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Original Article

Design, synthesis and antimycobacterial activity of some novel 3,5-dichloro-2-ethoxy-6-fluoropyridin-4 amine cyclocondensed dihydropyrimidines

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ARTICLE INFO

Article history:
Received 29 December 2012
Accepted 15 March 2013
Available online 9 April 2013

Keywords:
Antimycobacterial
Dihydropyrimidines
Heteroaryl aldehyde
Mycobacterium tuberculosis
CIP and H37Rv strain

ABSTRACT

Background/aim: Pyrimidine is found as a core structure in a large variety of compounds that exhibit important biological activity. Specifically, 2,4,5,6-tetrasubstituted dihydropyrimidines have shown potent antimycobacterial activity. The use of combinatorial approaches toward the synthesis of drug-like scaffolds is a powerful tool in helping to speed up drug discovery. Recently, we have developed a laboratory made para toluenesulfonic acid (PTSA) as an efficient catalyst to generate 2,4,5,6-substituted dihydropyrimidine libraries using a one-pot multicomponent reaction.

Methods: Based on the activity of compound 7a, a series of novel 2,4,5,6-pyrimidine derivatives were synthesized by reacting N-(3,5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-3-oxobutanamide, urea or thiourea and appropriate aldehyde in the presence of catalytic amount of PTSA as an efficient catalyst using modifications at the 4th-position of the dihydropyrimidine moiety. Synthesized compounds analyzed by melting point, thin layer chromatography (TLC), IR, ^{1}H NMR, mass spectra and *in vitro* antimycobacterial activity.

Results: Among the synthesized compounds, compound N-(3,5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-4-(4-fluorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (7j) was found to be the most potent against *Mycobacterium tuberculosis* CIP 103471 and *M. tuberculosis* H37Rv ATCC with minimum inhibitory concentration (MIC) 1.13 and 1.09 μg/ml respectively.

Conclusion: A series of novel Biginelli dihydropyrimidines of biological interest were synthesized and analyzed for their structures. Our present study makes it an interesting compound when compared to the current therapeutic agents and are considered the candidates to investigate further for the same.

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0974-6943/$ – see front matter
http://dx.doi.org/10.1016/j.jopr.2013.03.016

1. Introduction

Pyrimidine is found as a core structure in a large variety of compounds that exhibit important biological activity.[1] Many researchers have attempted to determine the synthetic routes and various biological activities of these compounds. These developments led to the preparation and pharmacological evaluation of dihydropyrimidines (DHPM).[2,3] The discovery during the 1930s that a dihydropyridine (dihydronicotinamide derivative, NADH), ''hydrogen-transferring coenzyme'' consequently became important in biological system, has generated numerous studies on the biochemical properties of dihydropyridines and their bioisosteres dihydropyrimidines.[4–6]

We have synthesized dihydropyrimidines that represent important and extensively studied compounds belonging to the class of antimycobacterial activity. The present interest for Biginelli dihydropyrimidines is mainly due to their close structural relationship to similar drugs and compounds reported in the literature for their antitubercular,[7–9] antagonists of the human adenosine A2A receptor,[10] cyclooxygenase-2 inhibitory activity,[11,12] tyrosine kinase inhibitors, antiangiogenic agents,[13] antiamoebic activity[14] and anticancer activities.[15,16] The use of combinatorial approaches toward the synthesis of drug-like scaffolds is a powerful tool in helping to speed up drug discovery. We have developed an efficient method to generate dihydropyrimidine libraries using a three-component one-pot reaction. In our continuing work on dihydropyrimidines,[7,8] we became interested to incorporate a 3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-amine group in dihydropyrimidine ring. The reason for this is that 3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-amine derivatives are gaining importance due to their different and significant biological activities.[8,9,14,17] We perceived that when two moieties, like 3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-amine and pyrimidine are joined the molecules might exhibit superior antimycobacterial activity. It is with this idea in mind that the present work was undertaken. Therefore, this paper describes the synthesis of eleven dihydropyrimidine derivatives (7a–7k) have not yet been reported in the literature.

2. Materials and methods

All chemicals were supplied by E. Merck (Germany) and S.D fine chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system ethanol, chloroform, ethyl acetate (7:2:1); the spots were located under iodine vapors or UV light. IR spectrums were obtained on a Perkin–Elmer 1720 FT-IR spectrometer (KBr Pellets). ^{1}H NMR spectra were recorded or a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO/$CDCl_3$. Mass spectra were obtained using Shimadzu LCMS 2010A under ESI ionization technique.

2.1. Experimental

2.1.1. Procedure

2.1.1.1. *Preparation of* N-*(3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-3-oxobutanamide (3)*. 3, 5-Dichloro-2-ethoxy-6-fluoropyridin-4-amine (1) (0.01 M) and ethyl acetoacetate (2) (0.01 M) were mixed and refluxed for approximately 6h. The colorless liquid formed was then heated on a water bath to remove the alcohol formed during the reaction.[9] After allowing the reaction mixture to cool, crude crystals were obtained. Purification was performed by stirring crude crystals with cold diethyl ether for approximately 10 min using a mechanical stirrer. Allowing it to stand for 20 min, followed by filtration, resulted in the third compound in a pure form of *N*-(3,5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-3-oxobutanamide(3).

2.1.1.2. *Preparation of dihydropyrimidines by one-pot multicomponent, Biginelli synthesis (7a–k)*. The mixture of allowing it to stand for 20 min, followed by filtration, resulted in the third compound in a pure form of *N*-(3,5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-3-oxobutanamide(3) (0.005 M), urea/thiourea (0.0075 M), and appropriate aldehyde (0.005 M) with catalytic amount of PTSA in 10 ml of ethanol was stirred for 18–26 h. The reactions were monitored through TLC using 30% ethyl acetate in pet ether as solvent system. After the reaction was complete, the reaction mixture was cooled in a refrigerator and filtered. The precipitate obtained was washed thoroughly with water to remove unreacted urea/thiourea and dried. The crude solid product was recrystallized with ethanol to give the pure compounds (7a–k) Scheme 1.

2.2. Analytical data

2.2.1. *N-(3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-3-oxobutanamide (3)*

Colorless crystalline solid, M.P: 162–164 °C, Yield – 52%, IR (KBr, cm^{-1}): 3254 (N–H), 3036 (Ht–ArC–H), 2856 (AliC–H), 1734 (C=O, ketone), 1646 (C=O, amide), 1542 (C=C), 1356 (C–N), 658 (C–F), ^{1}H NMR (DMSO-d6) d: 2.31 (s, 3H, CH3), 3.48 (s, 2H, CH2), 7.26 (d, 2H, ArH), 7.46 (d, 2H, ArH), 9.36 (s, 1H, NH), MS (*m/z*): M^+ calculated 195.19, found, 194.86.

2.2.2. *N-(3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-6-methyl-2-oxo-4-(pyridin-4-yl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (7a)*

Pale-yellowish solid, M.P: 245–247 °C, Reaction time – 23 h, Yield – 52%, IR (KBr, cm^{-1}): 3260 (N–H), 3172(ArC–H), 2960 (AliC–H), 1680 (C=O, amide), 1534 (C=C), 1190 (O–C), ^{1}H NMR (DMSO-d6) d: 2.04 (s, 3H, CH3), 3.42 (s, 5H, OC_2H_5), 5.36 (s, 1H, CH), 6.48–6.81 (d, 2H, ArH), 7.29–7.37 (m, 5H, ArH), 7.48 (d, 2H, ArH), 8.68 (s, 1H, NH), 8.86 (s, 1H, NH), 9.38 (s, 1H, NH). MS (*m/z*): M^+ calculated 439.06, found 438.96.

2.2.3. *N-(3, 5-dichloro-2-ethoxy-6-fluoropyridin-4-yl)-6-methyl-4-(pyridin-4-yl)-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (7b)*

Light-bluish colored solid, M.P: 272–274 °C, Reaction time – 22 h, Yield – 57%, IR (KBr, cm^{-1}): 3276 (N–H), 3143(ArC–H), 2964 (AliC–H), 1676 (C=O, amide), 1564 (C=C), 1168 (O–C), ^{1}H NMR (DMSO-d6) d: 2.02 (s, 3H, CH3), 3.52 (d, 5H, OC_2H_5), 5.74(s, 1H, CH), 6.52 (d, 2H, ArH), 7.34–7.48 (m, 5H, ArH), 7.74 (d, 2H, ArH), 9.24 (s, 1H, NH), 9.65 (s, 1H, NH), 9.88 (s, 1H, NH), MS (*m/z*): M^+ calculated 353, found 353.75. MS (*m/z*): M^+ calculated 455.03, found 455.09.