



**HAL**  
open science

## Cinnamic Acid Derivatives in Tuberculosis, Malaria and Cardiovascular Diseases - A Review

Prithwiraj De, Florence Bedos-Belval, Corinne Vanucci-Bacqué, Michel Baltas

► **To cite this version:**

Prithwiraj De, Florence Bedos-Belval, Corinne Vanucci-Bacqué, Michel Baltas. Cinnamic Acid Derivatives in Tuberculosis, Malaria and Cardiovascular Diseases - A Review. *Current Organic Chemistry*, 2012, 16 (6), pp.747-768. 10.2174/138527212799958020 . hal-02444262

**HAL Id: hal-02444262**

**<https://hal.science/hal-02444262v1>**

Submitted on 22 Jan 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# **Cinnamic acid derivatives in tuberculosis, malaria and cardiovascular diseases-**

## **A Review**

Prithwiraj De,<sup>a, b</sup> Florence Bedos-Belval,<sup>a, b</sup> Corinne Vanucci-Bacqu ,<sup>a, b</sup> Michel Baltas,<sup>\*a, b</sup>

<sup>a</sup> Universit  de Toulouse, UPS, LSPCMIB (*Laboratoire de Synth se et Physico-Chimie de Mol cules d'Int r t Biologique*), 118, Route de Narbonne, F-31062 Toulouse Cedex 9, France.

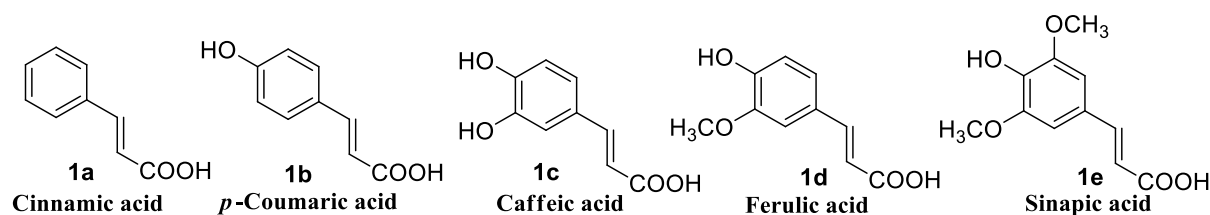
<sup>b</sup> CNRS, LSPCMIB (*Laboratoire de Synth se et Physico-Chimie de Mol cules d'Int r t Biologique*), 118, Route de Narbonne, F-31062 Toulouse Cedex 9, France.

**Abstract:** Cinnamic acid and its phenolic analogues are natural substances. Chemically, cinnamic acids or the 3-phenyl acrylic acids, offer three main reactive sites: substitution on the phenyl ring, addition on the  $\alpha,\beta$ -unsaturation and reactions of the carboxylic acid. Owing to these chemical aspects, cinnamic acid derivatives received much attention in medicinal research as traditional as well as valuable scaffolds in recent synthetic bioactive agents. In the last two decades, there has been huge attention towards various cinnamoyl derivatives and their biological efficacy. This review provides a comprehensive literature compilation concerning the synthesis of various cinnamoyl acids, esters, amides, hydrazides and related derivatives and their biological activity evaluations against diseases such as tuberculosis and malaria, which are frequent in developing countries and cardiovascular diseases, which cause a high mortality rate worldwide. We envisage that our effort in this review contributes a much needed and timely addition to the literature of medicinal research.

**Keywords:** Antituberculosis, antimalarial agents, cardiovascular diseases, cinnamic acid, cinnamide, cinnamoyl ester, cinnamic hydrazide.

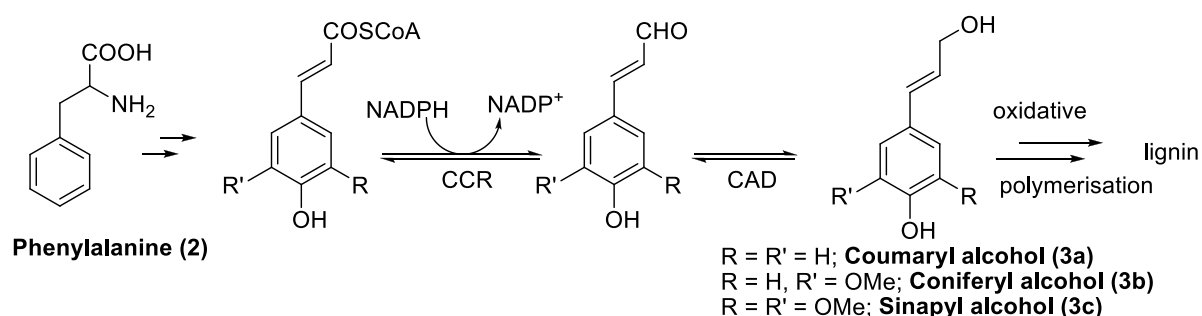
## **1. INTRODUCTION**

Cinnamic acid (**1a**) has a long history of human use as a component of plant-derived scents and flavourings [1].



**Fig. 1:** Cinnamic acid and its natural phenolic-analogues

It belongs to the class of auxin, which is recognized as plant hormones regulating cell growth and differentiation [2]. 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 [3]. The hydroxyl cinnamic acids such as *p*-coumaric acid (**1b**), caffeic acid (**1c**), ferulic acid (**1d**), sinapic acid (**1e**) (**Fig.1**) are natural products arising from the deamination of the phenyl alanine (**2**); they are important constituents in the biochemical pathway in plants leading to the lignin (**Scheme 1**) [4], the second most abundant biopolymer after cellulose [5], resulting mainly from the oxidative polymerization [6] of the three hydroxycinnamoyl alcohols, *i.e.*, coumaryl (**3a**), coniferyl (**3b**), sinapyl alcohols (**3c**).



**Scheme 1:** Lignin biosynthesis pathway

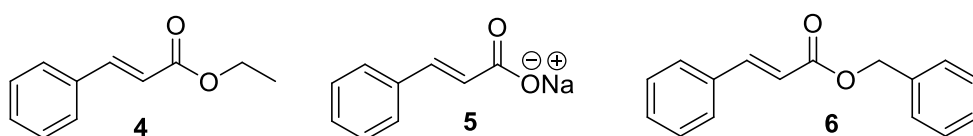
Natural hydroxyl cinnamates are extremely potent antitumor agents [3,7]. Chemically, cinnamic acid is an aromatic fatty acid composed of a phenyl ring substituted with an acrylic acid group, commonly, in the *trans*-geometry and has low toxicity in human exposure.

Cinnamic acids possess an  $\alpha,\beta$ -unsaturated carbonyl moiety, which can be considered as a Michael acceptor, an active moiety often employed in the design of drugs [8]. In recent years, *trans*-cinnamic acid derivatives have attracted much attention due to their antioxidative [9], antitumor [10a,b] and antimicrobial [11] properties. In this review, we will restrict our discussion on cinnamic type related derivatives, their synthesis and their reported biological activities in tuberculosis, malaria and cardiovascular diseases research.

## 2. CINNAMIC ACID DERIVATIVES AS ANTITUBERCULOSIS AGENTS

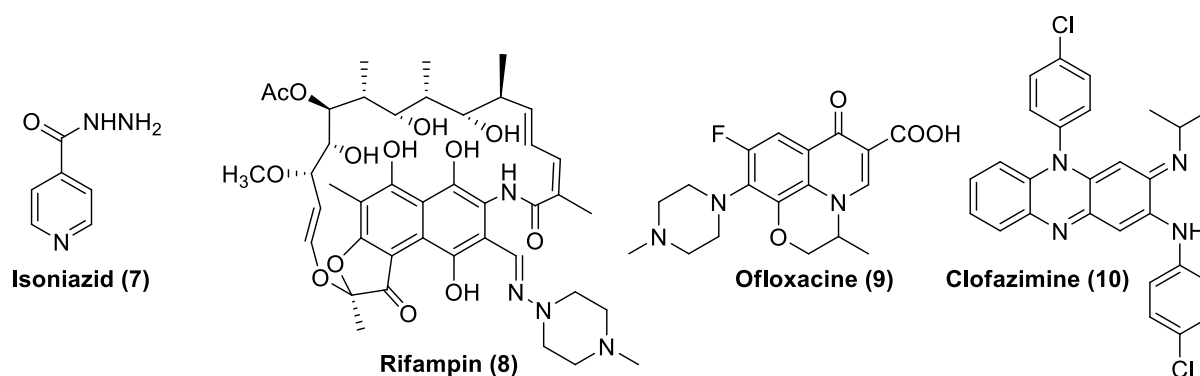
### 2.1. Introduction

Tuberculosis (TB) is a threat to worldwide public health. It is caused by *Mycobacterium tuberculosis* (*M.tb.*). 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 [12], the emergence of multi-drug-resistant (MDR-TB) strains [13a-c] 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 class of chemical compounds acting with different mechanisms from those currently used. In spite of that fact that cinnamic acid (**1a**) and derivatives have a century-old history as antituberculosis agents, for example, in 1894, Warbasse *et al.* [14] reported that gradual improvement was observed when the TB-patients were treated with cinnamic acid (**1a**) prepared from storax and in 1920s, ethyl cinnamate (**4**; **Fig. 2**) [15a], sodium cinnamate (**5**) [15b] and benzyl cinnamate (**6**) [15c] were reported to be efficacious in the treatment of TB, we feel that this class of molecules remained underutilized until recent years.



**Fig. 2:** Ethyl cinnamate, sodium cinnamate and benzyl cinnamate

In an attempt to develop a new strategy to circumvent MDR-TB by augmenting the potential of the existing drugs, Rastogi *et al.* [16] used *trans*-cinnamic acid (**1**) along with known antituberculous drugs (**Fig. 3**) such as isoniazid (**7**), rifampin (**8**), ofloxacin (**9**) or clofazimine (**10**). The synergistic increase in the activity of various drugs against *Mycobacterium avium* was observed. The same authors reported in 1998 [17] that the synergistic activity of *trans*-cinnamic acid with a variety of drugs was observed even with drug resistant isolates.



**Fig. 3:** Known antituberculous drugs

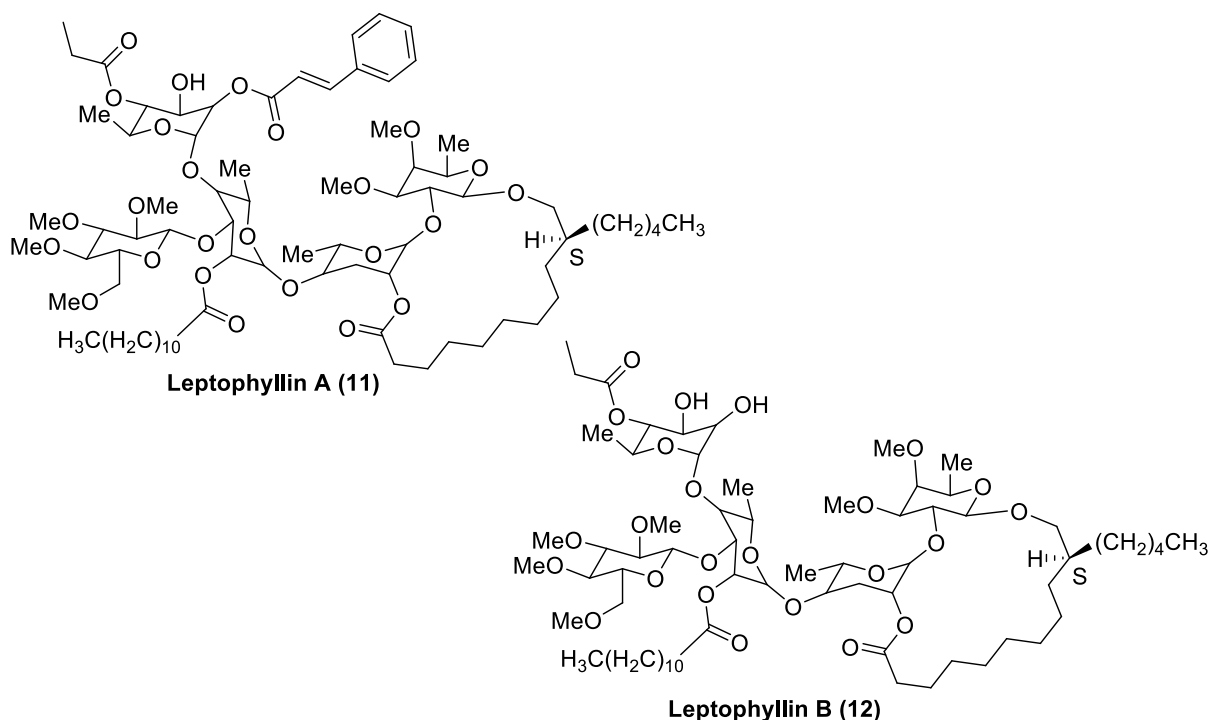
Although, *trans*-cinnamic acid (**1a**) was used to treat tuberculosis before antimycobacterial chemotherapy was used [18], this was the first example of MDR-TB activity in synergy with other drugs but the mechanism of action still remains unknown.

## 2.2. Natural Resources

### 2.2.1. Cinnamic ester derivatives

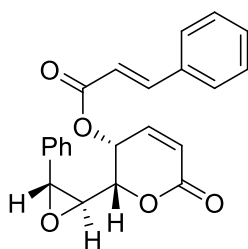
In another context, cinnamoyl ester was identified as an important frame in glycoside extracts of a native North American prairie plant named *Ipomoea leptophylla*. In fact, Manfredi *et al.* reported recently [19] that the organic soluble extracts from its leaves showed *in vitro* activity against *M. tb*. Through a bioassay-guided fractionation of these extracts the authors isolated leptophyllin A (**11**), a resin glycoside bearing a *trans*-cinnamic residue attached to one

rhamnose moiety. This compound (**Fig. 4**) showed 13% inhibition at 6.25  $\mu\text{g/mL}$  against *M. tb.* in the *in vitro* anti-tuberculosis assay. Furthermore, the bioassay results indicated that the cinnamic acid residue is required for the observed antimicrobial activity as an analogous compound leptophyllin B (**12**) also isolated from the same source without cinnamic acid residue showed no *in vitro* activity.



**Fig. 4:** Resin glycosides from *I. leptophylla*

Recently, Kanokmedhakul *et al.* [20] reported the identification of some bioactive styryllactones and alkaloids isolated from flowers of *Goniothalamus laoticus*. The authors isolated a styryllactone derivative, howiinin A (**13**; **Fig. 5**), by fractionation of the ethyl acetate and methanol extracts from the flowers of this species. This compound possessing a cinnamoyl ester moiety while inactive against *Plasmodium falciparum*, showed an interesting antituberculosis activity (MIC = 6.25  $\mu\text{g/mL}$ ) when tested against *M.tb.* strain H<sub>37</sub>Ra.



**Howiinin A (13)**

**Fig. 5:** Structure of Howiinin A.

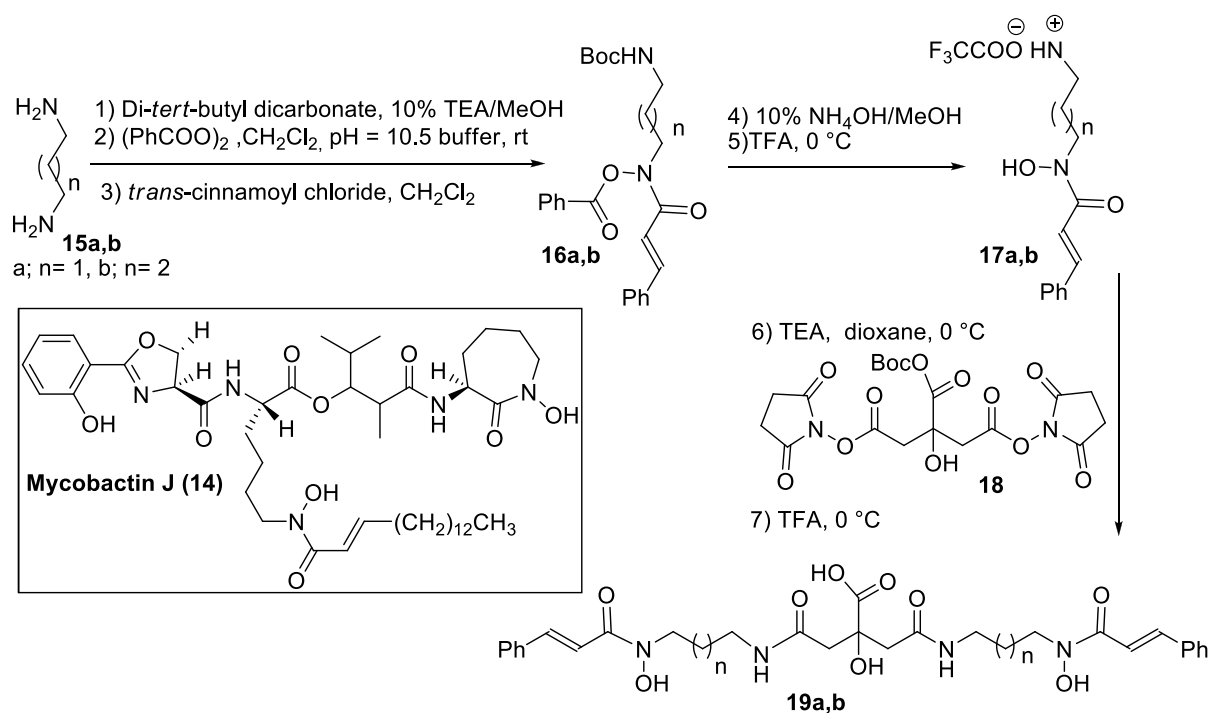
## 2.3. Synthetic compounds

### 2.3.1. Cinnamic hydroxamic acid derivatives

In 2002, Phanstiel and co-workers [21] used siderophores (produced by mycobacteria itself) 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 [22]. Further, the iron transport mechanism involves an “iron-handoff” between two siderophore families, the exochelins and the mycobactins. In low iron environments, *M. tuberculosis* biosynthesizes and secretes hydrophilic exochelins (e.g., Mycobactin J (**14**); **Scheme 2**) 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 [23]. The mycobactin associated iron either remains in the cell wall as an iron storage pool or is released into the cell by a mycobactin reductase [23].

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 understanding the molecular recognition events involved in mycobacterial iron transport. The authors synthesized different iron chelators containing  $\alpha,\beta$ -unsaturated hydroxamic acid

motifs appended to a citric acid platform such as Nannochelin A (**19b**) and compared its activities with the corresponding *trans*-octenoyl derivative.



**Scheme 2:** Synthesis of Nannochelin A

As shown in **Scheme 2**, the reaction of diamines (**15a,b**) with di-*tert*-butyl dicarbonate afforded the mono-Boc-protected diamines which were dissolved in a biphasic mixture containing carbonate buffer (pH 10.5) and benzoylperoxide dissolved in dichloromethane was added. After the oxidation step, the mixture was acylated with *trans*-cinnamoyl chloride to give the desired compounds **16a,b**. They were then treated with a 10%  $\text{NH}_4\text{OH}$  in methanol solution at 0 °C to deprotect hydroxamic acid and the resulting derivatives were treated with trifluoroacetic acid (TFA) at 0 °C to remove the Boc group and produce the TFA salts **17a,b**. As shown in **Scheme 2**, the condensation of **17a,b** with protected citric acid (**18**) in 1,4-dioxane followed by TFA treatment gave the chelators **19a,b**.

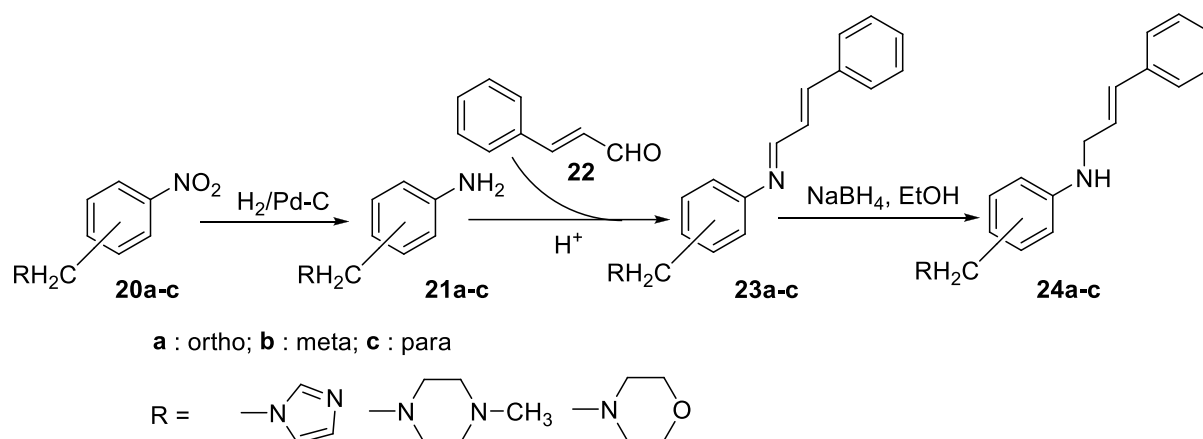
Notably, molecules that provided significantly higher growth index (GI) values than the native chelator mycobactin J (**14**) were identified as superior growth stimulants and more efficacious iron delivery agents. The systems containing longer tethers gave higher GI values



(e.g., GI= 0.76 for **19a** vs 1.5 for **19b**). It was envisaged by the authors that the longer tether allows for a more conformationally flexible ligand to properly coordinate to iron and provides an increase in hydrophobicity. However, the authors identified the derivative **19b** as superior growth stimulants and more efficacious iron delivery agents. 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.

### 2.3.2. Cinnamaldehyde Schiff's base derivatives

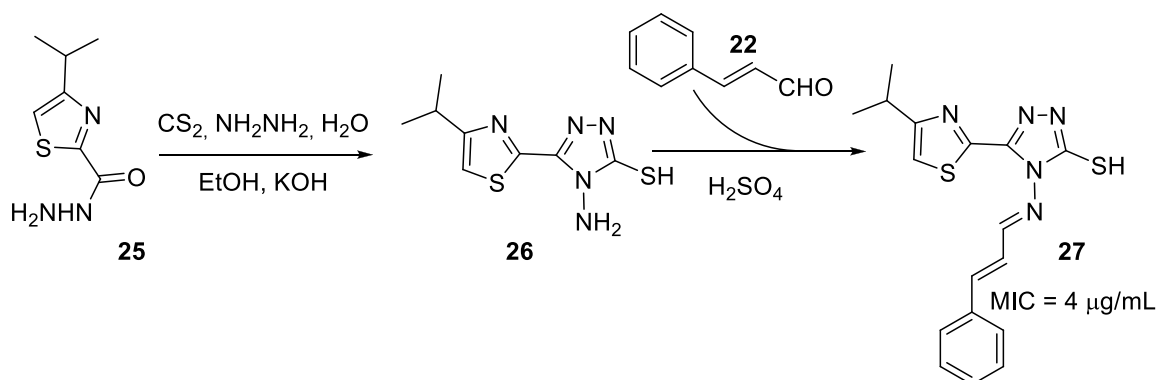
In 1997, Biava *et al.* [24] reported the synthesis and antimycobacterial efficacy of a new class of styryl derivatives (**Scheme 3**). *Ortho*, *meta* or *para*- aminotoluidine compounds possessing an imidazole, pyrazine or morpholine frame (**21a-c**) were obtained after reduction of the corresponding nitro derivatives (**20a-c**). These compounds were coupled under reductive amination conditions (**Scheme 3**) with cinnamaldehyde (**22**) affording the toluidine-styryl derivatives (**24a-c**).



### Scheme 3: Synthesis of toluidine derivatives

Among all synthesized compounds, derivatives **23c** (R=Imidazole) and **24a-c** (R=Imidazole) were the most active against five different *M. tb.* strains with MIC values ranging between 1 to 64  $\mu\text{g/mL}$ .

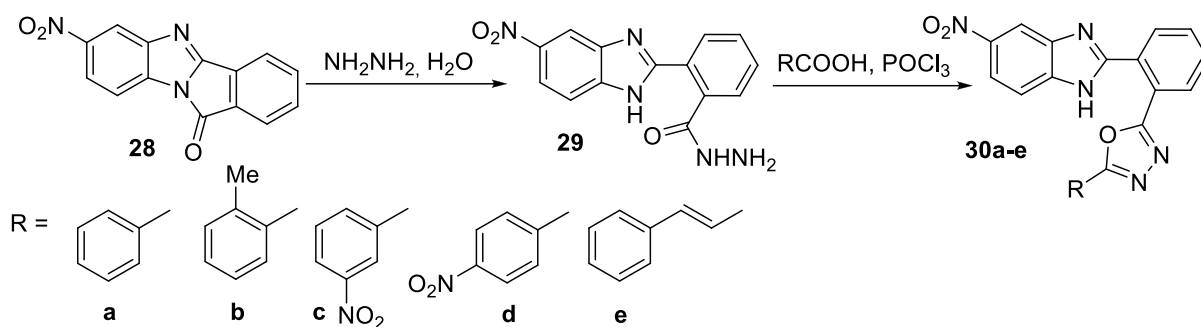
In 2010, Kumar and co-workers [25] synthesized 5-(4-isopropylthiazol-2-yl)-4-((*E*)-((*E*)-3-phenylallylidene)amino)-4*H*-1,2,4-triazole-3-thiol (**27**) (**Scheme 4**). 4-Isopropylthiazol-2-carbahydrazone **25** was converted into the corresponding potassium dithiocarbazinate, which on cyclization with hydrazine hydrate yields 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol **26**. The triazole **26** was condensed with **22** in the presence of catalytic amount of concentrated sulphuric acid in refluxing ethanol to afford **27**. Synthesized compound **27** was subjected for the evaluation of antitubercular activity against *M.tb.* strain H<sub>37</sub>Rv and resulted in a promising activity (MIC 4 µg/mL) profile.



**Scheme 4:** Synthesis of 2-substituted -5-[isopropylthiazole] clubbed 1,2,4-triazole

### 2.3.3. Cinnamic oxadiazole derivatives

In 1997, Parekh *et al.* [26] reported the synthesis of some 1,3,4-oxadiazoles and oxoimidazolines compounds as potent biologically active agents. The synthetic routes are presented in **Scheme 5**. The starting common precursor **29** was obtained through condensation of 5-nitro-*O*-benzoylene-2,1-benzimidazole (**28**) with hydrazine hydrate. The cyclocondensation reaction of different aromatic acids with **29** in the presence of  $\text{POCl}_3$  afforded the 1,3,4-oxadiazoles **30a-e**.



**Scheme 5:** Synthesis of 1,3,4-oxadiazoles and 5-oxo-imidazolines

Compounds **30a-d** were found to be more active against *M. tb.* than the cinnamic derivative **30e** (all activities were evaluated at 12.5 µg/mL against *M. tb.* H<sub>37</sub>Rv).

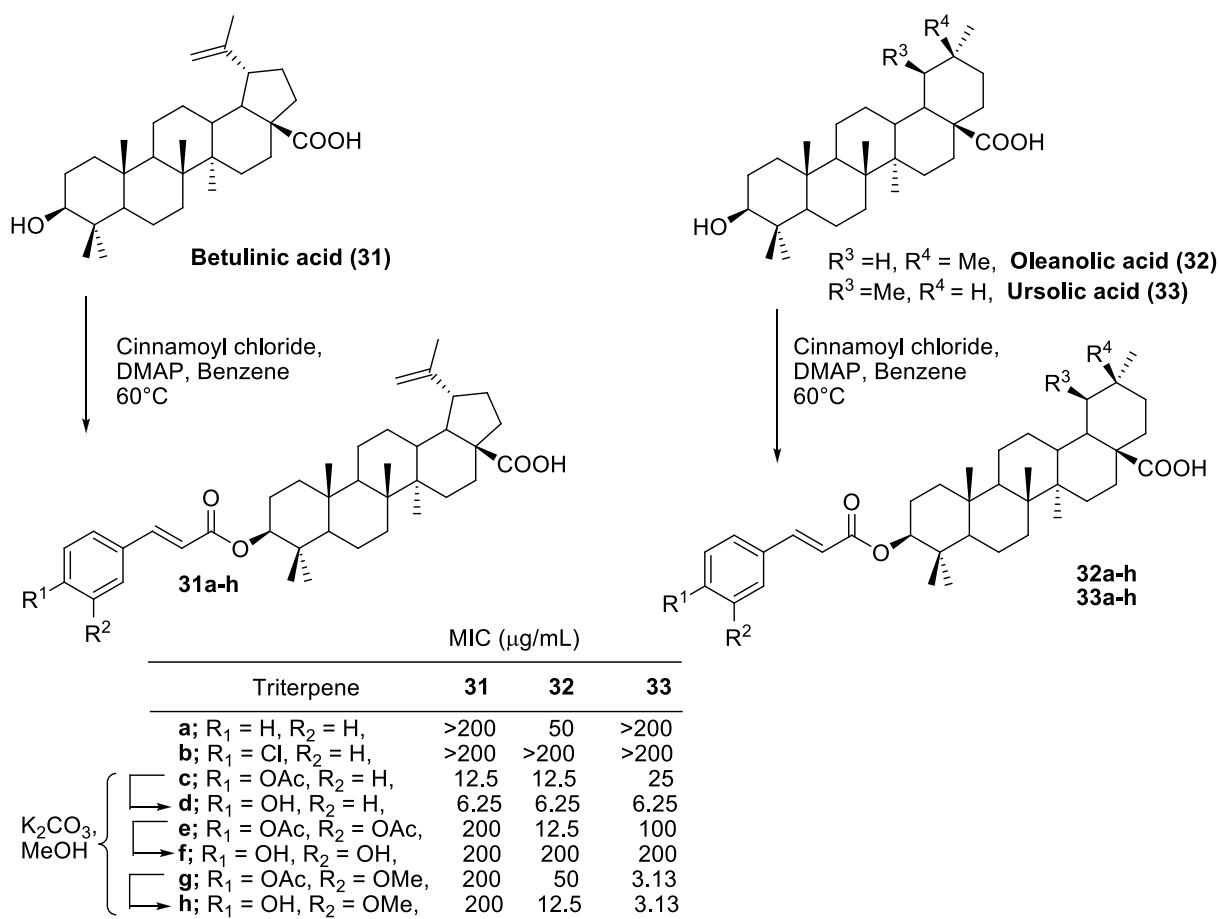
#### 2.4. Modified drugs with Cinnamic-residues

Structural modifications of known drugs by introduction of cinnamoyl or substituted cinnamoyl groups have been also explored with some success.

##### 2.4.1. Cinnamic ester derivatives

It is well known that triterpenes exhibit moderate to high *in vitro* antimycobacterial activity against *M. tb.* [27-29]. In 2008, Suksamrarn *et al.* reported [30] the modification of natural triterpenes such as betulinic acid (**31**), oleanolic acid (**32**) and ursolic acid (**33**) through introduction at the C-3 position of cinnamoyl frames (**Scheme 6**). Different cinnamoyl derivatives such as cinnamate, *p*-coumarate, ferulate, caffeate and *p*-chloro cinnamate 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 (**Scheme 6**). All the hydroxyl cinnamic acids were acetylated as a protection to the phenolic group before generating the corresponding acid chlorides followed by coupling with the triterpenes. However, the hydroxycinnamate derivatives of the triterpenes (**31d,f,h**; **32d,f,h**; **33d,f,h**) were obtained by deacetylation of the acetylated derivatives (**31c,e,g**; **32c,e,g**; **33c,e,g**) using K<sub>2</sub>CO<sub>3</sub> in methanol. The biological results indicated that the introduction of unsubstituted or

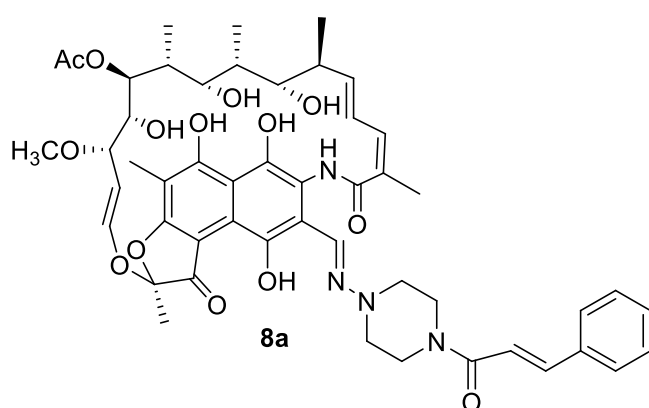
*p*-chlorinated cinnamate ester functionality (**31a,b**; **32a,b**; **33a,b**) led to inactive compounds (MIC > 200 µg/mL) or without any improvement in their antimycobacterial activity. Interestingly, the results also indicated that introduction of the *p*-coumarate moiety at the C-3 position of the triterpenes (**31d**, **32d**, **33d**) resulted in an 8-fold increase in antimycobacterial activity of the parent triterpenes **31** (MIC = 50 µg/mL) and **32** (MIC = 50 µg/mL), and a 2-fold increase in this activity of the triterpene **33** (MIC = 12.5 µg/mL). Introduction of a ferulate moiety (**31h**, **32h**, **33h**) resulted in a 4-fold increase in activity only in case of **33**. However, the *p*-hydroxyl group contributed to high antimycobacterial activity, while methylation and acetylation of the phenolic hydroxyl group, with the exception of the caffeate esters, decreased antimycobacterial activity.



**Scheme 6:** Cinnamate-based triterpenes and their biological activities

#### 2.4.2. Cinnamic amide derivatives

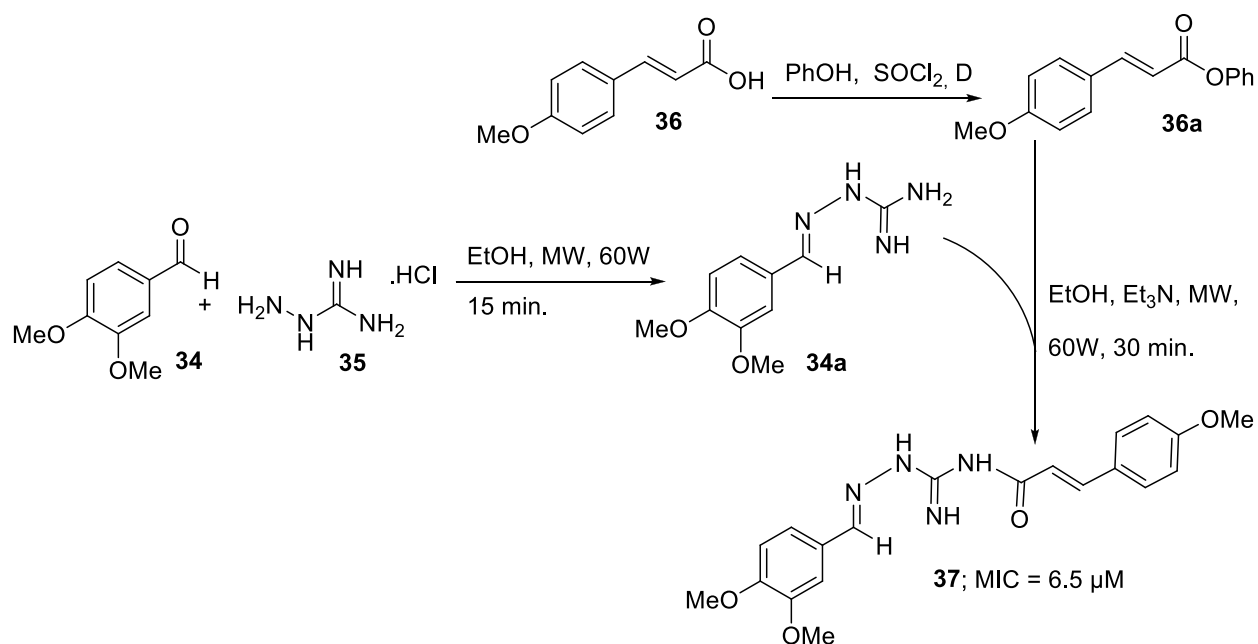
Rifampicin (RIF; **8**) is one of the most important drugs in TB treatment. In search for new compounds with structural modifications of existing lead drugs, Dimova *et al.* [31] reported in 1995 that the introduction of the cinnamoyl moiety on the piperazinyl frame of rifampicin that named rifamycin SV (T9) resulted in enhanced antimycobacterial activities. The antimycobacterial activities of 3-(4-cinnamylpiperazinyl-iminomethyl)rifamycin derivative (**8a**; **Fig. 6**) on 20 susceptible and MDR-strains of *M. tb.* and 20 *Mycobacterium avium* complex (MAC) strains were investigated by Reddy *et al.* [32]. 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  $\mu\text{g}/\text{mL}$ , respectively. Interestingly, **8a** had lower MICs against some RIF-resistant *M. tb.* strains. Compound **8a** had better activity against MAC strains, and the MIC at which 90% of the MAC strains were inhibited was <0.125  $\mu\text{g}/\text{mL}$ , and that of RIF was <2.0  $\mu\text{g}/\text{mL}$ . Compound **8a** 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, **8a** showed excellent *in vivo* activity against *M.tb.* H<sub>37</sub>Rv compared to RIF in both the lungs and spleens of C57BL/6 mice, indicating the potential therapeutic value of **8a** in the treatment of mycobacterial infections.



**Fig. 6:** Structure of Rifamycin SV

In an attempt to find novel compounds active against TB, Degani and coworkers [33] synthesized and evaluated a series of phenylacrylamides designed by molecular hybridization

of *trans*-cinnamic acids and guanylhydrazones (**Scheme 7**). 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 owing to their cationic nature [34-36]. *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 [37]. Biosynthesis of LAM is known to be a target for several antitubercular agents, including the first line antitubercular agent, ethambutol [38,39]. For the synthesis of the most active phenylacrylamide derivative (**37**; **Scheme 7**), guanylhydrazone (**34a**), required as starting material, was prepared by the microwave assisted reaction of 3,4-dimethoxybenzaldehyde (**34**) with guanyl hydrazine hydrochloride (**35**). The phenyl 4-methoxycinnamate (**36a**) was prepared by treating phenol and thionyl chloride to 4-methoxycinnamic acid (**36**). The reaction of equimolar quantities of guanylhydrazones (**34a**), with phenylcinnamates (**36a**), under microwave irradiation in the presence of triethylamine and ethanol as the solvent afforded the target derivative (*E*)-*N*-(((*E*)-2-(3,4-dimethoxybenzylidene)hydrazinyl)(imino)methyl)-3-(4-methoxyphenyl)acrylamide (**37**). This principle of the design was applied to obtain other phenylacrylamide derivatives. But compound **37** was found to be most active when tested on resazurin microtitre plate assay (REMA) against *M. tb.* H<sub>37</sub>Rv.



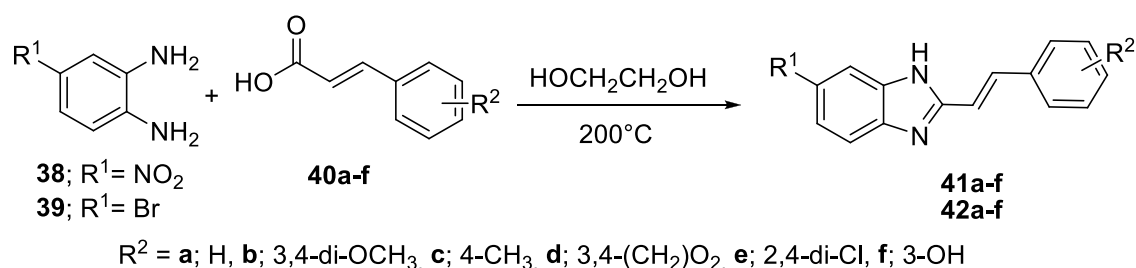
**Scheme 7:** Synthetic route for the synthesis of phenylacrylamide derivatives

Compound **37** showed MIC of 6.5  $\mu\text{M}$  along with good safety profile ( $\text{CC}_{50} = 340 \mu\text{M}$ ) in VERO cell line. Importantly, based on empirical structure–activity relationship data, it was observed that both steric and electronic parameters play major role in the activity of this series of compounds.

#### 2.4.3. Cinnamic benzimidazole derivatives

In 2009, Hosamani *et al.* [40] synthesized a new series of 5-(nitro/bromo)-styryl-2-benzimidazoles (**41a-f**, **42a-f**; **Scheme 8**) by condensation of 5-(nitro/bromo)-*O*-phenylenediamine (**38**, **39**) with *trans*-cinnamic acids (**40a-f**) in ethylene glycol for 6 h at around 200°C (**Scheme 8**). This work is based on the fact that benzimidazole and its derivatives were reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases like epilepsy, diabetes, anti-fertility [41, 42]. It is an important pharmacophore and privileged structure in medicinal chemistry [43, 44] encompassing a diverse range of biological activities. Screening for the *in vitro* anti-TB activities of these compounds (**41a-f**, **42a-f**) on the *M. tb.* strain H<sub>37</sub>Rv was conducted at 7.25

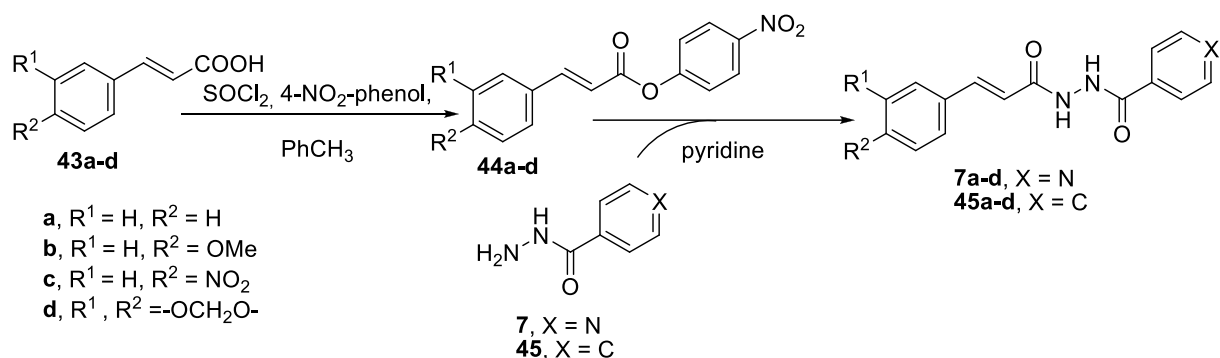
$\mu\text{g/mL}$  concentration and the inhibitory efficacies were determined. The benzimidazole derivatives wearing bromo-substituent (**42a-f**) exhibited the best results with 63-83% inhibition.



**Scheme 8:** Synthesis of styryl-2-benzimidazoles series

#### 2.4.4. Cinnamic acid hydrazide, thioester and other derivatives

Carvalho *et al.* [11b] presented the first *trans*-cinnamic acid hydrazide derivatives as potential antituberculous agents. The authors designed and explored the introduction of the *trans*-cinnamic moiety into isoniazid (**7**) core structure to ameliorate its activity. Isosteric substitution of the pyridine ring of **7** was also investigated by these authors. The synthetic route (**Scheme 9**) used for the preparation of the target compounds makes use of activation technique of cinnamic derivatives by formation of *p*-nitrophenyl esters.



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

These stable intermediates have been prepared by treating the appropriate cinnamic acids (**43a-d**) with thionyl chloride in the presence of 4-nitro-phenol resulting in the corresponding esters (**44a-d**). The target hydrazides (**7a-d, 45a-d; Scheme 9**) were obtained in good yields by nucleophilic substitution in the presence of acylhydrazides. The antimycobacterial activities of these compounds were assessed against *M. tb*. Almost all of the isonicotinic



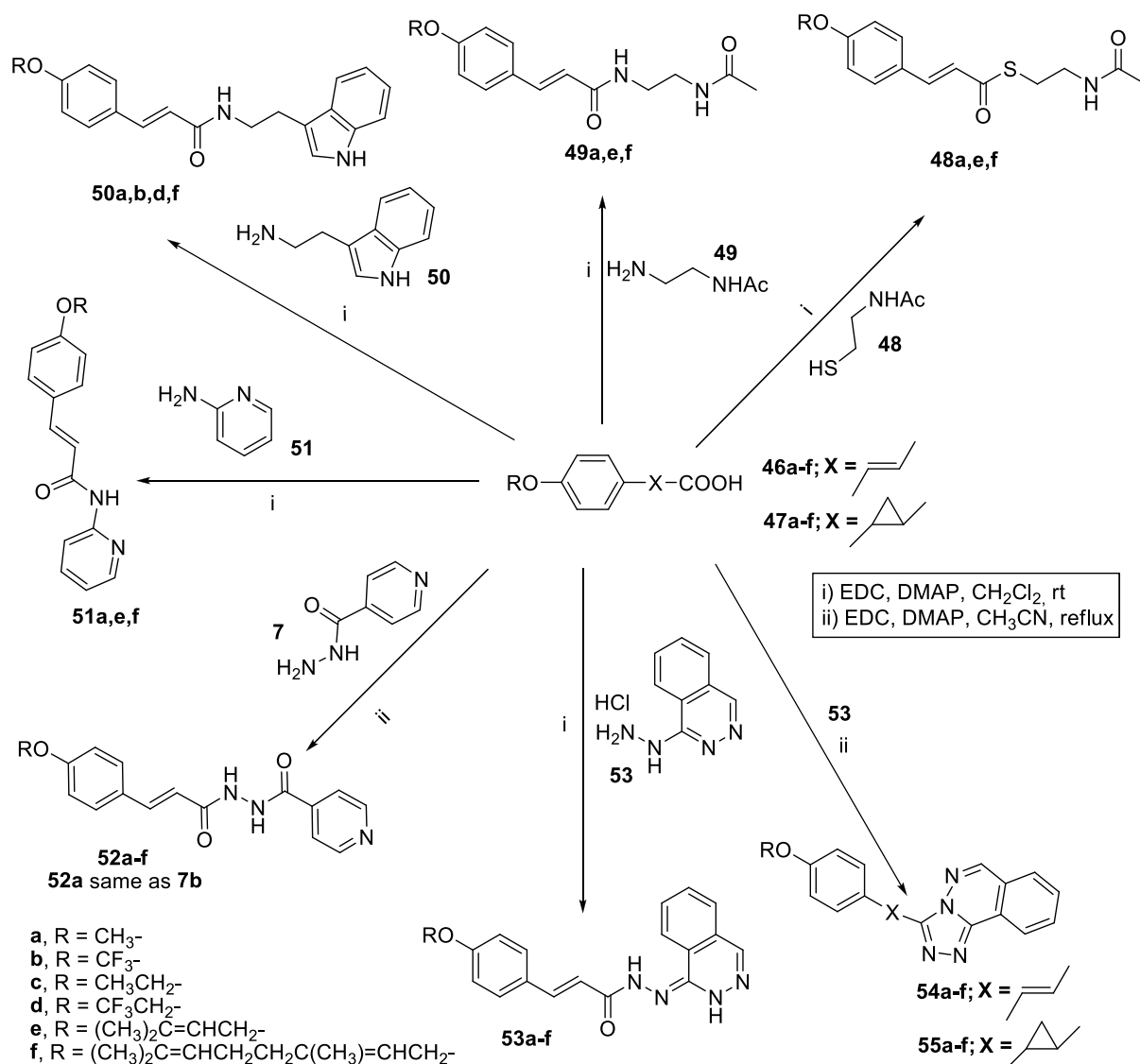
derivatives **7a-d** were sensitive in the minimum concentration tested (MIC= 3.12µg/mL) while all benzoic acid derivatives **45a-d** were much less active, thus reinforcing the pharmacophoric contribution of the isonicotinic moiety. Importantly, the authors identified the 4-methoxy cinnamic derivatives promoting better activities.

In our recent effort, we have synthesized some 4-alkoxycinnamic acid thio-ester, amides, hydrazides and triazolophthalazine derivatives [45a,b] and evaluated (MTT colorometric assay) their anti-TB efficacy. While 4-alkoxy substitutions were introduced to control the required lipophilicity following Lipinski's rules [46], their coupling partners were suitably chosen either to mimic biological intermediates or to modify any existing drug. 4-Alkoxycinnamic acids were coupled with *N*-acetylcysteamine (**48**, **Scheme 10**) to afford the corresponding thio-esters **48a,e,f** thereby mimicking the enoylacyl-ACP intermediate involved in the *M.tb.* fatty acid synthase II (FASII) cycle, an important step towards its cell wall biosynthesis. However, these thioesters showed poor anti-TB activities against *M.tb.* H<sub>37</sub>Rv possibly due to the weak C-S bond energy making these molecules labile under physiological conditions. In continuation, we introduced *N*-acetyethelenediamine **49** as coupling partner of cinnamic acids as a replacement of cysteamine moiety to afford compounds **49a,e,f** (**Scheme 10**). In spite of our concern regarding proteolytic instability of the cinnamides, (*E*)-*N*-(2-acetamidoethyl)-3-(4-geranyloxyphenyl)acrylamide (**49f**) showed a very good anti-TB activity (MIC = 0.24 µM, vs INH; MIC = 0.6 µM). Unfortunately, poor cytotoxicity profile of this class of compounds forced us to think otherwise. No other amide derivatives (**50a,b,d,f**; **51 a,e,f**) showed good biological activities. To alleviate the concern for the proteolytic instability we wanted to synthesize cinnamoyl hydrazides and thus, isoniazid became an immediate choice. To our delight, all six 4-alkoxycinnamoyl isonicotinyl hydrazides (**52a-f**) showed good anti-TB activities (MIC) and their cytotoxicity profile (IC<sub>50</sub>) were very much encouraging. At this point, it became absolutely necessary to test these

molecules against INH-resistant strains (MYC5165, 1400) to find out if these molecules are pro-drug of INH. Two representative INH-derivatives **52a** (same as **7b** in **Scheme 9**) and **52e** were tested on MYC5165, a *M.tb.* strain mutated in *InhA* and 1400 a *M.tb.* strain mutated in *katG*. The inhibitory activities of **52a** (MIC = 16  $\mu$ M: MYC5165; 320  $\mu$ M: 1400) and **52e** (MIC = 27  $\mu$ M: MYC5165; 68  $\mu$ M: 1400) were found to follow similar trends as that of INH (MIC = 18  $\mu$ M: MYC5165; 729  $\mu$ M: 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 **53**, an antihypertensive drug [47] of moderate potency, was coupled with acids **46a-f** in the presence of EDC.HCl, HOBt and triethylamine to afford (2*E*, *N'E*)-3-(4-alkoxyphenyl)-*N'*-[phthalazin-1-(2*H*)-ylidene]acrylohydrazides (**53a-f**).

In a different experimental condition, coupling of 4-alkoxyphenyl-cyclopropyl acids (**47a-f**) with 1-hydrazinophthalazine hydrochloride in acetonitrile under reflux for 48 h in presence of EDC.HCl, HOBt and triethylamine furnished the corresponding 3-(4-alkoxystyryl)-[1,2,4]triazolo[3,4- $\alpha$ ]phthalazines (**54a-f**). For the family of 1-phthalazino hydrazides (**53a-f**), MIC results were moderate but the trend of cytotoxic behaviour was not acceptable. Interestingly, the combination of isopentenyl-side chain as 4-alkoxy substituent with triazolophthalazine (**54e**), showed excellent antitubercular potency (MIC = 1.4  $\mu$ M), in comparison with other derivatives in the series (**54a-f**), and more importantly, with good cytotoxicity (IC<sub>50</sub> = 449  $\mu$ M) and selectivity index (SI = 320). Finally, to our great delight, compound **54e** showed 100-fold better *in vitro* activity against MYC5165 strain (**54e**; MIC= 0.2 $\mu$ M) and 1800-fold better activity against 1400 strain (**54e**; MIC= 0.4  $\mu$ M) compared to INH (MIC= 18 and 729  $\mu$ M respectively). The importance of the isopentenyl-side chain and triazolophthalazine part are evident from these biological results as none of the other triazolophthalazine derivatives (**54a-d**, **54f**) are active enough. Further, the radio-thin-layer

chromatography analysis revealed that compound **54e** 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, with an approach to replace the double bond by isosteric cyclopropyl moiety, we also synthesized 3-[2-(4-alkoxyphenyl)cyclopropyl]-[1,2,4]triazolo[3,4- $\alpha$ ]phthalazine (**55a-f**; racemates) and their *in-vitro* anti-TB potentiality were evaluated. Significantly, the MIC values of the compounds (**55a-f**) were found to be poor compared to their olefinic analogues (**54a-f**). In regard to the difference in activities between the enoyl and cyclopropyl series, a plausible explanation could be the respective Michael acceptor ability. Chew *et al.* [48a] have recently showed that cinnamaldehydes can act as Michael acceptors and inhibit thioredoxin reductase through nucleophilic addition of glutathione cystine –SH residues. In our case, from a chemical point of view, the compounds having electron withdrawing group in the *para*-position of the aromatic ring should be more active to Michael addition. It should be a clear structure activity relationship if this is the possible reason of their activity, i.e. 4-OCF<sub>3</sub> derivatives are expected to show better inhibitory activities compared to their 4-OCH<sub>3</sub> analogues. But this is not the case as compound **52a** has a 4-fold better activity (MIC=0.3  $\mu$ M) compared to **52b** (MIC=1.1  $\mu$ M) and similarly **54a** (MIC=53  $\mu$ M) exhibits approximately 15-fold better activity than **54b** (702  $\mu$ M). In view of these results, we can suggest that the Michael addition is not 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 [48b].



**Scheme 10:** Synthetic route for the preparation of different cinnamoyl derivatives

### 3. CINNAMIC ACID DERIVATIVES AS ANTIMALARIAL AGENTS

#### 3.1. Introduction

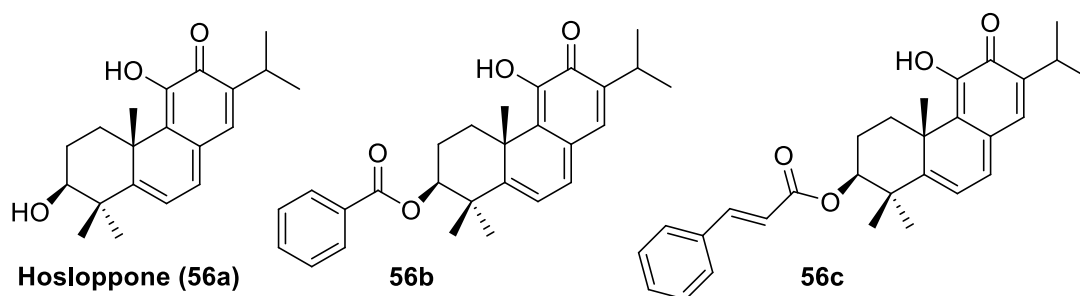
Malaria remains one of the most serious health threats in the world, affecting 300-400 million people and claiming approximately 3 million lives each year [49, 50a,b]. Malaria is generally caused by four species, including *Plasmodium falciparum*, *P. Vivax*, *P. Ovale* and *P. Malariae*, having the greatest toll in human health. For much of the twentieth century, malaria was treated with the fast-acting and inexpensive drugs chloroquine and pyrimethamine-sulphadoxine. From the 1960s onwards, these drugs progressively succumbed to the

appearance and spread of resistance around the world. By the early 1990s, malaria's percentage contribution to 'all-cause mortality' in African infants was climbing, in some areas accounting for nearly 50% of deaths. Currently, the only fully effective class of antimalarial drug is the artemisinins. As a result of the increasing prevalence of multidrug resistance of malaria parasites to standard chemotherapy, the discovery and use of nontraditional antimalarials with novel action mechanisms is becoming urgent [51a-c]. In this context, cinnamic derivatives from natural or synthetic sources form a class of drug candidates which we believe could be used as lead for the antimalarial drug discovery.

### 3.2. Natural Resources

#### 3.2.1. Cinnamic ester derivatives

In 1992, Nkunya and co-workers [52] isolated two new hosloppone derivatives, 3-*O*-benzoylhosloppone (**56b**), 3-*O*-cinnamoylhosloppone (**56c**) (**Fig. 7**), from the root bark of the antimalarial plant *Hoslundia opposita* Vahl. growing in East and West Africa. The crude *n*-hexane extract of the root bark was found to have significant *in vitro* activity against *Plasmodium falciparum* (*P. Falciparum*) (IC<sub>50</sub> = 5.6 µg/mL). In order to evaluate the active principles, different compounds were isolated and especially two esters (**56b,c**) of new abietane-type quinomethane alcohol named hosloppone (**56a**).

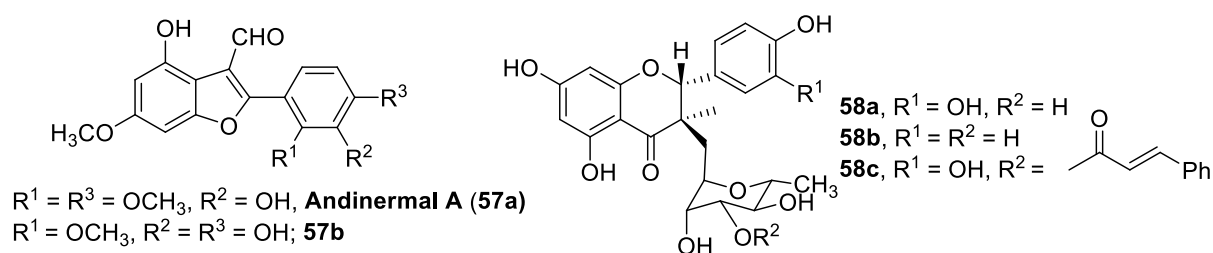


**Fig. 7:** Chemical structure of hosloppone derivatives

Compounds **56b** and **56c** showed significant *in vitro* activities against the multidrug resistant K1 strain of *P. falciparum* and against chloroquine sensitive strain NF 54 (IC<sub>50</sub> = 0.4 and 0.22

$\mu\text{g/mL}$  respectively). The better antimalarial activity of **56c** in comparison to **56a** and **56b** could be attributed to the presence cinnamoyl moiety in **56c**; this group is suspected to undergo Michael reaction with nucleophilic sites in the parasite cell DNA molecules, thereby inhibiting the growth of the *P. falciparum*.

During a screening program on antimalarial compounds from plant sources, Jenett-Siems and co-workers [53] investigated *Andira inermis*, a native from southern Mexico to northern South America. From crude lipophilic extracts of leaves showing moderate *in vitro* activity against *P. falciparum*, they isolated and elucidated the chemical structure as 2-arylbenzofuran-3-carbaldehydes (**57a,b**) along with new flavanonol glycosides (**58a,b,c**) (Fig. 8). *In vitro* antiplasmodial effects of the compounds were also assessed.

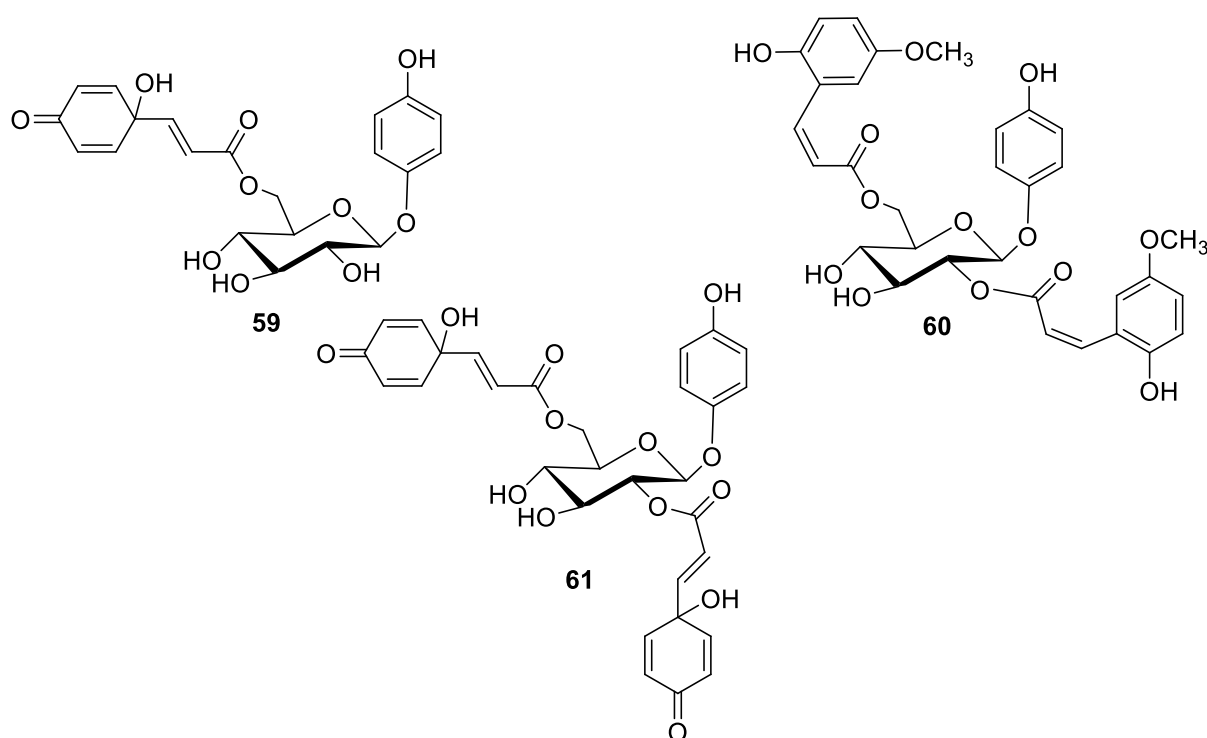


**Fig. 8:** Andinermal A (**57a**) and flavanonol glycosides isolated from *Andira inermis*

Andinermal A (**57a**) (Fig. 8) exhibited the strongest antiplasmodial activity with  $\text{IC}_{50}$  values of 2.3 mg/mL against poW and 3.9 mg/mL against Dd2 strains. Whereas the 3-*O*-rhamnosides **58a** and **58b** proved to be inactive, 3'-*O*-*trans*-cinnamoyl-astilbin (**58c**) showed a 50% growth inhibition at 10.4 mg/mL (poW) and 4.2 mg/mL (Dd2). Obviously the *trans*-cinnamoyl residue could enhance the antiplasmodial activity of the unsubstituted rhamnoside **58a**.

While screening a library of terrestrial plant and marine invertebrate extracts for their *in vitro* *P. falciparum* activity, Ovenden and co-workers [54] isolated an extract from the leaves and twigs of a *Gre Villea* "Poorinda Queen" displaying significant antimalarial activity. Subsequent bioassay-guided fractionation of this methanol extract allowed for the

identification of three new phenolic glycosides, robustasides E (**59**), F (**60**) and G (**61**) (**Fig. 9**).



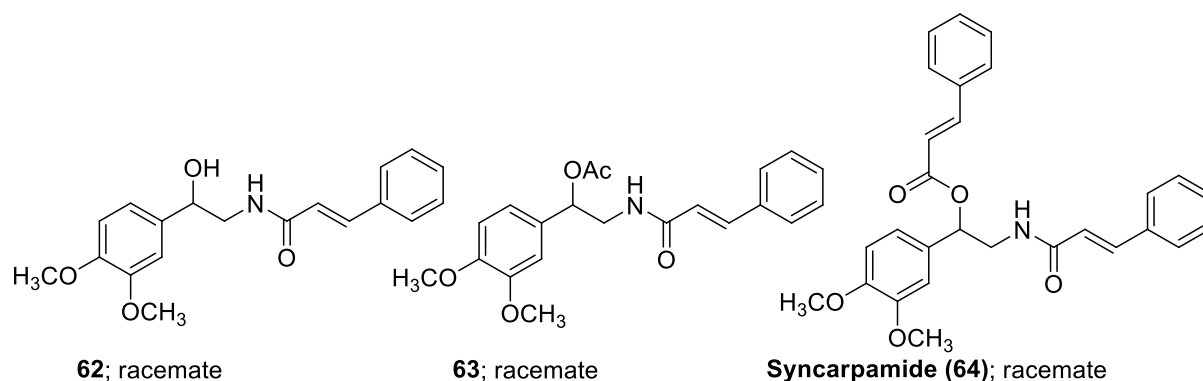
**Fig. 9:** Chemical structure of robustasides E (**59**), F (**60**), and G (**61**)

The *in vitro* antimalarial activities ( $IC_{50}$  values) of **59-61** on the *P. falciparum* chloroquine-sensitive D6 cell-lines were established. Compounds **59** and **60** were found to have only moderate *in vitro* activity ( $IC_{50}$  of 55.4 and 14.7  $\mu$ M), while **61** was the most active ( $IC_{50}$  of 4.7 $\mu$ M). However, the mechanism of action of these compounds and the role of the hemiquinone in the observed differences in antimalarial activities remained unknown.

### 3.2.2. Cinnamic amide derivatives

In 2005, Ross and co-workers [55] isolated three alkamides (**62-64**; **Fig. 10**) from the leaves of *Zanthoxylum syncarpum*, commonly called “prickly ash”, which is the largest genus in the family *Rutaceae* and comprises about 200 species of trees and shrubs, with a worldwide, but predominantly tropical, distribution. The antimalarial activity of the isolated racemic compounds (**62-64**) was evaluated against chloroquine-sensitive (D6, Sierra Leone) and

resistant (W2, Indochina) strains of *P. falciparum*. Compounds **62** and **63** were inactive, whereas compound **64** showed moderate activity, with IC<sub>50</sub> values of 4.2 and 6.1 μM against *P. falciparum* D6 clone, Sierra Leone, and *P. falciparum* W2 clone, Indochina, respectively. Artemisinin and chloroquine showed IC<sub>50</sub> values of 0.04 and 0.05 μM against *P. falciparum* D6 clone, respectively. Cytotoxicity was evaluated at an IC<sub>50</sub> of 4.7 μg/mL.



**Fig. 10:** Chemical structure of alkamides from leaves of *Zanthoxylum syncarpum*

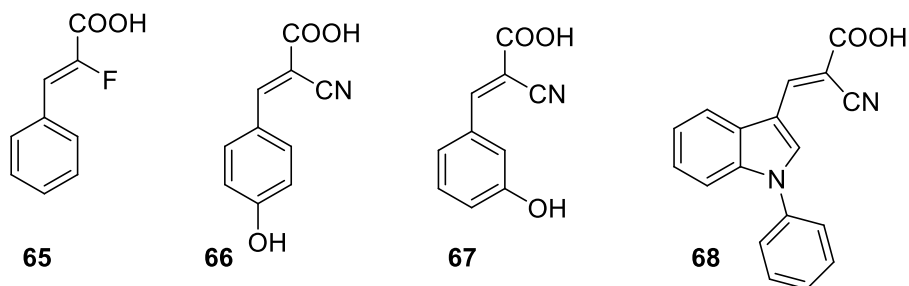
### 3.3. Synthetic compounds

#### 3.3.1 Cinnamic acid derivatives

Ginsburg et al. [56] reported that some cinnamic acid derivatives **65-68** (**Fig. 11**), obtained from commercial sources, inhibited the growth of intraerythrocytic *P. falciparum* in culture, which is in correlation with their hydrophobic character. It was found that all the derivatives also inhibit the translocation of carbohydrates and amino acids across the new permeability pathways induced in the host cell membrane by the parasite. This impediment correlated strictly with their effect on parasite growth. These drug-candidates caused a significant decline in ATP level in the parasite compartment, while they provoked only a small effect on ATP level in the intact cells and the host cell compartment. These observations suggest that these cinnamic derivatives (**65-68**) inhibit ATP production in the parasite and its utilization by the host cell. The authors studied the inhibition of *P. falciparum* growth and sorbitol uptake by  $\alpha$ -fluorocinnamate (**65**),  $\alpha$ -cyano-4-hydroxycinnamate (**66**),  $\alpha$ -cyano-3-hydroxycinnamate (**67**) and  $\alpha$ -Cyano- *p*-(1-phenylindol-3-yl) acrylate (**68**). The IC<sub>50</sub> values for parasite growth



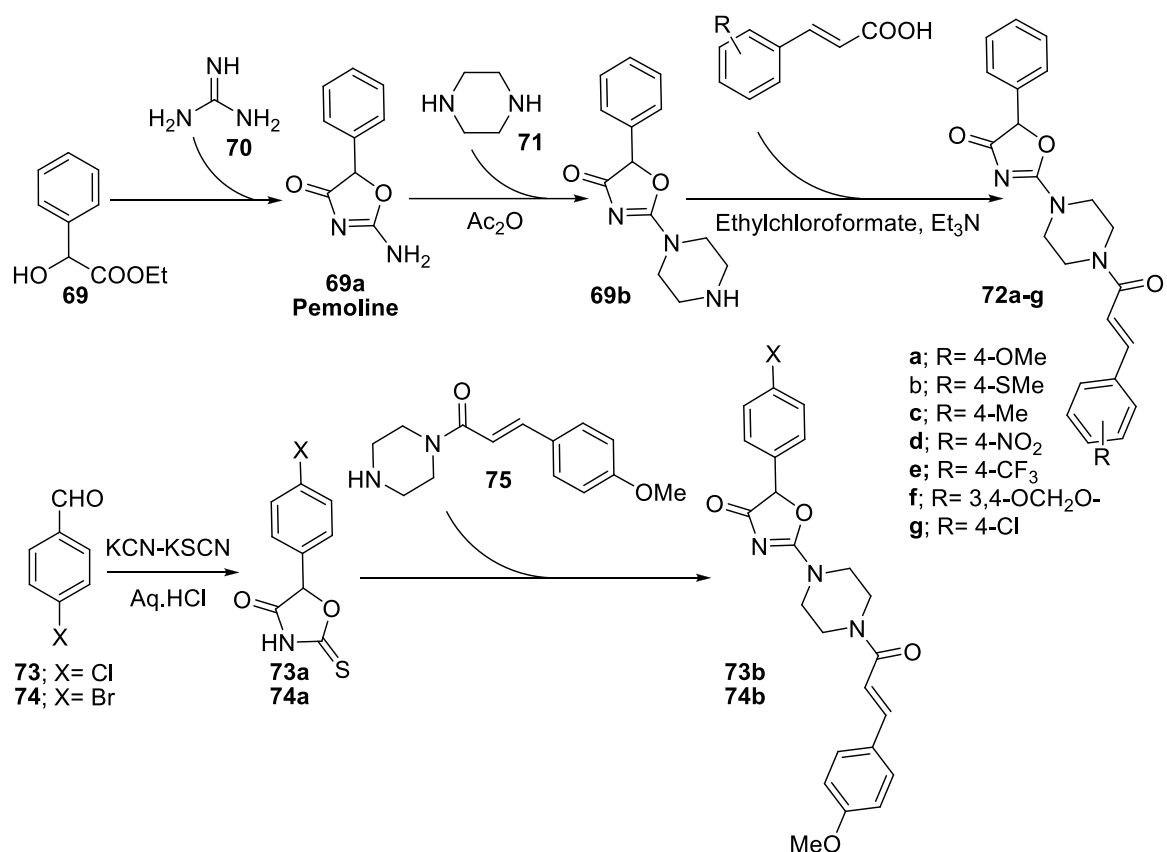
inhibition (**65**;  $0.612 \pm 0.084$  mM, **66**;  $1.126 \pm 0.0005$  mM, **67**;  $0.258 \pm 0.025$  mM, **68**;  $0.064 \pm 0.006$  mM) were found to be higher in comparison to their sorbitol uptake inhibition (**65**; 0.11 mM, **67**; 0.16 mM, **68**; 0.03 mM). These results indicated that the indolyl derivative (**68**) is the most efficient inhibitor. However, the fluorinated derivative (**65**) has a better sorbitol uptake inhibition profile than plasmodial growth inhibition.



**Fig 11:  $\alpha$ -Substituted cinnamic acid derivatives.**

### 3.3.2. Cinnamic amide derivatives

In 1975, Herrin and co-workers [57] used (4-oxo-2-oxazolin-2-yl)piperazine scaffold to synthesize different potential antimalarial agents. The starting material for the compounds was 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (**69b**). Condensation of ester **69** with guanidine (**70**) gave 2-amino-5-phenyl-2-oxazolin-4-one (pemoline; **69a**) (Scheme 12). Pemoline (**69a**) was activated by acylation with acetic anhydride to yield a monoacetyl derivative which reacted smoothly with piperazine (**71**) to give the piperazine pemoline **69b**. Cinnamoyl groups were introduced by activating the corresponding cinnamic acid through mixed anhydride formation using ethylchloroformate and triethylamine followed by reacting with pemoline-piperazine derivative (**69b**) to afford **72a-g**.

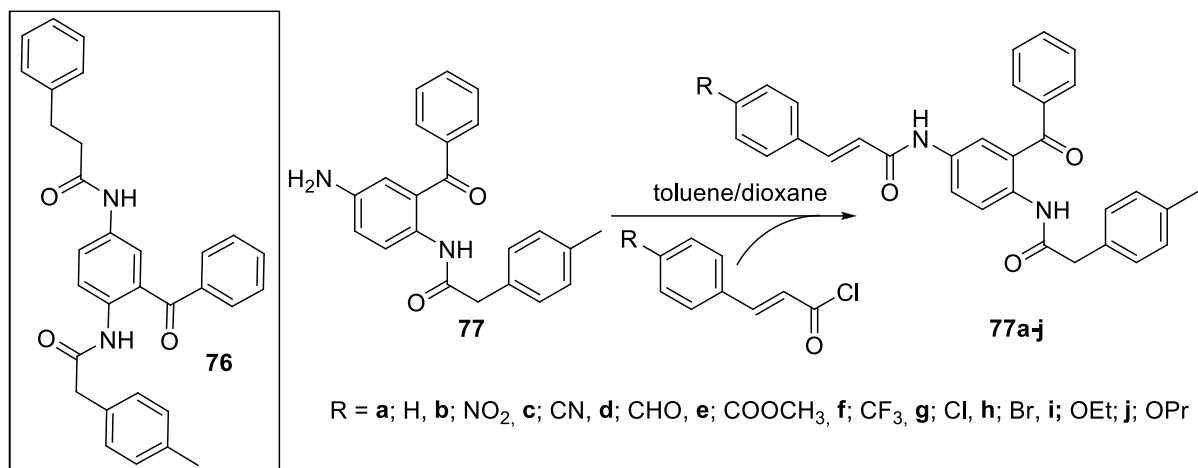


### Scheme 11: Synthesis of pemoline analogues

In another approach the 5-(4-halogenophenyl)-4-oxo-2-oxazolinyl derivatives (**73b**, **74b**; Scheme 11) were prepared by allowing 5-(4-halogenophenyl)-2-thio-2,4-oxazolidinediones (**73a**, **74a**) to react with monocinnamoylated piperazine (**75**). These molecules were evaluated for blood schizonticidal activity against *Plasmodium berghei* in mice. Untreated animals die within 6-8 days with a mean survival time of 6.2 days. Compounds possessing 4-chloro or bromo substitution (**73b**, **74b**) were most active against *Plasmodium berghei*. At 320 mg/Kg dose, mean survival time is 16 and 17 days respectively. In summary, the biological activity of these derivatives indicates that the (5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine moiety is a sensitive antimalarial pharmacophoric group.

By random screening, Schlitzer and co-workers identified compound **76** (Scheme 12) as a lead structure for a novel class of anti-malarial agents (IC<sub>50</sub>= 2.7 μM) [58-60]. In the course

of the establishment of structure-activity relationships, they replaced the phenylpropionyl residue of **76** by several *para*-substituted cinnamoyl moieties (**Scheme 12**). The target compounds (**77a-j**) were prepared from *N*-(4-amino-2-benzoylphenyl)-(4-methylphenyl)acetamide (**77**) and appropriate cinnamic acid chlorides (**Scheme 12**).



**Scheme 12:** Structures of the lead compound **76** and synthesis of benzophenonediamine derivatives (**77a-j**).

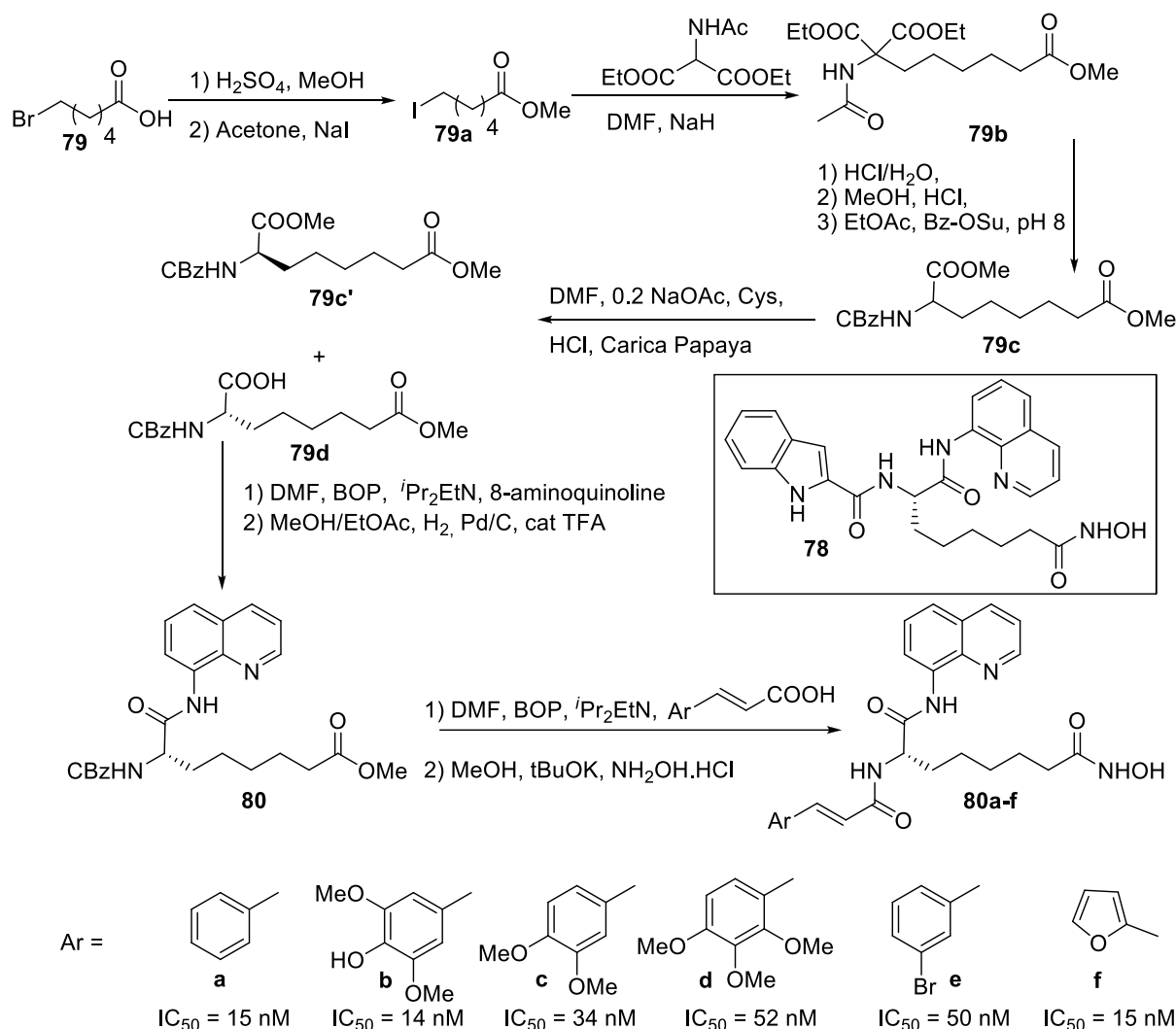
All derivatives, tested against multidrug resistant *P. falciparum* strain Dd2, exhibited activities in terms of IC<sub>50</sub> from 0.2 to >100μM. Replacement of the 3-phenylpropionyl moiety of the lead structure **76** by a 4-propoxycinnamoyl residue (**77j**) resulted in a 10-fold improvement in anti-malarial activity (**77j**; IC<sub>50</sub>= 0.2μM vs **76**; 2.7μM).

In 2006, Doerksen and co-workers [61] used the class of antimalarials developed by Schlitzer *et al.* [58-60] as plasmodial protein farnesyltransferase inhibitors. In order to investigate quantitatively the local physicochemical properties involved in the interaction between drug and biotarget, the 3D-QSAR methods CoMFA and CoMSIA were used to study some molecules of the series, including the screened lead compound **76** and cinnamic acid derivatives (**77a-j**). Steric, electrostatic, and hydrophobic properties of substituent groups were found to play key roles in the bioactivity of the series of compounds, while hydrogen

bonding interactions show no obvious impact. The results provided insight for optimization of this class of antimalarials for better activity and might prove helpful for further lead optimization. In this study, the hydrophobic property seemed to be most significant factor that is correlated with activity.

Effective treatment and control of malaria continues to be challenged by parasite resistance to antimalarial drugs. To this aim, histone deacetylase enzymes (HDACs) in malaria parasites may represent potential new targets for antimalarial drug development. HDACs are Zn-dependent enzymes that play crucial roles in modulating mammalian cell chromatin structure, transcription, and gene expression. Fairlie and co-workers [62] found that compounds derived from L-2-aminosuberic acid (Asu), like **78** and **80a** (**Scheme 13**), have potent antimalarial activity and also inhibited *P. falciparum* HDAC nuclear extracts in a dose-dependent manner (IC<sub>50</sub>= 78 nM and 87 nM, respectively). Compound **80a** was a lead compound with a cinnamic acid residue. A series of synthetically accessible derivatives of cinnamic acids was synthesized (**Scheme 13**). 6-Bromohexanoic acid (**79**) was protected as a methyl ester followed by iodide substitution forming methyl 6-iodohexanoate (**79a**). Alkylation of diethyl acetamidomalonate with **79a** gave 6-acetamido-7-ethoxy-6-(ethoxycarbonyl)-7-oxoheptanoic acid (**79b**), which was hydrolyzed under acidic conditions followed by protection of the acid as the methyl ester, and conversion of the amine to the benzylcarbamate (**79c**). Chiral resolution of **79c** was achieved using the cysteine protease, *Carica papaya* and stopped at 40% conversion to free acid **79d** and ester **79c'**. The acid functionality of **79d** was coupled with 8-aminoquinoline and terminal amine with cinnamoyl residues using standard coupling procedures to afford a series of inhibitors (**80a-f**).

The authors described a series of potent antimalarial cinnamates (**80a-f**) with IC<sub>50s</sub> <50 nM against a drug sensitive (3D7) strain of *P. falciparum*.

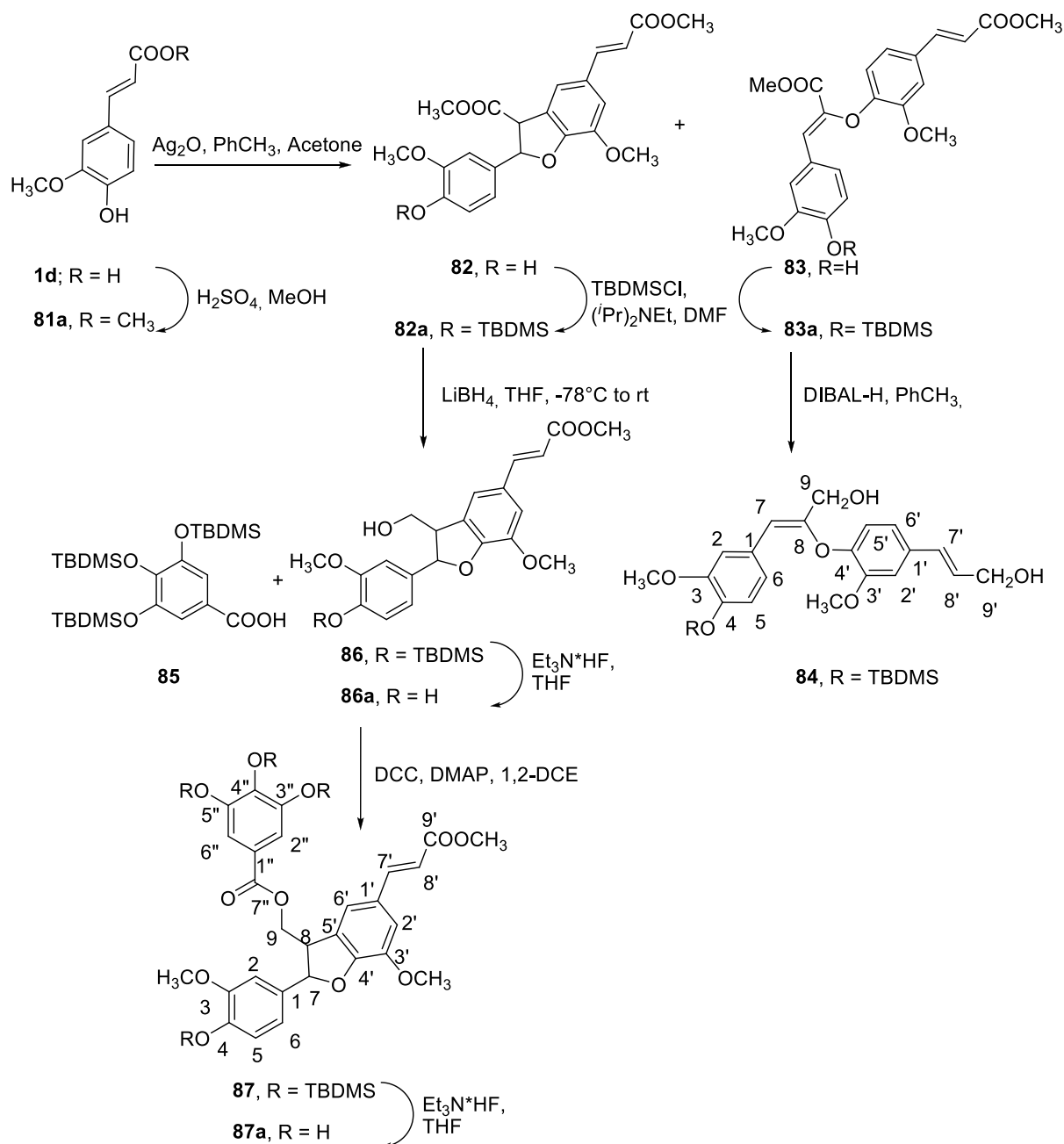


**Scheme 13:** Synthetic route to antimalarial HDAC inhibitors containing cinnamic residues

The inhibitors showed selectivity in killing the malarial parasite over normal cells and they caused hyperacetylation of *P. falciparum* histones. When docked in a *P. falciparum* HDAC (PfHDAC1) homology model, a preferred inhibitor binding mode revealed amide–NH H-bonding to PfHDAC1 Asp97. The inhibitors reported herein share a branch or fork at the chiral center, thereby enabling generation of compound libraries that can distinguish between HDAC surface contours at the entrance to the HDAC active sites, thereby enabling discrimination between different *P. falciparum* and human HDACs. This may be an important approach to enhancing selectivity over human HDAC enzymes. Together the data supports the case for targeting the PfHDAC1 enzyme to obtain novel antimalarial drugs.

### 3.3.3. Cinnamic ester derivatives

In 2007, Baltas and co-workers [63] investigated ferulic dimers to identify new class of antimalarials. The feruloyl dimers were prepared by the oxidative coupling of the feruloyl methyl ester (**81a**), obtained by treating ferulic acid (**1d**) with refluxing methanol in the presence of sulfuric acid (**Scheme 14**). The biomimetic oxidative coupling of **81a** was carried out using silver oxide Ag<sub>2</sub>O in toluene/acetone (2/1) mixture as solvent. Benzofuranic derivative **82** (sole diastereoisomer) was obtained as the major product along with some dimeric ferulic ester (**83**). The monoalcohol **86** was obtained by selective reduction of the benzofuranyl ester group of compound **82a** with 6 equivalents of LiBH<sub>4</sub> in THF at room temperature. Compound **86a**, obtained after TBDMS deprotection of **86**, was coupled with trisilylated gallic acid **85** in the presence of EDC/DMAP or DCC/DMAP to afford the gallate ester **87**. Finally, silyl group deprotection was performed by using Et<sub>3</sub>N.3HF complex in THF. Compound **83** possessing two allylic esters could not be reduced by lithium tetrahydroborate. The treatment of **83a**, the silylated derivative, with DIBAL-H afforded the diol **84**. The reaction was quite sluggish when compound **83** was used. Compounds **82**, **83**, **86a**, and **87a** were evaluated for their ability to inhibit *in vitro* *P. falciparum*, grown in asynchronous culture conditions. To this end, the chloroquine-resistant *Plasmodium* strain FCM29 was used. Compound **87a** exhibited antiplasmodial activities with an IC<sub>50</sub> value of 798 ± 12 nM. The standard reference drug chloroquine had an IC<sub>50</sub> value of 264 ± 11 nM. The remaining compounds **82**, **83**, and **86a** did not show significant antiplasmodial activities.



**Scheme 14:** Synthetic route to ferulic esters dimers

Interestingly, the presence of the galloyl moiety in compound **87a** led to the appearance of antiplasmodial effects with respect to the parent compound **86a**. A decrease in cytotoxicity from compound **82** to compound **87a** was noticed. Thus, gallate ester might be a good substitute to enhance the antimalarial activities of existing or potential drugs. Cytotoxicity activities of these compounds were also evaluated against the murine P388 leukaemia cells.

Compound **82** showed cytotoxicity activities against P388 cell lines with  $IC_{50}$  of  $772 \pm 21$  nM whereas the remaining compounds were devoid of such activities.

## **4. CINNAMIC ACID DERIVATIVES IN CARDIOVASCULAR DISEASES**

### **4.1. Introduction**

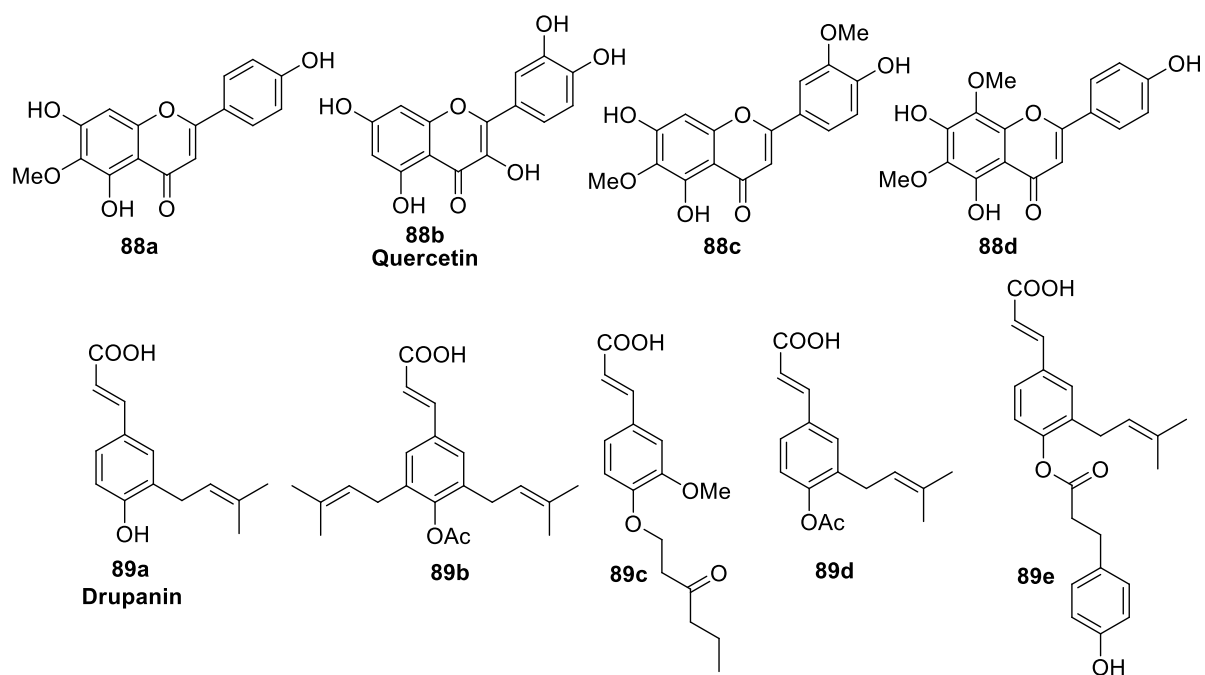
Heart diseases or cardiovascular diseases involve the heart or blood vessels (arteries and veins) [64]. While the term technically refers to any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial diseases). These diseases have similar causes, mechanisms, and treatments. Most countries face high and increasing rates of cardiovascular diseases. A large histological study showed vascular injury accumulates from adolescence, making primary prevention efforts necessary from childhood [65a,b]. By the time that heart problems are detected, the underlying cause (atherosclerosis) is usually quite advanced, having progressed for decades. There is therefore increased emphasis on preventing atherosclerosis by modifying risk factors, such as healthy eating, exercise and avoidance of smoking. In addition, low density lipoprotein (LDL) metabolism in human has a profound effect on atherosclerosis. Because LDL particles appear to be harmless until entering within the blood vessel walls and oxidized by free radicals [66], it is postulated that ingesting antioxidants and minimizing free radical exposure may reduce LDL's contribution to atherosclerosis, though results are not conclusive [67]. Naturally occurring polyphenolic cinnamic acid derivatives are known antioxidants and are traditional medicines for atherosclerosis-related diseases like hypertension. Our effort in this review is directed towards the understanding of natural and synthetic cinnamic derivatives in cardiovascular disease-related medicinal chemistry.

### **4.2. Natural sources**

#### **4.2.1. *Cinnamic acid derivatives and analogues***



Oxidative stress, the consequence of an imbalance of prooxidants and antioxidants in the organism, is gaining recognition as a key phenomenon in chronic illness like inflammatory and heart diseases, hypertension and some forms of cancer. Several gastrointestinal tract diseases seem to be induced by oxidative stress [68]. On the other hand, the traditional use of many *Baccharis*-species as hepatoprotective and digestive crude drugs have been reported [69]. Schmeda-Hirschmann *et al.* reported [70] that the exudate and seriated extracts from the aerial parts of *Baccharis grisebachii* (*Asteraceae*) which is recommended as a digestive and to relieve gastric ulcers in Argentina, showed activities as free radical scavengers and inhibited lipoperoxidation in erythrocytes. Assay guided isolation led to *p*-coumaric acid derivatives and flavonoids as the main active constituents of the crude drug (**Fig. 12**). The activity towards the superoxide anion was mainly arising due to the flavonoid constituents. 5,7,4'-Trihydroxy-6-methoxyflavone (**88a**) and quercetin (**88b**) presented high activity (64 and 79%) even at 12.5 µg/mL. The xanthine oxidase inhibitory effect of the extracts was related with the *p*-coumaric acid derivatives such as drupanin (**89a**), 4-acetyl-3,5-diprenylcinnamic acid (**89b**) and *trans*-ferulic acid *O*-hexan-3-onyl-ether (**89c**) which showed IC<sub>50</sub> values in the range 28–40 µg/mL. Both *p*-coumaric acid derivatives and flavonoids inhibited lipoperoxidation in erythrocytes. The highest activity was found for the *p*-coumaric acid derivatives such as 4-acetyl-3-prenyl-ethoxycinnamate (**89d**), 3-prenyl-4-(4'-hydroxydihydrocinnamoyloxy)-cinnamate (**89e**) and compound **89c** (69–82%), and for the flavonoids such as **88a**, **88b**, 5,7,4'-trihydroxy-6,3'- dimethoxyflavone (**88c**) and 5,7,4'-trihydroxy-6,8-dimethoxyflavone (**88d**) (64–84%) at 100 µg/mL. The most active free radical scavengers measured by the DPPH decoloration assay were the *p*-coumaric acid derivatives **89a** and *trans*-ferulic acid *O*-hexan-3-onyl-ether (**89c**)(27–35% at 10 µg/mL) and the flavonoid quercetin (97 and 23% at 10 and 1 µg/mL, respectively). The results support the use of *Baccharis grisebachii* in Argentinian traditional medicine.



**Fig. 12:** Active components isolated from *Baccharis grisebachii*.

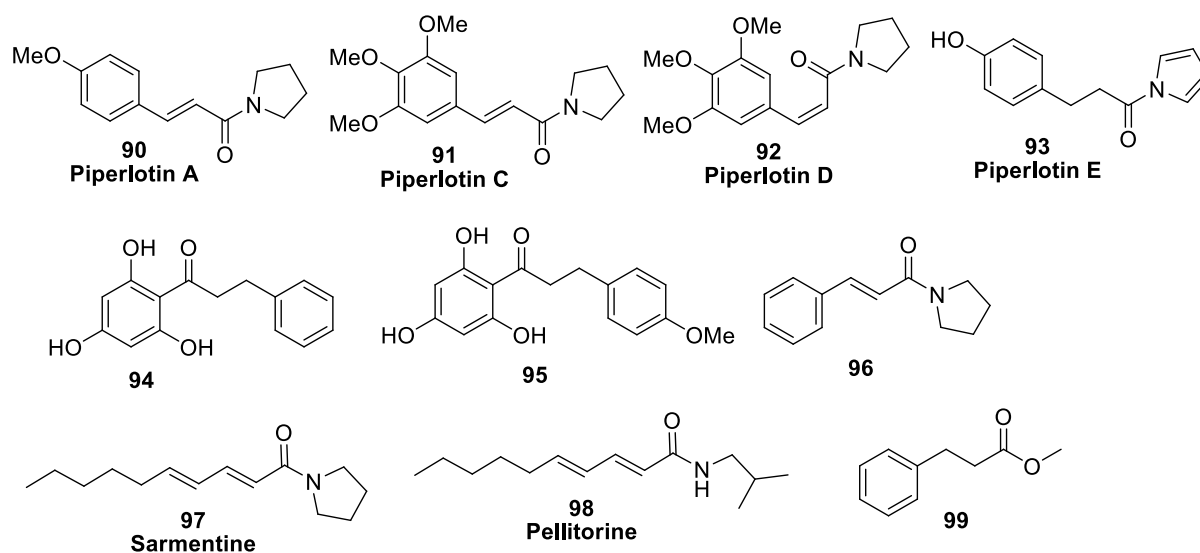
#### 4.2.2. Cinnamic ester derivatives

Hypertension is a lifestyle-related disease which often leads to serious ailments such as heart diseases and cerebral hemorrhage. Angiotensin II (Ang II) plays an important role in regulating cardiovascular homeostasis. Uemura *et al.* [71] found that EtOH extract from the resin of sweet gum *Liquidambar styraciflua* strongly inhibited Ang II signaling. The authors isolated benzyl benzoate and benzyl cinnamate (**6**) (**Fig. 2**) from this extract and found that these compounds inhibited the function of Ang II in a dose-dependent manner without cytotoxicity.

In 2006, Awang *et al.* [72] isolated ethyl cinnamate (**4**) (**Fig. 2**) through bioassay guided fractionation from *Kaempferia galanga* L., a common Malaysian Zingiberaceae species. The species is locally used as a spice and commonly prescribed for the traditional treatment of hypertension, rheumatism and asthma. However, the authors reported that the active component, **4**, has a vasorelaxant activity as it exhibited hypotensive activity by lowering the basal mean arterial pressure in anaesthetized rats.

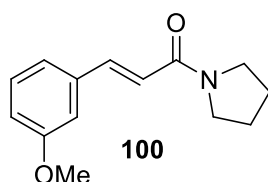
#### 4.2.3. Cinnamic amide derivatives and analogues

Thanh *et al.* reported [73] in 2007 that the methanolic extract of *Piper lolot*, showed potent inhibitory activity on platelet aggregation induced by arachidonic acid (AA) and platelet activating factor (PAF). Members of the *Piper* genus, widely distributed throughout the tropical and subtropical regions, have commercial, economical, and medicinal importance. Economically, the *Piperaceae* is employed for the production of pepper in worldwide spice markets. Plants from the *Piper* genus have been used for a number of practical applications, including remedies in many traditional medicinal systems, such as traditional Chinese medicine, the Indian Ayurvedic system, and folklore medicines of Latin America and the West Indies. Activity-guided isolation afforded amide alkaloids, piperlotine analogues, along with some known compounds (**Fig. 13**). The isolated compounds were tested for their inhibitory activity on the rabbit platelet aggregation. The compounds piperlotine A (**90**), piperlotine C (**91**), piperlotine D (**92**), piperlotine E (**93**), 3-phenyl-1-(2,4,6-trihydroxyphenyl)propan-1-one (**94**), 3-(4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one (**95**), 1-*trans*-cinnamoylpyrrolidine (**96**), sarmentine (**97**), pellitorine (**98**) and methyl 3-phenylpropionate (**99**) showed potent antiplatelet aggregation activity (100% antiplatelet aggregation at 100  $\mu\text{g/mL}$ ). Importantly, platelet aggregation plays a central role in thrombosis (clot formation). The presence of a thrombus in an artery providing blood to the heart is the most common cause of acute coronary syndromes such as myocardial infarction and angina. Inhibitors of aggregation can provide protection against these diseases and lower vascular disease mortality and stroke incidence in patients with unstable ischemic heart disease [74a,b].



**Fig. 13:** Active compounds isolated from *Piper lolot*

In the same year Liao *et al.* reported [75] the isolation of cinnamoyl amide derivatives from another piper-species; *Piper taiwanense*. Among them, 1-(3-methoxycinnamoyl)pyrrolidine (**100**; Fig. 14), a regioisomer of **90**, showed moderate inhibitory activity ( $IC_{50} = 17.4 \mu M$ ) of platelet aggregation induced by collagen.



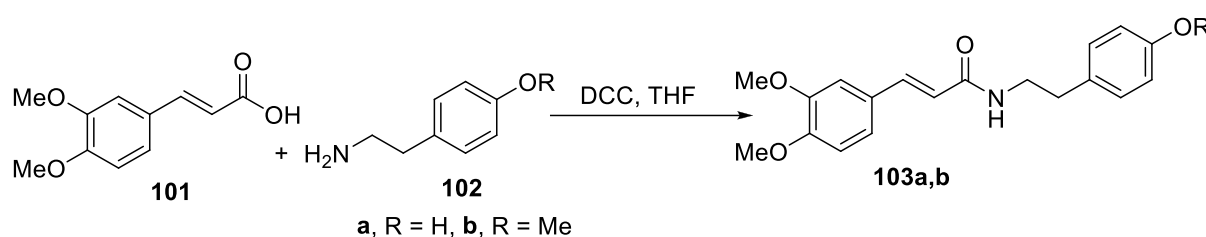
**Fig. 14:** 1-(3-Methoxycinnamoyl)pyrrolidine

### 4.3. Synthetic compounds

#### 4.3.1. Cinnamic amide derivatives

*N-p*-Coumaroyltyramine [76a,b] and *N-trans*-feruloyltyramine derivatives in *Allium bakeri* Reg. (*Lilliaceae*) were shown to be potent inhibitors against ADP-induced platelet aggregation [77]. Recently, PAF and its antagonists were extensively studied since PAF is known to play various pathophysiological roles including platelet aggregation, inflammation, asthma, endotoxic shock and hypotension [78a,b]. Based upon above background, Woo *et al.*

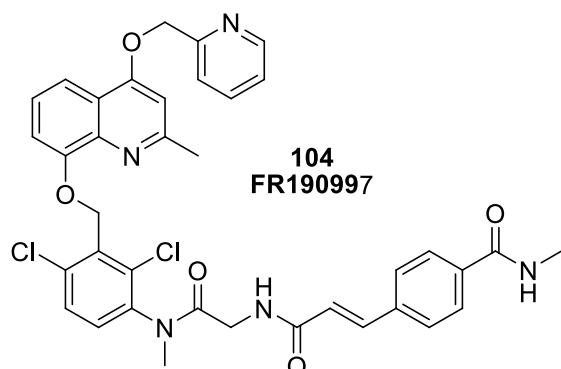
[79] synthesized (**Scheme 15**) some cinnamoyl-tyramine amide derivatives (**103a,b**) by DCC-coupling of substituted cinnamic acid (**101**) with tyramine or tyramine methyl-*l*-ether (**102a,b**) to evaluate PAF-receptor binding antagonistic activities and inhibitory activities on PAF-induced platelet aggregation with interest on structure-activity relations. The results show that both **103a** and **103b** have significant PAF-receptor binding antagonistic activity and platelet antiaggregatory activities.



**Scheme 15:** Synthesis of cinnamoyltyramine derivatives

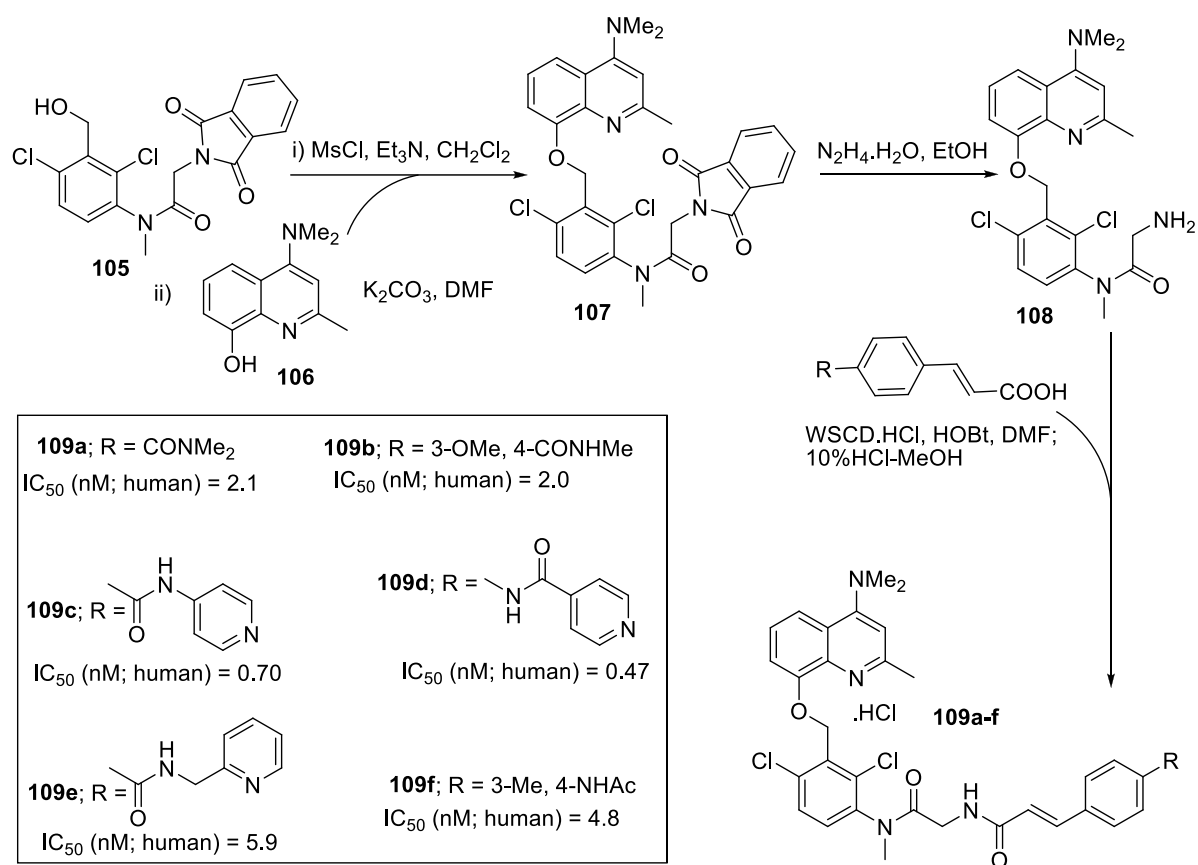
Kinins, members of a family of peptides released from kininogens by the action of kallikreins, have been implicated in a variety of biological activities including vasodilation, increased vascular permeability, contraction of smooth muscle cells and activation of sensory neurons. However, investigation of the physiological actions of kinins has been greatly hampered because its effects are curtailed by rapid proteolytic degradation. Aramori *et al.* [80] examined the pharmacological characteristics of the first nonpeptide bradykinin receptor agonist 8-[2,6-dichloro-3-[*N*-[(*E*)-4-(*N*-methylcarbamoyl)cinnamidoacetyl]-*N*-methylamino]benzyloxy]-2-methyl-4-(2-pyridylmethoxy)quinoline (**104**; FR190997; **Fig. 15**). Compound **104**, whose structure is quite different from the natural peptide ligand, potently and selectively interacts with the human B<sub>2</sub> receptor and markedly stimulates inositol phosphate formation in transfected Chinese hamster ovary (CHO) cells. Compound **104** induces concentration-dependent contraction of isolated guinea pig ileum. *In vivo*, compound **104** mimics the biological action of bradykinin and induces hypotensive responses in rats with prolonged duration, presumably as a consequence of its resistance to proteolytic degradation. Therefore,

**104** is a highly potent and subtype-selective nonpeptide agonist which displays high intrinsic activity at the bradykinin B<sub>2</sub> receptor.



**Fig. 15:** Structure of FR190997

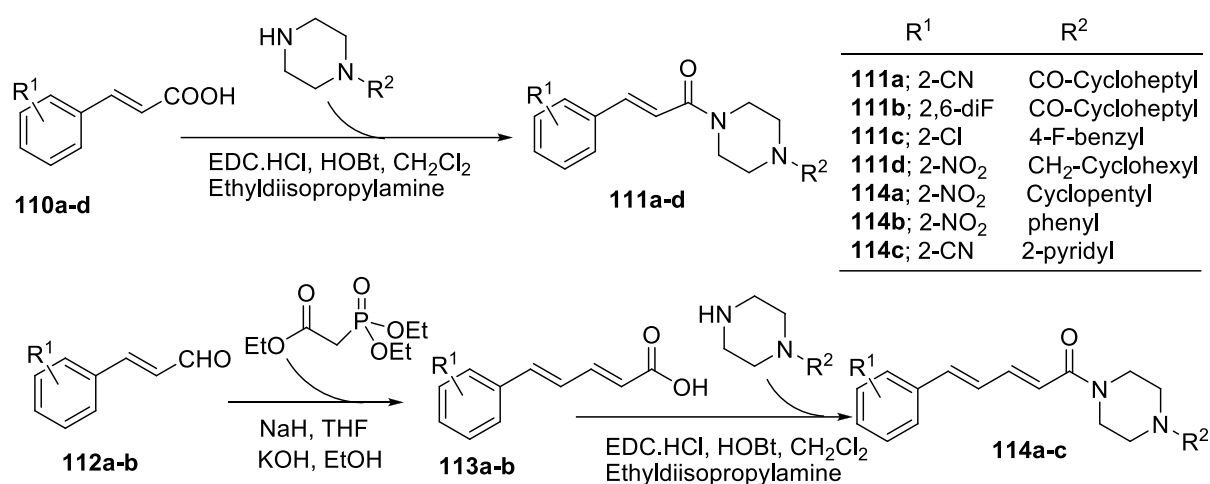
Recently, Kayahiri *et al.* reported [81] the synthesis and biological evaluation of a series of cinnamoyl derivatives (**109a-f**; **Scheme 16**) as nonpeptide bradykinin B<sub>2</sub> receptor ligands. These molecules are mainly analogues of **104**. Compound **105** was treated with methanesulfonyl chloride followed by the substitution reaction with 4-(dimethylamino)-2-methyl-8-quinolinol (**106**) to afford **107**. Removal of the *N*-phthaloyl group of **107** with hydrazine monohydrate and coupling with the (*E*)-4-(substituted)cinnamic acids using coupling reagent afforded the corresponding cinnamides (**109a-f**). Importantly, some of these compounds exhibited subnanomolar and nanomolar binding affinities for human and guinea pig B<sub>2</sub> receptors respectively, and significantly inhibited bradykinin induced bronchoconstriction in guinea pigs at a dose of 10 µg/Kg by intravenous administration.



### Scheme 16: Synthesis of cinnamoyl-quinoline derivatives and their biological activities

Protease activated receptors (PARs) or thrombin receptors constitute a class of G-protein coupled receptors (GPCRs) implicated in the activation of many physiological mechanisms. Thus, thrombin activates many cell types such as vascular smooth muscle cells, leukocytes, endothelial cells, and platelets *via* activation of these receptors. In humans, thrombin-induced platelet aggregation is mediated by one subtype of these receptors, termed PAR1. Perez *et al.* [82] reported the discovery of new antagonists of these receptors and more specifically two compounds: 2-[5-oxo-5-(4-pyridin-2-yl)piperazin-1-yl]penta-1,3-dienylbenzotrile (**114c**; F 16618) and 3-(2-chlorophenyl)-1-[4-(4-fluorobenzyl)piperazin-1-yl]propenone (**111c**; F 16357), obtained after optimization (**Scheme 17**). These cinnamoyl derivatives are able to inhibit SFLLR-induced human platelet aggregation and display antithrombotic activity in an arteriovenous shunt model in the rat after intravenous or oral administration. Notably, these compounds are devoid of bleeding side effects. Suitable piperazine derivatives were coupled

with substituted cinnamic acids (**110a-d**) in the presence of EDC.HCl, HOBt and ethyldiisopropylamine in dichloromethane to afford the cinnamides (**111a-d**; **Scheme 18**). Homologation of cinnamic-system was carried out by the treatment of ethyl diethylphosphonoacetate and NaH in THF to the corresponding cinnamaldehydes (**112a,b**) followed by saponification to obtain corresponding acids (**113a,b**). The acids were then coupled with piperazines to afford the target compounds (**114a-c**).

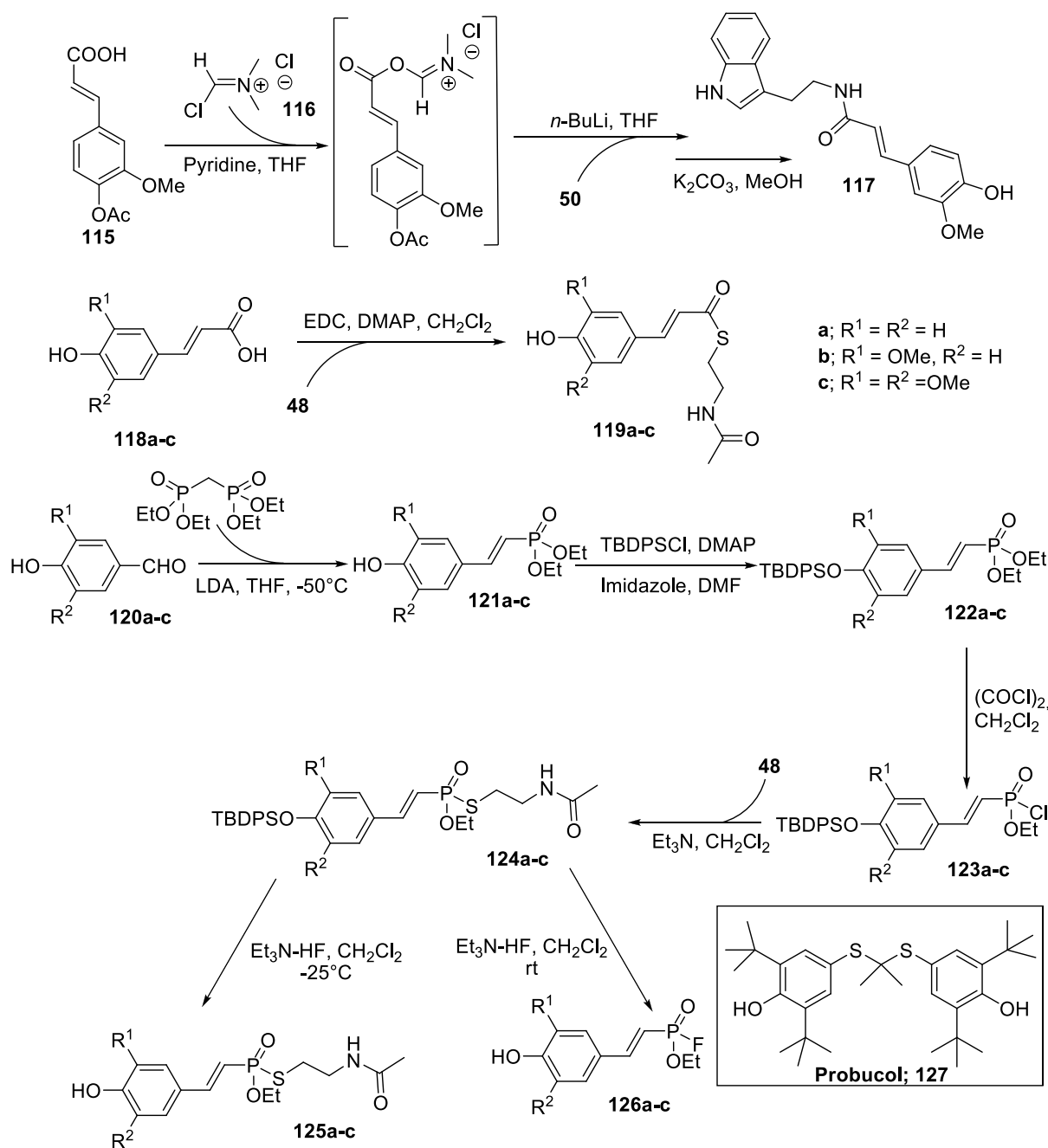


**Scheme 17:** Synthesis of cinnamic derivatives with antithrombotic activity

#### 4.3.2. Cinnamic thioester, amide and phosphono derivatives

A series of cinnamic and phosphonocinnamic derivatives have been synthesized (**Scheme 18**) and their ability to inhibit cell-mediated low density lipoprotein (LDL) oxidation and oxidized LDL (oxLDL)-induced cytotoxicity was investigated by our group [83a,b]. The involvement of oxidative modifications of LDL in the pathogenesis of atherosclerosis is clinically and experimentally evident [84]. A variety of lipid soluble antioxidants inhibit atherogenesis in the animal models of hypercholesterolemia [85] and a large number of antioxidants are phenolic compounds [86].





**Scheme 18:** Synthesis of cinnamic amide, thioester and phosphonate derivatives

Therefore, synthesis of coumaric acid derivatives, ferulic acid derivatives and sinapic acid derivatives were our obvious choice. The phenolic hydroxyl group of ferulic acid (**1d**) was protected by acetylation. The acetylated derivative (**115**) was then treated with *N,N*-dimethylchloroformaldiminium chloride (**116**) to activate the acid functionality followed by lithiated amine to afford the corresponding 2-(3-indolyl)ethylamide derivative (**Scheme 18**).

The product thus obtained was subsequently deprotected by saponification to obtain the feruloyl amide (**117**). With a view that thioester derivatives are a masked form of thiol group, a well-known scavenger of oxygen radical, we planned to test some *N*-acetylcysteamine derivatives (**119a-c**) of *p*-coumaric acid, ferulic acid and related cinnamic acids for their antioxidant efficacy. However, the cinnamic-phosphonates (**121a-c**), bioisosteric varieties of cinnamic acid derivatives, were prepared by reacting suitable aldehydes (**120a-c**) with tetraethylmethylenediphosphonate in the presence of LDA. These compounds (**121a-c**) were then chlorinated in order to incorporate the *N*-acetylcysteamine residue to afford compounds **124a-c**. But the protection of free phenolic functionality with silyl-group before chlorination became necessary due to messy reactions with oxalyl chloride, the chlorinating agent. The silyl-protection was then removed using the usual reagents at -25 °C to afford the cinnamic-phosphonothioesters (**125a-c**). However, the same deprotection procedure at room temperature afforded the corresponding fluorinated derivatives (**126a-c**). Among the synthesized compounds, the amide (**117**), thioester (**119c**), phosphonothioester (**125c**) and the fluorophosphonocinnamic acid analogue (**126c**) exhibited potent inhibitory effects against LDL-oxidation and subsequent toxicities mediated by cultured human microvascular endothelial cells (HMEC-1), with efficacies comparable to that observed with probucol (**127**), a known anti hyperlipidemic drug [87]. Synthesized antioxidants could either share both radical scavenger and metal chelator activities, or show antioxidant activity only as metal chelator since LDL-oxidation in HMEC-1 was done in the presence of copper (1 μM). However, electron donating substituents surrounding the 4-hydroxy group of the aromatic ring of these cinnamic derivatives seemed to play crucial role towards the observed antiatherogenic activity.

## 5. CONCLUSION AND PERSPECTIVES

Cinnamic acids are abundant in various natural resources. Cinnamic acid and its natural and synthetic analogues are unique as drug candidates in tuberculosis, malaria and cardiovascular diseases. Natural substances such as ethyl- (**4**) and benzyl- (**6**) cinnamates not only have anti-TB activities, they are traditional medicines for hypertension as well. With  $\alpha,\beta$ -unsaturated carboxyl functionality, cinnamic acids 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, at-least during cell wall biosynthesis, the presence of the cinnamoyl moiety certainly increased the antituberculosis efficacy in several occasions. For example, cinnamoyl-rifamycine (**8a**) has better *in vitro* anti-TB activity than rifamycine (**8**) itself and leptophyllin A (**11**) has better activity than its non-cinnamoylated analogue leptophyllin B (**12**). Similarly, the fact that naturally occurring cinnamoyl-hosloppone (**56c**) is a better antimalarial agent than hosloppone (**56a**) and its benzoyl-analogue (**56b**) reflects the importance of  $\alpha,\beta$ -unsaturated carboxyl functionality. 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, a frontline anti-TB drug, 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  $\alpha,\beta$ -unsaturation but also on the functionalization of the carboxyl part of the cinnamoyl derivatives. Similarly, the introduction of 4-propyloxycinnamoyl residue to the *N*-(4-amino-2-benzoylphenyl)-(4-methylphenyl)acetamide (**77**) resulted in a 10-fold enhancement of anti malarial activity compared to its phenethyl analogue (**76**). Notably, substituents at the benzene ring of the cinnamic acids also play a crucial role in the biological activities. While hydroxyl substitution in cinnamic acids and related derivatives confers antioxidative properties thereby making them useful in chronic illness such as inflammatory and heart diseases and hypertension, methoxy, isoprenyloxy and isoprenyl substituents also seem to

play useful roles in tuberculosis, malaria and cardiovascular diseases. For example, **33h**, **7b**, and **37** are methoxyphenyl derivatives and they all have significant anti TB activities. Syncarpamide (**64**) and its analogues, ferulic acid dimers (**86a**, **87a**) and 8-aminoquinoline derivatives such as **80b,c,d** have significant anti malarial activities and piperlotin-analogues (**90-92**, **100**) and tyramine derivative **103a,b** are important anti-platelet aggregation agents. Drupanin (**89a**) and its natural analogues (**89b-e**), with isoprenyl substitution on the aromatic ring, showed significant xanthine oxidase inhibitory effect and isoprenyloxy cinnamoyl-triazolophthalazine derivative (**54e**) showed extremely potent anti-TB activity when tested against INH-resistant strains. In summary, cinnamic acid derivatives are potent anti-TB agents, active against *P. falciparum* even in nanomolar concentration range and they showed antioxidant properties as well as antiplatelet aggregation activities. In spite of all these multi-activities of cinnamic acid derivatives their mode of action and understanding of molecular mechanisms remains unclear. We express hope to learn more about this versatile molecule and its derivatives in addition to the synthesis of new useful biologically important compounds in near future.

#### **ACKNOWLEDGEMENTS**

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.

#### **REFERENCES**

- [1] Hoskins, J.A. The occurrence, metabolism and toxicity of cinnamic acid and related compounds. *J. Appl. Toxicol.*, **1984**, *4*, 283-292.
- [2] Thimann, K.V. The auxins. In: Son, M.B. (ed.) *Physiology of plant growth and development*, **1969**, McGraw-Hill, London, pp 2-45.

- [3] Epifano, F.; Curini, M.; Genovese, S.; Blaskovich, M.; Hamilton, A.; Sebti, S.M. Prenyloxyphenylpropanoids as novel lead compounds for the selective inhibition of geranylgeranyl transferase I. *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 2639-2642.
- [4] (a) Boerjan, W.; Ralph, J.; Baucher, M. Lignin biosynthesis, *Annu. Rev. Plant Biol.*, **2003**, *54*, 519-546. (b) Humphreys, J.M.; Chapple, C.; Rewriting the lignin roadmap, *Curr. Opin. Plant Biol.*, **2002**, *5*, 224-229.
- [5] (a) Wardrop, A.B.; In: Sarkanen, K.V.; and Ludwig, C.H. (Eds), Lignins: occurrence, formation, structure and reactions. Wiley- Interscience, New-York, **1971**, pp. 43-94. (b) Whetten, R.W.; Mackay, J.J.; Sederoff, R.R. Recent Advances in Understanding Lignin Biosynthesis, *Ann. Rev. Plant Physiol Plant Mol. Biol.*, **1998**, *49*, 585-609.
- [6] Freudenberg, K. Biosynthesis and Constitution of Lignin. *Nature*, **1959**, *183*, 1152-1155.
- [7] (a) Kroon, P.A.; Williamson, G. Hydroxycinnamates in plants and food, *J. Sci. Food. Agri.*, **1999**, *79*, 355-361. (b) Prager, R.H.; Thregold, H.M. Some neutral constituents of *Acronychia baueri*. *Aust. J. Chem.*, **1966**, *19*, 451-454.
- [8] (a) Ahn, B.Z.; Sok, D.E. Michael Acceptors as a Tool for Anticancer Drug Design, *Curr. Pharm. Design*, **1996**, *2*, 247-262. (b) Zou, H.B.; Dong, S.Y.; Zhou, C.X.; Hu, L.H.; Wu, Y.H.; Li, H.B.; Gong, J.X.; Sun, L.L.; Wu, X.M.; Bai, H.; Fan, B.T.; Hao, X.J.; Stöckigt, J.; Zhao, Y. Design, synthesis, and SAR analysis of cytotoxic sinapyl alcohol derivatives. *Bioorg. Med. Chem.*, **2006**, *14*, 2060-2071.
- [9] Chung, H.S.; Shin, J.C. Characterization of antioxidant alkaloids and phenolic acids from anthocyanin-pigmented rice (*Oryza sativa* cv Heugjinjubyeo). *Food Chem.*, **2007**, *104*, 1670-1677.
- [10] (a) Bezerra, D.P.; Castro, F.O.; Alves, A.P.N.N.; Pessoa, C.; Moraes, M. O.; Silveira, E. R.; Lima, M.A.S.; Elmiro, F.J.M.; Costa-Lotufo, L.V. *In vivo* growth-inhibition of Sarcoma 180 by piplartine and piperine, two alkaloid amides from Piper *Braz. J. Med. Biol. Res.*, **2006**,

39, 801-807. (b) De, P.; Baltas, M.; Bedos-Belval, F. Cinnamic acid derivatives as anticancer agents-A Review. *Curr. Med. Chem.*, **2011**, In Press.

[11] (a) Naz, S.; Ahmed, S.; Rasool, S.A.; Sayeed, S.A.; Siddiqi, R. Antibacterial activity directed isolation of compounds from *Onosma hispidum*. *Microb. Res.*, **2006**, *161*, 43-48. (b) Carvalho, S.A.; da Silva, E.F.; de Souza, M.V.N.; Lourenço, M.C.S.; Vicente, F.R. Synthesis and antimycobacterial evaluation of new *trans*-cinnamic acid hydrazide derivatives. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 538-541.

[12] Nunn, P.; Williams, B.; Floyed, K.; Dye, C.; Elzinga, G.; Raviglione, M. Tuberculosis control in the era of HIV. *Nat. Rev. Immunol.*, **2005**, *5*, 819-826.

[13] (a) Bloch, A.B.; Cauthen, G.M.; Onorato, I.M.; Kenneth, G.; Dandbury, G.; Kelly, G.D.; Driver, C.R.; Snider, D.E. Nationwide Survey of Drug-Resistant Tuberculosis in the United States. *J. Am. Med. Asso.*, **1994**, *271*, 665-671. (b) Rastogi, N.; Kochi, A.; Vareldzis, B.; Styblo, K.; Crawford, J.T.; Jarvis, W.R.; McGowan, J.E. Jr.; Perrone, C.; David, H.L.; Zhang, Y.; Cohn, D.L.; Iseman, M.D. Multidrug-resistant tuberculosis and its control. *Res. Microbiol.*, **1993**, *144*, 103-158. (c) Rastogi, N.; Ross, B.C.; Dwyer, B.; Goh, K.S.; Clavel-Sérès, S.; Jeantils, V.; Cruaud, P. Emergence during unsuccessful chemotherapy of multiple drug resistance in a strain of *Mycobacterium tuberculosis*. *Eur. J. Clin. Microbiol. Infect. Dis.*, **1993**, *11*, 901-907.

[14] Warbasse, J.P. Cinnamic acid in the treatment of tuberculosis. *Annals of Surgery*, **1894**, *19*, 102-111.

[15] (a) Jacobson, M. J. Ethyl cinnamate in experimental tuberculosis. *Bull. mem. sac. med. hopitaux de Paris* (1919), *35*, 322-325. (b) Corper, H. J.; Gauss, H.; Gekler, W. A. Studies on the inhibitory action of sodium cinnamate in tuberculosis. *Colo. Am. Rev. Tuberc.*, **1920**, *4*, 464-473. (c) Bainsborough, H. Benzyl cinnamic ester in tuberculosis. The method of Jacobsen. *Lancet*, **1928**, *I*, 908-909.

- [16] Rastogi, N., Goh, K.S., Wright, E.L. and Barrow, W.W. Potential drug targets for *Mycobacterium avium* defined by using radiometric drug-inhibitor combination techniques. *Antimicrob. Agents Chemother.*, **1994**, 38, 2287-2295.
- [17] Rastogi, N.; Goh, K.S.; Horgen, L.; Barrow, W.W. Synergistic activities of antituberculous drugs with cerulenin and trans-cinnamic acid against *Mycobacterium tuberculosis*. *FEMS Immunol. Med. Microbiol.*, **1998**, 21, 149-157.
- [18] Ryan, F. The Forgotten Plague. Little, Brown and Company, Boston, MA, **1992**.
- [19] Barnes, C.C.; Smalley, M.K.; Manfredi, K.P.; Kindscher, K.; Loring, H.; Sheele, D.M. Characterization of an Anti-tuberculosis Resin Glycoside from the Prairie Medicinal Plant *Ipomoea leptophylla*. *J. Nat. Prod.*, **2003**, 66, 1457-1462.
- [20] Lekphrom, R.; Kanokmedhakul, S.; Kanokmedhakul, K. Bioactive styryllactones and alkaloid from flowers of *Goniothalamus laoticus*. *J. Ethnopharmacol.*, **2009**, 125, 47-50.
- [21] Guo, H.; Naser, S.A.; Ghobrial, G.; Phanstiel, O. Synthesis and Biological Evaluation of New Citrate-Based Siderophores as Potential Probes for the Mechanism of Iron Uptake in Mycobacteria. *J. Med. Chem.*, **2002**, 45, 2056-2063.
- [22] Xu, Y.; Miller, M.J. Total Syntheses of Mycobactin Analogues as Potent Antimycobacterial Agents Using a Minimal Protecting Group Strategy. *J. Org. Chem.*, **1998**, 63, 4314-4322.
- [23] Roosenberg, J.M., II; Lin, Y.-M.; Lu, Y.; Miller, M.J. Studies and Syntheses of Siderophores, Microbial Iron Chelators, and Analogues as Potential Drug Delivery Agents. *Curr. Med. Chem.*, **2000**, 7, 159-197.
- [24] Biava, M.; Fioravanti, R.; Porretta, G.C.; Sleiter, G.; Ettorres, A.; Deidda, D.; Lampis, G.; Pompei, R. New Toluidine Derivatives Antimycobacterial and Antifungal Activities. *Med. Chem. Res.*, **1997**, 7, 228-250.

- [25] Kumar, G.V. S.; Rajendraprasad, Y.; Mallikarjuna, B.P.; Chandrashekar, S.M.; Kistayya, C. Synthesis of Some Novel 2-Substituted-5-[Isopropylthiazole] Clubbed 1,2,4-Triazole and 1,3,4-Oxadiazoles as Potential Antimicrobial and Antitubercular Agents. *Eur. J. Med. Chem.*, **2010**, *45*, 2063-2074.
- [26] Joshi, D.G.; Oza, H.B.; Parekh, H.H. Synthesis of Some Novel 1,3,4-Oxadiazoles and 5-Oxoimidazolines as Potent Biologically Active Agents. *Heterocycl. Commun.*, **1997**, *3*, 170-174.
- [27] Cantrell, C.L.; Franzblau, S.G.; Fischer, N.H. Antimycobacterial plant terpenoids. *Planta Med.*, **2001**, *67*, 685-694.
- [28] Copp, B.R.; Pearce, A.N. Natural product growth inhibitors of *Mycobacterium tuberculosis*. *Nat. Prod. Rep.*, **2007**, *24*, 278-297.
- [29] Okunade, A.L.; Elvin-Lewis, M.P.F.; Lewis, W.H. Natural Antimycobacterial Metabolites: Current Status. *Phytochemistry*, **2004**, *65*, 1017-1032.
- [30] Tanachatchairatana, T.; Bremner, J.B.; Chokchaisiri, R.; Suksamrarn, A. Antimycobacterial Activity of Cinnamate-Based Esters of the Triterpenes Betulinic, Oleanolic and Ursolic Acids. *Chem. Pharm. Bull.*, **2008**, *56*, 194-198.
- [31] Reddy, V.M.; Nadadhur, G.; Daneluzzi, D.; Dimova, V.; Gangadharam, P. Antimycobacterial Activity of New Rifamycin Derivative, 3-(4-Cinnamylpiperazinyl Iminomethyl)Rifamycin SV (T9). *Antimicrob. Agents Chemother.*, **1995**, *39*, 2320-2324.
- [32] 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. *Recent Patents on Anti-Infective Drug Discovery*, **2010**, *5*, 76-90.
- [33] Bairwa, R.; Kakwani, M.; Tawari, N.R.; Lalchandani, J.; Ray, M.K.; Rajan, M. G. R.; Degani, M.S. Novel Molecular Hybrids of Cinnamic Acids and Guanylylhydrazones as Potential Antitubercular Agents. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 1623-1625.



- [34] Gadad, A.K.; Mahajanshetti, C.S.; Nimbalkar, S.; Raichurkar, A. Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives. *Eur. J. Med. Chem.*, **2000**, *35*, 853-857.
- [35] Khownum, K.; Wood, S.J.; Miller, K.A.; Balakrishna, R.; Nguyen, T.B.; Kimbrell, M. R.; Georg, G.I.; David, S.A. Novel endotoxin-sequestering compounds with terephthalaldehyde-bis-guanylhydrazone scaffolds. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1305-1308.
- [36] Wu, W.; Sil, D.; Szostak, M.L.; Malladi, S.S.; Warshakoon, H.J.; Kimbrell, M.R.; Cromer, J.R.; David, S.A. Structure-activity relationships of lipopolysaccharide sequestration in guanylhydrazone-bearing lipopolyamines. *Bioorg. Med. Chem.*, **2009**, *17*, 709-715.
- [37] Zhang, Y.; Broser, M.; Rom, W. N. Activation of the interleukin 6 gene by Mycobacterium tuberculosis or lipopolysaccharide is mediated by nuclear factors NF-IL6 and NF-kappa B. *Proc. Natl. Acad. Sci.*, **1994**, *91*, 2225-2229.
- [38] Scherman, M.; Weston, A.; Duncan, K.; Whittington, A.; Upton, R.; Deng, L.; Comber, R.; Friedrich, J.D.; Neil, M.R. Biosynthetic origin of mycobacterial cell wall arabinosyl residues. *J. Bacteriol.*, **1995**, *177*, 7125-7130.
- [39] Heijenoort, J.V. Formation of the glycan chains in the synthesis of bacterial peptidoglycan. *Glycobiology*, **2001**, *11*, 25R-36R.
- [40] Shingalapur, R.V.; Hosamani, K.M.; Keri, R.S. Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles. *Eur. J. Med. Chem.*, **2009**, *44*, 4244-4248.
- [41] Orjales, A.; Mosquera, R.; Labeaga, L.; Rodes, R. New 2-Piperazinylbenzimidazole Derivatives as 5-HT<sub>3</sub> Antagonists. Synthesis and Pharmacological Evaluation. *J. Med. Chem.*, **1997**, *40*, 586-593.

- [42] Grimmett, M.R. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds.; Pergamon Press, Oxford, **1996**; vol. 3, pp. 77-220.
- [43] Khalafi-Nezhad, A.; Rad, M.N.S.; Mohbatkar, H.; Asrari, Z.; Hemmateenejad, B. Design, synthesis, antibacterial and QSAR studies of benzimidazole and imidazole chloroaryloxyalkyl derivatives. *Bioorg. Med. Chem.*, **2005**, *13*, 1931-1938.
- [44] Evans, B.E.; Rittle, K.E.; DiPardo, R.M.; Freidinger, R.M.; Whitter, W.L.; Lundell, G.F.; Veber, D.F.; Anderson, P.S. Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists. *J. Med. Chem.*, **1998**, *31*, 2235-2246.
- [45] (a) Koumba Yoya, G., Bedos-Belval, F.; Constant, P.; Duran, H.; Daffé, M.; Baltas. M. Synthesis and Evaluation of a Novel Series of Pseudo-Cinnamic Derivatives as Antituberculosis Agents. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 341-343. (b) De, P.; Yoya, G.K.; Constant, P.; Bedos-Belval, F.; Duran, H.; Saffon, N. Daffé, M.; Baltas M. Design, synthesis and biological evaluation of new cinnamic derivatives as antituberculosis Agents. *J. Med. Chem.*, **2011**, In Press.
- [46] Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.*, **1997**, *23*, 3-25.
- [47] (a) Schroeder, H.A. Circulation: The effect of 1-hydrazinophthalazine in hypertension. *J. Am. Heart Asso.*, **1952**, *5*, 28-37. (b) Silas, J.H.; Ramsay, L.E.; Freestone, S. Hydralazine once daily in hypertension. *Br. Med. J.*, **1982**, *284*, 1602-1604.
- [48] (a) Chew, E.-H.; Nagle, A.A.; Zhang, Y.; Scarmagnani, S.; Palaniappan, P.; Bradshaw, T.D.; Holmgren, A.; Westwell, A.D. Cinnamaldehydes inhibit thioredoxin reductase and induce Nrf2: potential candidates for cancer therapy and chemoprevention. *Free Radic. Biol. Med.*, **2010**, *48*, 98-111. (b) Ma, Q.; Zhao, X.; Eddin, A.N.; Geerlof, A.; Li, X.; Cronan, J.E.;

Kaufmann, S.H.E.; Wilmanns, M. The Mycobacterium tuberculosis LipB enzyme functions as a cysteine/lysine dyad acyltransferase. *Proc. Nat. Acad. Sci.*, **2006**, *103*(23), 8662-8667.

[49] Walsh, J.A. Disease Problems in the World. *Ann. N.Y. Acad. Sci.*, **1989**, *569*, 1-16.

[50] (a) Torok, D.S.; Ziffer, H. Synthesis and Antimalarial Activities of N-Substituted 11-Azaartemisinins. *J. Med. Chem.*, **1995**, *38*, 5045-5050. (b) Fidock, D.A. Priming the antimalarial pipeline. *Nature*, **2010**, *465*, 297-298.

[51] (a) Posner, G.H.; O'Dowd, H.; Ploypradith, P.; Cumming, J.N.; Xie, S.; Shapiro, T.A. Antimalarial Cyclic Peroxy Ketals. *J. Med. Chem.*, **1998**, *41*, 2164-2167. (b) Gamo, F.-J.; Sanz, L.M.; Vidal, J.; de Cozar, C.; Alvarez, E.; Lavandera, J.-L.; Vanderwall, D.E.; Green, D.V.S.; Kumar, V.; Hasan, S.; Brown, J.R.; Peishoff, C.E.; Cardon, L.R.; Garcia-Bustos, J.F. thousands of chemical starting points for antimalarial lead identification. *Nature*, **2010**, *465*, 305-312. (c) Guiguemde, W.A.; Shelat, A.A.; Bouck, D.; Duffy, S.; Crowther, G.J.; Davis, P.H.; Smithson, D.C.; Connelly, M.; Clark, J.; Zhu, F.; Jiménez-Díaz, M.B.; Martinez, M.S.; Wilson, E.B.; Tripathi, A.K.; Gut, J.; Sharlow, E.R.; Bathurst, I.; Mazouni, F.E.; Fowble, J.W.; Forquer, I.; McGinley, P.L.; Castro, S.; Angulo-Barturen, I.; Ferrer, S.; Rosenthal, P.J.; DeRisi, J.L.; Sullivan Jr, D.J.; Lazo, J.S.; Roos, D.S.; Riscoe, M.K.; Phillips, M.A.; Rathod, P.K.; Voorhis, W.C.V.; Avery, V.M. Guy, R. K. Chemical genetics of *Plasmodium falciparum*. *Nature*, **2010**, *465*, 311-315.

[52] Achenbach, H.; R.; Nkunya, M.H.H.; Weenen, H. Antimalarial Compounds from *Hoslundia opposita*. *Phytochem.*, **1992**, *31*, 3781-3784.

[53] Krafta, C.; Jenett-Siems, K.; Siems, K.; Solisc, P.N.; Guptac, M.P.; Bienzled, U.; Eicha E. Andinermals A–C, antiplasmodial constituents from *Andira inermis*. *Phytochem.*, **2001**, *58*, 769–774.

- [54] Ovenden, S.P.B.; Cobbe, M.; Kissell, R.; Birrell, G.W.; Chavchich, M.; Edstein, M.D. Phenolic Glycosides with Antimalarial Activity from *GreWillea* "Poorinda Queen". *J. Nat. Prod.*, **2010**, doi : 10.1021/np100737q.
- [55] Ross, S.A.; Al-Azeib, M.A.; Krishnaveni, K.S.; Fronczek, F.R.; Burandt, C.L. Alkamides from the Leaves of *Zanthoxylum syncarpum*. *J. Nat. Prod.*, **2005**, *68*, 1297-1299.
- [56] Kanaani, J.; Ginsburg, H. Effects of Cinnamic Acid Derivatives on In Vitro Growth of *Plasmodium falciparum* and on the Permeability of the Membrane of Malaria-Infected Erythrocytes. *Antimicrob. Agents and Chemother.*, **1992**, *36*, 1102-1108.
- [57] Hemin, T.R.; Pauvlik, J.M.; Schuber, E.V.; Geiszler, A. Antimalarials. Synthesis and Antimalarial Activity of 1-(4-Methoxycinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine and Derivatives. *J. Med. Chem.*, **1975**, *18*, 1216-1223.
- [58] Wiesner, J.; Mitsch, A.; Wiüner, P.; Jomaaa, H.; Schlitzer, M. Structure-Activity Relationships of Novel Anti-Malarial Agents. Part 2: Cinnamic Acid Derivatives. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 423-424.
- [59] Wiesner, J.; Kettler, K.; Jomaaa, H.; Schlitzer, M. Structure-Activity Relationships of Novel Anti-Malarial Agents. Part 3: N-(4-Acylamino-3-benzoylphenyl)-4-propoxycinnamic Acid Amides. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 543-545.
- [60] Schlitzer, M.; Böhm, M.; Dahse, H.-M.; Sattler, I. Design, Synthesis and Early Structure-Activity Relationship of Farnesyltransferase Inhibitors which Mimic both the Peptidic and the Prenylic Substrate. *Bioorg. Med. Chem.* **2000**, *8*, 1991-2006.
- [61] Xie, A.; Sivaprakasama, P.; Doerksen, R.J. 3D-QSAR Analysis of Antimalarial Farnesyltransferase Inhibitors Based on a 2,5-Diaminobenzophenone Scaffold. *Bioorg. Med. Chem.*, **2006**, *14*, 7311-7323.

[62] Wheatley, N.C.; Andrews, K.T.; Tran, T.L.; Lucke, A.J.; Reid, R.C.; Fairlie, D.P. Antimalarial histone deacetylase inhibitors containing cinnamate or NSAID components. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 7080-7084.

[63] Rakotondramanana, D.L.A.; Delomenède, M.; Baltas, M.; Duran, H.; Bedos-Belval, F.; Rasoanaivo, P.; Negre-Salvayre, A.; Gornitzka, H. Synthesis of Ferulic Ester Dimers, Functionalisation and Biological Evaluation as Potential Antiatherogenic and Antiplasmodial Agents. *Bioorg. Med. Chem.*, **2007**, *15*, 6018-6026.

[64] Maton, A. *Human Biology and Health*. Englewood Cliffs, New Jersey: Prentice Hall 1993.

[65] (a) Rainwater, D.L.; McMahan, C.A.; Malcom, G.T.; Scheer, W.D.; Roheim, P.S.; McGill, H.C.; Strong, J.P. Lipid and apolipoprotein predictors of atherosclerosis in youth: apolipoprotein concentrations do not materially improve prediction of arterial lesions in PDAY subjects. *Arterioscler. Thromb. Vasc. Biol.*, **1999**, *19*, 753-761. (b) McGill, H.C.; McMahan, C.A.; Zieske, A.W.; Sloop, G.D.; Walcott, J.V.; Troxclair, D.A.; Malcom, G.T.; Tracy, R.E.; Oalman, M.C.; Strong, J.P. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. *Arterioscler. Thromb. Vasc. Biol.*, **2000**, *20*, 1998-2004.

[66] Teissedre, P.L.; Frankel, E.N.; Waterhouse, A.L.; Peleg, H.; German, J.B. Inhibition of in vitro human LDL oxidation by phenolic antioxidants from grapes and wines. *J-sci-food-agric.*, **1996**, *70*, 55-61.

[67] Esterbauer, H.; Puhl, H.; Dieber-Rotheneder, M.; Waeg, G. Rabl H. Effect of antioxidants on oxidative modification of LDL. *Annals of Medicine*, **1991**, *23*, 573-581.

[68] Oh, T.Y.; Lee, J.S.; Ahn, B.O.; Cho, H.; Kim, W.B.; Surch, Y.J.; Cho, S.W.; Hahm, K.B. Oxidative damages are critical in pathogenesis of reflux esophagitis implication of antioxidants in its treatment. *Free Radic. Biol. and Med.*, **2001**, *30*, 905-915.

[69] Gupta, M.P. (ed). 270 Plantas medicinales iberoamericanas. Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo y Convenio Andres Bello, **1995**, pp.73-84.

[70] Tapia, A.; Rodriguez, J.; Theoduloz, C.; Lopez, S.; Feresin, G.E.; Schmeda-Hirschmann, G. Free radical scavengers and antioxidants from *Baccharis grisebachii*. *J. Ethnopharmacol.*, **2004**, *95*, 155-161.

[71] Ohno, O.; Ye, M.; Koyama, T.; Yazawa, K.; Mura, E.; Matsumoto, H.; Ichino, T.; Yamada, K.; Nakamura, K.; Ohno, T.; Yamaguchi, K.; Ishida, J.; Fukamizu, A.; Uemura, D. Inhibitory effect of benzyl benzoate and its derivatives on angiotensin II-induced hypertension. *Bioorg. Med. Chem.*, **2008**, *16*, 7843-7852.

[72] Othman, R.; Ibrahim, H.; Mohd, M.A.; Mustafa, M.R.; Awang, K. Bioassay-guided isolation of a vasorelaxant active compound from *Kaempferia galanga* L. *Phytomedicine*, **2006**, *13*, 61-66.

[73] Li, C.-Y.; Tsai, W.-J.; Damu, A.G.; Lee, E.-J.; Wu, T.-S.; Dung, N.X.; Thang, T.D.; Thanh, L. Isolation and identification of antiplatelet aggregatory principles from the leaves of *Piper lolot*. *J. Agricultural and Food Chem.*, **2007**, *55*, 9436-9442.

[74] (a) Davies, M. J.; Thomas, M. B. Thrombosis and acute coronary lesions in sudden cardiac ischemic death. *N. Engl. J. Med.*, **1984**, *310*, 1137-1140. (b) Fuster, V. F.; Badimon, J. J.; Chesebro, J. H. Mechanisms of disease: the pathogenesis of coronary artery disease and the acute coronary syndromes. *N. Engl. J. Med.*, **1992**, *326*, 242-250.

[75] Chen, I.-S.; Chen, Y.-C.; Liao, C.-H. Amides with anti-platelet aggregation activity from *Piper taiwanense*. *Fitoterapia*, **2007**, *78*, 414-419.

[76] (a) Matano, Y.; Okuyama, T.; Shibata, S.; Hoson, M.; Kawada, T.; and Osada, H. Studies on coumarins of a Chinese drug "Quian-Hu" VII, Structures of new coumarin glycosides of Zi-Hua Quian-Hu and effect of coumarin glycosides on human platelet aggregation. *Planta Med.*, **1986**, *52*, 135-138. (b) Okuyama, T.; Kawasaki, C.; Shibata, S.; Hoson, M.; Kawada,

T.; Okuda, H.; Noguchi, T. Effect of oriental plant drugs on platelet aggregation II, Effect of Quian-Hu coumarins on human platelet aggregation. *Planta Med.*, **1986**, *52*, 132-134.

[77] Okuyama, T.; Shibata, S.; Hoson, M.; Kawada, T.; and Osada, H.; Noguchi, T. Effect of oriental plant drugs on platelet aggregation III, Effect of Chinesedrug "Xiebai" on human platelet aggregation. *Planta Med.*, 1986, *52*, 171-175.

[78] (a) Benveniste, J.; Henson, P. M.; Cochran, C. G. Leukocyte-dependent histamine release from rabbit platelets. The role of IgE, basophils and a platelet activating factor. *J. Exp. Med.*, 1972, *136*, 1356-1377. (b) Braquet, P.; Tongui, L.; Shen, T. Y.; Vargaftig, B.B. Perspectives in platelet-activating factor research. *Pharmacol Rev.*, **1987**, *39*, 97-145.

[79] Woo, N.T.; Jin, S.Y.; Cho, D.J.; Kim, N.S.; Bae, E.H.; Han, D.; Han, B.H.; Kang, Y.-H. Synthesis of substituted cinnamoyl-tyramine derivatives and their platelet anti-aggregatory activities. *Arch. Pharm. Res.*, **1997**, *20*, 80-84.

[80] Aramori, I.; Zenkoh, J.; Morikawa, N.; Asano, M.; Hatori, C.; Sawai, H.; Kayakiri, H.; Satoh, S.; Inoue, T.; Abe, Y.; Sawada, Y.; Mizutani, T.; Inamura, N.; Iwami, M.; Nakahara, K.; Kojo, H.; Oku, T.; Notsu, Y. Nonpeptide mimic of bradykinin with long-acting properties. *Immunopharmacology*, **1999**, *45*, 185-190.

[81] Swada, Y.; Kayakiri, H.; Abe, Y.; Mizutani, T.; Inamura, N.; Asano, M.; Aramori, I.; Hatori, C.; Oku, T.; Tanaka, H. A new class of nonpeptide bradykinin B<sub>2</sub> receptor ligand, incorporating a 4-aminoquinoline framework. Identification of a key pharmacophore to determine species difference and agonist/antagonist profile. *J. Med. Chem.*, **2004**, *47*, 2667-2677.

[82] Perez, M.; Lamothe, M.; Maraval, C.; Mirabel, E.; Loubat, C.; Planty, B.; Horn, C.; Michaux, J.; Marrot, S.; Metienne, R.; Pignier, C.; Bocquet, A.; Nadal-Wollbold, F.; Cussac, D.; de Vries, L.; Grand, B.L. Discovery of novel protease activated receptors 1 antagonists with potent antithrombotic activity in vivo. *J. Med. Chem.*, **2009**, *52*, 5826-5836.

[83] (a) Lapeyre, C.; Delmonède, M.; Bedos-Belval, F.; Duran, H.; Nègre-Salvayre, A.; Baltas, M. Design, synthesis and evaluation of pharmacological properties of cinnamic derivatives as anti atherogenic agents. *J. Med. Chem.*, **2005**, *48*, 8115-8124. (b) Baltas, M.; Bedos-Belval, F.; Duran, H.; Lapeyre, C.; Nègre-Salvayre, A.-E. Fluorophosphonocinnamic compounds, synthesis and uses for treating disorders caused by oxidative stress. Int. Pat. WO/2006/ 037869, April 2006.

[84] (a) Chisolm, G.M.; Steinberg, D. The Oxidative Modification Hypothesis of Atherogenesis: an Overview. *Free Radic. Biol. Med.*, **2000**, *28*, 1815-1826. (b) Heineke, J. W. Oxidants and Antioxidants in the Pathogenesis of Atherosclerosis: Implications for the Oxidized Low-Density Lipoprotein Hypothesis. *Atherosclerosis*, **1998**, *141*, 1-15. (c) Yokoyama, M. Oxidant Stress and Atherosclerosis. *Curr. Opin. Chem. Biol.*, **2004**, *4*, 110-115. (d) Harrison, D.; Griendling, K. K.; Landmesser, U.; Hornig, B.; Drexler, H. Role of Oxidative Stress in Atherosclerosis. *Am. J. Cardiol.*, **2003**, *91*, 7A-11A.

[85] (a) Berliner, J.A.; Heineke, J.W. The role of oxidized lipoproteins in atherogenesis. *Free Radic. Biol. Med.*, **1996**, *20*, 707-727. (b) Lynch, S.M.; Frei, B. Antioxidants as Anti-atherogens: Animal Studies. In *Natural antioxidants in human health and disease*; Frei, B., Eds.; Academic Press: Orlando, 1994. (c) Steinberg, D. Clinical Trials of Antioxidants in Atherosclerosis: are we Doing the Right Thing? *Lancet*, **1995**, *346*, 36-38. (d) Diaz, M.N.; Frei, B.; Vita, J.A.; Keaney, J.F. Antioxidants and Atherosclerotic Heart Disease. *New Eng. J. Med.*, **1997**, *337*, 408-416.

[86] Noguchi, N.; Niki, E. Phenolic Antioxidants: A Rationale for Design and Evaluation of Novel Antioxidant Drug for Atherosclerosis. *Free Radic. Biol. Med.*, **2000**, *28*, 1538-1546.

[87] Yamamoto, A. A unique hyperantilipidemic drug-Probucol. *J. Atheroscler. Thromb.*, **2008**, *15*, 304-305.



