Bioorganic & Medicinal Chemistry Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological evaluation of 1,3-diaryl pyrazole derivatives as potential antibacterial and anti-inflammatory agents

Ya-Ru Li, Chao Li, Jia-Chun Liu, Meng Guo, Tian-Yi Zhang, Liang-Peng Sun, Chang-Ji Zheng *, Hu-Ri Piao *

Key Laboratory of Natural Resources and Functional Molecules of the Changbai Mountain, Affiliated Ministry of Education, Yanbian University, College of Pharmacy, Yanji 133002, PR China

ARTICLE INFO

Article history:
Received 11 July 2015
Revised 8 October 2015
Accepted 10 October 2015
Available online xxxx

Keywords:
Pyrazole
Aminoguanidine
Furan
Antibacterial activity
Anti-inflammatory activity

ABSTRACT

Three series of 1,3-diaryl pyrazole derivatives bearing aminoguanidine or furan-2-carbohydrazide moieties have been synthesized, characterized and evaluated for antibacterial and anti-inflammatory activities. Most of the synthesized compounds showed potent inhibition of several Gram-positive bacterial strains (including multidrug-resistant clinical isolates) and Gram-negative bacterial strains with minimum inhibitory concentration values in the range of 1–64 μg/mL. Compounds **6g**, **6l** and **7l** presented the most potent inhibitory activity against Gram-positive bacteria (e.g. *Staphylococcus aureus* 4220), Gram-negative bacteria (e.g. *Escherichia coli* 1924) and the fungus, *Candida albicans* 7535, with minimum inhibitory concentration values of 1 or 2 μg/mL. Compared with previous studies, these compounds exhibited a broad spectrum of inhibitory activity. Furthermore, compound **7l** showed the greatest anti-inflammatory activity (93.59% inhibition, 30 min after intraperitoneal administration), which was more potent than the reference drugs ibuprofen and indomethacin.

The incidence of bacterial infection has increased rapidly during the past two decades.[1] Furthermore, many drug-resistant pathogens have emerged in recent years because of the increasing use or abuse of antibacterial agents for all kinds of human infectious diseases.[1–4] In addition to bacterial infection, many factors can lead to inflammation, such as biological agents, physical agents, chemical injuries and allergic reactions. Such conditions may lead to bacteremia, toxemia, septicemia and pyemia. As a result, the development of novel antibacterial and anti-inflammatory agents is crucial for ongoing effective therapeutic intervention.[5–8]

Pyrazoles occupy a distinct niche in heterocyclic chemistry and represent a key motif in medicinal chemistry because of their capability to exhibit an array of bioactivities such as antimicrobial,[9,10] anticancer,[11] anti-inflammatory,[12] antidepressant,[13] anticonvulsant,[14] antipyretic[15] and selective enzyme inhibitory[16] activities. In recent years, the guanidinium derivatives have been infrequently investigated as pharmaceutical antimicrobial agents.[17] In our previous work, we found that several pyrazole derivatives showed moderate to good activity against Gram-positive strains (including multidrug-resistant clinical isolates).[5,9] One of these derivatives, compound **A**, exhibited inhibitory activity with a minimum inhibitory concentration (MIC) value of 4 μg/mL (Fig. 1).[5] Unfortunately, however, none of these derivatives displayed any activity against Gram-negative bacteria, even at 64 μg/mL. Dibama et al. reported that compound **B** showed potent antibacterial activity against *Escherichia coli* with an MIC value of 32 μg/mL (Fig. 1).[18] In this work, as part of our ongoing studies toward the development of novel antibacterial agents, we designed new hybrid compounds in which the rhodanine moiety of **A** was replaced by a guanidine moiety or its isostere furan-2-carbohydrazide, simultaneously changing the substituents on the phenyl ring of the pyrazole, to investigate their effects on activity. Inspired from existing antibacterial agents bearing nitro groups, such as chloramphenicol that operates via inhibition of bacterial protein synthesis after the nitro group is metabolized to a hydroxyamino group, two nitro groups were introduced into the phenyl ring on the N^1 position of the pyrazole. Thus, three novel series of 1,3-diaryl pyrazole derivatives bearing aminoguanidine or furan-2-carbohydrazide moieties were designed, synthesized, and evaluated for their antimicrobial activities. Meanwhile, in light of the fact that some drugs contain a pyrazole moiety, such as phenazone and metamizole,[19] these compounds were also evaluated for their anti-inflammatory activity.

The synthesis of the target compounds is presented in Scheme 1.[22] Hydrazone derivatives (compounds **2** and **4**) were prepared by reacting substituted acetophenones with phenylhydrazine (or 2,4-dinitrophenylhydrazine) in the presence of glacial

* Corresponding authors. Tel.: +86 (433)243 6015; fax: +86 (433)243 5026 (C.-J.Z.); tel.: +86 (433)243 5003; fax: +86 (433)243 5026 (H.-R.P.).
E-mail addresses: zhengcj@ybu.edu.cn (C.-J. Zheng), piaohr@ybu.edu.cn (H.-R. Piao).

http://dx.doi.org/10.1016/j.bmcl.2015.10.028
0960-894X/

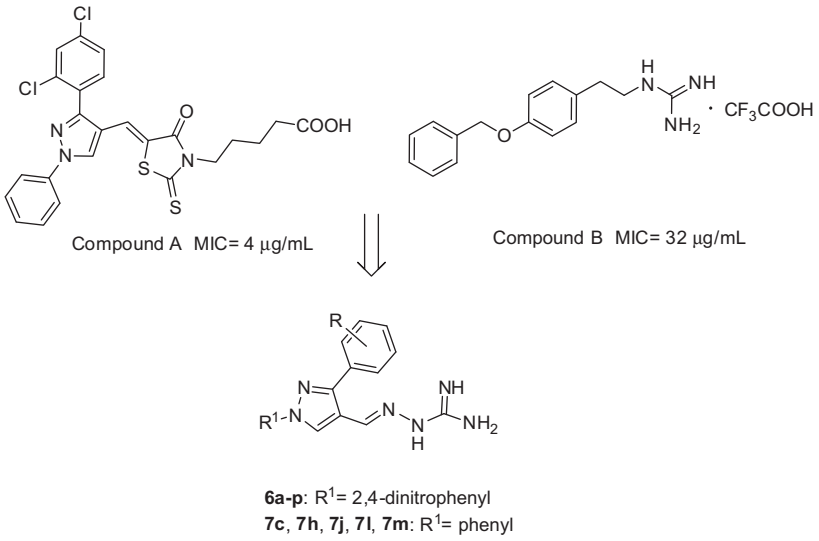
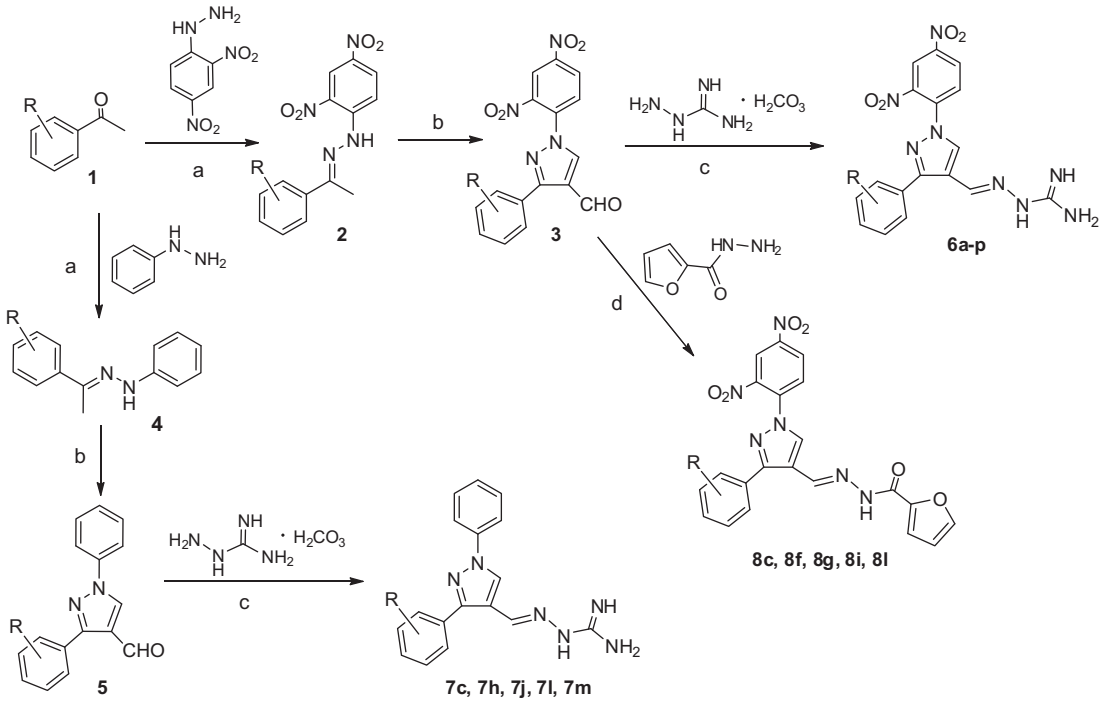


Figure 1. Previously reported compound **A**, **B** and the structure-based design of the target compounds.



Scheme 1. Synthetic scheme for the synthesis of compounds **6**–**8**. Reagents and conditions: (a) EtOH, AcOH or AcONa, reflux 5–7 h, (b) $POCl_3$, DMF, 0 °C 0.5 h, 80 °C 6 h, (c) EtOH, HCl, Reflux 20 h. (d) EtOH, reflux 3 h.

acetic acid in ethanol. Compound **2** (or compound **4**) reacted under Vilsmeier–Haack (DMF–$POCl_3$) conditions and afforded corresponding 4-carboxaldehyde functionalized pyrazole derivatives **3** (or **5**). In this reaction, four equivalents of the reagent, instead of three as described by Pascal Rathelot,[20] were necessary to obtain compounds **3** and **5** in good yield. Compounds **3** or **5** were then reacted with aminoguanidine bicarbonate in the presence of catalytic amounts of hydrochloric acid in ethanol to provide compounds in series **6** and **7**. Compounds in series **8** were prepared by reacting compounds **3** with furan-2-carbohydrazide in refluxing ethanol. The structures of the compounds synthesized were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

In vitro anti-bacterial activities of the synthesized compounds were evaluated using a 96-well microtiter plate and a serial dilution method to obtain the Minimum Inhibitory Concentration (MIC) values for different strains (including multidrug-resistant clinical isolates). Four Gram-positive strains (*Staphylococcus aureus RN* 4220, *S. aureus KCTC* 209, *S. aureus KCTC* 503, *Streptococcus mutans* 3065), five Gram-negative strains (*Escherichia coli KCTC* 1924, *Escherichia coli CCARM* 1356, *Pseudomonas aeruginosa* 2742,