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Aminothiazolomorphinans with Mixed Kappa and Mu Opioid Activity[a]

Tangzhi Zhang[†], **Zhaohua Yan**[†], **Anna Sromek**[†], **Brian I. Knapp**[‡], **Thomas Scrimale**[‡], **Jean M. Bidlack**[‡], and **John L. Neumeyer**[*,†]

[†] Alcohol & Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, Massachusetts 02478

[‡] Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York 14642

Abstract

A series of N-substituted and N′-substituted aminothiazole-derived morphinans (**5**) were synthesized for expanding the structure-activity relationships of aminothiazolo-morphinans. Although their affinities were somewhat lower than their prototype aminothiazolo-N-cyclopropylmorphinan (**3**), 3-aminothiazole derivatives of cyclorphan (**1**) containing a primary amino group displayed high affinity and selectivity at the κ and μ opioid receptors. [^{35}S]GTPγS binding assays showed that the aminothiazolomorphinans were κ agonists with mixed agonist and antagonist activity at the μ opioid receptor. These novel N′-monosubstituted aminothiazole-derived morphinans may be valuable for the development of drug abuse medications.

Introduction

The opioid system modulates several key physiological and behavioral processes, such as: pain perception, the stress response, the immune response, and neuroendocrine function.[1] With the discovery of the three different opioid receptors (κOR, μOR, and δOR), different functions and effects of the three receptor subtypes have been elucidated. Notably, it was found that the κ opioid receptor plays a role in the development of drug addiction, specifically by altering the dopamine reward pathway. Thus, the κ receptor has been implicated as a primary target for the development of pharmacotherapies for the treatment of cocaine dependence.[2,3] Recent behavioral studies suggested that κ/μ opioids may be useful for the treatment of cocaine abuse and dependence.[4] We reported that both acute and chronic treatment with mixed κ/μ opioids cyclorphan (**1**)[5] and butorphan,[5, 6] reduced cocaine self-administration dose-dependently and produced fewer side-effects than κ-selective agonists.[7] However, the opioid derivatives are not metabolically stable: the free phenolic hydroxyl group in cyclorphan (**1**) and butorphan is also a potential site for metabolism, conjugation, and excretion, resulting in low oral bioavailability and short duration of action.[1,8, 9] In an attempt to further extend the duration of action and to manipulate relative affinity and efficacy at κOR, modification of the phenolic hydroxyl group of cyclorphan has been performed, by incorporating 3-amino (**2**) [10], 3-aminothiazole (**3**, ATPM) [10], 2-aminooxazole (**4**) [11] isosteres (Figure 1).

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To whom correspondence should be addressed. Phone: 617-855-3388. Fax: 617-855-2519. Neumeyer@mclean.harvard.edu.
[†]Harvard Medical School
[‡]University of Rochester

Among this series, one compound, **3** (Figure 1), has been identified to possess high affinity at κOR (K_i = 0.049 nM), and mixed κ agonist and μ-agonist/antagonist.[10c] (Table 1). Previous studies have shown that **3** inhibited morphine-induced antinociceptive tolerance, with less potential to develop tolerance and reduce heroin self-administration with lower sedative effect.[12] However, recent *in vivo* studies of **3** in mice in the 55°C tail-flick test showed that this compound does not appear to have a longer duration of action than the phenolic compound **1**.[13] Aiming to extend duration of action and to improve oral bioavailability, a structure-activity relationship (SAR) study has been conducted to investigate the effect of modifications of N-substituent (R^3) and N′-3-amino-substituted (R^1, R^2) of the morphinan **5** (Figure 1).

Herein we report the synthesis and pharmacological evaluation of a series of N-substituted (R^3) and N′-3-amino-substituted (R^1, R^2) analogs of morphinan. The highly potent (−)-3-hydroxy-N-(*E*)-iodoallylmorphinan[14] suggested the replacement of the N-cyclopropylmethyl group in cyclorphan with a fluoropropyl group to make compounds **7c** and its analogs **9c, 11, 13c,** and **19c**, and introduced a trifluoroethyl substituent to the amino group of the aminothiazole component in **3** to make compound **15** (Scheme 1 and Scheme 2).

Chemistry

The synthesis of all target compounds was initiated from commercially available levorphanol tartrate, which, after conversion to its free base, could be demethylated to norlevorphanol (**6**). Next, **6** was alkylated with either cyclopropylmethyl bromide, cyclobutylmethyl bromide, fluoropropyl bromide, or (−)-(s) tetrahydrofurfuryl (R)-camphor-10-sulfonate to yield **7a–d,** respectively. Subsequent triflation of morphinans **7a–d** afforded triflates **8a–d**, which were subjected to palladium-catalyzed amination to afford amines **9a–d** in moderate yields. The aminothiazoles **3**, **10–12** were then synthesized in 55–61% yield according to literature procedure (Scheme 1).[6, 10]

For the synthesis of N′-methyl substituted aminothiazolomorphinans **13a–c**, aminothiazolomorphinans **3, 10** and **11** were formylated with freshly prepared formyl acetate (prepared by heating a mixture of HCOOH and Ac_2O), followed by reduction, yielding the novel N′-methyl-3-aminothiazolomorphinans **13a–c** in 34–45% yields (Scheme 2).[15] Treatment of **13a** and **13c** with paraformaldehyde and $NaBH_4$ yielded dimethyl substituted aminothiazolomorphinans **17a** and **17c** in 83–89% yields.[16] N′-Trifluoroethyl derivative **15** was prepared in 45% yield by treating **3** with trifluoroacetic anhydride in the presence of Et_3N, followed by reduction.[17] N′-ethyl substituted aminothiazolomorphinans **19a–c** were prepared analogously [17] in which compound **3**, **10**, and **11** were first acylated and then reduced. Treatment of **13a** and **19a** with acetic anhydride produced N′-disubstituted derivatives **14** and **20**. Compounds **3** and **11** were also condensed with propionaldehyde, followed by reduction of the resulting imines to N′-propyl substituted aminothiazolomorphinans **16a** and **16c** in 47–55% yields[18] (Scheme 2).

Using literature procedures,[19] **3** was reductively aminated to afford **21** and **22** in 65–68% yields. Methoxybenzylated derivative **21** was demethylated with BBr_3 to give **23** in 74% yield.[20] Furthermore, **3** was treated with EtSCN to yield thiourea **24** in 45% yield (Scheme 3).[21]

For preparation of aryl substituted derivatives **26** and **27**, **3** was converted to 3-bromothiazolo-N-cyclopropylmethylmorphinan **25** through the Sandmeyer reaction.[22] Compound **25** was treated with aniline and 2-aminopyridine, respectively, to yield **26** and **27** in 70–72% yields. Treatment of **25** with piperazine produced **28** in 63% yield (Scheme 4). [23]

Results and Discussion

Target compounds were screened for their affinity and selectivity for μ, κ, and δ opioid receptors with Chinese hamster ovary (CHO) cell membranes stably expressing the human opioid receptors. The data were summarized in Table 1. For comparison purposes, opioid binding affinity data for cyclorphan **1**, **2**, **3**, **4** and N-methyl-3-aminothiazolomorphinan (**29**) were also included.

Previous reports from our laboratories indicated that changing N-substituted group (R_3) in the aminothiazolomorphinan drastically altered potency and efficacy. Compared to the N-methyl derivative **29**, the N-cyclopropyl compound **3** displayed a much higher (130-fold) affinity at κ the receptor. From the data shown in Table 1, the N-fluoropropyl derivative **11** had high affinity at κ (0.30 nM) and good selectivity for κ over μ (9-fold) and δ (180-fold) receptor. N-Tetrahydrofurylmethylmorphinan **12** also showed high affinity at κ (0.83 nM) and moderate affinity at μ (2.4 nM). Introducing a small alkyl group at N′, **13a** had similar affinity with **3** at the κ receptor, with K_i value of 0.066 nM. Compound **13a** also displayed high selectivity for κ over μ (45-fold) and δ (380-fold) receptors. When the size of alkyl group at N′ increased, we observed a smooth decrease in affinity at κ and μ receptors in **19a**, **15**, **16a**. However, they still displayed high affinity at κ (K_i = 0.15–1.6 nM). N′-Acetyl aminothiazolomorphinan **18a** showed low affinity at κ (13 nM) and μ (57 nM), perhaps due to the lowered basicity of nitrogen in this analogue. When the N′-substituent on amine was either benzyl (**22**), 3-OH-benzyl (**23**), or 3-MeO-benzyl (**21**), binding affinities were low [K_i = 2.1–4.8 nM (κ) and K_i = 9.1–10 nM (μ)]. Analogues **26** and **27**, which contained N′-aryl and (hetero)aryl groups, were prepared. Compared to the alkyl substituted aminothiazole analogues (**13a**, **15**, **19a**), an unexpected decrease of affinity at κ and μ receptors was observed in **26** and **27**. The N′-piperazine substituted aminothiazolomorphinan displayed very low affinity at κ (110 nM) and at μ (2700 nM). To explore the possibility that incorporation of an additional polar group into the N′-substitution would further enhance affinity, we prepared a thiourea analogue as a probe. However, the N′-ethylthiourea analogue displayed low affinity at κ (18 nM) and at μ (130 nM).

It was found that N′-disubstituted aminothiazolo-N-cyclopropylmorphinans generally had lower affinity when compared to N′-monosubstituted- aminothiazolo-N-cyclopropylmorphinans. N′-Dimethyl substituted derivative (**17a**) was the most potent compound in the series of N′-disubstituted compounds synthesized, with an affinity of 0.45 nM at the κ receptor and 10 nM at the μ receptor. K_i values for N′-methyl derivative (**13b**) and N′-ethyl derivative (**19b**) were 2.4 and 3.7 nM for κ, respectively. N-fluoropropyl N′-methyl (**13c**) and N′-ethyl (**19c**) morphinan analogues were very potent, with K_i values being <1 nM for binding to the κOR. N-fluoropropyl N′-propyl (**16c**) and N′-dimethyl (**17c**) morphinan analogues showed low affinity at the κ and μ receptors. From a SAR perspective, the binding affinities of substituted aminothiazolomorphinan analogues at all three receptors were generally lower than the binding affinities of the aminothiazole precursors (**3**, **10**, **11**). However, most of the N′-monosubstituted analogues showed high affinities at κ (K_i = 0.06–0.94 nM).

To characterize the relative efficacy of these ligands, **1**, **3**, and **10**, were selected for the [^{35}S]GTPγS assay. The stimulation and inhibition of [^{35}S]GTPγS binding mediated by κ and μ opioid receptors are shown in Table 2 and Table 3, respectively.

These ligands produced maximal stimulation of [^{35}S]GTPγS binding (E_{max}) at κ comparable to that of ligand **3**. Ligands **13c**, **15**, **19a**, and **19c** produced a higher E_{max} than that of selective agonist U50,488. None of these compounds inhibited U50,488-stimulated [^{35}S]GTPγS at κ, demonstrating that all of these ligands were full κ agonists.

From the data shown in Table 3, ligands **11**, **13a**, and **17a** displayed partial agonist activity at μ receptor. Ligands **12**, **13c**, **19a** and **19c** showed full agonist activity at the μ receptor; they did not inhibit DAMGO-stimulated [^{35}S]GTPγS binding.

Conclusion

We have extended the structure-activity relationships of aminothiazolomorphinans by introducing different groups to N- and N′-positions. A series of aminothiazolomorphinans and their N′-mono- and di-substituted derivatives were synthesized, and their pharmacological properties at opioid receptors were evaluated. It was found that substituents at the aminothiazole nitrogen tended to reduce the affinity of the compounds, with the exception of the methyl group (**13a**), which retained high affinity at the κ receptor (0.066 nM) as well as good selectivity for κ over μ (45-fold) and δ (380-fold) receptor. N′-disubstituted aminothiazolo-N-cyclopropylmorphinan analogues **17a**, **14**, **20**, and **17c** had lower affinity at all three opioid receptors. However, N′-dimethyl aminothiazolo-N-cyclopropylmorphinan **17a** was also a potent and selective compound, with an affinity of 0.45 nM at the κ receptor and 10 nM at the μ receptor. The same pattern was observed with the replacement of the cyclopropylmethyl group in **1** with the fluoropropyl group. **13a**, **19a**, and **17a** may prove to be useful for the potential development as medications for cocaine or opioid abuse. The [^{35}S]GTPγS binding assay revealed that all new compounds were full agonists at the κ receptors, ligands **11**, **13a**, and **17a** were partial agonists at the μ receptors, and ligands **12**, **13c**, **19a**, and **19c** were full agonists at the μ receptors. Preliminary evaluation of **3** in non-human primates reduced self-administration and attenuated food intake, probably due to its kappa agonist properties.[24]

Experimental Section

General Synthetic Methods

^{1}H (and ^{13}C NMR) spectra were recorded at 300 MHz (75 MHz) on a Varian Mercury 300 spectrometer. Chemical shifts are given as δ value (ppm) downfield from tetramethylsilane as an internal reference. Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. Elemental analyses, performed by Atlantic Microlabs, Atlanta, GA, were within (0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2 micrometer Kieselgel 60F-254 silica gel plastic sheets (EM Science, Newark, NJ). Flash chromatography was used for the routine purification of reaction products. Eluent systems are described for the individual compounds.

General Procedure[6] for the Preparation of 3-Hydroxy-N-alkyl-morphinans 7a–d

The mixture of norlevorphanol (5 mmol), K_2CO_3 or $NaHCO_3$ (7.5 mmol), and either bromomethyl cyclopropane, bromomethyl cyclobutane, 1-bromo-3-fluoropropane, or (*S*)-tetrahydrofurfuryl (1*R*)-camphor-10-sulfonate (7.5 mmol) in 20 mL anhydrous DMF were stirred at 90–95 °C for overnight. After the reaction was judged complete by TLC, the reaction mixture was cooled, poured into water, extracted with $CHCl_3$. The organic phase washed by brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give crude product, purified by flash silica gel column (DCM: MeOH = 20:1 – 5:1) to give the corresponding morphinans **7a–d**. The analytical data for **7a–b**, **7d** was in agreement with literature values. [6]

3-Hydroxy-N-fluoropropylmorphinan (7c)

White crystals (73%); M.p. 148–150 °C. ^{1}H NMR (300 MHz, CDCl3) δ 7.04-6.88 (m, 1H), 6.71 (s, 1H), 6.66-6.55 (m, 1H), 4.64-4.53 (m, 1H), 4.49-4.37 (m, 1H), 2.97-2.83 (m, 2H),

2.71-2.48 (m, 5H), 2.33-2.24 (m, 1H), 2.15-2.01 (m, 1H), 1.97-1.58 (m, 5H), 1.54-1.07 (m, 7H). ^{19}F NMR (282 MHz, CDCl3) δ 29.21 (m). ^{13}C NMR (75 MHz, CDCl3) δ 154.35, 141.81, 128.72, 113.03, 111.91, 82.71 (d, *J* = 163.5 Hz), 56.44, 50.92 (d, *J* = 5.2 Hz), 45.61, 44.69, 41.63, 37.66, 36.51, 28.50 (d, *J* = 21.5 Hz), 26.82, 26.48, 24.20, 22.20, 22.11.

General Procedure[6,10] for the Preparation of Triflates 8a–d

3-Hydroxy-N-alkylmorphinan **7a–d** (3.5 mmol), was dissolved in anhydrous DCM (20 mL) and Et_3N (3.5 mL). The mixture was cooled to 0 °C, and then $PhNTf_2$ (1.94 g, 5.4 mmol) was added. The mixture was allowed to warm to rt overnight. The solution was diluted with DCM (40 mL), washed with 1N HCl followed by brine, and then dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* to afford the crude product, which was purified by flash silica gel column to give corresponding triflates. The analytical data for **8a–b** was in agreement with literature values. [6]

N-(Fluoropropyl)-morphinan-3-yl Trifluoromethanesulfonate (8c)

Yellow oil (99%). ^{1}H NMR (300 MHz, CDCl3) δ 7.17 (d, *J* = 8.6, 1H), 7.12 (d, *J* = 2.5, 1H), 7.02 (dd, *J* = 2.6, 8.4 Hz, 1H), 4.69-4.37 (m, 2H), 2.99 (d, *J* = 18.6 Hz, 1H), 2.93-2.85 (m, 1H), 2.74- 2.50 (m, 4H), 2.29 (d, *J* = 14.1 Hz, 1H), 2.07-1.51 (m, 7H), 1.47-1.14 (m, 5H), 1.11-0.98 (m, 1H). ^{19}F NMR (282 MHz, CDCl3) δ 29.21 (m), -73.22. ^{13}C NMR (75 MHz, CDCl3) δ 148.38, 143.51, 138.36, 129.33, 118.76 (d, *J* = 318.7 Hz), 118.23, 118.15, 82.58 (d, *J* = 162.8 Hz), 56.16, 50.77 (d, *J* = 5.2 Hz), 45.01, 44.65, 41.75, 38.10, 36.44, 28.80 (d, *J* = 19.5 Hz), 26.66, 26.37, 24.81, 21.85.

N-((*S*)-tetrahydrofurfuryl)-morphinan-3-yl Trifluoromethanesulfonate (8d)

Yellow oil (95%). ^{1}H NMR (300 MHz, CDCl3) δ 7.18 (d, *J* = 5.8 Hz, 1H), 7.12 (d, *J* = 1.8 Hz, 1H), 7.04 (m, 1H), 4.31-4.10 (m, 2H), 3.92-3.64 (m, 3H), 3.24-2.72 (m, 5H), 2.52-0.89 (m, 15H).

General Procedure[6,10] for the Preparation of Aminomorphinans 9a–d

The triflate **8a–d** (900 mg, 1.92 mmol) in 20 mL THF was added $Pd(OAc)_2$ (21 mg, 0.096 mmol), BINAP (95.4 mg, 0.151 mmol), $CsCO_3$ (936 mg, 2.88 mmol), and benzophenone imine (150 mg, 420 uL, 2.49 mmol) under N_2. The mixture was heated to reflux with stirring overnight. When starting material was consumed, the solvent was removed. The residue was diluted with EtOAc, washed with brine, dried and concentrated. The crude product was purified by flash silica gel column to yield the imine intermediate as yellow oil. To a solution of the imine intermediate in MeOH (50 mL) at rt was added NaOAc (654 mg, 8.4 mmol) and hydroxylamine hydrochloride (85 mg, 3.9 mmol). The mixture was stirred at room temperature for 36h. The solvent was removed and the residue was directly purified by flash silica gel column to yield corresponding amine. The analytical data for **9a–b** was in agreement with literature values. [6,10]

3-Amino-N-fluoropropyl-morphinan (9c)

Yellow oil (68%); ^{1}H NMR (300 MHz, CDCl3) δ 6.88 (d, *J* = 8.0, 1H), 6.61 (s, 1H), 6.55-6.44 (m, 1H), 4.69-4.32 (m, 2H), 3.52 (s, 2H), 2.87 (d, *J* = 18.0 Hz, 2H), 2.73-2.44 (m,, 4H), 2.30 (d, *J* = 9.2 Hz, 1H), 2.16-2.03 (m, 1H), 1.96-1.60 (m, 5H), 1.50 (s, 1H), 1.44-1.24 (m, 5H), 1.22-1.09 (m, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 144.44, 141.32, 128.38, 127.88, 113.15, 111.86, 82.81 (d, *J* = 165.0 Hz), 56.51, 50.83 (d, *J* = 5.2 Hz), 45.54, 45.32, 42.03, 37.58, 36.58, 28.85 (d, *J* = 19.5 Hz), 26.88, 26.61, 24.23, 22.28.

3-Amino-N-(*S*)-tetrahydrofurfuryl-morphinan (9d)

Yellow oil (41%); ^{1}H NMR (300 MHz, CDCl3) δ 6.88 (d, *J* = 5.8 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 6.50-6.47 (m, 1H), 4.02-3.96 (m, 1H), 3.88-3.71 (m, 2H), 3.50 (br, 2H), 3.94-2.86 (m, 2H), 2.68-2.48 (m, 4H), 2.28 (m, 1H), 2.16-1.10 (m, 15H). ^{13}C NMR (75 MHz, CDCl3) δ 144.31, 141.30, 128.22, 127.97, 112.99, 111.71, 77.47, 67.91, 60.06, 57.04, 45.93, 44.82, 41.77, 37.27, 36.42, 30.15, 26.72, 26.50, 25.30, 24.48, 22.19.

General Procedure[6,10] for the Preparation of Aminothiazolomorphinans 3, 10-12

The amine (1.1 mmol) and KSCN (426 mg, 4.4 mmol) were dissolved in 10 mL glacial acetic acid. A solution of Br_2 (180 mg, 1.1 mmol) in 2 mL of glacial acetic acid was added dropwise. The mixture was stirred for 48h, then basified with 10% NaOH and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash silica gel column to yield corresponding aminothiazole. The analytical data for **3**, **10** was in agreement with literature values. [10c]

Aminothiazolo[5,4-b]-N-fluoropropylmorphinan (11)

Slightly yellow solid (52%), M.p. 114–117 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.46 (s, 1H), 7.32 (s, 1H), 5.33 (s, 2H), 4.68-4.37 (m, 2H), 3.04 (d, *J* = 18.1 Hz, 1H), 2.92-2.82 (m, 1H), 2.80-2.38 (m, 5H), 2.13-1.99 (m, 1H), 1.96-1.59 (m, 5H), 1.55-1.29 (m, 6H), 1.22-1.03 (m, 1H). ^{19}F NMR (282 MHz, CDCl3) δ 9.72 (m). ^{13}C NMR (75 MHz, CDCl3) δ 164.97, 151.21, 139.04, 132.40, 129.09, 119.43, 115.92, 82.77 (d, *J* = 163.5 Hz), 56.52, 58.85 (d, *J* = 5.2 Hz), 45.39, 45.20, 42.40, 37.84, 36.81, 28.85 (d, *J* = 18.8 Hz), 26.90, 26.60, 25.13, 22.11. Anal. Calcd. for $C_{20}H_{26}FN_3S \cdot 3HCl \cdot 0.5H_2O$: C, 50.27; H, 6.33; N, 8.79. Found: C, 50.49; H, 6.58: N, 8.63.

Aminothiazolo[5,4-b]-N-(*S*)-tetrahydrofurylmethylmorphinan (12)

White solid (46%), M.P. 127–130 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.46 (s, 1H), 7.32 (s, 1H), 5.23 (s, 2H), 3.88 (m, 3H), 3.02 (m, 2H), 2.60 (m, 5H), 1.93 (m, 7H), 1.44 (m, 7H), 1.11 (m, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 164.83, 151.13, 139.23, 132.76, 129.03, 119.41, 115.95, 77.65, 68.08, 60.22, 57.01, 45.98, 44.94, 42.30, 37.66, 36.77, 30.28, 26.87, 26.61, 25.42 (2C), 22.14. Anal. Calcd. for $C_{22}H_{29}N_3OS \cdot 2HCl \cdot 1.4H_2O$: C, 54.86; H, 7.07; N, 8.72; Found: C, 54.85; H, 7.15: N, 8.44.

General Procedure for Synthesis of N′-Methyl-aminothiazolomorphinans 13a–c

At room temperature and under nitrogen atmosphere, freshly made HCOOAc (0.7 ml, 5.0 mmol, this reagent was prepared by heating a mixture of 1.8 mL HCOOH and 3.8 mL HOAc at 50 °C for two hours) was slowly added to a solution of 3-aminothiazolomorphinan (0.88 mmol). The mixture was stirred at room temperature for 24h. The resulting mixture was then concentrated to dryness and directly separated by flash silica gel column to give the intermediate formate. The intermediate (0.65 mmol) was dissolved in 5 mL anhydrous THF followed by addition of $LiAlH_4$ (50 mg, 1.3 mmol, added in one portion at 0 °C). Then resulting suspension was stirred at room temperature for 16h. After reaction was judged to be complete by TLC, 1 mL of water was added slowly to quench the reaction and followed by addition of 1 mL aqueous 2 N NaOH. The resulting olution was diluted with 50 mL of CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash silica gel column to give corresponding morphinans.

N′-Methylaminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (13a)

Slightly yellow foam (39%), M.P. (HCl salt) 212–215 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.50 (s, 1H), 7.30 (s, 1H), 5.27 (br, 1H), 3.19-3.07 (m, 4H), 3.05-2.94 (m, 1H), 2.81-2.64 (m, 2H), 2.58-2.28 (m, 3H), 2.11-1.97 (m, 1H), 1.96-1.74 (m, 2H), 1.69-1.59 (m, 1H), 1.55-1.32 (m, 6H), 1.25 (s, 1H), 0.96-0.80 (m, 1H), 0.58-0.45 (m, 2H), 0.19-0.07 (m, 2H).^{13}C NMR (75 MHz, CDCl3) δ 167.26, 151.62, 139.00, 131.58, 127.90, 119.31, 115.58, 59.94, 55.86, 45.73, 45.08, 42.22, 37.90, 36.82, 31.57, 26.94, 26.65, 24.65, 22.19, 9.36, 4.09, 3.64; Anal. Calcd. for $C_{22}H_{29}N_3S \cdot 2HCl \cdot 1.3H_2O$: C, 56.96; H, 7.30; N, 9.06. Found: C, 56.99; H, 7.14; N, 8.84.

N′-Methyl-aminothiazolo[5,4-b]-N-cyclobutylmethylmorphinan (13b)

White solid (45%), M.p. (HCl salt) >217 °C (dec). ^{1}H NMR (300 MHz, CDCl3) δ 7.49 (s, 1H), 7.32 (s, 1H), 5.33 (s, 1H), 3.14-3.01 (m, 4H), 2.89-2.37 (m, 6H), 2.15-1.58 (m, 11H), 1.53-1.27 (m, 6H). ^{13}C NMR (75 MHz, CDCl3) δ 167.31, 151.57, 138.98, 131.65, 127.86, 119.33, 115.54, 61.48, 55.98, 45.86, 45.01, 42.20, 37.74, 36.79, 34.85, 31.57, 27.91, 26.94, 26.61, 24.80, 22.17, 18.83; Anal. Calcd for $C_{23}H_{31}N_3S \cdot 2HCl \cdot 1.1H_2O$: C, 58.24; H, 7.48; N, 8.86. Found: C, 58.38; H, 7.47; N, 8.56.

N′-Methyl-aminothiazolo[5,4-b]-N-fluoropropylmorphinan (13c)

Slightly yellow foam (55%), M.p. (HCl salt) 205–207 °C (dec); ^{1}H NMR (300 MHz, CDCl3) δ 7.50 (s, 1H), 7.31 (s, 1H), 5.22 (br, 1H), 4.68-4.37 (m, 2H), 3.11 (s, 3H), 3.03 (d, *J* = 18.1 Hz, 1H), 2.92-2.83 (m, 1H), 2.80-2.40 (m, 5H), 2.14-2.01 (m, 1H), 1.97-1.59 (m, 5H), 1.54-1.10 (m, 7H). ^{13}C NMR (75 MHz, CDCl3) δ 167.29, 151.66, 138.93, 131.57, 127.97, 119.35, 115.62, 82.78 (d, *J* = 162.8 Hz), 56.59, 50.87 (d, *J* = 5.2 Hz), 45.44, 45.25, 42.41, 37.88, 36.83, 31.58, 28.86 (d, *J* = 19.5 Hz), 26.94, 26.64, 25.11, 22.20; Anal. Calcd for $C_{21}H_{28}FN_3S \cdot 2HCl \cdot 1.5H_2O$: C, 53.27; H, 7.03; N, 8.87. Found: C, 53.38; H, 7.20; N, 8.75.

Synthesis of N′-Acetyl-N′-methyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (14)

A solution of N′-Methyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (40mg, 0.11 mmol), acetic anhydride (0.5 mL) and pyridine (2 mL) was stirred at room temperature for 5h. After reaction was over, the volatile components were removed *in vacuo*. The residue was purified by flash silica gel column (Hexane:EtOAc: Et_3N = 10:10:0.5) to afford a white solid (40 mg, 90%). M.p. 67–70 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.76 (s, 1H), 7.51 (s, 1H), 3.79 (s, 3H), 3.15-3.06 (m, 2H), 2.82-2.68 (m, 2H), 2.54-2.48 (m, 2H), 2.45 (s, 3H), 2.36-2.29 (m, 2H), 2.04-1.78 (m, 3H), 1.64 (m, 1H), 1.55-1.11 (m, 6H), 0.88 (m, 1H), 0.52-0.49 (m, 2H), 0.16-0.07 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 170.55, 159.06, 147.21, 139.53, 134.33, 130.78, 119.28, 117.78, 59.97, 55.81, 45.67, 45.16, 42.57, 38.08, 36.87, 35.85, 26.95, 26.64, 24.87, 23.54, 22.19, 9.40, 4.04, 3.59; Anal. Calcd for $C_{25}H_{33}N_3OS \cdot 0.1H_2O$: C, 70.58; H, 7.87; N, 9.88. Found: C, 70.38; H, 7.91; N, 9.72.

Synthesis of N′-Trifluoroethyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (15)

Et_3N (0.6 mL) was added to the solution of aminothiazolo[5,4-b]-Ncyclopropylmethylmorphinan (71 mg, 0.2 mmol) in 1.5 ml toluene. Trifluoroacetic anhydride (0.6 mL) was added to the mixture, and then stirred at 100 °C for overnight. The volatile components were removed *in vacuo*. The residue was purified by flash silica gel column (EtOAc: MeOH: Et_3N = 60:1:1) to afford the intermediate. $LiAlH_4$ (10 mg, 0.25 mmol) was added to a solution of intermediate (50 mg, 0.11 mmol) in 2 mL THF. The mixture was stirred at room temperature overnight. Next, 0.2 mL water was added to quench the reaction, followed by the addition of 0.2 mL of 2 N aqueous NaOH. The resulting mixture was stirred for 30 min and then filtered. The resulting solid was washed with

CH_2Cl_2 (2×2 mL). The filtrate was concentrated *in vacuo*. The residue obtained was purified by flash silica gel column (Hex: EtOAc: Et_3N = 10:10:1) to afford a white foam (15mg, 31%), M.p. (HCl salt) >198 °C (dec); ^{1}H NMR (300 MHz, CDCl3) δ 7.53 (s, 1H), 7.32 (s, 1H), 4.19 (m, 2H), 3.12 (m, 1H), 3.01 (d, *J* = 18.2 Hz, 1H), 2.72 (m, 2H), 2.42 (m, 3H), 1.91 (m, 3H), 1.44 (m, 8H), 0.89 (m, 1H), 0.51 (dd, *J* = 1.4, 8.0 Hz, 2H), 0.11 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 164.93, 150.72, 139.46, 132.84, 128.06, 119.43, 116.38, 59.99, 55.82, 45.98, 45.69, 45.08, 42.25, 37.99, 36.81, 26.95, 26.64, 24.76, 22.19, 9.39, 4.09, 3.63. Anal. Calcd for $C_{23}H_{28}F_3N_3S \cdot 2HCl \cdot 1.9H_2O$: C, 50.90; H, 6.28; N, 7.74. Found: C, 51.10; H, 6.21; N, 7.24.

General Procedure for Synthesis of N′-Propyl-aminothiazolomorphinans 16a and 16c

The mixture of aminothiazolomorphinan (0.3 mmol), proponialdehyde (43 μL, 0.6 mmol) in 2 mL MeOH was stirred at 60 °C for overnight. The reaction was judged to be complete by TLC. Next, $NaBH_4$ (45.6 mg, 1.2 mmol) was added, and the resulting mixture was stirred at 60 °C for 8h. After this period, the solvents were removed *in vacuo*. The residue was then directly purified by flash silica gel column to give corresponding morphinans.

N′-Propyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (16a)

White foam (55%), M.p. (HCl salt) 212–214 °C (dec). ^{1}H NMR (300 MHz, CDCl3) δ 7.46 (s, 1H), 7.29 (s, 1H), 5.19 (s, 1H), 3.39 (s, 2H), 3.18-3.06 (m, 1H), 3.05-2.91 (m, 1H), 2.78-2.65 (m, 2H), 2.55-2.40 (m, 2H), 2.38-2.28 (m, 1H), 2.08-1.96 (m, 1H), 1.93-1.59 (m, 5H), 1.53-1.30 (m, 6H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 2H), 0.56-0.45 (m, 2H), 0.18-0.05 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 166.61, 151.60, 138.96, 131.51, 127.78, 119.28, 115.49, 59.94, 55.86, 47.11, 45.74, 45.10, 42.22, 37.90, 36.83, 26.95, 26.66, 24.66, 22.86, 22.19, 11.36, 9.37, 4.09, 3.64. Anal. Calcd for $C_{24}H_{33}N_3S \cdot 2HCl \cdot 2.1H_2O$: C, 56.93; H, 7.80; N, 8.30. Found: C, 57.19; H, 7.69; N, 7.84.

N′-Propyl-aminothiazolo[5,4-b]-N-fluoropropylmorphinan (16c)

White foam (47%), M.p. (HCl salt) 215-217 °C (dec). ^{1}H NMR (300 MHz, CDCl3) δ 7.46 (s, 1H), 7.31 (s, 1H), 5.49 (s, 1H), 4.71-4.36 (m, 2H), 3.39 (t, *J* = 6.6 Hz, 2H), 3.07-2.41 (m, 6H), 2.07 (t, *J* = 11.6 Hz, 1H), 1.97-1.58 (m, 7H), 1.54-1.23 (m, 8H), 1.06-0.95 (m, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 166.91, 151.59, 138.76, 131.22, 127.78, 119.33, 115.37, 82.73 (d, *J* = 163.5 Hz), 56.55, 50.82 (d, *J* = 5.2 Hz), 47.21, 45.44, 45.04, 42.24, 37.81, 36.77, 28.69 (d, J = 19.5 Hz), 26.90, 26.60, 25.08, 22.85, 22.16, 11.35. Anal. Calcd for $C_{23}H_{32}FN_3S \cdot 2HCl \cdot 0.9H_2O$: C, 56.29; H, 7.35; N, 8.56. Found: C, 56.24; H, 7.48; N, 8.19.

General Procedure for Synthesis of N′, N′-Dimethyl-aminothiazolomorphinans 17a and 17c

To a stirred mixture of N′-methyl-aminothiazolomorphinan (0.15 mmol), paraformaldehyde (44 mg, 1.5 mmol), and $NaBH_4$ (28.8 mg, 0.76 mmol) in THF (3 mL) at rt under nitrogen atmosphere was added dropwise trifluoroacetic acid (1.5 mL). The resulting mixture was stirred at rt for 24h, then poured into a mixture of 25% aqueous NaOH (5 mL) and ice to make strongly alkaline solution, which was then diluted with saturated NaCl solution (5 mL), and extracted with CH_2Cl_2. The combined extracts were dried by anhydrous Na_2SO_4, filtered, and concentrated in *vacuo* to afford a yellow solid. The solid was treated with 10% HCl. The aqueous layer was washed with CH_2Cl_2, and then added 10% NaOH to make the free base. The resulting aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine, and then dried by anhydrous Na_2SO_4, filtered, and concentrated in *vacuo* to give corresponding morphinans.

N′, N′-Dimethyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (17a)

Pale yellow solid (89%), M.p. (HCl salt) 193–195 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.51 (s, 1H), 7.31 (s, 1H), 3.19 (s, 6H), 3.15-3.10 (m, 1H), 3.04-2.93 (m, 1H), 2.82-2.64 (m, 2H), 2.57-2.26 (m, 3H), 2.11-1.74 (m, 3H), 1.70-1.58 (m, 1H), 1.54-1.30 (m, 6H), 1.26-1.10 (m, 1H), 1.00-0.79 (m, 1H), 0.61-0.42 (m, 2H), 0.19-0.06 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 168.25, 152.29, 138.99, 128.52, 119.14, 115.36, 59.99, 55.95, 45.80, 45.15, 42.26, 40.21, 37.94, 36.82, 26.97, 26.67, 24.65, 22.27, 22.21, 9.38, 4.09, 3.65; Anal. Calcd for $C_{22}H_{29}N_3S \cdot 3HCl \cdot H_2O$: C, 54.27; H, 7.13; N, 8.26. Found: C, 54.47; H, 7.18: N, 8.16.

N′, N′-Dimethyl-aminothiazolo[5,4-b]-N-fluoropropylmethylmorphinan (17c)

Pale yellow solid (83%), M.p. (HCl salt) 198–200 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.51 (s, 1H), 7.33 (s, 1H), 4.72-4.33 (m, 2H), 3.19 (s, 6H), 3.10-2.42 (m, 6H), 2.19-2.05 (m, 1H), 2.01-1.71 (m, 4H), 1.69-1.31 (m, 8H), 0.97-0.74 (m, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 168.31, 152.40, 138.65, 130.46, 128.68, 119.20, 115.36, 82.66 (d, *J* = 163.5 Hz), 56.71, 50.89 (d, *J* = 5.2 Hz), 45.55, 44.90, 42.12, 40.20, 37.79, 36.70, 29.68, 28.56 (d, *J* = 19.5 Hz), 26.88, 26.56, 25.04, 22.21; Analysis Calcd for $C_{22}H_{30}FN_3S{\cdot}2HCl \cdot 1.3H_2O$: C, 54.61; H, 7.21; N, 8.68. Found: C, 54.82; H, 7.30; N, 8.35.

General Procedure for Synthesis of N′-Acetyl-aminothiazolomorphinans 18a and 18c

The mixture of aminothiazolo-morphinan (0.41 mmol), pyridine (2.1 mL), and acetic anhydride (1.1 mL) was stirred at room temperature for 24h. The volatile components were removed *in vacuo*. The residue was purified by flash silica gel column to afford the corresponding morphinans.

N′-Acetyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (18a)

Slightly yellow solid (78%), M.p. 148–151 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.67 (s, 1H), 7.54 (s, 1H), 3.20-3.03 (m, 2H), 2.86-2.67 (m, 1H), 2.60-2.33 (m, 2H), 2.29 (s, 3H), 2.01-1.82 (m, 2H), 1.77-1.59 (m, 4H), 1.56-1.27 (m, 6H), 1.17-1.09 (m, 1H), 0.93-0.81 (m, 1H), 0.57-0.46 (m, 2H), 0.18-0.08 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 168.90, 159.47, 147.08, 140.31, 139.91, 129.48, 120.16, 117.18, 60.28, 56.03, 45.87, 45.40, 42.89, 38.40, 37.22, 27.19, 26.86, 25.17, 23.68, 22.38, 9.47, 4.32, 3.82; Analysis Calcd for $C_{23}H_{29}N_3OS \cdot 0.1H_2O$: C, 69.52; H, 7.41; N, 10.57. Found: C, 69.62; H, 7.58; N, 10.22.

N′-Acetyl-aminothiazolo[5,4-b]-N-fluoropropylmorphinan (18c)

Slightly yellow solid (60%), M.p. (HCl salt) 215–217 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 11.77 (s, 1H), 7.68 (s, 1H), 7.58 (s, 1H), 4.69-4.38 (m, 2H), 3.14 (d, *J* = 18.1 Hz, 1H), 2.98-2.39 (m, 5H), 2.28 (s, 3H), 2.10-1.98 (m, 1H), 1.96-1.08 (m, 13H). ^{19}F NMR (282 MHz, CDCl3) δ 9.59 (m). ^{13}C NMR (75 MHz, CDCl3) δ 168.62, 159.10, 146.86, 139.90, 134.48, 129.27, 119.97, 116.98, 82.69 (d, *J* = 162.8 Hz), 56.44, 50.85 (d, *J* = 5.2 Hz), 45.30, 45.13, 42.66, 38.05, 36.90, 28.83 (d, *J* = 19.5), 26.88, 26.56, 25.31, 23.48, 22.10; Anal. Calcd for $C_{22}H_{28}FN_3OS \cdot 2HCl \cdot 0.7H_2O$: C, 54.25; H, 6.50; N, 8.63. Found: C, 54.34; H, 6.41: N, 8.47.

General Procedure for Synthesis of N′-Ethyl-aminothiazolomorphinans 19a -c

At room temperature, a solution of N′-acetyl-aminothiazolomorphinan (N′-acetyl-2′-aminothiazolo-N-cyclobutylmorphinan **18b** was prepared using same procedure with **12a)** (0.31 mmol) in 1 mL of dry THF was added to a suspension of $LiAlH_4$ (24 mg, 0.62 mmol) in 2 mL of dry THF. After 24h of stirring, 0.2 mL of water was added to quench the reaction followed by the addition of 0.2 mL of 2 N aqueous NaOH. The resulting mixture was then stirred for 30 min and filtered, and the resulting solid was washed with CH_2Cl_2. The filtrate

was concentrated *in vacuo*. The resulting residue was then purified by flash silica gel column to afford the corresponding morphinans.

N′-Ethyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (19a)

White solid (86%), M.p. 95–98 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.47 (s, 1H), 7.30 (s, 1H), 5.81 (s, 1H), 3.54-3.43 (m, 2H), 3.21-2.90 (m, 2H), 2.83-2.64 (m, 2H), 2.57-2.30 (m, 3H), 2.07- 1.75 (m, 2H), 1.54-1.05 (m, 11H), 1.00-0.78 (m, 1H), 0.60-0.39 (m, 2H), 0.13 (s, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 166.61, 151.57, 138.73, 131.14, 127.73, 119.24, 115.29, 59.78, 55.81, 45.66, 44.85, 42.03, 40.06, 37.78, 36.74, 26.85, 26.56, 24.61, 22.10, 14.89, 9.16, 4.06, 3.63; Anal. Calcd for $C_{23}H_{31}N_3OS \cdot 2HCl \cdot 1.3H_2O$: C, 57.80; H, 7.51; N, 8.79. Found: C, 57.88; H, 7.50; N, 8.55.

N′-Ethyl-aminothiazolo[5,4-b]-N-cyclobutylmethylmorphinan (19b)

White solid (84%), M.p. (HCl salt) >220 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.47 (s, 1H), 7.31 (s, 1H), 5.23 (s, 1H), 3.57-3.42 (m, 2H), 3.06 (d, *J* = 17.9, 1H), 2.82 (s, 1H), 2.75-2.36 (m, 6H), 2.14-1.57 (m, 11H), 1.43-1.26 (m, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 166.40, 151.53, 139.00, 131.71, 127.73, 119.29, 115.49, 61.55, 55.97, 45.85, 45.15, 42.30, 40.09, 37.77, 36.83, 34.97, 27.91, 26.96, 26.65, 24.81, 22.18, 18.85, 14.96; Anal. Calcd for $C_{24}H_{33}N_3S \cdot 2HCl \cdot 1.\ 4H_2O$: C, 58.38; H, 7.72; N, 8.51. Found: C, 58.70; H, 7.60; N, 8.13.

N′-Ethyl-aminothiazolo[5,4-b]-N-fluoropropylmorphinan (19c)

White solid (93%), M.p. 113–115 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.48 (s, 1H), 7.31 (s, 1H), 5.24 (br, 1H), 4.68-4.38 (m, 2H), 3.57-3.40 (m, 2H), 3.03 (d, *J* = 18.1 Hz, 1H), 2.92-2.85 (m, 1H), 2.80- 2.40 (m, 5H), 2.15-2.00 (m, 1H), 1.97-1.59 (m, 5H), 1.54-1.10 (m, 11H); ^{19}F NMR (282 MHz, CDCl3) δ 9.24 (m); ^{13}C NMR (75 MHz, CDCl3) δ 166.42, 151.64, 138.85, 131.48, 127.86, 119.32, 115.53, 82.78 (d, *J* = 162.8 Hz), 56.58, 50.88 (d, *J* = 5.2 Hz), 45.45, 45.21,42.37, 40.08, 37.85, 36.81, 28.82 (d, *J* = 19.5 Hz), 26.91, 26.62, 25.07, 22.17, 14.96; Anal. Calcd for $C_{22}H_{30}FN_3S \cdot 2HCl \cdot 1.8H_2O$: C, 53.61; H, 7.28; N, 8.52. Found: C, 53.63; H, 7.25; N, 8.46.

Synthesis of N′-Acetyl-N′-ethyl-amino-thiazolo[5,4-b]-N-cyclopropylmethylmorphinan (20)

A solution of N′-ethyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (55mg, 0.14 mmol), acetic anhydride (0.5 mL) and pyridine (2 mL) was stirred at room temperature for 24h. After reaction was judged complete by TLC, the volatile components were removed *in vacuo*. The resulting residue was purified by flash silica gel column (EtOAc: Et_3N = 60:1) to afford a white solid (40 mg, 65%). M.p. 88–90 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.75 (s, 1H), 7.51 (s, 1H), 4.31 (m, 2H), 3.14-3.06 (m, 2H), 2.81-2.67 (m, 2H), 2.54-2.48 (m, 2H), 2.45 (s, 3H), 2.04-1.78 (m, 3H), 1.64 (m, 1H), 1.54 (m, 1H), 1.48-1.36 (m, 10H), 0.88 (m, 1H), 0.54-0.49 (m, 2H), 0.13-0.09 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 170.19, 147.48, 139.44, 134.31, 130.82, 119.21,117.86, 60.02, 55.85, 45.69, 45.28, 43.66, 42.62, 38.10, 36.89, 26.96, 26.66, 24.88, 22.95, 22.19, 13.77, 9.48, 4.04, 3.56; Anal. Calcd for $C_{24}H_{31}N_3OS{\cdot}0.2H_2O$: C, 69.76; H, 7.66; N, 10.17. Found: C, 70.00; H, 7.92; N, 9.80.

Synthesis of N′-Benzyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (22)

A mixture of ATPM (70 mg, 0.20 mmol), benzaldehyde (84 uL, 0.8 mmol) and a crystal of *p*-toluenesulfonic acid (20 mg) in 25 mL dry toluene was refluxed using a Dean-Stark apparatus for 18 h. Toluene was then removed *in vacuo*. The resulting residue was dissolved in 8 mL MeOH and $NaBH_4$ (31 mg, 0.8 mmol) was added. The resulting mixture was refluxed for 6 h. MeOH was then removed *in vacuo*. The residue was then dissolved in 10 mL 1N HCl and washed with ethyl acetate (10 mL × 2), then basified with ammonium hydroxide until pH ~ 11 was reached. The aqueous solution was then extracted with CH_2Cl_2

(10 mL × 3). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash silica gel column to give product **15** as a white foam (43 mg, 62%). M.P. (HCl salt) >216 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.48 (s, 1H), 7.35 (m, 6H), 5.77 (s, 1H), 4.65 (s, 2H), 3.11 (m, 1H), 2.99 (d, *J* = 18.3, 1H), 2.72 (m, 2H), 2.41 (m, 3H), 1.91 (m, 3H), 1.62 (s, 1H), 1.31 (m, 7H), 0.89 (m, 1H), 0.51 (m, 2H), 0.11 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 166.37, 151.42, 139.10, 137.65, 131.85, 128.76, 127.89, 127.77, 127.63, 119.33, 115.69, 59.98, 55.86, 49.16, 45.73, 45.13, 42.26, 37.92, 36.82, 26.96, 26.66, 24.69, 22.20, 9.40, 4.09, 3.62; Anal. Calc. for $C_{29}H_{35}N_3OS \cdot 2HCl \cdot 1.2H_2O$: C, 62.49; H, 7.00; N, 7.81. Found: C, 62.73; H, 6.92; N, 8.00.

Synthesis of N′-(3-Methoxybenzyl)-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (21)

A mixture of **3** (135 mg, 0.38 mmol), *m*-anisaldehyde (93 μL, 0.76 mmol) and a crystal of *p*-toluenesulfonic acid (20 mg) in 25 mL dry toluene was refluxed using a Dean Stark apparatus for 18 h. Toluene was then removed in *vacuo*. The residue was dissolved in 8 mL MeOH and $NaBH_4$ (31 mg, 0.8 mmol) was added. The resulting mixture was refluxed for 6 h. and then the solvent was removed in *vacuo*. The residue was dissolved in 10 mL 1N HCl and washed with ethyl acetate (10 mL × 2), then basified with ammonium hydroxide until pH ~ 11 was reached. The aqueous solution was extracted with CH_2Cl_2 (10 mL × 3). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash silica gel column to give product **21** as a white foam (122 mg, 68%), M.P. (HCl salt) 205-207 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.48 (s, 1H), 7.28 (m, 2H), 6.95 (m, 2H), 6.84 (dd, *J* = 2.2, 8.0 Hz, 1H), 5.77 (s, 1H), 4.62 (s, 2H), 3.79 (s, 3H), 3.05 (m, 2H), 2.71 (m, 2H), 2.40 (m, 3H), 1.74 (m, 11H), 0.88 (m, 1H), 0.50 (m, 2H), 0.10 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 166.35, 159.89, 151.37, 139.22, 139.13, 131.91, 129.81, 127.85, 119.81, 119.32, 115.67, 113.16, 60.02, 55.84, 55.22, 49.11, 45.74, 45.18, 42.31, 37.93, 36.83, 26.96, 26.66, 24.64, 22.20, 9.45, 4.09, 3.60; Anal. Calc. for $C_{29}H_{35}N_3OS \cdot 2HCl \cdot 1.2H_2O$: C, 61.30; H, 6.99; N, 7.40. Found: C, 61.33, H, 7.08; N, 7.28.

Synthesis of N′-(3-Hydroxybenzyl)-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (23)

To the solution of compound **21** (80 mg, 0.17 mmol) in 4 mL CH_2Cl_2 was added BBr_3 (1M in CH_2Cl_2, 3 mL) at 0 °C, then stirred at room temperature for 3.5 h. The reaction was quenched with MeOH, and then the solvent was removed *in vacuo*. The resulting dark oil was redissolved in MeOH and refluxed 15 min. MeOH was removed *in vacuo* and the residue was dissolved in 10 mL 1M HCl, washed with ethyl acetate twice, then basified with ammonium hydroxide, extracted with CH_2Cl_2, and dried over Na_2SO_4. The crude product was purified by flash silica gel column (EtOAc/MeOH/Et_3N = 50/1/1) to give product **17** as a white solid (57 mg, 74%). M.P. 180–182 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.42 (s, 1H), 7.29 (s, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.79 (m, 3H), 4.53 (s, 2H), 3.20 (m, 1H), 3.01 (d, *J* = 18.3 Hz, 1H), 2.78 (m, 2H), 2.46 (m, 3H), 2.09 (m, 1H), 1.54 (m, 11H), 0.56 (m, 2H), 0.16 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 168.15, 157.66, 151.66, 140.07, 138.77, 131.42, 130.14, 128.31, 119.94, 119.24, 115.19, 114.87, 114.81, 60.08, 56.21, 46.37, 45.00, 42.14, 38.22, 37.27, 27.43, 27.07, 25.04, 22.59, 8.95, 4.35, 4.18. Anal. Calc. for $C_{28}H_{33}N_3OS \cdot 0.6H_2O$: C, 71.48; H, 7.33; N, 8.93. Found: C, 71.52; H, 7.44; N, 8.89.

Synthesis of N′-ethylthiourea-thiazolo[5,4-b]-N-cyclopropylmethylmorphinan (24)

To a solution of **3** (141 mg, 0.4 mmol) in dry toluene (6 mL) were added Et_3N (33 μL, 0.22 mmol) and ethyl isothiocyanate (50 mg, 0.56 mmol). The reaction mixture was stirred in the microwave reactor (150W, 130 °C) for 150 mins. After cooled, the residue was directly

purified by flash silica gel column (hexanes/EtOAc/Et_3N 20/20/1) to give product **24** as a white foam (62 mg, 35%). M.P. (HCl salt) >255 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 11.10 (s, 1H), 7.62 (s, 1H), 7.41 (s, 1H), 3.94 – 3.76 (m, 2H), 3.16 (s, 1H), 3.05 (d, *J* = 18.5 Hz, 1H), 2.84-2.65 (m, 2H), 2.59-2.26 (m, 3H), 2.03-1.77 (m, 3H), 1.74-1.06 (m, 11H), 0.94- 0.82 (m, 1H), 0.52 (ps. d, *J* = 7.4 Hz, 2H), 0.21-0.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 177.54, 159.43, 148.79, 140.02, 134.81, 127.15, 119.60, 117.28, 59.93, 55.68, 45.60, 44.96, 42.35, 40.52, 38.03, 36.79, 26.89, 26.56, 24.89, 22.19, 14.01, 9.34, 4.09, 3.65; Anal. Calc. for $C_{24}H_{32}N_4S_2 \cdot HCl \cdot 1.5H_2O$: C, 57.18; H, 7.20; N, 11.11. Found: C, 57.41; H, 7.07; N, 10.72.

Synthesis of 3-Bromo-thiazolo[5,4-b]-N-cyclopropylmethylmorphinan (25)

t-Butyl nitrite (76 uL, 0.65 mmol) was added to the solution of $CuBr_2$ (145 mg, 0.65 mmol) in dry acetonitrile (8 ml). The reaction mixture was stirred for 10 minutes at room temperature. After 10 minutes **3** (115 mg, 0.32 mmol) was added in portions at 60 °C. The reaction mixture was left to stir at 60 °C for 30 minutes, and then an additional amount of *t*-butyl nitrite (76 uL, 0.65 mmol) was added. After 1.5 h of stirring at room temperature the reaction mixture was poured on water (30 ml) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, concentrated. The residue was purified twice by flash silica gel column (first with hexanes/EtOAc 1/3 then with hexanes/EtOAc/Et_3N 20/20/1) to give product **25** as a slightly yellow oil (60 mg, 45%). ^{1}H NMR (300 MHz, CDCl3) δ 7.90 (s, 1H), 7.51 (s, 1H), 3.18-3.02 (m, 2H), 2.82-2.67 (m, 2H), 2.54-2.42 (m, 2H), 2.37-2.26 (m, 1H), 2.02-1.79 (m, 3H), 1.70-1.22 (m, 8H), 0.95-0.82 (m, 1H), 0.57-0.48 (m, 2H), 0.17-0.06 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 151.65, 140.60, 137.61, 136.57, 134.51, 119.49, 119.12, 60.01, 55.62, 45.51, 44.94, 42.44, 38.14, 36.80, 26.93, 26.56, 24.97, 21.98, 9.44, 4.09, 3.61.

General Procedure for Synthesis of N′-Aryl-aminothiazolomorphinans (26–27) and 3-(piperazin-1-yl)-thiazolo[5,4-b]-N-cyclopropylmethylmorphinan (28)

To a solution of either aniline, 2-aminopyridine or piperazine (1.32 mmol) in dry THF (4 ml), NaH (55 mg; 1.32 mmol, ω = 0.6) was added and stirred for 30 minutes at 50 – 60 °C. Next, 2′-bromo-thiazolo[5,4-b]-N-cyclopropylmethyl-morphinan 25 (137 mg, 0.33 mmol) was added and the reaction mixture was left to stir for 4 hours. The reaction mixture was then concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated. The crude product was purified by flash silica gel column to give the corresponding morphinans 26–28.

N′-Phenyl-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (26)

Slightly yellow foam (72%). M.P. (HCl salt) >212 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.55-7.46 (m, 3H), 7.38 (m, 3H), 7.18-7.08 (m, 1H), 3.13 (s, 1H), 3.02 (d, *J* = 18.8 Hz, 1H), 2.74 (m, 2H), 2.58-2.44 (m, 1H), 2.43-2.25 (m, 2H), 2.11-1.74 (m, 4H), 1.62 (s, 1H), 1.42 (m, 7H), 0.89 (m, 1H), 0.51 (ps. d, *J* = 7.5 Hz, 2H), 0.12 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 163.45, 150.64, 139.97, 139.33, 132.59, 129.47, 127.39, 123.95, 119.86, 119.30, 116.13, 59.98, 55.86, 45.74, 45.05, 42.28, 37.96, 36.78, 26.95, 26.64, 24.77, 22.21, 9.37, 4.11, 3.66. Anal. Calc. for $C_{27}H_{31}N_3S \cdot HCl \cdot 1.6H_2O$: C, 65.53; H, 7.17; N, 8.49. Found: C, 65.34; H, 6.87; N, 8.30.

N′-(Pyridin-2-yl)-aminothiazolo[5,4-b]-N-cyclopropylmethylmorphinan (27)

Slightly yellow foam (39%); M.P. (HCl salt) >223 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 8.41 (d, *J* = 3.9, 1H), 7.63 (s, 1H), 7.57-7.48 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.94-6.87 (m, 1H), 3.17 (s, 1H), 3.10 (d, *J* = 18.4 Hz, 1H), 2.89-2.68 (m, 2H), 2.59-2.50 (m, 1H),

2.42-2.32 (m, 2H), 2.11-1.23 (m, 11H), 0.96-0.85 (m, 1H), 0.55-0.49 (m, 2H), 0.16- 0.13 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 161.20, 151.72, 147.90, 146.89, 139.14, 137.73, 132.47, 129.54, 119.56, 116.78, 115.66, 111.11, 59.93, 55.89, 45.76, 45.03, 42.47, 38.02, 36.79, 26.96, 26.66, 24.83, 22.39, 9.33, 4.10, 3.66. Anal. Calcd. for $C_{26}H_{30}N_4S \cdot 2HCl \cdot 2H_2O$: C, 57.88; H, 6.73; N, 10.38. Found: C, 58.21; H, 6.95; N, 9.97.

N′-(Piperazin-1-yl)-thiazolo[5,4-b]-N-cyclopropylmethylmorphinan (28)

White foam (63%); M.P. (HCl salt) >245 °C (dec.); ^{1}H NMR (300 MHz, CDCl3) δ 7.50 (s, 1H), 7.33 (s, 1H), 3.63-3.55 (m, 4H), 3.23 (s, 1H), 3.02-2.95 (m, 4H), 2.85-2.73 (m, 2H), 2.70-2.37 (m, 4H), 2.17-1.79 (m, 3H), 1.70-1.30 (m, 8H), 0.98-0.95 (m, 1H), 0.62-0.47 (m, 2H), 0.24-0.11 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 168.61, 151.77, 138.81, 130.94, 128.07, 119.24, 115.68, 59.59, 55.81, 49.50, 45.66, 45.44, 44.50, 41.82, 37.78, 36.65, 26.85, 26.53, 24.74, 22.17, 8.90, 4.08, 3.75. Anal. Calcd. for $C_{25}H_{34}N_4S \cdot 3HCl \cdot 3.1H_2O$: C, 51.08; H, 7.41; N, 9.53. Found: C, 51.37; H, 7.49; N, 9.05.

Opioid binding to the human κ, δ, and μ opioid receptors

Chinese hamster ovary (CHO) cells stably transfected with the human κ opioid receptor (hKOR-CHO), δ-opioid receptor (hDOR-CHO) were obtained from Dr. Larry Toll (SRI International, Palo Alto, CA), and the μ-opioid receptor (hMOR-CHO) were obtained from Dr. George Uhl (NIDA Intramural Program, Baltimore, MD). The cells were grown in 100-mm dishes in Dulbecco's modified Eagle's media (DMEM) supplemented with 10% fetal bovine serum (FBS) and penicillin–streptomycin (10,000 U/mL) at 37 °C in a 5% CO_2 atmosphere. The affinity and selectivity of the compounds for the multiple opioid receptors were determined by incubating the membranes with radiolabeled ligands and 12 different concentrations of the compounds at 25 °C in a final volume of 1 mL of 50 mM Tris–HCl, pH 7.5. Incubation times of 60 min were used for the κ-selective peptide [^{3}H]DAMGO and the j-selective ligand [^{3}H]U69,593. A 3-h incubation was used with the δ-selective antagonist [^{3}H]naltrindole.

[^{35}S]GTPγS binding studies to measure coupling to G proteins

Membranes from CHO cells stably expressing either the human κ or μ opioid receptor were used in the experiments. Cells were scraped from tissue culture plates and then centrifuged at 1000*g* for 10 min at 4 °C. The cells were resuspended in phosphatebuffered saline, pH 7.4, containing 0.04% EDTA. After centrifugation at 1000*g* for 10 min at 4 °C, the cell pellet was resuspended in membrane buffer, which consisted of 50 mM Tris–HCl, 3 mM $MgCl_2$, and 1 mM EGTA, pH 7.4. The membranes were homogenized with a Dounce homogenizer, followed by centrifugation at 40,000*g* for 20 min at 4 °C. The membrane pellet was resuspended in membrane buffer, and those transfected with the centrifugation step was repeated. The membranes were then resuspended in assay buffer, which consisted of 50 mM Tris–HCl, 3 mM $MgCl_2$, 100 mM NaCl, and 0.2 mM EGTA, pH 7.4. The protein concentration was determined by the Bradford assay using bovine serum albumin as the standard. The membranes were frozen at −80 °C until used.

CHO cell membranes expressing either the human κ opioid receptor (15 μg of protein per tube) or μ opioid receptor (7.5 μg of protein per tube) were incubated with 12 different concentrations of the agonist in assay buffer for 60 min at 30 °C in a final volume of 0.5 mL. The reaction mixture contained 3 μM GDP and 80 pmol of [^{35}S]GTPγS. Basal activity was determined in the presence of 3 μM GDP and in the absence of an agonist, and nonspecific binding was determined in the presence of 10 μM unlabeled GTPγS. Then, the membranes were filtered onto glass fiber filters by vacuum filtration, followed by three washes with 3 mL of ice-cold 50 mM Tris–HCl, pH 7.5. Samples were counted in 2 mL of Ecoscint A scintillation fluid. Data represent the percent of agoniststimulation [^{35}S]GTPγS binding over

the basal activity, defined as [(specific binding/basal binding) × 100] − 100. All experiments were repeated at least three times and were performed in triplicate. To determine antagonist activity of a compound at the μ opioid receptors, CHO membranes expressing the μ opioid receptor were incubated with the compound in the presence of 200 nM of the agonist DAMGO. To determine antagonist activity of a compound at the κ opioid receptors, CHO membranes expressing the κ opioid receptor were incubated with the compound in the presence of 100 nM of the κ agonist U50,488.

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Abbreviations

κOR	kappa opioid receptor
μOR	mu opioid receptor
δOR	delta opioid receptor
SAR	structure-activity relationship
ATPM	aminothiazolo-N-cyclopropylmorphinan
ATBM	aminothiazolo-N-cyclobutylmorphinan

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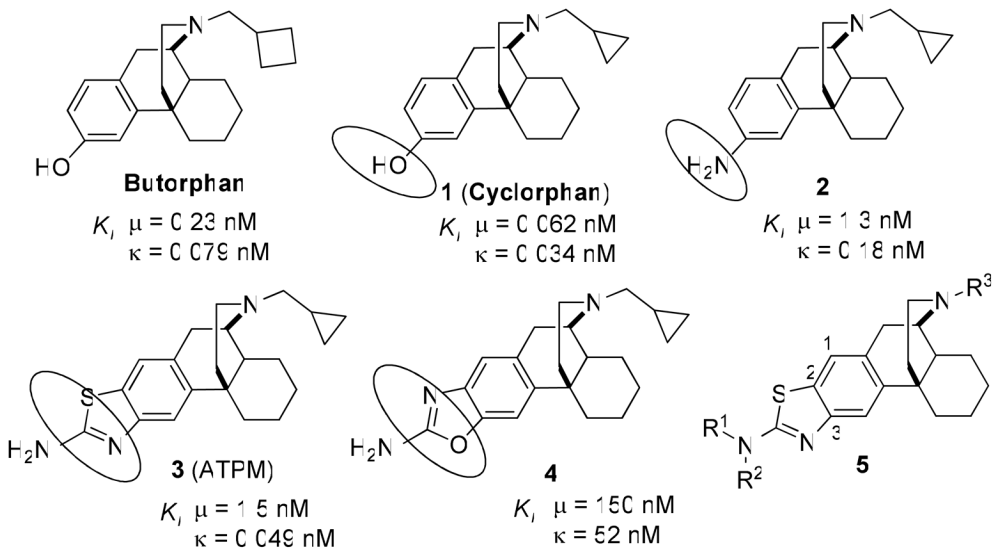
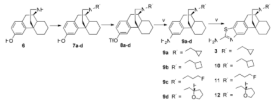
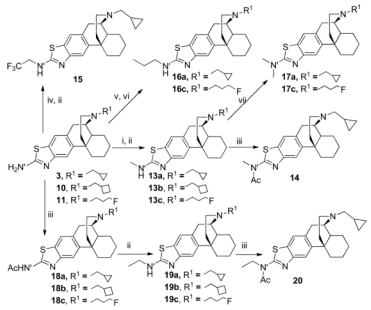


Figure 1.
Structures of opioid ligands butorphan and **1 – 5**



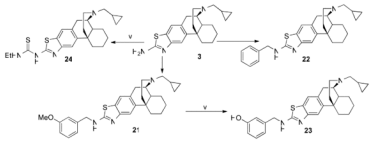
Scheme 1.

[a]reagents and conditions: (i) cyclopropylmethyl bromide, cyclobutylmethyl bromide, fluoropropyl bromide, or (−) – (s) tetrahydrofurfuryl (*R*)-camphor-10-sulfonate, K_2CO_3, DMF; (ii) $PhNTf_2$, Et_3N, CH_2Cl_2; (iii) $Ph_2C{=}NH$, BINAP, $Pd(OAc)_2$, Cs_2CO_3, THF; (iv) NaOAc, $NH_2OH.HCl$, MeOH; (v) KSCN, Br_2, AcOH.



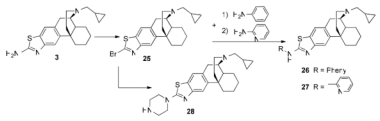
Scheme 2.

[a]reagents and conditions: (i) HCOOH, Ac_2O, THF; (ii) $LiAlH_4$, THF; (iii) Ac_2O, pyridine; (iv) $CF_3CO(O)OCCF_3$, Et_3N, toluene; (v) propionaldehyde, CH_3CN; (vi) $NaBH_4$, MeOH; (vii) (CHO)n, $NaBH_4$, TFA, THF.



Scheme 3.

[a]reagents and conditions: (i) benzaldehyde, *p*-toluenesulfonic acid, toluene; (ii) $NaBH_4$, MeOH; (iii) *m*-anisaldehyde, *p*-toluenesulfonic acid, toluene; (iv) BBr_3, CH_2Cl_2; (v) EtSCN, Et_3N, Toluene.

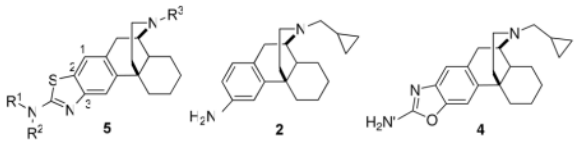


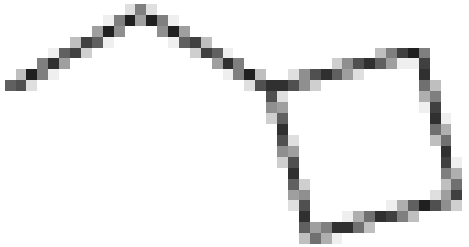
Scheme 4.

[a]reagents and conditions: (i) $CuBr_2$/*t*-Butyl nitrite, CH_3CN; (ii) NaH, THF; (iii) piperazine, NaH, THF.

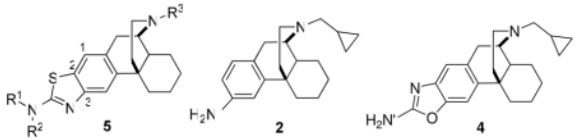
Table 1

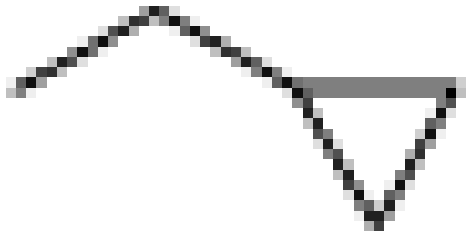
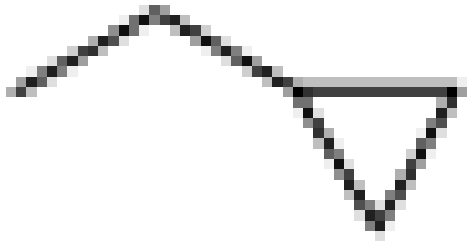
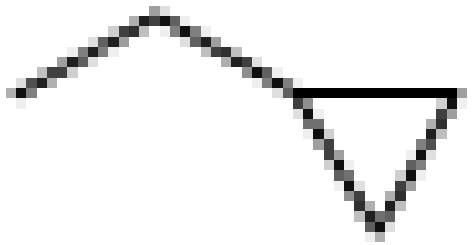
ffinities of Novel Compounds to Human κ, μ and δ Opioid Receptors[a]



	R^1	R^2	R^3	K_i (nM) ± SEM			Selectivity	
				[^{3}H]U69,593 (κ)	[^{3}H]DAMGO (μ)	[^{3}H]Naltrindole (δ)	μ/κ	σ/κ
phan)	--	--	--	0.034 ± 0.002	0.062 ± 0.003	1.9 ± 0.1	2	56
	--	--	--	0.18 ± 0.003	1.3 ± 0.029	150 ± 2.0		
)	H	H		0.049 ± 0.005	1.5 ± 0.2	29 ± 2	30	590
	--	--	--	52 ±1.0	150 ± 5.1	18% inh at 10 μM	3	>192
	H	H	CH_3	6.4 ± 0.5	1.1 ± 0.1	190 ± 10	0.17	30
M)	H	H		0.79 ± 0.02	7.1 ± 0.5	230 ± 21	9	290
	H	H		0.30 ± 0.011	2.7 ± 0.39	54 ± 1.5	9	180
	H	H		0.83 ± 0.10	2.4 ± 0.22	56 ± 7.2	3	67

J Med Chem. Author manuscript; available in PMC 2012 March 24.



			K_i (nM) ± SEM			Selectivity	
R[1]	**R[2]**	**R[3]**	**[3H]U69,593 (κ)**	**[3H]DAMGO (μ)**	**[3H]Naltrindole (δ)**	**μ/κ**	**σ/κ**
H	CH_3		0.066 ± 0.0037	3.0 ± 0.062	25 ± 1.5	45	380
H	CH_2CH_3		0.151 ± 0.0051	4.7 ± 0.23	43 ± 6.5	31	280
H	CH_2CF_3		0.84 ± 0.012	21 ± 0.94	180 ± 13	25	210

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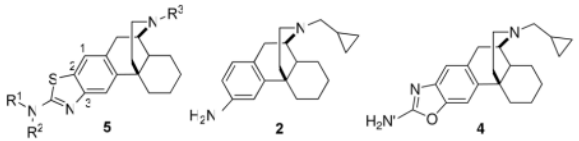
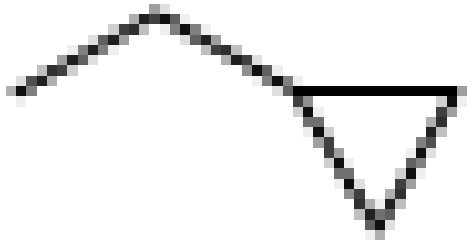
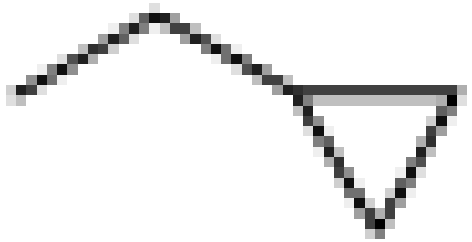


			K_i (nM) ± SEM			Selectivity	
R[1]	**R[2]**	**R[3]**	**[3H]U69,593 (κ)**	**[3H]DAMGO (μ)**	**[3H]Naltrindole (δ)**	**μ/κ**	**σ/κ**
H	$CH_2CH_2CH_3$		1.6 ± 0.096	17 ± 1.1	79 ± 3.6	11	49
H	CH_2CH_3		13 ± 1.1	57 ± 3.9	750 ± 64	4	58
H	C_6H_5		21 ± 0.20	180 ± 15	140 ± 11	9	7

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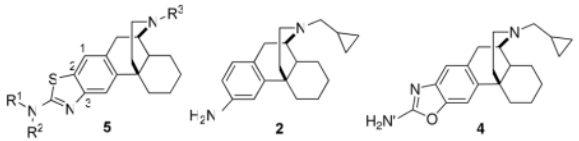
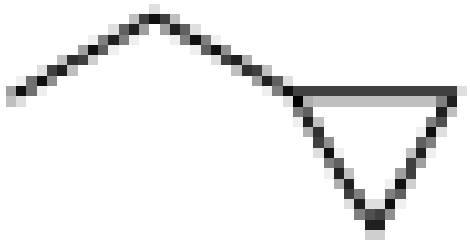
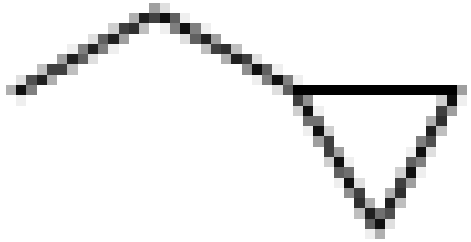


			K_i (nM) ± SEM			Selectivity	
R¹	**R²**	**R³**	**[³H]U69,593 (κ)**	**[³H]DAMGO (μ)**	**[³H]Naltrindole (δ)**	**μ/κ**	**σ/κ**
H	$C_6H_5CH_2$		2.1 ± 0.20	10 ± 1.3	41 ± 2.8	5	20
H	3-CH_3O-$C_6H_5CH_2$		4.8 ± 0.51	9.1 ± 1.2	34 ± 2.8	2	7
H	3-HO-$C_6H_5CH_2$		3.5 ± 0.085	9.9 ± 0.53	29 ± 3.4	3	8
H	C(O)NHEt		18 ± 1.6	130 ± 12	150 ± 13	7	8

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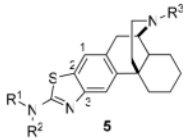
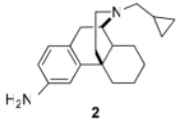
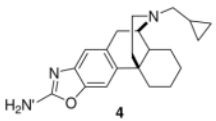
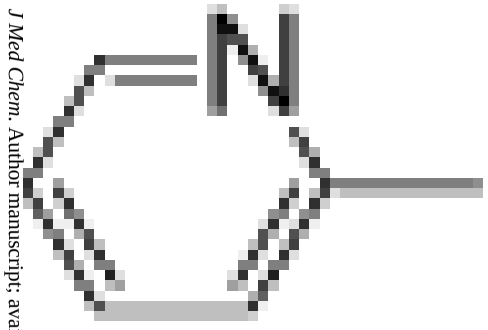
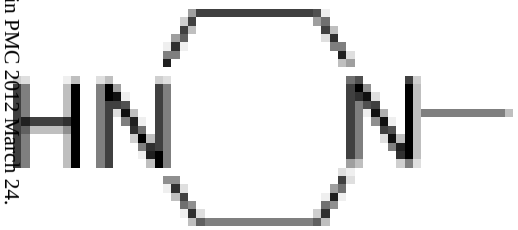
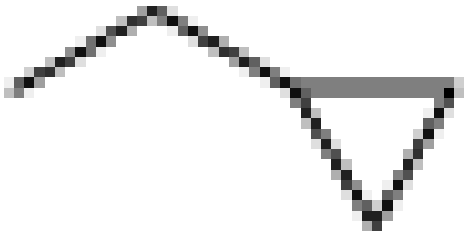
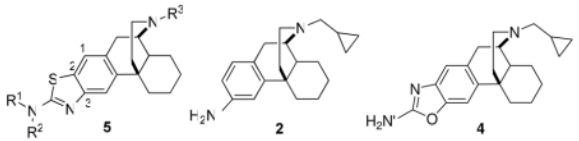
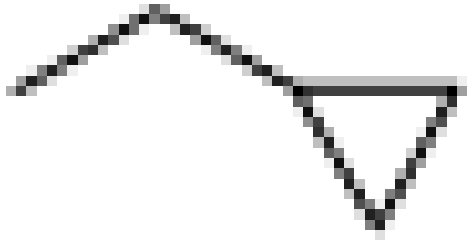
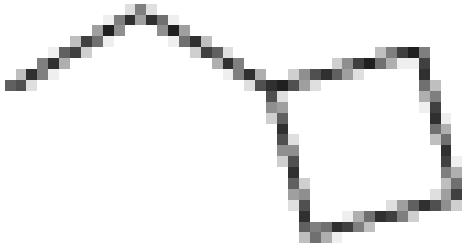


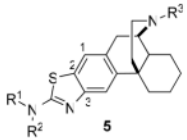


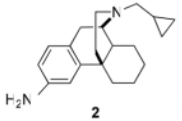


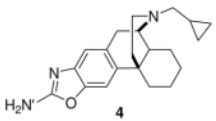
			K_i (nM) ± SEM			Selectivity	
R¹	**R²**	**R³**	**[³H]U69,593 (κ)**	**[³H]DAMGO (μ)**	**[³H]Naltrindole (δ)**	**μ/κ**	**σ/κ**
H			95 ± 9.7	610 ± 56	> 10 μM	6	>110
H			110 ± 16	2700 ± 320	> 10 μM	25	>91

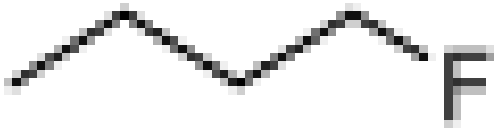


			K_i (nM) ± SEM			Selectivity	
R¹	**R²**	**R³**	**[³H]U69,593 (κ)**	**[³H]DAMGO (μ)**	**[³H]Naltrindole (δ)**	**μ/κ**	**σ/κ**
CH_3	CH_3		0.45 ± 0.065	10 ± 1.0	65 ± 1.0	22	140
CH_3	CH_2CH_3		6.9 ± 1.0	110 ± 5.3	1100 ± 66	16	160
CH_2CH_3	CH_2CH_3		13 ± 1.6	86 ± 5.1	740 ± 51	4	57
H	CH_3		2.4 ± 0.10	1.8 ± 0.029	47 ± 3.9	1	20
H	CH_2CH_3		3.7 ± 0.095	1.1 ± 0.15	91 ± 4.4	0.3	25
H	CH_3		0.71 ± 0.077	7.4 ± 0.93	50 ± 6.3	10	70
H	$COCH_3$		1.2 ± 0.11	15 ± 1.4	220 ± 16	13	180
H	CH_2CH_3		0.94 ± 0.13	4.0 ± 0.33	76 ± 6.8	4	81
H	$CH_2CH_2CH_3$		5.8 ± 0.71	24 ± 2.9	120 ± 17	4	21







			K_i (nM) ± SEM			Selectivity	
R[1]	**R[2]**	**R[3]**	**[3H]U69,593 (κ)**	**[3H]DAMGO (μ)**	**[3H]Naltrindole (δ)**	**μ/κ**	**σ/κ**
CH_3	CH_3		11 ± 1.4	76 ± 4.1	420 ± 22	7	38

rom Chinese hamster ovary cells, expressing either the human κ, μ, or δ opioid receptors, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific
25 °C, in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Nonspecific binding was determined using 10 μM naloxone.

mean values ± SEM from three experiments, performed in triplicate. Data for **1**, **2**, **3**, **4**, and **29** were obtained from the literature.[5c, 10c, 11]

Table 2

Pharmacological properties of compounds in stimulating [^{35}S]GTPγS binding mediated by the κ opioid receptor [a]

compound	E_{max} ± SEM (% maximal stimulation)	EC_{50} ± SEM nM)
(−)-U50,488	110 ± 2.0	46 ± 16
1[b] **(Cyclorphan)**	90 ±10	0.2 ± 0.0
3[b] **(ATPM)**	80 ± 6	2.4 ± 0.6
10[b] **(ATBM)**	80 ± 1	29 ± 4
11	100 ± 4.8	32 ± 5.5
12	190 ± 21	14 ± 1.5
13a	82 ± 10	14 ± 3.1
13c	170 ± 6.3	120 ± 6.7
15	120 ± 0.33	120 ± 16
17a	110 ± 14	46 ± 8.9
19a	190 ± 6.4	22 ± 5.1
19c	150 ± 3.9	89 ± 8.0

[a] Membranes from CHO cells that stably expressed the human κ opioid receptor were incubated with varying concentrations of the compounds in the presence of 0.08 nM [^{35}S]GTPγS. Data are the mean values ± SEM from three experiment, performed in triplicate. None of the compounds inhibited U50,488-stimulated [^{35}S]GTPγS binding, indicating that the compounds were agonists devoid of any antagonist properties at the κ opioid receptor.

[b] See Ref. 5c,10c.

Table 3

Agonist and antagonist properties of compounds in stimulating [^{35}S]GTPγS binding mediated by the μ opioid receptor[a]

compound	pharmacological properties	E_{max} (% maximal stimulation)	EC_{50} (nM)	I_{max} (% maximal inhibition)	IC_{50} (nM)
DAMGO	Agonist	120 ± 12	110 ± 9.0	NI[a]	NI
1[b] **(Cyclorphan)**	Partial agonist	40 ± 2.9	0.8 ± 0.1	50 ± 1.2	1.7 ± 0.40
3[b] **(ATPM)**	Agonist	45 ± 4	73 ± 5	NI	NI
10[b] **(ATBM)**	Partial agonist	26 ± 1	> 1 μM	29 ± 7.4	85 ± 5.8
11	Partial agonist	65 ± 1.4	130 ± 11	40 ± 1.4% inhibition at 10 μM	NA
12	Agonist	120 ± 15	71 ± 4.2	NI	NI
13a	Agonist	40 ± 0.87	47 ± 9.0	NI	NI
13c	Agonist	100 ± 5.3	420 ± 17	NI	NI
17a	Partial agonist	57 ± 4.7	140 ± 6.5	40 ± 0.73% inhibition at 10 μM	NA
19a	Agonist	83 ± 2.5	29 ± 4.6	NI	NI
19c	Agonist	97 ± 2.9	240 ± 12	NI	NI

[a]Membranes from CHO cells that stably expressed only the μ opioid receptor were incubated with varying concentrations of the compounds in the presence of 0.08 nM [^{35}S]GTPγS. Data are the mean values ± SEM from three experiment, performed in triplicate. NI = no inhibition; NA = not applicable; no value could be determined because a maximal inhibition of binding was not obtained.

[b]See Ref. 5c,10c.