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Design, synthesis, evaluation, and molecular docking of ursolic acid derivatives containing a nitrogen heterocycle as anti-inflammatory agents

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ABSTRACT

Ursolic acid derivatives containing oxadiazole, triazolone, and piperazine moieties were synthesized in an attempt to develop potent anti-inflammatory agents. Structures of the synthesized compounds were elucidated by ^{1}H NMR, ^{13}C NMR, and HRMS. Most of the synthesized compounds showed pronounced anti-inflammatory effects at 100 mg/kg. In particular, compound **11b**, which displayed the most potent anti-inflammatory activity of all of the compounds prepared, with 69.76% inhibition after intraperitoneal administration, was more potent than the reference drugs indomethacin and ibuprofen. The cytotoxicity of the compounds was also assessed by the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-*H*-tetrazolium bromide (MTT) assay, and no compounds showed any appreciable cytotoxic activity (IC_{50} >100 μmol/L). Furthermore, molecular docking studies of the synthesized compounds were performed to rationalize the obtained biological results. Overall, the results indicate that compound **11b** could be a therapeutic candidate for the treatment of inflammation.

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Inflammation is a complex biological process for modulation of the immune response against a diverse range of triggering factors, including infectious agents, allergens, free radicals, highly refined foods, and a sedentary lifestyle.[1] Exaggerated and prolonged inflammation may cause various diseases, which can seriously threaten human health, such as arthritis, sepsis, and even cancer.[2,3] At present, non-steroidal anti-inflammatory drugs (NSAIDs) are the most important class of widely used therapeutics for the treatment of inflammation and account for 35% of the global market for prescription pain medication.[4–6] Common NSAIDs, such as aspirin and indomethacin, can inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), causing significant toxicity to the gastrointestinal tract and kidney.[7–9] The gastrointestinal irritation, bleeding, and ulceration side effects of classical NSAIDs are caused by high COX-1 versus COX-2 selectivity, and may also be related to the acidity of classical NSAIDs.[10] The simple chemical derivatization (esterification or amidation) of the carboxylic function of representative NSAIDs has been shown to result, not only in reduction of the ulcerogenic effect, but also in increased anti-inflammatory activity.[11–17] Thus, there is a need to develop new anti-inflammatory drugs with decreased acidity and increased specificity for targeting COX-2.

Pentacyclic triterpenes are a very powerful class of natural products because of their wide range of biological activities and diversity of structures.[18,19] Ursolic acid (UA) is a well-known pentacyclic triterpene that is one of the major active components of many traditional Chinese medicines.[20] UA and its derivatives have been reported to have antihepatodamage,[21] anti-HIV,[22] antimalarial,[23] anti-inflammatory,[24] antidiabetic,[25] antimicrobial,[26] and antitumor[27] activity. However, the low bioavailability of UA *in vivo* restricts its clinical application. In recent years, chemical modification of UA has been widely investigated as a method of improving its biological activity and bioavailability. Research has shown that keeping a polar substituent at the C-3 position is essential for the pharmacological activity of UA.[28] The introduction of a nitrogen-containing heterocycle has been shown to be a useful tactic in the structural modification of natural products because the nitrogen atom can carry a positive charge and act as a hydrogen-bond acceptor or donor that can strongly influence the interaction between the molecule and its target.[29] Recent studies have used 1,3,4-oxadiazole as a pharmacophore because it is a good bioisostere of amides and esters, which can influence the pharmacokinetic

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properties of drugs by increasing the lipophilicity and thus the ability of drugs to reach their targets by transmembrane diffusion.[30] In addition, several 1,2,4-triazoles have been reported to possess potent antimicrobial[31] and anti-inflammatory[32] activity. Piperazine-based drug discovery has also attracted considerable attention in recent years. Studies have shown that the incorporation of a piperazine moiety can occasionally provide unexpected improvement in the bioactivity of compounds.[33–35] Furthermore, it has been reported that several ursolic acid, oxadiazole, triazole, and piperazine derivatives are COX-2 inhibitors and anti-inflammatory agents (Fig. 1).[36–39] These findings suggest that introducing oxadiazole, triazole, and piperazine heterocycles into the C-28 position, and keeping an hydroxy substituent at the C-3 position of the ursolic acid scaffold may produce novel UA derivatives targeting COX-2 with improved anti-inflammatory properties.

On the basis of the abovementioned reports, the present work aimed to synthesize novel derivatives of UA by introducing an 1,3,4-oxadiazole moiety, a piperazine ring, or a 4-phenyl-1*H*-1,2,4-triazol-5(4*H*)-one moiety to the UA nucleus with the objective of discovering potent anti-inflammatory agents that are devoid of gastrointestinal side effects. The substituents on the phenyl ring were simultaneously altered to investigate their contribution to the biological activity. Hence, four novel series of ursolic acid derivatives were synthesized and evaluated for anti-inflam-

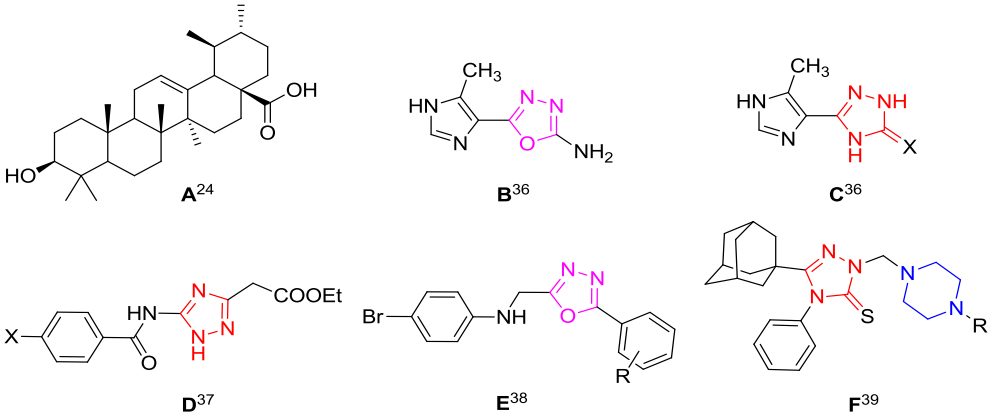
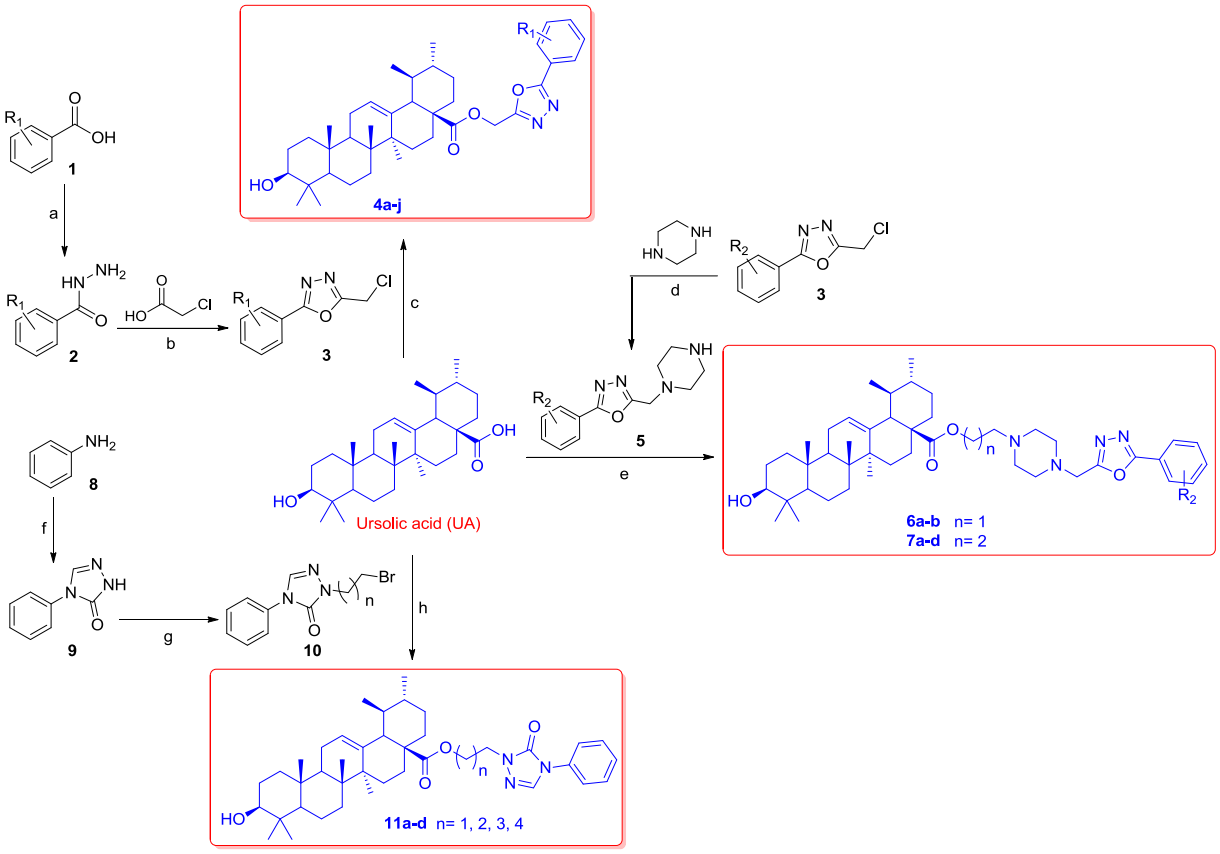


Fig. 1. Chemical structures of some previous reported compounds as COX-2 inhibitors and anti-inflammatory agents.



Scheme 1. Synthetic scheme for the synthesis of compounds **4a–j**, **6a–b**, **7a–d** and **11a–d**. Reagents and conditions: (a) MeOH, H_2SO_4; $NH_2NH_2{\cdot}H_2O$; (b) $POCl_3$; (c) K_2CO_3, KI, acetone, reflux, 10 h; (d) K_2CO_3, KI; (e) $Br(CH_2)_nBr$; K_2CO_3, KI, acetone, reflux, 10 h; (f) $NH_2NHCOOCH_3$, $CH(OC_2H_5)_3$; EtOH, MeONa, reflux, 48 h; (g) $Br(CH_2)_nBr$; K_2CO_3, KI; (h) K_2CO_3, KI, acetone, reflux, 10 h.

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