Available online at www.sciencedirect.com
ScienceDirect
Chinese Journal of Natural Medicines 2018, **16**(2): 0113–0124
Chinese Journal of Natural Medicines

Synthesis and biological evaluation of novel tanshinone IIA derivatives for treating pain

LI Qi-Nan[1Δ], HUANG Zhi-Peng[1Δ], GU Qin-Lan[2], ZHI Zhuo-Er[1], YANG Yu-Han[1], HE Long[1], CHEN Kai-Li[1], WANG Jin-Xin[1*]

[1] *Jiangsu Key Laboratory of Drug Design and Optimization, China Pharmaceutical University, Nanjing 211009, China;*
[2] *Higher Vocational School of Pharmacy, China Pharmaceutical University, Nanjing 211009, China*

Available online 20 Feb., 2018

[ABSTRACT] Due to ineffectiveness and side effects of existing analgesics, chronic pain has become one of the most complex and difficult problems in the clinic. Monoacylglycerol lipase (MAGL) is an essential hydrolase in the endocannabinoid system and has been identified as a potential target for the treatment of pain. In the present study, we designed and synthesized twelve tanshinone IIA analogs and screened their activity against MAGL. Selected compounds were tested for analgesic activity *in vivo*, with the acetic acid writhing test model. Among the test compounds, compound **III-3** (IC_{50} 120 nmol·L^{-1}) showed significant activity against MAGL and ameliorated the clinical progression in the mouse pain model. Additionally, compound **III-3**, substitution with *N*-methyl-2-morpholinoacetamide, demonstrated improved solubility relative to tanshinone IIA.

[KEY WORDS] Tanshinone IIA; MAGL inhibitors; Analgesic activity

[CLC Number] R284, R965 **[Document code]** A **[Article ID]** 2095-6975(2018)02-0113-12

Introduction

Pain is considered as an alert of underlying disease or injury in our body. However, when it develops into a chronic condition, the pain itself will become a tormenting disease. At present, clinical analgesic drugs mainly work through the activation of opioid receptors in the central nervous system (CNS), which often causes various side effects, such as poor tolerance, physical dependence, and respiratory dependence [1-2]. Accordingly, significant efforts have been made to identify novel pharmacological targets for chronic pain [3-4].

The endogenous cannabinoid system (ECS), as a novel analgesia mechanism, is involved in diverse processes like perceiving pain, appetite controlling, and limiting the growth and invasion of cancer cells [5-7]. Although many cannabinoid agonists have been suggested as a potential treatment for pain, their various psychotropic side effects render these treatments intolerable to patients [8]. Therefore, it is necessary to find alternative strategy to activate the ECS without impairing motor and cognitive functions. a major brain endogenous cannabinoids, 2-Arachidonoylglycerol (2-AG) acts as a full agonist for the cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2) [9-10]. The main downstream enzyme involved in 2-AG inactivation is monoacylglycerol lipase (MAGL), a 33-kDa serine hydrolase, which has recently become a focus of attention (Fig. 1) [11]. Several studies have proven that inhibition of MAGL could increase the 2-AG level and then indirectly act CB1 and CB2 [12-14]. Furthermore, as reported by Petrenko *et al.* [15] and Hernández *et al.* [16], next generation inhibitors may generate an analgesic effect without side effects, such as motor impairments, catalepsy, and pharmacological tolerance. Their results suggest that the inhibition of MAGL could be a hopeful novel strategy in treating pain. However, current inhibitors are relatively similar and the development of novel MAGL inhibitors is much imperative.

Tanshinone IIA, extracted from a Chinese herb Salvia miltiorrhiza Bunge, has been clinically used to treat diverse disorders such as inflammation, myocardial ischemia, and atherosclerosis. In 2014, tanshinone IIA was confirmed as a potent MAGL inhibitor for the first time and its potential

[Received on] 26-July-2017
[Research funding] This work was supported by the Key Research & Development Program in Jiangsu (No. BE2015683), and the Introduction Program of Leading Scientific and Technological Entrepreneurship in Nanjing (No. 2013B14007).
[*Corresponding author] E-mail: jinxinwang@163.com
[Δ]These two authors contributed equally to this paper.
These authors have no conflict of interest to declare.

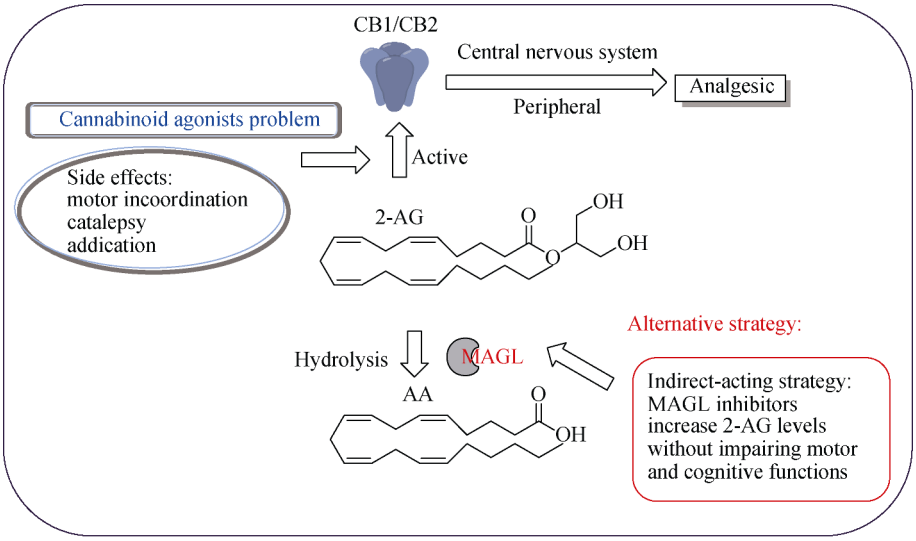

Fig. 1 MAGL inhibitors may induce analgesic effects without cannabinoid side effects

interactions were analyzed *in silico* [17]. To obtain more novel potent MAGL inhibitors and meet the demand for developing the traditional Chinese medicine tanshinone, we designed and synthesized a series of tanshinone IIA derivatives.

The active site of MAGL contains a classical catalytic triad (Ser122-Asp239-His269), an oxyanion hole (Met123-Ala51), and two hydrophobic pockets defined by amino acids Leu148, Ala164, Leu176, Ile179, Leu205, Val207, Ile211, Leu213, Leu214, VaL217, and Leu241 [18-19]. Several compounds targeting MAGL have been described before (Fig. 2). Through SAR analysis of the existing inhibitors, we have found that, besides a good leaving group such as multiple classes of carbamates or a hydrogen bond acceptor, bulky hydrophobic aromatic rings and heterocyclic linker are required to ensure their high activity and selectivity toward MAGL (Fig. 2) [20-24]. Recent studies have reported that tanshinone IIA includes constrained aromatic rings and hydrogen bond acceptors, which can occupy some parts of the hydrophobic region and form H-bonds like existing inhibitors. However, as illustrated in Fig. 3, tanshinone IIA is not bulky enough to fit well into the MAGL. In an attempt to improve its MAGL inhibitory activities, we extended structures with the 'linker' parts and hydrophobic heterocyclic. The compounds were designed as follows: (a) we extended the hydrophobic region with ester-connected dimethylamine, morpholine, and piperidine referred to the structure of endogenous cannabinoids 2-AG **(I**, **II**; Figs. 4A and 4B); (b) considering the absorption and penetration, we used an amide as an alternative linking part to increase its drug-like properties to obtain series **III**−**IV** (Figs. 4C and D).

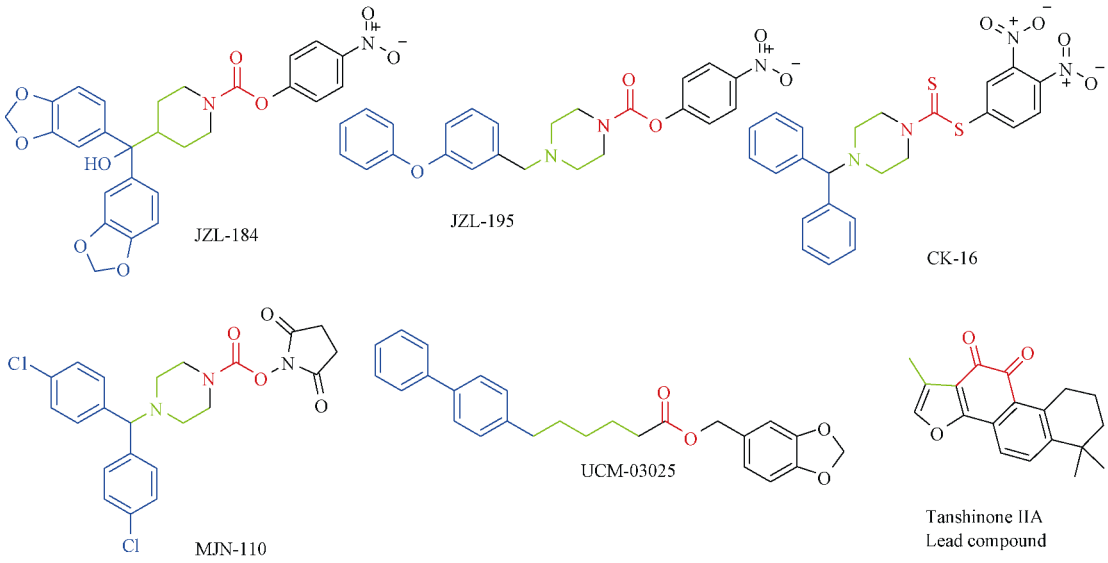

Fig. 2 Representative MAGL inhibitors and natural products tanshinone IIA, these inhibitor contains a bulky hydrophobic aromatic rings (blue), carbamates or hydrogen bond acceptor (red) and a linker (green)