Bioorganic & Medicinal Chemistry Letters 22 (2012) 5129–5133

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives

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ARTICLE INFO

Article history:
Received 7 April 2012
Revised 13 May 2012
Accepted 15 May 2012
Available online 24 May 2012

Keywords:
Antimicrobial
Antibacterial
Antitubercular
Antifungal
Hydrazone
Pyrazole
Azetidinone
Thiazolidinone

ABSTRACT

As a part of our research to develop novel antitubercular and antimicrobial agents, a series of 3-(4-chlorophenyl)-4-substituted pyrazoles have been synthesised. These compounds were tested for antitubercular activity in vitro against *Mycobacterium tuberculosis* H37R*v* strain using the BACTEC 460 radiometric system, antifungal activity against a pathogenic strain of fungi and antibacterial activity against gram-positive and gram-negative organisms. Among them tested, many compounds showed good to excellent antimicrobial and antitubercular activity. The results suggest that hydrazones, 2-azetidinones and 4-thiazolidinones bearing a core pyrazole scaffold would be potent antimicrobial and antitubercular agents.

Pyrazoles and their derivatives have attracted much attention due to diverse biological activities.[1,2] Enormous interest in the chemistry of pyrazoles is reflected by the design of new synthetic approaches due to their significant biological and therapeutic value. There has been overwhelming literature reports reflecting the immense biological potential of pyrazoles derivatives as antitumor, anti-HIV, anti-inflammatory and anti-microbial activities.[3]

Over the past few years continuous interest in the synthesis of C_2-substituted thiazolidinone derivatives for their significant activity,[4,5] thiazolidinones derivatives posses verities of bilogical activities like antibacterial,[6] antituberculosis,[7] antifungal,[8] and anticancer[9] has been observed. Azetidinones known[10] as a β-lactams since 1907, possess a four member ring system bearing internal amide linkage. The discovery of an azitidin-2-one ring in penicillin led to development of the compounds bearing this ring system. The powerful activity of penicillin[11,12] and the clinically more useful cephalosporin[13] led chemists and medicinal chemists to investigate the chemistry of the azetidinone ring system. The basic skeleton commonly encountered in β-lactam antibiotics are the penam and cepham and the high electrophilicity of the β-lactam ring system is responsible for the antibiotic activity of these compounds.

After a comprehensive literature survey our focus was to synthesise thiazolidinone and azetidinone derivatives as less toxic, more active antimicrobial and antituberculosis agents. (See Fig. 1)

Our efforts focused on the introduction of chemical diversity in the molecular framework in order to synthesise pharmacologically interesting compounds of different composition. This motivated us to design and synthesise new hydrazone, 2-azetidinones and 4-thiazolidinone templates bearing pyrazole moieties (Scheme 1).

A convenient method for the synthesis of the pyrazole compound was achieved starting from *p*-chloro acetophenone. According to a previously reported method[14] the *p*-chloro acetophenone upon tretment with diethyl oxalate in presence of base afforded ethyl 4-(4-chlorophenyl)-2,4-dioxobutanoate **(2)**. 3-(4-chlorophenyl)-1*H*-pyrazole-5-carbohydrazide **(3)** is previously reported compound,[15] was synthesised by the reaction of **(2)** with hydrazine hydrate under reflux condition. The hydrazone **(4)** was prepared by the condensation of hydrazide **(3)** and the appropriate aromatic aldehyde under reflex.[16] The Staudinger [2+2] cycloaddition reaction[17,18] of the hydrazone with chloroacetyl chloride to afford β-lactam **(5)** with a *trans*-configuration (On the basis of ^{1}H NMR, the coupling constant of the the protons on C3 and C4 is in the range of 2.0–2.4 Hz, indicating *trans*-configuration of the β-lactam). The reaction of the hydrazone **(4)** with mercaptoacetic acid in presence of sodium acetate and galcial acetic acid afforded racemic mixture of the thiazolidin-4-one **(6)**. The yields varied from

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http://dx.doi.org/10.1016/j.bmcl.2012.05.063

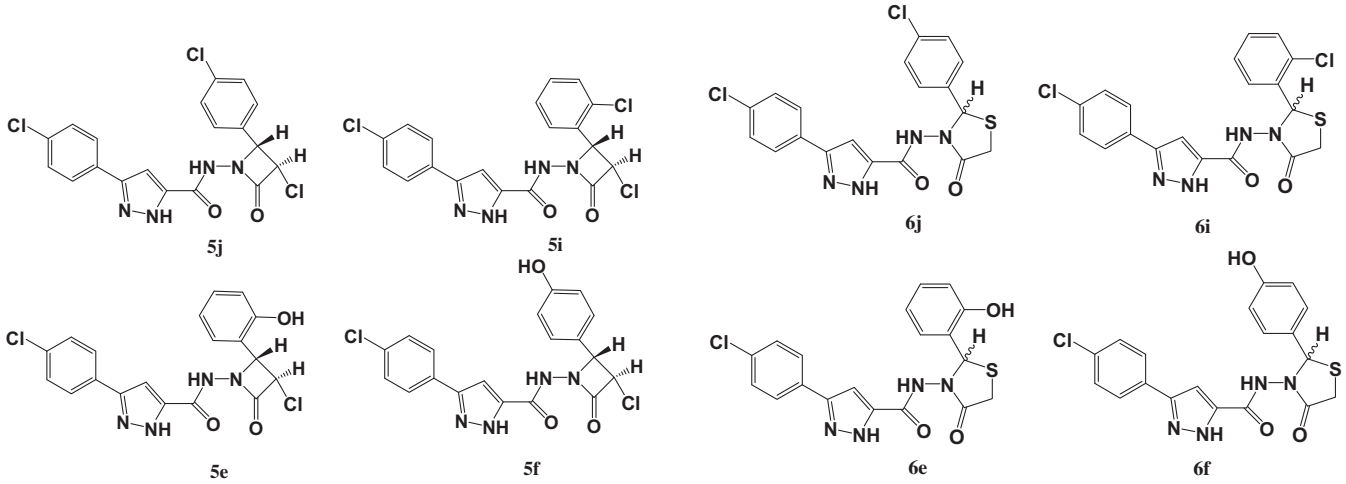
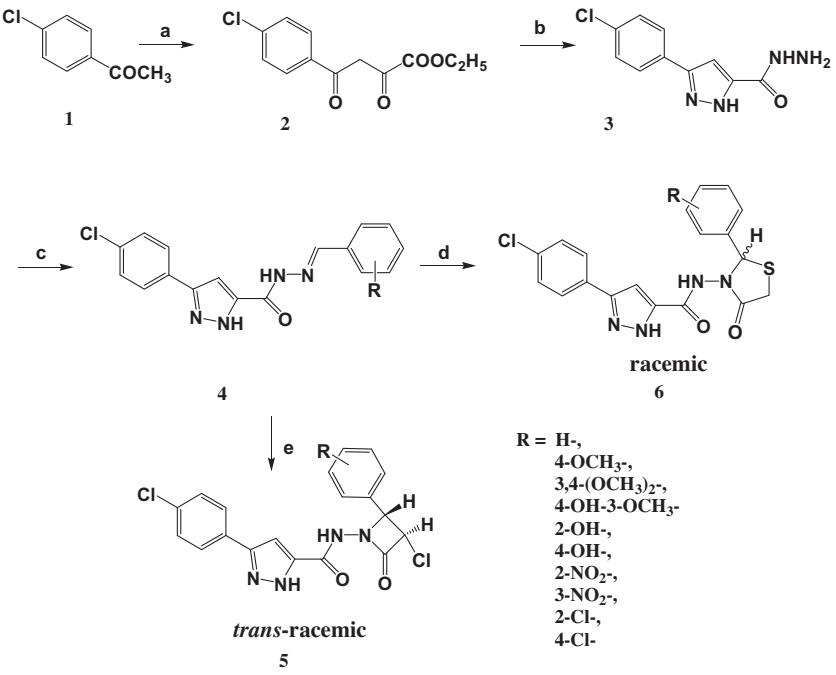


Figure 1. Structures of the most active compounds.



Scheme 1. Reagents and condition: (a) Diethyl oxalate (1.05 equiv), NaOMe (1.05 equiv), THF, rt, 1 h; (b) $NH_2NH_2{\cdot}H_2O$ (2.0 equiv), EtOH, reflux, 6 h; (c) aryl aldehyde (1.05 equiv), MeOH, glacial CH_3COOH, reflux, 6 h; (d) mercaptoacetic acid (1.05 equiv), NaOAc (2.1 equiv), glacial CH_3COOH, reflux, 10 h; (e) chloroacetyl chloride (1.2 equiv), Et_3N (1.2 equiv), DCM, rt, 2 h.

35% to 60% in case of hydrazone **(4)**; for the 2-azetidinones **(5)** the yields varied from 40% to 65% and from 25% to 50% for the 4-thiazolidinones **(6)**. All the compounds structures were confirmed by ^1H, ^{13}C, HR-MS and IR (refer to Supplementary data). All compounds were confirmed to be greater than 95% pure via LC–MS prior to their use in the evaluation of their biological efficacies.

All the compounds were evaluated for in vitro antibacterial activity against *Escherichia coli*, and *Staphylococcus aureus* and antifungal activity against pathogenic fungi. The MIC (minimum inhibitory concentration) values were determined by a comparison with ciprofloxacin (CIP), moxifloxacin (MFX) for antibacterial activity and fluconazole, 5-fluorocytosine for antifungal activity as standard agent. The activities reported as MICs were determined according to NCCLS method.[19–21]

As indicated in Table 1, most of sysnthesised compounds generally showed potent antifungal activity against all pathogenic fungal strains tested. Actully, the activity of compounds **5b**, **5c**, **6d**, **5e**, **6e**, **5f**, **5i**, **5j** and **6j** was superior or comparable to those of 5-fluorocytosine against some strain of fungai. In contrast, the compounds **5a**, **4b**, **4f**, **5g**, **5h** and **6h** did not show significant antifungal activity against all pathogenic fungal strain tested.

The substituents (−OH, −Cl) for the compounds **5** and **6** contribute significantly toward biological potency, Thus, the substituents appear to be an important factor in their antifungal activity. In addition, the compounds containing 2-azetidinone or 4-thiazolidinone showed more potent antifungal activity then the compounds containing hydrazones.

All the compounds were evaluated for in vitro antibacterial activity against *E. coli* ATCC 25922 and *S. aureus* ATCC 29213.

As indicated in Table 2, compounds **4e**, **4f**, **4i**, **4j**, **5e**, **5f**, **5i**, **5j**, **6e**, **6f**, **6i** and **6j** show excellent activity against the strains of bacteria. The substituents (−OH, −Cl) for the compounds **4**, **5** and **6** are