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AN UPDATE AND LITERATURE REVIEW: BENZIMIDAZOLES AS ANTI TUBERCULAR AGENTS

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ABSTRCTCT

Tuberculosis (TB) is a transmissible infectious disease caused by *Mycobacterium Tuberculosis.* It is transmit through the cough, sneeze and respiratory fluids of infectious person to another person through air. Overall 33% of peoples are suffering from the TB, 8.8 million peoples are reporting in every year, 52,000 deaths reporting in a week as well as nearly 7000 deaths are reporting in day. There are many drugs available treat tuberculosis however *Mycobacterium Tuberculosis* showing showing resistance against them. Hence there is a urgent requirement to development of new anti tubercula agents with significant pharmacological activity against *Mycobacterium Tuberculosis.* The review papers explains the literature review of benzimidazoles as antitubercular agents, it helpful to researchers to develop most active anti tubercular agents.

KEYWORDS: Tuberculosis, *Tuberculosis, Mycobacterium,* benzimidazoles.

INTRODUCTION

Tuberculosis (TB) is a transmissible infectious disease caused by *Mycobacterium Tuberculosis.* It is transmit through the cough, sneeze and respiratory fluids of infectious person to another person through air. It is also transmitted through the primary contact of the infectious person with tuberculosis.[1-2] Overall 33% of peoples are suffering from the TB, 8.8 million peoples are reporting in every year, 52, 000 deaths reporting in a week as well as nearly 7000 deaths are reporting in day.[3-4] Tuberculosis is the major problem in the African and Acian countries, above 80% of inhabitants are infected with TB, lessthan 10% peoples are reported in United states. There are many drugs available treat tuberculosis however *Mycobacterium Tuberculosis* showing resistance against them.[5] Hence there is a urgent requirement to development of new anti tubercula agents with significant pharmacological activity against *Mycobacterium Tuberculosis.* A variety of pharmacological activities shown by benzimidazoles along with anti tubercular activity.[16-46] In the present review papers explains the literature review (2000 to till date) of benzimidazoles as antitubercular agents, it helpful to researchers to develop most active anti tubercular benzimidazoles.

Chemistry of Benzimidazole Benzimidazole is a benzofused heterocyclic compound contain two Nitrogen atoms as hetero atom. The benzimiazole structure depicted in **Fig.1**. In which benzene ring fused with imidazole ring. It shows important role in medicine its shows many pharmacological activities like antitubercuar,[16-47] antitumor,[6] anti-microbial,[7] anti-inflammatory,[8] analgesis,[9] anti HIV,[10] antiviral,[11] anti-protozoal,[12] anti-malarial,[13] anti-leishmanial,[14] antibacterial.[15] Hence it is attracting many researchers to develop new benzimidazole derivatives with significant pharmacological activities.

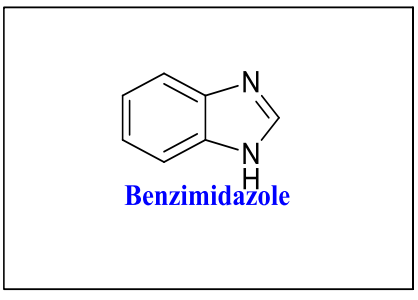

Fig. 1: Representation of structure of Benzimidazole.

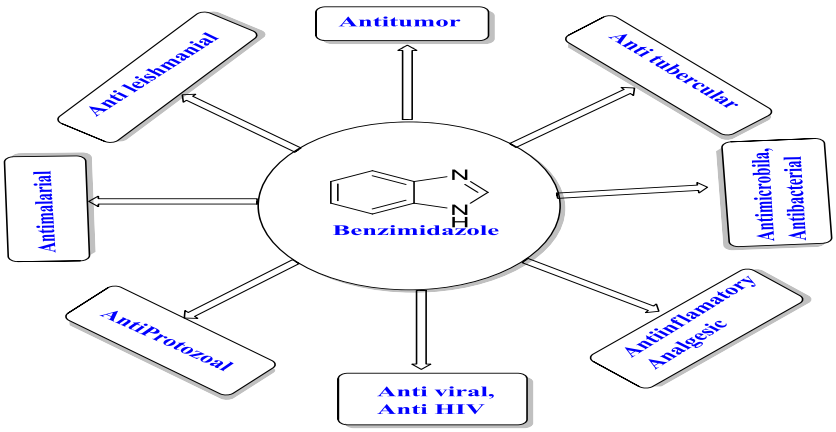

Fig. 2: Representation of pharmacological activities of Benzimidazoles.

Benzimidazole Derivatives As Anti Tubercular Agents

Senthilraja Manivannan *et al*, 2019, synthesized the Substituted benzimidazoles, evaluated the anti tubercular activity. Among all, the compound **1a, 1b** (**Fig. 3**) showed best anti tubercular activity with MIC value of (compound **1a**) 6.5 µg/mL, 6.5 µg/mL, 12.5µg/mL (compound **1b**) 6.5 µg/mL, 12.5µg/mL, 6.5 µg/mL against *Mycobaterium Tuberculosis* H37Rv, drug-resistant, drug-susceptible strains.[16]

Sujit *et al.*, 2018, synthesized the novel azo derivatives of benzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **2a** (**Fig. 3**) showed best anti tubercular activity with IC_{50} value of 0.119 µM/mL against *Mycobaterium Tuberculosis* compared with isoniazid.[17]

Snehlata *et al.*, 2017, synthesized the benzimidazole derivatives, evaluated the anti tubercular activity. Among all, the compounds **3a,3b,3c,3d, 3e,3f,3g,3h,3i (Fig. 3)** showed best anti tubercular activity with MIC value of 12.5µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with streptomycin.[18]

Jurupula *et al.*, 2015, synthesized the imidazo[2,1-b][1,3,4] thiadiazole-benzimidazole derivatives, evaluated the anti tubercular activity. Among all, the compounds **4a, 4b, 4c** (**Fig. 3**), **4d, 4e, 4f, 4g** (**Fig. 4**) showed best anti tubercular activity with MIC value of 3.125 µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv, Spec. 192, Spec. 210 compared with isoniazid, Ethambutol, Pyrazinamide.[19]

Yeong et al., 2015, synthesized the new benzimidazole aminoesters, evaluated the anti tubercular activity. Among all, the compounds **5a (Fig. 4)** showed best anti tubercular activity with IC_{50} value of 11.52 µM against *Mycobaterium Tuberculosis* strains of H37Rv compared with Amikacin, Cycloserin, Ethambutol, Isoniazid, Pyrimethamine, Rifampicin.[20]

Yaling *et al.*, 2014, synthesized the new **benzimidazoles**, evaluated the anti tubercular activity. Among all, the compound **6a (Fig. 4)** showed best anti tubercular activity with MIC value of 0.20 µg/mL, 0.049 µg/mL against non-replicating *Mycobaterium Tuberculosis* and replicating *Mycobacterium Tuberculosis* compared with rifampicin, pyrazinamide, isoniazid, ethambuthol.[21]

Shahul *et al.*, 2014, synthesized the new benzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **7a (Fig. 4)** showed best anti tubercular activity with MIC value of 0.19µM against fluoroquinolone-resistant strains of *Mycobaterium Tuberculosis* compared with isoniazid, rifampicin.[22]

Veerendra *et al.*, 2014, synthesized the 1-[(2E)-3-phenylprop-2-enoyl]-1*H*-benzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **8a, 8b, 8c (Fig. 4)** showed best anti tubercular activity with MIC value of 3.12 µg/mL, 3.12µg/mL, 1.6 µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with pyrazinamide, streptomycin, Refampicin.[23]

Bora *et al.*, 2014, synthesized the 2, 5, 6-trisubstituted benzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **9a (Fig. 4)** showed best anti tubercular activity with MIC value of 0.63 µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv.[24]

Katarzyna *et al.*, 2014, synthesized the 1*H*benzo[*d*]imidazole derivatives, evaluated the anti tubercular activity. Among all, the compounds **10a, 10b,10c,10d (Fig. 4)** showed best anti tubercular activity with MIC value of 0.75 µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv, Spec. 192, Spec. 210 compared with isoniazid, Pyrazinamide, Refampicin.[25]

Nandha *et al.*, 2013, synthesized the 1, 2,4-triazole substituted fluorobenzimidazoles, evaluated the anti tubercular activity. Among all, the compound **11a, 11b (Fig. 5)** showed best anti tubercular activity with MIC value of 12.5µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with isoniazid.[26]

Satish *et al.*, 2013, synthesized the amino alcohol derivatives of 2-methylbenzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **12a, 12b (Fig. 5)** showed best anti tubercular activity with MIC value of 6.25µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with isoniazid.[27]

Namrata *et al.*, 2013, synthesized the new benzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **13a, 13b (Fig. 5)** showed best anti tubercular activity with MIC value of 1.56µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with fluconazole, isoniazid, Ethambutol.[28]

Divya *et al.*, 2013, synthesized the Trisubstituted Benzimidazoles, evaluated the anti tubercular activity. Among all, the compound **14a (Fig. 5)** showed best anti tubercular activity with MIC value of 0.06 µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with isoniazid.[29]

Yeong *et al.*, 2013, synthesized the new benzimidazoles, evaluated the anti tubercular activity. Among all, the compound **15a** (Fig. 1) showed best anti tubercular activity with MIC value of 0.115µM, 6.12 µM against *Mycobacterium tuberculosis* H37Rv and INH-resistant *Mycobacterium Tuberculosis* compared with isoniazid.[30]

Karuvalam *et al.*, 2013, synthesized the 6-bromo-1-[(phenyl)sulfonyl]-2-[(4-nitrophenoxy) methyl]-1*H*benzimidazoles, evaluated the anti tubercular activity. Among all, the compounds **16a, 16b, 16c, 16d, 16e (Fig. 5)** showed best anti tubercular activity with MIC value of 1 µg/mL against *Mycobacterium Tuberculosis* H37Rv compared with isoniazid, Refampicin.[31]

Rahul *et al.*, 2012, synthesized the benzimidazolyl-1,3,4-oxadiazol-2ylthio-N-phenyl (benzothiazolyl) acetamides, evaluated the anti tubercular activity. Among all, the compound **17a, 17b, 17c (Fig. 5)** showed best anti tubercular activity with MIC value of 12.5µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with isoniazid, Refampicin, Ethambutol, Pyrazinamide.[32]

Chetan *et al.*, 2012, synthesized the synthesis of pyrido[1,2-a]benzimidazole derivatives of beta-aryloxyquinoline, evaluated the anti tubercular activity. Among all, the compound **18a (Fig. 5)** showed best anti tubercular activity with MIC value of 6.25µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with isoniazid, Refampicin.[33]

Katarzyna *et al.*, 2012, synthesized the new benzimidazoles, evaluated the anti tubercular activity. Among all, the compound **19a (Fig. 5)** showed best anti tubercular activity with MIC value of 3.1 µg/mL, 1.5µg/mL, 3.1 µg/mL against *Mycobaterium Tuberculosis* strains of H_{37}Rv, Spec. 192, Spec. 210 compared with isoniazid, Pyrazinamide, Refampicin.[34]

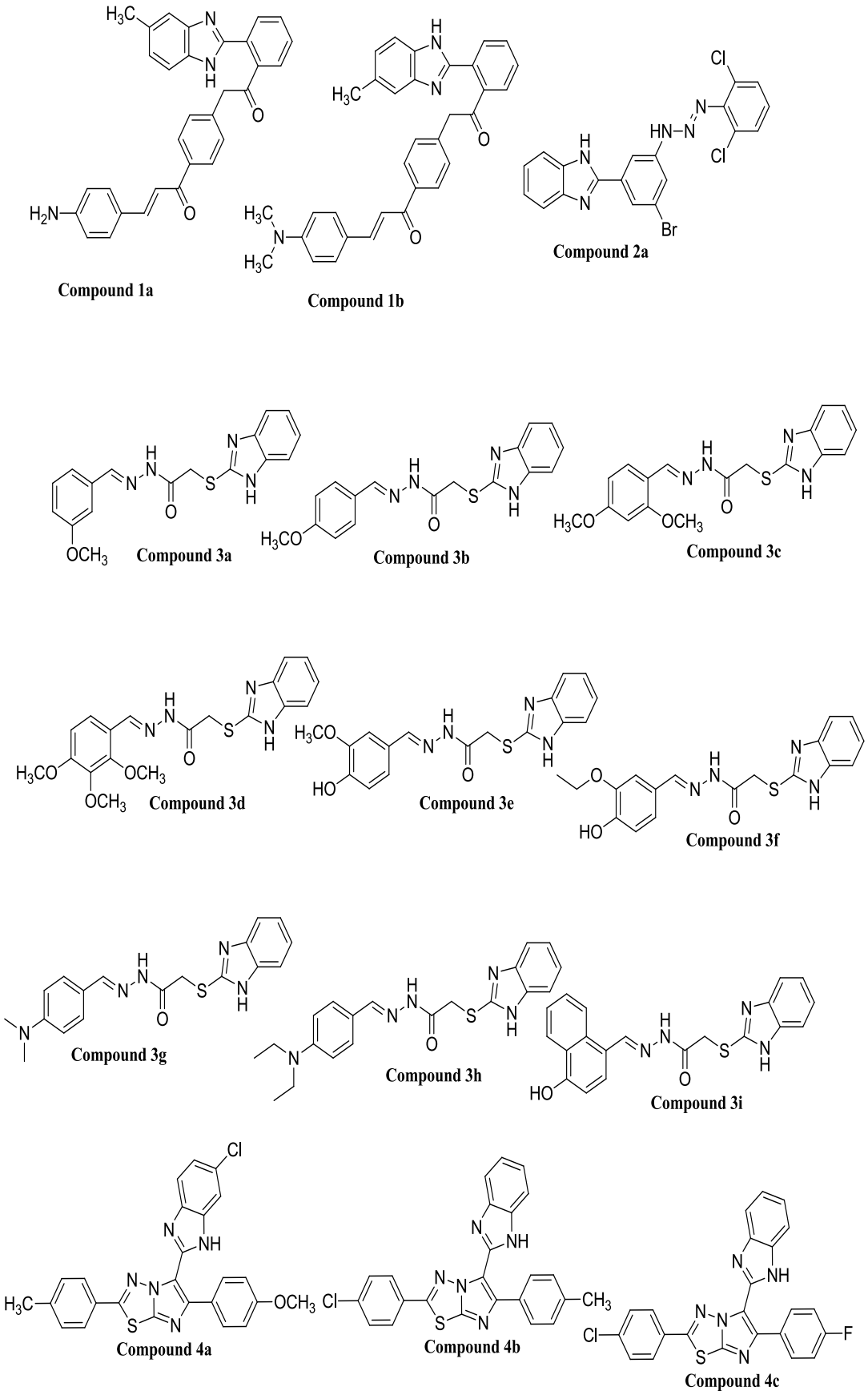

Fig. 3: Structures of effective antitubercular compounds (1a-1b, 2a, 3a-3i, 4a-4c).

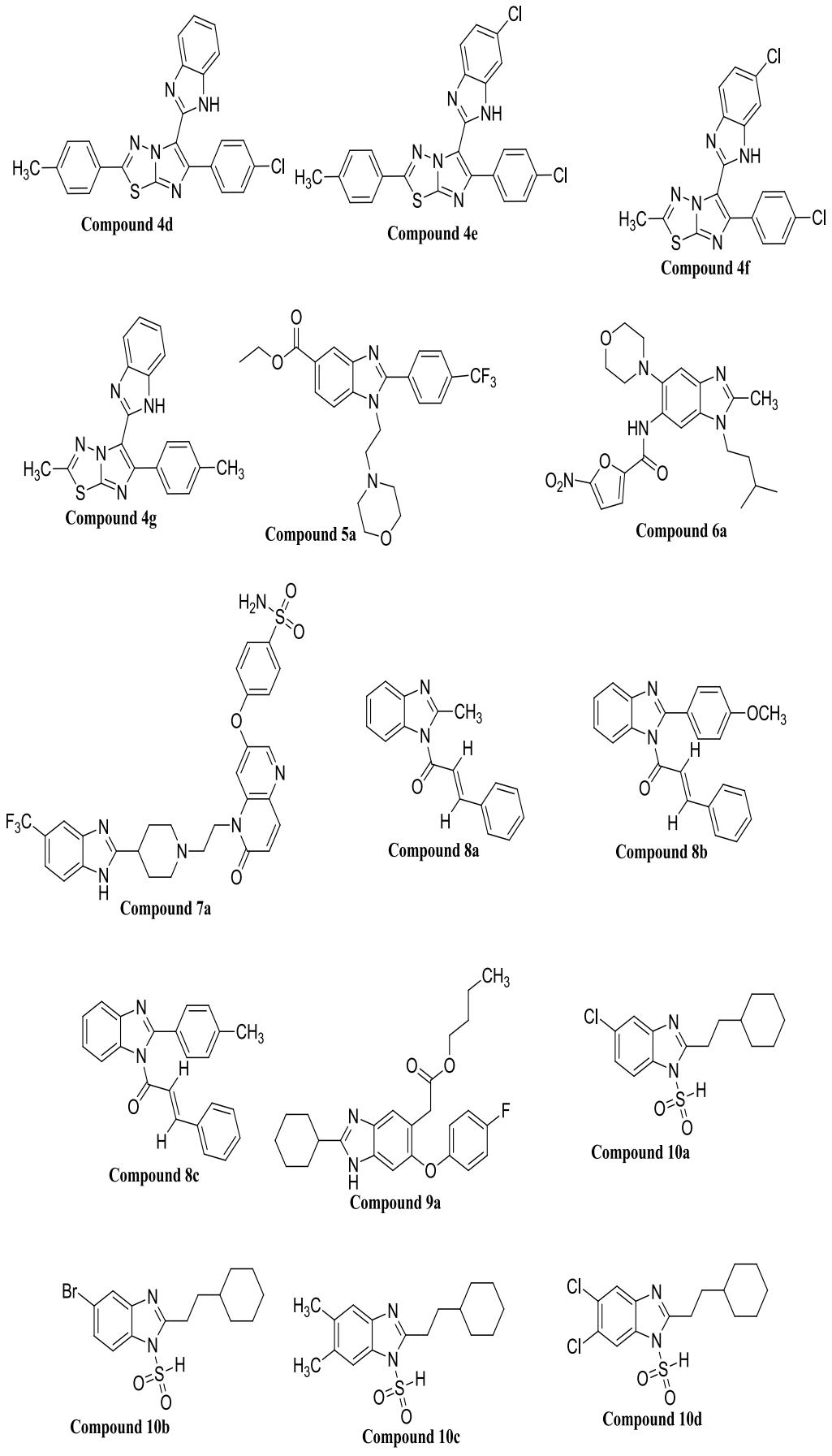

Fig.4. Structures of effective antitubercular compounds (4d-4f, 5a, 6a,7a,8a-8c, 9a, 10a-10d).

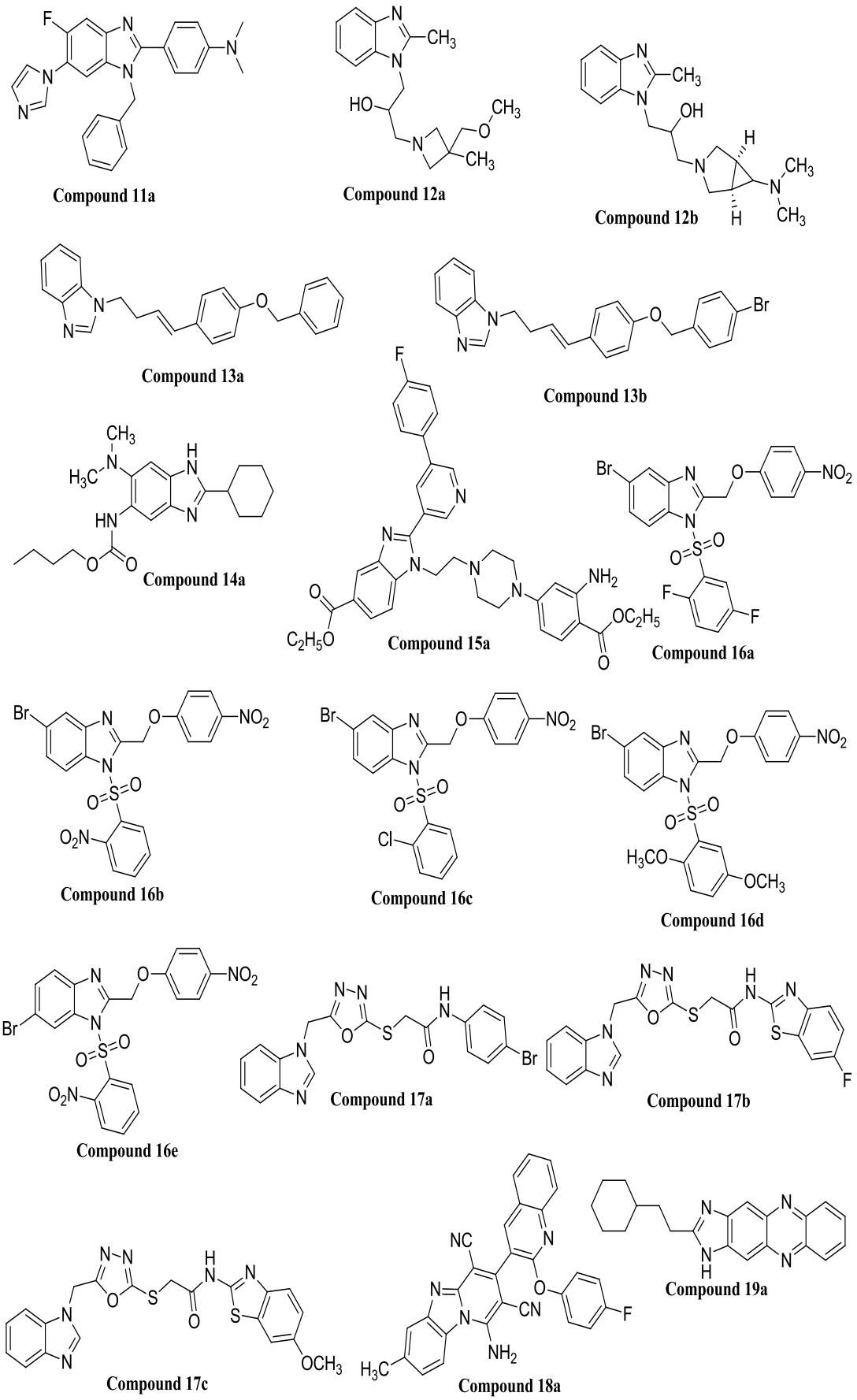

Fig.5. Structures of effective antitubercular compounds (11a, 12a-12b, 13a-13b, 14a, 15a, 16a-16e, 17a-17c, 18a, 19a).

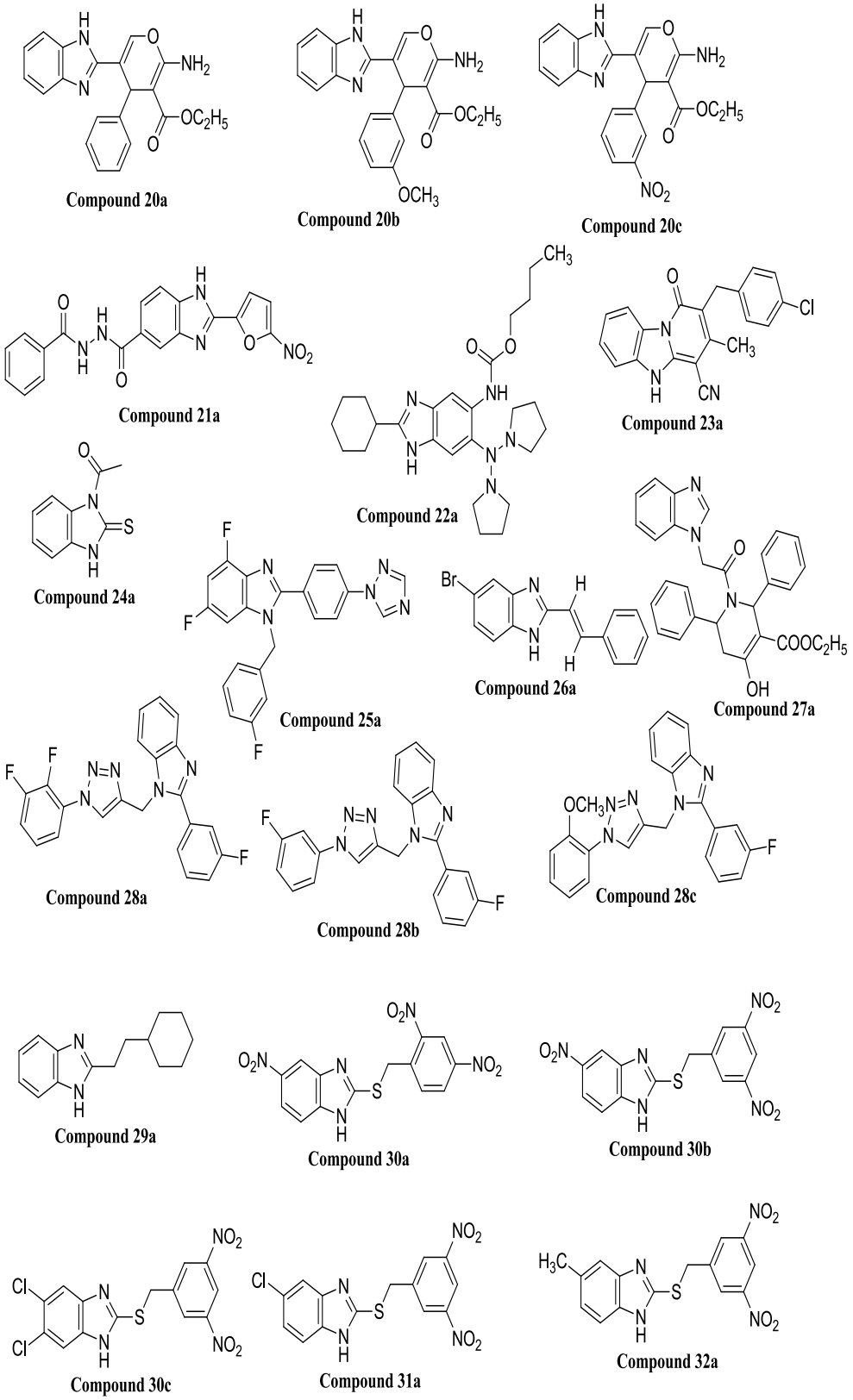

Fig.6. Structures of effective antitubercular compounds (20a-20c, 21a, 22a, 26a, 27a, 28a-28c, 30a-30c, 31a, 32a).

Francis *et al.*, 2011, synthesized the **6-benzimidazoyl pyrans**, evaluated the anti tubercular activity. Among all, the compound **20a, 20b, 20c (Fig. 6)** showed best anti tubercular activity at *at 10 and 100mcg/ml concentrations* against *Mycobaterium Tuberculosis* compared with isoniazid.[35]

José *et al.*, 2011, synthesized the benzimidazole-5-carbohydrazide derivatives, evaluated the anti tubercular

activity. Among all, the compound **21a (Fig. 6)** showed best anti tubercular activity bbknnnnwith MIC values of 12.5 µg/mL, 6.25 µg/mL against multidrug-resistant MDR, MTB strains compared with rifampicin.[36]

Kunal *et al.*, 2011, synthesized the trisubstituted benzimidazoles, evaluated the anti tubercular activity. Among all, the compound **22a (Fig. 6)** showed best anti tubercular activity with MIC_{99}values of 1.0 µM, 1.0 µM, 1.0 µM, 1.0 µM, 1.0 µM, 1.0 µM against *Mycobaterium Tuberculosis* strains of H37Rv, W210, NHN 20, NHN335, NHN382, TN587.[37]

Marco *et al.*, 2011, synthesized the pyrido[1,2-a] benzimidazoles, evaluated the anti tubercular activity. Among all, the compound 2**3a (Fig. 6)** showed best anti tubercular activity with MIC values of 0.5µg/mL, 1.0µg/mL, 8.0µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv by different assays MABA (Micro plate Alamar Blue assay), BD (Middlebrook broth dilu tion culture), Cytotoxicity against Vero cells compared with isoniazid.[38]

Mahalakshmi *et al.*, 2010, synthesized the benzimidazole thiones, evaluated the anti tubercular activity. Among all, the compound **24a (Fig. 6)** showed best anti tubercular activity with IC_{50} values of 9.2 ± 0.9 µM against *M. Tuberculosis.*[39]

Ganesh *et al.*, 2009, synthesized the clubbed [1,2,4]-triazolyl with fluorobenzimidazoles, evaluated the anti tubercular activity. Among all, the compound **25a (Fig. 6)** showed best anti tubercular activity with MIC value of 0.36µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with Refampicin.[40]

Ramya *et al.*, 2009, synthesized the 2-styryl benzimidazoles, evaluated the anti tubercular activity. Among all, the compound **26a (Fig. 6)** showed best anti tubercular activity with MIC value of 7.25µg/mL (83% Groth of inhibition) against *Mycobaterium Tuberculosis* compared with streptomycin.[41]

Gopalakrishnan *et al.*, 2008, synthesized the benzimidazoles containing piperidin-4-one and tetrahydropyridines, evaluated the anti tubercular activity. Among all, the compound **27a (Fig. 6)** showed best anti tubercular activity with MIC value of 16µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv compared with Refampicin.[42]

Charansingh *et al.*, 2008, synthesized the substituted benzimidazole by fluorine, triazoles, evaluated the anti tubercular activity. Among all, the compound **28a, 28b, 28c (Fig. 6)** showed best anti tubercular activity with MIC values found to be less than 6.25µg/mL(96% Groth of inhibition), 6.25µg/mL(96% Groth of inhibition), 6.25µg/mL(96% Groth of inhibition) against *Mycobaterium Tuberculosis* compared with rifampicin.[43]

Foks *et al.*, 2006, synthesized the benzimidazole derivatives, evaluated the anti tubercular activity. Among all, the compound **29a (Fig. 6)** showed best anti tubercular activity with MIC value of 3.1µg/mL, 6.2µg/mL, 6.2µg/mL against *Mycobaterium Tuberculosis* H37Rv, Drug-resistant and Drug-resistant strains.[44]

Agata *et al.*, 2005, synthesized the benzimidazole derivatives, evaluated the anti tubercular activity. Among all, the compound **30a, 30b, 30c (Fig. 6)** showed best anti tubercular activity with MIC value of 16µg/mL against *Mycobaterium Tuberculosis* strains of H37Rv and Mycobaterium Tuberculosis Isoniazid-resistantstraincompared with isoniazid.[45]

Kazimierczuk *et al*., 2005, synthesized the 2-substituted halogeno benzimidazole derivatives, evaluated the anti tubercular activity. Among all, the compound **31a (Fig. 6)** showed best anti tubercular activity with MIC values for 7, 14, 21 days found to be 2µmol/L, 2µmol/L, 4µmol/L against *Mycobaterium Tuberculosis* compared with isoniazid.[46]

Vera *et al.*, 2002, synthesized the new benzimidazole derivatives, evaluated the anti tubercular activity. Among all, the compound **32a (Fig. 6)** xshowed best anti tubercular activity with MIC values for 7, 14 days found to be 4µmol/L, 4µmol/L against *Mycobaterium Tuberculosis* compared with isoniazid.[47]

CONCLUSION

Benzimidazole is a bioactive heterocyclic compound, exhibit wide variety of biological activities. hence it attract the many researcher to synthesize bioactive compounds towards the target site. The present review focused on anti tubercular activity of many bioactive substituted benzimidazoles. It may serves as valuable source of information to researchers who wish to synthesize new benzimidazole derivative having antitubercular activity as well as further investigation.

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