2-Aminothiazole-Derived Opioids. Bioisosteric Replacement of Phenols

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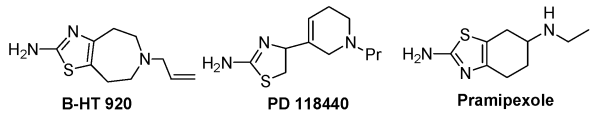
Abstract: A series of aminothiazole-derived morphinans, benzomorphans, and morphine were synthesized. Although their affinities were somewhat lower than their phenol prototypes, one compound (**9a**, ATPM) has been identified possessing high affinity and selectivity at the κ receptor. Functional assays showed that **9a** was a full κ but partial μ agonist; the efficacy at κ was significantly greater than at μ receptors. This novel compound may be valuable for the development of long-acting analgesics and drug abuse medication.

It is generally accepted that two sites, the basic nitrogen and the phenol moiety, are necessary for narcotic analgesic binding to its receptors.[1,2] The phenolic hydroxyl group is recognized as a requisite for the formation of a hydrogen bond with a dipolar site on the receptor and for good antinociceptive activity.[2,3] However, the free hydroxyl group is also a potential site for metabolism, conjugation, and excretion resulting in low oral bioavailability and short duration of action.[4,5] One of the approaches to improve the pharmacological properties of analgesics such as morphine and morphinan analogues is to modify this phenolic hydroxyl function. Recently, we have synthesized and identified several potent compounds by replacing the hydroxyl moiety of morphinans with other functional groups (amino, carboxamido, etc).[6] In the current communication, we investigated the replacement of the phenolic hydroxyl moiety by a heterocyclic bioisostere: 2-aminothiazole. The rationale for this approach was strengthened by the fact that the 2-aminothiazole functionality has been successfully applied as a heterocyclic bioisostere of the phenol moiety in dopamine agonists such as B-HT 920,[7] PD 118440,[8] and the widely used antiparkinsonian agent pramipexole[9−11] (Chart 1). These medications resulted in improved pharmacological properties including longer duration of action and better bioavailability. Although the 2-aminothiazole moiety, strictly speaking, cannot be considered as a bioisosteric replacement[12] of the phenol group, it can be viewed as an extension of the aromatic functionality of the molecule. The 2-amino group may effectively substitute the phenolic hydroxyl group to form a presumed hydrogen bond on its receptor binding site, which may result in improved pharmacological properties.

Chart 1



In our earlier report,[13] we synthesized two aminothiazole-derived morphinans **4** and **5** from commercially available levorphanol **1**, which was first triflated and then subjected to reduction followed by nitration (Scheme 1). The resulting two nitrated isomers (**2** and **3**) were separated and reduced to their corresponding amines followed by cyclization, which occurred selectively and produced the aminothiazole products **4** and **5**, respectively. However, the isolation of the nitro intermediates **2** and **3** was cumbersome and resulted in low yields that limited the application of this procedure to the synthesis of other aminothiazolomorphinans. Alternatively, a Pd-catalyzed amination approach was used in our current synthesis.[6a,14] Thus, the phenolic opioids including morphinans **6a** (cyclorphan), **6b**, and **6c** and benzomorphans **6d** and **6e** were employed as the substrates (Scheme 2). After triflation of phenols **6a**−**e**, the corresponding triflates **7a**−**e** were subjected to palladium-catalyzed amination yielding the amines **8a**−**e** in moderate yield. Upon cyclization of **8a**−**e** by a reported procedure,[13] the aminothiazoles **9a**−**e** were obtained in moderate yields. A similar strategy was used to prepare the aminothiazole-derived morphine **14** (Scheme 3). First, the phenolic hydroxyl function of morphine was selectively triflated followed by protection of the 6-hydroxyl group with a *tert*-butyldiphenylsilyl moiety (TBDPS). The resulting triflate **11** was subjected to the same amination procedure described above to yield the TBDPS-protected 3-aminomorphine **12**,[15] which was followed by the formation of aminothiazole ring to yield **13**. After deprotection of 6-hydroxyl group in **13** with tetrabutylammonium fluoride (TBAF), aminothiazole-derived morphine **14** was obtained in 62% yield.

All new compounds including **4**, **5**, **9a**−**e**, and **14** were evaluated for their binding affinity at all three opioid receptors (μ, κ, and δ) (Table 1) using a previously reported procedure.[6,16] For comparison purposes, opioid binding affinity data for the phenol precursors including **1**[16] (levorphanol), **6a**[6a] (cyclorphan) and its *N*-cyclobutylmethyl analogue **6b**,[6a] ketomorphinan **6c**,[6a] benzomorphan **6d**,[15] and morphine[15] were also included.

From the data shown in Table 1, the binding affinities of the 2-aminothiazole-derived opioids were generally lower than the binding affinities of the phenol precursors, but the selectivity for κ over μ and δ receptors was improved. A difference was observed between the regioisomers **4** and **5**. Compared to the phenol **1**, the 2,3-fused isomer **4** displayed only slightly lower affinity (3- to 5-fold) at κ and μ receptors, while a remarkable decrease (14- to 60-fold) in affinity was observed in the 1,2-fused isomer **5**, and the selectivity of μ over κ receptors was reversed. It is noteworthy that aminothiazole **9a** (ATPM), which is derived from the κ agonist cyclorphan **6a**, retained the same high affinity (K_i = 0.049 nM) at the κ receptor, although a decrease

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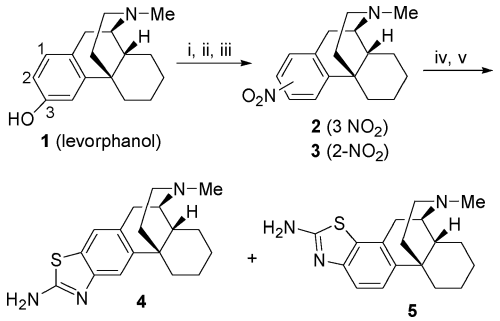
Table 1. K_i Values Inhibition of δ, κ, and μ Opioid Binding to Chinese Hamster Ovary Membranes by Novel Compounds[a]

	$K_i \pm$ SEM (nM)			selectivity	
compd	[^{3}H]DAMGO (μ)	[^{3}H]naltrindole (δ)	[^{3}H]U69,593 (κ)	μ:κ	δ:κ
1 (levorphanol)	0.21 ± 0.02	4.2 ± 2.3	2.3 ± 0.3	0.09	2
6a (cyclorphan)	0.062 ±0.003	1.9 ± 0.1	0.034 ± 0.002	2	60
6b (MCL-101)	0.23 ± 0.01	5.9 ± 0.6	0.079 ± 0.003	3	70
6c	3.3 ± 0.4	260 ± 55	0.48 ± 0.03	7	540
6d	0.32 ± 0.02	1.1 ± 0.0	0.18 ± 0.02	1.8	6.1
morphine	0.88 ± 0.14	140 ± 18	24 ± 2	0.04	5.8
5 (MCL-186)	130 ± 6	1100 ± 30	29 ± 1	4.5	38
4 (MCL-187)	1.1 ± 0.1	190 ± 10	6.4 ± 0.5	0.17	30
9a (ATPM)	1.5 ± 0.2	29 ± 2	0.049 ± 0.005	30	590
9b (ATBM)	7.1 ± 0.5	230 ± 21	0.79 ± 0.02	9.0	290
9c (MCL-168)	200 ± 43	>10 μM	13 ± 2	15	>770
9d (MCL-185)	48 ± 6	940 ± 19	6.7 ± 0.3	7.1	140
9e (MCL-184)	8.3 ± 0.2	93 ± 10	0.49 ± 0.03	17	190
14 (MCL-188)	30 ± 3	32 ± 3	220 ± 10	0.13	0.14

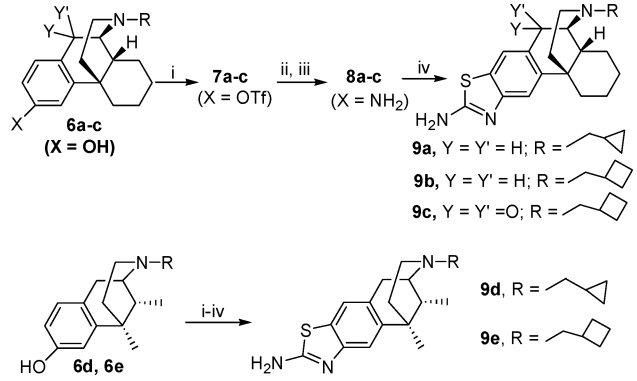
[a] Chinese hamster ovary membranes, 0.5 mg of protein/sample, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific radioligands at 25 °C, in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Nonspecific binding was determined using 10 μM naloxone. Data are the mean values ± SEM from three experiments, performed in triplicate. Data for **1** (levorphanol), **6a** (cyclorphan), **6b** (MCL-101), **6c**, **6d**, and morphine were obtained from the literature.[6a,15,16]

Scheme 1[a]



[a] Reagents and conditions: (i) $PhNTf_2$, Et_3N, CH_2Cl_2; (ii) Pd/C (10%), HCO_2NH_4; (iii) HNO_3, H_2SO_4, CH_3NO_2; (iv) Pd/C (10%), HCO_2NH_4; (v) KSCN, Br_2, AcOH.

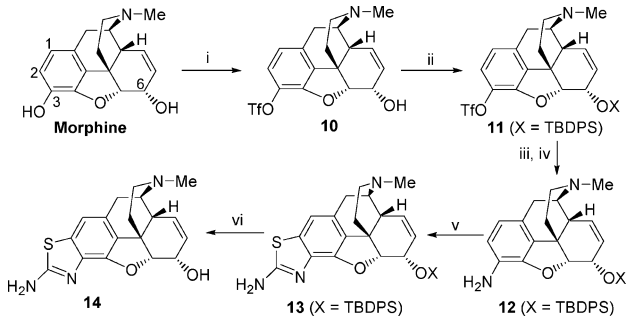
Scheme 2[a]



[a] Reagents and conditions: (i) $PhNTf_2$, Et_3N, CH_2Cl_2; (ii) $Ph_2C{=}NH$, BINAP, $Pd(OAc)_2$, Cs_2CO_3; (iii) NaOAc, $NH_2OH.HCl$; (iv) KSCN, Br_2, AcOH.

of 2.5-fold at μ and 15-fold at δ was observed. This resulted in a high selectivity for κ over μ (30-fold) and δ (590-fold) receptors. The cyclobutylmethyl analogue **9b** (ATBM), compared to the phenol **6b**, showed a 30- to 40-fold decrease in affinity at μ and δ but only 10-fold decrease at the κ receptor, which also displayed a good selectivity for κ versus μ and δ receptors. A pronounced decrease in affinity at all three receptors was observed in the aminothiazole-derived ketomorphinan **9c**. Similarly, an appreciable decrease in affinity (37- to 850-fold) was also observed in **9d**, which was derived from the benzomorphan **6d**. It is noteworthy that the cyclobutylmethyl analogue **9e** displayed higher affinity than the cyclopropylmethyl analogue **9d** at all three opioid receptors, especially at the κ receptor. The morphine derived aminothiazole **14** displayed a decrease of 34-fold at μ, 9-fold at κ, but a 4-fold increase at δ receptors. Compared to the high affinity and selectivity of morphine at the μ receptor, **14** was equipotent at μ and δ and 7-fold higher than at κ receptors. [^{35}S]GTPγS binding studies showed that **9a**, similar to phenol **6a**, was a full κ but partial μ agonist. It produced greater stimulation at κ than at μ receptors. Compared to the phenol **6b**, the cyclobutylmethyl analogue **9b** was a κ agonist with a very weak agonist activity at the μ receptor (Table 2).

Scheme 3[a]



[a] Reagents and conditions: (i) $PhNTf_2$, Et_3N; (ii) TBDSCl, imidazole, THF; (iii) $Pd(OAc)_2$, BINAP, $Ph_2C{=}NH$, Cs_2CO_3; (iv) NaOAc, $NH_2OH.HCl$; (v) KSCN, Br_2, AcOH; (vi) TBAF, THF.

In summary, a series of aminothiazole-derived morphinans, benzomorphans, and morphine were synthesized with a palladium-catalyzed amination as the key step. Although the affinity of this novel series was somewhat reduced from that of their phenol prototypes, one compound (**9a**) has been identified as possessing high affinity and selectivity at the κ receptor. The functional assays showed that **9a** was a full κ but partial μ agonist, and the efficacy at κ was considerably greater than at μ receptors. In view of the short duration of action of traditional narcotic analgesics and the successful application of the 2-aminothiazole functionality as a heterocyclic bioisostere of the phenol moiety in DA agonists, as well as the potential application of κ agonists as a treatment for cocaine abuse, this novel compound may be valuable for the development of long-

Table 2. E_{max} and EC_{50} Values for the Stimulation of [^{35}S]GTPγS by Novel Compounds[a]

compd	$E_{max} \pm$ SE (% stimulation)	$EC_{50} \pm$ SE (nM)
	κ Opioid Receptor	
6a[6b]	90 ± 10	0.2 ± 0.0
6b[6b]	80 ± 7	1.3 ± 0.4
9a (ATPM)	80 ± 6	2.4 ± 0.6
9b (ATBM)	80 ± 1	29 ± 4
	μ Opioid Receptor	
6a[6b]	40 ± 3	0.8 ± 0.1
6b[6b]	50 ± 2	1.6 ± 0.1
9a (ATPM)	45 ± 4	73 ± 5
9b (ATBM)	26 ± 1	>1 μM

[a] Chinese hamster ovary membranes, expressing either the κ or μ receptor, were incubated with varying concentrations of the novel compounds in the presence of 0.8 nM [^{35}S]GTPγS. Data are the mean values ± SE from three experiments, performed in triplicate.

acting analgesics and drug abuse medication. Further pharmacological evaluation is in progress.

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Supporting Information Available: Experimental details for the synthetic procedures for intermediates and final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. X-ray analytical reexamination of correlation of nitrogen lone-pair orientation with analgetic activity. *J. Med. Chem.* **1978**, *21*, 153.

(2) Portoghese, P. S. A New Concept on the Mode of Interaction of Narcotic Analgesics with Receptors. *J. Med. Chem.* **1965**, *8*, 609.

(3) Katsuura, K.; Yamaguchi, K.; Sakai, S.; Mitsuhashi, K. Thiazole Analogs of Benzomorphan. II. Synthesis of Novel Thiazolo[5,4-*f*]morphans. *Chem. Pharm. Bull.* **1983**, *31*, 1518.

(4) (a) Aldrich, J. V.; Vigil-Cruz, S. C. Narcotic Analgesics. In *Burger's Medicinal Chemistry and Drug Discovery*; Abraham, D., Ed.; John Wiley & Sons: New York, 2003. (b) Fries, D. S. Opioid Analgesics. In *Foye's Principles of Medicinal Chemistry*; Williams, D. A., Lemke, T. L., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, 2002; pp 453−479. (c) Zimmerman, D. M.; Leander, J. D. Selective Opioid Receptor Agonists and Antagonists: Research Tool and Potential Therapeutic Agent. *J. Med. Chem.* **1990**, *33*, 895.

(5) Hori, M.; Iwamura, T.; Morita, T.; Imai, E.; Oji, H.; Kataoka, T.; Shimizu, H.; Ban, M.; Nozaki, M.; Niwa, M.; Fujimura, H. Facile Synthesis of 8-Benzoylthio-2,6-methano-3-benzazocines and 3-Benzoylthiomorphinans Having Small-Ring Substituents. *Chem. Pharm. Bull.* **1989**, *37*, 2222.

(6) (a) Zhang, A.; Xiong, W.; Bidlack, J. M.; Hilbert, J. E.; Knapp, B. I.; Wentland, M. P.; Neumeyer, J. L. 10-Ketomorphinan and 3-Substituted-3-desoxymorphinan Analogues as Mixed κ and μ Opioid Ligands: Synthesis and Biological Evaluation of Their Binding Affinity at Opioid Receptors. *J. Med. Chem.* **2004**, *47*, 165. (b) Neumeyer, J. L.; Zhang, A.; Xiong, W.; Gu, X.; Hilbert, J. E.; Knapp, B. I.; Negus, S. S.; Mello, N. K.; Bidlack, J. M. Design and Synthesis of Novel Bivalent Morphinan Ligands for Opioid Receptors. *J. Med. Chem.* **2003**, *46*, 5162.

(7) Andén, N. E.; Nilsson, H.; Ros, E.; Thornström, U. Effects of B-HT 920 and B-HT 933 on Dopamine and Noradrenaline Autoreceptors in the Rat Brain. *Acta Pharmacol. Toxicol.* **1983**, *52*, 51.

(8) Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A. 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: a novel class of compounds with central dopamine agonist properties. *J. Med. Chem.* **1990**, *33*, 311.

(9) Mierau, J.; Schneider, F. J.; Ensinger, H. A.; Chio, C. L.; Lajiness, M. E.; Huff, R. M. Pramipexole Binding and Activation of Cloned and Expressed Dopamine D_2, D_3 and D_4 Receptors. *Eur. J. Pharmacol.* **1995**, *290*, 29.

(10) Schneider, C. S.; Mierau, J. Dopamine autoreceptor agonists: resolution and pharmacological activity of 2,6-diaminotetrahydrobenzothiazole and an aminothiazole analogue of apomorphine. *J. Med. Chem.* **1987**, *30*, 494.

(11) van Vliet, L. A.; Rodenhuis, N.; Wikström, H. Thiazoloindans and Thiazolobenzopyrans: A Novel Class of Orally Active Central Dopamine (Partial) Agonists. *J. Med. Chem.* **2000**, *43*, 3549.

(12) (a) Thornber, C. W. Isosterism and Molecular Modification in Drug Design. *Chem. Soc. Rev.* **1979**, *8*, 563. (b) Patani, G. A.; LaVoie, E. J. Bioisosterism: A Rational Approach in Drug Design. *Chem. Rev.* **1996**, *96*, 3147.

(13) Zhang, A.; Van Vliet, S.; Neumeyer, J. L. Synthesis of aminothiazole derived morphinans. *Tetrahedron Lett.* **2003**, *44*, 6459.

(14) (a) Hartwig, J. F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl halides and Triflates. *Tetrahedron Lett.* **1997**, *38*, 6367. (c) Wolfe, J. P.; Buchwald, S. L. Palladium-Catalyzed Amination of Aryl Triflates. *J. Org. Chem.* **1997**, *62*, 1264. (d) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *J. Org. Chem.* **1997**, *62*, 1268.

(15) Wentland, M. P.; Duan, W.; Cohen, D. J.; Bidlack, J. M. Selective Protection and Functionalization of Morphine: Synthesis and Opioid Receptor Binding Properties of 3-Amino-3-desoxymorphine Derivatives. *J. Med. Chem.* **2000**, *43*, 3558.

(16) Neumeyer, J. L.; Bidlack, J. M.; Zong, R.; Bakthavachalam, V.; Gao, P.; Cohen, D. J.; Negus, S. S.; Mello, N. K. Synthesis and Opioid Receptor Affinity of Morphinan and Benzomorphan Derivatives: Mixed κ Agonists and μ Agonists/Antagonists as Potential Pharmacotherapeutics for Cocaine Dependence. *J. Med. Chem.* **2000**, *43*, 114.

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