Indian Journal of Heterocyclic Chemistry
Vol. 33 - Number 02 (Apr-Jun 2023) 221-226
https://connectjournals.com/01951.2023.33.221
https://doi.org/10.59467/IJHC.2023.33.221

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

Synthesis and *In Vitro* Antimycobacterial Activity of Some New *N*-(5-Substituted Phenylthiazol-2-yl) Pyrimidine-5-Carboxamides

Mazen Almehmadi[1], Ahad Amer Alsaiari[1], Mamdouh Allahyani[1], Abdulelah Aljuaid[1], Supriyo Saha[2] and Mohammad Asif[3]*

[1]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia
[2]Department of Pharmaceutical Chemistry, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Prem Nagar, Dehradun, Uttarakhand, India
[3]Department of Pharmaceutical Chemistry, Era College of Pharmacy, Era University, Lucknow, Uttar Pradesh, India

ABSTRACT A series of *N*-(5-substituted phenylthiazol-2-yl)pyrimidine-5-carboxamide derivatives (**2a-j**) was synthesized by the reaction of 5-substituted phenylthiazol-2-amines (**1a-1j**) and pyrimidine-5-carboxylic acid. Compounds **1a-1j** were synthesized from acetophenones, thiourea, and iodine. The newly synthesized compounds **2a-j** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis and screened for their inhibitory effect against *Mycobacterium tuberculosis* H37Rv using the microplate Alamar blue assay method. Compounds **2i** and **2j** showed high antimycobacterial activity with MIC value of 6.25 µg/mL, and compound **2h** showed MIC value of 12.50 µg/mL when compared with isoniazid (MIC value of 3.125 µg/mL), pyrazinamide (MIC value 3.125 µg/mL), and streptomycin (MIC value 6.25 µg/mL) as reference drugs.

KEYWORDS Carboxamide derivatives, Aminothiazoles, Pyrimidine-5-carboxylic acid, *Mycobacterium tuberculosis*, Antimycobacterial activity.

How to cite this article: Almehmadi, M, Alsaiari, A.A., Allahyani, M., Aljuaid, A., Saha, S. Asif, M. Synthesis and *In Vitro* Antimycobacterial Activity of Some New *N*-(5-Substituted Phenylthiazol-2-yl) Pyrimidine-5-Carboxamides, *Indian J. Heterocycl. Chem.*, **2023**, *33*, 221–226. (https://doi.org/10.59467/IJHC.2023.33.221)

INTRODUCTION

One of the most widespread infectious diseases, tuberculosis (TB), is brought on by the airborne transmission of *Mycobacterium tuberculosis* (MTB). The MTB bacterium is a tiny, non-motile, aerobically obligate bacillus. It is the most prevalent infectious disease that both developed and developing countries.[1,2]

Thus, the primary focus is on the discovery of innovative anti-TB drugs with activity against latent TB, extensively drug-resistant (XDR) TB, and multidrug-resistant (MDR) TB.[3] The existing TB treatment involves 3–4 drugs for a 6–9-month period.[4] Hence, new anti-TB drugs are immediately required which can restrict long treatment and target MDR, XDR, and latent TB. In the current times, the occurrence of drug-resistant microbes is increasing at an alarming rate internationally.[5] TB is the second highest cause of death after human immunodeficiency virus (HIV) in infectious diseases.[6,7] Therefore, TB poses a challenge to chemists and scientists for the design and development of potent and novel drugs that can control MTB growth and are effective against drug-resistant strains with minimum side effects.[8,9] The increase in MTB resistance has attracted extensive interest in the design development of novel anti-TB agents.[10,11]

The 2-aminothiazole analogs have exhibited good anti-TB activity.[10,12] The structure of 2-aminothiazole analogs is comparable to that of thiolactomycin, a protein inhibitor of ß-ketoacyl-ACP synthase synthase[11] which is involved in the manufacture of mycolic acid, a key

*Corresponding author: Email: aasif321@gmail.com

Published & Hosted by :
Journal Homepage :
www.connectjournals.com/ijhc
www.connectjournals.com

against MTB H37Rv by MABA method. These compounds exhibited significant antimycobacterial activity. Compounds **2i** and **2j** showed the highest activity and compounds **2f**, **2g**, and **2h** showed moderate activity. These findings imply that there is a large potential for the *N*-arylthiazol-2-yl-pyrimidine-5-carboxamides as potent antimycobacterial drugs.

ACKNOWLEDGMENTS

The researchers would like to acknowledge the Deanship of Scientific Research, Taif University for the funding of this work.

CONFLICT OF INTEREST

There is no potential conflict of interest.

REFERENCES

[1] Martínez, R., Zamudio, G.J.N., Pretelin-Castillo, G., Torres-Ochoa, R.O., Medina-Franco. J.L., Pinzón, C.I.E., Miranda, M.S., Hernández, E. and Alanís-Garza, B. Synthesis and anti-tubercular activity of new N-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-(nitroheteroaryl) carboxamides, *Heterocycl. Comm*., **2019**, *25*, 52–59.

[2] Prasad, P.M.K. and Sundararajan, R. Design, synthesis, antitubercular and antimicrobial activities of novel thiazole substituted benzimidazole derivatives, *Der Pharm. Lett*., **2017**, *9*, 270–284.

[3] Thomas, B. and Harindran, J. Design, synthesis and evaluation of antitubercular activity of amino azetidinones from isoniazid, *Int. J. Pharm. Sci. Res*., **2016**, *7*, 2795–2804.

[4] Shingalapur, R.V., Hosamani, K.M. and Keri, R.S. Synthesis and evaluation of *in vitro* antimicrobial and antitubercular activity of 2-styryl benzimidazoles, *Eur. . Med. Chem*., **2009**, *44*, 4244–4248.

[5] Projan, S.J. and Bradford, P.A. Late-stage antibacterial drugs in the clinical pipeline, *Curr. Opin. Microbiol*., **2007**, *10*, 441–446.

[6] Bodige, S., Ravula, P., Gulipalli, K.C., Endoori, S., Cherukumalli, P.K.R., Chandra, N.S.J.N. and Seelam, N. Design, synthesis, antitubercular and antibacterial activities of pyrrolo[3,2-b]pyridine-3-carboxamide linked 2-methoxypyridine derivatives and *in-silico* docking studies, *Synth. Commun*., **2019**, *49*, 2219–2234.

[7] Rawat, B. and Rawat, D.S. Antituberculosis drug research: A critical overview, *Med. Res. Rev*., **2013**, *33*, 693–764.

[8] Rychtarcikova, Z., Krátky, M., Gazvoda, M., Komloova, M., Polanc, S., Kocevar, M., Stolarikova, J. and Vinsova, J. *N*-substituted 2-isonicotinoylhydrazine carboxamides-new antimycobacterial active molecules. *Molecules*, **2014**, *19*, 3851–3868.

[9] Pieroni, M., Wan, B., Cho, S., Franzblau, S.G. and Costantino, G. Design, synthesis and investigation on the structure-activity relationships of N-substituted 2-aminothiazole derivatives as antitubercular agents, *Eur. J. Med. Chem*., **2014**, *72*, 26–34.

[10] Kesicki, E.A., Bailey, M.A., Ovechkina, Y., Early, J.V., Alling, T., Bowman, J., Zuniga, E.S., Dalai, S., Kumar, N., Masquelin, T., Hipskind, P.A., Odingo, J.O. and Parish, T. Synthesis and evaluation of the 2-aminothiazoles as antitubercular agents, *PLoS One*, **2016**, *11*, e0155209.

[11] Vora, D., Upadhyay, N., Tilekar, K., Jain, V. and Ramaa, C.S. Development of 1,2,4-triazole-5-thione derivatives as potential inhibitors of enoyl acyl carrier protein reductase (InhA) in tuberculosis, *Iran. J. Pharm. Res*., **2019**, *18*, 1742–1758.

[12] Meissner, A., Boshoff, H.I., Vasan, M., Duckworth, B.P. and Barry, C.E. 3rd. and Aldrich, C.C. Structure-activity relationships of 2-aminothiazoles effective against *Mycobacterium tuberculosis*, *Bioorg. Med. Chem*., **2013**, *21*, 6385–6397.

[13] Aljamali, N.M., Almosawy, M.G.A.A., Hussein, A.A.A., Bahar, N.A.A.A., Ghafil, R.A.A. and Hamza, N.A. Review on chemical-biological applications of thiazole derivatives, *Forefront J. Eng. Technol*., **2020**, *2*, 9–22.

[14] Krishnan, G.P., Gnanaprakash, K. and Chandrasekhar, K.B. Design, synthesis, characterization and antitubercular activity of some novel 2,4-disubstituted thiazole derivatives, *Int. J. Res. Pharm. Sci*., **2015**, *10*, 1504–1509.

[15] Jiang, B. and Gu, X.H. Syntheses and cytotoxicity evaluation of bis (indolyl) thiazole, bis (indolyl) pyrazinone and bis(indolyl)pyrazine: Analogues of cytotoxic marine bis (indole) alkaloid. *Bioorg. Med. Chem*., **2000**, *8*, 363–371.

[16] Karuvalam, R.P., Haridas, K.R., Nayak, S.K., Row, T.N.G., Rajesh, P., Rishikesan, R. and Kumari, N.S. Design, synthesis of some new (2-amino-thiazole-4-yl) methyl ester derivatives as possible antimicrobial and antitubercular agents, *Eur. J. Med. Chem*., **2012**, *49*, 172–182.

[17] Karabasanagouda, T., Adhikari, A.V., Ramgopal, D. and Parameshwarappa, G. Synthesis of some new 2-(4-alkylthiophenoxy)-4-substituted-1,3-thiazoles as a possible anti-inflammatory and antimicrobial agents, *Ind. J. Chem*., **2008**, *47B*, 144–152.

[18] Amine, M.A.K., Rahman, D.E.A. and El-Eryani, Y.A. Synthesis and preliminary evaluation of some substituted coumarins as anticonvulsant agents, *Bioorg. Med. Chem*., **2008**, *16*, 5377–5388.

[19] Bhusari, K.P., Khedekar, P.B., Umathe, S.N., Bahekar, R.H. and Raghu, R.A. Synthesis of 8-bromo-9-substituted-1,3benzothi-zolo[5,1-b]1,3,4-triazoles and their anthelmintic activity, *Ind. J. Heterocycl. Chem*., **2000**, *9*, 275–278.

[20] Tripathi, A.C., Gupta, S.J., Fatima, G.N., Sonar, P.K., Verma, A. and Saraf, S.K. 4-Thiazolidinones: The advances continue, *Eur. J. Med. Chem*., **2014**, *72*, 52–77.

[21] Ghafil, R.A.A. and Rajaa, A.A.G. Schiff-Chalcone derivative spreparation, investigation, antibacterial assay, *Int. J. Pharm. Res*., **2019**, *11*, 657–666.

[22] Jawad, A.M. and Aljamali, N.M. Innovation, preparation of cephalexin drug derivatives and studying of (Toxicity & resistance of infection), *Int. J. Psychosoc. Rehabil*., **2020**, *24*, 3754–3767.

[23] Ajmal, R.B. Biological activity of pyrimidine derivatives: A review, *Org. Med. Chem. J*., **2017**, *2*, 555581.

[24] Bhat, A.R., Dongra, R.S. and Selokar, R.S. Potent *in-vitro* antibacterial and antifungal activities of pyrano[2,3-d]pyrimidine derivatives with quantitative yield, *Int. J. Pharma Bio. Sci*., **2014**, *5*, 422–430.

[25] Gomha, S.M. and Hassaneen, H.M.E. Synthesis and antimicrobial activity of some new pyrazoles, fused pyrazolo[3,4-d]-pyrimidine and 1,2-dihydroimidazo-[2,1-c][1,2,4]triazin-6-one derivatives, *Molecules*, **2011**, *16*, 6549–6560.

[26] Mudaraddi, K.T.Y., Nadagouda, M.N. and Aminabhavi, T.M. Pyrrolyl pyrazoline carbaldehydes as enoyl-ACP reductase inhibitors: Design, synthesis and antitubercular activity, *Open Med. Chem. J*., **2017**, *11*, 92–108.

[27] Radwan, M.A.A., Alminderej, F.M. and Awad, H.M. One-pot multicomponent synthesis and cytotoxic evaluation of novel 7-substituted-5-(1H-Indol-3-yl) tetrazolo[1,5-a]pyrimidine-6-carbonitrile, *Molecules*, **2020**, *25*, 255.

[28] Mokale, S.N., Shinde, S.S., Elgire, R.D., Sangshetti, J.N. and Shinde, D.B. Synthesis and anti-inflammatory activity of some 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl) propanoic acid derivatives, *Bioorg. Med. Chem. Lett*., **2010**, *20*, 4424–4426.

[29] Ibrahim, H.M., Behbehani, H. and Elnagdi, M.H. Approaches towards the synthesis of a novel class of 2-amino-5-arylazonicotinate, pyridazinone and pyrido[2,3-d]pyrimidine derivatives as potent antimicrobial agents, *Chem. Cent. J*., **2013**, *7*, 123.

[30] Kethireddy, S., Eppakayala, L. and Maringanti, T.C. Synthesis and antibacterial activity of novel 5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-2-carbohydrazide derivatives, *Chem. Cent. J*., **2015**, *9*, 51.

[31] Ugwu, D.I., Ezema, B.E., Eze, F.U. and Ugwuja, D.I. Synthesis and structural activity relationship study of antitubercular carboxamides, *Int. J. Med. Chem*., **2014**, *2014*, 614808.

[32] Alsayed, S.S.R., Lun, S., Luna, G., Beh, C.C., Payne, A.D., Foster, N., Bishai, W.R. and Gunosewoyo, H. Design, synthesis, and biological evaluation of novel arylcarboxamide derivatives as antitubercular agents, *RSC. Adv*., **2020**, *10*, 7523–7540.

[33] Lourenco, M.C.S., deSouza, M.V.N., Pinheiro, A.C., Ferreira, M., de L,Goncalves, R.B, Nogneira, T.C.M. and Peralta, M.A. Evaluation of anti-tubercular activity of nicotinic and isoniazid analogues, *Arkivoc*, **2007**, *15*, 181–191.

[34] Murugan, V., Shukla, M., Geetha, K.M., Ashwini, A.K. and Singh, V. Synthesis and biological activities of *N*-[(2'-Substituted phenyl)-1',3'-thiazol-5-one]-naphtho[2,1-b]furan-2-carboxamide derivatives, *Der Pharma Chem*., **2011**, *3*, 509–516.

[35] Prajapati, A.K. and Modi, V.P. Synthesis and biological activity of n-{5-(4-methylphenyl) diazenyl-4-phenyl- 1, 3-thiazol-2-yl}benzamide derivatives, *Quim. Nova*, **2011**, *34*, 771–774.

[36] Dhas, A., Kanagare, A., Kanetkar, M., Pansare, D., Deshmukh, S., Katariya, A. and Kakade, G. Rapid and efficient synthesis of 4-substituted 2-amino thiazole using copper silicate as a heterogeneous reusable catalyst, *Lett. Appl. NanoSci*., **2023**, *12*, 159.

Received: 31 Mar 2023; Accepted: 08 Jun 2023