ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Design, synthesis, characterization and antitubercular activity of some novel 2, 4-disubstituted thiazole derivatives

Gobala Krishnan P*[1], Gnanaprakash K[2], Chandrasekhar KB[3]

[1]Research Scholar, JNTUA, Anantapuramu – 515002, Andhra Pradesh, India
[2]Department of Pharmaceutical Chemistry, Saastra College of Pharmaceutical Education and Research, Nellore – 524 311, Andhra Pradesh, India
[3]Department of Chemistry, JNTUA, Anantapuramu – 515002, Andhra Pradesh, India

Article History:

Received on: 17.10.2018
Revised on: 15.03.2019
Accepted on: 18.03.2019

Keywords:

2-aminothiazole, Pyrazine 2-carboxylic acid, Mycobacterium tuberculosis (Mtb), b-Ketoacyl-ACP Synthase (KasA), Antimycobacterial action

ABSTRACT

Literature reviews reveal that thiazole and pyrazine carboxamide derivatives exhibit anticonvulsant**,** antimicrobial, anticancer and anti-tubercular activities due to the presence of –S-C=N- and-CO–NH- moiety. A series of thiazolyl pyrazine carboxamide derivatives (5a-j) were synthesized by condensation reaction between 2-amino, 4-substituted phenyl 2-amino thiazole and pyrazine 2-carboxylic acid. These synthesized thiazole derivatives (5a-j) were evaluated for their inhibitory activity against Mycobacterium tuberculosis (Mtb), $H_{37}Rv$ using microplate Alamar Blue assay (MABA). The compound, 5c and 5h showed high anti-mycobacterial activity with MIC value of 6.25 µg/ml, and the compound 5g also exhibited anti-mycobacterial activity with MIC value of 12.50 µg/ml. Molecular docking studies of these synthesized molecules with b-Ketoacyl-ACP Synthase (KasA) protein of Mycobacterium tuberculosis (Mtb) have been carried out to understand the mechanism of anti-mycobacterial action.

* Corresponding Author

Name: Gobala Krishnan P
Phone: +91-9840139923
Email: gopalintas2004@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v10i2.729

Production and Hosted by

IJRPS | https://ijrps.com

INTRODUCTION

Tuberculosis (TB) is one of the leading airborne infectious diseases in the world that are mainly caused by bacterium *Mycobacterium tuberculosis (Mtb)*, a species of genus Mycobacterium. *M.tb* is a small obligate aerobic non-motile bacillus, which was identified by Robert Koch in 1882. Eighteenth global TB report of the World Health Organization (WHO), stated that out of 8.6 million new infections, 1.3 million people died in 2012. It is the second highest cause of mortality from the infectious disease globally after Human Immunodeficiency Virus infection (HIV). Efforts to discover new anti-tuberculosis agents that will;

- shortens the duration of treatment
- Reduce the pill burden and lower dosing frequency
- be effective in treating latent, MDR and XDR TB
- be suitably formulated to manage pediatric TB
- be affordable for developing nations
- be effectively co-administered with other drugs for chronic illnesses, especially HIV.

Although there is an existing pipeline of new drugs under development that will bring new anti-tuberculosis agents into clinical use in the near future, it is still not sufficient to address the alarming rate at which the current drugs are becoming ineffective due to resistance, which stresses the need for a completely novel TB treatment regimen.

To solve the increase of TB, attempts have been made to understand the factors behind the evolution and existence of resistant strains of Mtb (C.U. Koser *et al.,* 2013; M.R. Farhat *et al.,* 2013; H. Zhang *et al.,* 2013). On the other hand, the synthesis and

high throughput screening of large chemical molecules with a wide spectrum of known and novel entities have also been carried out to identify the lead antitubercular molecules with maximum efficacy, unique and novel mode of actions (S. Ananthan *et al.,* 2009; R.C. Reynolds *et al.,* 2012; L.G. Dover *et al.,* 2011; A. Koul *et al.,* 2011). Among them, 2-aminothiazole derivatives have also exhibited good activity against Mtb, $H_{37}Rv$ (M. Pieroni *et al.,* 2014; A. Meissner *et al.,* 2013). 2-aminothiazole derivatives are found a similar structure to thiolactomycin (TLM) (G. Pappenberger *et al.,* 2007), ab-Ketoacyl-ACP Synthase (KasA) protein inhibitor (S.R. Luckner *et al.,* 2009). TLM acts by inhibiting enzyme KasA, which is responsible for the biosynthesis of mycolic acid, which is an essential component Mtb cell wall, (Q. Al-Balas *et al.,* 2009). Similarly, it is expected that thiazolyl pyrazine carboxamide derivatives may also inhibit the growth of Mtb by inhibiting the biosynthesis of mycolic acid.

Thiazoles have been reported to show several pharmacological activities. According to the literature survey, thiazoles were reported to have antimicrobial (El-S. T. Ali *et al.,* 2010; P. Karegoudar *et al.,* 2008), analgesic (T. Karabasanagouda *et al.,* 2008), anti-inflammatory (M. A. K. Amine *et al.,* 2008), anticonvulsant (A. Andreani *et al.,* 2000), cardiotonic (B. Jiang *et al.,* 2000), anticancer, antitubercular (R.P. Karuvalam *et al.,* 2012) and anthelmintic (K. P. Bhusari *et al.,* 2000) activities. Thiazoles are an important class of five-member heterocyclic compounds, found in many potent biologically active molecules such as Ritonavir (an antiretroviral drug), Sulfathiazole (antimicrobial drug), Abafungin (an antifungal drug), Bleomycin and Tiazofurin (antineoplastic drug).

MATERIALS AND METHODS

All the Chemicals were purchased from Sigma-Aldrich and Sd fine chemicals Ltd and Sigma-Aldrich as 'synthesis grade' and used without further purification. The purity of the compounds was checked by thin layer chromatography (TLC) using Hexane: Ethyl acetate (50:50) as a solvent system. Based on the literature survey, an attempt was made to design a series of thiazolyl pyrazine carboxamides. A literature review has been used to select the target protein and ligands. The ligands were docked with the enzyme KasA of Mtb (PDB code: 2WGD). The thiazolyl pyrazine carboxamides were designed, synthesized and characterized by using IR, ^{1}HNMR, mass spectra and evaluated for their antitubercular activity by Microplate Alamar Blue Assay (MABA).

Synthesis of thiazolyl pyrazine carboxamide derivatives

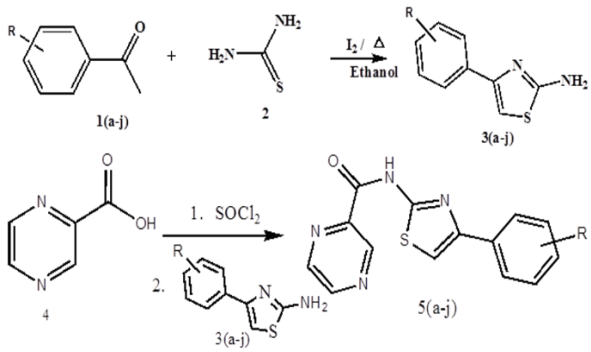

Figure 1: synthesis of thiazolyl pyrazine carboxamide derivatives

The scheme of synthesis of thiazolyl pyrazine carboxamide derivatives is shown in Figure 1.

The general method of Synthesis of 2-amino-4-phenylthiazole derivatives (3a-j)

A mixture 2.0g of substituted acetophenone (0.016 mol), 2.5g of thiourea (0.033 mol), 2.01g of Iodine (0.016 mol) and 50 ml of absolute ethanol was taken in a round bottom flask and refluxed for overnight. The mixture was diluted with 50ml of water and heated further to dissolve the solid and filtered. The filtrate was cooled in ice mixture and basified with aqueous ammonia. The resulting precipitate was filtered, washed with ether and recrystallized from ethanol (Yasser Hussein Eissa Mohammed *et al.,* 2018).

The general method of Synthesis of thiazolyl pyrazine carboxamide derivatives (5a-j)

Pyrazine-2-carboxylic acids (50.0 mmol) and thionyl chloride (5.5ml) were refluxed in dry toluene (20ml) for about 1h. The crude pyrazine acyl chloride dissolved in dry acetone (50 mL) was added dropwise to a stirred solution of the 2-aminothiazole derivatives (50.0 mmol) in dry pyridine (50 ml) kept at room temperature. After the addition was complete, stirring continued for another 30 minutes. Finally, the reaction mixture was then poured into cold water (100 ml), and the crude amide (thiazolyl pyrazine carboxamide) was collected and recrystallized from aqueous ethanol (Martin Dolezal *et al.,* 2006).

Spectral Characterization

N-(4-(4-methylphenyl) thiazol-2-yl) pyrazine-2-carboxamide (5a)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3352 (N-H); 2952 (Ar-H), 1669 (C=O), 1549 (C=N), 1458 (C=C), 1254 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 2.37 (3H, s, -CH_3); 7.15-7.17 (1H, d, Ar-H); 7.32-7.35 (1H, t, Ar-H); 7.74 (2H, d, Ar-H); 7.80 (1H, s, Ar-H); 8.85 (1H, d, Ar-H); 8.96 (1H, d, Ar-H); 9.33 (1H, s, Ar-H), 12.52 (1H, s, -NH). Mass: m/z = 297.2 (M+1).

N-(4-(4-methoxyphenyl) thiazol-2-yl) pyrazine-2-carboxamide (5b)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3358 (N-H); 2831 (Ar-H), 2034 (C-H), 1676 (C=O), 1529 (C=N), 1447 (C=C), 1239 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 3.79 (3H, s, -OCH_3); 6.99-7.01 (2H,d, Ar-H); 7.61 (1H, s, Ar-H); 7.87-7.89 (2H, d, Ar-H); 8.84 (1H, s, Ar-H); 8.95 (1H, d, Ar-H); 9.32 (1H, s, Ar-H), 12.47 (1H, s, -NH). Mass: m/z = 313.2 (M+1).

N-(4-(4-nitrophenyl) thiazol-2-yl) pyrazine-2-carboxamide (5c)

Off-white solid, FT-IR (KBr, cm^{-1}): 3302 (N-H); 2880 (Ar-H), 1669 (C=O), 1515 (C=N), 1454 (C=C), 1203 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 8.16 (1H, s, Ar-H); 8.23 (2H, d, Ar-H) 8.34 (2H, d, Ar-H); 8.86 (1H, d, Ar-H); 8.96 (1H, d, Ar-H); 9.33 (1H, d, Ar-H), 12.76 (1H, s, -NH). Mass: m /z = 328.2 (M+1).

N-(4-(3,4,5-trimethoxyphenyl) thiazol-2-yl) pyrazine-2-carboxamide (5d)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3538 (N-H); 3059 (Ar-H), 1671 (C=O), 1544 (C=N), 1454 (C=C), 1216 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 3.70-3.86 (9H, s, -OCH_3); 7.28 (2H, s, Ar-H); 7.81 (1H, s, Ar-H); 8.85 (1H, d, Ar-H); 8.96 (1H, d, Ar-H); 9.32 (1H, d, Ar-H), 12.53 (1H, s, -NH). Mass: m/z = 373.2 (M+1).

N-(4-(4-fluorophenyl) thiazol-2-yl) pyrazine-2-carboxamide (5e)

Off-white solid, FT-IR (KBr, cm^{-1}): 3358 (N-H); 2831 (Ar-H), 2034 (C-H), 1676 (C=O), 1529 (C=N), 1447 (C=C), 1239 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 7.26-7.29 (2H, d, Ar-H); 7.76 (1H, s, Ar-H); 7.99-8.00 (2H, d, Ar-H); 8.84 (1H, d, Ar-H); 8.95 (1H, d, Ar-H); 9.32 (1H, s, Ar-H), 12.53 (1H, s, -NH). Mass: m/z = 301.2 (M+1).

N-(4-(3-methoxyphenyl) thiazol-2-yl) pyrazine-2-carboxamide (5f)

Off-white solid, FT-IR (KBr, cm^{-1}): 3397 (N-H); 2835 (Ar-H), 1661 (C=O), 1593 (C=N), 1486 (C=C), 1240 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 3.82 (3H, s, -OCH_3); 6.91-6.93 (1H, m, Ar-H); 7.36 (1H, t, Ar-H); 7.55 (2H, d, Ar-H); 7.82 (1H, s, Ar-H); 8.85 (1H, s, Ar-H); 8.96 (1H, d, Ar-H); 9.33 (1H, s, Ar-H), 12.55 (1H, s, -NH). Mass: m/z = 313.2 (M+1).

N-(4-(4-bromophenyl) thiazol-2-yl) pyrazine-2-carboxamide (5g)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3324 (N-H); 2938 (Ar-H), 1960 (C-H), 1663 (C=O), 1508 (C=N), 1445 (C=C), 1284 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 7.51-7.57 (2H, d, Ar-H); 7.64-7.66 (2H, d, Ar-H); 7.73-7.74 (1H, s, Ar-H); 8.85 (1H, s, Ar-H); 8.95 (1H, d, Ar-H); 9.32 (1H, s, Ar-H), 12.59 (1H, s, -NH). Mass: m/z = 362.2 (M+1).

N-(4-(4-chlorophenyl) thiazol-2-yl) pyrazine-2-carboxamide (5h)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3450 (N-H); 2897 (Ar-H), 2317 (C-H), 1668 (C=O), 1541 (C=N), 1449 (C=C), 1287 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 7.51-7.53 (2H, d, Ar-H); 7.85 (1H, s, Ar-H); 7.98 (2H, d, Ar-H); 8.86 (1H, s, Ar-H); 8.95 (1H, d, Ar-H); 9.33 (1H, s, Ar-H), 12.62 (1H, s, -NH). Mass: m/z = 316.92 (M+1).

N-(4-(3-methoxy, 4-hydroxyphenyl) thiazol-2-yl) pyrazine-2-carboxamide (5i)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3326 (N-H); 2855 (Ar-H), 2079 (C-H), 1664 (C=O), 1545 (C=N), 1498 (C=C), 1209 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 3.88 (3H, s, -OCH_3); 7.37-7.39 (1H, d, Ar-H); 7.65 (1H, d, Ar-H); 7.78 (1H, s, Ar-H); 7.90 (1H, s, Ar-H); 8.86 (1H, d, Ar-H); 8.93-8.94 (1H, d, Ar-H); 9.01 (1H, s, Ar-H); 9.34 (1H, s, Ar-H), 12.59 (1H, s, -NH). Mass: m/z = 329.2 (M+1).

N-(4-(3,4-dimethoxyphenyl) thiazol-2-yl) pyrazine-2-carboxamide (5j)

Pale yellow solid, FT-IR (KBr, cm^{-1}): 3411 (N-H); 2836 (Ar-H), 2344 (C-H), 1661 (C=O), 1588 (C=N), 1448 (C=C), 1237 (C-N). ^{1}H-NMR (DMSO-d*6*): δppm: 3.79-3.84 (6H, d, -OCH_3); 7.01-7.03 (1H, d, Ar-H); 7.52 (1H, d, Ar-H); 7.54 (1H, d, Ar-H); 7.67 (1H, s, Ar-H); 8.84-8.85 (1H, d, Ar-H); 8.95 (1H, d, Ar-H); 9.32 (1H, d, Ar-H), 12.49 (1H, s, -NH). Mass: m/z = 343.2 (M+1).

RESULTS AND DISCUSSION

A series of heterocyclic thiazole derivatives (5a-j) were synthesized by condensation of 4-phenyl 2-aminothiazole derivative and pyrazine-2-carboxylic acid. The synthesized compounds were characterized by IR, ^{1}HNMR and mass spectra. Physical properties of the synthesized thiazoles were listed in table 1. Molecular Docking is an important tool in the rational design of drugs which helps to predict the interactions between a ligand and a receptor (protein) molecule in order to predict the activity and the affinity of the small molecules. Molecular docking studies of these synthesized thiazoles with b-Ketoacyl-ACP Synthase enzyme of Mycobacterium tuberculosis (Mtb) was conducted to understand the mechanism of anti-mycobacterial action. 2-aminothiazole derivatives are found a similar structure to thiolactomycin a b-Ketoacyl-ACP Synthase (KasA) protein inhibitor acts by inhibiting enzyme KasA which is responsible for the biosynthesis of mycolic acid, which is an essential component Mtb cell wall. Similarly, it is expected

Table 1: Physical properties of synthesized compounds (5a-j)

Compound Code	R	Molecular Formula	Molecular Weight	Melting Point (^{0}C)	R_f Value	% Yield
5a	4-CH_3	$C_{15}H_{12}N_4OS$	296.36	184-185	0.69	70.53
5b	4-OCH_3	$C_{15}H_{12}N_4O_2S$	312.35	186-188	0.52	57.94
5c	4-NO_2	$C_{14}H_9N_5O_3S$	327.32	207-209	0.48	56.87
5d	3,4,5-OCH_3	$C_{17}H_{16}N_4O_4S$	372.41	175-177	0.71	54.84
5e	4-F	$C_{14}H_9FN_4OS$	300.32	179-181	0.63	72.12
5f	3-OCH_3	$C_{15}H_{12}N_4O_2S$	312.35	194-195	0.53	64.22
5g	4-Br	$C_{14}H_9BrN_4OS$	361.22	208-210	0.42	56.53
5h	4-Cl	$C_{14}H_9ClN_4OS$	316.77	200-202	0.58	58.92
5i	3-OCH_3, 4-OH	$C_{15}H_{12}N_4O_3S$	328.35	197-198	0.68	66.25
5j	3-OCH_3, 4-OCH_3	$C_{16}H_{14}N_4O_3S$	342.38	218-220	0.64	52.56

Table 2: Binding energy and antimycobacterial activity of thiazoles against Mtb H37Rv

S No	Compound	Binding Energy (Δkcal/mol)	Antimycobacterial activity (µg/ml)
01	5a	-8.0	>100
02	5b	-7.9	>100
03	5c	-6.9	6.25
04	5d	-6.6	25
05	5e	-7.9	50
06	5f	-7.7	>100
07	5g	-7.7	12.5
08	5h	-7.1	6.25
09	5i	-7.9	>100
10	5j	-6.9	100
11	Pyrazinamide	5.2	3.125
12	Streptomycin	6.8	3.125
13	Ciprofloxacin	4.8	6.25

that thiazolyl pyrazine carboxamide derivatives may also inhibit the growth of Mtb by inhibiting the biosynthesis of mycolic acid. The protein structure of b-Ketoacyl-ACP Synthase (KasA) (PDB code: 2WGD) has been retrieved from Protein Data Bank (https://www.rcsb.org/). Thiazolyl pyrazine carboxamides are selected as potential leaders, and molecular docking study was conducted against of KasA of Mtb and snapshot of compound 5c and 5h are depicted in Figure 2. Binding energies of the docked compounds were listed in table 2.

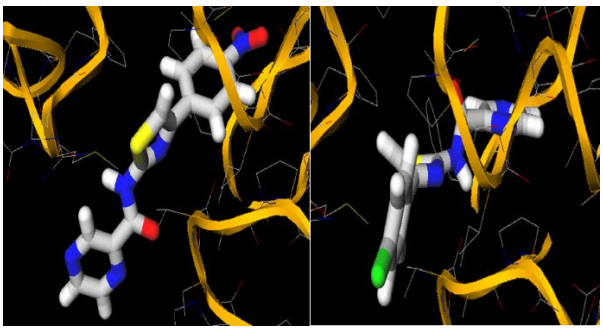

Figure 2: Snapshot of the binding pose of 5c & 5h compounds with enzyme b-Ketoacyl-ACP Synthase

Antimycobacterial activity: The antimycobacterial activity of synthesized thiazolyl pyrazine carboxamides (5a-k) was assessed against M. tuberculosis using Microplate Alamar Blue Assay (Maria C. S. Lourenco *et al.,* 2007). *Mycobacteria tuberculosis* $H37_{RV}$ strain): ATCC No- 27294 used as standard strain. MIC value of standard used, Pyrazinamide-3.125µg/ml Ciprofloxacin-3.125µg/ml Streptomycin-6.25µg/ml. The compound 5c and 5h showed good anti-mycobacterial activity with MIC value of 6.25 µg/ml, and the compound 5g also exhibited anti-mycobacterial activity with MIC value of 12.50 µg/ml. Compounds 5d, 5e and 5j, showed moderate anti-mycobacterial activity with MIC value at 25, 50 and 100 µg/ml when compared with standard drugs. The compounds 5c, 5h and 5g having electron withdrawing group like nitro, chloro and bromo substitution at the para position of phenyl ring at the fourth position of thiazole ring showed good anti-tubercular activity than other substituents.

CONCLUSION

A series of heterocyclic thiazole derivatives (5a-j) were synthesized by condensation of 4-substituted phenyl 2-aminothiazole derivative and pyrazine-2-carboxylic acid. These synthesized thiazole derivatives (5a-j) were evaluated for their inhibitory activity against Mycobacterium tuberculosis (Mtb), $H_{37}Rv$ using microplate Alamar Blue assay

(MABA). The compound 5c and 5h showed good anti-mycobacterial activity with MIC value of 6.25 µg/ml, and the compound 5g also exhibited anti-mycobacterial activity with MIC value of 12.50 µg/ml. Compounds 5d, 5e and 5j, showed moderate anti-mycobacterial activity with MIC value of 25, 50 and 100 µg/ml when compared with standard drugs. Molecular docking studies of these synthesized molecules with b-Ketoacyl-ACP Synthase (KasA) protein of Mycobacterium tuberculosis (Mtb) and binding energy of all synthesized thiazole compounds is more than that of standard drugs.

Acknowledgement

Authors acknowledge Vagdevi College of Pharmacy and Research Centre for its support to perform this effort. We also acknowledge, Dr K. G. Kishore Bhatt., Department of Pathology and Molecular biology, Marata Mandal Dental college, Belgaum for performing antitubercular Activity.

REFERENCES

A Andreani, M. Rambaldi, A. Leoni, A. Locatelli, R. Bossa, M. Chiericozzi, I. Galatulas, G. Salvatore," Synthesis and cardiotonic activity of imidazo[2,1-b] thiazoles bearing a lactam ring. Eur. J. Med. Chem. 31, 383-387, 1996.

A Koul, E. Arnoult, N. Lounis, J. Guillemont, K. Andries, The challenge of new drug discovery for tuberculosis, Nature 469 (2011) 483-490.

A Meissner, H.I. Boshoff, M. Vasan, B.P. Duckworth, C.E. Barry III, C.C. Aldrich, Structure-activity relationships of 2-aminothiazoles effective against Mycobacterium tuberculosis, Bioorg. Med. Chem. 21 (2013) 6385-6397.

B Jiang, X.– H. Gu, "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. 8, 363-371, 2000.

C.U. Koser, J.M. Bryant, J. Becq, M.E. Torok, M.J. Ellington, M.A. Marti-Renom, A.J. Carmichael, J. Parkhill, G.P. Smith, S.J. Peacock, Whole-genome sequencing for rapid susceptibility testing of M. tuberculosis, N. Engl. J. Med. 369 (2013) 290-292.

El-S. T. Ali, A. M. El. Kazak, "Synthesis and antimicrobial activity of some new 1,3-thiazoles, 1,3,4-thiadiazoles,1,2,4-triazoles and 1,3-thiazines are incorporating acridine and 1,2,3,4-tetrahydroacridine moieties". Eur. J. Chem. 1(1), 6-11, 2010.

G. Pappenberger, T. Schulz-Gasch, E. Kusznir, F. Muller, M. Hennig, Structure-assisted discovery of an aminothiazole derivative as a lead molecule for inhibition of bacterial fatty acid synthesis, Acta Crystallogr. Sect. D Biol. Crystallogr. 63 (2007) 1208-1216.

H. Zhang, D. Li, L. Zhao, J. Fleming, N. Lin, T. Wang, Z. Liu, C. Li, N. Galwey, Deng, Y. Zhou, Y. Zhu, Y. Gao, T. Wang, S. Wang, Y. Huang, M. Wang, Zhong, L. Zhou, T. Chen, J. Zhou, R. Yang, G. Zhu, H. Hang, J. Zhang, F. Li, Wan, J. Wang, X.-E. Zhang, L. Bi, Genome sequencing of 161 Mycobacterium tuberculosis isolates from China, identifies genes and intergenic regions associated with drug resistance, Nat. Genet. 45 (2013) 1255-1260.

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

L.G. Dover, G.D. Coxon, Current status and research strategies in tuberculosis drug development, J. Med. Chem. 54 (2011) 6157-6165.

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

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

M.R. Farhat, B.J. Shapiro, K.J. Kieser, R. Sultana, K.R. Jacobson, T.C. Victor, R.M. Warren, E.M. Streicher, A. Calver, A. Sloutsky, D. Kaur, J.E. Posey, Plikaytis, M.R. Oggioni, J.L. Gardy, J.C. Johnston, M. Rodrigues, P.K.C. Tang, Kato-Maeda, M.L. Borowsky, B. Muddukrishna, B.N. Kreiswirth, Kurepina, J. Galagan, S. Gagneux, B. Birren, E.J. Rubin, E.S. Lander, P.C. Sabeti, M. Murray, Genomic analysis identifies targets of convergent positive selection in drug-resistant Mycobacterium tuberculosis, Nat. Genet. 45 (2013) 1183-1189.

Maria C. S. Lourenco, Marcus V. N deSouza, Alessandra C Pinheiro, Marcelle de L. Fer reira, Rasnisb B, Goncalves, Thais Cristina M Nogneira, Monica A Peralta, Evaluation of anti-Tubercular activity of nicotinic and isoniazid analogues. ARKIVOC 2007 (xv), 181-191.

Martin Dolezal, Lukas Palek, Jarmila Vinsova, Vladimir Bucha, Josef Jampilek and Katarina Kralova, Substituted pyrazinecarboxamide: Synthesis and Biological Evaluation, Molecules 2006, 11, 242-256.

P. Karegoudar, M. S. Karthikeyan, D. J. Prasad, M. Mahalinga, B. S. Holla, N. S. Kumari, "Synthesis of

some novel 2,4-disubstituted thiazoles as possible antimicrobial agents". Eur. J. Med. Chem. 43, 261-267, 2008.

Q. Al-Balas, N.G. Anthony, B. Al-Jaidi, A. Alnimr, G. Abbott, A.K. Brown, R.C. Taylor, G.S. Besra, T.D. McHugh, S.H. Gillespie, B.F. Johnston, S.P. Mackay, G.D. Coxon, Identification of 2-aminothiazole-4-carboxylate derivatives active against Mycobacterium tuberculosis $H_{37}R_v$ and the b-ketoacyl-ACP synthase MtfabH, PLoS One 4 (2009) -5617.

R.C. Reynolds, S. Ananthan, E. Faaleolea, J.V. Hobrath, C.D. Kwong, C. Maddox, Rasmussen, M.I. Sosa, E. Thammasuvimol, E.L. White, W. Zhang, J.A. Secrist III, High throughput screening of a library based on kinase inhibitor scaffolds against Mycobacterium tuberculosis H37Rv, Tuberculosis 92 (2012) 72-83.

R.P. Karuvalam, K.R. Haridas, S.K. Nayak, T.N. Guru Row, P.Rajesh, R.Rishikesan, N. Suchetha Kumari, Design, synthesis of some new (2-aminothiazole-4-yl) methyl ester derivatives as possible antimicrobial and antitubercular agents, European Journal of Medicinal Chemistry, 49: 172-82, 2012.

S. Ananthan, E.R. Faaleolea, R.C. Goldman, J.V. Hobrath, C.D. Kwong, B.E. Laughon, J.A. Maddry, A. Mehta, L. Rasmussen, R.C. Reynolds, J.A. Secrist 3rd, N. Shindo, D.N. Showe, M.I. Sosa, W.J. Suling, E.L. White, High-throughput screening for inhibitors of Mycobacterium tuberculosis H37Rv, Tuberculosis 89 (2009) 334-353

S.R. Luckner, C.A. Machutta, P.J. Tonge, C. Kisker, Crystal structures of Mycobacterium tuberculosis KasA show mode of action within cell wall biosynthesis and its inhibition by thiolactomycin, Structure 17 (2009) 1004-1013.

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

Yasser Hussein Eissa Mohammed, Vikas H. Malojirao, Prabhu Thirusangu, Mohammed Al-Ghorbani, B.T. Prabhakar, Shaukath Ara Khanum, The Novel 4-Phenyl-2-Phenoxyacetamide Thiazoles modulates the tumour hypoxia leading to the crackdown of neoangiogenesis and evoking the cell death, European Journal of Medicinal Chemistry 143 (2018) 1826-1839.