15

Cinnamic Derivatives in Tuberculosis

Prithwiraj De[1,2], Damien Veau[1,2], Florence Bedos-Belval[1,2], Stefan Chassaing[1,2] and Michel Baltas[1,2]
[1]*Université de Toulouse, UPS, LSPCMIB (Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique),*
[2]*CNRS, LSPCMIB,*
France

1. Introduction

Tuberculosis (TB) is a threat to worldwide public health, mainly caused by *Mycobacterium tuberculosis* (*M.tb.*) bacteria species. Despite the availability of effective treatment, tuberculosis is responsible for more than three million deaths annually worldwide. The high susceptibility of human immunodeficiency virus-infected persons to the disease (Nunn et al., 2005), the emergence of multi-drug-resistant (MDR-TB) strains (Rastogi et al., 1992, Kochi et al., 1993; Bloch et al., 1994) and extensively drug-resistant (XDR-TB) ones have brought this infectious disease into the focus of urgent scientific interest. For this reason, there is a growing need and urgency to discover new classes of chemical compounds acting with different mechanisms from those currently used. Cinnamic acid (**1; Fig. 1**) and derivatives have a century-old history as antituberculosis agents. For example, gradual improvement was observed when the TB-patients were treated with cinnamic acid (**1**) prepared from storax (Warbasse, 1894). Furthermore, in 1920s, ethylcinnamate (**2**) (Jacobson, 1919), sodium cinnamate (**3**) (Corper et al., 1920) and benzylcinnamate (**4**) (Gainsborough, 1928) were reported to be efficacious in the treatment of TB (Fig. 1). Nevertheless, we feel that this class of molecules remained underutilized until recent years. Particularly in the last two decades, there has been huge attention towards various natural and unnatural cinnamic derivatives and their antituberculosis efficacy. This chapter provides a comprehensive literature compilation concerning the synthesis so as the antituberculosis potency of various cinnamic acid, cinnamaldehyde and chalcone derivatives. We envisage that our effort in this chapter contributes a much needed and timely addition to the literature of medicinal research.

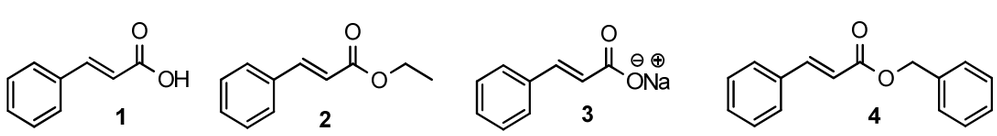


Fig. 1. Cinnamic acid, ethylcinnamate, sodium cinnamate and benzylcinnamate

2. Cinnamic acid derivatives as anti-TB agents

trans-Cinnamic acid (1) has a long history of human use as a component of plant-derived scents and flavourings (Hoskins, 1984). It belongs to the class of auxin, which is recognized as plant hormones regulating cell growth and differentiation (Thimann, 1969). The cinnamoyl functionality is also present in a variety of secondary metabolites of phenylpropanoid biosynthetic origin. Those containing a sesquiterpenyl, monoterpenyl and isopentenyl chain attached to a 4-hydroxy group represent quite a rare group of natural products (Epifano et al., 2007).

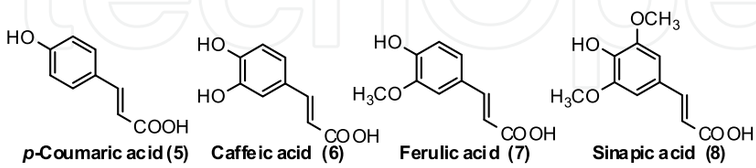
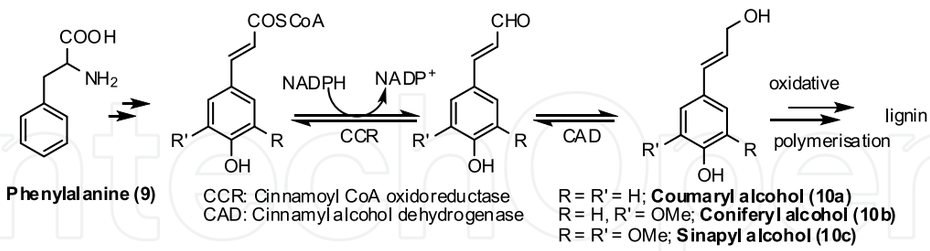


Fig. 2. Cinnamic acid and its natural phenolic-analogues

The hydroxyl cinnamic acids such as *p*-coumaric acid (**5**), caffeic acid (**6**), ferulic acid (**7**), sinapic acid (**8**) (**Fig. 2**) are natural products arising from the deamination of the phenyl alanine (**9**) (**Scheme 1**) (Kroon & Williamson, 1999). Besides, they are important constituents in the biochemical pathway in plants leading to the lignin (Humphreys & Chapple, 2002; Boerjan et al., 2003), the second most abundant biopolymer after cellulose (Whetten et al., 1998) resulting mainly from the oxidative polymerization (Freudenberg, 1959) of the three hydroxycinnamyl alcohols, namely coumaryl (**10a**), coniferyl (**10b**) and sinapyl alcohols (**10c**). These key cinnamyl alcohols are produced through two successive enzyme-catalyzed reductions starting from the corresponding cinnamyl SCoA-esters. In recent years, *trans*-cinnamic acid derivatives have also attracted much attention due to their antioxidative (Chung & Shin, 2007), antitumor (De et al., 2011a) and antimicrobial (Naz et al., 2006; Carvalho et al., 2008) properties.



Scheme 1. Lignin biosynthesis pathway

2.1 Cinnamic acid

In an attempt to develop a new strategy to circumvent MDR-TB by augmenting the potential of the existing drugs (Rastogi et al. 1994), *trans*-cinnamic acid (**1**) was used along with known antituberculous drugs such as isoniazid (**11**), rifampin (**12**), ofloxacine (**13**) or clofazimine (**14**) (**Fig. 3**). Interestingly, a synergistic increase was observed in the activity of various drugs against *Mycobacterium avium*. The synergistic activity of **1** (Rastogi *et al.* 1994) with a variety of drugs was manifested even with drug resistant isolates. Importantly, it was

proved that **1** is not bactericidal. The dose-dependent effect of cerulenin (**16**) and *trans*-cinnamic acid on *M.tb.* viability showed (Rastogi *et al.* 1996) that cinnamic acid was not bactericidal even at concentrations as high as 200 μg/mL, whereas cerulenin was bactericidal only at concentrations above 50 μg/mL.

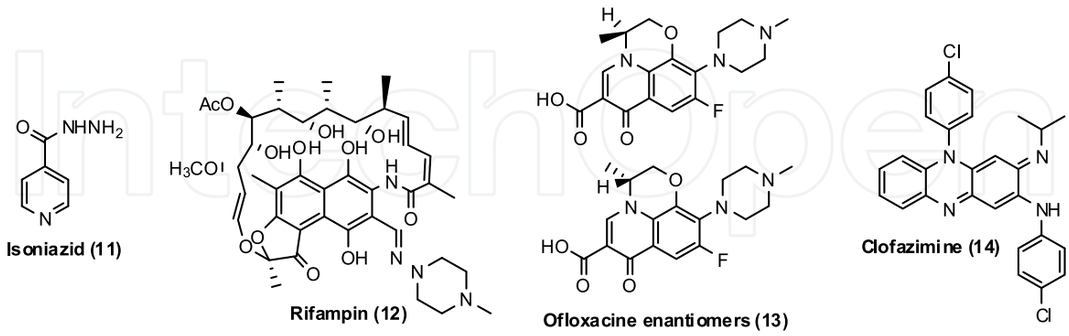


Fig. 3. Known antituberculosis drugs

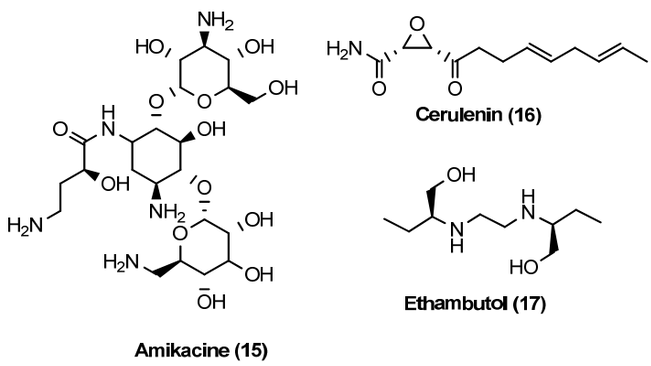


Fig. 4. Known antibiotics used in synergy studies

Thus, the sub minimum inhibitory concentrations (sub-MIC) of both **16** and **1** used in synergy experiments (fixed concentrations of only 1 μg/mL) were not due to any direct effect of these two inhibitors on *tubercle bacilli* (TB). Out of the various drug combinations screened, those with **1** gave the best results. For example, enhancement of drug activity was even observed with the drug-resistant strain 92-0492 (resistant to isoniazid (**11**) & rifampin (**12**)) when **1** at sub-MIC concentrations was used in combination with antibiotics such as ofloxacine (**13**), clofazimine (**14**) and amikacine (**15**). Cerulenin (**16**) is a known antifungal antibiotic that inhibits fatty acid and steroid biosynthesis. In fatty acid synthesis, **1** proved to bind in equimolar ratio to β-keto-acyl-ACP synthase, one of the seven moieties of fatty acid synthase, blocking the interaction of malonyl-CoA (Nomura et al., 1972; Omura, 1976). It is therefore likely that the inhibitory effects that were observed in the synergy study resulted from the inhibition of fatty acid synthesis. However, the mode of action for **1** is still unknown. In a previous study with *M. avium* (Rastogi et al., 1994), it was suspected that **1** might have inhibitory effects because of its structural similarity to phenylalanine. Because of that similarity, **1** would inhibit glycopeptidelipid (GPL) biosynthesis, therefore increasing cell wall permeability and enhancing the inhibitory effect of antimycobacterial drugs. As *M.tb.* does not synthesize GPL antigens, this reasoning does not fully fit with this bacterial species. Apparently other sites are also

being affected by **1**, which in turn enhance the susceptibility of the organism to the effects of the antimycobacterial drugs. Although, *trans*-cinnamic acid (**1**) was used to treat tuberculosis before antimycobacterial chemotherapy was used (Ryan, 1992), this was the first example of MDR-TB activity in synergy with other drugs but the mechanism of action still remains unknown.

2.2 Natural compounds

In another context, a cinnamoyl ester was identified to be important in glycoside extracts of a native North American prairie plant named *Ipomoea leptophylla*. In fact, the organic soluble extracts from its leaves showed (Barnes et al. 2003) *in vitro* activity against *M.tb*. Through a bioassay-guided fractionation of these extracts, the authors isolated leptophyllin A (**18**), a resin glycoside bearing a *trans*-cinnamic residue attached to one rhamnose moiety (**Fig. 5**). This compound showed 13% inhibition at 6.25 μg/mL against *M. tb.* in the *in vitro* anti-TB assay. Furthermore, the bioassay results indicated that the cinnamic acid residue is required for the observed antimicrobial activity as an analogous compound bearing no cinnamic acid residue, leptophyllin B (**19**), also isolated from the same source, showed no *in vitro* activity. Recently, some bioactive styryllactones and alkaloids were isolated from flowers of *Goniothalamus laoticus* (Lekphrom et al. 2009). In particular, the authors isolated a styryllactone derivative, namely howiinin A (**20**), by fractionation of the ethyl acetate and methanol extracts from the flowers of this species (**Fig**. **6**). While inactive against *Plasmodium falciparum*, this compound possessing a cinnamoyl ester moiety showed an interesting anti-TB activity (MIC = 6.25 µg/mL) when tested against *M.tb.* strain H_{37}Ra.

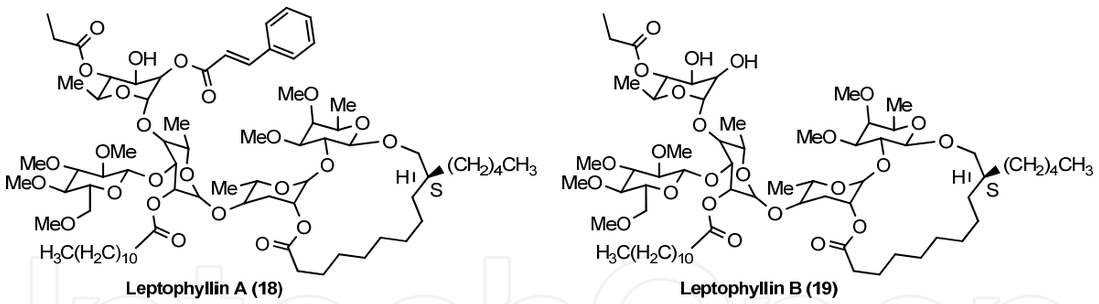


Fig. 5. Resin glycosides from *I. Leptophylla*

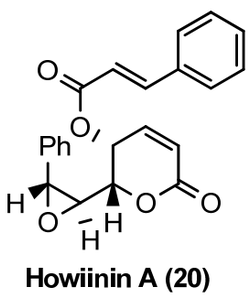
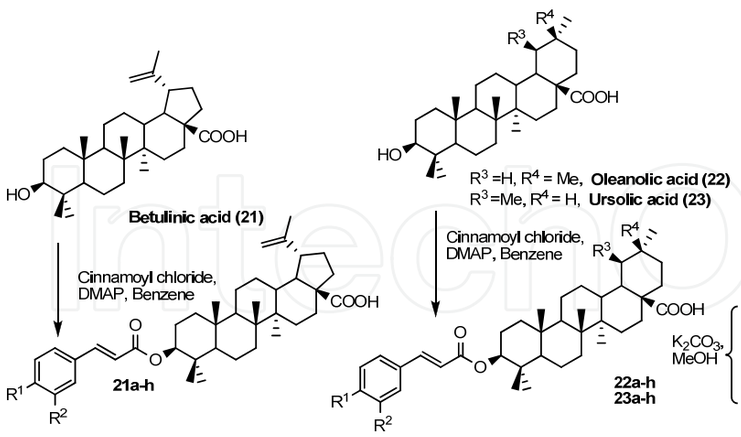


Fig. 6. Structure of Howiinin A

2.3 Synthetic compounds

2.3.1 Cinnamic ester derivatives

It is well known that triterpenes exhibit moderate to high *in vitro* antimycobacterial activity against *M. tb*. (Copp & Pearce, 2007; Okunade, Elvin-Lewis & Lewis, 2004). The modification of natural triterpenes such as betulinic acid (**21**), oleanolic acid (**22**) and ursolic acid (**23**) through introduction of cinnamoyl frames at the C-3 position has been reported (**Scheme 2**) (Tanachatchairatana et al., 2008). Different cinnamoyl derivatives such as cinnamate, *p*-coumarate, ferulate, caffeate and *p*-chlorocinnamate esters of the above mentioned triterpenes were synthesized by reacting with the suitable cinnamoyl chlorides in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) in benzene. All the hydroxyl-cinnamic acids were acetylated to protect the phenolic group before generating the corresponding acid chlorides followed by coupling with the triterpenes. The hydroxycinnamate derivatives of the triterpenes (**21d,f,h**; **22d,f,h**; **23d,f,h**) were easily obtained by deacetylation of the acetylated derivatives (**21c,e,g**; **22c,e,g**; **23c,e,g**) using K_2CO_3 in methanol. The biological results indicated that the introduction of unsubstituted or *p*-chlorinated cinnamate ester functionality (**21a,b**; **22a,b**; **23a,b**) led to inactive compounds (MIC>200 μg/mL) or without any improvement in the antimycobacterial activity of the native triterpenes. Interestingly, the results also indicated that introduction of the *p*-coumarate moiety at the C-3 position of the triterpenes (**21d**, **22d**, **23d**) resulted in an 8-fold increase in antimycobacterial activity of the parent triterpenes **21** (MIC = 50 μg/mL) and **22** (MIC = 50 μg/mL), and a 2-fold increase in the activity of the triterpene **23** (MIC = 12.5 μg/mL). Introduction of a ferulate moiety (**21h**, **22h**, **23h**) resulted in a 4-fold increase in activity only in case of **23**. However, the presence of a *p*-hydroxy group plays a crucial role on the high antimycobacterial activity because its methylation and acetylation proved to decrease antimycobacterial activity in a significant manner, caffeate esters **21e,g** and **22e,g** being the exceptions.



Triterpene	21	22	23
a; R_1 = H, R_2 = H,	>200	50	>200
b; R_1 = Cl, R_2 = H,	>200	>200	>200
c; R_1 = OAc, R_2 = H,	12.5	12.5	25
d; R_1 = OH, R_2 = H,	6.25	6.25	6.25
e; R_1 = OAc, R_2 = OAc,	200	12.5	100
f; R_1 = OH, R_2 = OH,	200	200	200
g; R_1 = OAc, R_2 = OMe,	200	50	3.13
h; R_1 = OH, R_2 = OMe,	200	12.5	3.13

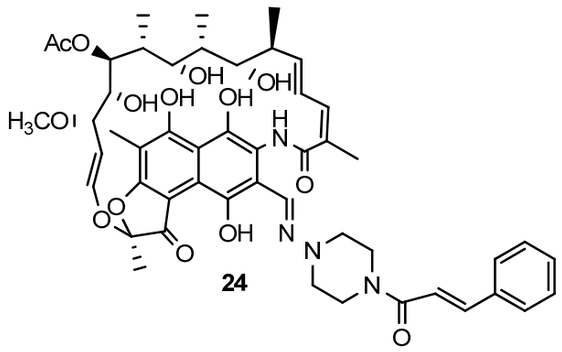
MIC (μg/mL)

Scheme 2. Cinnamate-based triterpenes and their biological activities

2.3.2 Cinnamic amide derivatives

Rifampin (RIF; **12; Fig. 3**) is one of the most important drugs in TB treatment. In search for new compounds with structural modifications of existing lead drugs, the presence of a cinnamoyl moiety on rifampin's piperazinyl framework instead of a methyl group,

furnishing 3-(4-cinnamylpiperazinyl-iminomethyl)rifamycin derivative (**24**; rifamycin SV (T9); **Fig. 7**), resulted in enhanced antimycobacterial activity (Reddy *et al*. 1995; Velichka et al. 2010). The antimycobacterial activities of **24** on 20 susceptible and MDR-strains of *M.tb.* and 20 *M. avium* complex (MAC) strains were investigated (Dimova *et al.* 2010). The radiometric MICs of T9 for *M.tb.* were significantly lower than those of RIF. The MICs of T9 and RIF at which 90% of the RIF-susceptible strains were inhibited were <0.25 and <0.5 µg/mL, respectively. Compound **24** had better activity against MAC strains, and the MIC at which 90% of the MAC strains were inhibited was <0.125 µg/mL, while that of RIF was <2.0 µg/mL. Compound **24** also showed high *in vitro* bactericidal and intracellular activities which were significantly superior to those of RIF against both *M.tb.* and MAC strains. More importantly, **24** showed excellent *in vivo* activity against *M.tb.* $H_{37}Rv$ compared to RIF in both the lungs and spleens of C57BL/6 mice, indicating the potential therapeutic value of **24** in the treatment of mycobacterial infections.

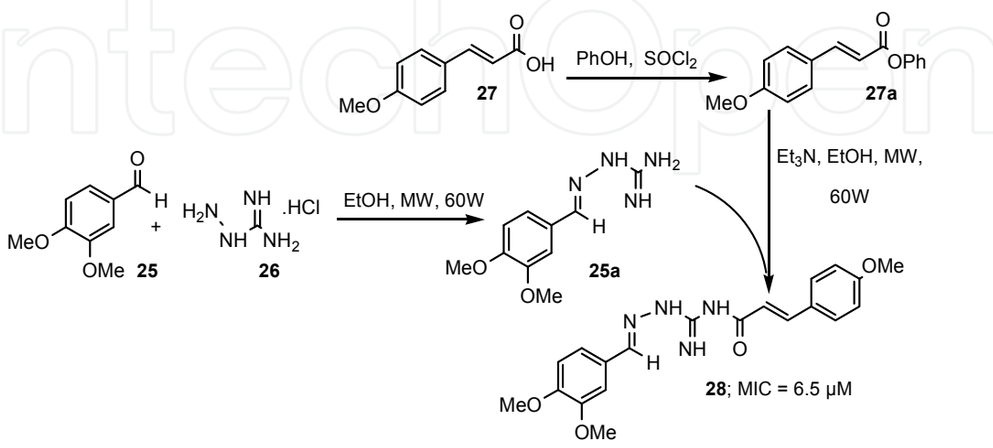


24

Fig. 7. Structure of Rifamycin SV(T9)

In an attempt to find novel compounds active against TB, a series of phenylacrylamides designed by molecular hybridization of *trans*-cinnamic acids and guanylhydrazones were synthesized and antiTB efficacy were evaluated (**Scheme 3**) (Bairwa et al., 2010). While cinnamic acids are already known for their antituberculosis efficacy, guanylhydrazones have been shown to have antimicrobial activity including an interesting gram-negative bacterial endotoxin lipopolysaccharide (LPS) sequestering activity (Gadad et al. 2000; Wu et al. 2009). *M. tb.* contains lipoarabinomannan (LAM), a complex lipid glycoprotein anchored to the cell membrane by phosphatidylinositol which has structural and functional similarity to LPS, including the presence of anionic phosphate groups (Zhang et al., 1994). Biosynthesis of LAM is known to be a target for several antituberculosis agents, including the first line antitubercular agent, ethambutol (**17**; **Fig. 4**) (Scherman et al. 1995; Heijenoort, 2001). For the synthesis of the most active phenylacrylamide derivative (**28**; **Scheme 3**), the required guanylhydrazone (**25a**) was prepared by the microwave-assisted reaction of 3,4-dimethoxy benzaldehyde (**25**) with guanylhydrazine hydrochloride (**26**). In parallel, the phenyl 4-methoxycinnamate (**27a**) was prepared by esterification of 4-methoxycinnamic acid (**27**) via its treatment by phenol and thionyl chloride. Finally, the coupling of equimolar quantities of guanylhydrazone (**25a**) with phenylcinnamate (**27a**), was performed under microwave irradiation in the presence of triethylamine and ethanol as solvent to afford the target derivative (*E*)-*N*-(((*E*)-2-(3,4-dimethoxybenzylidene)hydrazinyl)(imino)methyl)-3-(4-methoxyphenyl)acrylamide (**28**). Compound **28** was found to be active when tested on resazurin microtiter plate assay

(REMA) against *M. tb.* $H_{37}Rv$ (MIC = 6.5 µM) along with good safety profile (CC_{50} = 340 µM) in VERO cell line. Importantly, analysis of structure–activity relationships revealed that both steric and electronic parameters play major role in the activity of this series of compounds.

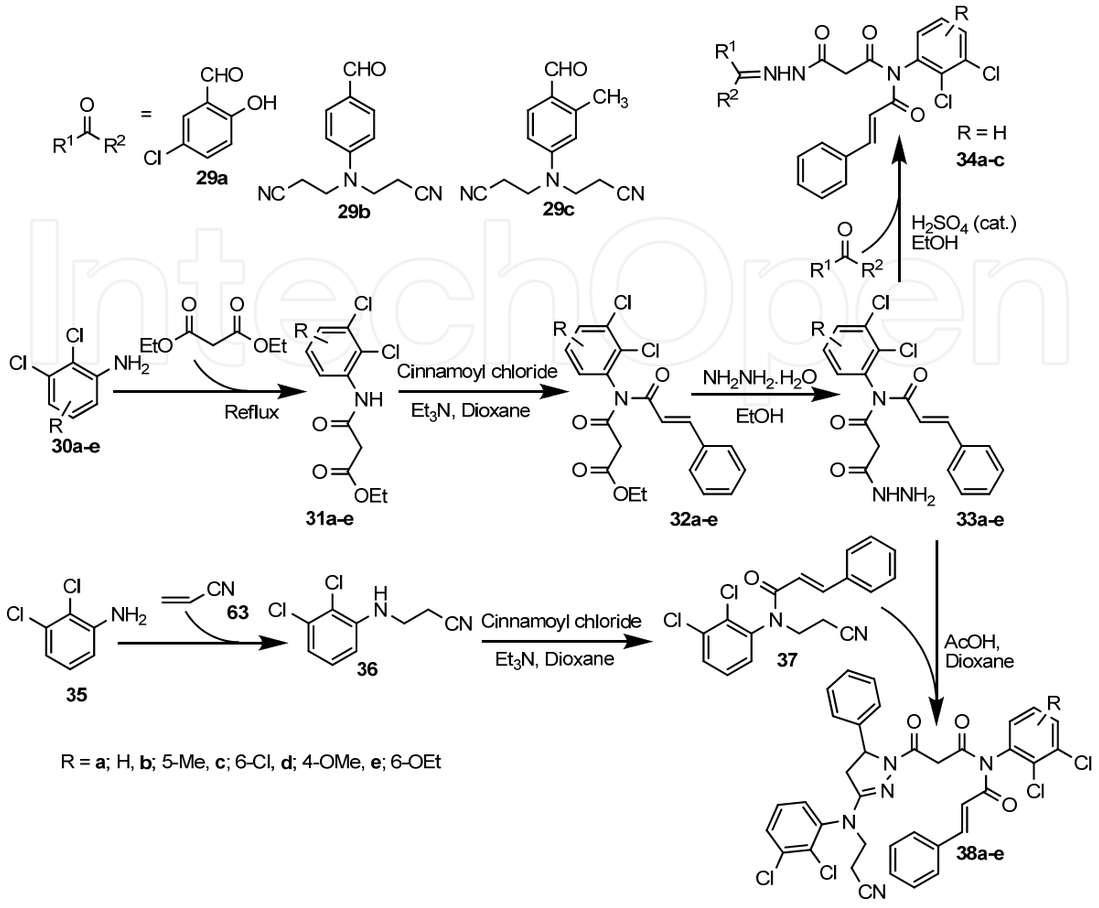


Scheme 3. Synthetic route for the synthesis of phenylacrylamide derivatives

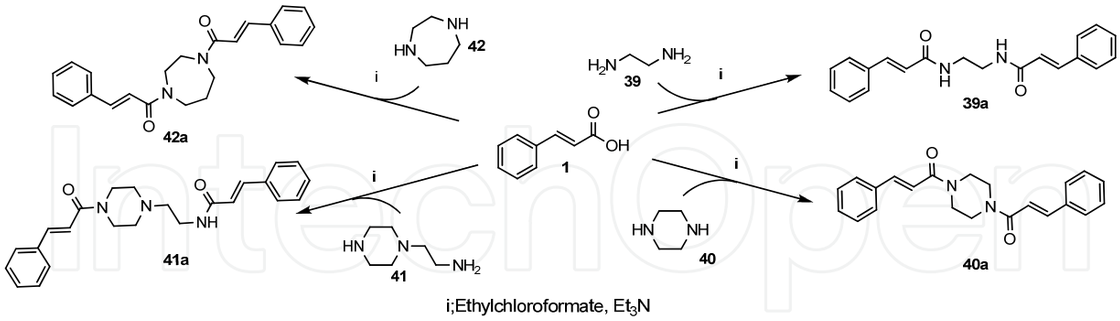
A series of 1-[(2,3-dichloroanilinomalonyl)-3-(*N*-2′-cyanoethyl)-2-(*N*-cinnamoyl) 2,3-Dichloroanilino)]-5-phenyl pyrazolines (**38a-e**) have been synthesized from *N*-cinnamoyl-*N*-2′-cyanoethyl-2,3-dichloroaniline (**37**) in the presence of 2-[(*N*-cinnamoyl) 2,3-dichloroanilido] acetohydrazides (**33a-e**) and acetic acid in dioxane (**Scheme 4**) (Sharma et al., 2010, 2011). These compounds have been tested for *in vitro* antitubercular activity on *M.tb***.** $H_{37}Rv$ strains.

The compounds (**38a-e**) inhibited the growth of *M.tb.* at 100 µg/mL concentration. The acylhydrazide (**33a**) was also coupled with some aromatic aldehydes (**29a-c**) in the presence of catalytic H_2SO_4 in ethanol. The resulting hydrazones (**34a-c**) were also found to have anti-TB activity.

Using a molecular hybridization approach, a series of cinnamide derivatives (**39a**-**42a**) was designed as potential antimycobacterial agents (Kakwani et al. 2011). The diamine moiety of ethambutol (**17; Fig. 4**) and its other analogs proved to be a key feature. Various diamines (**39-42**) were coupled with **1** using ethylchloroformate and triethylamine to obtain cinnamide derivatives (**39a**-**42a**) (**Scheme 5**). The MICs of all synthesized compounds were determined against *M.tb.* $H_{37}Rv$ using Resazurin Microtitre plate Assay (REMA) method. The synthesized molecules (**39a**-**42a**) showed good to moderate activities with MIC in the range of 5–150 µM and good safety profiles. The most potent compound **39a**, having MIC of 5.1 µM (cytotoxicity measured on VERO cells line C1008 (CC_{50}) = 618 µM) exhibited synergy with rifampin (**12**). Under similar conditions ethambutol (**17**) showed MIC of 15.3 µM with a CC_{50} value of 1470 µM.



Scheme 4. Synthesis of cinnamoyl pyrazolines and analogs

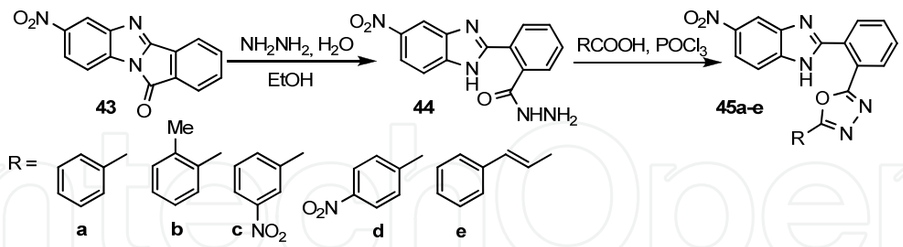


Scheme 5. Synthesis of cinnamides from diamines

2.3.3 Cinnamic oxadiazole derivatives

The synthesis of some 1,3,4-oxadiazoles and oxo-imidazolines compounds as potent biologically active agents has been reported (Joshi et al., 1997). The synthetic routes are presented in **Scheme 6**. The common precursor **44** was obtained through condensation of 5-nitro-*o*-benzoylene-2,1-benzimidazole (**43**) with hydrazine hydrate. The cyclocondensation reaction of different aromatic acids with **44** in the presence of $POCl_3$ afforded 1,3,4-

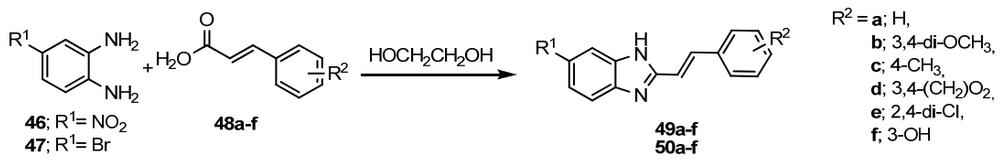
oxadiazoles **45a-e**. Compounds **45a-d** were found to be more active against *M.tb.* $H_{37}Rv$ than the cinnamic derivative **45e** at 12.5 μg/mL.



Scheme 6. Synthesis of various 1,3,4-oxadiazoles and 5-oxo-imidazolines

2.3.4 Cinnamic benzimidazole derivatives

Benzimidazole scaffold being an important pharmacophore and privileged structure in medicinal chemistry (Khalafi-Nezhad et al., 2005; Evans et al. 1988), a new series of 5-(nitro/bromo)-styryl-2-benzimidazoles (**49a-f, 50a-f**; **Scheme 7**) was synthesized (Shingalapur et al., 2009) by simple condensation of 5-(nitro/bromo)-*O*-phenylenediamine (**46, 47**) with *trans*-cinnamic acids (**48a-f**) in ethylene glycol for 6 h at around 200°C (**Scheme 7**). The *in vitro* anti-TB activities of compounds **49a-f** and **50a-f** on the *M.tb.* $H_{37}Rv$ were determined at 7.25 μg/mL concentration. Interestingly, the bromo-substituted benzimidazole derivatives (**50a-f**) exhibited the best results with 63-83% inhibition.

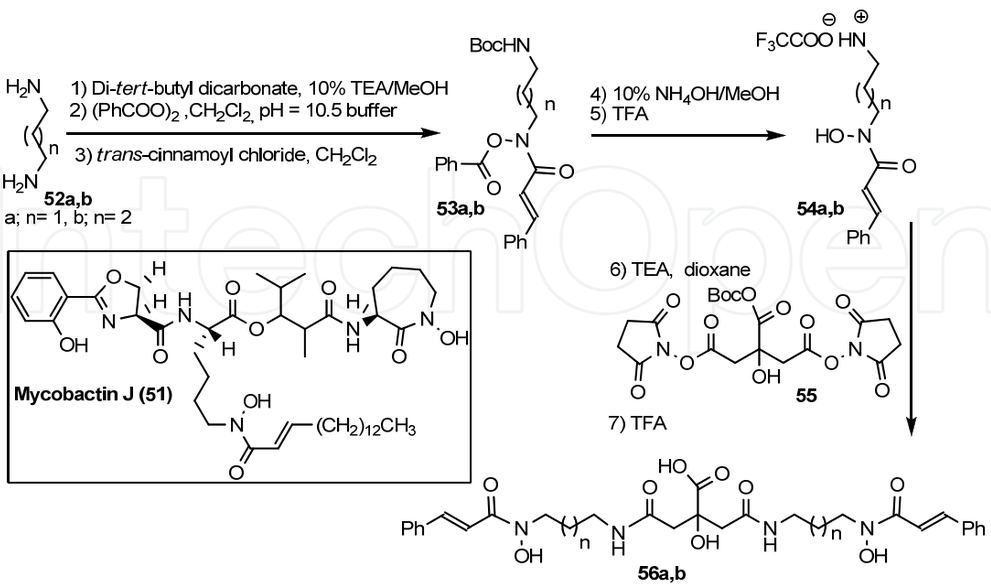


Scheme 7. Synthesis of styryl-2-benzimidazoles series

2.3.5 Cinnamic acid hydroxamic derivatives

The sequestration of iron is a part of the non-specific mammalian immune response and thus, metal uptake and regulation of metal-ion concentrations are the key features of host-pathogen interactions (Agranoff & Krishna, 2004). Siderophores are small, high-affinity iron chelating compounds secreted by microorganisms such as bacteria, fungi and grasses (Neilands, 1995; Cornelis & Andrews, 2010). Siderophores are considered amongst the strongest soluble Fe(III)-binding agents known. Siderophores, produced by mycobacteria itself, were used (Guo et al., 2002) to target iron transport processes essential for the growth and survival of *M. tb.* Targeting the iron transport processes of *M.tb.* is challenging for several reasons. The complexity of the mycobactin architecture itself poses a daunting synthetic challenge, which hampers the generation of conjugates (Xu & Miller, 1998). Further, the iron transport mechanism involves an "iron-handoff" between two siderophore families, the exochelins and the mycobactins. In low iron environments, *M.tb.* biosynthesizes and secretes hydrophilic exochelins (e.g., Mycobactin J (**51**); **Scheme 8**) to bind exogenous ferric ion. The iron-complex is then transferred to intracellular siderophores (*i.e.* the mycobactins) which are lipophilic chelators associated with the

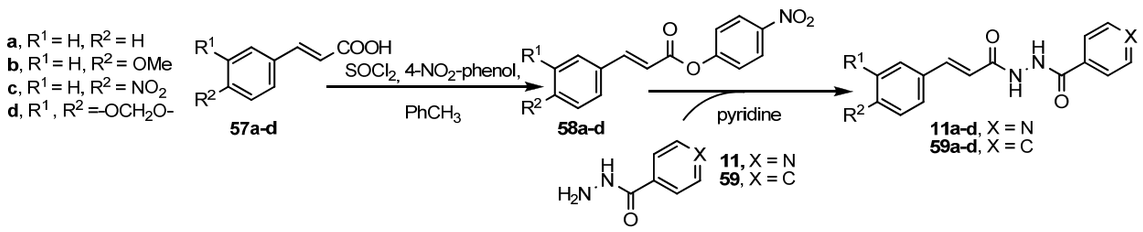
cytoplasmic membrane (Roosenberg et al., 2000). The mycobactin so-associated with iron either remains in the cell wall as an iron storage pool or is released into the cell by a mycobactin reductase. Therefore, the sequestration of the available iron into a form, which cannot be processed by *M.tb.* may be an alternative therapeutic way. The success of this approach relies on the understanding of the molecular recognition events involved in mycobacterial iron transport. In that context, the authors synthesized different iron chelators containing α,β-unsaturated hydroxamic acid motifs appended to a citric acid platform such as Nannochelin A (**56b**) and compared their activities with the corresponding *trans*-octenoyl derivative (**56a**). As shown in **Scheme 8**, the synthesis starts from diamines (**52a,b**) with a three-steps sequence to afford, after monoprotection, *N*-benzoylation and *N*-acylation with *trans*-cinnamoyl chloride, the dissymetric amino-compounds **53a,b**. **53a,b** were then treated with a 10% NH_4OH solution in methanol solution at 0 °C to deprotect the hydroxamic acid and the resulting derivatives were treated with trifluoroacetic acid (TFA) to produce the TFA salts **54a,b**. Finally, the condensation of **54a,b** with the activated Boc-protected citric acid (**55**) in 1,4-dioxane followed by TFA treatment gave the desired chelators **56a,b.** Notably, molecules that provided significantly higher growth index (GI) values than the native chelator **51** were identified as superior growth stimulants and more efficacious iron delivery agents. The systems containing longer tethers gave higher GI values (e.g., GI = 0.76 for **56a** *vs* 1.5 for **56b**). It was envisaged by the authors that the longer tether allows for a more conformationally flexible ligand to properly coordinate to iron thus providing an increase in hydrophobicity. However, the authors identified **56b** as a superior growth stimulant and a more efficacious iron delivery agent. Such ligands, which offer regulation of the initial iron delivery step, provide the opportunity to compare the iron transport mechanisms of both native and genetically modified mycobacteria.



Scheme 8. Synthesis of Nannochelin A

2.3.6 Cinnamic acid hydrazide, thioester and other derivatives

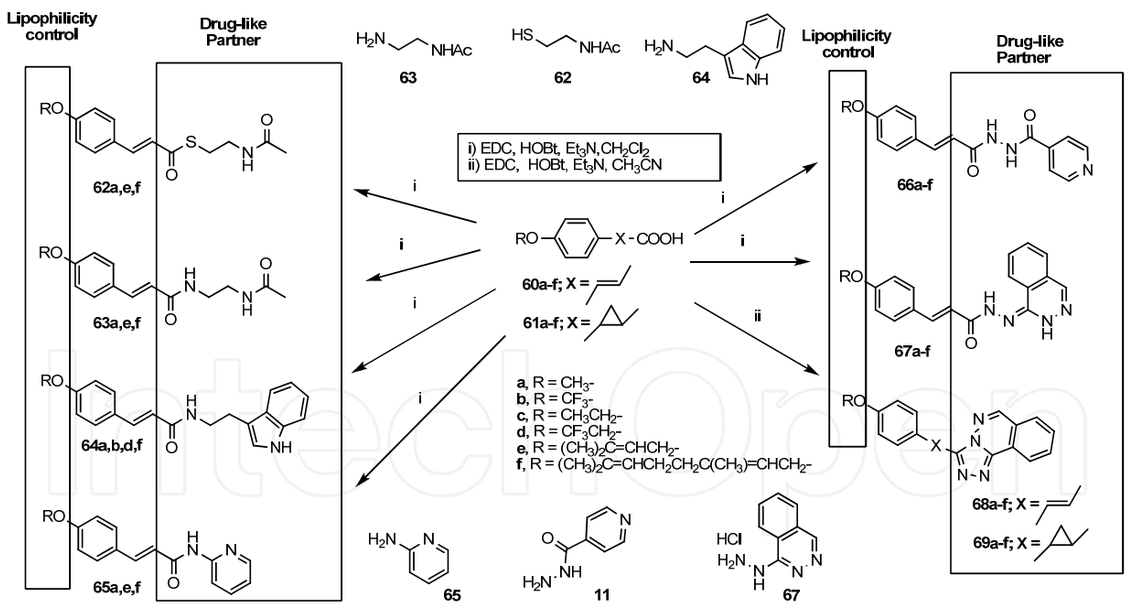
trans-Cinnamic acid hydrazide derivatives were presented as potential antituberculosis agents (Carvalho et al. 2008). The authors designed and explored the introduction of the *trans*-cinnamic moiety into isoniazid (**11**) core structure to ameliorate its activity. Isosteric substitution of the pyridine ring of **11** was also investigated by these authors. The synthetic route (**Scheme 9**) used for the preparation of the target compounds is rapid and relies on the formation/use of *p*-nitrophenyl esters (**58a-d**) as activated forms of cinnamic acid derivatives (**Scheme 9**). These stable intermediates (**58a-d**) were prepared by treating the appropriate cinnamic acid (**57a-d**) with thionyl chloride in the presence of 4-nitro-phenol. The target hydrazides (**11a-d**, **59a-d**; **Scheme 9**) were then obtained in good yields by coupling the so-formed activated acids (**58a-d**) with either acylhydrazide **11** or **59**. The anti-TB activities of these compounds were assessed against *M.tb*. Almost all of the isonicotinic derivatives **11a-d** were sensitive in the minimum concentration tested (MIC = 3.12 µg/mL). Nevertheless, all benzoic acid derivatives **59a-d** were much less active, thus reinforcing the pharmacophoric contribution of the isonicotinic moiety. Importantly, the authors identified that the 4-methoxycinnamic derivatives promote the better activity.



Scheme 9. Synthetic route for the preparation of the cinnamoyl hydrazides

In our recent effort, we have synthesized some 4-alkoxycinnamic acid thioesters, amides, hydrazides and triazolophthalazine derivatives (Yoya et al., 2009; De et al., 2011b) and evaluated their anti-TB efficacy **(Scheme 10)**. While 4-alkoxy substitutions were introduced to control the required lipophilicity following Lipinski's rules (Lipinski et al., 1997), their coupling partners were suitably chosen either to mimic biological intermediates or to modify any existing drug. Accordingly, various 4-alkoxycinnamic acids were coupled with *N*-acetylcysteamine (**62**) to afford the corresponding thioesters (**62a,e,f**) thereby mimicking the enoylacyl-ACP intermediate involved in the *M.tb*. fatty acid synthase II (FASII) cycle, an essential step towards mycolic acid (C_{26}-C_{56} fatty acids) biosynthesis. Mycolic acids are essential components of bacterial cell wall and notably, isoniazid is known to inhibit InhA (enoylacylreductase A; involved in FAS II cycle) thereby inhibiting the mycolic acid biosynthesis. The major advantage of FAS II-cycle as drug target is that it is an exclusive feature of prokaryotes. However, the synthesized thioesters (**62a,e,f**) showed poor anti-TB activities against *M.tb*. H_{37}Rv, possibly due to the weak C-S bond energy which makes these molecules labile under physiological conditions. No amide derivatives (**63a,e, 64a,b,d,f; 65a,e,f**) showed good biological activity except (*E*)-*N*-(2-acetamidoethyl)-3-(4-geranyloxyphenyl)acrylamide (**63f**) (MIC = 0.24 µM, *vs* INH; MIC = 0.6 µM). Unfortunately, they (**63a,e, 64a,b,d,f; 65a,e,f**) have poor cytotoxicity profile. To alleviate the concern for the proteolytic instability, we thus prepared a series of cinnamoylhydrazides (**66a-f**). All six 4-alkoxycinnamoyl isonicotinyl hydrazides (**66a-f**) showed good MIC and their cytotoxicity profile (IC_{50} ranging between 43-256 µM on THP-1 cell line) were very much encouraging.

Further, the radio-thin-layer chromatography analysis of **52e**, when introduced to the broth culture of *M.tb.,* revealed that this class of molecules inhibit the mycolic acid biosynthesis. Two representative INH-derivatives **66a** (same as **11b** in **Scheme 9**) and **66e** were tested on MYC5165, a *M.tb.* strain mutated in InhA and 1400 a *M.tb.* strain mutated in *katG*. The inhibitory activities of **66a** (MIC = 16 μM: MYC5165; 320 μM: 1400) and **66e** (MIC = 27 μM: MYC5165; 68 μM: 1400) were found to follow similar trends as that of INH (MIC = 18 μM: MYC5165; 729 μM: 1400) itself**,** thus not allowing at the moment to propose these compounds as isoniazid prodrugs or not. In order to explore the influence of other hydrazides, 1-hydrazinophthalazine hydrochloride **67**, an antihypertensive drug (Schroeder, 1952; Silas et al., 1982) of moderate potency, was coupled with acids **60a-f** in the presence of EDC.HCl, HOBt and triethylamine to afford phthalazinohydrazides (**67a-f**). For the family of 1-phthalazinohydrazides (**67a-f**), MIC results were moderate but the trend of cytotoxic behaviour was not acceptable. Under different experimental conditions, coupling of acids (**60a-f**) with **67** in acetonitrile under reflux furnished the corresponding 3-(4-alkoxystyryl)-[1,2,4]triazolo[3,4-α]phthalazines (**68a-f**). Interestingly, the combination of isopentenyl-side chain as 4-alkoxy substituent with triazolophthalazine (**68e**), showed excellent antitubercular potency (MIC = 1.4 μM), in comparison with other derivatives in the series (**68a-f**), and more importantly, with good cytotoxicity (IC_{50} = 449 μM on THP-1 cell line) and selectivity index (SI = 320). Finally, to our great delight, compound **68e** showed 100-fold better *in vitro* activity against MYC5165 strain (**68e**; MIC = 0.2 μM) and 1800-fold better activity against 1400 strain (**68e**; MIC= 0.4 μM) compared to INH.



Scheme 10. Synthetic route for the preparation of different cinnamoyl derivatives

Further, the radio-thin-layer chromatography analysis revealed that compound **68e** does not inhibit mycolic acid biosynthesis signifying a different mode of action than INH. In order to explore the importance of the enoyl-acyl backbone, the double bond was replaced by bioisosteric cyclopropyl moiety. Thus, 3-[2-(4-alkoxyphenyl)cyclopropyl]-[1,2,4]triazolo[3,4-α]phthalazine (**69a-f**; racemates) were synthesized and their *in-vitro* anti-TB activities were

also evaluated. Significantly, the MICs of the compounds (**69a-f**) were found to be poorer compared to **68a-f**. In regard to the difference in activities between the enoyl and cyclopropyl series, a plausible explanation could be the respective Michael acceptor ability. From a chemical point of view, 4-OCF_3 derivatives are expected to show better inhibitory activities compared to their 4-OCH_3 analogues. However, this is not the case as **66a** has a 4-fold better activity (MIC = 0.3 μM) compared to **66b** (MIC = 1.1 μM) and similarly **68a** (MIC = 53 μM) exhibits approximately 15-fold activity better than **68b** (702 μM). In view of these results, it was suggested that the Michael addition may not be the mode of action of these compounds. This view was also supported by the fact that mycobacterial lip B prefers to form thioester intermediate with deca-2-enoic acid during mycolic acid biosynthesis unlike *E.coli* lipB which forms a thioether *via* Michael addition (Ma et al.; 2006).

3. Cinnamaldehyde derivatives as anti-TB agents

Cinnamaldehyde (**70**), also biosynthesized starting from phenylalanine (**9**) in the process of lignin biosynthesis, occurs naturally in the bark of cinnamon trees and other species of the genus *Cinnamomum*. Owing to its typical odor and low toxicity to human exposure, cinnamaldehyde is used as food flavoring agent. It is also used as a fungicide, insecticide for mosquito larvae (Cheng et al., 2004) and has shown inhibitory activities towards proliferation, invasion and tumor growth in a murin A375 model of human melanoma (Cabello et al., 2009). Importantly, **70** and its derivatives have shown enormous potential as antimicrobial agents. For example, cinnamaldehyde is known to inhibit *E. coli* and *Salmonella typhimurium* growth (Helander et al., 1998). Its carbonyl group has affinity for proteins, preventing the action of decarboxylase amino acids on *E. aerogenes* (Wendakoon & Sakaguchi, 1995). From a chemical standpoint, worth precising is that **70** so as its 3-phenylacrylaldehydic congeners offer three main reactive sites: substitution on the phenyl ring, addition on the α,β-unsaturation and reactions of the aldehyde functionality. The α,β-unsaturated carbonyl moiety can be considered as a Michael acceptor (Chew et al., 2010), which is often employed in the design of drugs (Ahn & Sok, 1996).

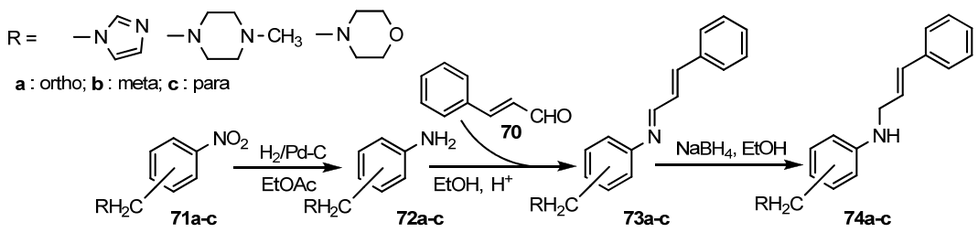
3.1 Cinnamaldehyde

The growth of *M. avium* subsp. paratuberculosis is inhibited by cinnamaldehyde (**70**) with a MIC of 25.9 μg/mL (Wong et al., 2008). Importantly, the authors suggest that the mechanism of antimicrobial activity of naturally occurring compounds such as cinnamaldehyde is specific rather than nonspecific since it is concentration dependent (Friedman et al., 2002). Possible modes of action include disruption of cell membranes, inhibition of essential enzymes, chelation of essential trace elements (such as iron), and targeting of cell membranes. Cinnamaldehyde (**70**) is also known to inhibit the bacterial cell division protein FtsZ (Domadia et al., 2007). FtsZ, a prokaryotic homolog of tubulin, regulates cell by assembling into the macromolecular structure called Z-ring at the site of cell division (Romberg & Levin, 2003). While cinnamaldehyde (**70**) proves to decrease the *in vitro* assembly reaction and bundling of FtsZ, **70** was also found to perturb the Z-ring morphology *in vivo* and to reduce the frequency of the Z ring per unit cell length of *Escherichia coli*. In addition, GTP-dependent FtsZ polymerization is inhibited by **70**, cinnamaldehyde (**70**) inhibiting the rate of GTP hydrolysis and binding FtsZ with an affinity constant of 1.0 ± 0.2 μM^{-1}. Isothermal titration calorimetry revealed that the binding of **70** to

FtsZ is driven by favorable enthalpic interactions. This signifies that **70** binds FtsZ, perturbs the cytokinetic Z-ring formation and inhibits its assembly dynamics. The authors suggested that **70**, a small molecule of plant origin, is a potential lead compound that can be developed as an anti-FtsZ agent towards drug design.

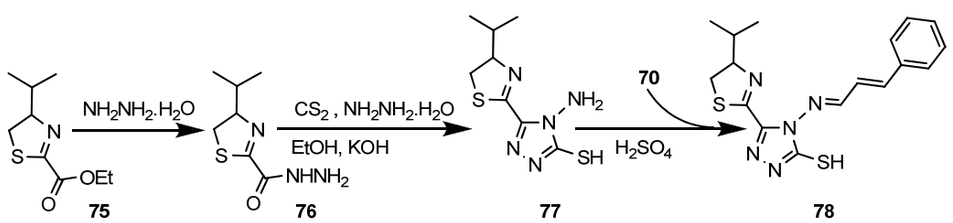
3.2 Cinnamaldehyde-derived hydrazones

The synthesis and antimycobacterial efficacy of a new class of styryl derivatives (**74a-c**) were reported (**Scheme 11**) (Biava et al., 1997). The desired styryl derivatives (**74a-c**) were prepared in a three-steps sequence that begins by the reduction of the starting nitro compounds (**71a-c**) furnishing *ortho-*, *meta-* or *para*-aminotoluidines possessing either an imidazole, pyrazine or morpholine frame (**72a-c**). The so-obtained compounds (**72a-c**) were then coupled under reductive amination conditions (**Scheme 11**) with cinnamaldehyde (**70**) to afford the toluidine-styryl derivatives (**74a-c**). Among all synthetized compounds, derivatives **73c** (R=Imidazole) and **74a-c** (R=Imidazole) were the most active against five different *M.tb.* strains with MIC values ranging between 1 to 64 µg/mL.

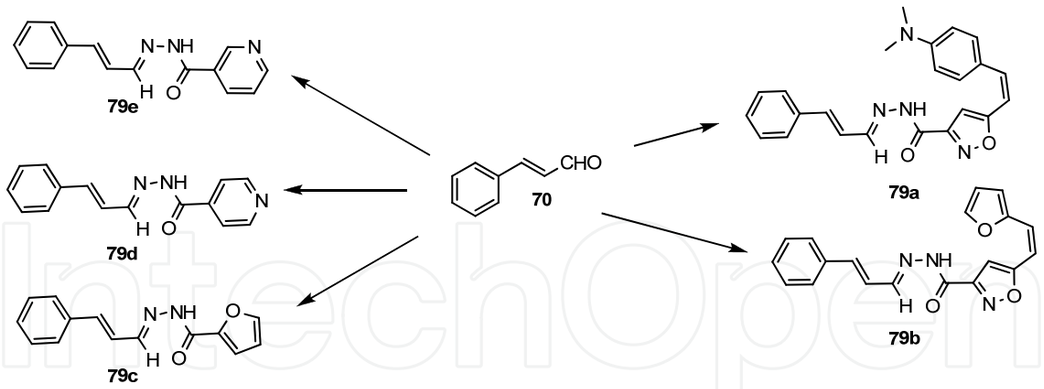


Scheme 11. Synthesis of toluidine derivatives

In 2010, a series of 5-(4-isopropylthiazol-2-yl)-4-((*E*)-((*E*)-3-phenylallylidene)amino)-4*H*-1,2,4-triazole-3-thiol (**78**; **Scheme 12**) was synthesized (Kumar *et al.* 2010). 4-Isopropylthiazol-2-carbahydrazide **76** was converted into the corresponding dithiocarbazinate, which upon cyclization with hydrazine hydrate yields 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol (**77**). The triazole (**77**) was condensed with **70** in the presence of catalytic amount of H_2SO_4 in refluxing ethanol to afford **78**. Synthesized compound **78** was evaluated (Shiradkar et al. 2007; Joshi et al. 2008) for its preliminary cytotoxicity and antitubercular activity against *M.tb.* $H_{37}Rv$ strain by broth dilution assay method and showed a promising activity (MIC = 4 µg/mL).

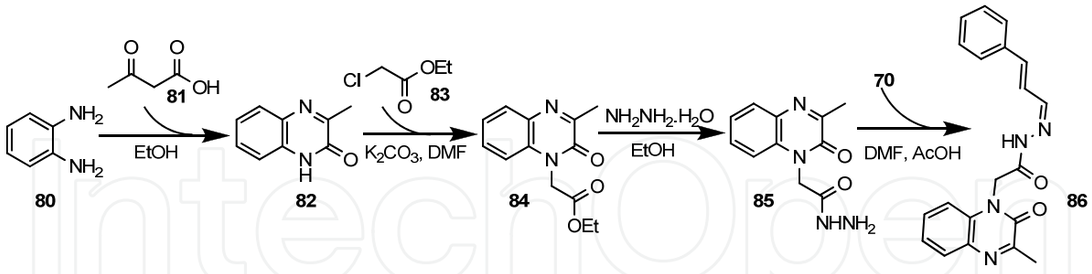


Scheme 12. Synthesis of 2-substituted -5-[isopropylthiazole] clubbed 1,2,4-triazole



Scheme 13. Different hydrazone derivatives synthesized from cinnamaldehyde

Several other hydrazone derivatives (**79a-e**) of cinnamaldehyde were made and their antiTB efficacy was also tested(**Scheme 13**) (Abdel-Aal et al. 2009). Among them, compound **79d**, arising from cinnamaldehyde (**70**) and isoniazid (**11**), showed maximum anti-TB activity (at 50 µg/mL) with the same MIC of the reference drug isoniazid (INH, 12.5 µg/mL).The synthetic hydrazone (**86**), exhibiting anti-TB activity (MIC = 25 µg/mL), was recently reported by Rao *et al.* (**Scheme 14**) (Rao et al., 2010). The authors synthesized **86** through 3-methyl-2-oxoquinoxalin (**82**) that is easily obtainable from *ortho*-diaminobenzene (**80**) by refluxing in ethanol along with acetylacetic acid (**81**). Treatment of **82** with 2-chloro ethylacetate (**83**) in the presence of K_2CO_3 in DMF gave the corresponding ethyl 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)acetate (**84**) which was converted to 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)acetohydrazide (**85**) by refluxing in ethanol in the presence of hydrazine hydrate (**Scheme 14**). Compound **85** was then coupled with **70** in DMF in the presence of acetic acid to furnish the desired hydrazone (**86**) which showed anti-TB activity (MIC = 25 µg/mL).

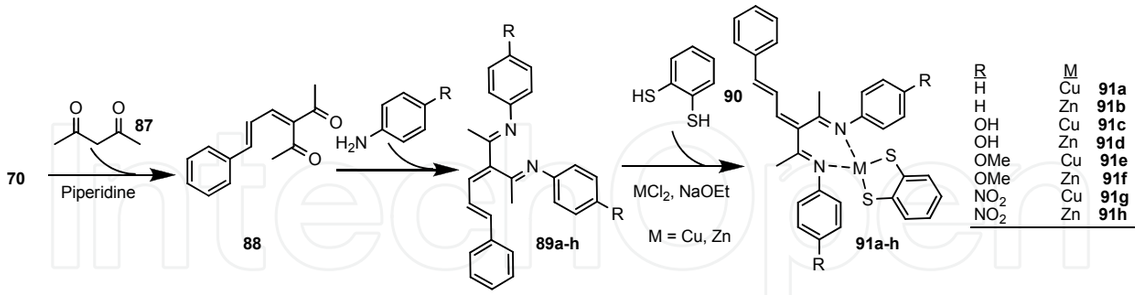


Scheme 14. Synthesis of a quinaxoline-derived cinnamaldehyde hydrazone

3.3 Cinnamaldehyde-derived metal complexes

A new series of copper(II) and zinc(II) complexes has been designed and synthesized using a new type of Schiff base (**89a-h**) derived from the reaction of 3-(3-phenyl-allylidene)-pentane-2,4-dione (**88**) with *para*-substituted aniline and benzene-1,2-dithiol (**90**) (**Scheme 15**) (Raman et al., 2010). The intermediate **88** was first obtained by aldol condensation between **70** and acetylacetone (**87**) using piperidine as base. The minimum inhibitory concentrations of the complexes have also been investigated against *M.tb.* strain $H_{37}Rv$. The lowest MIC values were obtained for -NO_2 group containing complexes (**91g**; MIC = 2.9

μg/mL, **91h**; MIC = 3.8 μg/mL) which are more active against $H_{37}Rv$ strain than the other complexes.



Scheme 15. Preparation of Cu(II) and Zn(II) complexes starting from cinnamaldehyde

4. Chalcone derivatives as anti-TB agents

Chalcones, one of the major classes of natural products with widespread distribution in fruits, vegetables, spices, tea and soya based foodstuffs, are of great interest for their interesting pharmacological activities (Di Carlo et al., 1999). Chalcones, or 1,3-diaryl-2-propen-1-ones, belong to the flavonoid family (Dimmock et al., 1999; Ni et al., 2004). From a structural standpoint, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl unit (**Fig. 8**). Interestingly, a vast number of naturally occurring chalcones are polyhydroxylated onto both aryl rings conferring them significant radical-quenching properties which have raised interest in using chalcones or chalcone-rich plant extracts as drugs or food preservatives (Nowakowska, 2007). Besides, Chalcones have been reported to possess many useful properties, including anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor and anticancer activities (Dimmock et al., 1999; Go, Wu & Liu, 2005).

4.1 Natural and synthesized chalcones

M.tb. , *M. bovis*, *M. kansasii*, *M. xenophii* and *M. marinum* were inhibited by licochalcone A (**92**; MIC = 20 mg /mL), extracted and purified from Chinese licorice roots (**Fig. 8**) (Friis-Møller et al. 2002). Besides, the presence of a halogen substituent on A-ring of 2'-hydroxychalcones proved to play a crucial role on anti-TB activity. It has indeed been found that chalcones substituted by a halogen atom at the 3-position demonstrate stronger anti-TB activity than those substituted by a halogen atom at the 2- or 4-position (Lin et al., 2002). In that manner, chalcones **93** and **94** with a 2'-hydroxyl group on B-ring and a 3-chloro- or 3-iodo-group on A-ring showed the strongest activity, with 90-92% inhibition against *M.tb.* $H_{37}Rv$ at a drug concentration of 12.5 mg/mL. The activity of 2'-hydroxychalcone (61% inhibition) was further enhanced by introducing a chloro (89%) or a methoxy group (78%) at the 4'-position of B-ring. Nevertheless, introduction of an additional substituent, such as a methoxy, amino, bromo or carboxyl group on B-ring led to a dramatic decrease or a complete loss of activity (Lin et al., 2002). Recently, the activities of some synthetic chalcones were also assayed against *M.tb.* protein tyrosine phosphatase A (PtpA) which is an enzyme associated with *M.tb.* infectivity (Chiaradia et al., 2008). Note that tyrosine phosphatases are secreted by pathogenic bacteria, and MPtpA is an example that was shown to be required

for growth of *M.tb.* in human macrophages (Bach et al., 2008). In the search for lead compounds, a series of 38 chalcones were prepared by aldol condensation between aldehydes and acetophenones and five of the so-prepared compounds (**95-99**) presented moderate to good activities (**Scheme 16**). The structure–activity analysis revealed that the predominant factor for the activity is the molecular planarity and/or hydrophobicity and the nature of the substituents. Later on, the molecular recognition of these inhibitors on PtpA was investigated through molecular modeling, these investigations revealing that the binding and the inhibitory activity of the chalcones are predominantly governed by the positions of the two methoxyl groups at the B-ring (Mascarello et al., 2010). Besides, the –OMe groups proved to establish key hydrogen bonds with the amino acid residues Arg17, His49 and Thr12 in the active site of PtpA while the 2-naphthyl A-ring undergoes л-stacking interaction with the Trp48 residue. Interestingly, reduction of mycobacterial survival in human macrophages upon inhibitor treatment suggests their potential use as novel therapeutics.

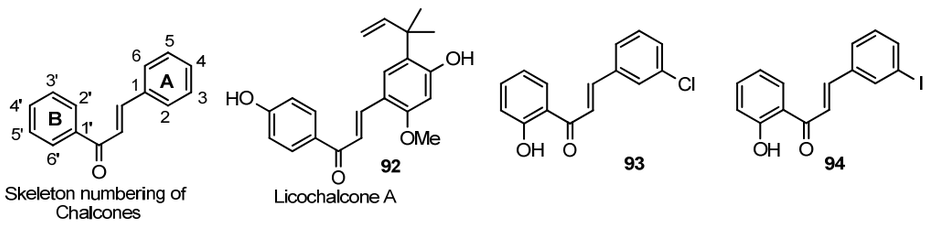
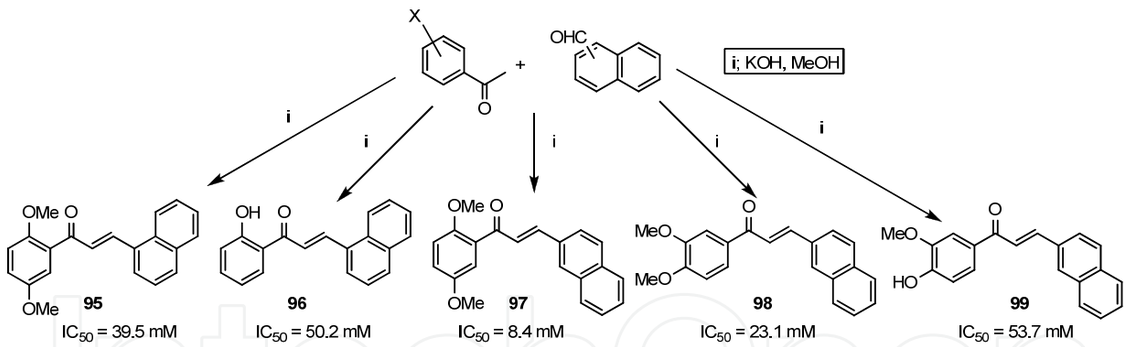


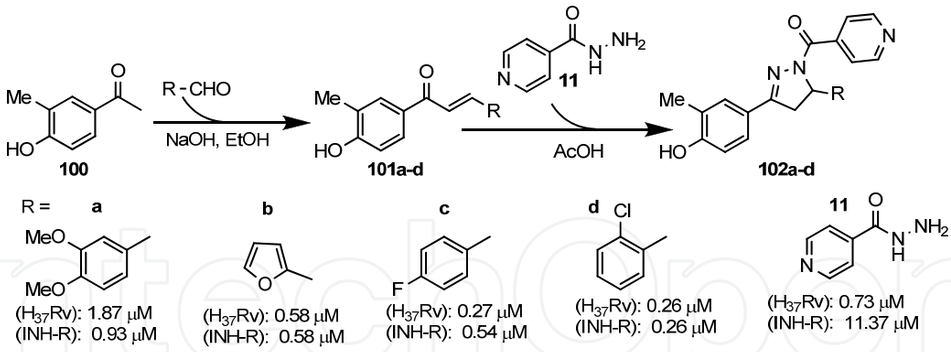
Fig. 8. Chalcones with antiTB activities



Scheme 16. General strategy for chalcone synthesis

4.2 Chalcone hydrazone derivatives

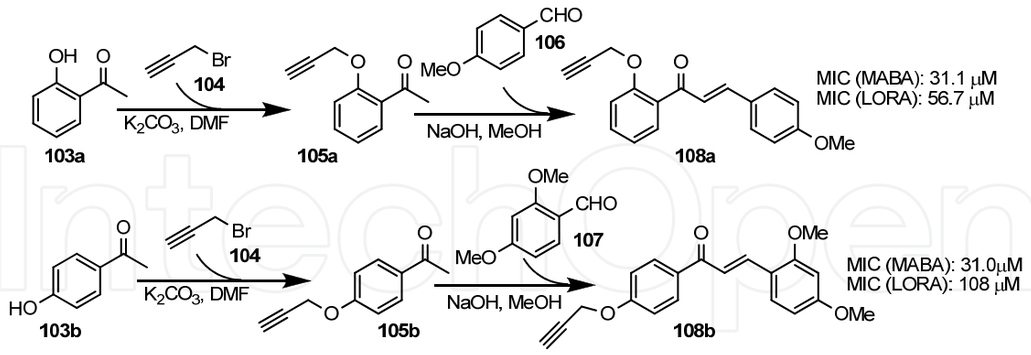
A series of *N*'-nicotinoyl-3-(4'-hydroxy-3'-methylphenyl)-5-(substituted phenyl)-2-pyrazolines (**102a-d**) were synthesized by the reaction between isoniazid (INH; **11**) and chalcones (**101a-d**) and were tested for their antimycobacterial activity *in vitro* against *M.tb.* H_{37}Rv and INH-resistant *M.tb.* (INHR- *M.tb.*) strains using the agar dilution method(**Scheme 17**) (Shaharyar et al. 2006). Among the synthesized compounds, *N*'-nicotinyl-3-(4'-hydroxy-3'-methyl phenyl)-5-(1''-chlorophenyl)-2-pyrazoline (**102d**) was found to be the most active agent against *M.tb.* and INHR- *M.tb.*, with minimum inhibitory concentration of 0.26 μM. When compared to INH-compound **102d** was found to be 2.8- and 43.7-fold more active against *M.tb.* H_{37}Rv and INHR-*M.tb.*, respectively.



Scheme 17. Synthesis and anti-TB activities of chalcone-derived pyrazoline compounds

4.3 Chalcones with substitutions at the aromatic ring

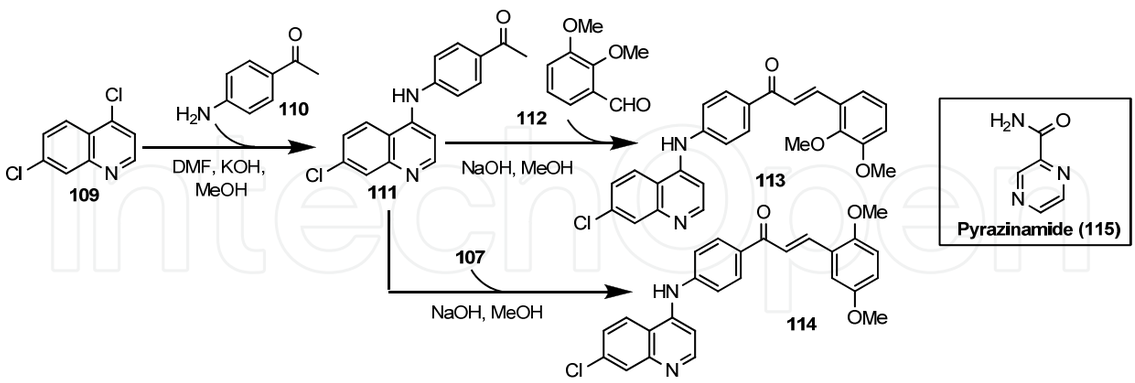
A series of acetylenic chalcones were evaluated for antituberculosis activity (**Scheme 18**) (Hans et al., 2010). The acetylenic functionality not only serves as a site for further chemical diversification but is also of great interest in medicinal chemistry and the pharmaceutical industry. Moreover, it functions as a key pharmacophoric unit in acetylenic antibiotics (Maretina & Trofimov, 2006) and its presence in anticancer (Siddiq & Dembitsky, 2008) and antitubercular (Deng et al. 2008) agents is noteworthy. From a synthetic standpoint, hydroxyacetophenones (**103a,b**) were treated with propargyl bromide (**104**) in the presence of K_2CO_3 in DMF to afford the respective propargyloxyacetophenones (**105a,b**) that were then treated with methoxybenzaldehydes (**106,107**) under basic conditions to provide the chalcones (**108a,b**) featuring the desired propargyloxy moiety. Most compounds were more active against non-replicating (MABA) than replicating (LORA) cultures of *M.tb.* $H_{37}Rv$, an unusual pattern with respect to existing anti-TB agents.



Scheme 18. Synthesis and anti-TB activities of acetylenic chalcones

The introduction of a quinoline moiety to chalcones as aromatic substituent was envisaged as an interesting way of designing new anti-TB agents. In that manner, a series of substituted quinolinyl chalcones (**113**, **114**) was synthesized under basic conditions and evaluated for their *in vitro* anti-TB activity against *M.tb.* $H_{37}Rv$ (**Scheme 19**) (Sharma et al., 2009). The structure–activity relationship analysis revealed that different physicochemical and structural requirements are needed for anti-TB activity. Two compounds **113** and **114** have shown anti-TB activity at MIC 3.12 μg/mL. By comparison, pyrazinamide (**115**), a

known antituberculosis drug, showed a MIC value of 50 μg/mL under similar assay. Moreover, these molecules were nontoxic against VERO and MBMDM cell lines.



Scheme 19. Synthesis of substituted quinolinyl chalcones

4.4 Physico-chemical study

Importantly, a quantitative structure activity relationship (QSARs) methodology has been developed (Sivakumar et al. 2007) for the reported anti-TB activity of chalcones, chalcone-like compounds, flavones and flavanones using a statistical technique called genetic function approximation (GFA). The generated equations in each model were analyzed, for both the goodness of fit and predictive capability. The analysis also points out to the importance of the hydrogen, PMI-mag and HOMO bond donors. The study indicated that the reported compounds are more lipophilic in nature and hence, as expected, exhibit good activity since *M.tb.* has a high concentration of lipid layer. These theoretical models deserve to be explored further to design potent, newer compounds having better anti-TB activity.

5. Conclusion

Cinnamic acids, cinnamaldehydes and chalcones are unique as drug candidates in tuberculosis. Natural cinnamic-based substances such as ethyl- (**2**) and benzyl- (**4**) cinnamates not only have anti-TB activities, they are traditional medicines for hypertension as well. Cinnamaldehyde and Licochalcone A also have good potentials as anti-TB agents. Sharing a common α,β-unsaturated carbonyl functionality, these molecules offer Michael-acceptor properties, particularly to the glutathione (GSH) and cystine residues. Although, mycobacteria, unlike *E.coli*, do not prefer the formation of Michael-adduct, the presence of the cinnamic moiety certainly increased the anti-TB efficacy on several occasions. Importantly, the replacement of the double bond with an isosteric cyclopropyl ring decreased the anti-TB efficiency of the triazolophthalazines. On the other hand, introduction of cinnamoyl moiety to isoniazid did not significantly alter the trend of biological activity or the mode of action. These observations indicate that the anti-TB activity depends not only on the α,β-unsaturation but also on the functionalization of the carbonyl part of the cinnamoyl derivatives. Several hydrazone derivatives of cinnamaldehyde and chalcones have notable anti-TB activities. Importantly, substituents at the benzene ring of the cinnamic acids also play a crucial role in the biological activities. Notably, Isoprenyloxy cinnamoyl-triazolophthalazine derivative (**68e**) and chalcone derived pyrazoline derivative (**102d**)

showed excellent anti-TB activity against INH-resistant strains. In summary, cinnamic acid, cinnamaldehyde and chalcone derivatives are regarded as potent anti-TB agents. Surprisingly, in spite of their relevant anti-TB activities, little is still known about the mode of action and understanding of the implicated molecular mechanisms. We hope to learn more about these versatile molecules and its derivatives in addition to the synthesis of new, useful biologically important compounds in the near future.

6. Acknowledgement

We thank "Université Paul Sabatier" for postdoctoral grant (P.D.). Thanks are due to the European Community (integrated project "New Medicines for Tuberculosis: NM4TB 018923") and CNRS (France) for financial support.

7. References

Abdel-Aal, W.S., Hassan, H.Y., Aboul-Fadl, T. & Youssef, A.F. (2009). Solution-Phase Synthesis of Small Schiff Bases Combinatorial Library with Potential Antitubercular Activity, *Der Pharma Chemica*, Vol.1, No.2, pp. 1-13, ISSN 0975-413X

Agranoff, D. & Krishna, S. (2004). Metal ion Transport and Regulation in *Mycobacterium tuberculosis*, *Frontiers in Bioscience*, Vol.9, pp. 2996-3006, ISSN 1093 4715

Ahn, B.Z., Sok, D.E. (1996). Michael Acceptors as a Tool for Anticancer Drug Design, *Current Pharmaceutical Design*, Vol.2, No.3, pp. 247-262, ISSN 1381-6128

Bach, H., Papavinasasundaram, K.G., Wong, D., Hmama, Z. & Av-Gay, Y. (2008) *Mycobacterium tuberculosis* Virulence Is Mediated by PtpA Dephosphorylation of Human Vacuolar Protein Sorting 33B, *Cell Host & Microbe*, Vol.3, No.5, pp. 316- 322, ISSN 1931 3128

Bairwa, R., Kakwani, M., Tiwari, N.R., Lalchandani, J., Ray, M.K., Rajan, M. G. R. & Degani, M.S. (2010) Novel Molecular Hybrids of Cinnamic Acids and Guanylhydrazones as Potential Antitubercular Agents, *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.5, pp. 1623-1625, ISSN 0960-894X

Barnes, C.C., Smalley, M.K., Manfredi, K.P., Kindscher, K., Loring, H. & Sheele, D.M. (2003) Characterization of an Anti-tuberculosis Resin Glycoside from the Prairie Medicinal Plant *Ipomoea leptophylla*, *Journal of Natural Products*, Vol.66, No.11, pp. 1457-1462, ISSN 1520 6025

Biava, M., Fioravanti, R., Porretta, G.C., Sleiter, G., Ettorres, A., Deidda, D., Lampis, G. & Pompei, R. (1997). New Toluidine Drivatives Antimycobacterial and Antifungal Activities, *Medicinal Chemistry Research*, Vol.7, No.4, pp. 228-250, ISSN 1554 8120

Bloch, A.B., Cauthen, G.M., Onorato, I.M., Kenneth, G., Dansbury, G., Kelly, G.D., Driver, C.R. & Snider Jr, D.E. (1994). Nationwide Survey of Drug-Resistant Tuberculosis in the United States, *Journal of the American Medical Association*, Vol.271, No.9, pp. 665-671, ISSN 0098-7484

Boerjan, W., Ralph, J. & Baucher, M. (2003). Lignin Biosynthesis, *Annual Review of Plant Biology,* Vol.54, pp. 519-546, ISSN 1543-5008

Cabello, C.M., Bair III, W.B., Lamore, S.D., Ley, S., Bause, A.S., Azimian, S. & Wondrak, G.T. (2009). The Cinnamon-derived Michael Acceptor Cinnamic Aldehyde Impairs Melanoma Cell Proliferation, Invasiveness, and Tumor Growth, *Free Radical Biology & Medicine,* Vol.46, No.2, pp. 220–231, ISSN 0891-5849

Carvalho, S.A., da Silva, E.F., de Souza, M.V.N., Lourenço, M.C.S. & Vicente, F.R. (2008). Synthesis and Antimycobacterial Evaluation of New *trans*-Cinnamic Acid Hydrazide Derivatives, *Bioorganic & Medicinal Chemistry Letters*, Vol.18, No.2, pp. 538-541, ISSN 0960-894X

Chiaradia, L.D., Mascarello, A., Purificação, M. Vernal, J., Cordeiro, M.N.S., Zenteno, M.E., Villarino A., Nunes, R.J., Yunes, R.A. & Terenzi, H. (2008). Synthetic Chalcones as Efficient Inhibitors of *Mycobacterium tuberculosis* Protein Tyrosinephosphatase PtpA, *Bioorganic & Medicinal Chemistry Letters*, Vol.18, No.23, pp. 6227-6230, ISSN 0960-894X

Cheng, S.-S., Liu, J.-Y., Tsai, K.-H., Chen, W.-J. & Chang, S.-T. (2004). Chemical Composition and Mosquito Larvicidal Activity of Essential Oils from Leaves of Different *Cinnamomum osmophloeum* Provenances, *Journal of Agricultural & Food Chemistry,* Vol.52, No.14, pp. 4395–4400, ISSN 0021-8561

Chew, E.-H., Nagle, A.A., Zhang, Y., Scarmagnani, S., Palaniappan, P., Bradshaw, T.D., Holmgren, A. & Westwell, A.D. (2010) Cinnamaldehydes Inhibit Thioredoxin Reductase and Induce Nrf2: Potential Candidates for Cancer Therapy and Chemoprevention, *Free Radical Biology & Medicine*, Vol.48, No.1, pp. 98-111, ISSN 0891-5849

Chung, H.S. & Shin, J.C. (2007). Characterization of Antioxidant Alkaloids and Phenolic Acids from Anthocyanin-pigmented Rice (*Oryza sativa cv Heugjinjubyeo*), *Food Chemistry*, Vol.104, No.4, pp. 1670-1677, ISSN 0308-8146

Copp, B.R. & Pearce, A.N. (2007) Natural Product Growth Inhibitors of *Mycobacterium tuberculosis*, *Natural Product Reports*, Vol.24, No.2, pp. 278-297, ISSN 1460 4752

Cornelis, P. & Andrews, S.C. (editor) (2010). *Iron Uptake and Homeostasis in Microorganisms*, Caister Academic Press, ISBN 978-1-904455-65-3, Norfolk, UK

Corper, H.J., Gauss, H. & Gekler, W.A. (1920). Studies on the Inhibitory Action of Sodium Cinnamate in Tuberculosis. *Colorado American Review of Tuberculosis*, Vol.4, pp. 464-473

a) De, P., Baltas, M. & Bedos-Belval, F. (2011). Cinnamic Acid Derivatives as Anticancer Agents- A Review, *Current Medicinal Chemistry*, Vol.18, No.11, pp. 1672-1703, ISSN 0929-8673

b) De, P., Yoya, G.K., Constant, P., Bedos-Belval, F., Duran, H., Saffon, N., Daffé, M. & Baltas M. (2011). Design, Synthesis and Biological Evaluation of New Cinnamic Derivatives as Antituberculosis Agents, *Journal of Medicinal Chemistry*, Vol.54, No.5, pp. 1449 -1461, ISSN 0022 2623

Deng, S., Wang, Y., Inui, T., Chen, S.-N., Farnsworth, N.R., Cho, S., Franzblau, S.G. & Pauli, G.F. (2008). Anti-TB Polyynes from the Roots of *Angelica sinensis, Phytotherapy Research,* Vol.22, No.7, pp. 878-882, ISSN 1099 1573

Di Carlo, G., Mascolo, N., Izzo, A.A. & Capasso, F. (1999). Flavonoids: Old and New Aspects of a Class of Natural Therapeutic Drugs, *Life Science*, Vol.65, No.4, pp. 337-353, ISSN 0024 3205

Dimmock, J.R., Elias, D.W., Beazely, M.A. & Kandepu, N.M. (1999). Bioactivities of Chalcones, *Current Medicinal Chemistry*, Vol.6, No.12, pp. 1125-1149, ISSN 0929-8673

Dimova, V., Atanasova, I., Tomioka, H., Sato, K., Reddy, V., Nadadhur, G., Daneluzzi, Gangadharam, P., Kantardjiev, T., Dhople, A., Feshchenko, Y., Yashina, L., Tourmanov, A., Zhirvkova, Z. & Sano, C. (2010). Experimental and Clinical Studies on Rifacinna® - The New Effective Antituberculous Drug (Review), *Recent Patents on Anti-Infective Drug Discovery*, Vol.5, No.1, pp. 76-90, ISSN 1574 891X

Domadia, P., Swarup, S., Bhunia, A., Sivaraman, J. & Dasgupta, D. (2007). Inhibition of Bacterial Cell Division Protein FtsZ by Cinnamaldehyde, *Biochemical Pharmacology*, Vol.74, No.6, pp. 831-840, ISSN 0006-2952

Epifano, F., Curini, M., Genovese, S., Blaskovich, M., Hamilton, A. & Sebti, S.M. (2007). Prenyloxyphenylpropanoids as Novel Lead Compounds for the Selective Inhibition of Geranylgeranyl Transferase I, *Bioorganic & Medicinal Chemistry Letters*, Vol.17, No.9, pp. 2639-2642, ISSN 0960-894X

Evans, B.E., Rittle, K.E., DiPardo, R.M., Freidinger, R.M., Whitter, W.L., Lundell, G.F., Veber, D.F. & Anderson, P.S. (1988). Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists, *Journal of Medicinal Chemistry*, Vol.31, No.12, pp. 2235-2246, ISSN 0022 2623

Freudenberg, K. (1959). Biosynthesis and Constitution of Lignin. *Nature*, Vol.183, No.4669, pp. 1152-1155, ISSN 0028-0836

Friedman, M., Henika, P. R. & Mandrell, R. E. (2002). Bactericidal Activities of Plant Essential Oils and Some of Their Isolated Constituents against *Campylobacter jejuni*, *Escherichia coli*, *Listeria monocytogenes*, and *Salmonella enteric*, *Journal of Food Protection,* Vol.65, No.10, pp. 1545–1560. ISSN 0362-028X

Friis-Møller, A., Chen, M., Fuursted, K., Christensen, S.B. & Kharazmi, A. (2002). *In Vitro* Antimycobacterial and Antilegionella Activity of Licochalcone A from Chinese Licorice Roots, *Planta Medica,* Vol.68, No.5, pp. 416-419, ISSN 0032 0943

Gadad, A.K., Mahajanshetti, C.S., Nimbalkar, S. & Raichurkar, A. (2000). Synthesis and Antibacterial Activity of Some 5-Guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide Derivatives, *European Journal of Medicinal Chem*istry, Vol.35, No.9, pp. 853-857, ISSN 0223-5234

Gainsborough, H. (1928). A Note on the Use of Benzyl Cinnamic Ester in Tuberculosis, The method of Jacobsen. *Lancet*, Vol.211, No.5462, pp. 908-909, ISSN 0140-6736

Go, M.L., Wu, X. & Liu, X.L. (2005). Chalcones: An Update on Cytotoxic and Chemoprotective Properties, *Current Medicinal Chemistry,* Vol.12, No.4, pp. 483-499, ISSN 0929-8673

Guo, H., Naser, S.A., Ghobrial, G. & Phanstiel, O. (2002). Synthesis and Biological Evaluation of New Citrate-Based Siderophores as Potential Probes for the Mechanism of Iron Uptake in Mycobacteria. *Journal of Medicinal Chemistry,* Vol.45, No.10, pp. 2056-2063, ISSN 0022 2623

Hans, R.H., Guantai, E.M., Lategan C., Smith, P.J., Wan, B., Franzblau, S.G., Gut, J., Rosenthal, P.J. & Chibale, K. (2010). Synthesis, Antimalarial and Antitubercular Activity of Acetylenic Chalcones, *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.3, pp. 942-944, ISSN 0960-894X

Helander, I.M., Alakomi, H.L., Latva-Kala, K., Mattila-Sandholm, T., Pol, I., Smid, E.J., Gorris, L.G.M. & Wright, A.V. (1998). Characterization of the Action of Selected Essential Oil Components on Gram-negative Bacteria, *Journal of Agricultural & Food Chemistry,* Vol.46, No.9, pp. 3590-3595, ISSN 0021-8561

Hoskins, J.A. (1984). The Occurrence, Metabolism and Toxicity of Cinnamic Acid and Related Compounds, *Journal of Applied Toxicol*gy, Vol.4, No.6, pp. 283-292, ISSN 0260-437X

Humphreys, J.M. & Chapple, C., (2002). Rewriting the Lignin Roadmap, *Current Opinion in Plant Biology,* Vol.5, No.5, pp. 224-229, ISSN 1369-5266

Jacobson, M.J. (1919). Ethylcinnamate in Experimental Tuberculosis, *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, Vol.35, pp. 322-325. Accession Number 1919:9620 CAN 13: 9620 CAPLUS

Joshi, D.G., Oza, H.B. & Parekh, H.H. (1997). Synthesis of Some Novel 1,3,4-Oxadiazoles and 5-Oxoimidazolines as Potent Biologically Active Agents, *Heterocyclic Communications*, Vol.3, No.2, pp. 169-174, ISSN 0793 0283

Joshi, S.D., Vagdevi, H.M., Vaidya, V.P. & Gadaginamath, G.S. (2008). Synthesis of New 4-Pyrrol-1-yl benzoic Acid Hydrazide Analogs and Some Derived Oxadiazole, Triazole and Pyrrole Ring Systems: A Novel Class of Potential Antibacterial and Antitubercular Agents, *European Journal of Medicinal Chemistry*, Vol.43, No.9, pp. 1989–1996, ISSN 0223-5234

Kakwani, M.K., Suryavanshi, P., Ray, M., Rajan, M.G.R., Majee, S., Samad, A., Devarajan, P. & Degani, M.S. (2011), Design, Synthesis and Antimycobacterial Activity of Cinnamide Derivatives: A Molecular Hybridization Approach, *Bioorganic & Medicinal Chemistry Letters*, Vol.21, No.7, pp. 1997-1999, ISSN 0960-894X

Khalafi-Nezhad, A., Rad, M.N.S., Mohbatkar, H., Asrari, Z. & Hemmateenejad, B. (2005). Design, Synthesis, Antibacterial and QSAR Studies of Benzimidazole and Imidazole hloroaryloxyalkyl Derivatives, *Bioorganic & Medicinal Chemistry*, Vol.13, No.6, pp. 1931-1938, ISSN 0968-0896

Kochi, A., Vareldzis, B., Styblo, K. (1993). Multidrug-resistant Tuberculosis and Its Control, *Research in Microbiology*, Vol.144, No.2, pp. 103-158, ISSN 0923-2508

Kroon, P.A. & Williamson, G. (1999). Hydroxycinnamates in Plants and Food, *Journal of the Science of Food & Agriculture*, Vol.79, No.3, pp. 355-361, ISSN 1097 0010

Kumar, G.V.S., Rajendraprasad, Y., Mallikarjuna, B.P., Chandrasekhar, S.M. & Kistayya, C., (2010). Synthesis of Some Novel 2-Substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as Potential Antimicrobial and Antitubercular Agents. *European Journal of Medicinal Chemistry*, Vol.45, No.5, pp. 2063-2074, ISSN 0223-5234

Lekphrom, R., Kanokmedhakul, S. & Kanokmedhakul, K. (2009). Bioactive Styryllactones and Alkaloid from Flowers of *Goniothalamus laoticus*, *Journal of Ethnopharmacology*, Vol.125, No.1, pp.47-50, ISSN 0378 8741

Lin, Y.-M., Zhou, Y., Flavin, M.T., Zhou, L.-M., Nie, W. & Chen, F.-Ch. (2002). Chalcones and Flavonoids as Anti-tuberculosis Agents, *Bioorganic & Medicinal Chemistry,* Vol.10, No.8, pp. 2795-2802, ISSN0968-0896

Lipinski, C.A., Lombardo, F., Dominy, B.W. & Feeney, P.J. (1997). Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings, *Advanced Drug Delivery Reviews*, Vol.23, No.1-3, pp. 3-25, ISSN 0169 409X

Ma, Q., Zhao, X., Eddine, A.N., Geerlof, A., Li, X., Cronan, J.E., Kaufmann, S.H.E. & Wilmanns, M. (2006). The *Mycobacterium tuberculosis* LipB Enzyme Functions as A Cysteine/Lysine Dyad Acyltransferase. *Proceedings of the National Academy of Science of the USA*, Vol.103, No.23, pp. 8662-8667, ISSN 0027 8424

Maretina, I.A. & Trofimov, B.A. (2006). Enediyne Antibiotics and Their Models: New Potential of Acetylene Chemistry, *Russian Chemical Reviews,* Vol.75, No.9, pp. 825-845, ISSN 1468 4837

Mascarello, A., Chiaradia, L.D., Vernal, J., Villarino A., Guido, R.V.C., Perizzolo, P., Poirier, V., Wong, D., Martins, P.G.A., Nunes, R.J., Yunes, R.A., Andricopulo, A.D., Av-Gay, Y. & Terenzi, H. (2010) Inhibition of *Mycobacterium tuberculosis* Tyrosine

Phosphatase PtpA by Synthetic Chalcones: Kinetics, Molecular Modeling, Toxicity and Effect on Growth. *Bioorganic & Medicinal Chemistry,* Vol.18, No.11, pp. 3783-3789, ISSN0968-0896

Naz, S., Ahmad, S., Rasool, S.A., Sayeed, S.A. & Siddiqi, R. (2006). Antibacterial Activity Directed Isolation of Compounds from *Onosma hispidum*, *Microbiological Research*, Vol.161, No.1, pp. 43-48, ISSN 0944-5013

Neilands, J.B. (1995). Siderophores: Structure and Function of Microbial Iron Transport Compounds, *Journal of Biological Chemistry*, Vol.270, No.45, pp. 26723–26726, ISSN 1083 351X

Ni, L., Meng, Q.C. & Sikorski, J.A. (2004). Recent Advances in Therapeutic Chalcones, *Expert Opinion on Therapeutic Patents*, Vol.14, No.12, pp. 1669-1691, ISSN 1744-7674

Nomura, S., Horiuchi, T., Omura, S. & Hata, T. (1972). The Action Mechanism of Cerulenin : I. Effect of Cerulenin on Sterol and Fatty Acid Biosyntheses in Yeast, *Journal of Biochemistry*, Vol.71, No.5, pp. 783-796. ISSN 0021-924X

Nowakowska, Z. (2007). A Review of Anti-infective and Anti-inflammatory Chalcones, *European Journal of Medicinal Chemistry,* Vol.42, No.2, pp. 125-137, ISSN 0223-5234

Nunn, P., Williams, B., Floyd, K., Dye, C., Elzinga, G. & Raviglione, M. (2005). Tuberculosis Control in the Era of HIV, *Nature Reviews Immunology*, Vol.5, No.10, pp. 819-826, ISSN 1474 1733

Okunade, A.L., Elvin-Lewis, M.P.F. & Lewis, W.H. (2004). Natural Antimycobacterial Metabolites: Current Status, *Phytochemistry*, Vol.65, No.8, pp. 1017-1032, ISSN 0031 9422

Omura, S. (1976). The Antibiotic Cerulenin, A Novel Tool for Biochemistry as an Inhibitor of Fatty Acid Synthesis, *Bacteriological Review,* Vol.40, No.3, pp. 681-697, ISSN 0005-3678

Raman, N., Jeyamurugan, R., Senthilkumar, R., Rajkapoor, B. & Franzblau, S.C. (2010). *In vivo* and *in vitro* Evaluation of Highly Specific Thiolate Carrier Group Copper(II) and Zinc(II) Complexes on Ehrlich Ascites Carcinoma Tumor Model. *European Journal of Medicinal Chemistry,* Vol.45, No.11, pp. 5438-5451, ISSN 0223-5234

Rao, G.K., Kotnal, R.B. & Pai, P.N.S. (2010). Synthesis and Biological Evaluation of 2-(3-Methyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*'-(substituted phenylmethyledene /ethylidene) Acetohydrazides, *E-Journal of Chemistry*, Vol.7, No.4, pp. 1435-1439, ISSN 0973-4945

Rastogi, N., Ross, B.C., Dwyer, B., Goh, K.S., Clavel-Sérès, S., Jeantils, V. & Cruaud, P. (1992). Emergence During Unsuccessful Chemotherapy of Multiple Drug Resistance in a Strain of *Mycobacterium tuberculosis*, *European Journal of Clinical Microbiology & Infectious Diseases*, Vol.11, No.10, pp. 901-907, ISSN 0934-9723

Rastogi, N., Goh, K.S., Wright, E.L. & Barrow, W.W. (1994). Potential Drug Targets for *Mycobacterium avium* Defined by Radiometric Drug-inhibitor Combination Techniques, *Antimicrobial Agents & Chemotherapy*, Vol.38, No.10, pp. 2287-2295, ISSN 0066-4804

Rastogi, N., Goh, K.S., Van Ginkel, S.Z., Wright, E,L. & Barrow, W.W. (1996). Identification of New Drug Targets in *Mycobacterium avium* and *Mycobacterium tuberculosis*, *Research in Microbiology,* Vol.147, No.1-2, pp. 97-105, ISSN 0923 2508

Rastogi, N., Goh, K.S., Horgen, L. & Barrow, W.W. (1998). Synergistic Activities of Antituberculous Drugs with Cerulenin and *trans*-Cinnamic Acid Against *Mycobacterium tuberculosis, FEMS Immunology & Medical Microbiology*, Vol.21, No.2, pp. 149-157, ISSN 0928-8244

Reddy, V.M., Nadadhur, G., Daneluzzi, D., Dimova, V. & Gangadharam, P. (1995). Antimycobacterial Activity of New Rifamycin Derivative, 3-(4-Cinnamylpiperazinyl Iminomethyl)Rifamycin SV (T9), *Antimicrobial Agents & Chemotherapy*, Vol.39, No.10, pp. 2320-2324, ISSN 1098 6596

Romberg, L & Levin, P.A. (2003). Assembly Dynamics of the Bacterial Cell Division Protein FtsZ : Poised at the Edge of Stability, *Annual Review of Microbiology*, Vol.57, pp.125-154. ISSN 0066-4227

Roosenberg II, J.M., Lin, Y.-M., Lu, Y. & Miller, M.J. (2000). Studies and Syntheses of Siderophores, Microbial Iron Chelators, and Analogs as Potential Drug Delivery Agents, *Current Medicinal Chemistry,* Vol.7, No.2, pp. 159-197, ISSN 0929-8673

Ryan, F. (1992). *The Forgotten Plague*, Little, Brown and Company, ISBN 0316763802, Boston, MA.

Scherman, M., Weston, A., Duncan, K., Whittington, A., Upton, R., Deng, L., Comber, R., Friedrich, J.D. & McNeil, M.R. (1995). Biosynthetic Origin of Mycobacterial Cell Wall Arabinosyl Residues, *Journal of Bacteriology*, Vol.177, No.24, pp. 7125-7130, ISSN 1098 5530

Schroeder, H.A. (1952). The effect of 1-hydrazinophthalazine in hypertension, *Circulation: Journal of the American Heart Association*, Vol.5, No.1, pp. 28-37. ISSN 0009 7322

Shaharyar, M., Siddiqui, A.A. Ali, M.A., Sriram D. & Yogeeswari, P. (2006). Synthesis and *in vitro* Antimycobacterial Activity of N^1-nicotinoyl-3-(4'-hydroxy-3'-methyl phenyl)-5-[(sub)phenyl]-2-pyrazolines, *Bioorganic & Medicinal Chemistry Letters,* Vol.16, No.15, pp. 3947-3949, ISSN 0960-894X

Sharma, M., Chaturvedi, V. Manju, Y.K. Bhatnagar, S., Srivastava, K., Puri, S.K. & Chauhan, P.M.S. (2009). Substituted Quinolinyl Chalcones and Quinolinyl Pyrimidines as A New Class of Anti-infective Agents, *European Journal of Medicinal Chemistry,* Vol.44, No.5, pp. 2081-2091. ISSN 0223-5234

Sharma, R.N., Sharma, K.P. & Dikshit, S.N. (2010). Synthesis, Characterization and Biological Activities of Some New Acidhydrazones Derived from Ethyl-2-[(*N*-cinnamoyl)-2,3-dichloroanilido]acetohydrazide, *Der Chemica Sinica*, Vol.1, No.1, pp. 57-66, Available from www.pelagiaresearchlibrary.com

Sharma, R.N., Sharma, K.P. & Dikshit, S.N. (2011). Synthesis, Characterization, and Biological Activities of New 1-[(2,3-dichloroanilinomalonyl)-3-(*N*-2′-cyanoethyl)-2-(*N*-cinnamoyl) 2, 3-dichloroanilino)]-5-phenyl Pyrazoline Derivatives, *Advances in Applied Science Research*, Vol.2, No.1, pp. 178-192, ISSN 0976-8610

Shingalapur, R.V., Hosamani, K.M. & Keri, R.S. (2009). Synthesis and Evaluation of *in vitro* Anti-microbial and Anti-tubercular Activity of 2-Styrylbenzimidazoles, *European Journal of Medicinal Chemistry*, Vol.44, No.10, pp. 4244-4248, ISSN 0223-5234

Shiradkar, M.R., Murahari, K.K., Gangadasu, H.R., Suresh, T., Kalyan, C.A., Panchal, D., Kaur, R., Burange, P. & Ghogare, J. (2007). Synthesis of New S-derivatives of Clubbed Triazolyl Thiazole as Anti-*Mycobacterium tuberculosis* Agents, *Bioorganic & Medicinal Chemistry*, Vol.15, No.12, pp. 3997–4008, ISSN 0968-0896

Sivakumar, P.M., Babu, S.K.G. & Mukesh D. (2007). QSAR Studies on Chalcones and Flavonoids as Anti-tuberculosis Agents Using Genetic Function Approximation (GFA) Method, *Chemical & Pharmaceutical Bulletin,* Vol.55, No.1, pp. 44-49, ISSN 1347-5223.

Siddiq, A. & Dembitsky, V. (2008). Acetylenic Anticancer Agents, *Anti-cancer Agents in Medicinal Chemistry,* Vol.8, No.2, pp. 132-170, ISSN 1871 5206

Silas, J.H., Ramsay, L.E. & Freestone, S. (1982). Hydralazine Once Daily in Hypertension, *British Medical Journal*, Vol.284, No.6329, pp. 1602-1604. ISSN 0959 8138

Tanachatchairatana, T., Bremner, J.B., Chokchaisiri, R. & Suksamrarn, A. (2008). Antimycobacterial Activity of Cinnamate-Based Esters of the Triterpenes Betulinic, Oleanolic and Ursolic Acids, *Chemical & Pharmaceutical Bulletin*, Vol.56, No.2, pp. 194-198. ISSN 1347 5223

Thimann, K.V. (1969). The auxins. In: *Physiology of Plant Growth and Development*, M.B. Wilkinson (ed.), pp 2-45, Accession Number 1970:51751 CAN: 72:51751 CAPLUS McGrew-Hill, London.

van Heijenoort, J. (2001). Formation of the Glycan Chains in the Synthesis of Bacterial Peptidoglycan, *Glycobiology*, Vol.11, No.3, pp. 25R-36R, ISSN 1460 2423

Velichka, D., Ivana, A., Haruaki, T., Katsumasa, S., Venkata, R., Nadadhur, G., Donna, D., Patisapu, G., Todor, K., Arvind, D., Yurii, F., Ljudmila, Y., Toumanov, A., Zvetana, Z. & Chiaki, S. (2010). Experimental and Clinical Studies on Rifacinna® - The New Effective Antituberculous Drug (Review). *Recent Patents on Anti-Infective Drug Discovery*, Vol.5, No.1, pp. 76-90, ISSN 1574 891X

Warbasse, J.P. (1894). Cinnamic Acid in the Treatment of Tuberculosis, *Annals of Surgery*, Vol.19, pp. 102-117. ISSN 1528 1140

Wendakoon, C.N. & Sakaguchi, M. (1995). Inhibition of Amino Acid Decarboxylase Activity of *Enterobacter aerogenes* by Active Components in Spices, *Journal of Food Protection* Vol.58, No.3, pp. 280-283, ISSN 0362-028X

Whetten, R.W., Mackay, J.J. & Sederoff, R.R. (1998). Recent Advances in Understanding Lignin Biosynthesis, *Annual Review of Plant Physiology & Plant Molecular Biology*, Vol.49, pp. 585-609. ISSN 0066-4294

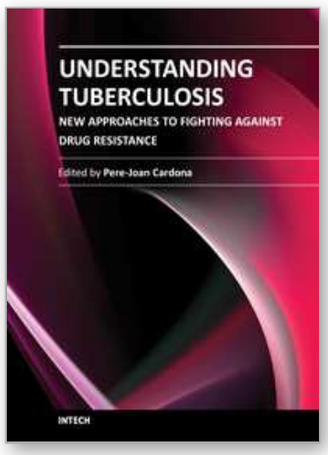
Wong, S.Y.Y., Grant, I.R., Friedman, M., Elliot, C.T. & Chen, S. (2008). Antibacterial Activities of Naturally Occurring Compounds against *Mycobacterium avium* subsp. *Paratuberculosis, Applied & Environmental Microbiology*, Vol.4, No.19, pp. 5986-5990, ISSN 0099-2240

Wu, W., Sil, D., Szostak, M.L., Malladi, S.S., Warshakoon, H.J., Kimbrell, M.R., Cromer, J.R. & David, S.A. (2009) Structure-activity Relationships of Lipopolysaccharide Sequestration in Guanylhydrazone-bearing Lipopolyamines, *Bioorganic & Medicinal Chemistry*, Vol.17, No.2, pp. 709-715, ISSN 0968-0896

Xu, Y. & Miller, M.J. (1998). Total Syntheses of Mycobactin Analogues as Potent Antimycobacterial Agents Using a Minimal Protecting Group Strategy, *Journal of Organic Chemistry*, Vol.63, No. 13, pp. 4314-4322, ISSN 1520 6904

Yoya, G. K., Bedos-Belval, F., Constant, P., Duran, H., Daffé, M. & Baltas. M. (2009) Synthesis and Evaluation of a Novel Series of Pseudo-Cinnamic Derivatives as Antituberculosis Agents, *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.2, pp. 341-343, ISSN 0960-894X

Zhang, Y., Broser, M. & Rom, W.N. (1994). Activation of the Interleukin-6 Gene by *Mycobacterium tuberculosis* or Lipopolysaccharide is Mediated by Nuclear Factors NF-IL6 and NF-kappa β, *Proceedings of the National Academy of Science of the USA*, Vol.91, No.6, pp. 2225-2229, ISSN 0027 8424



Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance

Edited by Dr. Pere-Joan Cardona

ISBN 978-953-307-948-6
Hard cover, 376 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

In 1957, a Streptomyces strain, the ME/83 (S.mediterranei), was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphael, France. This drug was the base for the chemotherapy with Streptomicine. The euphoria generated by the success of this regimen lead to the idea that TB eradication would be possible by the year 2000. Thus, any further drug development against TB was stopped. Unfortunately, the lack of an accurate administration of these drugs originated the irruption of the drug resistance in Mycobacterium tuberculosis. Once the global emergency was declared in 1993, seeking out new drugs became urgent. In this book, diverse authors focus on the development and the activity of the new drug families.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Prithwiraj De, Damien Veau, Florence Bedos-Belval, Stefan Chassaing and Michel Baltas (2012). Cinnamic Derivatives in Tuberculosis, Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance, Dr. Pere-Joan Cardona (Ed.), ISBN: 978-953-307-948-6, InTech, Available from: http://www.intechopen.com/books/understanding-tuberculosis-new-approaches-to-fighting-against-drug-resistance/cinnamic-derivatives-in-tuberculosis

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen