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Design, synthesis and biological evaluation of N-hydroxy- aminobenzyloxyarylamide analogues as novel selective κ opioid receptor antagonists

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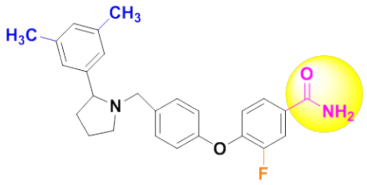
Graphical abstract



The selectivity of (±)**LY2456302** for KOR

μ K_i = 93.7±8.1 nM

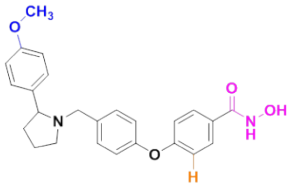
κ K_i = 14.0±0.7 nM

δ K_i = 105.2±5.6 nM

μ/κ = 6.7

δ/κ = 7.5

In binding affinities K_i values



Compound **1c** is a most selectivity for KOR

μ K_i = 2311±43.5 nM

κ K_i = 179.9±6.7 nM

δ K_i > 10000 nM

μ/κ = 12.8

δ/κ > 55.5

Design, synthesis and biological evaluation of *N*-hydroxy-aminobenzyloxyarylamide analogues as novel selective *κ* opioid receptor antagonists

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Abstract:

Aminobenzyloxyarylamide derivatives **1a-i** and **2a-t** were designed and synthesized as novel selective *κ* opioid receptor (KOR) antagonists. The benzoyl amide moiety of LY2456302 was changed into *N*-hydroxybenzamide and benzisoxazole-3(2*H*)-one to investigate whether it could increase the binding affinity or selectivity for KOR. All target compounds were evaluated in radioligand binding assays for opioid receptor binding affinity. These efforts led to the identification of compound **1c** (*κ* K_i = 179.9 nM), which exhibited high affinity for KOR. Moreover, the selectivity of KOR over MOR and DOR increased nearly 2-fold and 7-fold, respectively, compared with (±)LY2456302.

Keywords: *κ* opioid receptor; LY2456302; *N*-hydroxy-aminobenzyloxyarylamide antagonists; Novel; Selective

Depression has become a threat to human diminishing people's living standard [1-2]. The pathogenesis of depression is complicated, leading to a lack of effective drugs. Opioid receptors, a family of G-protein coupled receptors (GPCRs) comprising kappa (KOR or *κ*), mu (MOR or *μ*), delta ((DOR or *δ*), and opioid-like (ORL-1) receptors, play an important role in multiple physiological activities, including pain management, reward mechanisms, gastrointestinal (GI) motility, hormone release, and eating behavior [3-5]. Numerous studies have demonstrated that activation of KOR leads to depression and cocaine relapse, so blocking KOR activation may be effective in treating depression and drug abuse [6-7].

Over the past few decades, increasing efforts have been made to develop KOR antagonists for the treatment of depression. KOR antagonists such as norBNI, JDTic, PF-04455242 and LY2456302 have showed anxiolytic and anti-depressant-like

activity in clinical studies (**Fig. 1**) [8-12]. Among them, LY2456302 is a short-acting, high-affinity selective KOR antagonist, which is currently in phase II trial for the treatment of major depressive disorder [13-17]. However, the selectivity of LY2456302 between KOR and MOR receptors is not good [18-21], which may produce neither reliable antidepressant- nor anxiolytic-like effects in treatment. Thus, developing selective KOR antagonist is a promising strategy to treat depression.

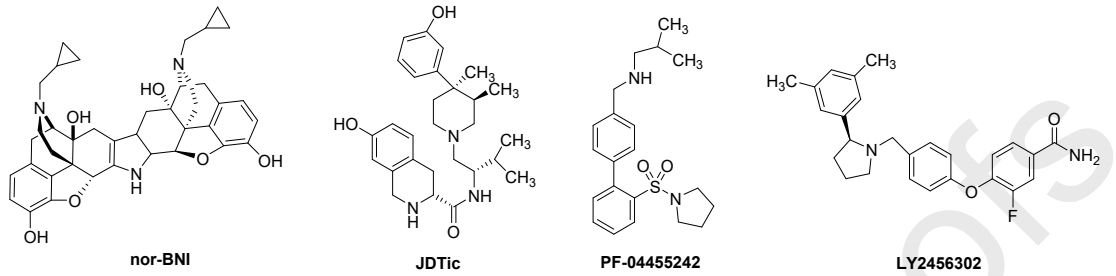


Fig. 1 Structures of representative KOR antagonists

In our previous work [22], a series of aminobenzyloxyarylamide derivatives were designed, synthesized and evaluated as κ opioid receptor antagonists based on the structural modification of LY2456302. We studied the effects on activity brought about by different substituents on both ring A and ring B and obtained one potent and selective candidate compound [22]. In this work, we continue to explore the chemical space of LY2456302 in the hope to identify more potent KOR antagonists with better selectivity profile. As shown in Fig 2, we mainly focus on the modification of its terminal amide moiety. The benzamide moiety of LY2456302 was switched to *N*-hydroxybenzamide and benzisoxazole-3(*2H*)-one bioisosterically, maintaining the presence of a hydrogen bond donor while exploring possible influences on activity and selectivity of the compounds associated with these structural changes.

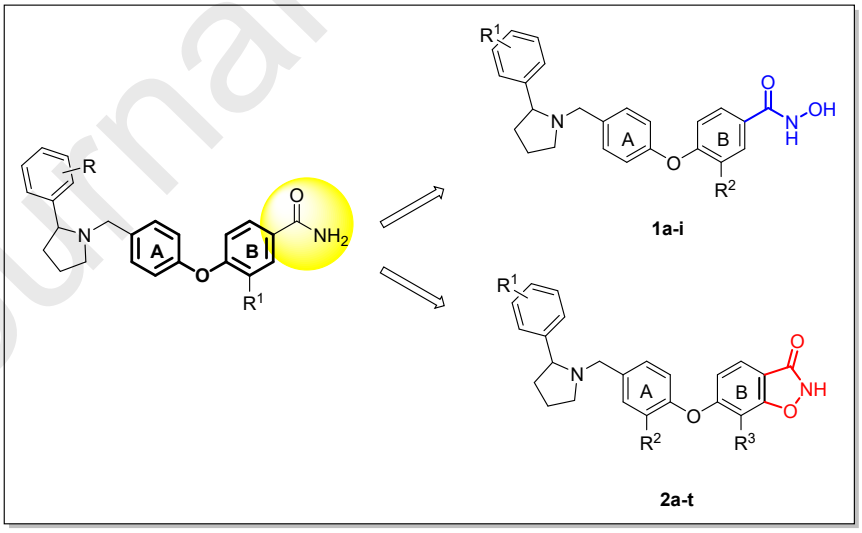


Fig. 2 Rational design of novel KOR antagonists.

In order rationalize our design strategy, modeling studies of compound **1c** and LY2456302 in the ligand binding pocket of KOR (PDB code: 4DJH and depicted using MOE 2013.08) were carried out. As predicted by the docking model, the replacement of the amide moiety in LY2456302 with hydroxamic acid in **1c** should not compromise the key hydrogen bonding interaction with His291. Moreover, the

hydroxyl group of the hydroxamic acid moiety in **1c** could form an additional hydrogen bond with the carbonyl of His291, which may contribute to a higher binding affinity.

Encouraged by the docking results, a series of *N*-hydroxybenzamide and benzisoxazole-3(*2H*)-one derivatives containing an aminobenzyloxyarylamide scaffold were synthesized as shown in Scheme 1 and Scheme 2. Benzoic acid derivatives **3a-m** were refluxed with thionyl chloride in ethanol to give intermediates **4a-m**, which were than coupled with *N*-Vinylpyrrolidone using sodium hydrogen as base to form **5a-m**. Intermediates **5a-m** was heated in hydrochloric acid to give **6a-m**. Reduction of **6a-m** with sodium borohydride provided intermediates **7a-m**. The reductive amination of aromatic aldehyde derivatives with **7a-m** gave intermediates **8a-m**. Etherification of intermediates **8a-j** with **9a-b** provided **10a-i**, which reacted with hydroxylamine hydrochloride gave target compounds **1a-i**.

Esterification of 4-fluoro-2-hydroxybenzoic acid derivatives **11a-c** with ethanol provided **12a-c**, which reacted with hydroxylamine hydrochloride gave 4-fluoro-*N,*2-dihydroxybenzamide derivatives **13a-c**. 6-fluorobenzo[*d*]isoxazol-3(2*H*)-ones **14a-c** were synthesize through the intermolecular condensation of **13a-c** under the condition of *N,N′*-carbonyldiimidazole (CDI), and then reaction with triphenylmethyl chloride gave **15a-c**. Obtained *N*-protected products **15a-c** were etherified with **8a-m** to give intermediates **16a-t**. Finally, the target benzisoxazole-3(*2H*)-one derivatives **2a-t** were obtained by the deprotection of triphenylmethyl group under the presence of zinc chloride. The synthesized *N*-hydroxybenzamide and benzisoxazole-3(*2H*)-one compounds have been confirmed by ^{1}H-NMR, ^{13}C-NMR, IR and HR-MS.

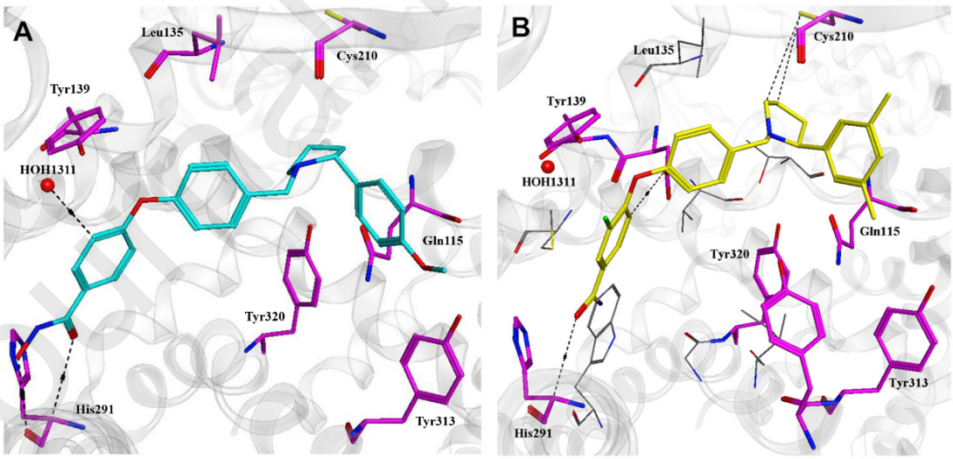
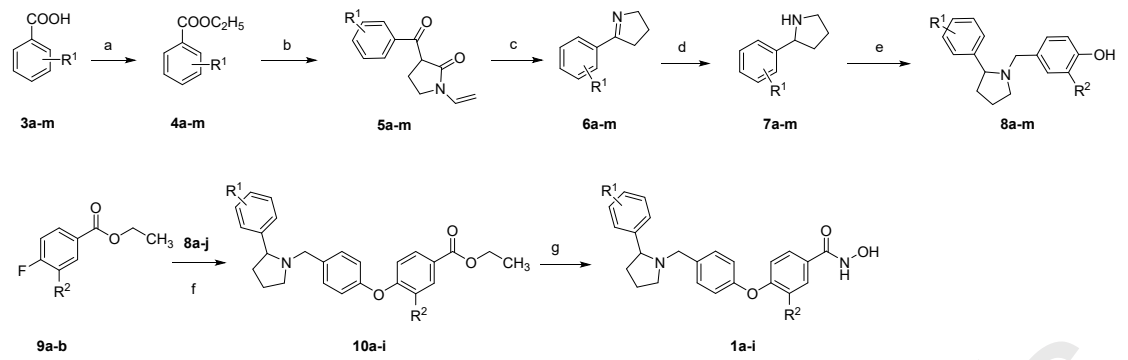


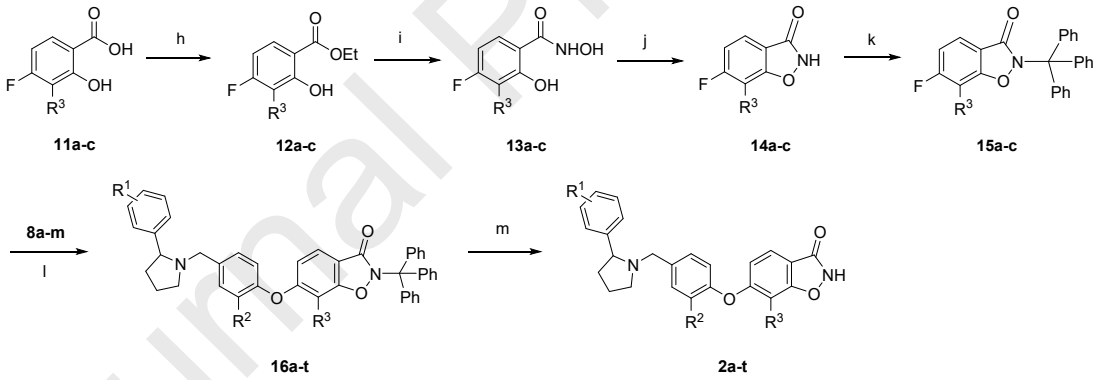
Fig. 3 Docking mode of **1c** (A) and LY2456302 (B). The H-bonds were shown as black dot lines and the key residues in the active site of KOR were shown as purple red. (A) The docking pose of **1c** in KOR crystal structure (PDB: 4DJH), and the ligand were shown as blue. (B) The docking pose of LY2456302 in KOR crystal structure (PDB: 4DJH), and the ligand were shown as yellow.



Synthesis route for target compounds **1a-i**. Regents and conditions: (a) $SOCl_2$, EtOH, reflux, 2 h, 94.4~98.8%; (b) *N*-Vinylpyrrolidone, NaH, THF, r.t.-60 °C, 3 h, 85.7~94.2%; (c) HCl, THF, reflux, 12 h, 82.8~87.2%; (d) $NaBH_4$, AcOH, MeOH, r.t., 1 h, 43.7~55.6%; (e) Aldehyde, $NaBH_3CN$, AcOH, MeOH, r.t., 12 h, 72.7~86.7%; (f) K_2CO_3, DMF, N_2, 120 °C, 12 h, 38.4~55.7%; (g) NH_2OH•HCl, KOH, MeOH, 40 °C, 10 h, 38.4~55.7%.

Cmpd	R^1	R^2	1e	4-Cl	F
1a	3,5-CH_3	H	**1f**	3-Cl	F
1b	H	H	**1g**	3-F	F
1c	4-OCH_3	H	**1h**	3-OCH_3	F
1d	3-OCH_3	H	**1i**	4-OCH_3	F

Scheme 1. Syntheses of *N*-hydroxybenzamide derivatives **1a-i**



Synthesis route for target compounds **2a-t**. Regents and conditions: (h) $SOCl_2$, EtOH, reflux, 18 h, 72.5~78.3%; (i) NH_2OH•HCl, NaOH, H_2O/Dioxane, r.t., 12 h, 72.2~80.3%; (j) CDI, THF, reflux, 2 h, 82.2~86.2%; (k) Triphenylmethyl chloride, $CHCl_3$, reflux, 12 h, 40.8~48.4%; (l) K_2CO_3, DMF, N_2, 120 °C, 12 h; (m) $ZnCl_2$, acetone, reflux, 1 h, 15.2~34.8% in two steps.

Cmpd	R^1	R^2	R^3	2k	3-OCH_3	H	F
2a	3, 5-CH_3	H	H	**2l**	3-OCH_3	H	Cl
2b	4-OCH_3	H	H	**2m**	3-F	H	F
2c	4-Cl	H	H	**2n**	3-F	H	Cl
2d	3, 5-CH_3	Cl	H	**2o**	4-Cl	H	F

2e	3, 5-CH_3	OCH_3	H	**2p**	4-Cl	H	Cl
2f	3, 5-CH_3	F	H	**2q**	4-OCH_3	H	F
2g	3-Cl	H	F	**2r**	4-OCH_3	H	Cl
2h	3-Cl	H	Cl	**2s**	3, 5-CH_3	Cl	F
2i	3, 5-CH_3	H	F	**2t**	3, 5-CH_3	F	F
2j	3, 5-CH_3	H	Cl				

Scheme 2. Syntheses of benzisoxazole-3(*2H*)-one derivatives **2a-t**

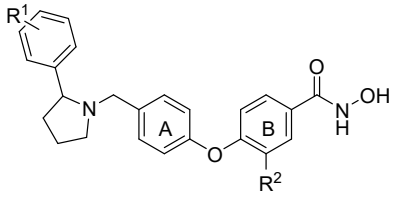
In order to evaluate the *in vitro* receptor binding affinity of above two series compounds, we used the radioligand binding assays analysis for MOR, KOR and DOR, using [^{3}H]-DAMGO, [^{3}H]-U69,593 and [^{3}H]-DPDPE, respectively [22-24]. As showed in **Table 1** and **Table 2**, compounds **1a-i**, **2a-g** and **2t** exhibited moderate binding affinities with KOR inhibition rates > 50% at the concentration of 10 μM, while the KOR inhibition rates of compounds **1b**, **1c** and **2a-c** were greater than 50% at the concentration of 1 μM. Among them, compound **2a** exhibited the strongest binding affinity, with KOR inhibitory rate > 90% at 10 μM and > 70% at 1 μM. It is noteworthy that the binding affinities of all compounds for MOR and DOR were much weaker compared with KOR, with inhibition rates constantly below 50% at 1 μM.

According to the above receptor binding affinity results, the compounds of **1c**, **1g**, **1h** and **2a** were selected to further test their K_i values for opioid receptors (**Table 3**). The affinities of these four compounds for MOR ([^{3}H]-DAMGO was used), KOR ([^{3}H]-U69,593 was used) and DOR ([^{3}H]-DPDPE was used) were weaker than those of **(±)LY2456302**. Although the binding affinities were less than satisfactory, we found that the KOR selectivity of **1c** over MOR and DOR was 12.8- and >55-fold, respectively, which eclipsed that of **(±)LY2456302.**

The above results indicate that changing the benzamide moiety into benzisoxazole-3(*2H*)-one did not improve the activity or selectivity. However, the replacement of benzamide with *N*-hydroxybenzamide increased the selectivity of KOR over MOR and DOR, especially over DOR. Among compounds **1a-i**, when R^2 group was fluorine, 3-methoxy substituted derivative **1g** exhibited more potent KOR binding affinity and higher KOR selectivity than 4-methoxy substituted derivative **1h**. However, when R^1 group was 4-methoxy, fluorine substituted derivative **1h** showed weaker KOR binding affinity and lower KOR selectivity than its unsubstituted counterpart **1c**.

Table 1

In vitro receptor binding affinity of *N*-hydroxybenzamide derivatives **1a-i** and **(±)LY2456302**.



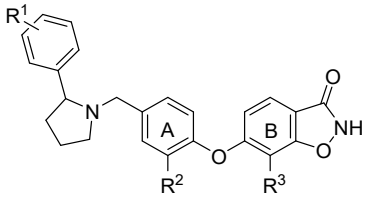
1a-i

Compd	Binding (%)					
	μ^a		κ^b		δ^c	
	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM
1a	36.0±1.3	10.7±2.7	84.7±0.3	39.5±0.5	6.5±0.5	0
1b	45.9±1.3	21.9±2.8	85.3±0.8	51.6±1.1	13.8±2.5	0
1c	40.4±3.1	12.8±0.6	86.0±0.6	52.3±0.1	24.4±1.8	3.9±0.3
1d	31.6±2.0	13.5±1.4	84.3±0.4	33.8±0.1	7.1±1.7	0
1e	25.8±1.6	0	74.3±1.4	46.1±0.8	34.4±2.0	25.6±1.4
1f	57.3±0.3	16.5±0.4	54.7±1.9	30.9±0.7	26.4±0.4	0
1g	73.2±0.2	25.8±1.5	80.6±0.5	45.8±0.8	28.4±2.1	16.8±1.1
1h	64.4±0.1	22.6±0.1	80.4±0.8	42.5±1.1	17.1±1.5	7.0±1.0
1i	43.1±2.3	11.0±0.4	77.4±0.9	34.9±0.6	15.8±0.4	6.2±0.8
(±)LY2456302	87.2±1.2	52.7±0.4	100±0.3	96.2±0.8	90.2±1.1	49.5±0.4

[a] [^{3}H]-DAMGO was used; [b] [^{3}H]-U69,593 was used; [c] [^{3}H]-DPDPE was used.

Table 2

In vitro receptor binding affinity of benzisoxazole-3(*2H*)-one derivatives **2a-t** and **(±)LY2456302**.



2a-t

Compd	Binding (%)					
	μ^a		κ^b		δ^c	
	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM
2a	74.0±1.4	49.4±0.5	91.6±0.4	70.6±0.5	54.8±2.0	33.9±1.0
2b	50.6±0.7	42.2±0.1	66.9±0.7	55.7±0.1	40.7±0.9	33.3±0.7
2c	54.5±1.6	47.0±0.1	83.5±0.3	57.6±1.6	35.9±0.6	15.7±1.1

2d	9.8±2.3	0	69.8±0.2	23.8±0.9	16.9±1.8	0
2e	59.2±0.2	14.3±1.4	73.2±0.1	38.4±0.3	49.1±0.9	11.6±0.4
2f	9.5±1.7	0	85.2±0.9	37.2±0.9	10.7±0.4	0
2g	0	0	57.2±0.1	20.0±0.3	38.2±0.4	0
2h	32.5±1.0	19.2±0.1	45.4±2.0	0	44.9±1.2	0
2i	21.1±2.6	0	36.4±0.4	0	33.3±0.2	0
2j	0	0	11.6±1.9	0	22.3±0.0	0
2k	6.2±0.3	0	29.0±0.9	9.7±0.2	28.4±0.3	0
2l	0	0	0	0	60.6±1.6	19.7±0.8
2m	0	0	24.8±2.4	0	52.5±0.6	20.7±0.1
2n	0	0	16.2±0.3	0	37.9±4.5	8.5±0.5
2o	35.8±0.1	22.5±3.8	39.2±0.2	0	9.6±1.0	0
2p	41.1±0.5	21.7±3.2	0	0	52.2±2.2	23.9±3.9
2q	41.0±2.3	19.2±2.5	19.1±4.3	0	49.7±6.2	23.7±2.3
2r	32.2±1.6	17.7±0.3	39.9±2.1	18.8±0.1	39.3±0.3	18.0±0.2
2s	45.7±0.1	21.4±1.6	47.4±3.8	20.1±0.2	32.9±0.1	18.0±0.4
2t	37.3±0.8	9.4±0.1	56.9±1.8	26.7±0.3	49.3±2.1	17.2±1.5
(±)LY2456302	87.2±1.2	52.7±0.4	100±0.3	96.2±0.8	90.2±1.1	49.5±0.4

[a] [^{3}H]-DAMGO was used; [b] [^{3}H]-U69,593 was used; [c] [^{3}H]-DPDPE was used.

Table 3

The binding affinities K_i values of **1c**, **1g**, **1h**, **2a** and **(±)LY2456302**.

Compd	K_i (nM)			Selectivity	
	μ^a	κ^b	δ^c	μ/κ	δ/κ
1c	2311±43.5	179.9±6.7	>10000	12.8	>55.5
1g	2797±17.0	497.6±34.7	>10000	4.6	>20.0
1h	4763±178.0	2154±27.0	>10000	2.2	>4.6
2a	1481±23.0	1411±125.8	5008±45.5	1.0	3.5
(±)LY2456302	93.7±8.1	14.0±0.7	105.2±5.6	6.7	7.5

[a] [^{3}H]-DAMGO was used; [b] [^{3}H]-U69,593 was used; [c] [^{3}H]-DPDPE was used.

Furthermore, to further evaluate compound **1c** *in vitro* antagonist activity, we utilized inhibition of agonist stimulated [^{35}S]GTP-γ-S binding with cloned human opioid receptors expressed in CHO cells for MOR and KOR or HEK293 cells for

DOR [16,22]. According to the [^{35}S]GTP-γ-S binding assays results showed in **Table 4**, **1c** with κ IC_{50} = 178 nM and μ IC_{50} = 201.5 nM that showed moderate κ antagonist potency and selectivity. Although its potency proved to be much weaker than **(±)LY2456302**, the result demonstrates intriguingly that **1c** is an antagonist of KOR and MOR but not of DOR.

Table 4

In vitro [^{35}S]GTP-γ-S binding values of **1c** and **(±)LY2456302**.

Compd	μ IC_{50} (nM)[a]	κ IC_{50} (nM)[b]	δ IC_{50} (nM)[c]	μ/κ	δ/κ
1c	201.5±10.61	178.0±22.80	> 5000	1.1	>28
(±)LY2456302	29.4±3.54	7.7±1.27	108.9±5.36	3.8	14.1

[a] DAMGO was used; [b] U69,593 was used; [c] DPDPE was used. The IC_{50} is reported as the mean ± SEM of at least three independent experiments.

In summary, a series of *N*-hydroxybenzamide derivatives **1a-i** and benzisoxazole-3(*2H*)-one derivatives **2a-t** were designed and synthesized to search novel KOR antagonists. All compounds were evaluated the binding affinities of towards opioid receptors, and typical compounds were biologically evaluated the antagonist potency for opioid receptors *in vitro*. The results showed that *N*-hydroxybenzamide may be an effective pharmacophore to improve the selectivity of KOR. Although the KOR binding affinity of compound **1c** (κ K_i =179.9 nM) was weaker than that of **(±)LY2456302** (κ K_i = 14.0 nM), the KOR selectivity of **1c** over MOR and DOR was nearly improved 2-fold and 7-fold, respectively. Meanwhile, in GTP-γ-S functional assays, compound **1c** also showed moderate KOR antagonist potency *in vitro*.

Acknowledgments

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Highlights:

- Opioid receptors are a family of G-protein coupled receptors and involved in multiple physiological activities.
- A series of κ opioid receptor antagonists were designed and synthesized based on the scaffold of aminobenzyloxyarylamide.
- All target compounds were evaluated in radioligand binding assays for opioid receptor binding affinity.

- Compound **1c** exhibited high affinity for KOR.
- The selectivity of compound **1c** for KOR was improved, compared with (±)LY2456302.