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Synthesis and biological evaluation of chalcone derivatives containing aminoguanidine or acylhydrazone moieties

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ABSTRACT

Three novel series of chalcone derivatives containing an aminoguanidine or acylhydrazone moiety were designed, synthesized and evaluated in terms of their antibacterial, antifungal and anti-inflammatory activities. Most of the synthesized compounds showed potent inhibitory activity towards various bacteria and one fungus with minimum inhibitory concentrations (MICs) ranging from 1 to 8 μg/mL. Compared with our previously reported chalcone derivatives (MICs >64 μg/mL), these compounds exhibited improved antibacterial activities (MICs = 2 μg/mL) against Gram-negative bacterial strains (*Escherichia coli* 1924 and 1356). Compounds **4f** and **4h** were found to be the most potent with an MIC value of 1 μg/mL against the Gram-negative bacterial strains *Salmonella typhimurium* 1926 and the fungus *Candida albicans* 7535. In addition, compound **4f** displayed the most potent anti-inflammatory activity of all of the compounds prepared in the current study with 92.45% inhibition after intraperitoneal administration, making it more potent than the reference drugs indomethacin and ibuprofen. The cytotoxic activity of the compound **4f** was assessed in HeLa, Hep3B and L02 cells.

Numerous research groups throughout the world are currently involved in an urgent search for novel antibacterial and antifungal agents to overcome the emergence of new infectious diseases and the increasing number of multidrug-resistant microbial pathogens.[1,2] Although several classes of antimicrobial agents are currently available, pathogenic bacteria and fungi have developed resistance to these drugs in the majority of cases.[3,4] Additionally, there is a strong relationship between bacterial infection and inflammation.[5] Furthermore, inflammation remains a common and poorly controlled clinical problem that can be life threatening in extreme cases, including allergic reaction, autoimmune disease and organ rejection following transplantation surgery.[6] There is, therefore, an urgent need to develop novel antibacterial, antifungal and anti-inflammatory agents to address these issues.

Chalcones belong to the flavonoid class of natural products and have attracted considerable interest because of their relatively simple structures and wide variety of pharmacological activities.[7–11] For example, chalcone-based compounds have been reported to exhibit anticancer,[12] anti-inflammatory,[13] anti-ulcerative,[14] analgesic,[15] antiviral,[16] antifungal,[17] antimalarial[18] and antibacterial activities.[19] Aminoguanidine derivatives have recently captured the attention of numerous researchers because of their diverse range of biological properties, including their antibacterial,[20] antifungal[21] and anti-inflammatory activities.[22] Acylhydrazones have also received considerable interest from researchers working in a variety of different fields because they possess a broad range of pharmacological properties, including antibacterial[23,24] and anticancer activities.[25] In our previous work, we reported the development of a series of chalcone derivatives that showed potent activity against Gram-positive bacterial strains, including multidrug-resistant clinical isolates.[26] Unfortunately, none of these compounds are active against Gram-negative bacteria. Aminoguanidine derivatives were reported as antifungal agents with a potency of 100 μg/mL.[21] In a continuation of our research towards the discovery and development of increasingly potent antibacterial agents, we report herein the structure-based design of chalcone derivatives containing an aminoguanidine or acylhydrazone moiety. In this way, we have developed three novel series of chalcone derivatives (Fig. 1), totaling 26 compounds, which were designed, synthesized and screened for their antibacterial, antifungal and anti-inflammatory activities

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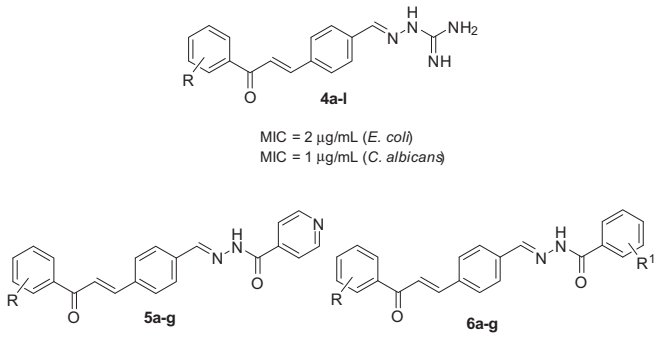


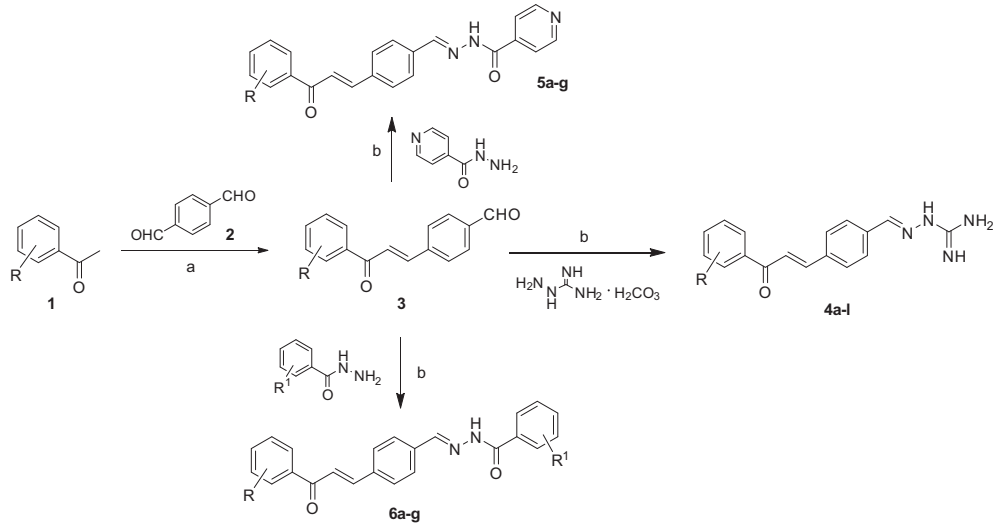
Fig. 1. The structures of the target compounds.

in vitro. The substituents on the phenyl ring were simultaneously changed to investigate their contribution to the biological activity.

The route used for the synthesis of compounds **4a**–**l**, **5a**–**g** and **6a**–**g** is shown in Scheme 1. The key intermediate **3** was prepared by the Claisen–Schmidt condensation of terephthalaldehyde (**2**) with a substituted acetophenone (**1**) using a previously described method.[26,27] Compounds **4a**–**l** were prepared by the reaction of **3** with aminoguanidine bicarbonate in the presence of concentrated hydrochloric acid in refluxing ethanol. Compounds **5a**–**g** and **6a**–**g** were prepared by the reactions of compound **3** with isonicotinic acid hydrazide and substituted benzoyl hydrazine, respectively, in the presence of catalytic amounts of hydrochloric acid in ethanol.[22] The structures of the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS and MS analyses.[28]

The *in vitro* antimicrobial and antifungal activities of the synthesized compounds were evaluated against a variety of strains of bacteria and one fungus (including multidrug-resistant clinical isolates), using a 96-well microtiter plate screening format to obtain their minimum inhibitory concentration (MIC) values.[29] Gatifloxacin, moxifloxacin, fluconazole, norfloxacin and oxacillin were used as positive controls. The compounds were screened against four Gram-positive strains (*S. aureus* 4220, *S. aureus* 209, *S. aureus* 503 and *Streptococcus mutans* 3065), four clinical isolates of multidrug-resistant Gram-positive bacterial strains (MRSA 3167 and 3506, and QRSA 3505 and 3519), four Gram-negative strains (*Escherichia coli* 1924, *E. coli* 1356, *Salmonella typhimurium* 1926 and *Pseudomonas aeruginosa* 2742) and one fungus (*Candida albicans* 7535).

The *in vitro* antibacterial and antifungal activities of the synthesized compounds are shown in Tables 1 and 2. Most of the synthesized compounds showed potent inhibitory activities against the different bacteria and the one fungus tested in the current study with MICs ranging from 1 to 64 μg/mL. Almost all of the compounds in series **4** exhibited potent antibacterial activity with MICs ranging from 1 to 16 μg/mL, except for **4i** and **4l** against the *E. coli* 1356 strain (MIC = 32 μg/mL). Compounds **4f** and **4h** exhibited the highest activity of all the compounds synthesized in series **4** against *S. typhimurium* 1926 with an MIC value of 1 μg/mL, making them 2-fold more potent than gatifloxacin and equipotent to moxifloxacin. Against the Gram-positive strains (*S. aureus* 503 and *S. aureus* 209) and Gram-negative *E. coli* 1924, these two compounds showed equipotent or more potent to the standard drugs gatifloxacin and moxifloxacin with an MIC value of 2 μg/mL. Against the fungus *C. albicans* 7535, compound **4f** displayed the strongest potency of all of the compounds synthesized in series **4** with an MIC value of 1 μg/mL, which was equal to that of fluconazole. Notably, we have shown for the first time the development of chalcone derivatives exhibiting good antibacterial activity against four Gram-negative bacteria, especially *S. typhimurium* 1926 and *P. aeruginosa* 2742, with MICs ranging from 1 to 16 μg/mL (except **4i** and **4l**). These compounds also exhibited antifungal activity against *C. albicans* 7535 with MICs ranging from 1 to 8 μg/mL, making them more potent than our previously reported chalcone derivatives.[26] The position of the substituents on the phenyl ring of compounds **4a**–**l** had a pronounced effect on their activities, which varied according to the following orders: 3-Br > 4-Br > 2-Br for the bromo-substituted compounds; 2,4-Cl_2 > 4-Cl > 3-Cl > 2-Cl for the chloro-substituted compounds; and 4-CH_3 > 2,4-$(CH_3)_2$ > 4-OCH_3 for compounds bearing an electron-donating group. Compounds in series **5** and **6** generally showed weak activity against all of the strains tested in the current study with MICs ranging from 16 to 64 μg/mL. Notably, compound **5f** bearing a 2,4-Cl_2 substituted phenyl ring showed moderate activity against all of the strains tested in this study with MICs ranging from 4 to 32 μg/mL, except for the Gram-negative strains *S. typhimurium* 1926 and *P. aeruginosa* 2742. For the compounds in series **6**, only those bearing a Cl substituent on the phenyl ring of their benzoyl hydrazone (**6e**, **6f**, **6g**) showed moderate antimicrobial activity.



Scheme 1. Synthetic scheme for the synthesis of the target compounds. Reagents and conditions: (a) NaOH, EtOH, 23 °C, 3–4 h; (b) Aminoguanidine bicarbonate or isoniazide or benzoylhydrazine, EtOH, HCl, 50–60 °C, reflux, 8–12 h.