a New Class of Potent and Selective δ Ligands, the Pyrrolomorphinans*; 29th International Narcotic Research Conference; Garmisch-Partenkirchen: Germany, 1998; Fr22.

(5) Quick, J.; Herlihy, P.; Razdan, R. K.; Howes, J. F. *J. Med. Chem.* **1982**, *25*, 983.

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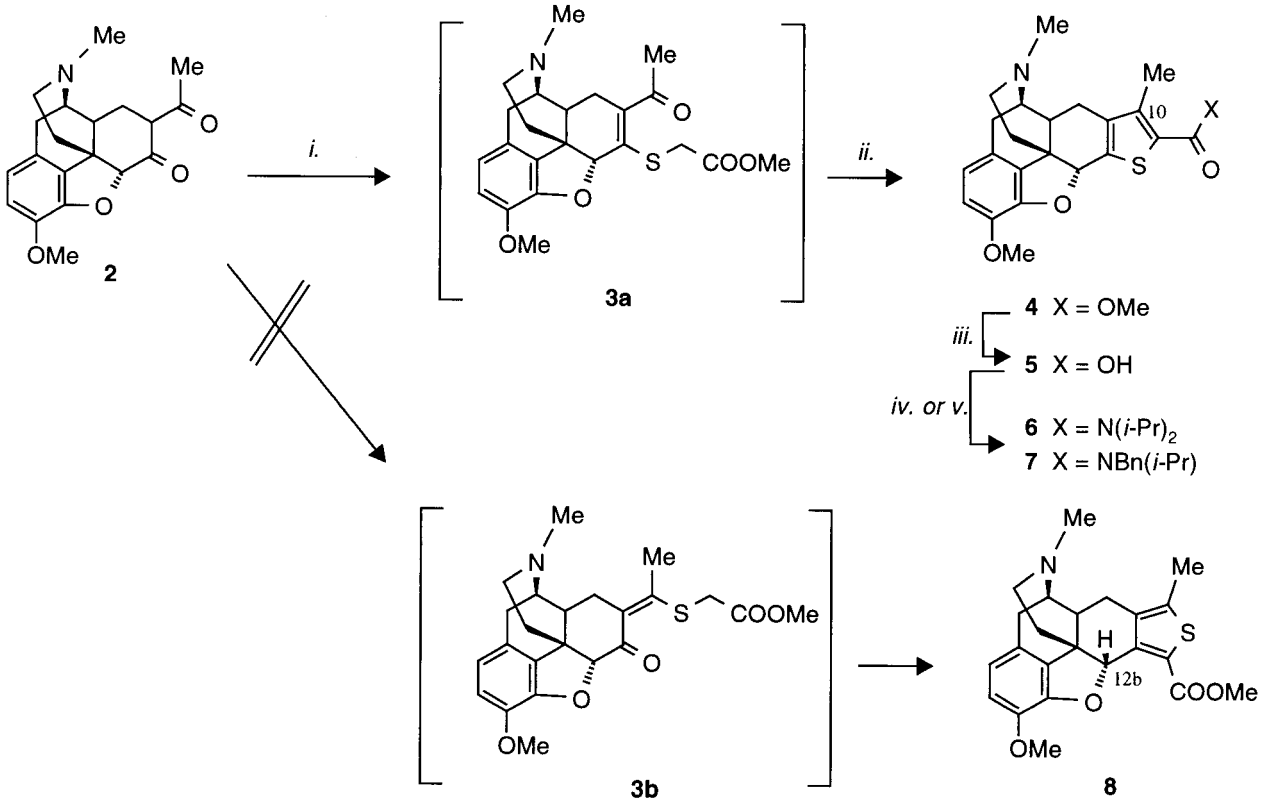
Scheme 1. Synthesis of Thienomorphinans[a]



[a] Reagents and conditions: (i) mercaptoacetic acid, HCl gas, MeOH, rt, 6 days; (ii) 2 N NaOMe/MeOH, rt, 24 h; (iii) 15% NaOH, reflux, 2 h; (iv) $(COCl)_2$, DCM, rt, 16 h, then $(i\text{-Pr})_2NH$, DCM, rt, 4 h, *v*. $(COCl)_2$, DCM, rt, 16 h, then Bn(*i*-Pr)NH, DCM, rt, 4 h.

Reaction of **2** with mercaptoacetic acid in MeOH/H^+ afforded the intermediate enol thioether **3a** which was subsequently cyclized by treatment with 2 N NaOMe in MeOH.[6] Despite the possible formation of two intermediate thioethers **3a** and **3b** during the S-nucleophilic attack on the two different carbonyl moieties of **2**, affording in principle compounds **4** and **8**, respectively, only product **4** was isolated from the reaction.

Simple proton and carbon NMR experiments[7] did not allow us to distinguish between the structures **4** and **8**; in fact, no useful ^1H-^1H nOe contacts were observed. Moreover, the ^{13}C chemical shifts of the thiophene ring in the two possible structures should be, in principle, very similar, as indicated by the ^{13}C data of the model compounds 2-carboxy-3-methyl- and 2-carboxy-5-methylthiophenes, thus precluding an unequivocal assignment.[8]

The structure of **4** was determined definitely by considering the long-range $^1H-^{13}C$ couplings. These couplings are known to have detectable values (4−8 Hz) when the coupled nuclei are separated by two or three bonds.[9] Thus the carbon adjacent to the carbomethoxy group should be a quartet (three-bond coupling with the methyl group CH_3-10 only) for the structure **4** and a doublet for the structure **8** (three-bond coupling with hydrogen H-12b only). In the aromatic region of the coupled ^{13}C spectrum of the final product, no doublets referring to quaternary carbons were detected, whereas three quartets were present at 163.6 (*C*$OOCH_3$, ^3J (COO, OCH_3) = 3.5 Hz), 139.3 (C-12a, ^2J (C-12a, H-12b), and ^3J (C-12a, H-9) = ∼4.0 Hz), 128.0 (C-11, ^3J (C-11, CH_3-10) = 4.0 Hz) ppm. A COLOC experiment, optimized for a long-range coupling constant of 6 Hz, showed a correlation of the carbon at 128.0 ppm with the hydrogens of CH_3-10 (2.45 ppm), clearly demonstrating that the compound under evaluation is the [2,3]-condensed thiophene **4**.

(6) Donoso, R.; Jordan de Urries, P.; Lissavetzky, J. *Synthesis* **1992**, 526.

(7) Spectroscopic data for compound **4**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, J = 8.1 Hz, 1H, H-2), 6.63 (d, J = 8.1 Hz, 1H, H-3), 5.51 (s, 1H, H-12b), 3.82 (s, 3H, COOCH_3), 3.81 (s, 3H, OCH_3), 3.26 (dd, J = 2.3 and 6.0 Hz, 1H, H-8), 3.08 (d, J = 18.5 Hz, 1H, H-14ax), 2.58 (ddd, J = 1.6, 4.5 and 12.0 Hz, 1H, H-6eq), 2.58−2.45 (m, 3H, H-14eq, H-8ax, H-9eq), 2.53 (s, 3H, NCH_3), 2.45 (s, 3H, CH_3-10), 2.34 (td, J = 4.0 and 12.0 Hz, 1H, H-6ax), 2.02 (td, J = 5.0 and 12.0 Hz, 1H, H-5ax), 1.92 (ddd, J = 1.6, 4.0 and 12.2 Hz, 1H, H-5eq), 1.83 (dd, J = 10.5 and 14.8 Hz, 1H, H-9ax); ^{13}C NMR (100 MHz, $CDCl_3$) δ (multeplicity is given only for the quaternary ^{13}C of interest) 163.6(q, ^3J (OCH_3) = 3.5 Hz, COO), 144.9 (C-13a), 144.1 (q, ^2J (CH_3) = ∼6.0 Hz, C-10), 143.5 (C-1), 139.8 (C-9a), 139.3 (q, ^2J (H-12b) and ^3J (H-9) = ∼4.0 Hz, C-12a), 128.9 (C-4a), 128.0 (q, ^3J (CH_3-10) = 4.0 Hz, C-11), 127.4 (C-4), 119.5 (C-3), 114.7 (C-2), 86.5 (C-12b), 59.9 (C-8), 57.1 (−OCH_3), 52.0 (COOCH_3), 47.0 (C-6), 43.7 (C-4b), 43.4 (−NCH_3), 40.5 (C-8a), 36.0 (C-5), 24.8 (C-9), 20.6 (C-14), 13.9 (CH_3-10).

(8) Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^1H FT NMR Spectra*; Aldrich Chemical: Milwaukee, WI; 1st ed.; 1992; Vol. III.

(9) Marshall, J. L. In *Carbon−Carbon and Carbon-Proton NMR Couplings: Application to Organic Stereochemistry and Conformational Analysis*; Marshand, A. P., Ed.; Verlag Chemie International: New York, NY,1983.

Once the thiophene ring had been constructed on the natural framework, the amides **6** and **7** were synthesized by converting the ester **4** into the acid **5** via a basic hydrolysis and then coupling the corresponding acyl chloride with the appropriate amine.

Thienomorphinans **6** and **7** were evaluated in ligand binding assay at μ-, δ-, and κ-opioid receptors in human cell lines.[10] Both compounds showed nanomolar affinity for the δ-opioid receptor [(**6**) $K_i = 1.4 \pm 1$ nM; (**7**) $K_i = 2.0 \pm 0.2$ nM], selectivity ratios of ~100-fold versus the μ-receptor and negligible affinity for the κ-receptor. These values of binding potency and selectivity are in line with those found for the corresponding pyrrolomorphinans,[4] thus demonstrating that the pyrrole ring has not a role per se in the interaction with the opioid receptors.

Lipophilicity of compound **6** was also estimated measuring its Δ log P parameter.[11] A value of 1.3, lower than that obtained for the corresponding pyrrolomorphinan (3.3), clearly indicates a marked increase in lipophilicity and, possibly, an increased capability to overcome the BBB.

In summary, synthesis and characterization of novel thieno derivatives of morphinan alkaloids have been described. This class of compounds, with low nanomolar δ-binding affinity and high lipophilicity, could be relevant in the search for novel and safe analgesic agents.

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(10) Binding experiments were performed using membranes from CHO cells expressing δ and μ human receptors and mouse brain for the κ-receptors: Dondio, G.; Ronzoni, S.; Eggleston, D. S.; Artico, M.; Petrillo, P.; Petrone, G.; Visentin, L.; Farina, C.; Vecchietti, V.; Clarke, G. D. *J. Med. Chem.* **1997**, *40*, 3192.

(11) Young, R. D.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R.; Griffiths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E.; Wilks, T. J. *J. Med. Chem.* **1996**, *39*, 982.