Short Communication

Synthesis, Crystal Structural and Pharmacological Study of *N*-Cyclopropylmehtyl-7α-[(*R*)-1-hydroxyl-1-methyl-3-(thien-2-yl)propyl]-6,14-endoethanotetrahydronooripavine

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Abstract

N-Cyclopropylmethyl-7α-[(*R*)-1-hydroxyl-1-methyl-3-(thien-2-yl)propyl])-6,14-endoethanotetrahydrooripavine (thienorphine, **I**), has been synthesized and evaluated for its in vivo analgesic activities. Thienorphine was structurally characterized by infrared (IR), NMR spectra, FAB-MS and X-ray diffraction. The crystal structure indicates that thienorphine maintained the main rigid structure of morphine and contains a C_6-C_{14} enthano bridge. The C_7 substituent is 1-hydroxyl-1-methyl-3-(thien-2-yl)propyl group adopting R-configuration. The cyclopropylmethyl group is located at the equatorial position as expected. The packing diagram of thienorphine showed the presence of the intramolecular and intermolecular O–H•••O hydrogen bond linking the molecules into an infinite quasi-one-dimensional chain structure. In vivo pharmacological study thienorphine exhibited excellent analgesic activity.

Key words: crystal structure, oripavine derivative, analgesic

Introduction

Opioid analogues still remain important drugs for the relief of severe pain and morphine is still the drug of choice in such situations. For many years, the search for new opioid derivatives that act on the CNS and have pain-relieving properties and devoid of undesired side effects, such addiction, has been the goal of a large number of scientists.[1,2] The abuse of cocaine and other stimulant drugs is becoming a significant social and public health concern in the world.[3] Consequently, a wide variety of modifications of the well-known alkaloids morphine, codeine and oripavine have been described.[4] The synthesis and pharmacological of 6,14-endoethanomorphinan derivatives have been extensively studied. The typical examples of the pharmacological active compounds reported in the literature such as buprenorphine (Temgesic),[5] etorphine(Immobilon)[6] and dihydroetorphine.[7] These kinds of compounds are characterized by a 6,14-endoethano bridge and a lipophilic substituted in position 7α of the C-ring.

We have engaged in the synthesis and biological activity study of oripavine derivative for many years, and have found *N*-Cyclopropylmethyl-7α-[1-(*R*)-1-hydroxy-1-methyl-3-(thien-2-yl)propyl]-6,14-endoethanotetrahydrooripavine (thienorphine, **I,** in chart 1), is a very potent oripavine derivative with mixed agonist and antagonist opiate receptor activities. Thienorphine showed very good analgesic activity in mouse using the acetic acid writhing model, mouse heat radiant tail-flick assay, and mouse heat plate test.

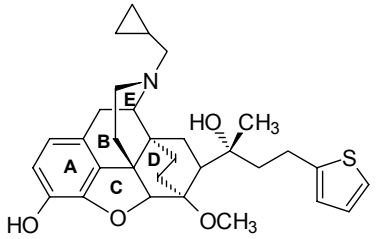


Chart 1. Thienorphine, **I**.

Results and discussion

Description of the crystal structure

The X-ray ORTEP structure of **I** with atomic labeling is shown in Figure 1. The crystal structure of **I** maintains the main rigid structure of morphine as described in the literature, such as morphine,[8] 3-methoxyetorphine,[9] and buprenorphine.[10] A rigid pentacyclic structure consisting of a benzene ring **A**, partially unsaturated six-membered ring **B** and cyclohexane ring **D**, a piperidine ring **E**, a dihydrofuran ring **C** and the C_6-C_{14} ethano bridge. Rings **A**, **B** and **D** are the phenanthrene ring system that has little conformational flexibility. The shape of the title compound likes a three-dimensional "T" with rings **A**, **B** and **C** forming a near perfect vertical plane and rings **E** and **D** forming a more distorted horizontal plane. The piperidine ring **E** is in the chair conformation and the **D** ring is boat with the atoms 6 and 14 fore and aft. The new ethano

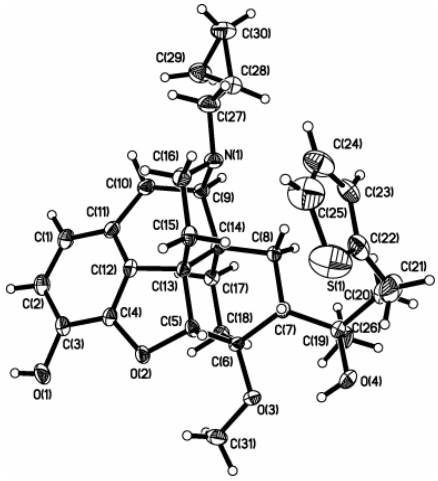


Figure 1. ORTEP view of the thienorphine with 50% thermal ellipsoid probability.

Table 1. Analgesic activity of **I** and buprenorphine.

Test model	Compound	ED_{50}(mg/kg)	
		S.C.	P.O.
Rat acetic acid writhing	buprenorphine	0.02	0.37
	I	0.08	0.64
Rat hot plate test	buprenorphine	1.01	12.52
	I	0.57	3.10
Rat tail-flick model	buprenorphine	8.75	–[a]
	I	1.75	2.61

[a] Maximal analgesic efficacy < 30%.

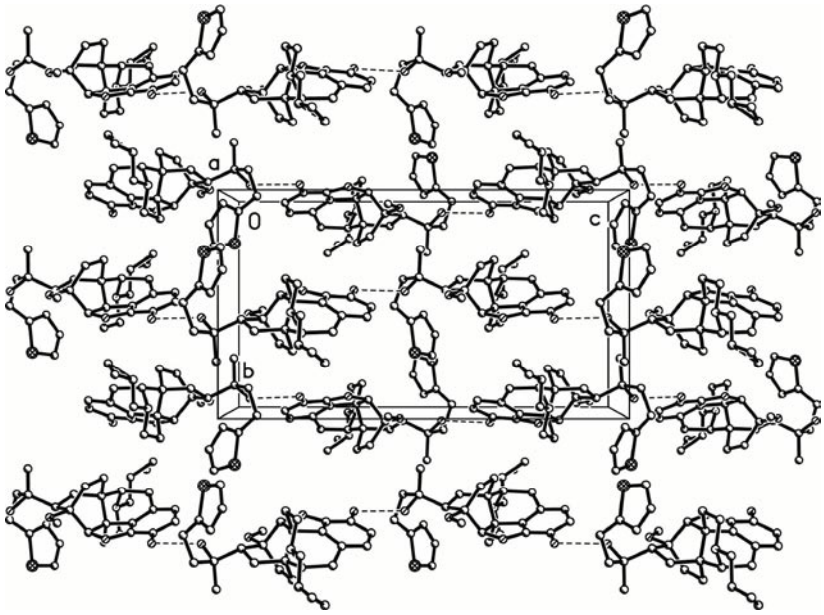
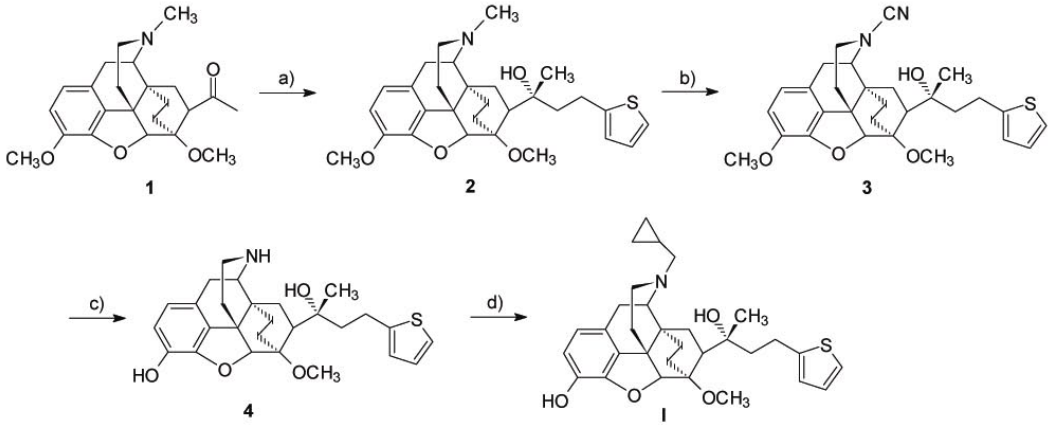


Figure 2. Packing diagram of the thienorphine showing hydrogen bonds.

bridge the original boat-shape ring **D** formed the bicycle[2,2,2]octane cage. The 1-hydroxyl-1-methyl-3-(thien-2-yl)propyl group on C_7 position adapted *R*-configuration. The Grignard reaction shows a remarkably high degree of stereoselectivity and strictly obeyed the Cram's rules(Scheme 1),[11] as a result the *R*-configuration was the almost sole product. Since the cyclopropylmethyl group on N is large than an electron pair or a protonated electron pair, it is predominantly equatorial (as shown), the stereostructrue would be important in determining relative agonist potencies as discussed in the literature.[12] The hydroxyl group O(4) is included by forming an intramolecular hydrogen bond with methyl ether oxygen O(3), and the distance between O(4) and O(3) is 2.586 Å with the H···O separation is 1.870 Å, falling into the normal range of the O···O separation for hydrogen bonding,[13] the bond angle is 145.15°.

As shown in Figure 2, an infinite quasi-one-dimensional chain structure was formed through O···H–O intermolecular hydrogen bonds in which the O atoms of the hydroxyl group links another hydroxyl group of benzene ring in the adjacent molecule. The O···O separation is 2.733 Å with the O···H separation is 1.914 Å, the bond angles are 176.67°.



Scheme 1. Synthesis of Thionorphine **I**. Reagents and conditions: a) 2-(thien-2-yl)ethylmagnesium bromide, anhydrous Et_2O. b) CNBr, CH_2Cl_2. c) KOH, diethylene glycol. d) Cyclopropylmethyl bromide, $NaHCO_3$, DMF.

Analgesic activity of thienorphine

The results in Table 1 clearly show that compound **I** and buprenorphine displayed definite analgesic activity. Buprenorphine is a potent opioid analgesic that is being developed as a treatment for the opiate abuse and dependence.[5,14] Compared with the analgesic activity of two compounds, **I** exhibited higher analgesic activity in rat hot plate test model and rat tail-flick model. It was 2 or 4 time more potent than buprenorphine.

Experimental

General

All the reagents for syntheses were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on JNM-ECA-400 400 MHz instrument in the solvent indicated below. Chemical shift values are reported in parts per million (ppm) relative to that for tetramethylsilane used as an internal reference standard. Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Elemental analysis was carried at the CarloErba-1106. IR spectra were measured on a FT-IR 170SX (Nicolet) spectrometer with KBr pellets.

Synthesis

Thienorphine **I** was prepared by a modified method as described in the literature.[15] According to Scheme 1, 7α-acetyl-6,14-endoethanotetrahydrothebaine **1** was coupled with Grignard reagent, 2-(thiophen-2-yl)ethylmagnesium bromide, to give 7α-[(*R*)-1-Hydroxy-1-methyl-3-(thien-2-yl)propyl]-6,14-endoethanoetrahydrothebaine **2**. This Grignard reaction shows a remarkably high degree of stereoselectivity. The *R* isomer was the almost sole product, whereas the *S* isomer was not afforded. A mixture of the intermediate **2** and cyanogens bromide in dried methylene chloride was refluxed to obtain *N*-Cyano-7α-[(*R*)-1-hydroxy-1-methyl-3-(thien-2-yl)propyl]-6,14-endoethanotetrahydronorthebaine **3**. 7α-[1-(*R*)-1-Hydroxy-1-methyl-3-(thien-2-yl)propyl]-6,14-endoethanotetrahydronororipavine **4** was obtained by treating **3** with KOH in diethylene glycol at 205–210 °C.

A mixture of **4** (7.0 g, 0.015 mol), cyclopropylmethyl bromide (4.1 g, 0.030 mol) and dried sodium bicarbonate (4.0 g, 0.048 mol) in *N*,*N*-dimethylformamide (200 mL) was vigorously stirred at 70–80 °C under nitrogen gas for 16 h. The mixture was filtered. The filtrate was evaporated to dryness. The residue was dissolved with CH_2Cl_2, dried (Na_2SO_4) and evaporated to obtain a crude product. The crude product was purified by chromatography on silica gel column, eluting with a CH_2Cl_2/MeOH mixture (20:1) to give white solid, then recrystallized from methanol to give colorless crystal **1** (3.8 g). Yield: 48.4%, mp 170–172 °C. IR (KBr): 3406, 3224, 2989, 2926, 1634, and 1609. ^{1}H NMR ($CDCl_3$) δ 8.98 (1H, s, Ar-OH), 7.29 (1H, d, *J* 5.0Hz, ArH), 6.93 (1H, m, ArH), 6.85 (1H, m, ArH), 6.73 (1H, d, *J* 8Hz, ArH), 6.55 (1H, d, *J* 8 Hz, ArH), 4.61 (1H, s, OH), 4.39 (1H, s,), 3.41 (3H, s, -OCH_3), 2.85–2.98 (4H, m), 2.58–2.76 (2H, m), 2.10–2.27 (4H, m), 1.80–2.05 (4H, m), 1.66–1.76 (2H, m, CH_2), 1.45–1.55 (2H, m, CH_2), 1.30 (3H, s, -CH_3), 1.18–1.24 (1H, m, CH), 1.07 (1H, m, CH), 0.75 (1H, m, Cprop-CH), 0.58 (1H, m), 0.44 (2H, m, Cprop-CH_2), 0.08 (2H, m, Cprop-CH_2). ^{13}C NMR ($CDCl_3$) δ 3.48, 3.97, 9.39, 17.7, 23.2, 23.9, 29.8, 31.6, 35.6, 35.9, 43.5, 43.6, 45.7, 47.2, 52.8, 58.3, 59.8, 75.8 (C16, C19), 80.5, 97.4, 116.5, 117.4, 119.5, 122.7, 123.9, 126.7, 128.1, 132.2, 145.5, 146.0. ESI-MS: 522.1(M+1). Anal. Calcd For $C_{31}H_{39}NO_4S$: C 71.37, H 7.53, N 2.68. Found: C 71.17, H 7.63, N 2.46.

Table 2. Crystallographic data and structure refinement summary for thienorphine.

Empirical formula	$C_{31}H_{39}NO_4S$
Molecular weight	521.69
Measured temperature	293(2) K
Crystal size (mm^3)	$0.32 \times 0.25 \times 0.20$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 11.304(4) Å
	b = 11.481(4) Å
	c = 20.534(5) Å
Volume V ($Å^3$)	2664.8(15)
Z	4
D_{calcd} (g cm^{-3})	1.300
μ (mm^{-1})	0.159
F (000)	1120
θ range(°)	1.98 – 26.46°
Completeness to θ	99.5 %
h/k/l	–10/14, –14/11, –20/25
Reflection collected/unique	15140 / 5477
Parameters refined	339
R_{int}	0.0368
Final R indices [$I \geq 2\sigma(I)$]	$R1$= 0.0467,
	$wR2$ = 0.1045
Goodness of fit	1.021
Residual electron densities (e $Å^{-3}$)	0.305 and –0.265

X-Ray diffraction analysis

Single-crystal X-ray diffraction measurement was carried out on a Bruker Smart 1000 CCD diffractometer. The determination of unit cell parameters and data collections was performed with Mo Kα radiation (λ = 0.71073 Å) and unit cell dimensions were obtained with least-squares refinements. The structure was solved by direct methods with SHELXL-97 program[16] and all data were corrected by using semi-empirical absorption corrections (SADABS) method. All the other non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was carried out by full matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were added theoretically, and riding on the concerned atoms and refined with fixed thermal factors. Further details of the structure analyses are given in Table 2. Positional parameters and atomic coordinates are given in Table 3, whereas bond distances and angles are listed in Table 4, respectively. Further details of the crystal structure investigation are available from the Cambridge Crystallographic Center with quotation number CCDC 212447.[17]

Table 3. Atomic coordination and equivalent isotropic displacement parameters for thienorphine.

	x	y	z	U(eq)
S(1)	3333(1)	7240(1)	4767(1)	120(1)
N(1)	2308(2)	4666(2)	6872(1)	36(1)
O(1)	8083(2)	5641(2)	8244(1)	51(1)
O(2)	6899(1)	5603(2)	6998(1)	35(1)
O(3)	7317(1)	4582(2)	5631(1)	41(1)
O(4)	6244(2)	4414(2)	4523(1)	55(1)
C(1)	5117(2)	4453(3)	8622(1)	45(1)
C(2)	6256(3)	4885(2)	8706(1)	45(1)
C(3)	6930(2)	5317(2)	8193(1)	36(1)
C(4)	6361(2)	5363(2)	7590(1)	31(1)
C(5)	6007(2)	5398(2)	6485(1)	30(1)
C(6)	6281(2)	4364(2)	6035(1)	30(1)
C(7)	5192(2)	4343(2)	5561(1)	28(1)
C(8)	4095(2)	3861(2)	5925(1)	29(1)
C(9)	3182(2)	3789(2)	7089(1)	31(1)
C(10)	3461(2)	3835(2)	7831(1)	38(1)
C(11)	4557(2)	4518(2)	8017(1)	36(1)
C(12)	5190(2)	5071(2)	7534(1)	30(1)
C(13)	4819(2)	5140(2)	6829(1)	27(1)
C(14)	4313(2)	3923(2)	6662(1)	27(1)
C(15)	3892(2)	6088(2)	6688(1)	34(1)
C(16)	2722(2)	5854(2)	7006(1)	40(1)
C(17)	5245(2)	2978(2)	6804(1)	31(1)
C(18)	6412(2)	3261(2)	6440(1)	33(1)
C(19)	5355(2)	3765(2)	4881(1)	37(1)
C(20)	4235(3)	3850(3)	4464(1)	49(1)
C(21)	3866(4)	5069(4)	4232(2)	79(1)
C(22)	3098(3)	5784(3)	4662(1)	55(1)
C(23)	2029(2)	5489(2)	4993(1)	47(1)
C(24)	1536(3)	6438(4)	5300(2)	79(1)
C(25)	2103(4)	7404(4)	5220(3)	101(2)
C(26)	5755(3)	2498(3)	4916(1)	53(1)
C(27)	1110(2)	4534(3)	7137(2)	51(1)
C(28)	641(2)	3330(3)	7113(2)	52(1)
C(29)	613(3)	2583(3)	7721(2)	58(1)
C(30)	–522(3)	3062(3)	7455(2)	64(1)
C(31)	8431(2)	4718(3)	5933(1)	52(1)

Pharmacology

Experiments were performed according to three methods: rat acetic acid writhing model, rat hot plate test model and rat tail-flick model as described in the literature,[17] which are the sensitive and predictive animal models for analgesic drugs as shown by the good correlation between values obtained in rats and analge-

Table 4. Bond lengths(Å), angles(°) of the thienorphine.

Bond lengths:					
S(1)-C(25)	1.684(5)	O(3)-C(6)	1.456(3)	C(4)-C(12)	1.370(3)
S(1)-C(22)	1.706(3)	C(1)-C(2)	1.390(4)	C(27)-C(28)	1.481(4)
N(1)-C(27)	1.467(3)	C(2)-C(3)	1.392(4)	C(11)-C(12)	1.377(3)
N(1)-C(9)	1.479(3)	C(6)-C(18)	1.522(3)	O(4)-C(19)	1.452(3)
O(1)-C(3)	1.359(3)	C(6)-C(7)	1.569(3)	C(1)-C(11)	1.397(3)
O(2)-C(4)	1.386(3)	N(1)-C(16)	1.468(3)	C(3)-C(4)	1.396(3)
O(2)-C(5)	1.477(3)	C(8)-C(14)	1.534(3)		
O(3)-C(31)	1.413(3)	C(9)-C(10)	1.556(3)		
Bond angles:					
C(25)-S(1)-C(22)	92.9(2)	N(1)-C(9)-C(14)	108.10(18)	C(17)-C(14)-C(9)	112.61(18)
C(27)-N(1)-C(16)	108.8(2)	C(12)-C(13)-C(15)	113.99(18)	C(13)-C(14)-C(9)	105.48(18)
C(27)-N(1)-C(9)	115.8(2)	C(15)-C(13)-C(5)	111.74(19)	C(16)-C(15)-C(13)	113.1(2)
C(16)-N(1)-C(9)	111.29(19)	C(12)-C(13)-C(14)	105.55(18)	N(1)-C(16)-C(15)	111.5(2)
C(4)-O(2)-C(5)	107.15(17)	C(15)-C(13)-C(14)	110.21(18)	C(14)-C(17)-C(18)	110.08(18)
C(12)-C(4)-O(2)	113.50(19)	C(20)-C(19)-C(7)	112.1(2)	C(6)-C(18)-C(17)	110.77(19)
O(2)-C(5)-C(6)	114.51(18)	C(5)-C(13)-C(14)	113.09(18)	O(4)-C(19)-C(26)	108.0(2)
O(2)-C(5)-C(13)	107.26(16)	C(8)-C(14)-C(17)	105.35(19)	O(4)-C(19)-C(20)	104.8(2)
C(6)-C(5)-C(13)	107.56(18)	C(8)-C(14)-C(13)	108.65(18)	C(26)-C(19)-C(20)	109.4(2)
C(8)-C(7)-C(19)	112.02(19)	C(17)-C(14)-C(13)	109.92(18)	O(4)-C(19)-C(7)	108.5(2)
C(19)-C(7)-C(6)	118.03(19)	C(8)-C(14)-C(9)	114.80(19)	C(26)-C(19)-C(7)	113.6(2)

sic doses in humans. As regards the experiments carried out in vivo, test compounds were administered as S.C. and P.O. methods. The experiments were performed on Wistar rats (180–200 g) of both sexes, kept at ambient temperature on a 12 h light/dark schedule, with free access to food and water before the experiments. The experimental groups consisted of 5–8 animals each. Statistical analysis used Kruskal–Wallis/Mann–Whitney. Differences in pre-and post-drug latencies were analyzed by the Wilcoxon test.

Acknowledgements

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Povzetek

Sintetizirali smo “thienorphine” (**I**) ter *in vivo* testirali njegove analgetske lastnosti. Strukturo **I** smo določili na osnovi IR in NMR analiz in rentgenske difrakcijske analize.