Letters

Discovery of Novel Triazole-Based Opioid Receptor Antagonists

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Abstract: We report the computer-aided design, chemical synthesis, and biological evaluation of a novel family of δ opioid receptor (DOR) antagonists containing a 1,2,4-triazole core structure that are structurally distinct from other known opioid receptor active ligands. Among those δ antagonists sharing this core structure, **8** exhibited strong binding affinity (K_i = 50 nM) for the DOR and appreciable selectivity for δ over μ and κ opioid receptors (δ/μ = 80; δ/κ > 200).

Opioid analgesics are the mainstay for treatment of moderate to severe pain. Research on opioids and their receptors has remained active over the past decade.[1] Three opioid receptor subtypes, designated as δ, κ, and μ, have been identified in the central nervous system (CNS) and periphery[2,3] and are products of three distinct and extensively studied genes. Recent evidence suggests that subtype-selective opioid receptor agonists and antagonists offer great potential as therapeutic agents devoid of the numerous adverse side effects (e.g., respiratory depression, physical dependence, and gastrointestinal effects) associated with morphine.[4] In particular, δ-selective antagonists have been shown to modulate the development of tolerance[5,6] and dependence on μ agonists such as morphine,[7] to offset the behavioral effects of drugs of abuse such as cocaine,[8] and to elicit favorable immunomodulatory[9] and emotional effects.[10] On the other hand, δ-selective agonists have been shown to elicit the prototypical analgesic effects of clinically available opioids.[4] They may also provide unique benefits as cardioprotective and neuroprotective agents[11] and as treatments for depression and anxiety.[12,13]

In view of their broad range of pharmacological applications, the δ-selective opioids have attracted interest in our laboratory and elsewhere. Given the paucity of high-quality X-ray crystal structure data for GPCRs such as the opioid receptor, our drug design strategy has relied on ligand-based molecular modeling approaches. An additional component of our drug discovery paradigm is the proprietary Shape Signatures computational tool that provides unique capabilities for scaffold hopping in the search for new lead compounds.[14,15]

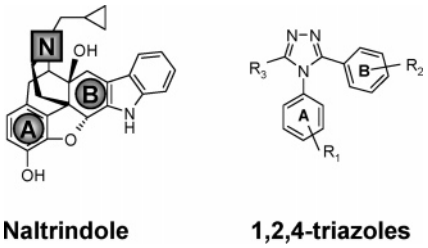

Figure 1. Comparison of the structures of naltrindole and the present 1,2,4-triazoles.

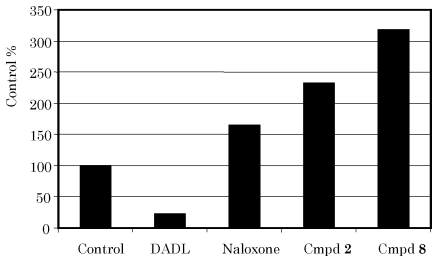

Figure 2. Up-regulation results of compounds **2** and **8**.

A three-point pharmacophore was extracted by overlaying a series of high-affinity opioid receptor ligands including the δ-antagonist naltrindole.[16] This pharmacophore model (Figure 1, gray) comprised the basic nitrogen atom, the centroid of the phenol ring (A), and the centroid of the hydrophobic ring (B). Virtual screening of an in-house database of ~1.2 million commercially available small-molecule chemicals was conducted to identify structures matching this three-point pharmacophore. Additional molecular models were developed for a distinct series of DOR-selective agonists[17] and antagonists[18] to demonstrate the structural requirement for δ selectivity. Promising chemical entities were then subjected to filters using an expanded Lipinski rule of five[19] hierarchical scheme. The substituted 1,2,4-triazoles (Figure 1) emerged from this scheme as an interesting core structural framework for our DOR active agents. In selecting appropriate substitution patterns for the 1,2,4-triazole ring to confer δ binding affinity and selectivity, we exploited the "message−address" concept[20,21] associated with classical morphine-like opioids. For instance, a sterically bulky group (e.g., *tert*-butyl) was attached to the B aryl group to mimic the δ "address" in our 1,2,4-triazoles. Several di- and trisubstituted 1,2,4-triazoles (Table 1) were selected for chemical synthesis and biological evaluation. Structural alignment of naltrindole and **8** in the conformation adopted in its X-ray crystal structure reveals good overlap between the *tert*-butyl group of **8** and the δ "address" of naltrindole (Figure 2, Supporting Information).

Three separate reaction schemes were developed for the synthesis of the 1,2,4-triazoles (Scheme 1) with thioamides as key intermediates. In most cases, thioamides were synthesized from the corresponding amides.[22,23] For **1**, **2**, **10**, and **16**, a coupling reaction of arylmagnesium reagents with isothiocyanates was conducted to synthesize the thioamides.[24,25] Amidrazones could be efficiently prepared by reaction of thioamides

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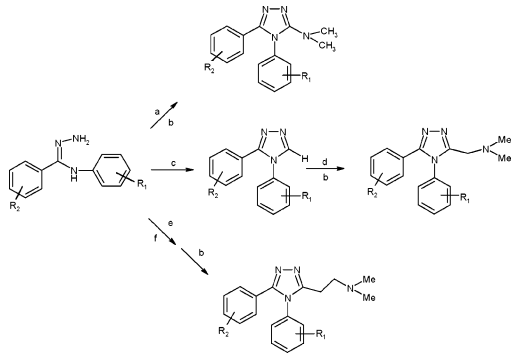
Table 1. Structures and Opioid Receptor Binding Affinities for Substituted 1,2,4-Triazoles

				% inhibition[a]			K_i (nM)[b]			selectivity ratio	
compd	R_1	R_2	R_3	δ	μ	κ	δ	μ	κ	δ/μ	δ/κ
1	3-OCH_3	3-*tert*-butyl	H	31	11	5	>10000	>10000	>10000	na	
2	3-OH	3-*tert*-butyl	H	91	78	66	230	850	1500	3.70	6.52
3	3-OCH_3	4-*tert*-butyl	H	8	9	8	>10000	>10000	>10000	na	
4	3-OH	4-*tert*-butyl	H	54	16	16	~10000	>10000	>10000	na	
5	3-OH	3-phenyl	H	84	84	42	140	1000	>10000	7.14	>71.4
6	3-OH	4-phenyl	H	75	60	46	1500	>10000	>10000	>6.66	>6.66
7	3-OH	3,4-(CH=CH)$_2$	H	68	48	27	2100	>10000	>10000	>4.76	>4.76
8	3-OH	4-*tert*-butyl	$N(CH_3)_2$	94	32	6	50	4000	>10000	80	>200
9	3-OCH_3	4-*tert*-butyl	$N(CH_3)_2$	28	50	3	>10000	>10000	>10000	na	
10	3-OH	3-*tert*-butyl	$N(CH_3)_2$	76	19	6	1050	>10000	>10000	>9.5	>9.5
11	3-OH	3-phenyl	$N(CH_3)_2$	86	23	8	150	>10000	>10000	>66.6	>66.6
12	3-OH	4-phenyl	$N(CH_3)_2$	82	15	11	130	>10000	>10000	>76.9	>76.9
13	3-OH	3,4-(CH=CH)$_2$	$N(CH_3)_2$	68	48	27	480	>10000	>10000	>20.8	>20.8
14	4-OH	4-*tert*-butyl	$N(CH_3)_2$	27	8	21	>10000	>10000	>10000	na	
15	3-OH	4-*tert*-butyl	$N(CH_2CH_2)_2NCH_3$	18	5	12	>10000	>10000	>10000	na	
16	3-OH	3-*tert*-butyl	$CH_2N(CH_3)_2$	65	27	10	2600	>10000	>10000	>3.86	>3.86
17	3-OH	4-*tert*-butyl	$CH_2N(CH_3)_2$	88	20	9	460	>10000	>10000	>21.6	>21.6
18	3-OH	4-*tert*-butyl	$(CH_2)_2N(CH_3)_2$	90	23	19	900	>10000	>10000	>11.1	>11.1

[a] Compounds, initially screened at 10 μM, are expressed as percentage inhibition of the reference compound which is normalized to 100%. (−)-[9-3*H*]bremazocine was used as the radiolabeled ligand. [b] Inhibitory effect to (−)-[9-3*H*]bremazocine on membranes isolated from HEK 293 cells stably transfected with mouse (δ and μ) or rat (κ) opioid receptors. K_i values are the average of two to three independent experiments.

Scheme 1. General Synthesis of Substituted 1,2,4-Triazoles[a]



[a] See Table 1 for examples of R1, R2, and R3. (a) Viehe's salts, DCM, room temp, 5 h; (b) BBr3, DCM, room temp, 3 h; (c) trimethyl orthoformate, HOAc/DMF, room temp, 3 h; (d) Eschenmoser's salt, DMF, 80 °C, 8 h; (e) *N*,*N*-dimethylaminopropionic acid hydrochloride, DCC, toluene, room temp; (f) reflux, 8 h.

with excess hydrazine at room temperature. Cyclization of amidrazones with different reagents led to products with methoxyl groups at the R_2 positions. **1**−**7** were obtained using trimethyl orthoformate as the cyclization reagent,[26] while **8**−**15** involved cyclization of amidrazones with phosgeninium salts (Viehe's salts), which were easily synthesized from the corresponding amines.[27] Compounds **16** and **17** were synthesized from **1** and **3**, respectively, through reaction with Eschenmoser's salt.[28,29] Compound **18** was prepared directly by condensation of amidrazone with 3-*N*,*N*-dimethylaminopropionic acid hydrochloride in the presence of dicyclohexyldiimide (DCC) (Scheme 1). For most of the products, the final step of cleaving methoxyl groups at R_2 was completed easily by reaction with BBr_3 in dichloromethane. Where hydrolysis of the methoxyl group was incomplete using the above BBr_3 procedure, excess NaSH was added to achieve ether cleavage in acceptable yields.

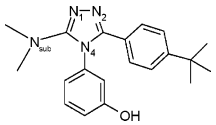
Initially, **1**−**4** were synthesized to evaluate the feasibility of our approach (Table 1). Radioligand binding assays revealed that **2** binds to all three opioid receptors with K_i values of 230 (δ), 850 (μ), and 1500 (κ) nM, respectively. As anticipated, it exhibited some subtype selectivity for the δ over μ and κ opioid receptors. Structural analogues (**5**−**18**) were synthesized in order to increase the δ binding affinity and selectivity (Table 1). Several of the subject compounds (e.g., **5**, **8**, **11**, **12**) exhibited selectivity for the δ over μ and κ opioid receptors, which concurs with our initial design strategy to confer δ selectivity. The inhibitory activity was much greater at all three opioid receptors for compounds with R_1 = OH (**2** and **4**) compared with R_1 = OCH_3 (**1** and **3**). In fact, the latter compounds showed very limited inhibitory activity for any of the opioid receptors even at 10 μM. Comparison of **8** and **14** indicates that the binding affinity for all three opioid receptor subtypes was virtually abolished when the hydroxyl substituent at R_1 is moved from the meta to para position on the aromatic ring. Although this single example precludes making generalizations, the strong preference for the meta over para phenolic moiety is consistent with the familiar SAR of morphine-like opioids.[30−33]

For **1**−**7**, R_2 substitutions were preferred at the meta position over the para position (e.g., $K_i(\delta)$ = 230 nM for **2** vs ~10 000 nM for **4**). For compounds with R_3 substitutions, namely **8**−**17**, the opposite trend was observed in cases exhibiting an appreciable affinity difference (see **8** vs **10**). Compound **8** ($K_i(\delta)$ = 50 nM), with R_2 = *p*-*tert*-butyl and R_3 = $N(CH_3)_2$, yielded the best results overall among this first generation of triazole-based opioid receptor active agents in terms of δ binding affinity and subtype selectivity. It is worth noting that introduction of groups more highly constrained than *tert*-butyl at R_2 failed to increase binding affinity for the δ receptor. For example, the δ binding affinity was poorer for **11**, **12** and **13** (K_i = 150, 130, and 480 nM, respectively) than for **8** (K_i = 50 nM).

The functional activity of our substituted 1,2,4-triazoles on the opioid receptors was determined by receptor up-regulation assays. Incubation of the δ opioid receptor with **2** and **8** produced a sharp increase in receptor expression, suggesting that the subject compounds are δ opioid antagonists (Figure 2). Interestingly, **8** exhibited >3-fold up-regulation of the δ opioid receptor in this assay. The pharmacological significance of this observation is currently under investigation in our laboratory.

In fact, a *N*,*N*-dimethylamino group at R_3 did produce a sharp increase in binding affinity to the δ receptor. Compare, for example, the $K_i(\delta)$ of **8** (50 nM, R_3 = $N(CH_3)_2$) with its simple homologue **4** (~10 000 nM, R_3 = H). One might reasonably attribute the greater activity of **8** over **4** to the strong basicity

Table 2. Relative Energies of Protonation[a] Obtained from HF/6-31G** ab Initio Calculations on Compound **8** Assuming Vacuum and Aqueous Conditions



protonation site	vacuum[a]	aqueous[a]
N_1	1.07	0.00
N_2	0.00	0.25
N_4	56.85	53.28
N_{sub}	25.29	13.30

[a] In units of kcal/mol.

of the N atom at R_3. Nevertheless, **8** is only slightly more basic than **4** (pK_a(pred) = 3.36 vs 2.18).[17] Ab initio quantum mechanical calculations on **8** at the HF/6-31G** level of theory, in vacuum and aqueous (implicit solvation) conditions, indicated that the most basic atom is not the N in $R_3 = N(CH_3)_2$ (i.e., N_{sub}) but rather N_1 or N_2 in the triazole ring (Table 2). Among the four N atoms in **8**, the rank of basicity is $N_1 \sim N_2 > N_{sub} > N_4$. These results suggest that N_{sub} is less basic than the triazole-ring atoms N_1 and N_2, although it should be restated that all of the N atoms in **8** are weakly basic. It is evident that the basicity of the $N(CH_3)_2$ group is mitigated by its strong conjugation with the triazole ring. One might suspect that disrupting this conjugation by extension of the substituent group would afford a basic N atom and thereby enhance binding affinity. However, **17** ($R_3 = CH_2N(CH_3)_2$) and **18** ($R_3 = (CH_2)_2N(CH_3)_2$) showed >6-fold decrease in binding affinity to the DOR compared with **8**.

In conclusion, we report here a novel family of δ-selective opioid receptor antagonists containing the 1,2,4-triazole core structure. The subject compounds are chemically and structurally distinct from the classical opioids such as morphine and other known small-molecule opioids (e.g., (+)-4-[(α)*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC80)). Moreover, these compounds are synthetically accessible as pure compounds in high yield and, uncommon among opioids, lack chiral centers. Compound **8**, the most active among this first generation of substituted 1,2,4-triazoles, exhibited strong binding affinity (K_i = 50 nM) and appreciable selectivity (selectivity ratio: $\delta/\mu = 80$; $\delta/\kappa > 200$) for the δ opioid receptor. The weak basicity of **8** (pK_a(pred) = 3.36) favors the neutral (unprotonated) form under physiological conditions (pH 7.4). Virtually all known opioids, whether agonists or antagonists, contain at least one basic N atom. The only exception to our knowledge is the κ agonist salvinorin A, a natural compound extracted from *S. divinorum*,[34] and a series of cyclic peptides reported by Schiller et al.[35] that act as δ and μ receptor antagonists. The present compounds thus represent the first nonpeptidic δ-selective opioid antagonists lacking a basic N atom.

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Supporting Information Available: Experimental procedures for the synthesis of all new compounds, details on the molecular modeling and in vitro assays, and the X-ray crystal structure of **8** together with the crystallographic structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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