Bioorganic & Medicinal Chemistry 24 (2016) 2964–2970

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis and biological evaluation of novel tetrahydroisoquinoline quaternary derivatives as peripheral κ-opioid receptor agonists

Ting Guo [a,†], Zongjie Gan [a,b,†], Jie Chen [c], Dechuan Wang [a,*], Ling He [d], Qiao Song [a,b], Yungen Xu [a,b,*]

[a] Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China
[b] Jiangsu Key Laboratory of Drug Design and Optimization, China Pharmaceutical University, Nanjing 210009, China
[c] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[d] Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, China

ARTICLE INFO

Article history:
Received 23 February 2016
Revised 30 April 2016
Accepted 2 May 2016
Available online 3 May 2016

Keywords:
Tetrahydroisoquinoline quaternary derivatives
Peripheral
κ-Opioid receptor agonists

ABSTRACT

A novel series of tetrahydroisoquinoline quaternary derivatives **4** were synthesized as peripheral κ-opioid receptor agonists. All the target compounds were evaluated in κ-opioid receptor binding assays, and compounds **4l**, **4m**, and **4n** exhibited high affinity for κ-opioid receptor. Furthermore, compound **4l** (κK_i = 0.94 nM) produced potent antinociceptive activity in the mouse acetic acid-induced writhing assay, with lower sedative side effects than the parent compound MB-1c.

1. Introduction

It is well established that μ-opioid receptor agonists such as morphine have been widely used due to their powerful analgesia potency. However, they have been of limited clinical use because of some undesirable side effects such as tolerance, addiction and respiratory depression.[1] During the past decades, there has been a move to develop κ-opioid receptor (KOR) agonist which may provide a strong analgesia free from the abuse potential and the adverse effects of μ-agonists. However, increasing evidence indicates that central κ-opioid receptor agonists usually produce some CNS side effects such as sedation and anxiety, thus prevented their further development as analgesic therapeutics.[2] More recently, the presence of opioid receptors in the peripheral nervous system has been described, and it has been proved that activation of peripheral κ receptors could produce antinociceptive effects without centrally-mediated side effects.[3] Therefore, in the search for alternative analgesics to morphine, much considerable attention has been focused on the development of peripherally selective κ-agonists.

A variety of peripheralization strategies have been utilized in the searching for peripheral kappa receptor agonists: (1) synthesizing zwitterions, such as ICI-204448.[4] (2) Introducing hydrophilic substituents, such as GR-94839.[5] (3) Combining features of lipophilicity and hydrophilicity in the same molecule for the design of amphiphilic compounds, such as asimadoline.[6] However, quaternary ammonium derivatives are rarely reported as peripheral kappa receptor agonists. It should be noted that quaternarization of the N-moiety to restrict the passage of compounds across the blood–brain barrier has been successfully employed in many drugs. Methylnaltrexone bromide[7] (Fig. 1) is a novel quaternary derivative of naltrexone that does not cross the blood–brain barrier and acts as a selective peripheral μ-opioid receptor antagonist. It can selectively block peripherally μ-receptors to avoid the side effects such as constipation, without reversing the antinociceptive activity produced by central μ-agonists.[8] Now methylnaltrexone bromide is approved for the treatment of opioid-induced constipation (OIC) in clinical. Therefore, synthesizing quaternary derivatives would be a potential way to provide potent peripherally selective κ-opioid agonists.

Previously, our research group had reported MB-1c[9] (Fig. 1), a novel tetrahydroisoquinoline κ-opioid receptor agonist with high affinity and selectivity for κ-receptor (κK_i = 0.033 nM, $\mu K_i/\kappa K_i$ = 21,151). Nevertheless, it was quite disappointed to note that, sedative evaluation experiment had also proved that MB-1c had an

* Corresponding authors. Tel.: +86 25 83271244.
E-mail address: xu_yungen@hotmail.com (Y. Xu).
† Both authors contributed equally to this work.

http://dx.doi.org/10.1016/j.bmc.2016.05.002
0968-0896/

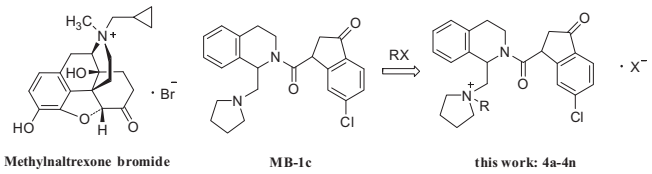


Figure 1. The structure of methylnaltrexone bromide, MB-1c and this work.

obvious centrally mediated side effect of sedation as the classic central κ-receptor agonists. Therefore, encouraged by the successful development of methylnaltrexone bromide, the structure of MB-1c was modified in this work by *N*-alkylation to afford a series of new quaternary compounds, which was expected to be beneficial to minimize or eliminate the CNS side effects associated with MB-1c while hopefully maintaining its antinociceptive activity in periphery.

2. Results and discussion

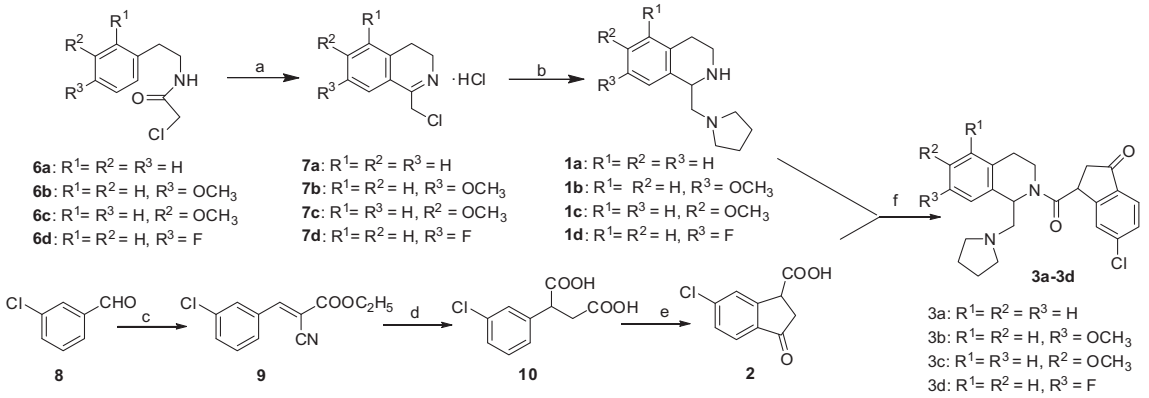
2.1. Chemistry

The desired compounds 1-(pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4- tetrahydroisoquinoline derivatives **3a**–**3d** were prepared by condensing different diamines **1a**–**d** with 6-chloro-3-oxo-2,3-dihydro-1*H*-indene-1-carboxylic acid **2**, and these intermediates were respectively obtained by convenient methods in advance.[10] The synthesis of diamines **1a**–**d** was carried out following the literature methods in two steps as depicted in Scheme 1. Compound **6** was cyclized in refluxing xylene to afford **7**, **7** were reacted with pyrrolidine to afford an intermediate, which was reduced by $NaBH_4$ to give **1**. Commercially available 3-chlorobenzaldehyde **8** was subjected to the Knoevenagel condensation with 2-cyanoacetate in the presence of piperidine to afford **9**. Treatment of **9** with potassium cyanide in aqueous ethanol followed by hydrolysis in refluxing 36% hydrochloric acid gave the corresponding succinic acid **10**, **10** was then subjected to Friedel–Crafts acylation using aluminum chloride as catalyst to give the key intermediate **2**. **3a**–**3d** were synthesized in moderate yields (about 40%), from indan acid **2** by condensation with diamines **1a**–**d** using dicyclohexylcarbodiimide (DCC) as coupling agent, and 4-(dimethylamino)-pyridine (DMAP) as catalyst. *N*-Alkylation of **3a**–**3d** with corresponding halogenated hydrocarbon under refluxing condition afforded the target compounds **4a**–**4n**. (Scheme 2) It should be noted that, there are two pairs of enantiomers existed in one compound, however, it was found that only one pair of enantiomers were generated as the main products during the synthetic process, while the other pair enantiomers were barely generated and obtained. Therefore, compound **4a**–**4n** reported in our manuscript were just represented one pair of enantiomers, and we have also explained this phenomenal in our previously work.[9]

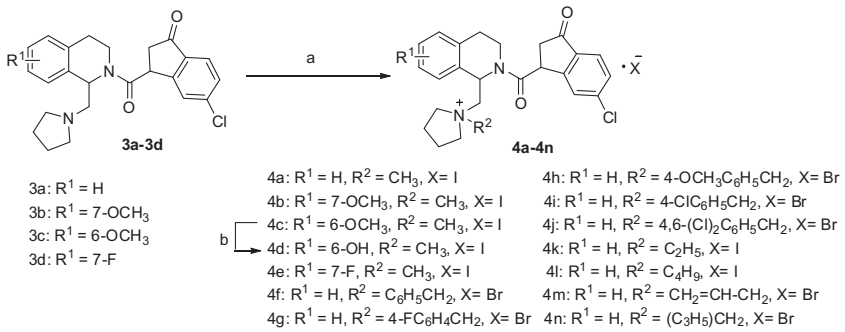
3. Pharmacological results and discussion

3.1. Affinity of the synthesized compounds

Tetrahydroisoquinoline quaternary derivatives **4a**–**4n** were evaluated in the in vitro opioid receptor binding assays. Binding affinity and selectivity of target compounds for κ and μ receptors



Scheme 1. Reagents and conditions: (a) a. P_2O_5, xylene, reflux, N_2. b. $HCl/C_2H_5OC_2H_5$; (b) a. pyrrolidine, CH_3OH, 0 °C, N_2. b. $NaBH_4$, CH_3OH, 0 °C; (c) $CNCH_2COOC_2H_5$, piperidine, glacial acetic acid, methylbenzene, reflux; (d) a. KCN, C_2H_5OH, H_2O, reflux or rt. b. HCl, reflux; (e) a. $SOCl_2$, reflux. b. anhydrous $AlCl_3$, CH_2Cl_2, rt; (f) DCC, DMAP, rt, 4 h.



Scheme 2. Synthesis of the target compounds. Regents and conditions: (a) R^2X, acetone or acetonitrile, rt or reflux, 3–8 h. (b) 48% HBr, reflux, 2 h.