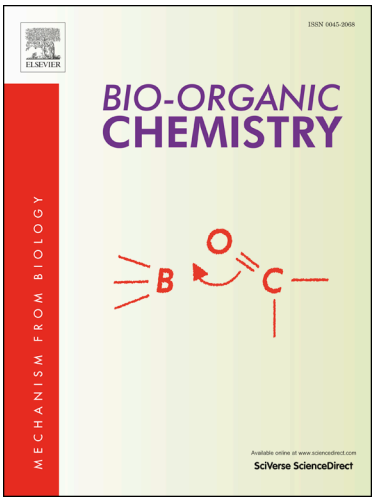

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Mingxiang Gao, Cunbin Nie, Jinyu Li, Beibei Songm, Xinru Chengm, Erying Sun, Lin Yan, Hai Qian

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Design, synthesis and biological evaluation of N^1-(isoquinolin-5-yl)-N^2-phenylpyrrolidine-1,2-dicarboxamide derivatives as potent TRPV1 antagonists

Mingxiang Gao[a], Cunbin Nie[a], Jinyu Li[a], Beibei Song[a], Xinru Cheng[a], Erying Sun[a], Lin Yan[a*], Hai Qian[b*]

[a] Institute for innovative drug design and evaluation, School of Pharmacy, Henan University, N. Jinming Ave., Kaifeng, Henan 475004, China

[b] State Key Laboratory of Natural Medicines, Center of Drug Discovery, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing, Jiangsu, 210009, China

ABSTRACT

Reported herein is the design, synthesis, and pharmacologic evaluation of a class of TRPV1 antagonists constructed on a N^1-(isoquinolin-5-yl)-N^2-phenylpyrrolidine-1,2-dicarboxamide platform that evolved from a 5-aminoisoquinoline urea lead. Advancing the SAR of this series led to the eventual identification of **3b**, comprising a *p*-Br substituted phenyl. In a TRPV1 functional assay, using cells expressing recombinant human TRPV1 channels, **3b** displayed potent antagonism activated by capsaicin (IC_{50} = 0.084 μM) and protons (IC_{50} = 0.313 μM). In the preliminary analgesic and body temperature tests, **3b** exhibited good efficacy in capsaicin-induced and heat-induced pain models and without hyperthermia side-effect. On the basis of its superior profiles, **3b** could be considered as the lead candidate for the further development of antinociceptive drugs.

Keywords: analgesic, transient receptor potential vanilloid type 1, 5-aminoisoquinoline urea, hyperthermia.

1. Introduction

Transient receptor potential vanilloid 1 (TRPV1) is an ion channel expressed on sensory neurons triggering an influx of cations, which is selectively activated by a wide range of stimuli such as exogenous ligands (e.g., capsaicin or resiniferatoxin), heat (>43 °C), acid (pH <6.8), and endogenous substances (e.g., anandamide and oxidative metabolites of linoleic acid) [1-4]. Activation of this channel is associated to chronic inflammatory pain and peripheral neuropathy [5]. Therefore, inhibition of TRPV1 function represents a strategy for the treatment of a variety of disease states, particularly in the management of chronic intractable pain [6, 7]. Over the past decade, a number of potent and selective small molecule TRPV1 antagonists has confirmed that pharmacological blockade of this receptor provided analgesic efficacy in several models of inflammatory and neuropathic pain [8-10]. However, the tendency of some TRPV1 antagonists to induce hyperthermia side-effect in preclinical models turned out to be a hurdle and led to its withdrawal from clinical development [11]. As a result, pharmacological separation of analgesic and hyperthermic effects became the key challenge in developing TRPV1 antagonists as therapeutic agents for pain management. Recently, efforts to eliminate hyperthermia led to the identification of the relative responses of TRPV1 to various stimulatory modulators, where

* Corresponding authors.

E-mail addresses: yanlin0378@163.com (L. Yan), qianhai24@163.com (H. Qian).