*THINK INDIA JOURNAL*

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

# A Review on Anti Tubercular Compounds

Pankaj Wadhwa[1*], Sanjeev Sahu[1], Amit Mittal [1], Suraj Pal Verma [1]

[1]Lovely School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab)-144401, India

**Abstract**

In current scenario, the number of infectious disease such as HIV, TB etc. has tremendously increases. It was also observed that continuous use of first line therapy against these infectious cases leads to resistance. Here, in the present work, we deals with designs, synthesis and evaluation of anti tuberculosis compounds along with their biological activities. This will help the reader in successful designing of new drugs against different strains of mycobacterium tuberculosis.

**Keywords:** Tuberculosis, Isoniazid, Minimum Inhibitory Concentration

* Corresponding author. Dr. Pankaj Wadhwa
School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab)-144401, India
Tel.: +91 9461754780. E-mail address: pankaj.23400@lpu.co.in

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

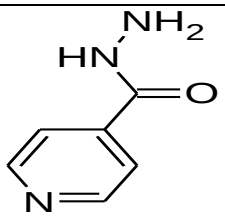
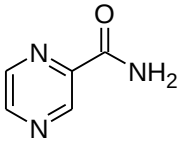
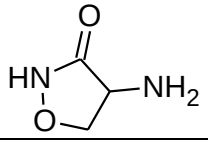
## Introduction

Different infectious diseases such as HIV, tuberculosis (TB) have serious impact on human health as well as growth of developing countries. To tackle these problems various types of combination therapies are used. As it is stated that TB is most serious infectious lungs disease, which is responsible for 10 million new TB cases as well as deaths of 1.3 millions HIV-negative people. It extends via inhaling tubercle bacillus droplet nuclei which after reaching at alveoli of lung are ingested by alveolar macrophages. It usually spreads through lymphatic channels or the bloodstream to more other parts of body and is more prevalent in poor and under developed countries, especially in the South East Asian and African region [1-2]. In the present work, we will discusses about available treatments and the research going on to find the lead for drug design.

## Available treatments for TB

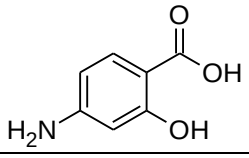
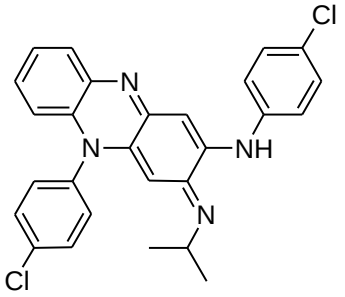
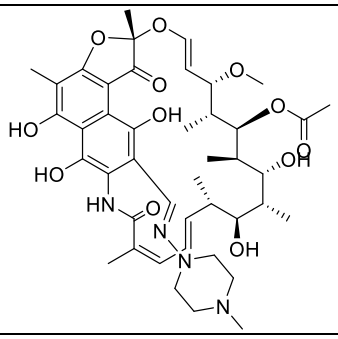
Multi-drug resistance tuberculosis is a stage where infectious *mycobacterium tuberculosis* strain is anti to many first-line drugs such as isoniazid and rifampin. For this purpose, mixtures of second-line/ new drugs, such as the fluoroquinolones are prefered [3-4]. Here, we have shown few molecules in table 1 along with their mechanism of action.

**Table 1**: Available treatments for TB action

| NAME | STRUCTURE | MECHANISM OF ACTION |
|---|---|---|
| Isoniazid |  | It inhibits the main component ofmycobacterial cell wall that is mycolic acid synthesis. |
| Pyrazinamide |  | It acts via its active form pyrazinoic acid. |
| Cycloserine |  | It acts as a cyclic analogue of D-Alanine. |

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

| | | |
|---|---|---|
| Para-aminosalicylic acid |  | An inhibitor of dihydrofolate reductase (DHFR) enzymatic activity. |
| Clofazimine |  | It binds with bacterial DNA guanine bases and inhibits bacterial proliferation. |
| Rifampicin |  | It is an inhibitor of DNA-dependent RNA polymerase. |

**Reported molecules as an anti TB compound**

In this section, we will discuss about reported molecules of different heterocyclic containing compounds as an inhibitors of tuberculosis life cycle.

Mangasuli and their group members. (2018) observed that **compound 1,** which is an member of coumarin-theophylline derivative exhibited activity at minimum inhibitory concentration of 0.12 μg/mL. It showed interactions with Lys 165, Ala 198, Leu 197 and Thr 196 [5]. Fan *et al.* (2018) evaluated different analogues of oxime-functionalized nitrofuranylamides and observed that two **compounds 2 and 3** bearing piperidinyl moiety showed significant activity at minimum inhibitory concentration values of 0.291 along with 0.158 μg/mL, respectively. Both of them also significant potent activity against MDR-TB 16833 and 16995 targets with an minimum inhibitory concentration values of 0.207–0.482 μg/mL, respectively [6].

Sager and his co workers (2018) synthesized four derivatives of triazole Schiff's Base (**compounds 4, 5, 6 and 7**) were found to be active as they controlled the growth of the Mycobacteria bacteria [7]. Later, Yang and his group members (2017) reported that that **compound 8 and 9** exerted cell anti mycobacterial activity through DHFR inhibition [8].

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

Linciano *et. al.* (2017) investigated thiadiazole analogues against trypanosoma brucei and found that a biphenyl-thiadiazole-2,5-diamine derivative (**Compound 10)** exhibited its activity at $IC_{50}$ value of 16 μM [9]. Ouyang *et. al.* (2017) stated that compound **11** exhibited inhibitory activity at minimum inhibitory concentration value of 6.25 μg/mL against vero cells via binding to glycerol (GOL) binding site [10].

Wavhale and co-workers (2017) uses scaffold hopping and shape based similarity for identifying new leads against Mycobacterium tuberculosis. They concluded that analogue of parent molecule BM212 (**compound 12)** exhibited significant activity at minimum inhibitory concentration 2.3 μg/ml against HepG2 cell [11]. In the same year, by using the similar scaffold hopping approach and structure activity relationship, Surase *et. al.* (2017) identified the hits and found that three derivatives (**compounds 13, 14 and 15)** were found to have improved activity against MTb.H37Rv [12].

Abdu-Allah *et. al.* (2016) synthesized and checked anti TB activity of substituted salicyl - hydrazones and found that **compound 16** as a important lead for further development. [13].

Nandha and his group members (2016) evaluated a series of substituted fluorobenzimidazoles with structural motifs present for their antitubercular activity. Their result showed that **compounds 17 and 18** become known as promising derivatives, characterized by minimum inhibitory concentration lower than that determined for sesamin against the pathogenic H37Rv strain [14].

Pitta *et. al.* (2016) reported that benzoxazole ring containing **compound 19** exhibited good blood stability and no hERG affinity [15]. Scalacci and his co workers (2016) synthesized thioridazine derivatives and found that the indole derivative **compound 20** showed an antimycobacterial activity which proved better than thioridazine and 15 times lower cytotoxicity [16]. Tanwar *et. al.* (2016) evaluated various quinoline-based compounds against ATCC 27294 strain of Mycobacterium tuberculosis H37Rv. Their result concluded that two compounds (**compounds 21 and 22**) displayed significant activity with minimum inhibitory concentration values of 0.2 and 0.39 μg/mL, respectively, [17].

Kumar *et. al.* (2014) reported that two compounds (**compounds 23 and 24**) of imidazo-azines class exhibited highest binding energy against four targets such as Pf-dihydrofolate reductase, Pf-protein kinase 7, Pf-enoyl acyl carrier protein reductase, and Mt-pantothenate synthetase [18]. Nagesh and his group members (2014) evaluated a series of substituted piperazine and reported that **compound 25** prevents 99% growth of M. tuberculosis H37Rv

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

strain significant activity at an minimum inhibitory concentration value of 1.56 mg/mL [19]. Naqvi *et. al.* (2014) reported that three **compounds 26, 27 and 28** showed significant anti TB activity as well as good binding energies via interacting with an active site [20].

Addla *et al.* (2013) evaluated different novel substituted phenothiazine-1,2,3-triazoles and found that three analogs (**compound 29, 30 and 31)** were most active as antitubercular agents at minimum inhibitory concentration values of 6.25 mg/mL [21].

Ranjith and co workers. (2013) reported that three molecules such as **compounds 32, 33 and 34** were most potent compounds against Mycobacterium tuberculosis H37Rv strain [22].

More and his group members. (2013) reported that novel pyrrole hydrazine derivative, Compound **35** was most active at minimum inhibitory concentration value of 0.2 mg/mL via forming hydrogen bonding interactions with Tyr158 [23]. De and his co workers (2012) reported that analogue of 4-isopentenyloxycinnamyl triazolophthalazine class **(compound 36)**, was 100-1800 times more active than isoniazid (INH) when tested against INH-resistant M. tuberculosis strains [24].

In same year, Breda *et al.* (2012) found that analogue of various pyrimidin-2(1H)-ones based derivatives (**compound 37**) exhibited promising activity against orotate phosphoribosyltransferase (OPRT) enzyme of *M. tuberculosis* at 0.19 $\pm$ 0.01 UM [25].

Lu *et. al.* (2011) evaluated various analogues of 2-acylated and 2-alkylated substituted thiophene-3-carboxylic acid and found that four compounds, **38, 39 40 and 41** exhibited their mycobacterium tuberculosis (Mtb) inhibitory activities at minimum inhibitory concentration values between 1.9 and 7.7 mM [26]. Fadl *et. al.*(2010) concluded that Schiff bases of 1H-indole-2,3-diones (For example **compound 42**) exhibited significant potent activity at an MIC 0.625 mg/ml. They further reported that **compound 42** showed 20 times greater activity comparable to standard drug isoniazid, INH, (minimum inhibitory concentration value of 12.5 mg/ml) [27].

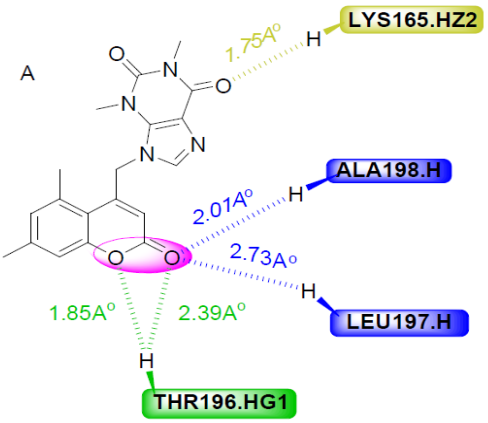
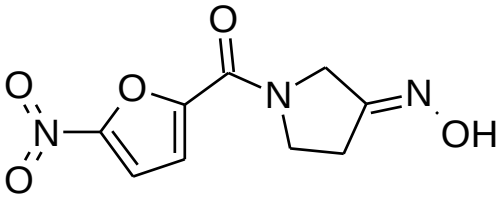
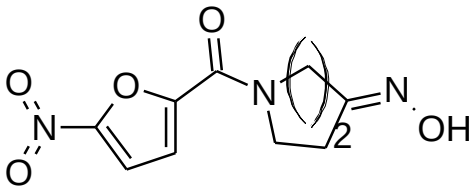
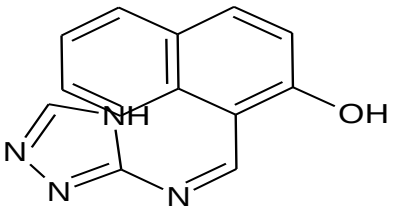
Huang *et. al.* (2009) evaluated 5-(2-methylbenzothiazol-5-yloxymethyl) isoxazole-3-carboxamide derivatives against TB strain and found that two **compounds 43 and 44** exhibited their anti Mtb growth activities at minimum inhibitory concentration values of 1.4 and 1.9 μM, respectively [28]. Bedia and their group members. (2006) evaluated hydrazide–hydrazones against of *M. Tuberculosis* strain and found that **Compound 45** was most potent among all [29]. Kamal and *et. al.* (2005) evaluated a series of substituted benzothiadiazine 1,1-dioxide derivatives were synthesized and reported that **compounds 46**, exhibited potent

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

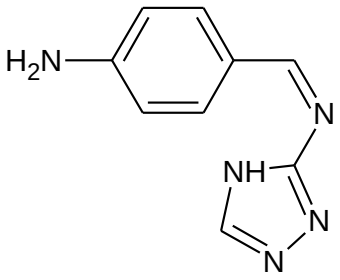
in vitro anti-tubercular activity. It was also reported that in vivo results were not so successful due to its low bioavailibity nature [30].

**Table 2:** Representation of anti TB compounds reported during 2005-2018

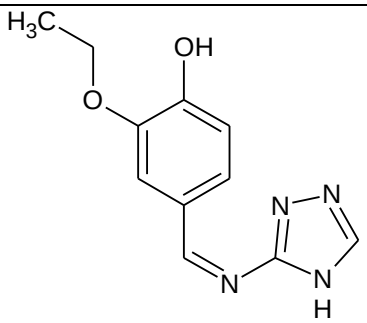
| | |
|---|---|
|  **Compound 1** |  **Compound 2** |
|  **Compound 3** |  **Compound 4** |

ISSN: 0971-1260

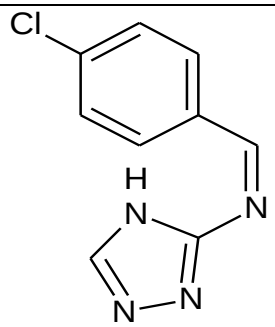
Vol-22-Issue-17-September-2019



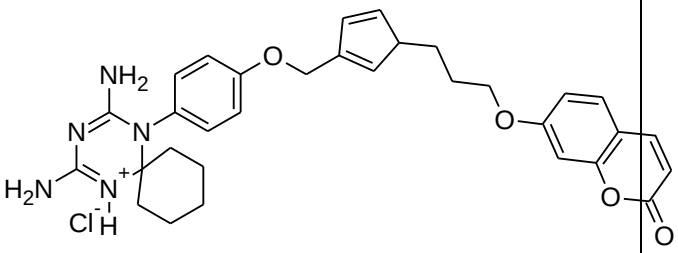
**compound 5**



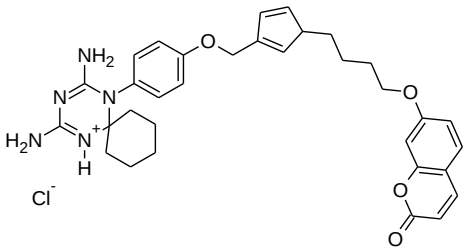
**Compound 6**



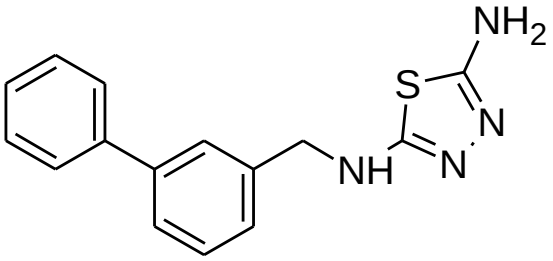
**Compound 7**



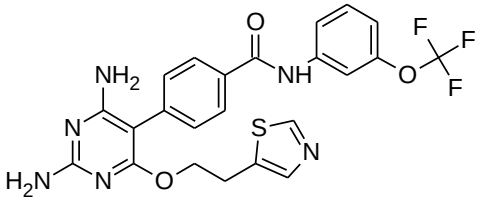
**Compound 8**

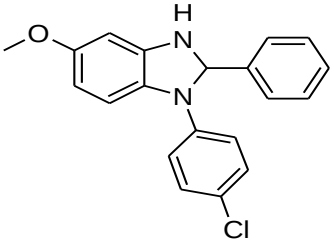


**Compound 9**



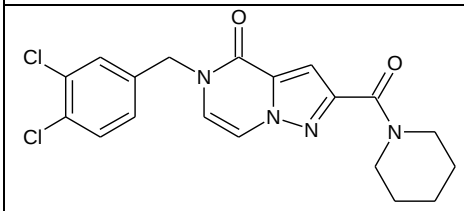
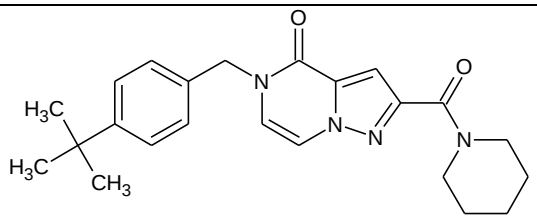
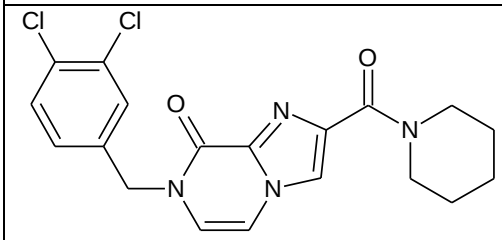
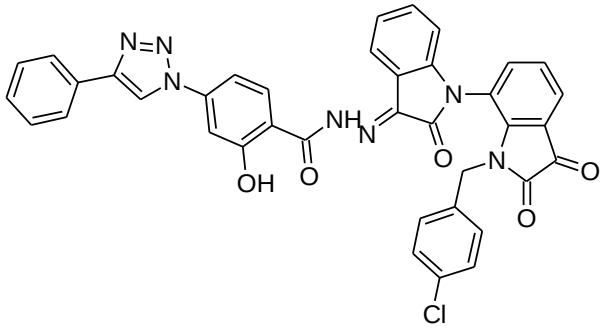
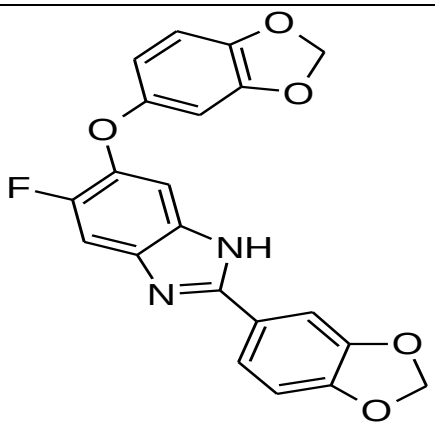
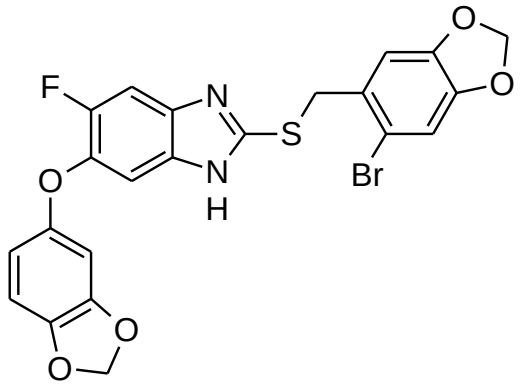
**Compound 10**





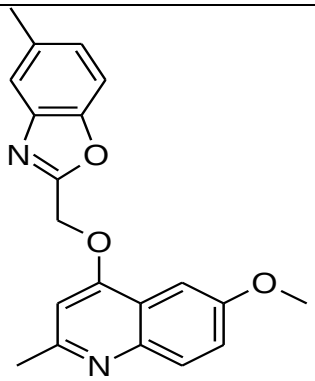
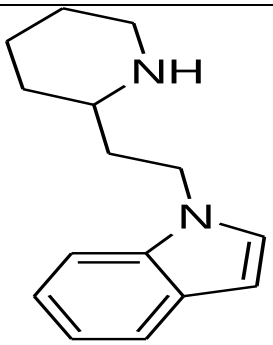
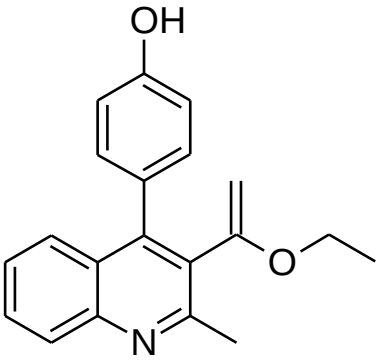
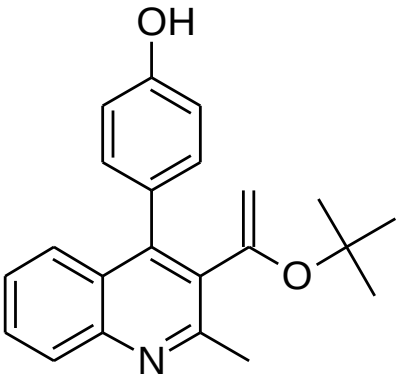
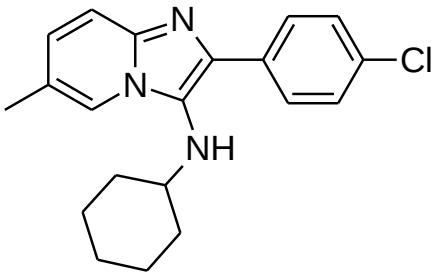
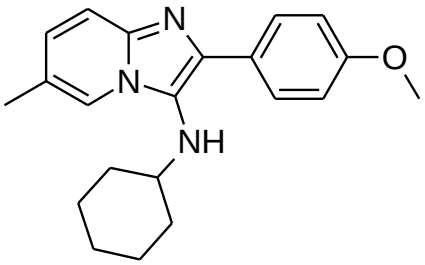
ISSN: 0971-1260

Vol-22-Issue-17-September-2019

| **Compound 11** | **Compound 12** |
|---|---|
|  **Compound 13** |  **Compound 14** |
|  **Compound 15** |  **Compound 16** |
|  **Compound 17** |  **Compound 18** |

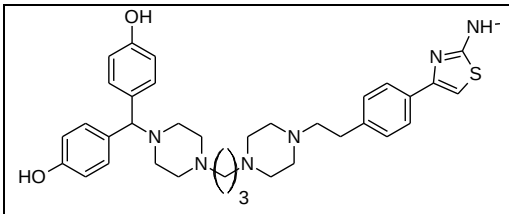
ISSN: 0971-1260

Vol-22-Issue-17-September-2019

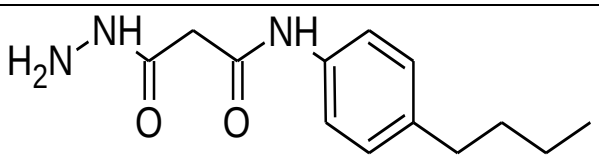
| | |
|---|---|
|  **Compound 19** |  **Compound 20** |
|  **Compound 21** |  **Compound 22** |
|  **Compound 23** |  **Compound 24** |

ISSN: 0971-1260

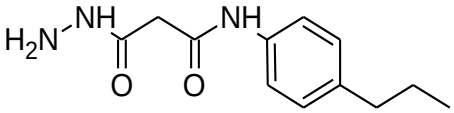
Vol-22-Issue-17-September-2019



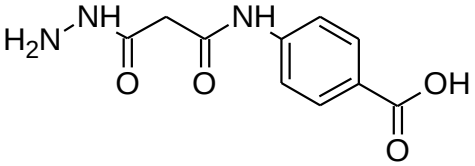
**Compound 25**



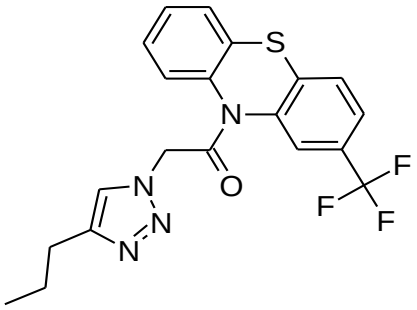
**Compound 26**



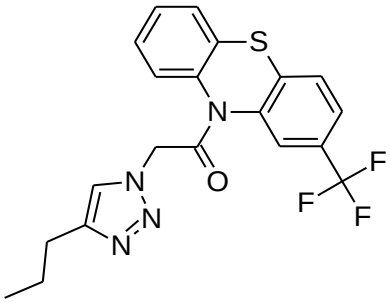
**Compound 27**



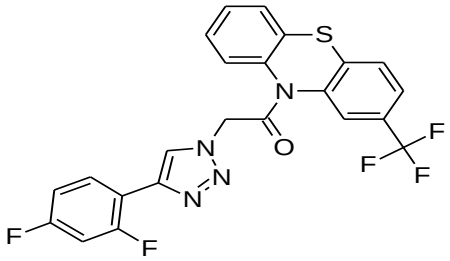
**Compound 28**



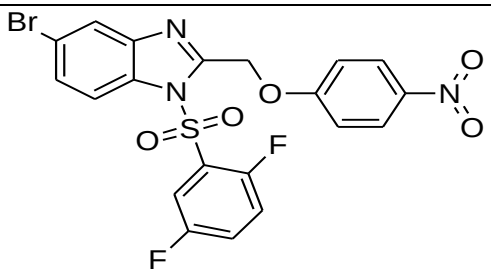
**Compound 29**



**Compound 30**



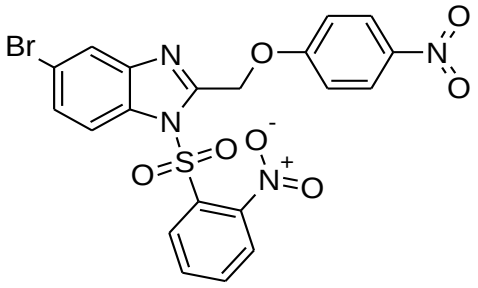
**Compound 31**



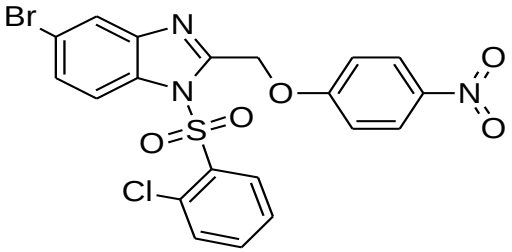
**Compound 32**

ISSN: 0971-1260

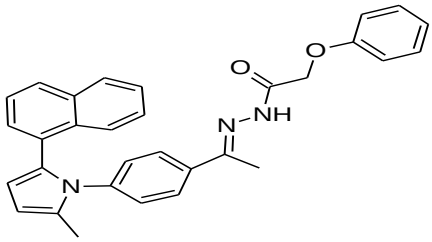
Vol-22-Issue-17-September-2019



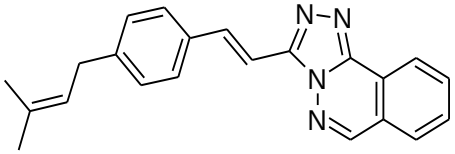
**Compound 33**



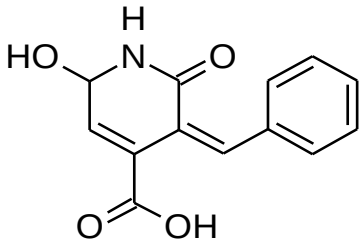
**Compound 34**



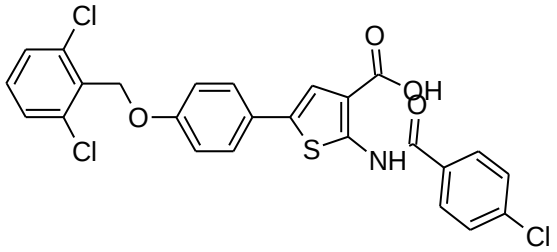
**Compound 35**



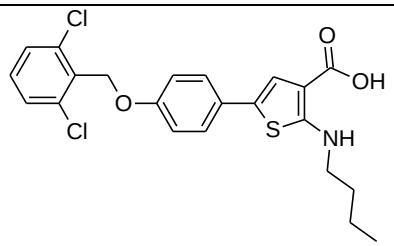
**Compound 36**

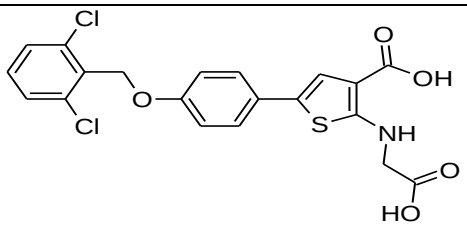


**Compound 37**



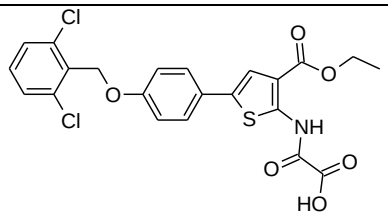
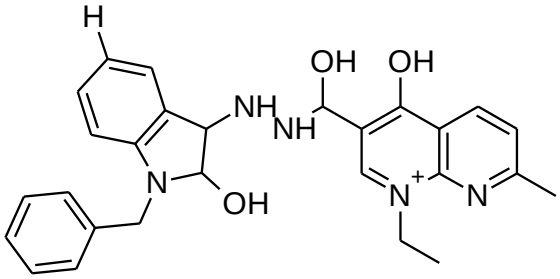
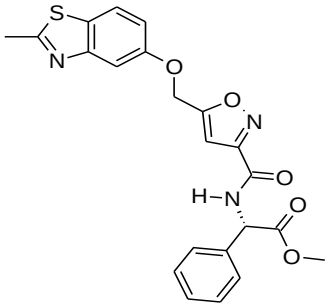
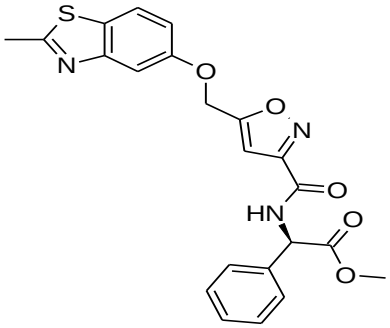
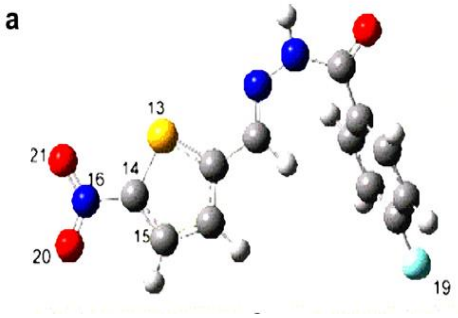
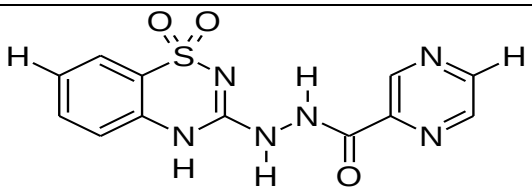
**Compound 38**





ISSN: 0971-1260

Vol-22-Issue-17-September-2019

| Compound 39 | Compound 40 |
|---|---|
|  **Compound 41** |  **Compound 42** |
|  **Compound 43** |  **Compound 44** |
|  **Compound 45** |  **Compound 46** |

## Conclusion

In this present work, we have discussed about combination therapies to tackle TB. Apart from this, it was also understood that different groups of scientists have prepared different

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

heterocyclic derivatives against various strains of mycobacterium tuberculosis. Their minimum inhibitory concentration against standard drugs along with their chemical structures are also reported here. This work will help the scientist in drug designing against various targets of TB.

**References**

1. Y. L. Janin, "Antituberculosis drugs: ten years of research," *Bioorganic & medicinal chemistry,* vol. 15, no. 7, pp. 2479-2513, 2007.
2. M. Möller, E. De Wit, and E. G. Hoal, "Past, present and future directions in human genetic susceptibility to tuberculosis," *FEMS Immunology & Medical Microbiology,* vol. 58, no. 1, pp. 3-26, 2010.
3. A. Kumar, A. Farhana, L. Guidry *et al.*, "Redox homeostasis in mycobacteria: the key to tuberculosis control?," *Expert reviews in molecular medicine,* vol. 13, 2011.
4. A. Rendon, S. Tiberi, A. Scardigli *et al.*, "Classification of drugs to treat multidrug-resistant tuberculosis (MDR-TB): evidence and perspectives," *Journal of thoracic disease,* vol. 8, no. 10, pp. 2666, 2016.
5. S. N. Mangasuli, K. M. Hosamani, H. C. Devarajegowda *et al.*, "Synthesis of coumarin-theophylline hybrids as a new class of anti-tubercular and anti-microbial agents," *European journal of medicinal chemistry,* vol. 146, pp. 747-756, 2018.
6. Y.-L. Fan, J.-B. Wu, X. Ke *et al.*, "Design, synthesis and evaluation of oxime-functionalized nitrofuranylamides as novel antitubercular agents," *Bioorganic & medicinal chemistry letters,* vol. 28, no. 18, pp. 3064-3066, 2018.
7. A. A. Sager, Z. S. Abood, W. M. El-Amary *et al.*, "Design, Synthesis and Biological Evaluation of Some Triazole Schiff's Base Derivatives as Potential Antitubercular Agents," *The open medicinal chemistry journal,* vol. 12, pp. 48, 2018.
8. X. Yang, W. Wedajo, Y. Yamada *et al.*, "1, 3, 5-triazaspiro [5.5] undeca-2, 4-dienes as selective Mycobacterium tuberculosis dihydrofolate reductase inhibitors with potent whole cell activity," *European journal of medicinal chemistry,* vol. 144, pp. 262-276, 2018.
9. P. Linciano, A. Dawson, I. Pöhner *et al.*, "Exploiting the 2-amino-1, 3, 4-thiadiazole scaffold to inhibit Trypanosoma brucei pteridine reductase in support of early-stage drug discovery," *ACS omega,* vol. 2, no. 9, pp. 5666-5683, 2017.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

10. Y. Ouyang, H. Yang, P. Zhang *et al.*, "Synthesis of 2, 4-Diaminopyrimidine Core-Based Derivatives and Biological Evaluation of Their Anti-Tubercular Activities," *Molecules,* vol. 22, no. 10, pp. 1592, 2017.
11. R. D. Wavhale, E. A. Martis, P. K. Ambre *et al.*, "Discovery of new leads against Mycobacterium tuberculosis using scaffold hopping and shape based similarity," *Bioorganic & medicinal chemistry,* vol. 25, no. 17, pp. 4835-4844, 2017.
12. Y. B. Surase, K. Samby, S. R. Amale *et al.*, "Identification and synthesis of novel inhibitors of mycobacterium ATP synthase," *Bioorganic & medicinal chemistry letters,* vol. 27, no. 15, pp. 3454-3459, 2017.
13. H. H. Abdu-Allah, B. G. Youssif, M. H. Abdelrahman *et al.*, "Synthesis and anti-mycobacterial activity of 4-(4-phenyl-1H-1, 2, 3-triazol-1-yl) salicylhydrazones: revitalizing an old drug," *Archives of pharmacal research,* vol. 40, no. 2, pp. 168-179, 2017.
14. B. Nandha, L. G. Nargund, S. L. Nargund *et al.*, "Design and Synthesis of Some Novel Fluorobenzimidazoles Substituted with Structural Motifs Present in Physiologically Active Natural Products for Antitubercular Activity," *Iranian journal of pharmaceutical research: IJPR,* vol. 16, no. 3, pp. 929, 2017.
15. E. Pitta, M. K. Rogacki, O. Balabon *et al.*, "Searching for new leads for tuberculosis: design, synthesis, and biological evaluation of novel 2-quinolin-4-yloxyacetamides," *Journal of medicinal chemistry,* vol. 59, no. 14, pp. 6709-6728, 2016.
16. N. Scalacci, A. K. Brown, F. R. Pavan *et al.*, "Synthesis and SAR evaluation of novel thioridazine derivatives active against drug-resistant tuberculosis," *European journal of medicinal chemistry,* vol. 127, pp. 147-158, 2017.
17. B. Tanwar, A. Kumar, P. Yogeeswari *et al.*, "Design, development of new synthetic methodology, and biological evaluation of substituted quinolines as new anti-tubercular leads," *Bioorganic & medicinal chemistry letters,* vol. 26, no. 24, pp. 5960-5966, 2016.
18. M. Kumar, B. Makhal, V. K. Gupta *et al.*, "In silico investigation of medicinal spectrum of imidazo-azines from the perspective of multitarget screening against malaria, tuberculosis and Chagas disease," *Journal of Molecular Graphics and Modelling,* vol. 50, pp. 1-9, 2014.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

19. H. N. Nagesh, A. Suresh, S. D. S. S. Sairam *et al.*, "Design, synthesis and antimycobacterial evaluation of 1-(4-(2-substitutedthiazol-4-yl) phenethyl)-4-(3-(4-substitutedpiperazin-1-yl) alkyl) piperazine hybrid analogues," *European journal of medicinal chemistry,* vol. 84, pp. 605-613, 2014.
20. A. Naqvi, R. Malasoni, A. Srivastava *et al.*, "Design, synthesis and molecular docking of substituted 3-hydrazinyl-3-oxo-propanamides as anti-tubercular agents," *Bioorganic & medicinal chemistry letters,* vol. 24, no. 22, pp. 5181-5184, 2014.
21. D. Addla, A. Jallapally, D. Gurram *et al.*, "Rational design, synthesis and antitubercular evaluation of novel 2-(trifluoromethyl) phenothiazine-[1, 2, 3] triazole hybrids," *Bioorganic & medicinal chemistry letters,* vol. 24, no. 1, pp. 233-236, 2014.
22. P. K. Ranjith, P. Rajeesh, K. R. Haridas *et al.*, "Design and synthesis of positional isomers of 5 and 6-bromo-1-[(phenyl) sulfonyl]-2-[(4-nitrophenoxy) methyl]-1H-benzimidazoles as possible antimicrobial and antitubercular agents," *Bioorganic & medicinal chemistry letters,* vol. 23, no. 18, pp. 5228-5234, 2013.
23. U. A. More, S. D. Joshi, T. M. Aminabhavi *et al.*, "Design, synthesis, molecular docking and 3D-QSAR studies of potent inhibitors of enoyl-acyl carrier protein reductase as potential antimycobacterial agents," *European journal of medicinal chemistry,* vol. 71, pp. 199-218, 2014.
24. P. De, G. Koumba Yoya, P. Constant *et al.*, "Design, synthesis, and biological evaluation of new cinnamic derivatives as antituberculosis agents," *Journal of medicinal chemistry,* vol. 54, no. 5, pp. 1449-1461, 2011.
25. A. Breda, P. Machado, L. A. Rosado *et al.*, "Pyrimidin-2 (1H)-ones based inhibitors of Mycobacterium tuberculosis orotate phosphoribosyltransferase," *European journal of medicinal chemistry,* vol. 54, pp. 113-122, 2012.
26. X. Lu, B. Wan, S. G. Franzblau *et al.*, "Design, synthesis and anti-tubercular evaluation of new 2-acylated and 2-alkylated amino-5-(4-(benzyloxy) phenyl) thiophene-3-carboxylic acid derivatives. Part 1," *European journal of medicinal chemistry,* vol. 46, no. 9, pp. 3551-3563, 2011.
27. T. Aboul-Fadl, F. A. Bin-Jubair, and O. Aboul-Wafa, "Schiff bases of indoline-2, 3-dione (isatin) derivatives and nalidixic acid carbohydrazide, synthesis, antitubercular activity and pharmacophoric model building," *European journal of medicinal chemistry,* vol. 45, no. 10, pp. 4578-4586, 2010.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

28. Q. Huang, J. Mao, B. Wan *et al.*, "Searching for new cures for tuberculosis: design, synthesis, and biological evaluation of 2-methylbenzothiazoles," *Journal of medicinal chemistry,* vol. 52, no. 21, pp. 6757-6767, 2009.

29. K.K. Bedia, O. Elçin, U. Seda *et al.*, "Synthesis and characterization of novel hydrazide–hydrazones and the study of their structure–antituberculosis activity," *European journal of medicinal chemistry,* vol. 41, no. 11, pp. 1253-1261, 2006.

30. A. Kamal, K. S. Reddy, S. K. Ahmed *et al.*, "Anti-tubercular agents. Part 3. Benzothiadiazine as a novel scaffold for anti-Mycobacterium activity," *Bioorganic & medicinal chemistry,* vol. 14, no. 3, pp. 650-658, 2006.