ANVESHA-A Multidisciplinary E-Journal for all Researches Volume 3, Issue 2,December, 2022
Bi annual, Bi lingual, Peer reviewed, Referred Journal

Available online on: www.anveshaejournal.com e-ISSN 2582-6719

DOI-10.55183/amjr.2022.vo3.i.02.003

Some recent advances in Nitrogen and Sulphur containing antitubercular

Noopur Srivastava[a*], Baban Mohan Mulik[a,b], Dhananjay Pendharkar [b]
[a]Department of Chemistry and Biochemistry, Sharda School of Basic Sciences & Research, Sharda University, Greater Noida, UP, India, 201310
[b]Integral Biosciences, Noida, UP, India, 201310,
E-mail address: noopursriv@gmail.com, https://orcid.org/0000-0002-9195-5448

Abstract:

Disease responsible for the highest number of deaths across the world is tuberculosis. Despite the use of BCG vaccine, MDRTB and XDRTB is still prevalent across the globe. TB co-infection with HIV is yet another issue which is barrier in complete eradication of this disease. Some of the recently reported antitubercular compounds and their synthesis have been reported in the present article.

Keywords: Infectious diseases, MTb, EMB, INH, MABA, LORA

Introduction:

According to world health organization (WHO) and Center for Disease Control and Prevention (CDCP) more than 80 percent of deaths occur in low and average income countries due to tuberculosis.[1,2] People who are addicted to tobacco or alcohol for long term are more likely to be TB positive. Patients with autoimmune disease, diabetes, kidney disorders, malnourishment and cancer are prone to have tuberculosis. Two types of treatments are currently being used to treat TB. First-line treatment involve use of anti-tubercular drug[3,4] *viz.* (EMB) Ethambutol, (INH) Isoniazid. Whereas second-Line treatment uses drugs[5,6] *viz.* Fluoroquinolones, PAS, ethionamide. The drugs used in second line treatment are less reactive compared to first-line treatment.[7] Generally drugs in second-line treatment have side effects after treatment, therefore are not being used extensively.

Tuberculosis (TB) is a medical condition caused by *Mycobacterium tuberculosis*[8,9](MTB) that affects the lungs and symptoms observed are – fever, chest pain, chronic cough, night sweat, weight loss, shortness of breath**.** MTB infection is due to inhalation of infectious aerosol particle released from close contacts. Most infections show no symptoms (bacteria becoming dormant) this condition referred as LTB (latent tuberculosis). Current research in the past years provided valuable insight into TB transmission, diagnosis and treatment which led to decrease in TB burden but still more improvement is required on same disease because around 10% cases are that of re-infection. BCG (*Bacillus-Calmette Guerin*) vaccine developed in 1908 and development anti-TB drugs since 1943 have resulted in decline of the TB cases. As per the WHO[10,11] reports one-third world's population infected with TB. It is responsible for 2.5% deaths in the world over, major infection rates are higher in hospitals and jails. A HIV infected person has high chances of getting TB infection.[5,12]Majority of people have latent infection (LTB) hence development of new diagnostic and screening tools become necessary to control disease. Some popular tests used are - (IGRAs) Interferon-gamma release assays to diagnose LTB and TST tuberculin skin test. They work by measuring the response of T cell to TB antigens. IGRA are more sensitive & specific (80% compared to 70% sensitivity for TST) but are expensive. They detect the release of cytokine IFN- r from T cells that react to antigens not found in BCG vaccine.

There are a number of nitrogen and sulphur containing heterocyclic scaffolds which show promising antitubercular activity e.g. thiadiazole and 2-Nitroimidazopyrazinone.[13,14] Thiadiazole has been used for anti-cancer treatment as well. The Oxazolidinones is yet a new class of antibacterial protein synthesis inhibitors which block transition through a unique mechanism by binding to 23S RNA in the 50S ribosomal sub units of bacteria. Fluorine containing Benzoxazinyl-Oxazolidinones[15,16] has been reported for the treatment of MDR tuberculosis by Chinese Academy of Medical Sciences. Linezolid [2,17] is oxazolidinone developed to treat complicated MDR-TB. Linezoid belonging to oxazolidinone class of antibacterials[11,18] has been approved by FDA. It is highly active agent to most chemically relevant gram-positive bacteria and in the treatment of MDR and XDR tuberculosis. Sutezolid is in clinical studies. We hereby report the synthesis of some of the recent scaffolds reported with anti-TB activity.

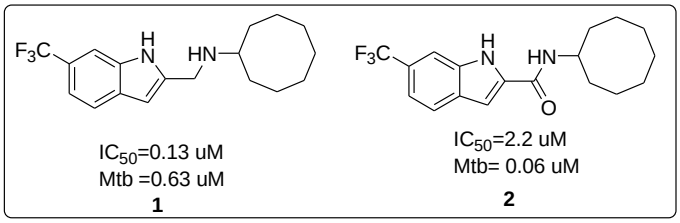
Some recently reported anti-TB scaffolds and their synthesis

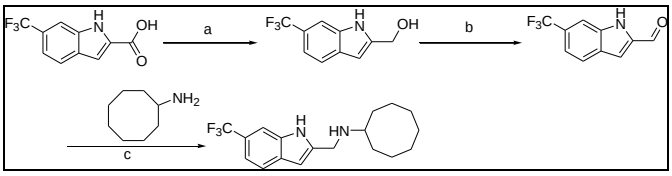
Available online on: www.anveshaejournal.com e-ISSN 2582-6719

DOI-10.55183/amjr.2022.vo3.i.02.003

(A) Amide-Amine Indole-2-carboxamides

Tan *et al* developed a poorly soluble indole carboxamide with good antitubercular activity.[19] Some solubility issues were overcome by replacing the indole ring with benzothiophene. Sulphur increased the solubility and excellent bactericidal activity against *Mycobacterium tuberculosis*.

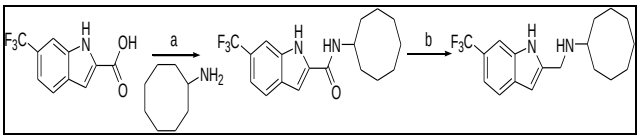




Reagents and conditions: *(a) ethyl thioglycolate ,K_2CO_3, DMF, 100°C, 16h, (b) NaOH, EtOH , RT, 4h, (c) EDC-HCl, HOBt, DIPEA, DMF, RT, 16 h, (d) LAH ,THF, 60°C, 4 h.*

Scheme 1a

The synthesis was carried out by cyclization of 2-Fluro-4 trifluromethyl benzaldehyde with ethyl thioglycolate, followed by the hydrolysis of the ester group with NaOH. The acid thus obtained was subjected to peptide coupling with cyclooctyl amine. Finally the amide was reduced to methyl amine using $LiAlH_4$(Scheme 1a).

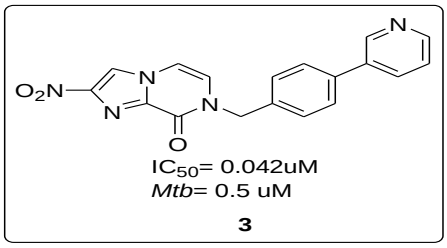


Reagents and conditions: *(a) EDC-HCl, HOBt, DIPEA, DMF, RT, 16h (b) LAH ,THF, 60°C, 4h*

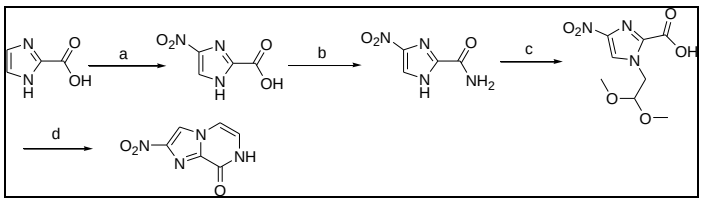
Scheme 1b

In another pathway the commercially available chemical 6-Trifluoromethyl-benzo[*b*] thiophene-2-carboxylic acid was reduction reaction done with LAH to give alcohol. The resultant alcohol was oxidized to aldehyde using MnO_2. The aldehyde obtained was then coupled with 1-amino octane to get the target by reductive amination(Scheme 1b).

(B) 2-Nitroimidazopyrazinone



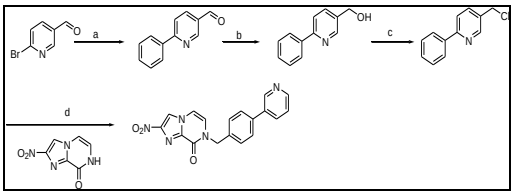
Bicyclic core scaffolds 2-Nitroimidazopyrazinone is biologically active against *MTb*. It shows excellent bactericidal and sterilizing activity, with MIC values of 0.006–0.024 μg/mL against both drug-susceptible and drug-resistant *Mycobacterium tuberculosis* under normoxic conditions.[13]



Reagents and conditions: *(a) H_2SO_4/HNO_3, 60 °C (b) oxalyl chloride, catalytic DMF, DCM, 0 °C → rt, then concentrated NH_4OH, 0 °C → rt (c) bromoacetaldehyde diethyl acetal, K_2CO_3, MW 180 °C (d) 2 M HCl/1,4-dioxane, MW 120°C*

Scheme 2a

1H-imidazole-2-carboxylic acid was converted to 4-nitro-1*H*-imidazole-2-carboxylic acid using nitrating mixture. The acid was converted to amide using acid chloride in presence of ammonia. In the next step bromoacetaldehyde diethyl acetal was coupled in presence of K_2CO_3 to finally give 2-nitroimidazo[1,2-a]pyrazin-8(7H)-one cyclized in presence of dil HCl(Scheme 2a). This was further coupled with the pyridine part in the next step(Scheme 2b).



Available online on: www.anveshaejournal.com e-ISSN 2582-6719

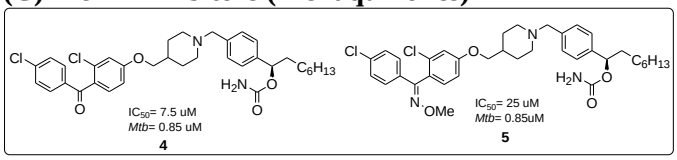
DOI-10.55183/amjr.2022.vo3.i.02.003

Reagents and conditions: *(a) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3,THF, 80°C,16h (b) $NaBH_4$, ETOH, RT,2h (c) $SOCl_2$, DCM , 0°C-RT,4h (d) K_2CO_3,MeOH,RT*

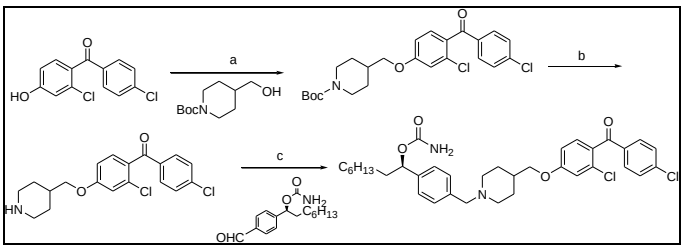
Scheme 2b

The synthesis of this compound was carried out by the Suzuki coupling of 6-bromo nicotinaldehyde with phenyl boronic acid. The product aldehyde was reduced to alcohol using $NaBH_4$. Further on treatment of alcohol with thionyl chloride 5-(chloromethyl)-2-phenylpyridine was obtained. Final target was synthesized using 2-Nitro-7H-imidazo[1,2-a]pyrazin-8-one in presence of K_2CO_3(Scheme 2b).[13]

(C) MenA inhibitors (Menaquinones)



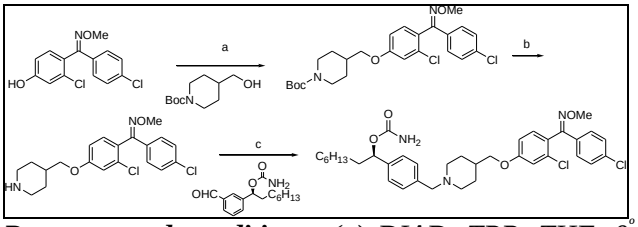
Joy Debnath et al. synthesized Mena Quinone biosynthesis inhibitors 4 and 5 against MTb. 1.4-dihydroxy-2-naphthoate prenyltransferase (Mena) inhibitors shows increase in potency of killing MTB in LORA (low oxygen recovery assay).20



Reagents and conditions: *(a) DIAD, TPP, THF, 0°C RT (b)TFA , DCM (c) STAB, DCM, 0°C,RT*

Scheme 3a

Synthesis was carried out by Mitsunobu reaction of the phenol, followed by Boc deprotection and finally reductive amination. The phenolic alcohol was subjected to the Mitsunobu reaction(using Diisopropyl azodicarboxylate) with Boc-protected piperidin-4-ylmethanol to provide the piperidinyl ethers. After deprotection of the Boc group reductive amination of NH was carried out with aldehyde(Scheme 3a). The same procedure was used to prepare the corresponding N-methoxy oxime derivative 5(Scheme 3b).

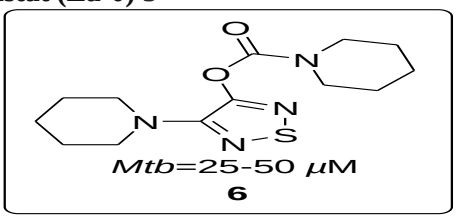


Reagents and conditions: *(a) DIAD, TPP, THF, 0°C RT (b)TFA , DCM (c) STAB, DCM, 0°C,RT*

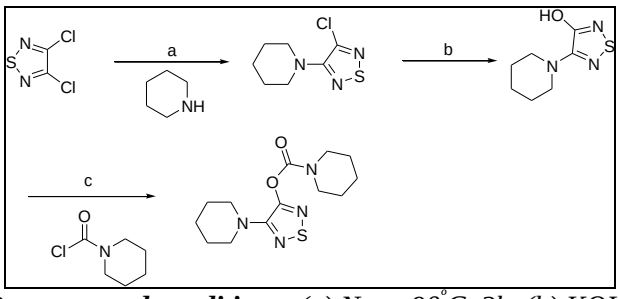
Scheme 3b

Synthesis was carried out by Mitsunobu reaction using Diisopropyl azodicarboxylate, followed by Boc deprotection and finally reductive amination.

(D) Lalistat (La-0) 5



Lehmann et.al. reported synthesis of 4- piperdine-1-yl 1,2,5 thiadizol-3-yl piperdine-1- carboxylate 6 using 3,4 dichloro1,2,5 thiadiazole. The route involves displacement of chloro using piperdine is a neat reaction and further substitution of the other chloro by OH using KOH. Finally the hydroxylated compound is treated with piperdine 1-carboxyl chloride to obtain the final ester(Scheme 4). Minimal inhibitory concentrations (MICs) were determined by addition of La-0 to diluted cultures of M. tuberculosis H37Rv and utilizing the resazurin assay. The compound exhibited a MIC of 25–50 μM exceeding the potency of previously studied orlistat ~30 μM.21



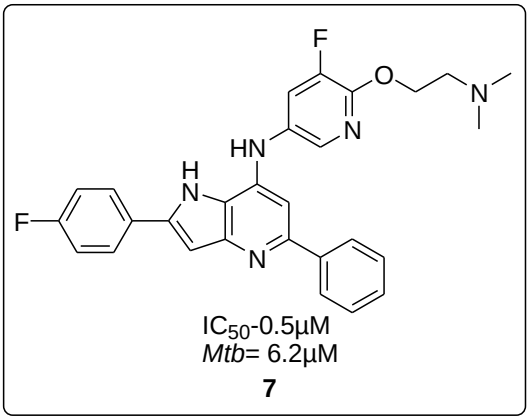
Reagents and conditions: *(a) Neat, 90°C, 2h, (b) KOH, DMSO, 100°C, 4h, (c) KOtBu, THF, RT, 16h.*

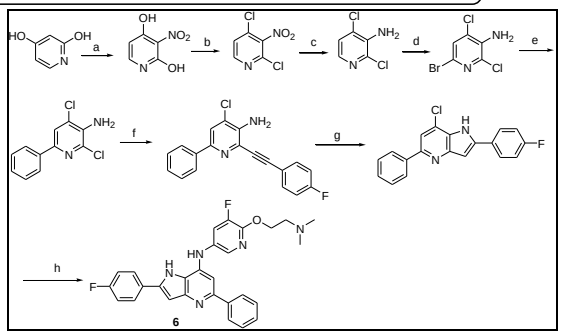
Available online on: www.anveshaejournal.com e-ISSN 2582-6719

DOI-10.55183/amjr.2022.vo3.i.02.003

Scheme 4

(E) Aminopyrazolopyrimidine 7

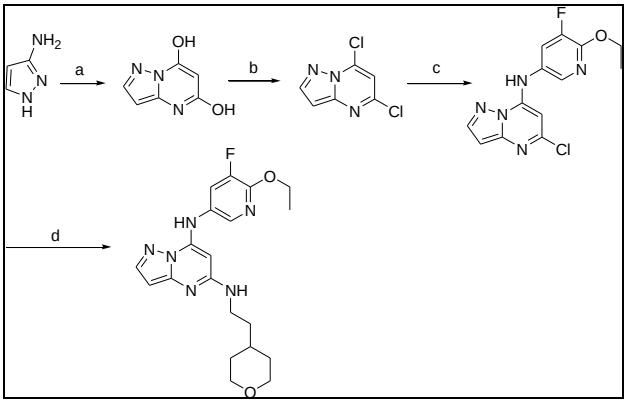




Scheme 5a

Reagents and conditions: *(a) HNO_3, H_2SO_4, 0°C, 0.5 h, 85% (b) $POCl_3$, 135°C, 12h, 72%(c) Fe, NH_4Cl, EtOH-H_2O, (4:1) 80°C, 5h, 82%; (d) NBS, DMF, 0-25°C, 1h, 47% (e) Phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O,85 °C, 12h, 81% (f) 1-ethynyl-4-fluorobenzene, $Pd(Ph)_2Cl_2$, CuI, TEA, 80°C, 5h, 45% (g) KOt-Bu, THF, MW, 100 °C, 1h, 78% (h) 1d, t-BuXPhos, THF, NaOt-Bu, MW,100°C, 2h, 63%*

Aminopyrazolopyrimidine 7 was prepared by nitration reaction on pyridine-2-4-diol was carried out using HNO3 and H2SO4 at 0°C. The nitro intermediate was then treated with POCl3 to yield the dichloro intermediate. Then nitro was reduced to amine with Fe/NH4Cl Et-OH/ Water at 80°C gives 82% yield. After bromination was carried out with NBS in DMF at 0°C to RT in 1 hr. on intermediate -4 Suzuki coupling with phenyl boronic and using Tetris catalyst In step - 6 Sonogashira coupling reaction done using diskis and CuI then cyclization reaction with potassium t-butoxide the final Buchwald coupling reaction give the target molecule 6(Scheme 5a).22



Scheme 5b

Reagents and conditions: *(a) Na, EtOH, 85 °C, 18h, 62%(b) $POCl_3$, 120 °C, 3h, 30% (c) 6-ethoxy-5-fluoropyridin-3-amine, NaH, DMF, 75 °C, 2h, 94% (d) 2-(tetrahydro-2H-pyran-4-yl)ethanamine, Na_2CO_3, DIPEA, n-BuOH, MW, 170°C, 1.25h, 36%*

Condensation of 1H- pyrozol-3- amino with diethyl malonate using sodium methoxide gave the cyclized product which was further treated with POCl3 to obtain dichloro compound as the intermediate. One chloro was substituted by 6-ethoxy-5-fluoropyridin-3-amino and another by 2-(tetrahydro-2H-pyran-4-yl)ethanamine gives the final target(Scheme 5b).22

Conclusion

This review aims to summarize the synthesis of the potent antitubercular compounds reported in recent times. This study maybe helpful for the development and preparation of new intermediates with promising ant-TB activity.

Abbreviations:

MABA - Microplate alamar blue assay
DIAD - Diisopropylazodicarboxylate,
MIC - Minimum Inhibitory Concentration
TFA – Trifluroacetic acid
IGRA - Interferon-gamma release assays
LORA - Low oxygen recovery assay
MDR - Multi Drug Resistant
XDR - Extensively Drug Resistant
TB - Tuberculosis

Available online on: www.anveshaejournal.com e-ISSN 2582-6719

DOI-10.55183/amjr.2022.vo3.i.02.003

NMR - Nuclear Magnetic Resonance,
DMSO - Dimethyl sulfoxide
HIV - Human Immunodeficiency Virus
MBC - Minimum bacterial Concentration.
DIPEA- N,N,diisopropyl ethyl amine.
HOBt - Hydroxybenzotriazole.
MnO_2- Manganese dioxide

References

1) Zhao, H., Lu, Y., Sheng, L., Yuan, Z., Wang, B., Wang, W., Li, Y., Ma, C., Wang, X., Zhang, D. and Huang, H., 2017. Discovery of fluorine-containing benzoxazinyl-oxazolidinones for the treatment of multidrug resistant tuberculosis. ACS Medicinal Chemistry Letters, 8(5), pp.533-537.

2) Fogel, N., 2015. Tuberculosis: a disease without boundaries. Tuberculosis, 95(5), pp.527-531.

3) WHO, Global tuberculosis report 2016.

4) J Sloan, D., R Davies, G. and H Khoo, S., 2013. New drugs and treatment regimens. Current Respiratory Medicine Reviews, 9(3), pp.200-210.

5) Zhang, N.N., Liu, Z.Y., Liang, J., Tang, Y.X., Qian, L., Gao, Y.M., Zhang, T.Y. and Yan, M., 2018. Design, synthesis, and biological evaluation of m-amidophenol derivatives as a new class of antitubercular agents. Med Chem Comm, 9(8), pp.1293-1304.

6) Koch, A., Cox, H. and Mizrahi, V., 2018. Drug-resistant tuberculosis: challenges and opportunities for diagnosis and treatment. Current Opinion in Pharmacology, 42, pp.7-15.

7) Tesfaye, F., Sturegård, E., Walles, J., Winqvist, N., Balcha, T.T., Karlson, S., Mulleta, D., Isberg, P.E., Jansson, M. and Björkman, P., 2020. Alternative biomarkers for classification of latent tuberculosis infection status in pregnant women with borderline Quantiferon plus results. Tuberculosis, 124, p.101984.

8) Kavková, V., 2016. Příprava derivátů tetrazolu s vysokou antimykobakteriální aktivitou a základní in vitro hodnocení jejich toxicity.

9) Saxena, N., Srivastava, N., Shukla, P. and Tripathi, G.K., 2019. The drug discovery development for treatment of tuberculosis. Journal of Drug Delivery and Therapeutics, 9(3-s), pp.802-819.

10) World Health Organization, 2013. Global tuberculosis report 2013. World Health Organization.

11) Scorpio, A., Lindholm-Levy, P., Heifets, L., Gilman, R., Siddiqi, S., Cynamon, M. and Zhang, Y., 1997. Characterization of pncA mutations in pyrazinamide-resistant Mycobacterium tuberculosis. Antimicrobial Agents and Chemotherapy, 41(3), pp.540-543.

12) Tantry, S.J., Shinde, V., Balakrishnan, G., Markad, S.D., Gupta, A.K., Bhat, J., Narayan, A., Raichurkar, A., Jena, L.K., Sharma, S. and Kumar, N., 2016. Scaffold morphing leading to evolution of 2, 4-diaminoquinolines and aminopyrazolopyrimidines as inhibitors of the ATP synthesis pathway. Med Chem Comm, 7(5), pp.1022-1032.

13) Ang, C.W., Tan, L., Sykes, M.L., AbuGharbiyeh, N., Debnath, A., Reid, J.C., West, N.P., Avery, V.M., Cooper, M.A. and Blaskovich, M.A., 2020. Antitubercular and antiparasitic 2-nitroimidazopyrazinones with improved potency and solubility. Journal of Medicinal Chemistry, 63(24), pp.15726-15751.

14) Rizal, R.A., Purba, N.O., Siregar, L.A., Sinaga, K. and Azizah, N., 2020. Analysis of Tuberculosis (TB) on X-ray Image Using SURF Feature Extraction and the K-Nearest Neighbor (KNN) Classification Method. JAICT, 5(2), pp.9-12.

15) Nuermberger, E., 2016. Evolving strategies for dose optimization of linezolid for treatment of tuberculosis. The International Journal of Tuberculosis and Lung Disease, 20(12), pp.S48-S51.

16) Hunter, R.L., 2016. Tuberculosis as a three-act play: A new paradigm for the pathogenesis of pulmonary tuberculosis. Tuberculosis, 97, pp.8-17.

17) Mota, F., Jadhav, R., Ruiz-Bedoya, C.A., Ordonez, A.A., Klunk, M.H., Freundlich, J.S. and Jain, S.K., 2020. Radiosynthesis and biodistribution of 18F-linezolid in Mycobacterium tuberculosis-infected mice using positron emission tomography. ACS infectious diseases, 6(5), pp.916-921.

18) Nikiforov, P.O., Surade, S., Blaszczyk, M., Delorme, V., Brodin, P., Baulard, A.R., Blundell, T.L. and Abell, C., 2016. A fragment merging approach towards the development of small molecule inhibitors of Mycobacterium tuberculosis EthR for use as ethionamide

Available online on: www.anveshaejournal.com e-ISSN 2582-6719

DOI-10.55183/amjr.2022.vo3.i.02.003

boosters. Organic & Biomolecular Chemistry, 14(7), pp.2318-2326.

19) Tan, Y.J., Li, M., Gunawan, G.A., Nyantakyi, S.A., Dick, T., Go, M.L. and Lam, Y., 2020. Amide–amine replacement in indole-2-carboxamides yields potent mycobactericidal agents with improved water solubility. ACS Medicinal Chemistry Letters, 12(5), pp.704-712.

20) Debnath, J., Siricilla, S., Wan, B., Crick, D.C., Lenaerts, A.J., Franzblau, S.G. and Kurosu, M., 2012. Discovery of selective menaquinone biosynthesis inhibitors against Mycobacterium tuberculosis. Journal of Medicinal Chemistry, 55(8), pp.3739-3755.

21) Lehmann, J., Vomacka, J., Esser, K., Nodwell, M., Kolbe, K., Rämer, P., Protzer, U., Reiling, N. and Sieber, S.A., 2016. Human lysosomal acid lipase inhibitor lalistat impairs Mycobacterium tuberculosis growth by targeting bacterial hydrolases. Med Chem Comm, 7(9), pp.1797-1801.

22) Subramanian J.T. et.al.(2016), Scaffold Morphing Led to Evolution of 2,4-Diaminoquinolines and Aminopyrazolopyrimidines As Inhibitors of ATP Synthesis Pathway, Med Chem Comm,7 ,1022-1032.