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Synthesis, biological evaluation and molecular modeling of novel thienopyrimidinone and triazolothienopyrimidinone derivatives as dual anti-inflammatory antimicrobial agents ☆

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ABSTRACT

New thienopyrimidinone and triazolothienopyrimidinone derivatives have been synthesized. These compounds were subjected to anti-inflammatory and antimicrobial activity screening aiming to identify new candidates that have dual anti-inflammatory and antimicrobial activities.

Compounds **5**, **7** and **10a** showed minimal ulcerogenic effect and high selectivity towards human recombinant COX-2 over COX-1 enzyme. Their docking outcome correlated with their biological activity and assured the high selectivity binding towards COX-2. In addition, they could act safely up to 80 mg/kg orally or 40 mg/kg parentrally. The antimicrobial screening showed that compound **10a** displayed distinctive inhibitory effect on the growth of *Escherichia coli* comparable to that of ampicillin. Moreover, compounds **5**, **7**, **9** and **12a** possessed 50% of the inhibitory activity of ampicillin against *E. coli*. Thus, compounds **5**, **7** and **10a** represent promising dual acting anti-inflammatory and antimicrobial agents. This work provides rewarding template enriching the chemical space for dual anti-inflammatory antimicrobial activities.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) keep on to be the main treatment of inflammatory diseases. However, they have been linked with many adverse effects such as gastrointestinal mucosal damage and bleeding [1]. The discovery of the inducible enzyme COX-2 has pushed the searching for anti-inflammatory agents forward that specifically target COX-2 and avoid the undesirable side effects accompanied by treatment with classical non selective NSAIDs [2]. Marketed COX-2 inhibitors have an exceptional importance as a potent and gastrointestinal safe anti-inflammatory agent [2]. Furthermore, the increasing microbial resistance to currently available antimicrobial agents has reached an alarming level in many countries [3]. There has been a rapid spread in the primary and opportunistic fungal infections because of the increased number of immunocompromised patients. *Candida albicans* is one of the most common opportunistic fungi responsible for such infection [4].

The co-administration of multiple drugs for treating inflammatory conditions associated with microbial infections might amend some secondary health problems particularly in patients with impaired kidney and/or liver functions. Therefore, from pharmacoeconomic perspective, and to better patient compliance, a dual anti-inflammatory/antimicrobial agent with minimal adverse effects and high safety margin is greatly needed. Significant confirmation accumulated in literature showed the efficacy of thienopyrimidine derivatives as anti-inflammatory [5–9], and antimicrobial agents [10–14].

Inspired by the above mentioned findings and as an extension of our ongoing program to synthesize compounds with dual antimi crobial/anti-inflammatory activities [15–21], new thienopyrimidinone and triazolothienopyrimidinone derivatives were prepared. This would enrich the chemical space for the desired activities, [22] and provide rewarding template for further lead optimization efforts in the future. The synthesized compounds were screened

☆ This work is dedicated to the memory of Professor Ragab M. Shafik.

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for their possible anti-inflammatory and antimicrobial activities aiming to identify dual acting candidates.

2. Results and discussion

2.1. Chemistry

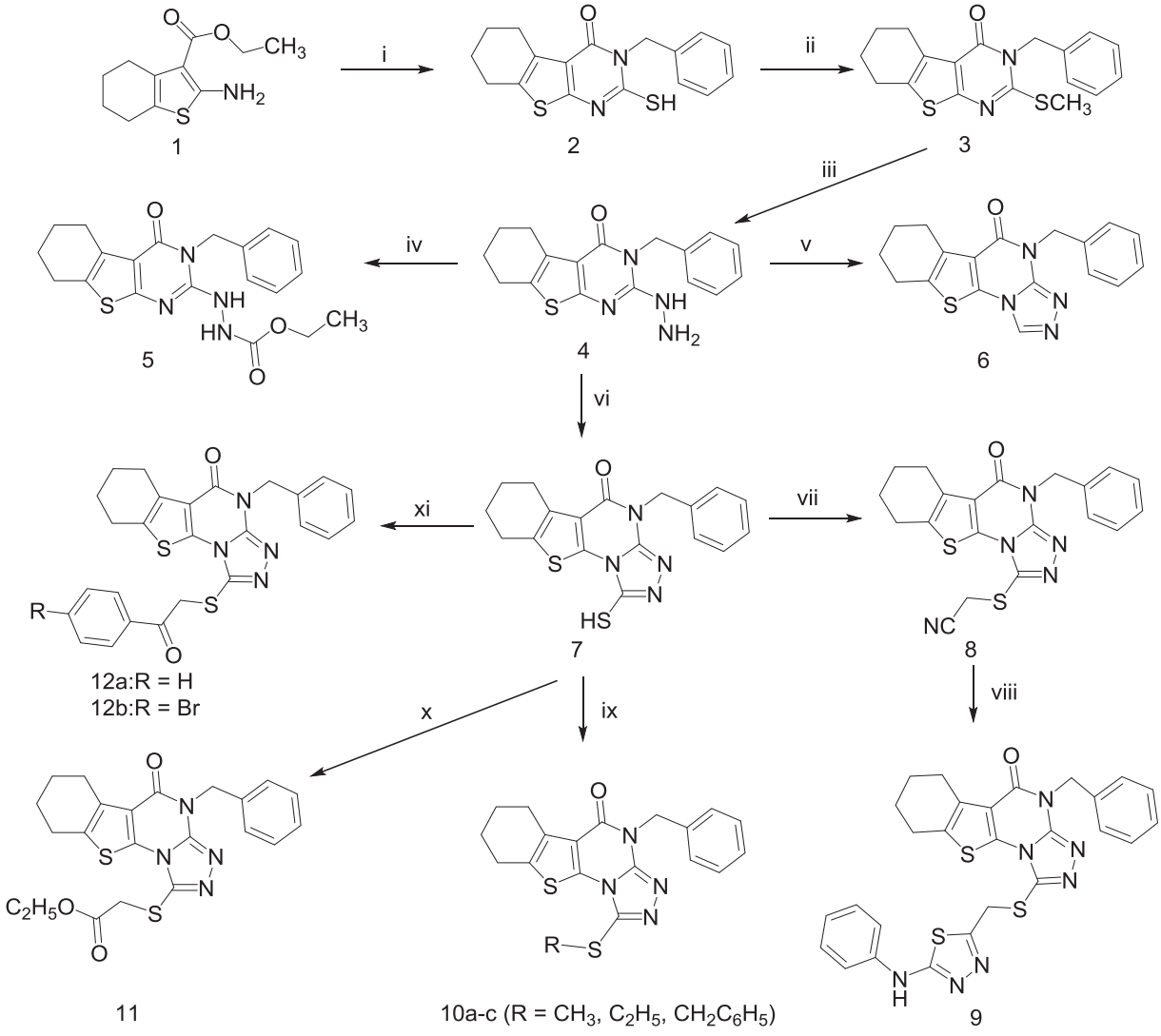
Synthesis of the intermediate and target compounds was accomplished according to the steps depicted in Scheme 1. The starting key compound was 3-Benzyl-2-sulfanyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-d]pyrimidin-4(3*H*)-one **2**.

Synthesis of 2-sulfanyl derivative **2** was reported [23,24]. However, it was prepared in our laboratory starting from the aminoester **1** using a new method that was adopted for the preparation of other similar derivatives [25]. In addition, methylsulfanyl derivative **3** was also prepared in our laboratory via S-alkylation of compound **2** using methyl iodide [21].

Moreover, hydrazinolysis of compound **3** to give 2-hydrazino derivative **4** was adopted by refluxing 2-methylsulfanyl derivative **3** with hydrazine hydrate 98% [21]. Reaction of the 2-hydrazino derivative **4** with ethyl chloroformate in dry pyridine yielded the open chain counterpart **5**. Trials to cyclize the open chain counterpart **5** to the corresponding oxotriazolo derivative either by increasing the reflux time in pyridine or by heating above its melting point were unsuccessful. ^{1}H NMR spectrum of compound **5** revealed two deuterium exchangeable singlets each integrated for one proton due to two NH groups. The spectrum also exhibited a triplet and a quartet assigned for CH_2CH_3 protons.

Moreover, treating the hydrazino derivative **4** with formic acid or carbon disulfide/sodium hydroxide yield the cyclized unsubstituted triazolo derivative **6** [21] or the 1-sulfanyltriazolo derivative **7**, respectively. In addition, reaction of the 2-hydrazino derivative **4** with isothiocyanate derivatives did not yield the corresponding phenylthiosemicarbazone derivatives. Instead, compound **7** was obtained. This is in agreement with previously reported data [26–28]. ^{1}H NMR spectrum of compound **7** showed a downfield deuterium exchangeable singlet characteristic for the thiol group. Electron impact mass spectrum (EI-MS) of compound **7** showed the molecular ion peak (M^+) at *m*/*z* 368 and the base peak at *m*/*z* 91 most probably corresponding to the tropylium carbocation.

The sulfanyl derivative **7** was alkylated using chloroacetonitrile, alkyl or aralkyl halides, ethyl chloroacetate or phenacyl bromides to the corresponding sulfanyl acetonitrile derivative **8**, S-alkyl or S-aralkyl derivatives **10a–c**, ethoxycarbonylmethylsulfanyl



Scheme 1. Synthesis of some thieno- and triazolothienopyrimidinone derivatives **2**–**12**. Reagents and conditions: (i) $C_6H_5CH_2NCS$, DMF, NaOH; (ii) CH_3I; (iii) $NH_2NH_2{\cdot}H_2O$ 98%; (iv) $ClCOOC_2H_5$; (v) HCOOH; (vi) CS_2, NaOH or RNCS, R = C_6H_5, 4-$CH_3C_6H_4$; (vii) $ClCH_2CN$, KI, K_2CO_3; (viii) = $C_6H_5NHCSNHNH_2$; (ix) = RX; (x) = $ClCH_2COOC_2H_5$/DMF/ K_2CO_3 or $BrCH_2COOC_2H_5$ /C_2H_5ONa; (xi) = 4-$RC_6H_4COCH_2Br$.