Chapter 2

Literature review

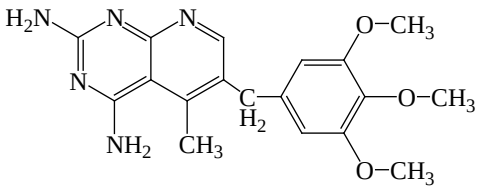
2.1 The latest discovery

Tuberculosis (TB) remains as a global pandemic that is aggravated by a lack of health care, the spread of HIV, and the emergence of MDR-TB) and XDR-TB strains. New anti-TB drugs are urgently required to shorten the long 6-12 month treatment regimen and to battle drug-resistant MTB strains. Many researchers have tried to elucidate possible structure-activity relationships (SAR), the effect of a drug or toxic chemical on an animal, plant, or the environment can be related to its molecular structure that might lead to new drug discovery. This review attempts to review the literatures that studied on SAR, in order to show structural requirements implicated in the antituberculosis activity, which might help to rationalize their development as antituberculosis agents.

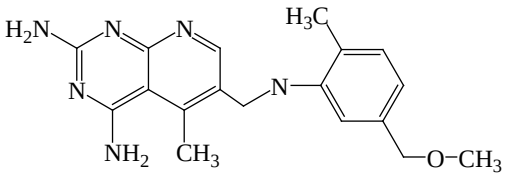
2.1.1 Deazapteridines analogs

According to the study of lipophilic 2,4-diamino-5-methyl-5-deazapteridine derivatives and trimethoprim **(Figure 11)** synthesized by Suling and co-workers (1998). It showed that 2,4-diamino-5-methyl-5-deazapteridines, with aryl groups substitutions at the 6-position linked through a CH_2NH bridge, were active against both *M. tuberculosis* H37Rv and H37Ra. Also, both antimycobacterial activity and *Vero* cells toxicity could vary depending on the type and position of the phenyl group substitutions and whether or not the bridge was methylated. Two compounds, 2-methyl-5-methoxy phenyl derivative **17** and 2-methoxy-5-trifluoromethyl phenyl derivative **18**, were very active against M. *tuberculosis* H37Rv with MIC 3.13 and 1.56 mg/L, respectively. Also, the derivatives **17** (1.28-12.8 mg/L) and **18** (0.128-1.28 mg/L) were found active against M. *tuberculosis* H37Ra. These compounds were more active against mycobacteria more than trimethoprim (against M. *tuberculosis* H37Ra with MIC > 128 mg/L but it was not determined for M. *tuberculosis* H37Rv). Two of the 5-deazapteridine derivatives **17** and **18** also exhibited cytotoxicity towards *Vero* cells with IC_{50} value 222 and 1.03 mg/L, respectively. The compounds **27** and

18 were reported to have good selectivity for the enzyme dihydrofolate reductase (DHFR) over the mammalian enzyme that is an important for medicinal chemistry (Suling, et al., 1998).



Trimethoprim



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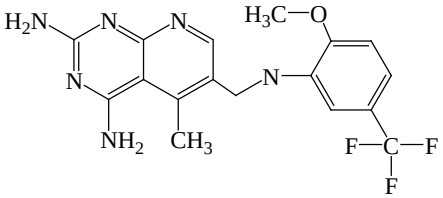

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Figure 9. Deazapteridines analogs

2.1.2 Toluidine derivatives

Biava and co-workers (1999) synthesized new *ortho*-, *meta*- and *para*-toluidine derivatives. Some of them showed an interesting in *vitro* activity against *Mycobacterium tuberculosis.* The study found that the amino derivatives were generally more active than the corresponding amides and it was probably due to both the presence of a non-hindered lone pair of nitrogen atoms and the increased rigidity conferred upon the structure. Most of the compounds with *ortho* and *para* derivatives were the most active than *meta* derivative. The replacement of the imidazole with *N*-methylpiperazine, morpholine and thiomorpholine moieties did not notice particular differences, whereas the activity against atypical mycobacteria increases when imidazole or *N*-methylpiperazine or morpholine moieties and *p*-Cl-phenyl or biphenyl ones are simultaneously introduced in the molecule. Compound **(Figure 10)** showed moderate to good antimycobacterial activity with MIC 4 µg/ml (Biava, et al., 1999). However, no toxicity data and the mode of action were reported.

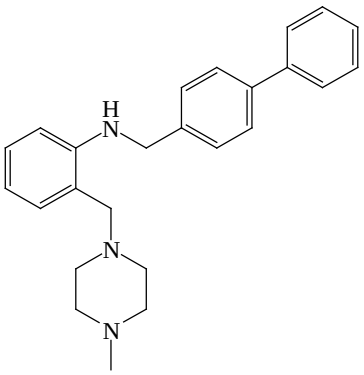


Figure 10. Toluidine derivatives

2.1.3 9-Benzylpurines

Bakkestuen and co-workers (2000) synthesized a series of 9-benzylpurines with a variety of substituents of the 2-, 6- and/or 8-positions. High inhibitory activity against M. *tuberculosis* was found for 9-benzylpurines carrying a phenylethynyl, *trans*-styryl or aryl substituents in the 6-position. Generally chlorine at the 2-position tends to increase activity, whereas compounds with a 2-amino substituent in most instances exhibit lower activity than their C-2 unsubstituted analogs. The result showed that 2-chloro-4(2-furanyl)-9-benzylpurine **(Figure 11)** has potently inhibited M. *tuberculosis* H37Rv *in vitro* with a MIC value of 0.78 µg/ml. It also exhibited low cytotoxicity towards *Vero* cells (IC_{50} value 8.1 µg/ml) (Bakkestuen, Gundersen, Langli, Liu, & Nolsoe, 2000). These compounds are unknown mode of action.

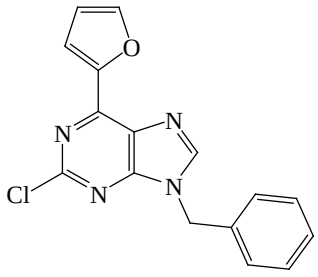


Figure 11. 2-Chloro-4-(2-furanyl)-9-benzylpurine

2.1.4 Fulleropyrrolidines

The study of the biological properties of fullerenes and fullerene derivatives has developed widely in recent years. After the first account on inhibition of HIV-protease, several interesting reports have dealt with potential activity in photodynamic therapy, neuroprotection and apoptosis. However, a main issue when dealing with fullerenes is the absolute lack of solubility in any polar solvent for biological evaluation. For this reason fullerenes have to be chemically modified in such a way that they acquire solubility and versatility. Jaju and co-workers (2000) interested a series of fullerene derivatives. Compound **(Figure 12)** displayed anti-mycobacterial activity. It inhibited the growth of *M. tuberculosis* strain H6/99, a human clinical isolate, with a MIC value of 5 µg/ml, and strain H37Rv with a MIC value of 50 µg/ml. However, the presence of the quartenary nitrogen atom in fullerene derivatives suggests that toxicity issues might be a problem. In addition, the large size of these molecules probably precludes oral absorption (SB Jaju, et al., 2009).

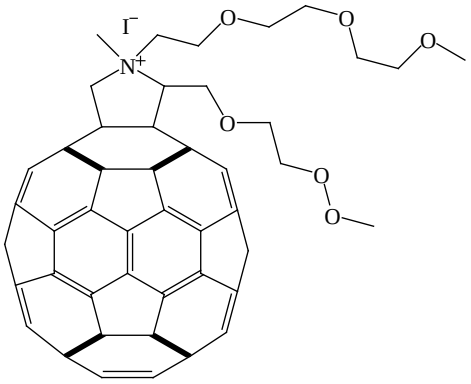
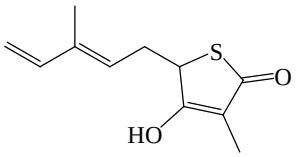


Figure 12. Fulleropyrrolidines

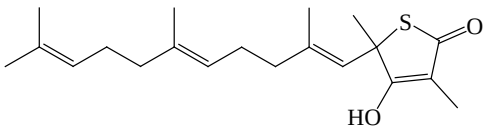
2.1.5 Thiolactomycin analogs

Thiolactomycin (TLM) is a natural product isolated from *Nocardia spp*. which belongs to a family of thiolactone-containing antibiotics. This compound selectively inhibited the mycobacterial acyl carrier protein-dependent type II fatty acid synthase (FAS-II) but not the multifunctional type I fatty acid synthase (FAS-I) present in mammals. It also has been shown to block long-chain mycolate synthesis in a dose-dependent manner in purified, cell wall-containing extracts of Mycobacterium

smegmatis (Kremer, et al., 2000). Douglas and co-workers (2002) reported that compounds **19** and **20** have greater activity than the parent thiolactomycin (MIC_{90} = 125 μM) in inhibiting M. *tuberculosis* H37Rv *in vitro* with MIC_{90} 29 μM. It indicated that a number of TLM analogues with different side chains in position 5 of the thiolactone ring gave enhanced activity. It was also appeared that altering the hydrophobicity of the side chain via length and saturation generates more potent TLM derivatives against *M. tuberculosis* (Douglas, et al., 2002). There was no report about cytotoxicity.



Thiolactomycin



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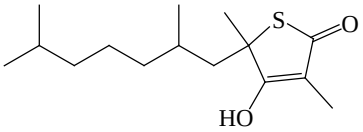

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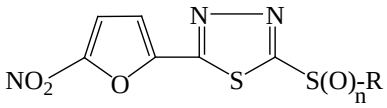
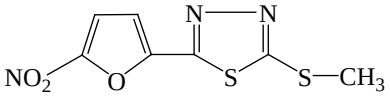
Figure 13. Thiolactomycin and analogs

2.1.6 2-(5-nitro-2-furyl)-1,3,4-thiadiazole derivatives

Foroumadi and co-workers (2002) studied 2-(5-nitro-2-furyl)-1,3,4-thiadiazole derivatives **(Figure 14)** for *in vitro* anti-tuberculosis activity against M. *tuberculosis* strain H37Rv.



2-(5-nitro-2-furyl)-1,3,4-thiadiazole derivatives



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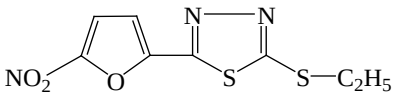

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n = 0, 1, 2

R = CH_3, C_2H_5, C_7H_7, 4-C_7H_6Cl, 4-C_7H_6N, 2,6-C_7H_5ClF, 2,5-$C_7H_5(CH_3)_2$

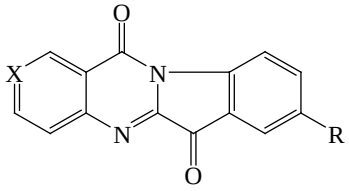
Figure 14. 2-(5-Nitro-2-furyl)-1,3,4-thiadiazole derivatives

The result showed that the compounds having methylthio or ethylthio group attached to the 1,3,4-thiadiazole ring were able to inhibit *in vitro* growth of MTB with MIC values of 6.25 μg/ml for **21** and 0.78 μg/ml for **22**. Replacement of methyl or ethyl group with a benzyl group resulted in a compound devoid of antituberculosis activity. It indicated that the hydrophobic effect on 1,3,4-thiadiazole ring results in a reduction of this activity. Considered methylthio or ethylthio group attach to the 1,3,4-thiadiazole ring. It showed that the oxidation of thio group to sulfoxide maintained the antituberculosis activity when n = 0. On the other hand, the activity was decreased when n=2. (Foroumadi, Soltani, Jabini, Moshafi, & Rasnani, 2004)

2.1.7 Tryptanthrin and analogs

Tryptanthrin **(Figure 15)** is a structurally novel indoloquinazolinone alkaloid, first isolated by Chinese scientists. It has been tested against various strains of *M. tuberculosis* with MIC = 0.5-1 μg/ml whereas INH was active from 0.03 to 0.06 mg/l. Clearly INH was superior against ordinary cultures. When a panel of multiply drug-resistant strains was utilized, however, INH decreased in activity (4.0 to 16.0 mg/L) whereas tryptanthrin retained its potency (0.5–1.0 mg/L) (Agrawal, et al., 2007). Many analogues of this lead structure have been synthesized and evaluated for their potential in tuberculosis chemotherapy. Hudson and co-workers (2003) synthesized

tryptanthrin ananlogs and evaluated in vitro and in vivo for their potential in the chemotherapy of human infections. Compound **23** showed potent in *vitro* activity towards M. tuberculosis H37Rv (MIC 0.015 µg/ml). However, to date it is not been possible to identify a compound sufficiently efficacious in animal models to warrant further progression. It is lack of toxicity data and the mode of action of the tryptanthrins is not known. (Hudson, Imamura, Gutteridge, Kanyok, & Nunn, 2003)



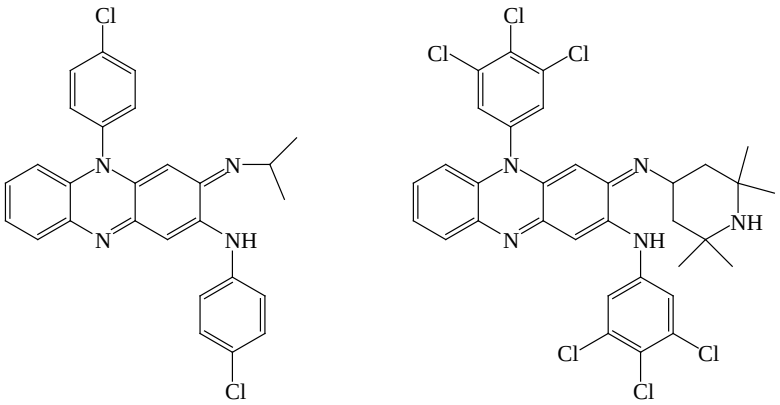
Tryptanthrin: R = H, X = CH

R = $CH(Me)(CH_2)_5Me$, X = N **23**

Figure 15. Tryptanthrin and analogs

2.1.8 Tetramethylpiperidino phenazines

A series of novel tetramethylpiperidinophenazines closely related to the antileprosy drug clofazimine **(Figure 15)** has been studied for the anti-TB activity. The intra- and extra-cellular activities of these compounds were compared to clofazimine and rifampicin against M. *tuberculosis* H37Rv. One of the phenazine derivatives **40** potently inhibited the bacterium with an MIC value of 0.015 µg/ml, while corresponding value for clofazimine was 0.06 µg/ml. The compounds **24** and **25** were also more active than clofazimine against a range of clinical *M. tuberculosis* isolates including multidrug-resistant strains. Another phenazines, such as **25**, showed significant intracellular activity against M. *tuberculosis* infected monocyte-derived macrophages at 0.001 µg/ml (van Rensburg, Jooné, Sirgel, Matlola, & O'Sullivan, 2000). There is no information as to mode of action although they might be expected to participate in a variety of redox reactions. (Hudson, et al., 2003)



Clofazimine **24**

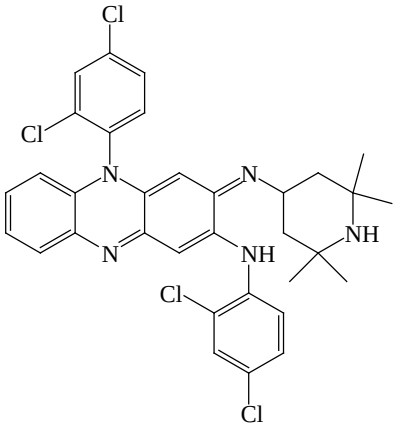


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Figure 16. Tetramethylpiperidino phenazines

2.1.9 1,2,3 –Triazoles analogs

1,2,3-Triazoles are an important class of heterocyclic compounds due to their wide range of applications including as pharmaceutical agents. Literature described triazoles as antiplatelet agents, dopamine D2 receptor ligands related to schizophrenia, anti-inflammatory agents, anticonvulsants, β-lactamase inhibitors, and antiviral and antimicrobial agents. Various *N*-substituted-phenyl-1,2,3-triazole-4-carbaldehydes have been synthesized and evaluated against M. *tuberculosis* H37Rv by Hisashi and co-workers (2003). Compounds **26** and **27** exhibited the best activity with MIC values of 2.5 µg/ml and 100% inhibiton. The study of SAR indicated the importance of the hydrogen bond acceptor subunit, the position in the aromatic ring, the planarity of triazole and phenyl rings in these compounds, and a correlation between the uniform

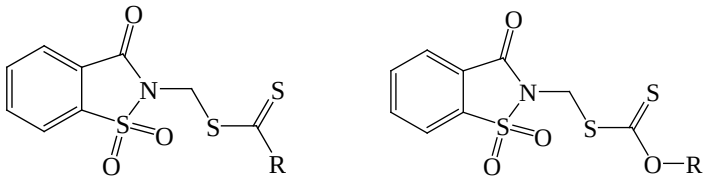
HOMO coefficient distribution and the anti-tubercular activity. Although the Osiris risk alerts (program for calculating and comparing the fragment based druglikeness of compounds) are not a fully reliable toxicity prediction, the theoretical low-toxicity profile of these compounds reinforces the significant activity and pointed them as promising lead molecules for further synthetic and biological exploration (Janin, 2007). No mode of action of these derivatives. (Costa, et al., 2006)

26 **27**

Figure 17. 1,2,3 –Triazoles analogs

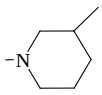
2.1.10 Dithiocarbamate and dithiocarbonate derivatives

Güzel et al. (2006) synthesized and evaluated dithiocarbamate **28** and dithiocarbonate **29** derivatives possessing different alkyl or cycloalkyl groups to obtain new and more potent antituberculosis agents.



28 **29**

28a R =



28b

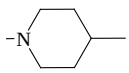
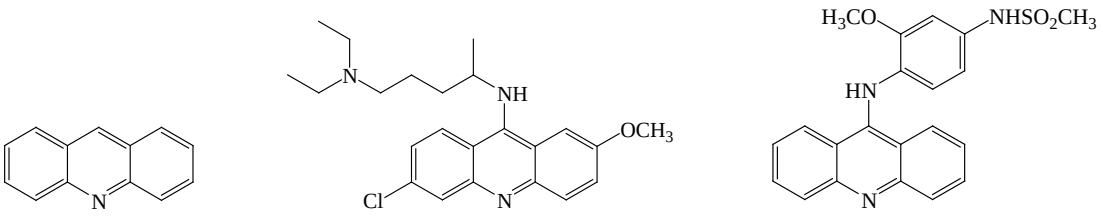


Figure 18. Dithiocarbamate **28** and dithiocarbonate **29** derivatives

The study showed that all compounds exhibited activity against M. *tuberculosis* H37Rv strain with MIC 0.78 to 3.13 μg/ml. Dithiocarbamate derivatives **28** were more active than dithiocarbonate derivatives **29**. Among dithiocarbamates, highest activity resided in compounds bearing 3-methyl piperidine, 4-methyl piperidine, and pyrrolidine residues. Ring opening, demethylation, 2-methyl substitution or introduction of a second heteroatom decreased activity. Substitution with benzyl, phenyl, and bulky groups was not tolerated and thus these structural modifications resulted in inactive derivatives. Compound **28a** and **29b** showed the most activity with MIC 0.78 μg/ml. (Güzel & Salman, 2006)

2.1.11 Acridine derivatives

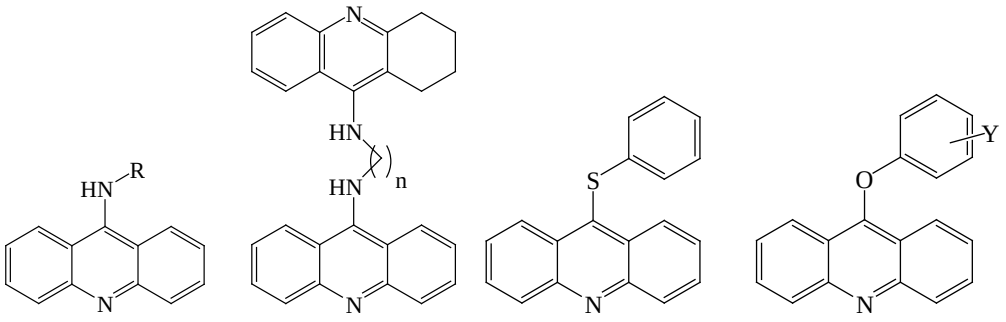
During world war-II, acridine derivatives **(Figure 19)** have been reported in antimalarials and anti-bacterial activities. It has been established that amino acridines having electronic conjugation between the ring nitrogen and the amino group are the most active antibacterial agents. However, there were only few reports about the use of acridines as antimycobacterial agent. Moreover, tetrahydroacridines have never been reported activity against M. *tuberculosis.*



acridine **28** **29**

Figure 19. Acridine and their derivatives

Therefore, in 2006 Tripathi and co-workers interested to synthesize 1,2,3,4-tetrahydroacridines **(Figure 20)** having substituents at C-9. They also evaluated effect of these compounds on anti-tubercular profile.



30 **31** **32** **33**

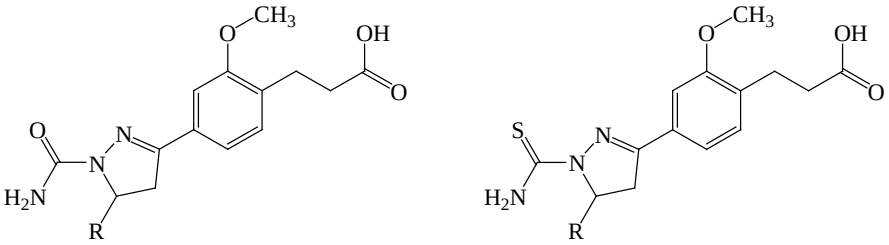
30a R= $-C_8H_{17}$ Y = 4-chloro, 3,4-dimethyl, 4-fluoro, 2,4-dichloro

Figure 20. Tetrahydroacridine derivatives

The results showed that tetrahydroacridines having 9-amino substituents **30** and **31** were more active than thiophenyl **32** or phenoxy **33** substituents. Compound **30a** with 8 carbon chain length of *N*-alkyl substituent was most active against M. *tuberculosis* strain H37Ra with 1.56 µg/ml, while it has MIC 3.125 µg/ml against M. *tuberculosis* strain H37Rv. Compound with a chain of 12 carbons as the aminoakyl substituent was the most potent with 0.78 µg/ml against H37Rv strain, while it has MIC 6.25 µg/ml against H37Ra strain. Instead of 9-aminoalkyl group **30**, substitution with aromatic ring did not offer any significant inhibition to the bacterial growth. Considered *bis*-acridinyl diamino alkanes **31**, compound with 10 carbon chain exhibited with MIC 3.125 µg/ml against H37Ra strain. The other compounds have MIC value either 12.5 or >12.5 µg/ml. It indicated that incoperation of one more acridine unit in such molecule is not beneficial. It was also evident from the activity data that replacement of aminoalkyl group at C-9 with thiophenyl **32** or phenoxy **33** group results incomplete loss activity. It indicated that N atom at C-9 is essential for antitubercular activity (Tripathi, et al., 2006).

2.1.12 Phenoxyacetic acid derivatives

The chemistry of heterocyclic compounds has been an interesting field for study by Ali and co-workers (2007). Phenoxyacetic acid derivatives **(Figure 21)** with encouraging antimycobacterial activity M. *tuberculosis* H37Rv and INH-resistant M. *tuberculosis* have been synthesized.



34 **35**

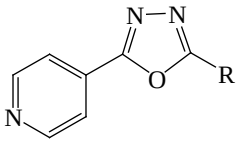
R = Phenyl, 4-Hydroxy phenyl, 4-Nitro phenyl, 4-Fluoro phenyl, 4-Methyl phenyl, 4-Chloro phenyl, 2-Chloro phenyl, 4-Amino phenyl, Benzyl, 2-Hydroxy phenyl

Figure 21. Phenoxyacetic acid derivatives

They reported that phenoxyacetic acid compound with electron-withdrawing group substituted analogs such as 4-chloro phenyl, 2-chloro phenyl and 4-hydroxyl phenyl enhanced the antimycobacterial activity. However, the electron-withdrawing group such as 4-fluoro phenyl and nitrophenyl-substituted analogs produced moderate inhibitory activity. On the other hand, the electron-donating group substituted analogs showed low to moderate inhibitory activity. Pyrazoline analogs **34** with (C=S) group substitution at N-1 improve the antitubercular activity more than analogs **34** with (C=O) substitution at N-1. The most active compound was 4-chloro phenyl (R position) substituted and (C=S) group at N-1 of pyrazoline ring **35**. It was reported with MIC 0.06 μg/ml (Ali & Shaharyar, 2007).

2.1.13 1,3,4-Oxadiazoles

Gabriel and co-workers (2007) studied 1,3,4-oxadiazoles. They were an important class of heterocyclic compounds with a wide range of biological activities such as antiviral, tyrosinase inhibitors, antimicrobial, cathepsin K inhibitors, fungicidal and antineoplasic properties.



R = -CH_3, -CF_3, CH_2Cl, -$C_{15}H_{31}$, -$C_{17}H_{35,}$ -C_6H_5, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 3,5-$(NO_2)_2C_6H_3$, 3,4,5-$(NO_2)_3C_6H_3$, 4-$N(NO_2)_2C_6H_3$, 4-Pyridyl

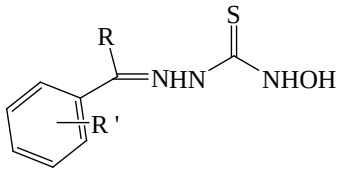
Figure 22. 1,3,4-Oxadiazoles

They synthesized 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines derivatives **(Figure 22)** and evaluated activity against M. *tuberculosis* H37Rv strain. The results showed that 5-arylsubstituted compounds possessed moderate activity, whereas alkyl and haloalkyl (-CH_3, -CF_3 and –CH_2Cl) substituted derivative did not show significant activity. Apparently, it was necessary to increase the steric hindrance at position 5 of oxadiazole moiety to improve the biological of these derivatives. It also implied that lipophilicity was an important in the antimycobacterial activity of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines derivatives. The most active compound was possessed high lipophilic chain (-$C_{15}H_{31}$ substituted) bond to the 5-position of oxadiazole moiety. It was reported with MIC 0.12 μg/ml. These result indicated that the present lipophilicity of these compounds was an important for antimycobacterial activity. (Navarrete-Vázquez, et al., 2007)

2.1.14 Thiosemicarbazone derivatives

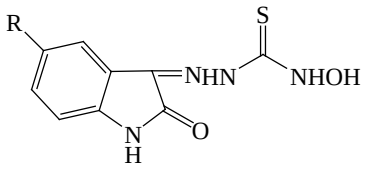
Thiosemicarbazone derivatives have been reported as antimycobacterial agents. *N*-hydroxythiosemicarbazone **36** and **37** were synthesized and evaluated for activity against M. *tuberculosis* H37Rv by Sriram and co-workers (2007). The results revealed that all compounds exhibited very good antimycobacterial activity with MIC ranging from 0.097 to 12.48 μg/ml. The most active compound was **36a** with MIC 0.097 μg/ml. It was more active than isoniazid and almost equally active as rifampicin. Consideration of benzaldehyde and actophenone derived thiosemicarbazone **36**, it showed that substituents with strongly deactivating electron withdrawing groups, such as nitro and trifluoromethyl group in the phenyl ring,

showed excellent antimycobacterial activity and followed by weakly deactivating electron withdrawing groups such as halogen derivatives. Electron donating group (methyl and methoxy) reduced the activity. The order of activity was found to be (4-bromo)diphenylbenzophenone > (sub)acetophenone > (sub)benzadehyde > isatin (Sriram, Yogeeswari, Dhakla, Senthilkumar, & Banerjee, 2007).



36

36a R = C_6H_5, R' = 4-Br



37

R = H, F

R = H, CH_3, C_6H_5

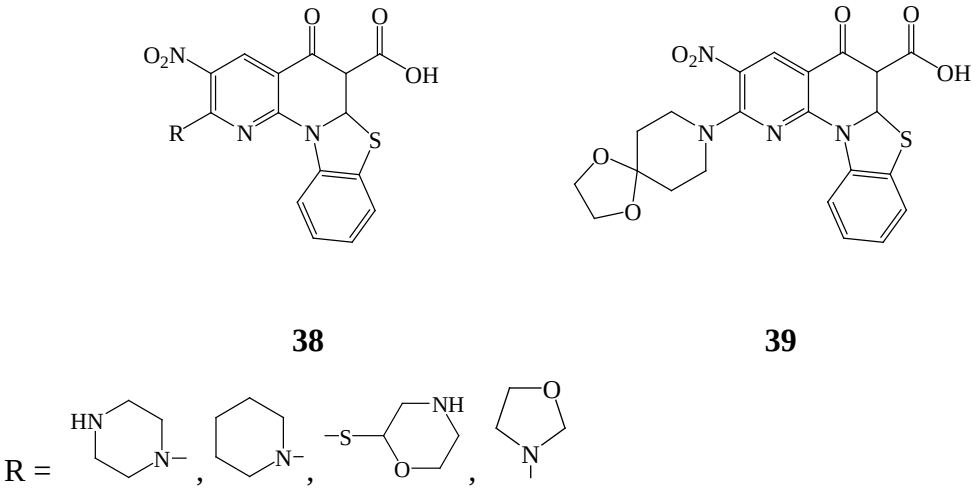
R′ = H, 2-OH, 4-OH, 4-$N(CH_3)_2$, 4-OCH_3, 4-CH_3

3-OCH_3, 4-NO_2, 2-NO_2, 4-Br

Figure 23. Thiosemicarbazone derivatives

2.1.15 Benzothiazolo naphthyridone carboxylic acid derivatives

Dinakaran and co-workers (2009) identified benzothiazolo naphthyridone carboxylic acid derivatives **38** for studied activity against M. *tuberculosis* H37Rv. All of the compounds showed excellent activity against both MTB with MIC of $\leq$12 μM. Compound **39** was the most active compound with MIC 0.19 μM. It is more active than isoniazid (MIC 0.36 μM). The researchers studied structure activity relationship on C-2 position with various substituents. On comparison of the substitution pattern at C-2, the order of activity was found to be substituted piperidines > (thio)morpholines > fused piperazines and piperidines > oxazolidine > substituted piperazines (Dinakaran, Senthilkumar, Yogeeswari, & Sriram, 2009).



38 **39**

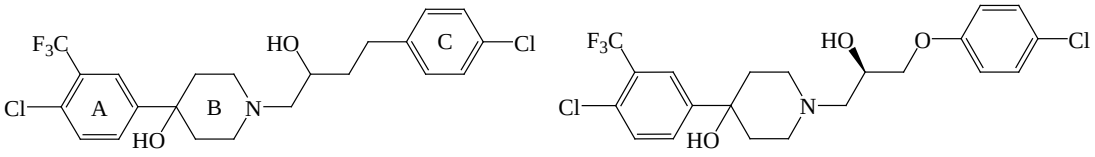
R =

Figure 24. Benzothiazolo naphthyridone carboxylic acid derivatives

2.1.16 Piperidinol derivatives

Sun and co-workers (2009) also reported piperidinol derivatives **40** because piperidinol was structurally similar to existing orally bioavailable drugs. There has been reported bioactivity of a number of piperidinol compounds as antivirals, antibacterials, mu receptor agonists and nociceptin receptor ligands that it is a biologically useful scaffold for a variety of targets. There were no reports of similar compounds with anti-tuberculosis activity. Thus, the researchers design and synthesized a series of analogs related to **40** for anti-tuberculosis activity. They reported that all derivatives achieved activity against *Mycobacterium tuberculosis* with MIC ranging from 1.4 to 18.8 μg/ml. The most active compound was **41** (MIC 1.4 μg/ml) with *R* stereochemistry at the central secondary hydroxyl group and chloro substitution at *para* position to the aryl C ring. The effect of stereochemistry at the central secondary hydroxyl group was considered and found that it was no correlation or preference between stereochemistry at the central secondary hydroxyl. The effect of phenoxy C ring, compounds with 4-chloro and 3-CF_3 groups enhanced activity more than 2,5-dimethyl substituted analogs. Removal of either of these groups led to the significant loss of activity. This demonstrated the importance of 4-chloro and 3-CF_3 groups. In addition, the tertiary hydroxyl group also has a significant effect on activity as well. Replacement of it with a cyano group resulted in a more active

compound and replacement with a dehydration product results led to a complete loss of anti-tuberculosis activity (Sun, et al., 2009).

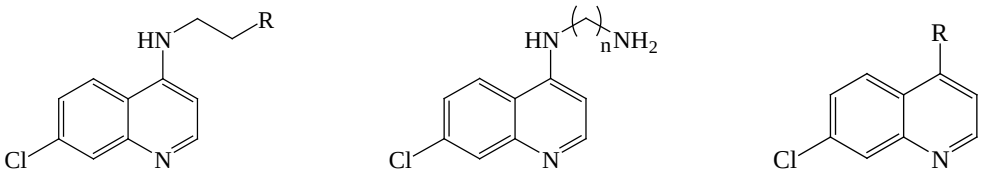


40 ***S*-41**

Figure 25. Piperidinol derivatives

2.1.17 Quinoline derivatives

Souza and co-workers (2009) studied quinoline derivatives, which an important class of heterocyclic compounds with a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, antiobesity, and anti-inflammatory. They synthesized and evaluated quinoline derivatives **(Figure 26)** and evaluated *in vitro* antibacterial activity against M. *tuberculosis* H37Rv.



42 **43** **44**

43a n = 10

R = OH, Cl, N_3, NHMe, NHPr, $NHCH_2CH_2OH$, NH*i*-Pr, NHBu, NHBn, CN

n = 2, 3, 4, 6, 8, 10

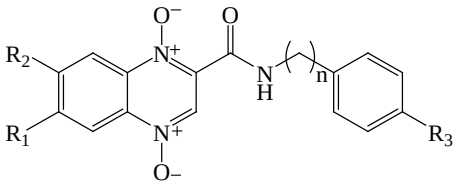
R = N_3, NH_2, NHMe, NH*i*-Pr, NHBu, NHPrOH, NHPr $NH(R)CH(Et)CH_2OH$ $NH(S)CH(Et)CH_2OH$

Figure 26. Quinoline derivatives

7-Chloro-4-amino-quinolines series **42** showed the most active derivative when a chorine atom in a terminal position. The antimycobacterial activity decreases when chorine atom is replaced by other groups, such as azide or other amines. It indicates the relevance of chorine atom for the biological activity in this series of compounds. For the 7-chloro-4-diamino-quinolines derivatives **43**, the addition of carbon atoms in the alkyl chain led to improving biological activity. The lipophilicity was an important parameter to the biological activity in this series. In the series of compounds **44**, the length of the alkyl chain was also a critical factor for increased anti-TB activity. The biological activity of quinoline derivatives increased due to the bulky or number of carbon atom of the alkyl chain. It was also show that the presence of a hydroxyl group in the structure of compounds could be responsible for the decrease of biological activity. The presence of chorine atom at position C-7 in the quinoline was also essential for the anti-TB activity. In the study, compound **43a** was found to be the most active with MIC 3.12 μg/ml (de Souza, et al., 2009).

2.1.18 1,4-di-*N*-oxide-3-methylquinoxaline-2-carboxylic acid aryl amide derivatives

Ancizu and co-workers (2010) interested 1,4-di-*N*-oxide-3-methylquinoxaline-2-carboxylic acid aryl amide derivatives **45**. They synthesized and evaluated these derivatives as potential anti-tubercular agents against MTB H37Rv strain.

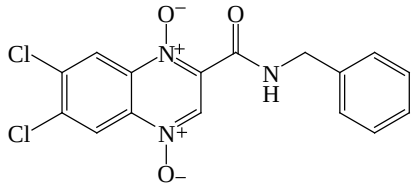


n = 1, 2

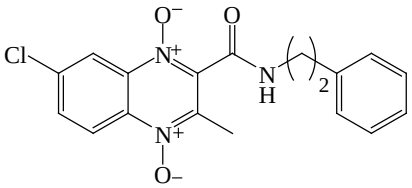
R_1, R_2 = H, Cl, F, OCH_3, CH_3, CF_3

R_3 = H, OCH_3

45



46



47

Figure 27. 1,4-Di-*N*-oxide-3-methylquinoxaline-2-carboxylic acid aryl amide derivatives

This study showed that compounds **46** and **47** were identified as the most interesting derivatives with great anti-tubercular activity. They were reported with same MIC values as < 0.2 μg/ml. The researchers explored the structure–activity relationships of these compounds. The introduction of an electron-withdrawing substituent in the quinoxaline ring resulted in an increment in the anti-tubercular activity of the derivatives. On the contrary, the insertion of an electro-releasing moiety resulted in a reduction of this activity. It was concluded that the insertion of an electron-withdrawing moiety in the quinoxaline ring is an essential requirement to improve the anti-tubercular activity (Ancizu, et al., 2010).

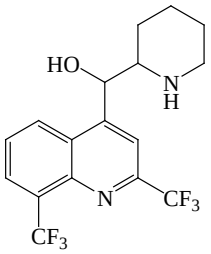
2.1.19 Mefloquine and analogs

Mefloquine (4-aminoquinoline methanol) **(Figure 28)** and several analogues have been reported for their activities against a variety of bacteria including *Mycobacterium*. In the year 2007, Mao and co-workers explored the SARs of mefloquine-based analogs as anti-TB agents. The modifications included introduction of the hydrazone linker into mefloquine at 4-position, replacement of the piperdine with a piperazine, and extension of the basic terminus of the piperazine ring at the

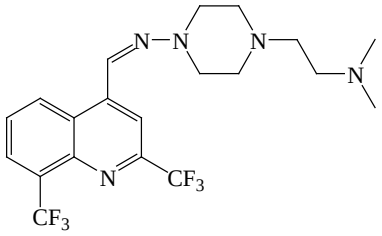
4-position. Compound **48** was found to have improved anti-TB activity. Moreover, the isoxazole scaffold emerged as one of the most potent hits in a high throughput screen against M. *tuberculosis* in their laboratory. Both compound **48** and the isoxazole hits consisted of an aromatic ring, and a two-atom linker with either a five or six membered ring. Based on these similarities, compound **49** was designed using a chemical hybridization strategy. Initially, they expected to develop potent anti-TB mefloquine-based ligands with an isoxazolecarboxamide moiety. Compound **49** was identified with excellent antituberculosis activity and devoid of detectable cytotoxicity. It was reported with MIC in the microplate Alamar Blue assay (MABA) and the low oxygen recovery assay (LORA) was 0.9 µM (0.4 µg/ml) and 12.2 µM (5.3 µg/ml), respectively (Mao, Wang, Wan, Kozikowski, & Franzblau, 2007). In the year 2010, Mao and co-workers modified compound **70** on the ester and the quinoline ring for improve the antituberculosis activity. The ester group was replaced by various bioisosteres [1], such as amides and the oxadiazole. The results showed that compound **49** was found to be active against M. *tuberculosis* both intracellularly and extracellularly, and its activity was specific for members of the *M. tuberculosis* complex. Various ester analogs were active against *M. tuberculosis* in both MABA and LORA. The compounds with small ester substituents, such as propyl and butyl esters, were as active as the lead compound **49**. However, none of the ester bioisosteres, including the isomeric ester, amides, and the oxadiazole analogs, showed any activity. These observations suggested that the ester may be acting as a prodrug. 2,8-Bis(trifluoromethyl) substitutions on the quinoline were found to be favored, and the phenyl ring in the quinoline was important for its antituberculosis activity. The 6- and 7-positions were better than the 4-position for location of the oxymethylene linker. It also suggested that the isoxazole carboxylic acid ester moiety forms a key

[1] **Bioisosteres** are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound. In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.

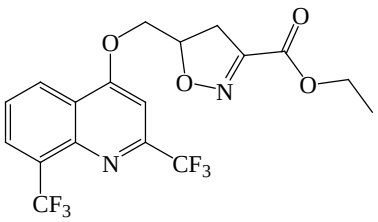
interaction with the active site of the putative target, which is crucial for activity, while the quinoline ring may be less important (Mao, et al., 2010).



Mefloquine



48



49

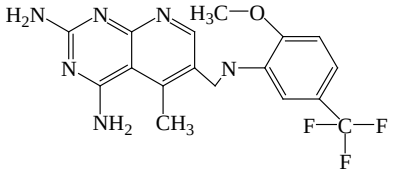
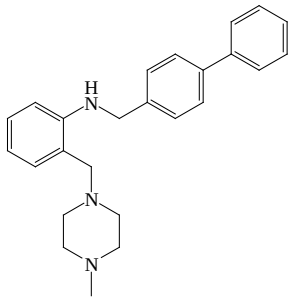
Figure 28. Mefloquine and analogs

We attempted to compile the literature studying structure-activity relationships (SAR) on antituberculosis that could be useful to develop antituberculosis agents. As a result of the literature reviews **(Table 2)** we found that most of compounds obtained benzene ring, nitrogen atom and halogen atom. The electron donating and electron withdrawing groups have significant effect on anti-TB activity. Ali and co-workers reported that compounds with electron-withdrawing substitution enhanced the antimycobacterial activity for phenoxyacetic acid analogs. Sriram and co-workers (2007) also reported that strongly deactivating electron withdrawing groups in the phenyl ring of *N*-hydroxythiosemicarbazone analogs showed excellent antimycobacterial. The study of SAR indicated the importance the position in the aromatic ring. (Costa, et al., 2006) Most of compounds with *ortho* and *para* derivatives of toluidine analogs are the most active than *meta* derivative. (Biava, et al., 1999) The present lipophilicity of thiolactomycin analogs was an important for antimycobacterial activity. (Douglas, et al., 2002) and (Navarrete-Vázquez, et al.,

2007) Foroumadi and co-workers found that hydrophobic effect of 2-(5-nitro-2-furyl)-1,3,4- thiadiazole analogs was results in a reduction of this activity. (Foroumadi, et al., 2004) On the other hand, Souza and co-workers report that the length of the alkyl chain is a critical factor for increased anti-TB activity for quinoline analogs. (de Souza, et al., 2009)

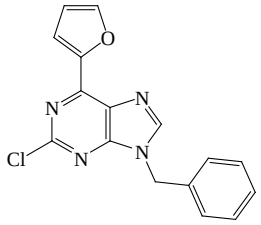
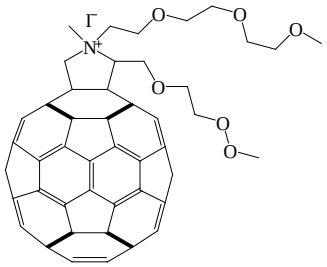
TABLE 2.

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
1998	Suling et al	Deazapteridines		1.56 mg/L	0.128-1.28 mg/L
1999	Biava et al	Toluidine		4 µg/ml	-

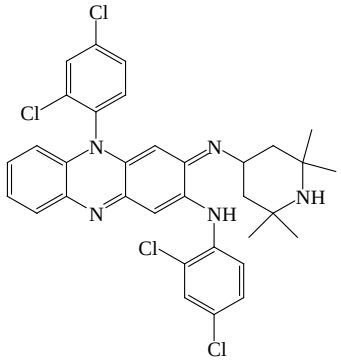
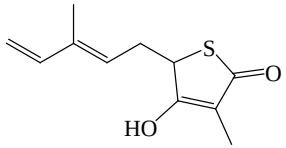
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2000	Bakkestuen et al	9-Benzylpurines		0.78 µg/ml	-
2000	Jaju et al	Fulleropyrrolidines		50 µg/ml	-

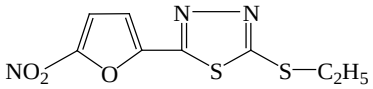
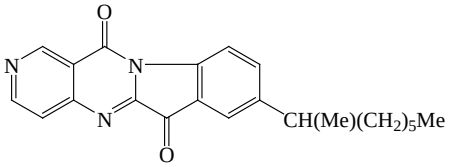
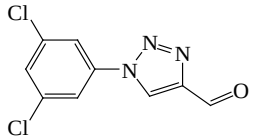
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2000	Van Rensburg et al	Tetramethylpiperidin phenazines		0.001 µg/ml.	-
2002	Douglas et al.	Thiolactomycin		29 µM (MIC_{90})	-

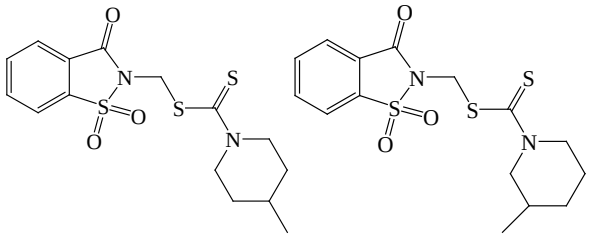
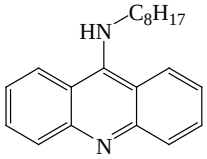
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2002	Foroumadi et al.	Thiadiazole		0.78 µg/ml	-
2003	Hudson et al.	Tryptanthrin		0.015 µg/ml	-
2003	Hisashi et al	1,2,3 –Triazoles		2.5 µg/ml	-

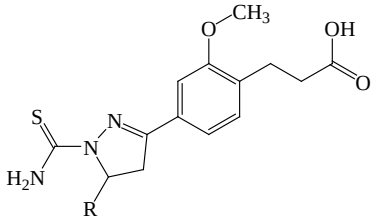
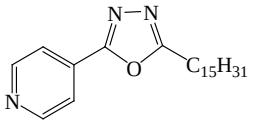
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2006	Güzel et al.	Dithiocarbamate and dithiocarbonate		0.78 µg/ml	-
2006	Tripathi et al.	Acridine		3.125 µg/ml	1.56 µg/ml

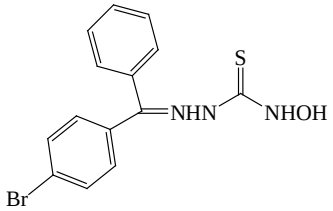
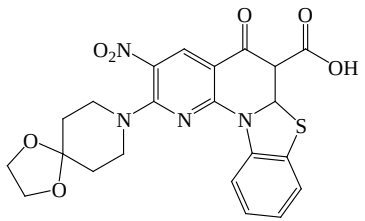
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2007	Ali et.al.	Phenoxyacetic acid		0.06 µg/ml	-
2007	Gabriel et.al.	1,3,4-Oxadiazoles		0.12 µg/ml	-

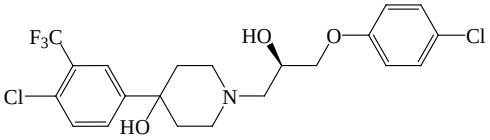
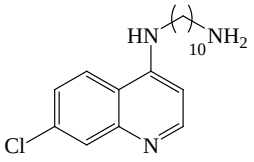
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2007	Sriram et.al	Thiosemicarbazone		0.097 μg/ml	-
2009	Dinakaran et.al.	Benzothiazolo naphthyridone carboxylic acid		0.19 μM.	-

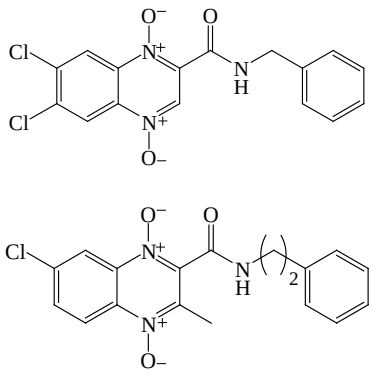
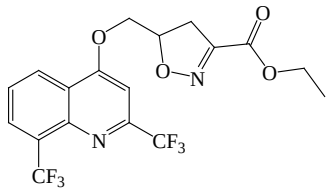
Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2009	Sun et.al.	Piperidinol		1.4 μg/ml	-
2009	Souza et.al.	Quinoline		3.12 μg/ml	-

Continued

A SUMMARY OF THE LITERATURES ON DEVELOPMENT OF ANTI-TUBERCULOSIS DRUGS (continued)

Year	References	Type of derivative	The most active compound	MIC	
				MTB H37Rv	MTB H37Ra
2010	Saioa et.al.	1,4-di-N-oxide-3-methylquinoxaline-2-carboxylic acid aryl amide		< 0.2 µg/ml	-
2010	Mao et al	Mefloquine		0.4 µg/ml	-

2.2 Galangal

Alpinia galangal (L.) Sw. (Zingiberaceae) is a perennial herb with rhizomatous root stocks and tall leafy stems. It is commonly known as greater galangal. The plant was found throughout the Western Ghats, Mysore, Goa, Malabar and Gujarat and also found in other countries such as Thailand, Indonesia, China and Malaysia. Roots are adventitious, in groups, fibrous, persistent in dried rhizomes, about 0.5 to 2.0 cm long and 0.1 to 0.2 cm in diameter and yellowish brown in color. Rhizomes **(figure 29)** are cylindrical, branched, 2 to 8 in diameter, longitudinally ridged with prominent rounded warts (remnants of roots) marked with fine annulations, scaly leaves arranged circularly, externally reddish brown, internally orange yellow, odour pleasant and aromatic, spicy and sweet in taste. (Bosi, Da Ros, Castellano, Banfi, & Prato, 2000)

Source: http://www.celtnet.org.uk/recipes/spice-entry.php?term=Galangal

Figure 29. Rhizome of *Alpinia galangal*

Alpinia galangal is reported to be rich in essential oils such as cineole, methyl cinnamate, myrecene, and methyl eugneol and is also contain various flavones such as galangin, alpinin, kampferide and 3-dioxy-4-methoxy galangal (SB Jaju, et al., 2009). The biological and aroma effects of the main and minor compound of the four essential oils of *Alpinia galangal* are discussed in terms of their possible use in medicine, cosmetics and foods (Jirovetz, Buchbauer, Shafi, & Leela, 2003).

In many countries, galangal is used distinctly. In most South East Asian countries dried galangal is employed only in the absence of fresh galangal whereas in Indonesia slices or powder of the fresh or dried rhizome are used frequently. The rhizome is used against rheumatism, bronchial catarrh, bad breath, and ulcers whooping colds in children, throat infections, to control incontinence, fever and dyspepsia. The root has been used in Europe as a spice for over a thousand years, having probably been introduced by Arabian or Greek physicians, but it has now largely gone out of use except in Russia and India. The rhizomes have been used as flavours in native dishes and ingredients in many traditional medicines to treat various ailments, such as stomach disorders and skin diseases. In India the rhizomes have many applications in traditional medicines such as for skin diseases, indigestion, colic, dysentery, enlarged spleen, respiratory diseases, mouth and stomach cancer. Rhizomes show antibacterial, anti-fungal, anti-protozoal, and expectorant activities. It is used as a body deodorizer and halitosis remedy ("Alpinia Galanga: Greater Galanga: Kulanjan," 2010).

2.3 Researches on 1´*S*-1´-acetoxylchavicol acetate (*S* -ACA)

1´*S*-1´-acetoxylchavicol acetate (*S*-ACA) is a natural compound that found in some plants in the family *Zingiberaceae* especially in greater galingale (*Alpinia galangal* (Linn.) Sw.) and big galingale (*Alpinia nigra* (Gaertn.) B. L. Burtt). The chemical configuration of naturally occurring 1´*S*-1´-acetoxylchavicol acetate naturally is in *S*-form (Yasuhara, et al., 2009). *S*-ACA exhibits a unique pungent sensation [1], which is less intense than that of capsaicin [2] and without a lingering effect. Applications of *S*-ACA were used in beverages, sweet goods, dressings, and personal care products. In many applications, 1´*S*-1´-acetoxylchavicol acetate is preferred to other pungent ingredients. *S*-ACA is not stable in aqueous solutions and undergoes hydrolysis/isomerization reactions. Therefore, *S*-ACA was absent in galangal essential oil obtained by steam distillation. However, *S*-ACA was found as

[1] **Pungent sensation** is a sharp sensation, as of the taste, smell, or feelings.

[2] **Capsaicin** is the active component of chili peppers, which are plants belonging to the genus *Capsicum.H*

one of the major volatile components of the galangal rhizomes by headspace GC analysis. Despite its simple structure, *S*-ACA has been reported to bear a variety of important biological activities**.**

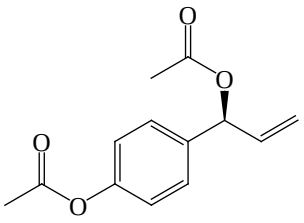


Figure 30. 1′*S*-1′-Acetoxychavicol acetate

Janssen and co-workers (1985) have reported the essential oils from fresh and dried rhizomes of *Alpinia galangal*. It showed antimicrobial activity against gram-positive bacteria, yeast and some dermatophytes. Moreover, 1′*S*-1′-acetoxychavicol acetate, 1′-acetoxyeugenol acetate and 1′-hydroxychavicol acetate displayed the antifungal activity. Acetoxychavicol acetate was active against seven fungi tested and its MIC value for dermatophytes ranged from 50 to 250 µg/ml (Janssen & Scheffer, 1985).

Murakami and co-workers (2000) investigated *S*-ACA **72** and its 16 derivatives in an inhibitory test of tumor promoter teleocidin B-4-induced Epstein−Barr virus (EBV) [1] activation in Raji cells. The study showed that: (1) the absolute configuration at the 1′-position does not affect activity; (2) hydrogenation of the terminal methylene group abolishes activity; (3) both phenolic and alcoholic hydroxyl groups are compulsorily acetylated, and it is necessary that the former is oriented only at the position *para* to the side chain; (4) an additional acetoxyl group is allowed to locate at the *ortho* or *meta* position; and (5) substitution of the hydrogen atom at the 1′-position by a methyl group reduces activity. Upon esterase blockade in

[1] **Epstein-Barr Virus** is a cancer-causing virus of the herpes family, which includes *herpes simplex virus* 1 and 2, and is one of the most common viruses in humans) activation

Raji cells, 1′*R*,*S*-ACA suppressed EBV activation, the extent of which was the same as tested in the control, suggesting that ACA bearing two acetoxyl groups is an intracellular structure prerequisite for activity exhibition. This study suggested that nucleophilic attack to the 3′-position was important and involved in the interaction of ACA with an unidentified target molecule(s) participating in the process of EBV (Murakami, Toyota, Ohura, Koshimizu, & Ohigashi, 2000).

Matsuda and co-workers (2003) reported a case of antiallergic activity. 1´-acetoxylchavicol acetate and 1´*S*-1´-acetoxyeugenol acetate exhibited potent inhibitory activity with IC_{50} values of 15 and 19 μM. They also inhibited ear passive cutaneous [1] anaphylaxis reactions in mice and the antigen-lgE-mediated TNF-alpha and IL-4 production, both of which participate in the late phase of [2] type l allergic reactions, in RBL-2H3 cells (H. Matsuda, Morikawa, Managi, & Yoshikawa, 2003). In the same year, Matsuda and co-workers found ACA was essential for strong gastroprotective effect. It inhibited the ethanol-induced gastric mucosal lesions (ED_{50} = 0.61 and ca. 0.90 mg/kg). In addition, 1´*S*-1´-acetoxychavicol acetate inhibited the lesions induced by 0.6 M HCl (ED_{50} = 0.73 mg/kg) but it did not show a significant effect on indomethacin-induced gastric lesions and acid output in pylorus-ligated rats at doses of 0.5–5.0 mg/kg (H. Matsuda, Pongpiriyadacha, Morikawa, Ochi, & Yoshikawa, 2003).

Matsuda et al. (2005) continues to study ACA from the rhizomes of *Alpinia galangal*. It showed potent inhibitory effect on the production of nitric oxide (NO) in lipopolysaccharide-activated mouse peritoneal macrophages with an IC_{50} value of 2.3 μM. To clarify the structure-activity relationship of 1'*S*-1'-acetoxychavicol acetate, various natural and synthetic phenylpropanoids and synthetic phenylbutanoids were examined, and the following structural requirements were clarified. (1) The para or

---

[1] **Passive cutaneous anaphylaxis** is a sensitive reaction for detecting very small quantities of antibodies and is also a method for studying the mechanisms of immediate hypersensitivity.

[2] **type l allergic reactions** an allergic reaction that becomes apparent in a sensitized person only minutes after contact

ortho substitution of the acetoxyl and 1-acetoxypropenyl groups at the benzene ring was essential. (2) The *S* configuration of the 1'-acetoxyl group was preferable. (3) The presence of the 3-methoxyl group and disappearance of the 2'-3' double bond by hydrogenation reduced the activity. (4) The substitution of acetyl groups with propionyl or methyl groups reduced the activity. (5) Lengthening of the carbon chain between the 1'- and 2'-positions reduced the activity (Hisashi Matsuda, Ando, Morikawa, Kataoka, & Yoshikawa, 2005).

Ying and Ali (2006) showed that ACA, a small molecular compound isolated from the rhizomes of *Alpinia galangal*, inhibited Rev transport at a low concentration by binding to chromosomal region maintenance and accumulating full-length HIV-1 RNA in the nucleus, resulting in a block in HIV-1 replication in peripheral blood mononuclear cells. Additionally, ACA and didanosine acted synergistically to inhibit HIV-1 replication (Ye & Li, 2006).

Azuma and co-workers (2006) interested 1´-acetoxychavicol acetate (ACA) for apoptotic activity against human leukemia HL-60 cells. They investigated optically active ACA and various racemic ACA analogs. Natural-type (or with different acyl group) ACA showed a high apoptotic activity, but the *ortho* or *meta* isomers, 4-deacetoxy analogue, and the 2´–3´ dehydrogenated derivative had no effect, or a weak activity. The study showed that the essential moieties of ACA for apoptotic activity against HL-60 cells are both the presence of a 4-acetoxyl group and an unsaturated double bond between C-2´ and C-3´ that the configuration at the 1´-position is unrelated to activity (H. Azuma, et al., 2006).

2.4 Alcohol Synthesis

Alcohols are organic compounds containing hydroxyl (-OH) groups. They are some of the most common and useful compounds in nature, in industry, and around the house. Because of their hydrogen bonding, alcohols have much higher boiling points than hydrocarbons of similar molecular weights. Small alcohols are relatively soluble in water because the hydroxyl group of the alcohol forms hydrogen bonds with water. (Glaser, et al.) Alcohols can be prepared by hydration of alkenes,

hydrolysis of alkyl halides, reduction of aldehydes, ketones, acids, and esters, and reactions of organometallic compounds with carbonyl compounds. (Metcalf, 2011)

An enantiomer is one of two stereoisomers that are mirror images of each other that are non-superposable much as one´s left and right hands are "the same" but opposite. (McNaught & Wilkinson, 1997) Enantiomers of each other often show different chemical reactions with other substances that are also enantiomers. Since many molecules in the body of living beings are enantiomers themselves, there is often a marked difference in the effects of two enantiomers on living beings. In drugs, the working substance is often one of two enantiomers, while the other one is responsible for adverse effects.

An enantiopure drug is a pharmaceutical that is available in one specific enantiomeric form. Most biological molecules (proteins, sugars, etc.) are present in only one of many chiral forms so different enantiomers of a chiral drug molecule bind differently to target receptors. One enantiomer of a drug may have a desired beneficial effect while the other may cause serious and undesired side effects, or sometimes even beneficial but entirely different effects. (Ariëns, 1984)

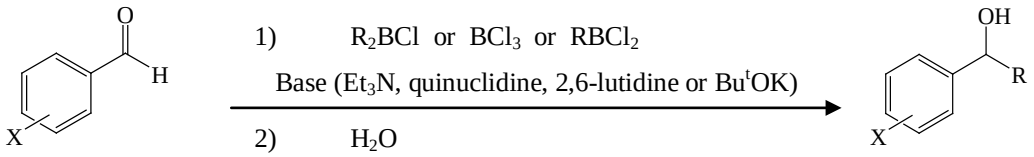
For this reason, there were many researches studied to develop the preparation procedure of enantiopure compounds. There are two main strategies for the preparation of enantiopure compounds. The first is known as chiral resolution (nonenantioselective synthesis). This method involves preparing the compound in racemic form, and separating it into its isomers. The second strategy is asymmetric synthesis (enantioselective synthesis). This method uses various techniques to prepare the desired compound in high enantiomeric excess. Techniques encompassed include the use of chiral starting materials (chiral pool synthesis), the use of chiral auxiliaries and chiral catalysts, and the application of asymmetric induction. The use of enzymes (biocatalysis) may also produce the desired compound.

2.4.1 Chiral resolution

Chiral resolution or nonenantioselective synthesis is a process for the separation of racemic compounds into their enantiomers (Porter, 1991). It is an important tool in the production of optically active drugs. One disadvantage of chiral resolution of racemic compounds compared to direct asymmetric synthesis of one of

the enantiomers is that only 50% of a desired enantiomer is obtained. There are several methods to separate racemate mixure such as resolution by crystallization, chiral resolving agents and chiral column chromatography.

Kabalka and co-workers (2001) studied the reaction of aryl aldehydes with alkylboron chlorides to produce the corresponding alcohols in good yields **(Scheme 1)**.



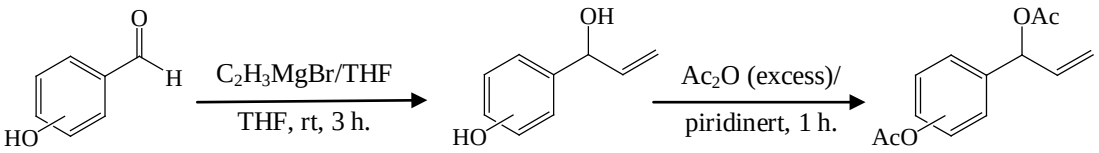
50 **51**
(20-90 %yield)

X = H, Naphthyl, 2-Cl, 2-Me, 4-F, 4-Cl, 4-Br, 4-Me, 4-MeO, 4-CN, 4-CHO
R = Cyclohexyl, Norbonyl, *s*-Butyl, 1-Hexyl

Scheme 1. Alkylation of aromatic aldehydes with alkylboron chloride derivatives

The reaction occurs under mild reaction conditions and tolerates a variety of functional groups. It was limited to aldehydes that do not possess α-hydrogens due to the well-known enolization reactions that occur with dialkylboron halides. Benzyl alcohols were formed in small quantities along with the desired products. This reaction predominates if the more hindered organoboranes, such as diisopinocampheylboron chloride, dinorbornylboron chloride, and di-(3-methyl-2-butyl)boron chloride were utilized. Organoboron chlorides containing secondary alkyl groups tended to give higher yield of alkylation products. Bulkier bases also led to higher yield of alkylated products. The best compound was synthesized via reaction of 4-fluorobenzaldehyde with dicyclohexylboron chloride that give cyclohexyl(4-fluorophenyl)methanol 90 %yield. (Kabalka, Wu, & Ju, 2001)

Lee and co-workers (2000) identified 1′-acetoxychavicol acetate and its positional (*meta* and *ortho*) as an anti-ulcer and insecticidal agent. They synthesized racemic analogs through Grignard reaction **(Scheme 2).**

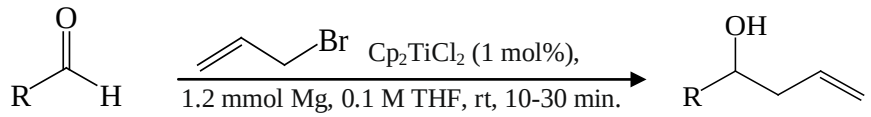


52 **54** **54**

Scheme 2. Synthesis of 1′-acetoxychavicol acetate and its positional isomer

They obtained *para*-isomer, *meta*-isomer, *ortho*-isomer with 49, 52 and 46 % yield, respectively. These racemic mixtures were resolved by HPLC equipped with a chiral column (Chiralpak AS or AD). They used 4 and 6% 2-propanol in *n*-hexane as the solvent and the flow rate of 0.5 ml/min. Both enantiomers of each compound showed almost the same insecticidal activity against the adzuki bean weevil (Lee & Ando, 2001).

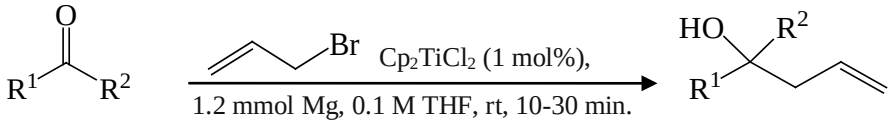
Fleury and co-workers (2010), synthesized allyl Grignard reagents *via* titanocene-catalyzed activation of allyl halides under very mild conditions through the catalytic activation and subsequent reductive transmetallation of the corresponding allyl halide in the presence of 1 mol % Cp_2TiCl_2 (titanocene dichloride) and unactivated magnesium turnings. The conditions allow for the *in situ* allylation of a wide variety of carbonyl derivatives, including aldehydes, ketones, and esters, in excellent yield (84–99%) within minutes at room temperature **(Scheme 3).** The allylation of 4-dimethylaminobenzaldehyde and (*E*)-Cinnamaldehyde gave the best yield with >99 %yield (Fleury & Ashfeld, 2010).



55 **56**

(84-99 %yield)

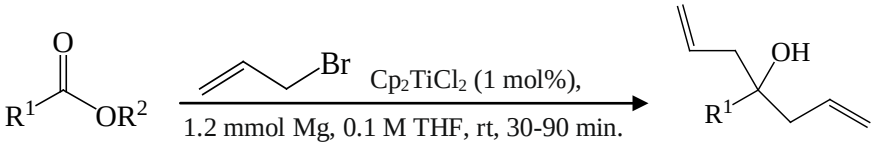
Aldehyde = Benzaldehyde, 4-Tolualdehyde, 4-Anisaldehyde, Hexanal,
4-Fluorobenzaldehyde, 4-Dimethylaminobenzaldehyde,
4-Trifluoromethylbenzaldehyde, 4-Chlorobenzaldehyde
4-Fluorobenzaldehyde, (*E*)-Cinnamaldehyde



57 **58**

(94-98 %yield)

Ketone = Acetophenone, (*E*)-4-MeO-C_6H_4-CH=CH-C(O)CH_3,
(*E*)-4-HO-C_6H_4-CH=CH-C(O)CH_3, (*E*)-4-CF_3-C_6H_4-CH=CH-C(O)CH_3,
(*E*)-4-Cl-C_6H_4-CH=CH-C(O)CH_3, (*E*)-4-c-C_6H_{11}-CH=CH-C(O)CH_3,
2-Cyclohexanone, Me_2C-=CH-C(O)CH_3, Me_2C-=CH-C(O)C_6H_5



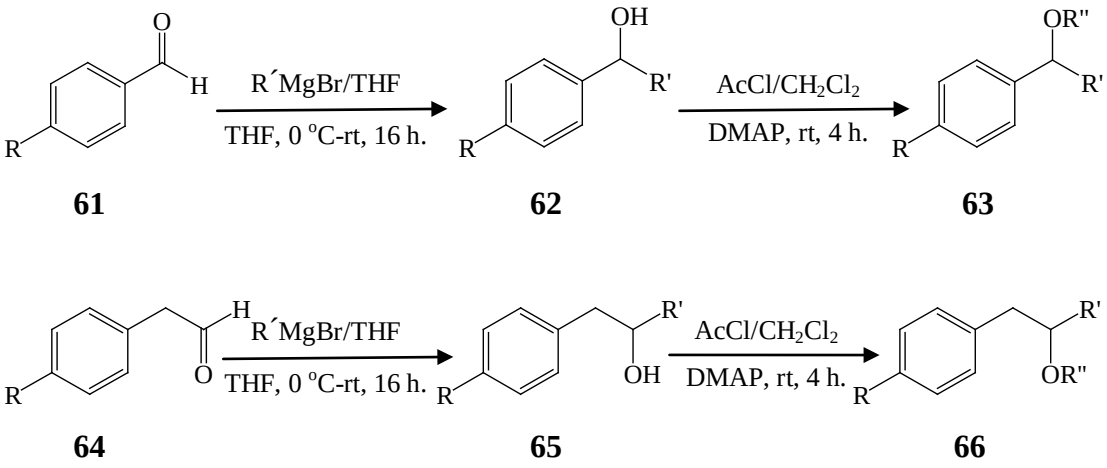
59 **60**

(92-97 %yield)

Ester = (*E*)-PhCH=$CHCO_2$-Me, 2-Me-$C_6H_4CO_2$Me, (*E*)-4-MeO-C_6H_4CH=$CHCO_2$Me
(*E*)-4-Cl-C_6H_4CH=$CHCO_2$Me

Scheme 3. Allylation of a wide variety of carbonyl derivatives

According to previous research showed that 1´*S*-1´-acetoxychavicol acetate (*S*-ACA) that isolated from rhizomes *Alpinia galangal*. It was shown to possess a potent inhibitory activity against M. *tuberculosis* H37Rv by a MIC value of 0.43 – 2.13 µM. However, it has been reported side effect. (Palittapongarnpim, Kirdmanee, Kittakoop, & Ruksaree, 2002) Therefore, Singkhonrat and co-workers (2000) tried to synthesis 1´-acetoxylchavicol acetate (ACA) analogs as anti-tuberculosis agents to enhance activity against MTB with low toxicity profiles. Alcohol analogs by Grignard reaction and following by acetylation **(Scheme 4)** were synthesized.



R = Cl, Br, CH_3, H

R´ = C_2H_3, C_3H_5, C_5H_9, C_7H_7

R´´ = Ac

Scheme 4. Pathway to synthesis of 1´-acetoxychavicol acetate analogs

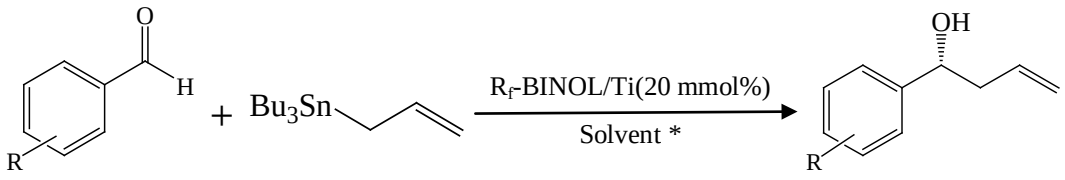
The synthesized compounds were evaluated for in *vitro* anti-mycobacterial activity against M. *tuberculosis* H37Ra. The results showed that anti-TB activity was increased when electron withdrawing group presented at *para*- position of benzene ring. The analogs with allyl substitution at position 1´ of chavicol were highly active than vinyl substitution. Moreover, compounds with hydroxyl group at position 1´ of chavicol trend to have activity than compounds with alkoxide groups at position 1´ of chavicol. The best result (MIC = 13.78 µM) was obtained with compound containing

bromide atom at *para*- position of benzene ring, hydroxyl group and allyl substitution at position 1´ of chavicol (Singkhonrat, Bunthitsakda, Kedpokasiri, & Nuampipat, 2010).

2.4.2 Asymmetric synthesis

Asymmetric synthesis also called enantioselective synthesis, chiral synthesis, or stereoselective synthesis, is organic synthesis that introduces one or more new and desired elements of chirality. This is important in the field of pharmaceuticals because the different enantiomers or diastereomers of a molecule often have different biological activity.

Yin and co-workers (2002) studied the 6,6´-bis(1*H*, 1*H*, 2*H*, 2*H*-perfluorooctyl)-1, 1´-bi-2naphthol (Rf_6-BINOL) **70** and 6,6´-bis(1*H*, 1*H*, 2*H*, 2*H*-perfluorodecyl)-1, 1´-bi-2naphthol (Rf_8-BINOL) **71** catalyzed the allylation of aldehydes in fluorous biphase system **(Scheme 5)**. Only substrate with strong electron withdrawing groups showed good yields and enantioselectivities. The conversions of *p*-chloro, *p*-bromo and 2,4-dichloro-benzaldehydes were rather poor and most of the substrates were recovered. Aldehydes with electron donating groups showed no better results. 4-Fluorobenzaldehyde and 3-fluorobenzaldehyde give the best result in this experiment with %yields 91 and 86 with high majority of *R*-configured homoallyl alcohols in 80.9 and 87.6 %ee, respectively (Yin, Zhao, Qian, & Yin, 2003).



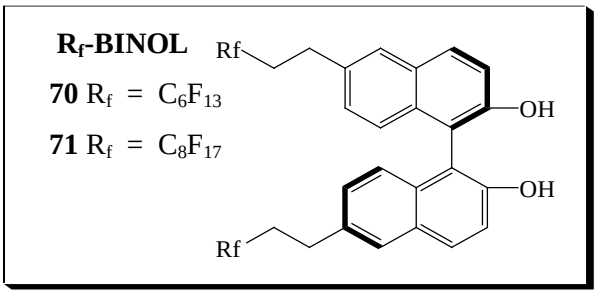
67 **68** **69**

(26-85 %yield, 49-90 %ee)

R = 3-F, 4-F, 3-F-5-CH_3F, 4-Cl, 4-Br, 3-Br, 2-Cl, 2,4-Dichloro, 4-OCH_3, 4-C_2H_5

* Solvent (homogenous) = Hexane, CH_2Cl_2, Toluene, $C_6H_5CF_3$

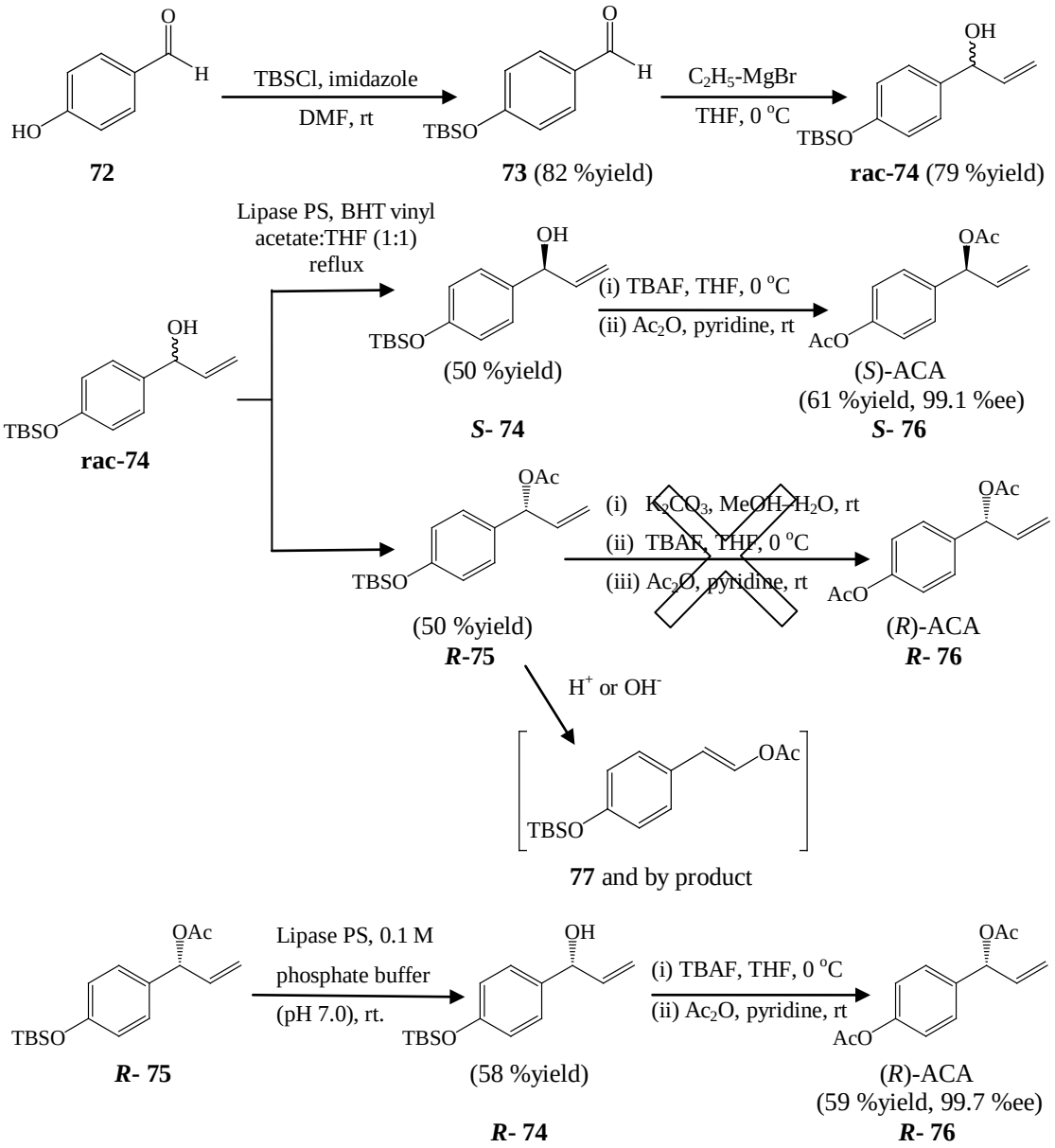
(biphase) = CH_2Cl_2:$C_{10}F_{18}$, Hexane:$C_{10}F_{18}$, Hexane:$C_6F_{11}CF_3$, Hexane:FC-72, Toluene:FC-72



Scheme 5. Asymmetric allylation of benzaldehyde in fluorous biphase system

Azuma and co-workers (2006) studied structure–activity relationships of 1´-acetoxychavicol acetate (ACA) for apoptotic activity against human leukemia HL-60 cells. They investigated using optically active ACA and various racemic ACA analogues. Optically active *S*-ACA ***S*-76** and *R*-ACA ***R*-76** were prepared by a lipase-catalyzed esterification **(Scheme 6)**. They synthesized racemic alcohol (**rac-74)** by treatment of *p*-hydroxybenzaldehyde **95** with *tert*-butyldimethylsilyl chloride in the presence of imidazole followed by a Grignard reaction with vinylmagnesium bromide to give the 4-O-protected alcohol ***rac*-74**. They used racemic alcohol ***rac*-74** as the substrate and lipase-catalyzed enantioselective esterification was carried out using various conditions. *S*-ACA ***S*-76** was obtained after the deprotection of the TBS group of the unreacted ***S*-74** by treatment with TBAF followed by acetylation. The acetylated product ***R*-75** was unstable, as the 1´-acetoxy group of ***R*-75** easily rearranges during the purification process using silica gel column chromatography to

give the structurally stable 3´-isomer **77**. This rearrangement also occurred during the deprotection of the TBS group using TBAF or under acidic conditions. Thus, it was not possible to isolate the desirable ***R*-76** after acetylation. Therefore, the deacetylation of ***R*-74** was attempted before deprotection of the 4-TBS group. However, even under very weakly alkaline conditions, rearrangement of the 1´-acetoxy group occurred. Therefore, they carried out the lipase-catalyzed hydrolysis. In phosphate buffer (pH 7), the enzymatic hydrolysis of ***R*-74** proceeded smoothly without the undesired rearrangement. This reaction, a mixture of vinyl acetate–tetrahydrofuran (1:1 v/v) as a solvent at refluxing temperature has high % enantiomer excess which optically pure ***S*-76** and ***R*-76** were obtained (99.7% ee and 99.1% ee, respectively) (Hideki Azuma, et al., 2006).



Scheme 6. Synthesis of *S*-ACA and *R*-ACA

Matsumura and co-workers (2006) reported *N*-formyl-α´-(2,4,6-triethylphenyl)-L-proline **(Figure 31)** as an activator for highly enantioselective reduction of aromatic ketones by trichlorosilane **(Scheme 7)**. The stereoselectivity for the reduction of ketones to corresponding alcohols was very high (93-97 %ee) and the absolute configuration of enantiomerically enriched alcohols was *R* in every case (Matsumura, Ogura, Kouchi, Iwasaki, & Onomura, 2006).

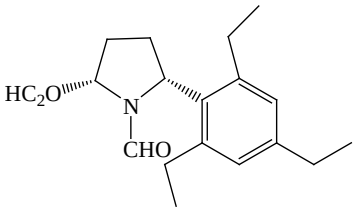
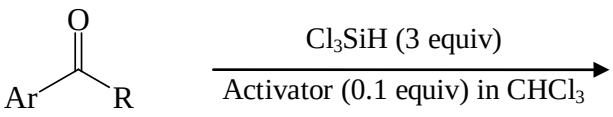


Figure 31. The structure of *N*-formyl-α´-(2,4,6-triethylphenyl)-L-proline (activator)



78 **79**

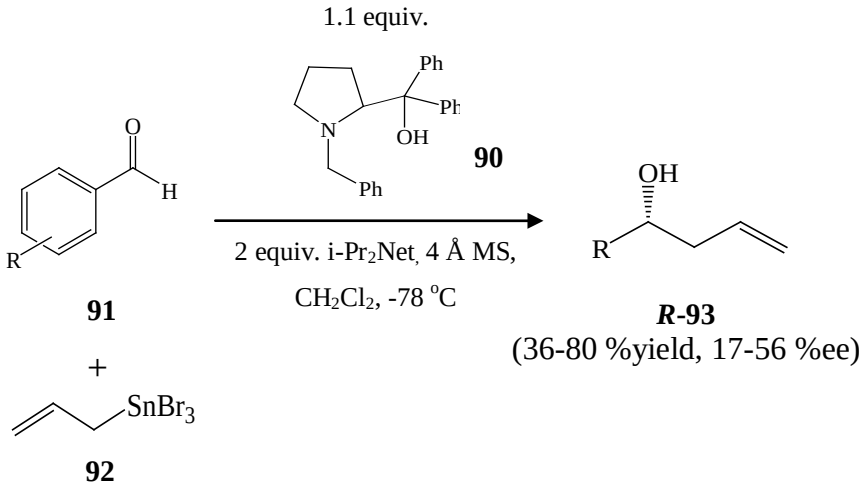
(93-97 %ee)

Ar = Ph, R = Me
Ar = Ph, R = Et
Ar = Ph, R = *n*-Pr
Ar = 4-ClPh, R = Me
Ar = 2-ClPh, R = Me
Ar = 4-FPh, R = Me
Ar = 4-NO_2Ph, R = Me
Ar = 4-MePh, R = Me
Ar = 2-MePh, R = Me
Ar = 4-*t*-BuPh, R = Me
Ar = 4-PhPh, R = Me

Scheme 7. Enantioselective reduction of aromatic ketones by trichlorosilane

Liu and co-workers (2007) reported the asymmetric allylation of benzaldehyde by using the various L-proline derivative as a chiral promoter in dichloromethane in the presence of a Lewis base. ((*S*)-1-benzylpyrrolidin-2-yl)diphenylmethanol **90** was the most active chiral promoter in the allylation of benzaldehyde with tribromoallyltin **(Scheme 8)**. Various optically active homoallylic alcohols were obtained in high yields with moderate enantioselectivities. The results showed that aldehyde with strong electron-donating group at the *para*-position gave a lower enantiomeric excess than those with an electron-withdrawing group in the *para*-position except for *p*-fluorobenzaldehyde. The aromatic aldehydes with substituent at the *otho*-position gave lower yields but higher enantioselectivities than those with the corresponding substituent at the *para*-position. This may be due to the larger steric hindrance of

otho-position than that of *para*- position. However, *o*-chloro benzaldehyde was an exception. A strong electron-withdrawing group at *meta*-position influenced the enantioselectivity. The best enantiomericselectivities (62%) of *R*-configured homoallyl alcohols was observed in case of *o*-fluorobenzaldehyde with 54 %yield (Liu, Sun, Liu, Chang, & Li, 2007).



R = Ph, Ph-CH=CH-, *p*-FC_6H_4, *o*-FC_6H_4, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, 2,4-dichloroC_6H_3, *p*-BrC_6H_4, *o*-BrC_6H_4, *p*-MeC_6H_4, *m*-$CF_3C_6H_4$, *p*-$CF_3C_6H_4$, *m*-$CF_3C_6H_4$, *p*-$NO_2C_6H_4$, *o*-$NO_2C_6H_4$, 3-methoxy—5-hydroxy-C_6H_5, Citral, *p*-$NH_2C_6H_4$, *p*-HOC_6H_4

Scheme 8. Asymmetric allylation of various aldehydes with tribromoallyltin

Appelt and co-workers (2008) developed many different systems for enantioselective allylation of benzaldehydes and substituted benzaldehydes **(Scheme 9)**. They studied the influence of chiral promoter, metal and substituted aromatic aldehydes in the reaction. They used saccharose **94** or β-cyclodextrin **95** as the chiral promoter. Zinc, indium or tin were used for enantioselective addition of in *situ* generated allylmetal reagents to aldehydes. The desired products were obtained in moderate to excellent yields and with up to 93% enantiomeric excess with β-cyclodextrin as the chiral agent and zinc as metal. High ee of 93% in the formation of

R-configured homoallyl alcohols by reaction with *p*-anisaldehyde in 90 %yield was obtained (Appelt, et al., 2008).

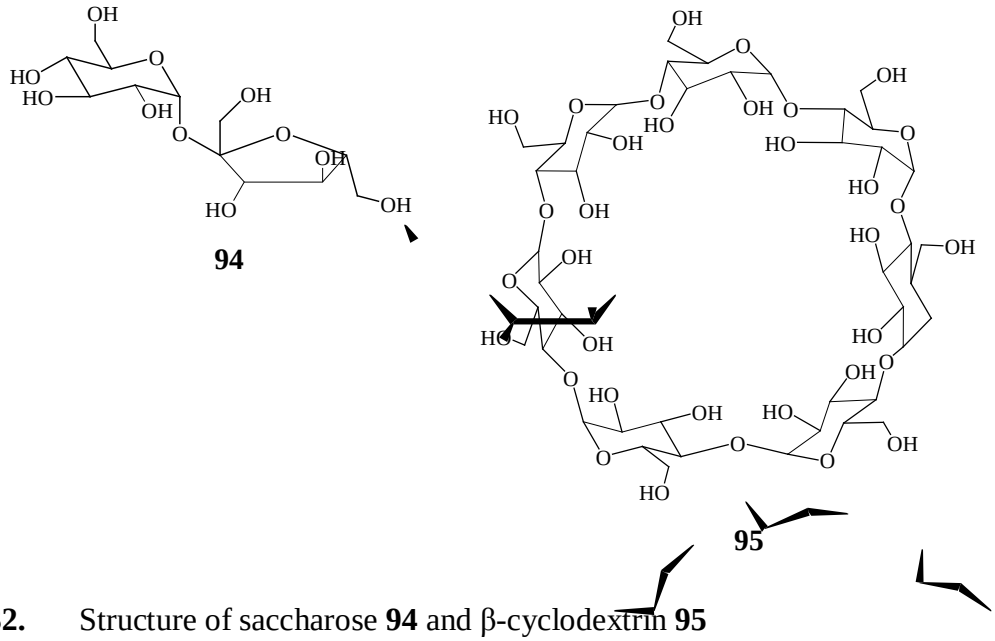
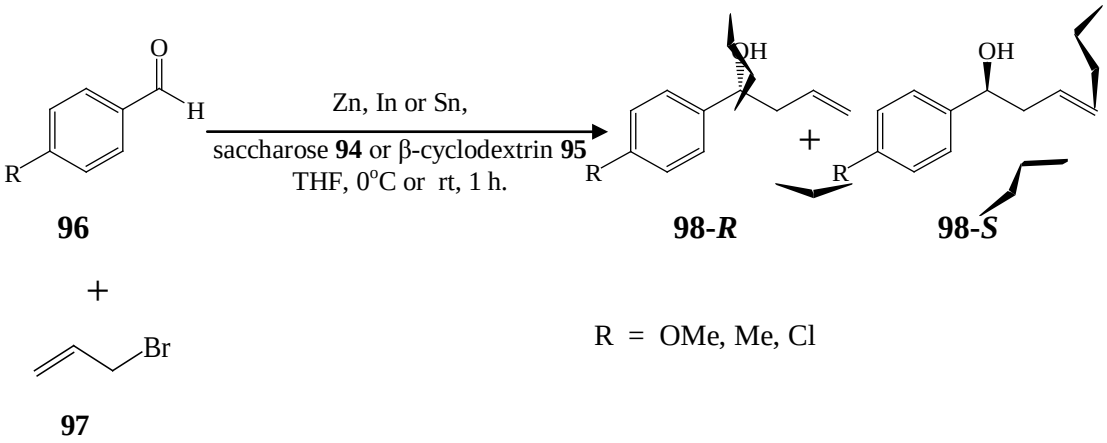


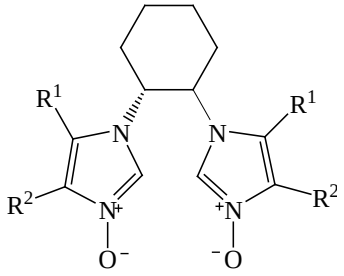
Figure 32. Structure of saccharose **94** and β-cyclodextrin **95**



Scheme 9. Enantioselective allylation of benzaldehydes derivatives

Kwiatkowski and co-workers (2009) interested chiral Lewis bases containing imidazole-*N*-oxide for purpose of asymmetric catalysis. Bisimidazole-*N*-oxides **(Figure 33)** were optimized and used as catalysts in the allylation reaction of aromatic aldehydes with allyltrichlorosilane **(Scheme 10)**. It is well known that highly nuclephilic amine *N*-oxides can act as efficient activators of organosilicon reagents.

The allylation of benzaldehyde with allyltrichlorosilane was selected as a test reaction of catalysts. The best enantioselectivity (55% ee) was achieved using the catalytic amount of **92** bearing two phenyl groups at C-4 and C-5. It led to formation of *S*-configured homoallyl alcohols. Then the reaction occurred efficiently with different aromatic aldehyde. The best enantiomericselectivities (80 %ee) was observed in case thiophene-2-carbaldehyde. (Kwiatkowski, Mucha, Mloston, & Jurczak, 2009)



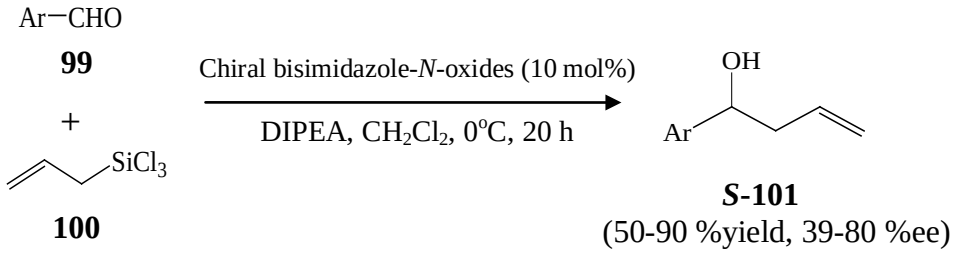
$R^1 = R^2 = Me$

$R^1 = Me, R^2 = Ph$

$R^1 = R^2, R^2 = Me$

$R^1 = R^2 = Ph$

Figure 33. Chiral bisimidazole-*N*-oxides



Ar = Me, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, β-naphtthyl, α–naphtthyl, , furan-2-yl, thien-2-yl

Scheme 10. Allylation reaction of aromatic aldehydes catalyzed by chiral bisimidazole-*N*-oxides

Our previous studies (Singkhonrat, et al., 2010) showed that a number of 1´-acetoxylchavicol acetate (ACA) analogs with halide atom at *para*- position of benzene ring significantly enhanced activity against M. *tuberculosis* H37Ra. The best result was obtained when using 1-(4-bromophenyl)but-3-en-1-ol with bromine atom

at *para*- position of benzene ring and allyl substitution at position 1´ of chavicol (MIC = 13.78 µM). Herein, we approached to synthesize and investigate a new series of ACA analogs as antituberculosis agents to enhance activity against M. *tuberculosis* H37Ra with low toxicity profiles by following structural requirements 1) the presence of electron withdrawing group (chloride atom) at *ortho*-, *meta*- or *para*- position of benzene ring 2) the presence of electron donating group (hydroxyl group) at *para*-position of benzene ring 3) the replacement of alkyl substitution at position 1´ of chavicol 4) the presence or absence of protecting group for hydroxyl group and 5) the presence of other aromatic rings**.**