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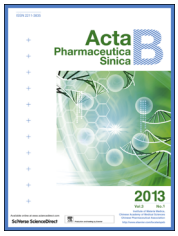

ORIGINAL ARTICLE

Synthesis and activity of novel indole derivatives as inhibitors of CD38

Dongying Wu[a], Kaiyiu Ting[b], Yaokai Duan[a], Na Li[a], Jianguo Li[a], Liangren Zhang[a,*], Honcheung Lee[b], Lihe Zhang[a]

[a]*State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China*
[b]*Department of Physiology, University of Hong Kong, Hong Kong, China*

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KEY WORDS

CD38;
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Abstract CD38 is a multifunctional enzyme/receptor expressed in a variety of mammalian tissues, regulating a wide range of physiological functions. Beginning with the previously reported compound **1**, an inhibitor of human CD38 NADase, we synthesized a series of indole-based NH-substituted derivatives with modifications on alkyl chains, changes in substituent groups on aromatic rings, and differences in carbon chain lengths. Compounds **10**, **13**, **16** and **34** exhibited moderate inhibition of human CD38 NADase. Analysis of the structure-activity relationships showed that the phenylpropionyl moiety was very important for the inhibitory activity. This study provides information for the rational design of CD38 inhibitors.

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Abbreviations: EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride; HOBt, 1-hydroxybenzotriazole; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide

*Corresponding author. Tel.: +86 10 82802567.
E-mail address: liangren@bjmu.edu.cn (Liangren Zhang).

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1. Introduction

CD38 is a 45-kD transmembrane protein firstly identified by monoclonal antibody typing of lymphocytes and thus is thought of as a lymphocyte-specific antigen[1]. It has now been established that it is not lymphocyte-specific, but is ubiquitously expressed in virtually all mammalian tissues examined[2].

As a multi-functional protein and a member of the ADP-ribosylcyclase family, CD38 can synthesize cyclic adenosine diphosphate ribose(cADPR) and ADPR from nicotinamide adenine dinucleotide (NAD^+), and nicotinic acid adenine dinucleotide phosphate (NAADP) from NAD phosphate ($NADP^+$)[3–5]. The likely mechanism has been informed by X-ray crystallographic analysis[6].

The membrane-bound enzyme CD38 exists in two opposing orientations, type II and type III[7], both of which can catalyze the synthesis of cADPR and NAADP. As Ca^{2+} messenger molecules, cADPR and NAADP have been shown to regulate a wide range of physiological functions[8]. Gene knockout studies have established that CD38 plays a critical role in a wide range of physiological functions from insulin secretion[9], immune response to bacterial infection[10], to modulate neuronal oxytocin secretion to affect behavior in mice[11]. It has been proved that CD38 is directly involved in many diseases, such as diabetes[12], AIDS[13] and chronic lymphocytic leukemia[14]. It is thus of great interest to develop specific and generally applicable inhibitors of CD38.

A series of CD38 inhibitors based on a computer-aided virtual screening approach and structural optimization were studied by our group previously. Compound **1** is the most active non-covalent inhibitor of human CD38 NADase reported to date[15]. Because the indole ring of compound **1** has an important π–π stacking with CD38 and the *para*-benzoate feature is required by the activity, we chose compound **1** as a lead compound and synthesized a series of indole-based NH-substituted derivatives. Molecular docking studies suggested the importance of the propylbenzyl group of compound **1** on binding, and to gain a better understanding of this structure-activity relationship (SAR), modification was mainly focused on varying the alkyl chain length, placing substituent groups on the aromatic ring, and altering the ring constituents (Fig. 1).

2. Results and discussion

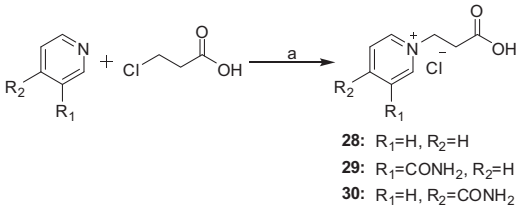
2.1. Synthetic routes

Compounds **5–27** were synthesized by a strategy similar to that reported previously[15] (Scheme 1), in a four-step reaction including carboxylation, esterification, reduction and amidation.

1-(3-Propionic acid) pyridium derivatives (**28–30**) were synthesized as described in Scheme 2.

Compounds **31–35** were obtained after the deprotection of the benzoxycarbonyl (Cbz) protecting group or the reduction of nitro-group by catalytic hydrogenation (Scheme 3).

In this paper, we investigated and optimized the synthetic routes of hydrogenation and amidation reactions reported in the literature[15]. When THF was used as the solvent for the Pd/C catalytic hydrogenation reaction, byproduct **36** was generated easily along with the main product, compound **4** (Scheme 4). The generation of



Scheme 2 Synthesis of compounds **28–30**. Reagents and conditions: (a) Anhydrous CH_3CN, reflux, 12 h.

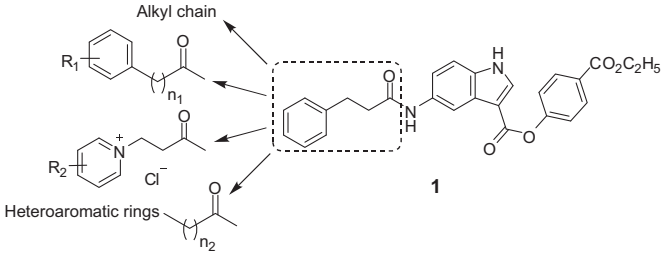
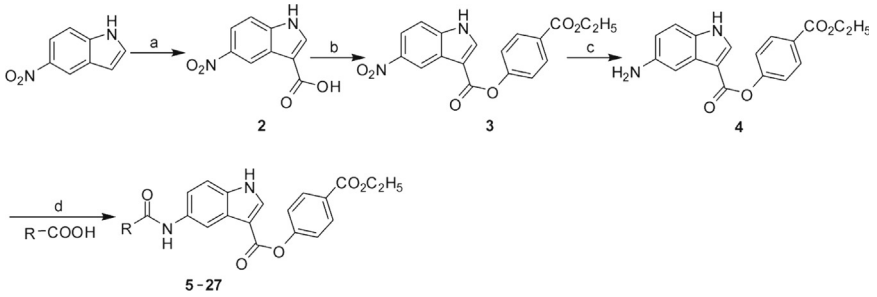


Figure 1 Design of indole-based NH-substituted derivatives.



Scheme 1 Synthesis of compounds **5–27**. Reagents and conditions: (a) 1: Oxalylchloride, ether, 0 °C→r.t., 24 h. 2: KOH, H_2O, 90 °C, 1 h. 3: HCl, 30% H_2O_2, reflux, 3 h; (b) Ethyl 4-hydroxybenzoate, EDCI, DMAP, DMF, 0 °C→r.t., 8 h; (c) H_2, Pd/C, DMF/MeOH, r.t., 12 h; (d) EDCI, THF or DMF, 0 °C→r.t., 48 h.

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