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Full Length Article

Design and synthesis of 3-(4-aminophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide/carbothioamide analogues as antitubercular agents

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ARTICLE INFO

Article history:
Received 23 October 2014
Accepted 5 January 2015
Available online 18 March 2015

Keywords:
Antitubercular agents
Claisen Schmidt condensation
Pyrazolines

ABSTRACT

Emergence of multi-drug resistant tuberculosis (MDR-TB) and HIV-TB co-infections potentiate the development of newer antitubercular agents to combat against tuberculosis, a dreadful disease. In the present investigation a series of pyrazoline analogues were designed and synthesized based on the structure of known antitubercular agent thiacetazone, in hope of obtaining new and safe antitubercular agents. The target molecules were synthesized in two steps, starting with the condensation of 4-aminoacetophenone and *p*-anisidine in methanolic sodium hydroxide solution followed by the cyclization of intermediate chalcones with appropriate semicarbazide/thiosemicarbazide in glacial acetic acid. All the synthesized compounds were characterized by ^{1}H NMR, IR and mass spectral data and the purity of the compounds was checked by elemental analysis. Their antimycobacterial activity was evaluated by two folds serial dilution method. 3-(4-Aminophenyl)-N-(4-chlorophenyl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazole-1-carboxamide (**4i**) showed maximum activity against *Mycobacterium tuberculosis* H37Rv with minimum inhibitory concentration (MIC) of 7.41 μM.

1. Introduction

Mycobacterium tuberculosis (MTB), one among the dreadful pathogens is mainly responsible for tuberculosis (TB) in human. An estimated 8.6 million new cases of TB and 1.3 million deaths occurred globally in 2012 (World Health Organization, Global Tuberculosis Report; 2013). After 40 years since the discovery of rifampin, US-FDA has granted conditional approval of TMC207 as a part of combination therapy to treat adults with multi-drug resistant (MDR-TB) in December 2012 and then later approved by European Medicine Agency (EMA) in March 2014 (Kamal et al., 2006; http://www.fda.gov; http://www.ema.europa.eu). However nausea,

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Peer review under the responsibility of Beni-Suef University.
http://dx.doi.org/10.1016/j.bjbas.2015.02.006

diarrhoea, athralgia, dizziness, hyper uricaemia, eye disorders, and QT interval prolongation has been detected in patients receiving this drug (Matteelli et al., 2010). EMA has also granted conditional approval of delamanid for the treatment of MDR-TB in April 2014 (Ryan and Lo, 2014; http://www.ema.europa.eu/docs/en). The emergence of MDR-TB and HIV-TB co-infection reduces the success rate of Directly Observed Treatment Short course (DOTS) in controlling TB. Also the combination of second line drug with DOTS has significant side effects. Hence it is clear that development of newer antitubercular drugs with novel mechanism of action is today's urgent need to fight against TB.

Pyrazoline analogues are an important class of heterocycles and possess significant biological activities including anticonvulsant (Ahsan et al., 2013, 2012a; Ahsan, 2013), antimicrobial (Dawane et al., 2010; Ahsan et al., 2012a), anticancer (Ahsan, 2012), antitubercular (Ahsan et al., 2011a, 2011b, 2011c, 2012b), anti-inflammatory (Sharma et al., 2010), antiviral (Ahsan et al., 2012a; Mui et al., 2002), antidepressant (Bilgin et al., 1993), antiarrhythmic (Turan-Zitouni et al., 2000), neuroprotective (Ahsan, 2013) etc. In the present investigation the pharmacophore of thiacetazone was taken and pyrazoline analogues were synthesized. The design of the pyrazoline scaffold is shown in Fig. 1.

2. Experimental

2.1. General

All chemicals were either supplied by E. Merck (Germany) or S. D. Fine Chemicals (India). The melting point of the compounds was determined by open tube capillary method and is uncorrected. The progress of reactions was monitored by TLC plates (silica gel G) using eluants benzene–acetone (9:1), and the spots were identified by iodine vapours or UV light. IR spectra were recorded on a Schimadzu 8201 PC, FT-IR spectrometer (KBr pellets). ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker AC 400 MHz spectrometer using TMS as internal standard and mass spectra were recorded on a Bruker Esquire LCMS using ESI.

2.2. General procedure for the synthesis of (2E)-1-(4-aminophenyl)-3-(4-methoxyphenyl)prop-2-ene-1-one (3)

4-aminoacetophenone (50 mmol; 6.76 g) with 4-methoxybenzaldehyde (50 mmol; 6.81 g) in diluted methanolic sodium hydroxide solution was stirred under room temperature for 4 h. The resulting solution was allowed to stand overnight and then the reaction mixture was poured into cold water and neutralized with dilute HCl. The solid was filtered, dried and recrystallized with ethanol to obtain the (2E)-1-(4-aminophenyl)-3-(4-methoxyphenyl)prop-2-ene-1-one (**3**).

2.3. General procedure for the synthesis 3-(4-aminophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide/carbothioamide analogues (4a-l)

1-(4-Aminophenyl)-3-(4-methoxyphenyl)prop-2-ene-1-one (**3**) (2 mmol; 0.51 g) and thiosemicarbazide/semicarbazide/substituted phenyl semicarbazides (2 mmol) in 20 ml glacial acetic acid was refluxed for 12 h. The excess of solvent was removed under reduced pressure and then the reaction mixture was poured into the crushed ice. The solid mass was filtered, dried and recrystallized with ethanol furnished the 3-(4-Aminophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide/carbothioamide analogues (**4a-l**).

2.3.1. 3-(4-Aminophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (4a)

(Thitipone et al., 2013).

2.3.2. 3-(4-Aminophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (4b)

^{1}H NMR (400 MHz, DMSO d_6): δ_H (ppm) 3.04 (1H, dd, J = 3.07, 10.91 Hz, H_a), 3.77 (3H, s, OCH_3), 3.78 (1H, dd, J = 6.14, 11.84 Hz, H_b), 5.45 (1H, t, J = 7.46 Hz, H_x), 6.41 (2H, s, NH_2), 6.85–6.87 (2H, d, J = 8.31 Hz, ArH), 7.08–7.10 (2H, d, J = 7.89 Hz, ArH), 7.67–7.72 (4H, m, ArH), 6.52 (2H, bs, $CONH_2$); ^{13}C NMR (100 MHz, DMSO d_6): δ_H (ppm) 162.1, 158.6, 151.7, 150.6, 135.9, 130.1, 128.0, 124.1, 116.5, 114.0, 61.1, 55.8, 39.5; IR (KBr) (ν_{max}, cm^{-1}): 3304 (NH), 1665 (C=O), 1594 (C=N); EI-MS, m/z: 310 (M^+).

2.3.3. 3-(4-Aminophenyl)-5-(4-methoxyphenyl)-N-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (4c)

(Sayed et al., 1996).

2.3.4. 3-(4-Aminophenyl)-5-(4-methoxyphenyl)-N-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (4d): ^{1}H NMR (400 MHz, DMSO d_6)

δ_H (ppm) 2.09 (3H, s, CH_3), 3.04 (1H, dd, J = 3.06, 10.99 Hz, H_a), 3.79 (1H, dd, J = 3.84, 11.02 Hz, H_b), 3.82 (3H, s, OCH_3), 5.41 (1H, t, J = 7.89 Hz, H_x), 6.49 (2H, s, NH_2), 7.00–7.02 (2H, d, J = 8.33 Hz, ArH), 7.70–7.84 (8H, m, ArH), 8.10–8.13 (2H, d, J = 8.77 Hz, ArH), 10.29 (1H, s, CONH); IR (KBr) (ν_{max}, cm^{-1}): 3302 (NH), 1667 (C=O), 1591 (C=N); EI-MS, m/z: 400 (M^+).

2.3.5. 3-(4-Aminophenyl)-5-(4-methoxyphenyl)-N-(o-tolyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (4e)

^{1}H NMR (400 MHz, DMSO d_6): δ_H (ppm) 2.11 (3H, s, CH_3), 3.03 (1H, dd, J = 3.16, 11.83 Hz, H_a), 3.78 (1H, dd, J = 3.81, 11.01 Hz,

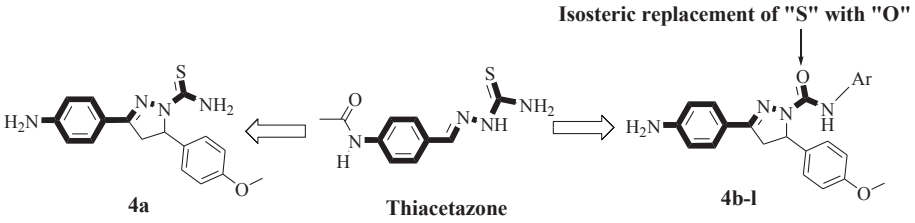

Fig. 1 – Design of the title compounds (4a-l) based on the structure of thiacetazone.