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Review

Antituberculosis drugs: Ten years of research

Yves L. Janin*

URA 2128 CNRS-Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris Cedex 15, France

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Abstract—Tuberculosis is today amongst the worldwide health threats. As resistant strains of *Mycobacterium tuberculosis* have slowly emerged, treatment failure is too often a fact, especially in countries lacking the necessary health care organisation to provide the long and costly treatment adapted to patients. Because of lack of treatment or lack of adapted treatment, at least two million people will die of tuberculosis this year. Due to this concern, this infectious disease was the focus of renewed scientific interest in the last decade. Regimens were optimized and much was learnt on the mechanisms of action of the antituberculosis drugs used. Moreover, the quest for original drugs overcoming some of the problems of current regimens also became the focus of research programmes and many new series of *M. tuberculosis* growth inhibitors were reported. This review presents the drugs currently used in antituberculosis treatments and the most advanced compounds undergoing clinical trials. We then provide a description of their mechanism of action along with other series of inhibitors known to act on related biochemical targets. This is followed by other inhibitors of *M. tuberculosis* growth, including recently reported compounds devoid of a reported mechanism of action.

Contents

Keywords: Tuberculosis; *Mycobacterium tuberculosis*; Antimycobacterial; Antituberculosis.
* Tel.: +33 (0) 6 85 42 49 47; fax: +33 (0) 1 45 68 84 04; e-mail: yljanin@pasteur.fr

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1. Introduction

In conjunction with the spread of HIV infection,[1] tuberculosis is today amongst the worldwide health threats. As resistant strains of *Mycobacterium tuberculosis* have slowly emerged, treatment failure is too often a fact,[2] especially in countries lacking the necessary health care organisation to provide the long and costly treatment adapted to patients. Because of lack of treatment or lack of adapted treatment, at least two million people will die of tuberculosis this year. From the mid-1990s, this infectious disease was the focus of renewed scientific interest. In the last 10 years, the research on *M. tuberculosis*, the causative agent of tuberculosis, has undergone much progress. Regimens were optimized along with the implementation of the directly observed therapy short course (DOTS) initiative. At the laboratory level, the genome of *M. tuberculosis* was unravelled[3,4] and much work provided insights into the mechanisms of action of the antituberculosis drugs currently used. Renewed screenings for antimycobacterial substances were made leading to many original growth inhibitors.[5,6] Recently published work on the measurement of transcriptional responses[7] or a review[8] illustrates the number of classes of compounds with an effect on *M. tuberculosis*. Extensive listing of the natural products displaying antimycobacterial properties has been published recently.[9–13] Other works, reviewing the drug candidates and the possible biological targets, were also published.[14–21] We first present the drugs currently used in antituberculosis treatments and then the most advanced compounds undergoing clinical trials. We then provide a description of their mechanism of action along with other series of inhibitors known to act on related biochemical process. This is followed by other inhibitors of *M. tuberculosis* growth, including recently reported compounds devoid of a reported mechanism of action.

2. Current antituberculosis regimen and compounds under clinical trials

2.1. Antituberculosis drugs

As described recently,[22] the chemotherapy of tuberculosis has much evolved along the years since it started with the introduction of streptomycin (**1**) in 1946. By 1955, the combination of streptomycin (**1**), *p*-aminosalicylic acid (**2**) and isoniazid (**3**) was adopted as a standard treatment by the western world. The minutes of a congress held in 1968 illustrate quite well what the clinical research concerns were at that time[23] (Fig. 1).

It will never be emphasized enough that the full observance of the treatment is probably at least as important as the level of efficiency of the drugs administered for a proper cure. Even worse, the lack of treatment observance is likely to become the main cause of the occurrence and spread of multi drug resistant strains of *M. tuberculosis*.[24,25] Two regimens emerged from the many trials[22,24] and involve first a two-month long treatment with four drugs; either: streptomycin (**1**), isoniazid (**3**), rifampin (**4**) and pyrazinamide (**5**) or: isoniazid (**3**), rifampin (**4**), pyrazinamide (**5**) and ethambutol (**6**). This is then followed by four months of isoniazid (**3**) and rifampin (**4**). Side effects, especially hepatotoxicity, are an issue which in some cases forces an untimely treatment termination.[26] Patients following this regimen become non-infectious after the first few weeks but the remaining months are crucial to eradicate a slow growing fraction of the bacilli and also to allow time for the host immune system action to achieve a clinical cure (Fig. 2).

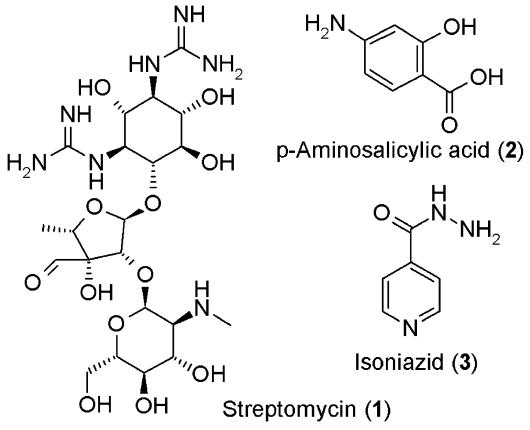
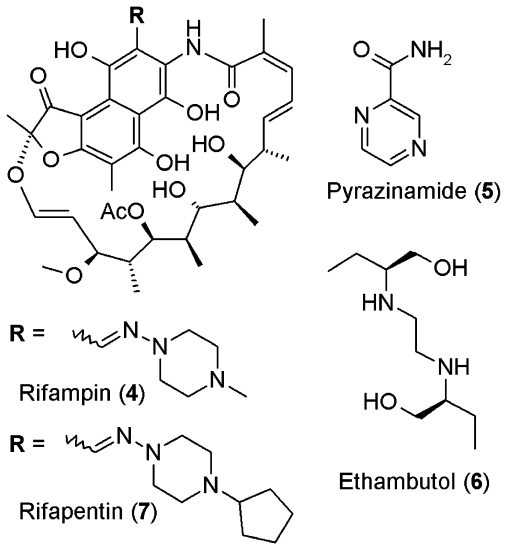


Figure 1.



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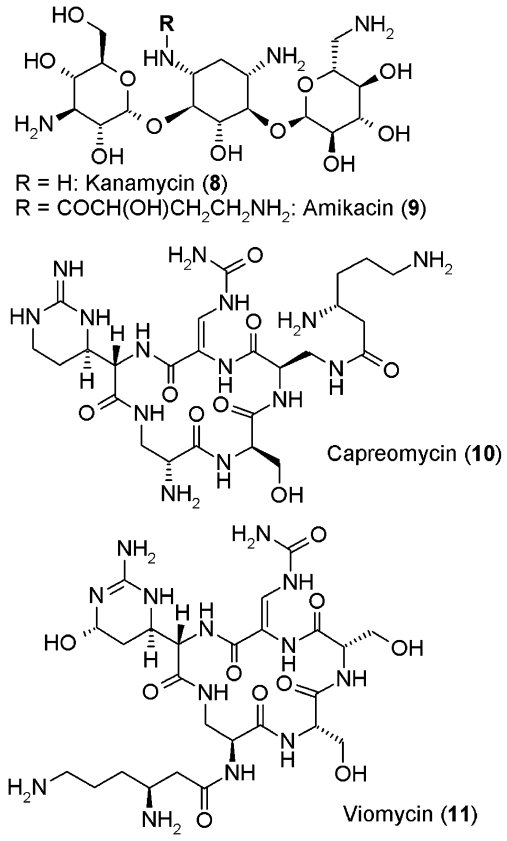


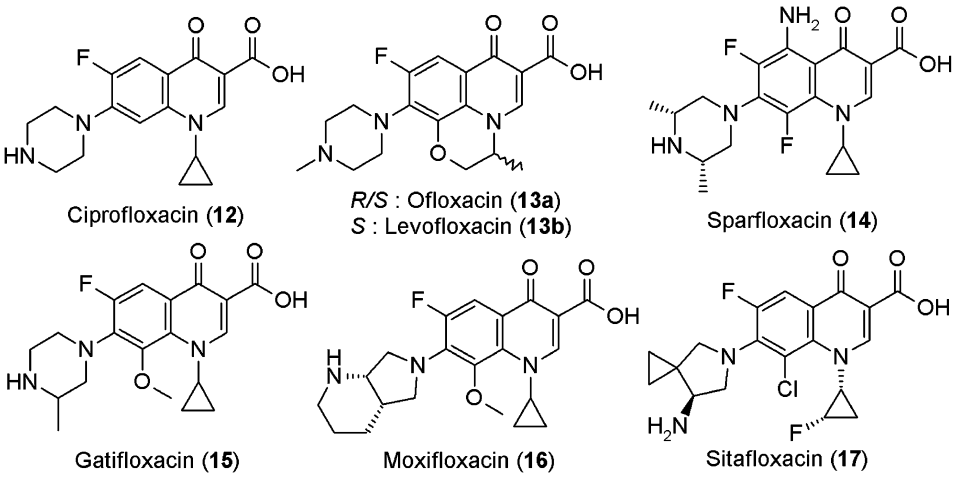
Figure 3.

The 14th edition of the Merck index lists 30 different tuberculostatics. Many of them are analogues or prodrugs of the first line drugs mentioned above and others fell out of use. Amongst rifamycin derivatives,[27] rifapentin (**7**)[28] is noteworthy as it is currently investigated as an alternative to rifampin (**4**) with a longer serum half life which would simplify treatments especially when following protocols requiring the direct observation of patient compliance.[29] However, the occurrence of multidrug resistant (MDR) strains of *M. tuberculosis*, at least resistant to the action of isoniazid (**3**) and rifampin (**4**), implies recourse to other compounds. In year 2000, an estimated 3.2% of all the tuberculosis new cases (between 185,000 and 414,000) were multiresistant.[30] Treatment guidelines for these cases have much less easily been established and are complicated by drug side effects and co-infections with HIV-1.[31–33] The clinical isolates' cross resistance monitoring provides insights in designing regimen strategies.[34] A recent survey of cohort studies, or more recent clinical data,[35–39] has led to some recommendations although, as mentioned by these authors, a full comparison of all the clinical data is not possible.[33] This survey recommends the use of a regimen of at least five adequate antituberculosis drugs. The choice of these drugs will be driven by the actual or presumed (in view of past failed treatment) resistance characteristic of the strains of *M. tuberculosis* considered. In order of preference they can be chosen from the following. (i) In any case, the first line agents still active on the patient: isoniazid (**3**), rifampin (**4**), pyrazinamide (**5**) and ethambutol (**6**). (ii) This is followed by the group of injectable drugs: streptomycin (**1**), kanamycin (**8**), amikacin (**9**), capreomycin (**10**) or viomycin/tuberactinomycin B (**11**) and the related tuberactinomycins A, N and O (Fig. 3).

(iii) One of the many related antibacterial fluoroquinolones such as ciprofloxacin (**12**), ofloxacin (**13a**), levofloxacin (**13b**), or the more recent sparfloxacin (**14**), gatifloxacin (**15**), moxifloxacin (**16**) and sitafloxacin (**17**) should be included in the regimen. This class of antibiotics has now[40] been proven as indispensable treatment for MDR tuberculosis.[41] Moreover, some of these drugs may leads to shorter antituberculosis regimens[29,42,43] although their use in monotherapy also lead to the occurrence of fluoroquinone-resistant strains of *M. tuberculosis*.[44–46] An actual preference between fluoroquinolones **12**–**17**, especially between the latest generation, for the specific treatment of MDR tuberculosis is still the matter of preclinical[47] and clinical research[48] (Fig. 4).

(iv) Second line bacteriostatics, with established clinical efficacy,[33] usually have more important side effects.[49] They are *p*-aminosalicylic acid (**2**), ethionamide (**18a**) (the propyl analogue prothionamide (**18b**) is also used) and cycloserine (**19**). (v) Other drugs are also considered. Their use is the subject of debate[33] and only time and proper observations will provide the necessary data. Clofazimine (**20**) is among these compounds and is also used against *Mycobacterium leprae* (Fig. 5).

The combination of amoxicillin (**21**) and the penicillinase inhibitor clavulanic acid (**22**) has an antimycobacterial effect in vitro. The same is true for clarithromycin (**23**) although its clinical efficacy remains to be established.[33] The use of rifabutin (**24**) is a matter of debate as, although in vitro, some *M. tuberculosis* strains



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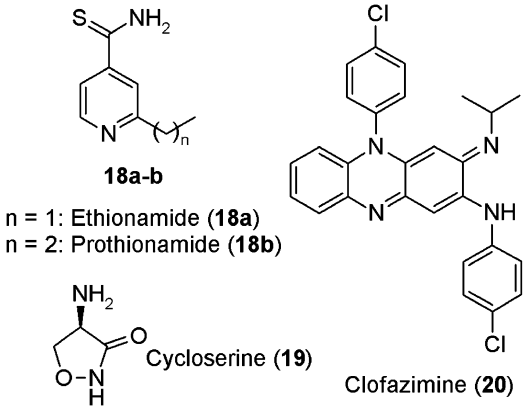


Figure 5.

resistant to rifampin (**4**) are still sensitive to rifabutin (**24**), its routine clinical use in MDR cases has not demonstrated any further usefulness.[33] Thiacetazone (**25**) has a high rate of side effect, especially with HIV-1 bearing patients. Moreover, cross-resistance is observed with ethionamide (**18a**)[50–53] (Fig. 6).

2.2. Compounds under clinical trials

Aside from some of the above-mentioned fluoroquinolones which are still in the process of being established as second line antituberculosis drugs, the oxazolidinone class of antibiotics is under study. The first antibiotic of this class approved, linezolid (**26**), was also studied for the treatment of MDR tuberculosis.[54] A clinical study which, for some cases, went well beyond the recommended 28 days-long treatment took place under a compassionate-use programme. Among the side effects reported three cases of peripheral neuropathy were mentioned.[55] Later reports,[56] including two focused on long MDR antituberculosis treatment,[57,58] demonstrated an antituberculosis effect on patients but also consistently mentioned peripheral neuropathies that remain to be studied more thoroughly, especially its reversibility. This illustrates all too well one of the nightmarish problems arising from the so far absolute necessity of long regi-

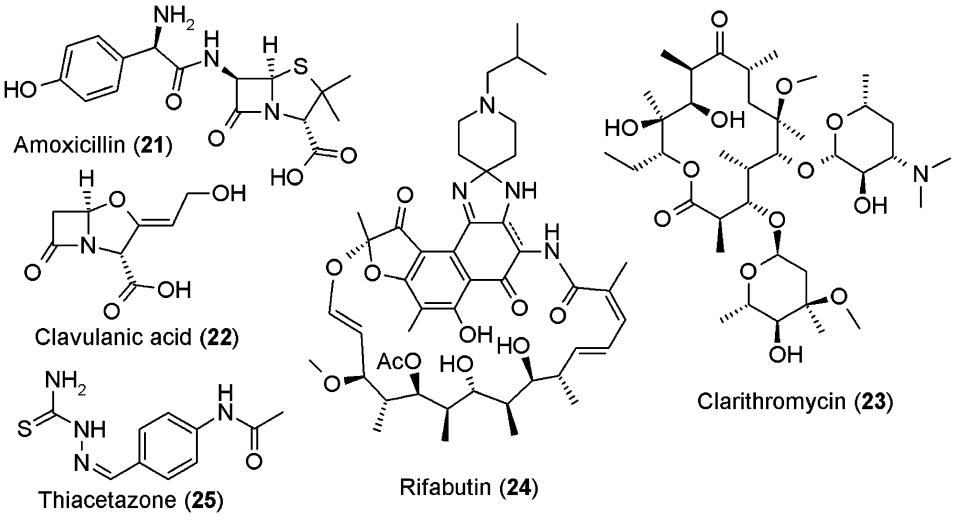


Figure 6.

men for the treatment of tuberculosis. This is due to the almost quiescent nature of a small mycobacterial subpopulation[59–66] that still needs to be eradicated for a complete cure. Any potential antituberculosis compound which undergoes human trials will be used for long regimen and this is bound to reveal previously unsuspected side effects. A remarkable series of diarylquinolines, illustrated by the structure of R207910/TMC207 (**27**), have a very good level of in vitro activity on *M. tuberculosis* growth (MIC_{99} = 0.06 μg/mL for **27**). The very short time (less than 3 years) existing between the patent application[67] and the first phase I human trials of **27** (on healthy human volunteers) is also noteworthy[68] (Fig. 7).

The first bicyclic nitro-bearing imidazoles were reported in the late 1970s for their eventual use as radiosensitizer.[69] Further work led to recognize their effect on *M. tuberculosis* and this led to PA-824 (**28**). Concerns about the potential. carcinogenicity of nitro-bearing molecules were probably at the origin of the slow development of this type of compound, although metronidazole, amongst other nitro-bearing compounds, is a commonly used anaerobic antibacterial.[70] As metronidazole, PA-824 (**28**) is not mutagenic on the Ames test and does not seem to be metabolized by the human cytochrome P450 into potentially carcinogenic substances.[29] Moreover, preclinical study on murine models demonstrated a good level of activity on resistant strains.[71,72] Thus, PA-824 (**28**) is currently undergoing clinical trials as an antituberculosis drug.[73,29] Moreover, further research led to a series of structurally related nitroimidazo[2,1-*b*]oxazoles,[74,75] such as OPC-67683 (**29**). This compound is undergoing clinical trials since 2004[29,76] (Fig. 8).

A series of antimycobacterial pyrroles were reported in the late 1990s. From the initial compound BM 212[77] identified, further structure–activity studies were undertaken in vitro and compound **30** was shown to have an effect on the mycobacterial growth inside the macrophages.[78] However, more recent work led to the conclusion that the analogues so far made could not be considered as potential clinical candidates.[79] On the other hand, another research group also undertook

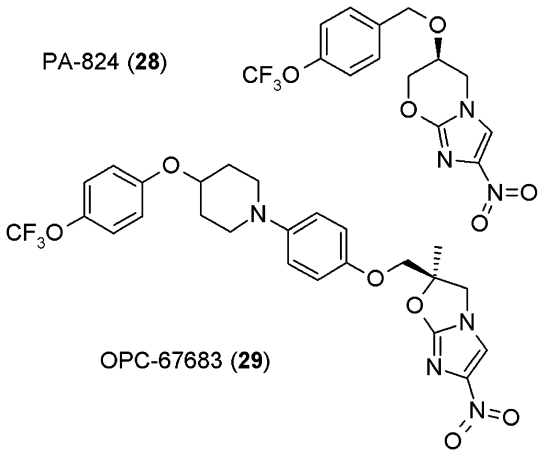


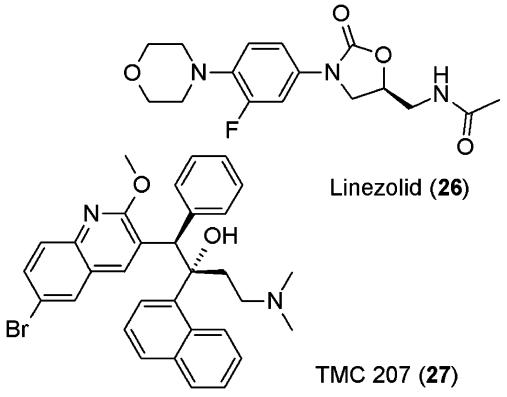
Figure 8.

structural optimization studies and the isoniazid-bearing derivative **31** was shown to be active in vivo on a murine model even infected with resistant *M. tuberculosis* strains.[80,81] Although no scientific results are yet publicly available, this series of compounds was placed in this section as a phase 1 clinical trial may have been initiated by the same research group; apparently with a pyrrole derivative[29] (Fig. 9).

From the structure of ethambutol (**6**), a modern chemical approach was undertaken leading to the synthesis of many chemical libraries of diaminated analogues.[82–84] Remarkably, SQ109 (**32**) turned out to be a very efficient antimycobacterial, also effective on MDR strains. Moreover, the favourable pharmacological properties of compound **32**[85] as well as a synergistic effect with other antituberculosis drugs[86] should lead to clinical trials which were scheduled to start in 2006 (Fig. 10).

3. Mechanisms of action of antituberculosis drugs or antimycobacterials

The determination of the biochemical processes targeted by antituberculosis drugs is still undergoing and has



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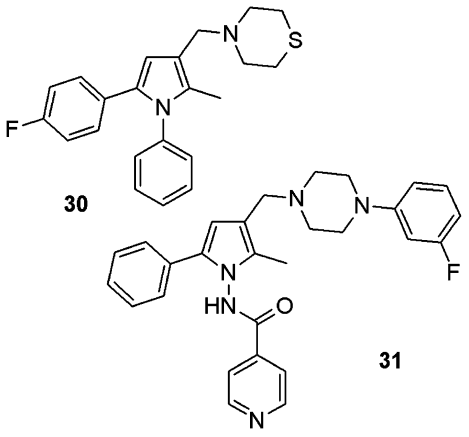

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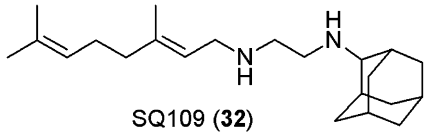


SQ109 (**32**)

Figure 10.

been reviewed in the recent past.[14,87,88] This is one of the many fascinating facets of this field as many antituberculosis drugs have been used for decades with little or no knowledge of their mechanism of action. This 'deorphaning' of antituberculosis drugs is today of prime importance, as it can lead to the identification of already validated biological targets of *M. tuberculosis*. These targets can then be used for the search of better inhibitors (longlasting or overcoming the resistance of mutated strains) starting with the use of modern fast screening of chemical libraries. In many instances the classification of these mechanisms of action was difficult as no clear-cut pictures were yet available. For instance, isoniazid (**3**) is, so far, likely to inhibit three NADH-using enzymes involved in fatty acid biosynthesis; but will the latter aspect hold true in some years? We strove to provide an overall view of the past and present studies which are sometime in contradiction. In this regard, the following is probably missing a table or two, although, we believe this would oversimplify the sum of the investigations reviewed and would ignore many antimycobacterials of interest. Moreover, our suggested biochemical targets for some compounds described below are sometimes only based on structural similarities and must be taken with the proverbial grain of salt.

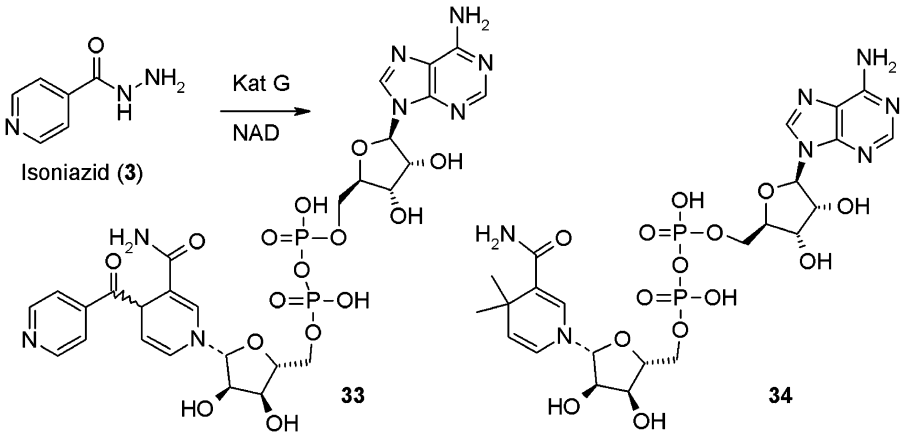
3.1. Fatty acid biosynthesis inhibitors

The mycolic acids, which are covalently linked to arabinogalactam, are components of the complex (and thick) mycobacterial envelope. These exceptionally long fatty acids are probably part of the keys[66] for the mycobacterial ability to withstand chemical injury such as the one produced by macrophage phagolysosome. Moreover, the acid-fast staining, characteristic of mycobacteria, is actually caused by the mycolic acids. To produce these branched fatty acids, the mycobacteria use two types of fatty acid synthase pathways, a eukaryotic type of fatty acid synthase (FAS I pathway) and an array of prokaryotic type of enzymes (FAS II pathway). The first type is a single large multifunctional enzyme which produces C16 and C24/26 fatty acids in four steps. The prokaryotic type group of enzymes will then elongate these acids to lengths as long as C56. Amongst the enzymes of the second type are: (i) MabA (also called FabG) and InhA (also called FabI) which are NADH-dependent enoyl acyl carrier protein reductases, catalysing the reduction steps of fatty acid synthesis (respectively, the β-carbonyl reduction and the α-β-insaturation reduction). (ii) FabH as well as Kas A or Kas B which are three different β-keto-acyl-carrier protein synthases, catalysing the condensation steps of fatty acid synthesis. Following this, many enzymatic transformations (desaturation, cyclopropylation, hydroxylation, etc.) can take place, thus giving rise to at least 500 different compounds.[89–91] Relevant schemes for all the biochemistry described above, which is still the matter of research, would be beyond the scope of this work. However, reviews excellently summarize the current knowledge on mycobacterial envelope.[89,90,92–95]

Many antibacterials are acting on fatty acid biosynthesis[96–99] and this is also true for compounds effective on *M. tuberculosis*. Moreover, 2-methoxy,[100] cyclopropane[101] or acetylenic-containing[102] fatty acids were reported for their antimycobacterial properties and some unsaturated fatty acids used as antibacterials[103] were recently demonstrated to inhibit FabI.[104] The first enzyme in this process is the acyl-CoA carboxylase carboxyltransferase which produces malonyl-CoA. Following a study on *Escherichia coli* enzyme,[105] a virtual screening using the X-ray derived structure of the mycobacterial enzyme led, amongst other compounds, to the identification of a diazo-containing inhibitor.[106]

3.1.1. Isoniazid (3). The quest to elucidate the mechanism of action of the 50-year-old antituberculosis drug isoniazid (**3**) was instrumental in demonstrating that the mycolic acid synthesis pathway of mycobacteria is a target of choice. As early as 1976, it was recognized that treating mycobacteria with tritium-labelled isoniazid would give rise to tritium-containing compounds related to NAD.[107] The gene *inhA* was demonstrated to code for one of the targets of isoniazid (**3**) in 1994.[108] Further work pointed out the role of KatG, an endogenous catalase-peroxidase,[109] and an X-ray derived structure of the NAD-isoniazid adduct (**33**) bound to InhA, the enoyl acyl carrier protein (ACP) reductase coded by *inha*, was then obtained in 1998.[110] From this, many puzzle pieces came into place; recent reviews further describe the many facets of isoniazid antimycobacterial mechanism of action.[88,111] Thus, the biological activity of isoniazid requires first an activation by Kat G[112,113] into an unstable intermediate which reacts with NAD to give compounds such as **33**. The resulting adduct then binds the NAD(H) recognition site of InhA and this leads to the antimycobacterial effect (Scheme 1).

This explains the long known correlation between isoniazid resistance and catalase-peroxidase activity of the *M. tuberculosis* strains[114,115] which was altered by mutations of the catalase KatG. The mutations of this enzyme are actually at the source of at least one-third of the *M. tuberculosis* strains resistant to isoniazid.[116–122] Further analysis and biological evaluation of the adducts arising from the reaction between isoniazid, an oxidizing agent, and NAD proved that compounds with a related structures are also inhibitors.[123] Few synthetic analogues of NAD bearing a double substitution on the nicotinamide moiety such as **34** have actually been patented for their antimycobacterial properties[124,125] and further work along this line has been initiated.[126,127] Moreover, two other NADH-using enzymes of mycobacteria: MabA[128] and dihydrofolate reductase[129] are also inhibited by some of these isoniazid-NAD adducts. This mechanism of action does raise the question whether any future rational drug design methodologies



Scheme 1. One of the isoniazid-NADH adducts and structure of an analogue.

will ever provide such exquisitely elegant antibacterials from scratch. A central feature to this activation mechanism, which recurrently appears in antituberculosis drugs, is in the present case an oxidation process, rather specific to mycobacteria, which leads to active compounds from the corresponding prodrugs. On the other hand, a whole series of nitro-bearing antimycobacterial prodrugs, described below, require a reduction to be active.

Many other analogues featuring the structure of isoniazid (**3**) have been synthesized and this is still the subject of works;[130–138] a critical review of such approaches has been published recently.[139] A database search of isoniazid-containing structures comes out with more than 3000 compounds, about 2000 of them being hydrazones. Moreover, six of these isoniazid-derived hydrazones (furonazide, glyconiazide, opioniazide, salinazid, streptonicozid and sulfoniazide) dating from the 1950s are still listed as tuberculostatics in the 13th edition of the Merck index although they are probably not much prescribed these days. Along with aroylhydrazides recently reported[140], the preclinical and clinical development of such isoniazid analogues will require a very substantial benefit when compared to isoniazid (**3**) itself. This improvement may exist for analogues capable of avoiding an *N*-acetyltransferase[141,142] at the source of a metabolic pathway for isoniazid elimination.[143,144]

Triclosan (**35**) has been used for at least 30 years as a broad spectrum biocide with the belief that its antimicrobial activity was due to cell wall disruption. However, from 1998,[145] it was established that triclosan is a large spectrum inhibitor of the FabI, the bacterial NADH-dependent enoyl acyl carrier protein reductases, including, although with lesser strength,[146–148] the FabI/InhA of *M. tuberculosis*. The X-ray structures obtained further demonstrated that the inhibition takes place via the occurrence of a ternary complex between FabI, NAD and triclosan.[149–152] This finding triggered syntheses of structural analogues of **35** focused on *M. tuberculosis*[153,154] or malarial[155,156] enoyl acyl carrier protein reductases. Amongst the few compounds reported so far, the octyl-bearing analogues **36** turned out to be 200-fold more active on an enzyme inhibition model than triclosan (**35**).[154] Reports have described an antimycobacterial activity of the anti-inflammatory drug diclofenac (**37**).[157,158] This leads us to point out its structural similarities with triclosan (**35**). However, such structural considerations may be risky as hexachlorophene (**38**), another antibacterial structurally very close from **35**, may act on some bacteria through a different mechanism of action.[159] The diazaborine class of antibacterials[160] such as compound **39** also turned out to covalently bind the FabI–NAD+ complex.[161] The structure–activity relationship studies undertaken with this class of inhibitors provided much insights into the FabI binding pocket conformation.[162] However, an inherent toxicity seems to prevent their pharmaceutical use.[163,160] On the other hand, the topical use of related boron-containing structures against fungal infections is being considered[164] and a patent from the same research group may have addressed this toxicity issue[165] (Fig. 11).

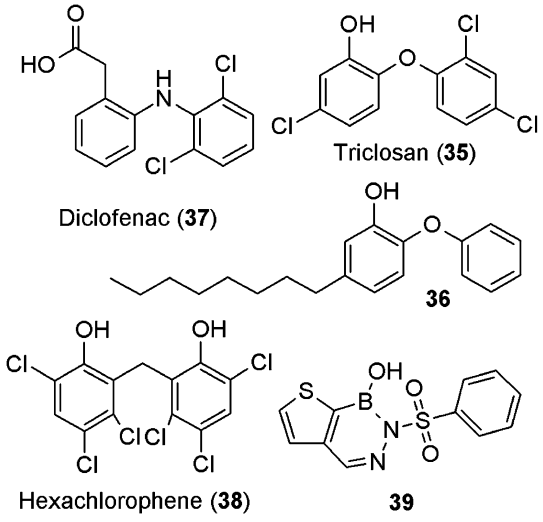


Figure 11.

Screenings against FabI enzymes have also led to the discovery of new series of antibacterial agents.[98,99] However, few of these reports mention if these series are active on mycobacteria.[149] On the other hand, as these inhibitors are binding FabI on the same site as triclosan (**35**), it is likely that they also have an effect on *M. tuberculosis* although tempered by differences in binding and cell wall permeability. The polyphenolic epigallocatechin gallate was reported to inhibit, amongst other targets,[166] FabI reductase,[167] and a survey of the effect of flavonoids on FabG, FabZ and FabI of *Plasmodium falciparum* was published recently.[168] Compounds **40** and **41** are two representatives of the structure–activity relationships found for these families of inhibitors.[169–172,149] The quite unrelated compound **42a**[173] was reported to also inhibit this reductase. This leads us to suggest a target for a previously reported series of pyrimidine-containing antimycobacterials illustrated by compound **42b**.[174] It is noteworthy that compound **40**–**42a**,**b** as well as the inhibitor **43**[175] or **44**[149] share only little common structural features. This is a good illustration of how chemically diverse inhibitors can be and still act on the same biological target. The recent report of another original class of inhibitors emphasizes this aspect even more[176] (Fig. 12).

Thiolactomycin (**45**) is a natural product isolated from *Nocardia* spp.[177] which belongs to a family of thiolactone-containing antibiotics.[178–183] This compound acts by inhibiting the condensing fatty acid synthase type II enzymes[184,185] (FabH, Kas A and Kas B in the case of *M. tuberculosis*[186,187]). Other natural compounds inhibiting the FAS systems are the irreversible[188] inhibitor cerulenin (**46a**),[189] the remotely related exomethylene-bearing compound C75 (**46b**) and the recently reported platensimycin (**47**)[190,191] However, the first two are probably of a lesser interest from a chemotherapeutic point of view[192] and no assay of platensimycin (**47**) on *M. tuberculosis* growth has been reported yet. The cyclic β-carbonyl structure of **45** was suggested to mimic the thiomalonate portion of the malonyl-acyl carrier protein.[193] This compound was at the origin of many structure–activity studies aimed at the design of bacterial,[186,187,194–198] mammalian[193] or parasite[199] fatty acid synthase inhibitors. Concerning *M. tuberculosis* growth inhibition, it turns out that a methyl on carbon 3 confers a selectivity of inhibition for FAS type II enzymes.[193] Further selectivity remains the subject of research as inhibition of FabH may not be relevant in the case of *M. tuberculosis*,[197] although it is for other bacteria.[200] For instance, it has been demonstrated that only very little modifications are allowed on carbon 5 position.[194,197] Removal of this side chain and alkylation of the oxygen on position 4 leads to an active analogue[196] reminiscent of antimycobacterial C75 (**46b**) derivatives[201] although these compounds may act by inhibiting the FAS type I enzyme. The *N*-octanesulfonylacetamide (**48**) was originally designed to inhibit β-keto-acyl-carrier protein synthases of mycobacteria by mimicking one of the transition states arising from the condensation reaction.[202,203] However, it appears that this compound probably acts on a different biochemical target.[204] A related compound (if not **48**) is considered for preclinical trials under the name FAS20013 (Fig. 13).

3.1.2. Pyrazinamide (5). From 1985, this compound became the third most important antituberculosis drug.[205] Until very recently, it should not have been placed in this part of the review as no specific biological target has been found for pyrazinamide (**5**). In any case, for the reasons described below, we placed it here. The

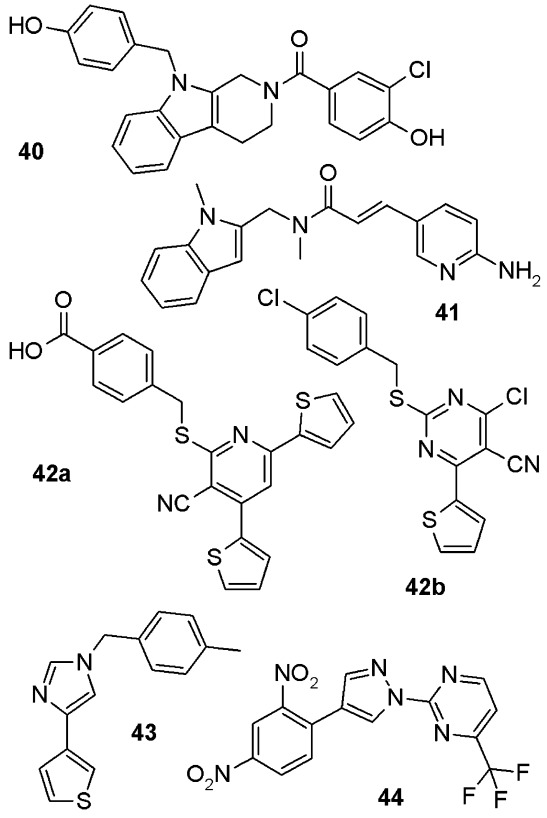


Figure 12.

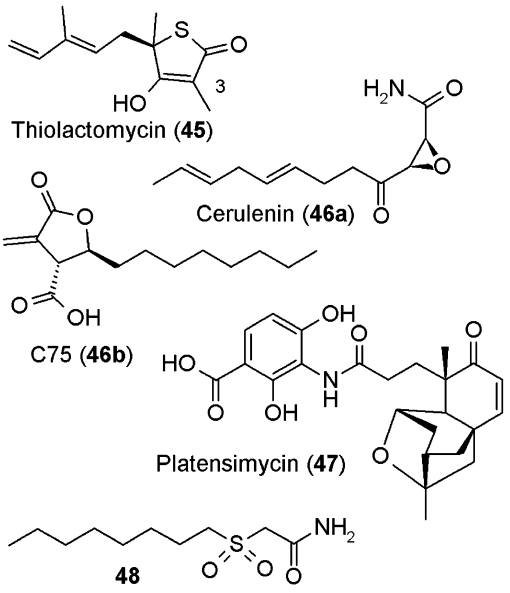


Figure 13.

similarity of structure of this antituberculosis drug with isoniazid (**3**) is one of the puzzling facts surrounding this compound.[206] Another is that pyrazinamide (**5**) is not active in vitro on many *Mycobacterium* strains, whereas pyrazinoic acid (**49**), which can result from a pyrazinamidase-catalysed hydrolysis of **5**, is active in vitro on most.[207,208] A third fact about this antituberculosis drug is that, along with rifampin (**4**), it is effective on the non-growing persistent baccilli.[64] The story behind its discovery can be summarized in two points. First, it had been found that nicotinamide (**50**) had an activity against *M. tuberculosis* so structure–activity relationship studies were initiated.[209] Second, in vitro tests were, regardless of their results, followed by in vivo assays on a murine model which, contrary to the in vitro, were very good for pyrazinamide (**5**).[206] From these facts, one can wonder if such compound would be identified today by modern drug screening strategies. Structure activity relationship studies reported antimycobacterial properties for 5-chloropyrazinamide (**51**),[207] esters of the pyrazinoic acid (**49**)[210,211] or related derivatives.[212,213] In another approach, the carboxylic moiety of compound **49** was replaced by isosteres of a carboxylic group as for the tetrazole-containing prodrug **52**.[214,215] The quinoxaline prodrug **53** and its pyrazine homologue were also reported to be active on *M. tuberculosis* growth.[216] The mechanism of action of pyrazinamide (**5**) is still the matter of researches which are quite hampered by the following peculiarity of this drug. Across the years, it was shown that in vitro assays of **5** have to take into account culture parameters[206] such as acidity of the medium (ammonia will be released),[217] an eventual low oxygen content[218] or even iron concentration.[219] The vast majority of the characterized *M. tuberculosis* strains resistant to pyrazinamide (**5**) have developed alterations on the *pncA* gene which code for a pyrazinamidase,[220,206] but these strains are still sensitive to pyrazinoic acid (**49**).[208,210] Matter got a bit more confusing as 5-chloropyrazinamide (**51**) was demonstrated to inhibit the FAS type I pathway,[221] whereas pyrazinamide (**5**) or pyrazinoic acid (**49**), which had been suspected to have a different mechanism of action,[207] did not.[222] On the other hand, a very recent study on replicating bacilli seems to contradict this in the case of pyrazinoic acid (**49**).[223] These results do render quite complex the analysis of any structure–activity relationship results reported in this series. Moreover, the esters of pyrazinoic acid (**49**), which had been developed to circumvent the alteration of the pyrazinamidase activity, turned out to be of little interest in vivo; possibly because of their poor stability.[206] In any case, a mechanism of action of pyrazinamide currently suggested[206] is based on the release of pyrazinoic acid (**49**) in situ. This causes an intake of proton (as protonated pyrazinoic acid) which leads to a complete dysfunction of the pH balance for the group of mycobacteria (which include *M. tuberculosis*) that are lacking an efflux pump capable of dealing with this salt.[224] This 'death by acidification' mechanism also explains why this drug is efficient on dormant bacilli as, aside from a pyrazinamidase, it does not require much metabolic activity. The very recent report describing the effect of pyrazinoic acid on replicating bacilli and palmitic

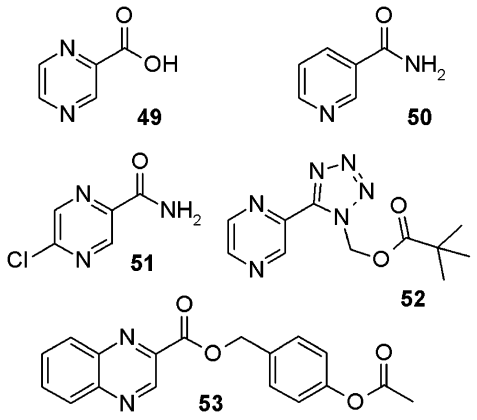


Figure 14.

acid biosynthesis guarantees further mechanistic studies[223] (Fig. 14).

3.1.3. Ethionamide (18a), prothionamide (18b) and thiacetazone (25). These compounds are characterized by clinical cross resistances which have been noted for patients infected with *M. leprae*[225,226] or *M. tuberculosis*.[50–52] An original approach currently aims at suppressing the repression of the expression of EthA (a flavoprotein monooxygenase) which is at the source of this resistance.[227,228] In the last six years it was confirmed that these compounds are prodrugs and that they are oxidized by EthA which can also be mutated in some resistant strains.[229–232] Oxidation of ethionamide (**18a**) by this enzyme leads to the sulfinic acid (**54**) which is likely to be further transformed as amide (**55**) and alcohol (**56**) were characterized.[230] In the case of thiacetazone (**25**), the sulfenic derivative (**57**) and the carbodiimide (**58**) were identified.[232,231] A sulfenic acid equivalent to ethionamide (**18a**) is likely to occur in the case of **25** although its strong reactivity has precluded its characterization.[232] Moreover, it had been known

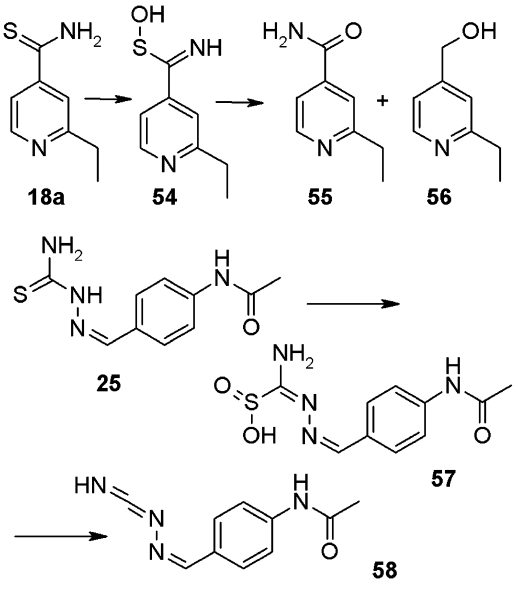
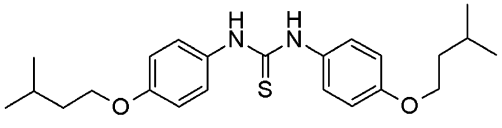


Figure 15.

that the sulfinic acid **54** was as active on mycobacterial growth in vitro as ethionamide (**18a**)[233–237] (Fig. 15).

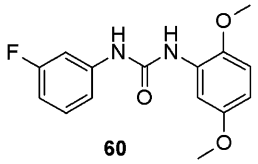
Thus as for isoniazid (**3**), which is activated by KatG, it has been established that another enzyme endogenous to *M. tuberculosis*, EthA, transforms ethionamide (**18a**) or thiacetazone (**25**) into highly reactive species. These intermediates are prone to react with any nucleophile. In the case of thiacetazone (**25**), a glutathione adduct arose when adding this thiol in the reaction medium[232] and an unidentified adduct of ethionamide (**18a**) has been seen by NMR techniques.[238,239] Hopefully, what is likely to be discovered in the near future are the actual mycobacterial enzymes targeted by these probable adducts. In the case of ethionamide (**18a**), or prothionamide (**18b**), the target is likely to be InhA as some *M. tuberculosis* strains resistant to isoniazid and ethionamide displayed a mutation on *inhA*.[240]

Isoxyl/thiocarlide (**59**), another thiocarboxyl-containing antituberculosis drug, has been used clinically in the past[241–243] before being supplanted by better drugs. This compound has also a history of cross resistance with ethionamide (**18a**) or thiacetazone (**25**)[244,52,51,245] which was confirmed more recently.[246,230] Recent studies demonstrated that one of the biological targets of **59** is DesA3, a Δ9-desaturase responsible for the synthesis of oleic acid from stearoyl-CoA.[247] Since sterculic acid, an inhibitor of Δ9-desaturase,[248] did not produce all the effects of isoxyl (**59**) on fatty acid synthesis, a second target is also suspected. Moreover, as all this work was conducted with whole cell extracts,[247] it remains to be proven that isoxyl (**59**) is (or not) a prodrug oxidized by EthA. An oxidation would probably lead to the corresponding carbodiimide and thus to adducts which would be the actual inhibitors of enzymes involved in oleic and mycolic acid biosynthesis. The remotely related dicyclohexylcarbodiimide was found to inhibit several enzymes involved in cation transport[249] and this compound as well as other hydrophobic carbodiimides were reported to inhibit bacterial membrane ATPase.[250] (Fig. 16).



Isoxyl (**59**)

Figure 16.



60

Figure 17.

Analogues of isoxyl (**59**) with a better antimycobacterial activity have been prepared recently.[251] However, if this prodrug aspect were confirmed, the inherent toxicity caused by a concurrent host flavoprotein monooxygenase activation may be a factor hampering a clinical development. On the other hand, this activation question remains open as it was observed[247] that the structurally related biaryl urea (**60**) is an inhibitor of a Δ5-desaturase[252] in rodents. It is noteworthy that remotely related aryl urea have also been reported recently for its antibacterial activity.[253] Finally, a very recent structure–activity relationship study of isoxyl analogues tends to suggest the existence of more than one biochemical target for this class of compounds[254] (Fig. 17).

In conclusion, as DesA3 is functionally analogous to the highly studied mammalian stearoyl-CoA desaturase, it would be quite remarkable if the research on antiobesity drugs (focusing on this mammalian desaturase[255,256] or on other enzymes of fatty acid metabolism) would come out with an original antituberculosis drug. This aspect has actually not escaped the attention of patent offices[257–262] as well as researchers who use tetrahydrolipstatin, an antiobesity drug, in their investigations on mycobacterial lipids.[263]

3.1.4. PA-824 (28) or OPC-67683 (29). Their mechanisms of action have not been reported yet. However, the following led us to place these compounds in this section. A bioreductive activation of the nitroimidazooxazine-bearing PA-824 (**28**) by a combination of the low redox potential F_{420}-dependent glucose 6-phosphate dehydrogenase and a previously unstudied protein (Rv3547) acting as the electron transfer mediator has been suggested.[264] The fact that this mediator has a PA-824 (**28**) specificity (two nitroimidazooxazoles related to OPC-67683 (**29**) were still active on RV3547-mutated strains resistant to PA-824) does complicate the overall picture of nitro-bearing activation of antibacterials.[264] Thus, the actual nature of the biochemical target of any of the resulting partially reduced (nitroso or hydroxylamine) or fully (amino) reduced metabolites is still the matter of research. Recent poster communication on OPC-67683 (**29**) reported the lack of cross-resistance with antituberculosis drugs[265] and the inhibition of the synthesis of mycolic acid at the stage of methoxy- and the keto-mycolic acid syntheses.[266] That is the reason why we have placed the very much related compounds **28** and **29** in this section. However, the vast array of nitrated antimycobacterials reported,[267–271] all of them probably being prodrugs to be reduced,[272] does raise the question whether the corresponding active species are all acting on a single or on many biochemical targets.

3.2. Arabinogalactam and peptidoglycan biosynthesis inhibitors

It would be beyond the scope of this review to attempt to describe the complexity of the glycosides present in mycobacteria envelope.[92,89,94,273] A central feature is a polysaccharide made of arabinose and galactose (arabinogalactam) which acts as the intermediate binding

scaffold between the many types of mycolic acids and the inner peptidoglycan. A general pathway for its biosynthesis has been suggested.[274,273,275] Moreover, quite a few other cell wall glycolipids or complex lipids are 'extractable' and thus not bonded to the peptidoglycan. The determination of the role and places in the mycobacteria envelope of these lipid-containing compounds (phtiocerol dimycocerosate, dimycolyltrehalose, sulfolipids, phosphatidylinositolmannans, lipomannans and lipoarabinomannans)[94] probably constitute one of the future challenges for structural biology. Only general features are known about the structure of mycobacteria peptidoglycan. It is shared by the *Corynebacterium* and the *Nocardia*, it contains D-alanine and differs from other groups of bacteria by the fact that *meso*-diaminopimelic acid constitutes the diaminoacid component. Moreover, the muramic acid component which, due to experimental artefact, was though to always bear an *N*-glycolyl,[276] can actually be N-acetylated as well.[277] As for other bacteria, a central feature in peptidoglycan synthesis is the cytosolic UDP-muramyl-pentapeptide (**61**) which can be considered as a building block. From UDP-Glc-NAc, this cofactor requires at least six distinct enzymes (MurA to MurF) for its synthesis.[278] The enzyme responsible for the transformation of the *N*-acetyl into an *N*-glycolyl is, as the stage it takes place, still the matter of investigations[273] (Fig. 18).

A great number of enzymes participate in the biosynthesis of all the components of this envelope. Genomic was instrumental in identifying many of them but their biochemical studies is in many instances still undergoing.[94,273] A review on the design of original inhibitors of bacterial cell wall biosynthesis was published recently.[279]

3.2.1. Ethambutol (6). This antituberculosis drug constitutes the proof of principle that an inhibitor of the biosynthesis of the glycoside of this envelope makes an excellent antituberculosis drug. The actual enzymatic target of this drug is still investigated as, although its effect is focused on arabinan biosynthesis, alterations can be observed on many envelope metabolites.[280–286] More important, its effect on cell wall improves the efficiency of other antibiotics, for instance clarithromycin (**23**), which are usually inefficient on *M. tuberculosis*.[287,288] This uncertainty regarding the biochemical target of ethambutol (**6**) did not deter the chemists who were armed with the facts that even simple ethylenediamines, such as **62**,[289] or unsaturated analogues[290] are effective inhibitors of mycobacterial growth. Thus, using a modern medicinal chemistry approach, they undertook the synthesis of chemical libraries featuring a central 1,2-ethylenediamine component.[82–84] Out of the 100,000 plus compounds prepared, the remarkable SQ109 (**32**) mentioned above was found as well as at least 26 analogues as active as ethambutol (**6**). For instance, piperazine or homopiperazine-containing compounds **63** and **64** were noted for their effect on *M. tuberculosis*.[84] Remarkably (but nothing seems to be simple in the field of antimycobacterials), these two compounds as well as SQ109 (**32**) do not seem to act on the mycobacterial envelope as ethambutol (**6**)[7] thus suggesting another biochemical target. On the other hand, as measured by an assay monitoring the activation of the promoter Rv0341, some compounds related to these analogues have an effect on biochemical targets involved in mycobacterial cell wall synthesis.[84] The pharmacoproteomic effect of this compound may also orientate the research on its target.[291] To even further complicate the matter, the pharmacokinetics studies of SQ109 (**32**) with human liver microsomes demonstrated a very quick metabolism of this compound (58.3 % in 10 min).[292] As an antituberculosis effect is still observed on animal models,[85] it is thus plausible that SQ109 (**32**) is, one more (!), antituberculosis prodrug and that the corresponding oxidized metabolites are the active species[86] (Fig. 19).

Attempts were made to prepare compounds featuring an arabinogalactam skeleton which would inhibit a glycosyl transferase activity.[293–296] The results are of interest, although some of the active compounds turned out to bear lipophilic hydroxy-protecting groups.[295] This is actually reminiscent of other furan or pyran-containing compounds featuring protected hydroxyl groups with an antimycobacterial activity.[297,298] This trend is actually especially true for an acetal-protected pyran containing a large hexadecyl side chain[299] or aza analogues of arabinose bearing a thiobenzylic moiety.[300] Amongst the 'extractable' cell wall component, the 6,6′-dimycolyltrehaloses, also named cord factor, have the general formula

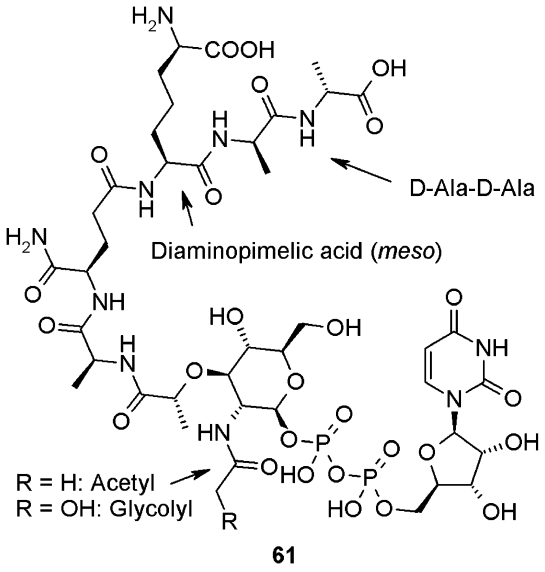


Figure 18.

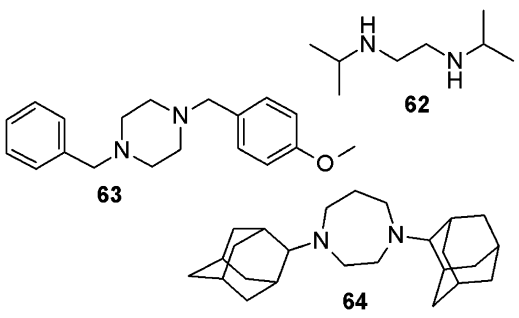


Figure 19.

65. Recent research has demonstrated the existence of structural variations of the mycolic side chains which are specific to the mycobacteria type.[301] These trehalose esters were the focus of many studies because of their strong effect on host immune response.[302] The synthesis of analogues which would interfere with their biosynthesis was also undertaken. Compounds such as 6-azido trehalose derivatives[303] and other structural analogues were thus prepared.[304–306] Sulfonamide derivatives[304] or the highly water-insoluble inverse bisamide **66**, featuring C8 side chains much shorter than the C70–C90 branched mycolic acid, turns out to be quite effective on *Mycobacterium smegmatis* growth on a diffusion assay.[306] The mycolyl transferase (antigen 85B) as well as the closely related antigen 85A or 85C[307] are responsible for the biosynthesis of **65**. As the X-ray-derived crystal structure of 85C was reported,[308] this led to suggestions for the design of original inhibitors.[309,310] This may be of great interest as the inactivation of antigen 85C was shown to lead to major alterations of the cell wall properties because of a change in its mycolic acid composition[311] (Fig. 20).

The four enzymes (RmlA to RmlD) catalysing the biosynthesis of deoxythymidine-diphosphate-rhamnose, which is the providing cofactor for rhamnose incorporation into mycobacterial cell wall, were the focus of a screening of potential inhibitors. The unspecified rhodanine with the general structure **A** was found to inhibit this synthetic pathway as well as *M. tuberculosis* growth.[312] Another research group reported modest antimycobacterial thiazolidinones, such as **67**, targeting the same synthetic path.[313] These structures are reminiscent of the series of antimycobacterial arylidenehydantoins[314] or other antibacterials such as the benzylidenethiazolidinedione (**68**) and some thio-analogues, for which no mechanism of action has been reported yet.[315] On the other hand, other bacteria produce rhamnose but do not incorporate it into their cell wall.[312] Moreover, related antibacterial rhodanines are class C β-lactamase inhibitors[316] (Fig. 21).

The arabinosyltransferases, which incorporate arabinose into the mycobacteria cell wall, use the decaprenol-

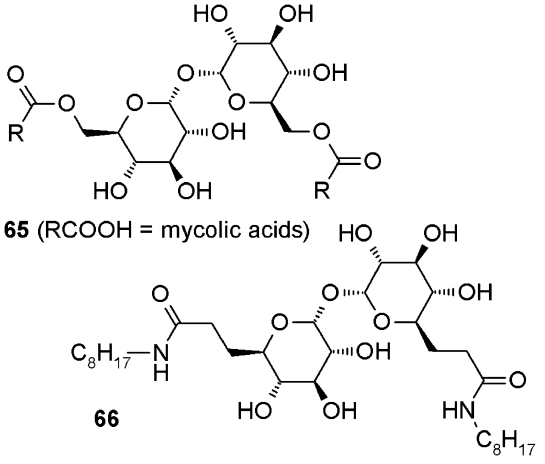


Figure 20.

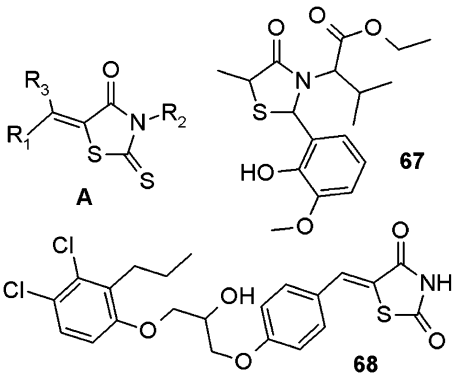


Figure 21.

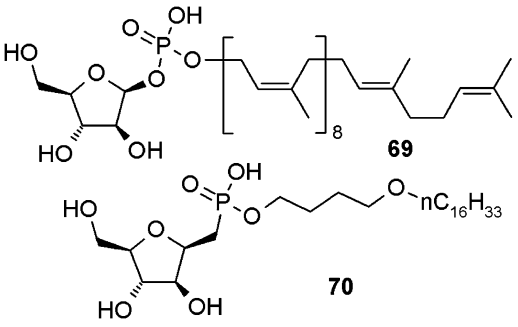


Figure 22.

phosphoarabinose (**69**) as a cofactor. Phosphonate, phosphinic and sulfone analogues of **69** were prepared and phosphonate **70** turned out to be an inhibitor of mycobacterial growth.[317,318] An aza-ribose analogue was reported more recently[319] (Fig. 22).

The necessity of attaching a long prenylphosphate side chain to cofactor prior to their incorporation into the cell wall exists also in the case of UDP-muramyl-pentapeptide (**61**). This cofactor thus undergoes a translocation, catalysed by the corresponding translocase, into an undecaprenyl derivative. Inhibition of such translocase was reported for series of natural compounds such as tunicamycin, liposidomycin B, mureidomycin A,[320] capuramycins[321–323] and caprazamycins[324] which feature a uridine moiety as well as large side chains. It is noteworthy that analogues of capuramycin (**71**) as well as far more functionalized caprazamycins[324] are now studied for their inhibition of *M. tuberculosis* growth.[321,325,326] The structure–activity relationship studies led, in one avenue, to the removal of the azepanone moiety and its replacement with aromatic group. An intranasal assay on a mice model was performed with the most active compounds, such as **72**, and led to the conclusion that human trials should be considered[327] (Fig. 23).

Upstream of the muramyl-pentapeptide incorporation into peptidoglycan, inhibitors of the UDP-muramyl-pentapeptide (**61**) biosynthesis was the focus of research of antibacterials. Inhibitors of the six enzymes, MurA to MurF, mentioned above, have been reviewed recent-

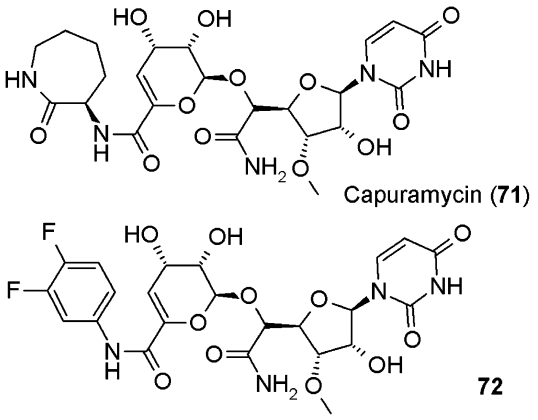


Figure 23.

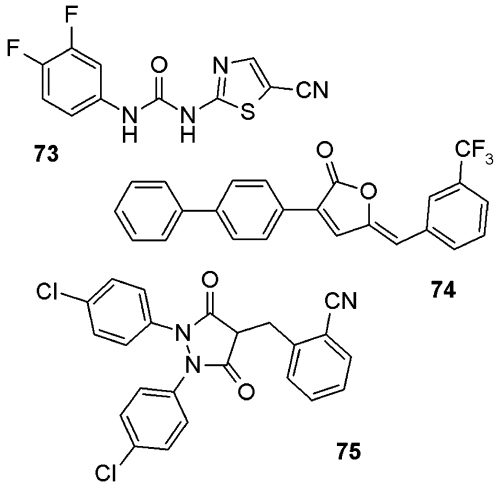


Figure 24.

ly.[278] More recent results were reported[328–335] although, as the preceding examples of inhibitors, their effect on mycobacteria growth has not been reported yet. Some of the MurB inhibitors may feature in their structure a heterocyclic moiety which mimics the diphosphate part of UDP-Glc-NAc.[336,329] Other compounds, such as **73**, inhibit MurA as well as MurB and are active against both Gram-positive and Gram-negative bacteria.[331] Pulvinone **74** is an inhibitor of MurA, MurB and MurC active on Gram-positive bacteria.[335] Pyrazolinediones, such as **75**, were investigated for their effect on MurB and were found active on Gram-positive and Gram-negative bacteria[333,334] (Fig. 24).

If the MurA-F enzymes have not yet been the focus of (published) research on antimycobacterials, much work is focused today on the determination of enzymes involved in the biosynthesis of the cell wall glycosides. As some of these enzymes are essential for mycobacterial growth, these researches should lead to the identification of original antimycobacterials.[274,275,337]

3.2.2. D-Cycloserine (19). Contrary to series of alanine analogues which are inhibitors of MurC,[338–340] D-cycloserine (**19**) was found to inhibit the D-alanine racemase

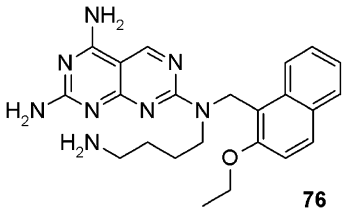


Figure 25.

and the D-alanine D-alanine ligase necessary for the synthesis of UDP-muramyl-pentapeptide (**61**). Which of these two enzymes is the main target of D-cycloserine causing *M. tuberculosis* growth inhibition remains the matter of research[341–344] although both seem to be validated targets for the design of antituberculosis treatment. However, the structural similarity of D-cycloserine (**19**) with neuroexcitatory amino acids is probably at the source of its marked central nervous system toxicity.[49,345] This structurally inherent problem does limit approaches based on the synthesis of analogues. On the other hand, the recent publication[346] of the X-ray derived crystal structure of alanine racemase from *M. tuberculosis* along with dynamic studies[347] will hopefully lead to allosteric inhibitors devoid of structural analogy with D-cycloserine. It is noteworthy that hydroxamate-containing derivatives inhibiting alanine racemase were recently claimed by the same research group.[348] Moreover, a patent claimed inhibitors of D-alanine D-alanine ligase such as compound **76**[349] (Fig. 25).

3.2.3. Amoxicillin (21). This compound has also to be placed here as this compound is amongst the latest β-lactam bearing compounds analogous to penicillin with an antibacterial property. Their main mechanism of action is the inhibition of the transpeptidase that cross-links the peptide side chains making the peptidoglycan. On the other hand, the, so far, weak activity of this class of compounds on mycobacteria put them beyond the scope of this review.[350,351]

3.2.4. Clofazimine (20). This compound and other riminophenazines which have been reviewed[352] could be placed at the very end of this section. As mentioned above, clofazimine (**20**) is effective against *M. Leprae* and its use in the treatment of tuberculosis has been suggested.[353] However, no specific mechanism of action has been established. A recent study suggests a 'generalized membrane-disrupting effect'[354] which would account for much of the observations previously reported.[355,356] Few structural alterations of this antimycobacterial have been reported recently.[357,358] This renewed interest may lead in the future to an elucidation mechanism of action.

3.3. Inhibitors of protein synthesis

As mentioned in an excellent review,[359] ribosome is the biggest (2 MDa) and the most ancient enzyme; it has been present in all living cells for the last 3 billion and a half years. Across this time, its function, translating the code of mRNA into proteins, has not changed as well as the general organisation of its 50 plus

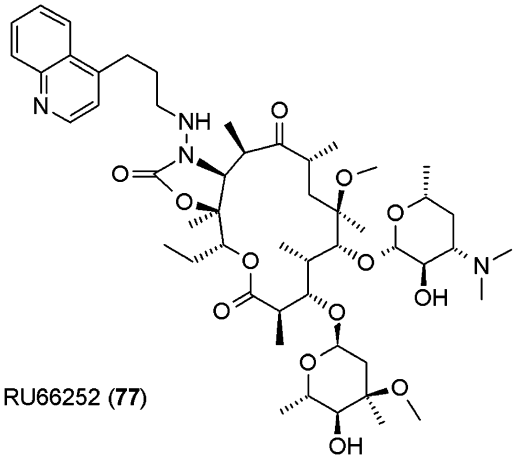
components assembled, in the case of bacteria, into a 30S and a 50S subunits. Amongst other remarkable facts about the ribosome is that these subunits are made of interlaced proteins and RNA (rRNA) and that the closest protein is about 18 Angstroms from the peptide-bond formation catalytic site.[360] These X-ray derived data confirmed the unimaginable suggestion, to a 'peptidocentric' world, that RNA could have a catalytic activity. Thankfully, evolution across these aeons has led to mutations and thus to differences in the mode of interactions between the ribosome components. This allows for the selectivity of action of the many antibiotics targeting the bacterial ribosome.[361,359] Very schematically, these inhibitors can be classed in three groups. Series that interact with the 30S subunits make the first group and the second is the inhibitors that interact with the 50S subunit. The last group is made of the compounds that inhibit the function of aminoacyl-tRNA synthetases. Each of the aminoacyl-tRNAs features a specific amino acid which is bound to the ribose of the tRNA stem by a specific aminoacyl-tRNA synthetase.[362] The aminoacyl-tRNAs can then transport and fit the proper amino acids for their incorporation into the nascent peptide by the ribosome machinery.

It is often suggested[363] that, was it not for the thick mycobacteria cell wall, all the antibiotics used for more classic infection could be efficient. In this respect, approaches based in the use of cell wall altering substances, such as ethambutol (**6**), could restore an efficacy for some of these compounds on *M. tuberculosis*.[287,288] However, this approach was not effective on some other mycobacteria.[364] Specific efflux pumps may explain these observations.[365]

3.3.1. Streptomycin (1), kanamycin (8), amikacin (9), capreomycin (10) and viomycin (11). The first three drugs are belonging to the aminoglycoside[366] family and these, as well as the cyclic peptides capreomycin (**10**) and viomycin (**11**), are targeting the 30S subunit[367] of ribosome and their use can lead to the selection of overlapping cross resistant *M. tuberculosis* strains.[368] Analysis of resistant *M. tuberculosis* strains to capreomycin (**10**) and viomycin (**11**) suggests that these compounds binds at the interface between the ribosomal subunits.[369] Somewhat surprisingly, the mycobacteria cell wall permeability does not seem to hamper the entrance of these five highly hydrophilic antibiotics.[370] Porins, useful for the mycobacteria intake of hydrophilic nutrient,[371,372] do explain this fact.[363,373,374] Moreover, many resistant strains bear mutation on ribosomal proteins or rRNA[375,376] and only low levels of resistances are suggested to be the result of permeability alteration as these could be reversed with Tween 80.[377] Thus, for these particular classes of antibiotic, it seems that the cell wall permeability is not an issue. The recent determination of X-ray derived structures of some these inhibitors inside their biochemical target should lead to the design of better drugs.[359,378–384] However, in the case of *M. tuberculosis*, the porin-based entrance process may be sensitive to important analogue structural alteration which would then complicate any structure–activity relationship study. Moreover, the inherent reactivity of these polyfunctionalized natural compounds may sometime limit the hemisynthetic transformations planned to obtain the most relevant structures.

3.3.2. Clarithromycin (23). Contrary to many related macrolides targeting the 50S ribosomal subunit, clarithromycin (**23**) inhibits *M. tuberculosis* growth in vitro.[385] However, in vivo studies pointed out only a weak effect[386] and thus, as mentioned above, its clinical efficacy remains to be established.[33] A synergy with cell wall altering substances, such as ethambutol (**6**) or pyrazinamide (**5**), could be an approach to improve these disappointing results.[387,288,388] The latest generation of macrolides (i.e., telithromycin) was designed to overcome bacterial resistances resulting from methylation of the rRNA. However, these compounds are no more effective than their precursors on *M. tuberculosis* growth. On the other hand, the quinoline-bearing RU 66252 (**77**) has a better in vivo effect on a murine model.[385] Further structure–activity relationship studies of this type of macrolides may lead to better antimycobacterials although, again, their rate uptake[389] by *M. tuberculosis* as well as the possibility of hemisynthesis[390,391] will have to be taken into account (Fig. 26).

3.3.3. Linezolid (26). This compound is amongst the very few fully artificial antibacterials targeting the 50S ribosomal subunit.[392–395] As this oxazolidinone represents the first completely new class of antibacterials to be marketed in 25 years, a very important number of structure–activity relationship studies were undertaken in many pharmaceutical companies.[396–400,384] Concerning the use of this class against tuberculosis, many active compounds were found.[401–406] However, the long term use of linezolid (**26**) may be plagued with forbidding side effects.[397,407] In any case, clinical trials with better oxazolidinones[397] are needed before a large scale trial can specifically address the treatment of tuberculosis. According to the publicly available information (much is proprietary), the most advanced oxazolidinone in this regard is ranbezolid/RBx 7644 (**78**)[408] which has undergone phase 1 clinical trials in 2004.[409] This compound has an excellent antibacterial spectrum[410] and an effect



RU66252 (**77**)

Figure 26.

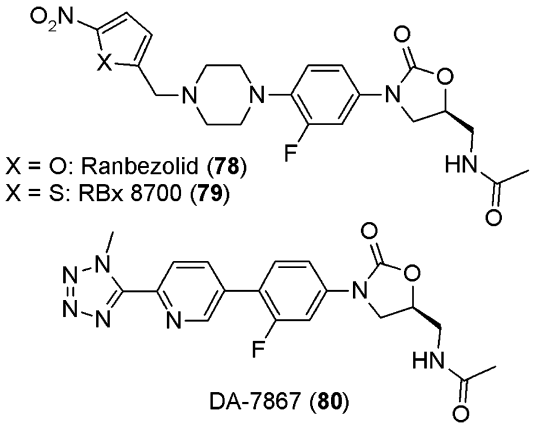


Figure 27.

on *M. tuberculosis* was noted, although the thiophene analogue RBx 8700 (**79**) seems even better.[411,412] Moreover, the presence of a nitro group on its structure raises the question whether their activity is due to an inhibition of the ribosome or to another mechanism related to the many nitro-bearing antibacterials[413,399,271] such as PA-824 (**28**) and OPC-67683 (**29**). The tetrazole-bearing oxazolidinones such as DA-7867 (**80**), are very efficient on Gram-positive aerobes as well as *M. tuberculosis*.[414,415] Although this compound was reported to have a low solubility leading to the design of more soluble prodrugs[415] it may have been selected for clinical studies[416–418] (Fig. 27).

From the recent structural knowledge gained with the use of crystallography, assays have been designed to find compounds targeting other part of the component of the 50S ribosomal subunit. Inhibition of the bacterial translation elongation factor were the focus of a screening that led to original structures with an effect on Gram-positive and Gram-negative bacteria although some of them also displayed an effect on DNA, RNA as well as cell wall synthesis.[419] From an initial hit originated by a 'structure–activity relationship by mass spectroscopy', the more classic chemist approach was undertaken. This led to, for instance, compound **81**, which inhibits the bacterial translation and is also active on bacteria[420] (Fig. 28).

The pleuromutilin class of antibiotics of which tiamulin and valdemulin are used in veterinary medicine[421] also

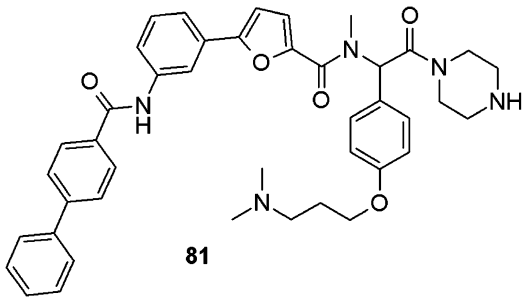


Figure 28.

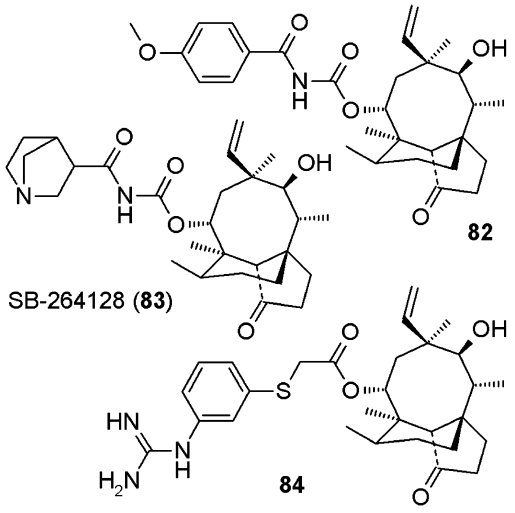


Figure 29.

targets the 50S ribosome subunit.[422–424] Renewed interest[425–428] in this class of antibiotics led, via one of the 'vagaries of mutilin chemistry', to the remarkable *N*-benzoyl carbamate derivative **82** (the corresponding ketoesters and malonamides were also patented[429,430]) which seems, so far, superior to previous hemisynthetic analogues.[425] This type of side chain provides so much more affinity to the ribosome that analogue SB-264128 (**83**) is even active on bacterial strains resistant to the older pleuromutilin derivative valdemulin.[423] Future publications will hopefully report the effect of these pleuromutilins on *M. tuberculosis* growth as other analogues, such as compound **84**, were the subjects of a recent patent for their antimycobacterial properties[431] (Fig. 29).

Nocathiacins, a series of fairly complex thiazol-containing peptides, should also be mentioned here as one of them is about 30 times more active than streptomycin (**1**) on *M. tuberculosis* growth and strains resistant to them were shown to present mutation on the 50S subunit.[432]

The significant evolutionary differences of aminoacyl tRNA synthetases[362] as well as their essential aspect make these biochemical targets attractive. Several reviews[433–437] describe antibacterials inhibiting these targets and additional inhibitors were reported more recently.[438–449] As an illustration, mupirocin (**85**) is today the most used topical antibiotic for treatment of methicillin-resistant *Staphylococcus aureus* infections. Remarkably, this substance actually inhibits isoleucyl-tRNA synthetase by competing with its normal substrate, isoleucyl-AMP (**86**).[450–452] Even if the previous generation of aminoacyl tRNA synthetases inhibitors exhibited a poor antibacterial activity or lacked selectivity,[437] much research is still undergoing. For instance, the potent antibacterial compound **87** is the result of extensive structure–activity relationship research on methionyl tRNA synthetase inhibitors.[441] (Fig. 30).

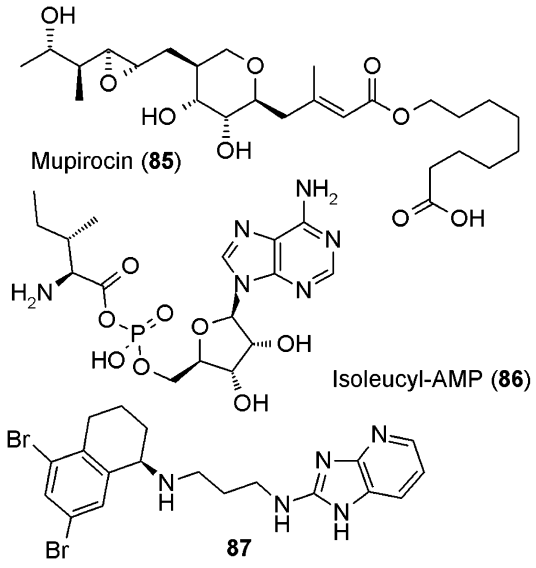


Figure 30.

Inhibitors of peptide deformylase which removes the N-terminal formyl group of newly synthesized peptides were found to be effective on *M. tuberculosis* growth. This result thus validates this biochemical process as a target for antituberculosis drugs.[453–455]

3.4. Inhibitors of DNA-based processes

3.4.1. Rifampin (4) and rifapentin (7). This class of drugs inhibits bacterial RNA synthesis by binding to the β-subunit of the DNA-dependent polymerase. Remarkably, rifamycins are the only clinically used antibiotics with this mechanism. Various alterations of the core structure were reviewed recently.[27] As for rifapentin (**7**), these modifications were designed to obtain compounds with better pharmacokinetics. However, with the exceptions of rifapentin (**7**) and the more recent rifametane, which is undergoing phase II clinical trials,[456,27] these analogues do not seem to offer an improvement when compared to rifampin (**4**). From a collection of rifampin-resistant *Staphylococcus aureus*, a research group screened these strains against other known RNA-polymerase inhibitors.[457] If the active compounds found were of little interest so far, this approach is probably sound as developing new inhibitors of mycobacteria DNA-dependent polymerase will require first of all to be better than the rifamycins. From the chemistry point of view, it could be that much of the possible alterations of the rifamycins have been tried. By modifying the gene cluster responsible for the biosynthesis of geldanamycin, another member of the ansamycin family antibiotics, biologists were able to produce remarkable analogues quite difficult to obtain otherwise.[458] It may well be that applying this strategy (if it is possible) to the preparation of rifamycin analogues would lift the apparent limits reached by the chemists and lead to better antimycobacterials. In a completely different approach, a recent patent describes carboxylic indole derivatives, such as compound **88**, which turned out to be inhibitors of *M. tuberculosis* RNA polymerase and thus useful for treating tuberculosis[459] (Fig. 31).

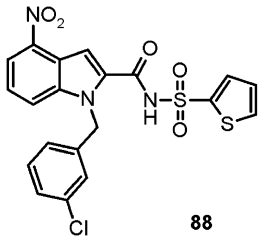


Figure 31.

3.4.2. Fluoroquinolones 12–17. The fluoroquinolones mentioned in this review are only a few representatives of the family of at least 25 related antibacterials currently used spanning four generations of analogues.[460–464] These compounds originated from a batch impurity which led first to nalidixic acid and, following an intense competition in the antibacterial field, to many related antibiotics.[461,462] The analogues made addressed the side effects, improved the pharmacokinetics, simplified dosing and extended the activity spectrum to many bacteria, including mycobacteria. As depicted in the first part of this review, many fluoroquinolones can be considered for the treatment of tuberculosis and only time and extensive clinical trials will orientate an eventually clear-cut choice. Their antibacterial mechanism of action is due to a dual inhibition of an ATP-dependent DNA gyrase (topoisomerase II) as well as, in most Gram positive bacteria, an ATP-dependent topoisomerase IV.[465–467] The detailed picture of their mode of their action is still the matter of studies.[462] Concerning their effect on *M. tuberculosis*, it can only be due to the inhibition of a topoisomerase II as no topoisomerase IV exists in this pathogen.[4,468] Recent biochemical studies actually demonstrated that this particular topoisomerase II had somewhat of a polyvalent activity and could relax supercoiled DNA as well as decatenate DNA; although less efficiently than a bacterial topoisomerase IV.[469] This fact may imply that a large spectra antibacterial quinolone may not be fine-tuned for a good effect on *M. tuberculosis* not only for the unavoidable reason of its cell wall permeability but also because of suboptimal inhibition of this specific topoisomerase II. This last aspect was addressed recently for 22 different quinolones.[468] Depending on the assay used, this work demonstrated that a correlation ($R^2 = 0.9$) exists between their inhibition of topoisomerase II and their effect on the growth of *M. tuberculosis*. The six quinolones **12**, **13b**–**17** depicted above, along with clinafloxacin (**89**), were amongst the best inhibitors according to the classification resulting from this work.[468] However, it is noteworthy that quinolone **89** had to be withdrawn from advanced clinical assessment because of unacceptable side effects (hypoglycaemia; phototoxicity).[470,471] More recently, the compound **90** bearing a remarkable side chain has been patented[472] and turns out to be at least 10-fold more active, on a panel of bacteria, than some of the currently used quinolones. A related compound (if not **90**) is undergoing preclinical trials as an antituberculosis

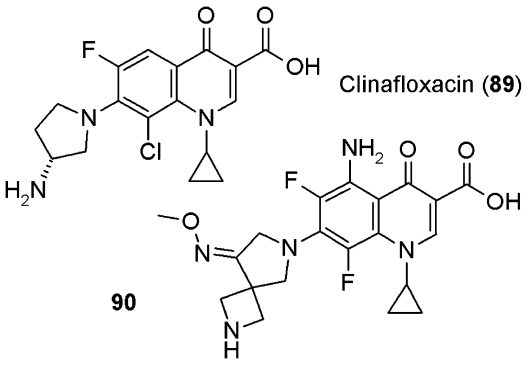


Figure 32.

drug under the name DW-224.[473] So far, few other quinolones were reported specifically for their antimycobacterial potential[474,475] (Fig. 32).

The bacterial DNA gyrase/topoisomerase II was also the subject of the research of compounds binding the ATP recognition site of the enzyme which has been reviewed.[476] As these enzymes structurally belong to the GHKL super-family, which feature a Bergerat ATP-binding fold, it is quite possible that inhibitors identified by screening programme of, for example, the mammalian heat shock protein 90,[477] are potential antibacterials.[478] On the other hand, the issue of selectivity of action of such inhibitors will have to be addressed even more than for other bacterial targets. Amongst the inhibitors recently reported,[479–486] compounds such as **91**–**93** turned out to have a good antibacterial activity and inhibited both bacterial topoisomerases II and IV. Moreover, in the case of compound **93**, very little cross resistance was observed with strains resistant to quinolones or the ATP binding site competitor novobiocin.[480] This last observation suggests another site of action, on the topoisomerases II and IV, for some of these compounds (Fig. 33).

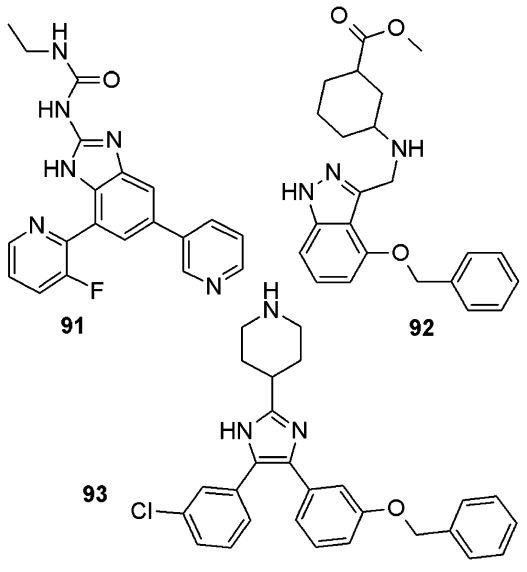


Figure 33.

The *M. tuberculosis* NAD-dependant DNA ligase has recently been the focus of research which led to dimeric pyrans of furan-bearing inhibitors.[487–489] Further work will hopefully lead to the validation of this target for the design of original antimycobacterials.

3.5. Inhibitors of dihydrofolate reductase or siderophore biosynthesis

3.5.1. *p*-Aminosalicylic acid (2). The mechanism of action of *p*-aminosalicylic acid (**2**) is still the subject of research. Recently, some of the *M. tuberculosis* strains resistant to this compound were found to have developed a reduced thymidylate synthase activity which interferes in fine with folate levels.[490] Previously suggested mechanism involved an interference with salicylic acid metabolism which would interfere in fine with *M. tuberculosis* iron intake.[491–493] As (a) a direct inhibition of any enzyme has not yet been demonstrated; (b) seven out of the ten clinical *M. tuberculosis* isolates mentioned above did not have a reduced thymidylate synthase activity,[490] further investigations are probably necessary. Aside from Schiff base conjugates,[494] little has been reported about analogues of *p*-aminosalicylic acid (**2**). On the other hand, as described below, research on the inhibition of mycobacterial dihydrofolate reductase[495,496] and on inhibition of the iron chelating siderophore biosynthesis[497–500] met some success.

The dihydrofolate reductase inhibitors have been reviewed recently.[496] Amongst noteworthy features, the antibacterials trimethoprim (**94**) or epiroprim (**95**) are poorly effective on mycobacteria.[501,502] Many folate analogues were made[503] and compound **96** is a good inhibitor of *Mycobacterium avium* complex growth with a quite high selectivity of action on mycobacteria versus human dihydrofolate reductase.[504] Surprisingly, a related series of analogues, such as **97**, are inhibiting

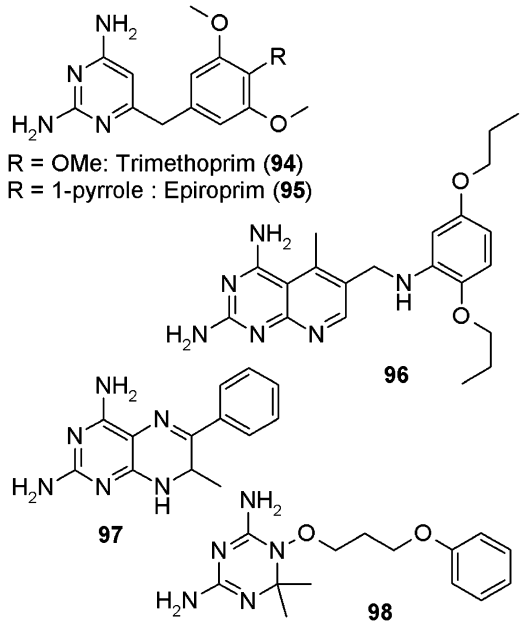


Figure 34.

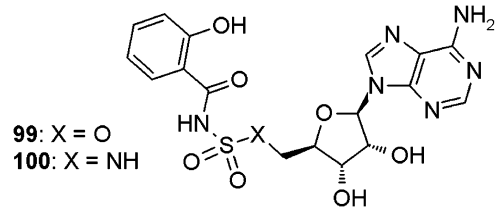


Figure 35.

M. tuberculosis growth in vitro but do not inhibit mycobacterial dihydrofolate reductase.[505] Triazines such as **98** were reported for their inhibition of dihydrofolate reductase and of mycobacterial growth in vitro.[506] However, antimalarial trials with a related analogue[507] pointed out gastrointestinal side effects[508] that prevented any further development.[496] A high throughput screening of inhibitors of *E. coli* dihydrofolate reductase was partially reported; remarkably, some of the inhibitors found were devoid of the recurrent diaminated pyrimidine pharmacophore (or its open form). Moreover, as mentioned above, isoniazid-NAD adducts such as **33** also inhibits this enzyme[129] (Fig. 34).

The inhibition of mycobactin biosynthesis, the iron chelating siderophores of *M. tuberculosis* critical for its growth in macrophage[509] and virulence,[510] has been the subject of some studies.[511,493,512] The two closely related compounds **99** and **100** were recently reported to inhibit the incorporation of salicylic acid in the mycobactin structure by mimicking the normal substrate (the phosphate homologue).[499,500] These compounds are also inhibitors of *M. tuberculosis* growth (Fig. 35).

3.6. Inhibitors of the proton pump $F_0F_1H^+$ATPase

3.6.1. TMC 207 (27). The antituberculosis mechanism of action of these diarylquinolines is the inhibition of mycobacterial proton pump $F_0F_1H^+$ATPase.[68] Remarkably, four additional patents are claiming structurally distinct diarylquinolines such as **101**,[67,513–515] and the same research group has obtained X-ray derived structures of this enzyme[516] and has reported structural researches in this regard.[517] Moreover, another patent claimed ATP synthase inhibitors, most of them of a peptidic nature, for the specific treatment of mycobacterial infections.[518] Also of great interest are the facts that the antimalarial mefloquine (**102**) is also active on *M. tuberculosis* growth[519–521] and that it inhibits the proton pump $F_0F_1H^+$ATPase of *Streptococcus pneumoniae*.[522] Some analogues were made and for instance, compound **103** is also inhibiting the proton pump $F_0F_1H^+$ATPase of *S. pneumoniae*.[522] These results triggered renewed structure–activity relationship studies of mefloquine (**102**) analogues and the more active hydrazone derivative **104** was reported.[523] It is very tempting to mention here the many quinoline derivatives,[524–530] such as **105**, that have been reported for their antimycobacterial activity in the last four years and for which no mechanism of action has been published yet. Probably unrelated to all these compounds, the most simple

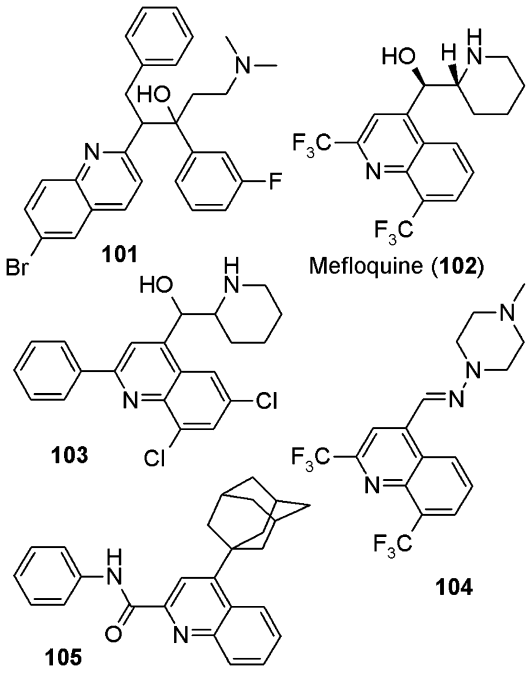


Figure 36.

5-chloroquinolin-8-ol was also recently reported for its remarkable antimycobacterial properties.[531] From the structural point of view, some tantalizing similarities between compounds **101**–**105** exist, although further studies are required to establish the hypothesis that all these compounds interfere with the mycobacterial proton pump $F_0F_1H^+$ATPase (at first look, TMC 207 (**27**) is quite different from **101**) (Fig. 36).

3.7. Inhibitors of mycobacterial cytochrome P450 mono-oxygenases

From the results of the assays of some antifungal and antihelmintic drugs on the growth of *M. tuberculosis*,[532] it turned out that the azole class of antifungal, such as econazole (**106**) or clotrimazole (**107**) were of interest against mycobacteria.[533–535] It is likely that their target in mycobacteria is the P450 mono-oxygenase homologue to the eukaryotic 14α-sterol demethylases (CYP51)[533,534] and that the imidazole moiety is binding the iron of these haem-containing enzymes.[536] X-ray derived structures of this enzyme were obtained[537,538] and econazole was reported to have an antituberculosis activity in vivo on a murine model.[539] Moreover, the recently reported X-ray structure of a *M. tuberculosis* P450 CYP121-fluconazole complex will probably lead to specific structure activity relationship studies.[540] Some original inhibitors were reported for their specific activity against mycobacteria.[541,542] Compound **108** featuring the 2,4-dichloro and 4-chlorophenyl pattern has a slightly better activity than compound **106** or **107**.[541] Moreover, the so far, targetless antimycobacterial hydantoin **109**[543] and a much less related pyrazolone[544] could deserve to be placed in this section too (Fig. 37).

Concerning structural similarities, the imidazole-containing analogue **110** was reported some time ago for

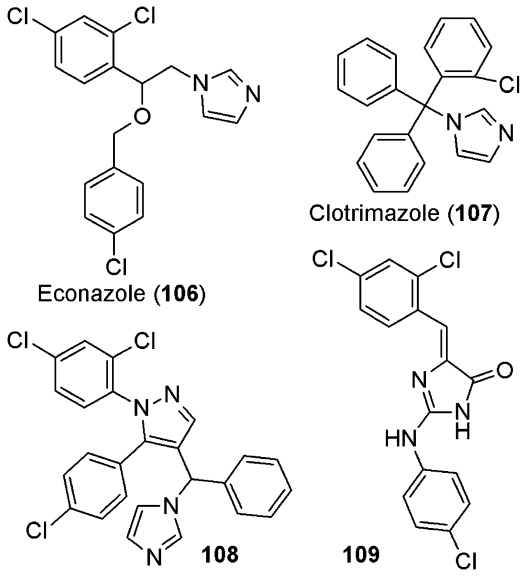


Figure 37.

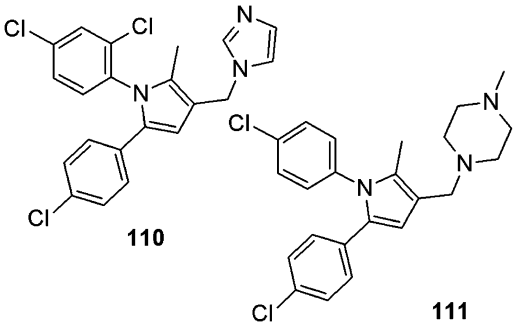


Figure 38.

its inhibition effect on *Candida* growth.[545] Further work pointed out that this imidazole moiety could be replaced by a piperazine.[546] From these considerations, we do suggest that the pyrrole series of antimycobacterials such as compound **30**, eventually **31** and other imidazole-containing derivatives[547] are inhibitors of at least one of the *M. tuberculosis* cytochrome P450 monooxygenases. Thus, the thiomorpholine group of **30** or the *N*-methylpiperazine moiety of other more toxic derivatives, such as BM212 (**111**),[77,79] would play the iron-binding role of the imidazole moiety (Fig. 38).

3.8. FtsZ targeting compounds

The FtsZ protein is the bacterial tubulin homologue and thus crucial for cell division.[548,549] From this, tubulin polymerisation inhibitors were tested on mycobacterial growth[550–553] For instance, the antihelmintic tubulin polymerisation inhibitors albendazole or thiabendazole are weakly effective on mycobacterial FtsZ polymerisation.[532,554] Moreover, many screenings of inhibitors were designed.[555–561] The antibacterial thioether-bearing compound **112** is one of the results of a screening for bacterial cytokinesis inhibitors.[560] Remarkably, a taxane derivative with a similar diphenylthioether moiety was

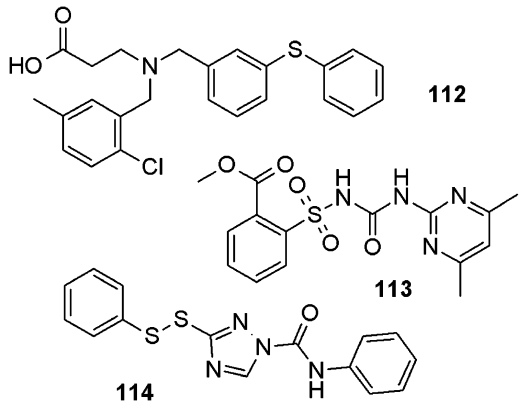


Figure 39.

also reported for its inhibition of *M. tuberculosis* growth.[562] Of note are carbamoyl-bearing pteridines originally designed to target dihydrofolate reductase; as well as related pyridines, which turned out to inhibit FtsZ.[550,551] Moreover, the biochemical processes regulating *M. tuberculosis* functions of this protein are still unknown and thus the subject of recent investigations.[563,564]

3.9. Inhibitors of branched-chain amino acid biosynthesis

The herbicides, such as sulfometuron methyl (**113**) which inhibits the branched-chain amino acid biosynthesis, were found to have an effect on mycobacterial growth.[565,566] More recent results were reported starting with the use of a cloned *M. tuberculosis* acetohydroxyacid synthase. This work confirmed that this enzyme is the target of **113**. Moreover, the modestly antimycobacterial disulfide **114** is one of the reported inhibitors resulting from the ensuing screening of chemical libraries[567] (Fig. 39).

3.10. Nucleoside monophosphate kinase inhibitors, pyrimidine or purine nucleoside analogues

The thymidine kinase of *M. tuberculosis* sequence is reasonably different (only 22% homology) from the human homologue to represent an original target for the design of antituberculosis drugs.[568] Moreover, X-ray derived structures[569,570] provided starting points for computer-based inhibitor design.[571] Thymidine analogues were

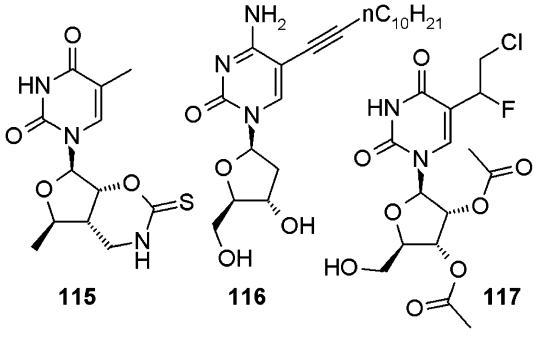


Figure 40.

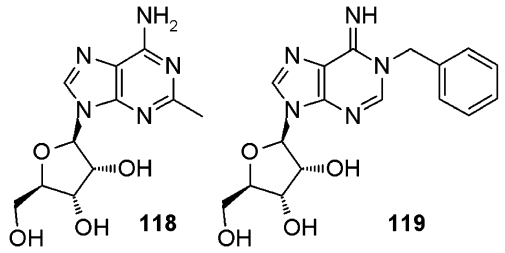


Figure 41.

thus prepared and some turned out to inhibit the *M. tuberculosis* thymidine kinase.[572–577,571,578] If the first enzyme inhibitors were devoid of antimycobacterial properties, probably because of a lack of solubility, the more lipophilic bicyclic thymine derivative **115** is a weak inhibitor of *Mycobacterium bovis* growth.[578] More recently, benzyl pyrimidine derivatives devoid of a ribose moiety have been patented for their inhibition of this enzyme.[579] Following a completely different non-focused strategy, analogues of pyrimidine nucleoside were assayed for their potential inhibition of mycobacteria growth. A series of 5-substituted alkynylpyrimidines turned out to be of interest and dodecynyl-bearing cytidine analogue **116** or the acetylated derivative **117** are amongst the most effective of the series.[580,581] It would, of course, be of interest to determine what is (are) the biochemical target(s) of these last two compounds; but can we even assume that these targets are involved in pyrimidine nucleoside chemistry? (Fig. 40).

In a similar fashion, purine nucleoside analogues were tested for their activity on *M. tuberculosis* and 2-methyladenosine (**118**) is an inhibitor of its growth.[582] Remarkably, it appears that its mechanism of action is associated with DNA synthesis.[583] In a more mechanism-focused approach, adenosine analogues were assayed for their inhibition of *M. tuberculosis* adenosine kinase. This study confirmed that methyladenosine (**118**) is a substrate of this kinase and that the *N*-benzyl derivative (**119**) is amongst the inhibitors. Further structure activity relationship studies of adenosine analogues inhibiting this enzyme have been reported recently.[584,585] (Fig. 41).

3.11. Signalling kinase inhibitors

It is likely that the survival of *M. tuberculosis* against the macrophage phagocytosis relies not only on a thick cell wall[586] but also on many of the mycobacterial kinases (or phosphates) which disrupt the host-cell defence mechanism against such parasitism.[65] The intensive research existing in the kinase inhibitors in general may well lead to antimycobacterial compounds hampering these processes.

- Bacterial two component signal transduction system, which involves a histidine kinase, was the focus of research of original antibacterials.[587–592] Concerning the specific inhibition of such signal transduction system in mycobacteria, a series of antimycobacterial salicylanilides were recently reported[593,594] as related compounds had been reported to inhibit the two component signal system of other bacteria.[595,596] Inhibiting this regulatory system probably remains a worthy research subject since a regulation of this type is involved in the virulence of *M. tuberculosis* in mice.[597]
- Eleven putative eukaryotic-like protein serine-threonine kinases (Pkn A to L) involved in signal transduction were identified in *M. tuberculosis* H37Rv genome.[4,598–600] Moreover, the 'generic' kinase inhibitor **120**[601] as well as other more complex compounds[602] were shown to inhibit the growth of some mycobacteria. This last result provided an impetus for the research of more specific inhibitors. The X-ray derived structures of the catalytic domains of PknB and PknE were reported,[603–605] the existence of a predicted transmembrane helix in their peptidic sequence greatly hampers the crystallisation of the full enzyme. On the other hand, PknG does not have a transmembrane domain and could be a secreted protein enabling the mycobacteria survival within the macrophages.[606] This suggestion[607,608] is probably very important as there would thus be no need for a PknG inhibitor to pass the mycobacterial cell wall to reach this enzyme. In the case of PknB, it was recently reported to be essential for *M. tuberculosis* growth[609] and the antitumural drug mitoxantrone was found to be an inhibitor by binding to its ATP recognition site.[610] Concerning PknG, the specific inhibitor benzothiophene **121** was reported to be inactive on the growth of *M. tuberculosis* in vitro but to have a dose dependent inhibition effect on mycobacteria grown inside macrophages.[606,611] Moreover, benzoquinoxalines such as **122** were patented by the same research group for their inhibition of PknB, PknG and PknH as well as for their effect on mycobacterial growth.[612] This last compound is actually reminiscent of quinoxalin 1,4-dioxyde derivatives such as **123** reported only for their antimycobacterial effect.[613–615] (Fig. 42).
- Although no such enzymes exist in mycobacteria, tyrosine kinase inhibitors for the treatment of pathogenic (including mycobacteria) were mentioned in a patent.[616] A subsequent report by the same research

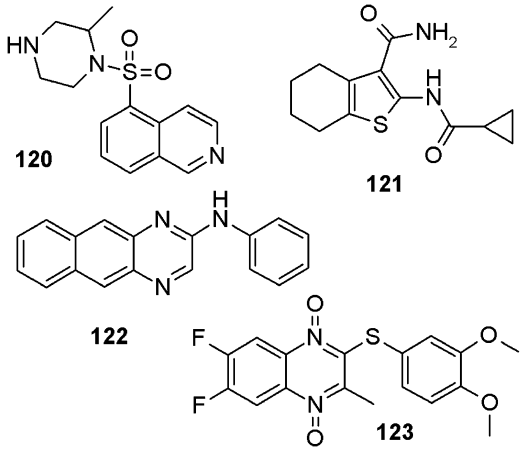


Figure 42.

group describes the inhibition of Abl-family tyrosine kinases for the inhibition of poxvirus pathogenesis by STI-571 (Gleevec).[617] In an 'opposite' approach, mycobacterial tyrosine phosphatase inhibitors, which are secreted by mycobacteria,[618] have been suggested for the research of new antimycobacterials.[65] Two reports describing two families of cyclic peptides were published recently.[619,620] An ensuing fragment-based approach as well as a screening led to the identification of several low molecular weight hits in one instance. However, eventual results of inhibition assays on the *M. tuberculosis* growth were not mentioned.[619]

3.12. Miscellaneous mechanism-based inhibitors

The probably too weak antituberculosis properties of the phenothiazine derivative (**124**) were investigated.[621,622] However, since these compounds are inhibitors of type II NADH:menaquinone oxidoreductase, further research in this direction may be of interest.[623] The study of the effect of gemfibrozil (**125**), a drug used for hyperlipidemia and a peroxisome proliferation inducer, on *M. tuberculosis* metabolism may herald further work on some of its oxidoreduction-based processes.[624] The co-administration of IMiD3 (**126**), a thalidomide analogue, in the course of the treatment of an experimental model of tuberculous meningitis pointed out a potential benefit. The immunomodulatory mechanism of action of thalidomide which is still the matter of research may be explaining an indirect effect of **126** on *M. tuberculosis* growth in vivo.[625] (Fig. 43).

3.13. Recently reported antimycobacterials devoid of a mechanism of action

A complete list of all the series of antimycobacterials reported in the last decade would only attempt to copy a recent report which did a really good work of reviewing them.[8] We will only provide here a selection of original compounds reported after the publication of this work.

From the result of a screening, tetracyclic structures such as the aminated derivative **127** were prepared. However, if this analogue is still an antimycobacterial it also remains quite cytotoxic.[626] This is unfortunately

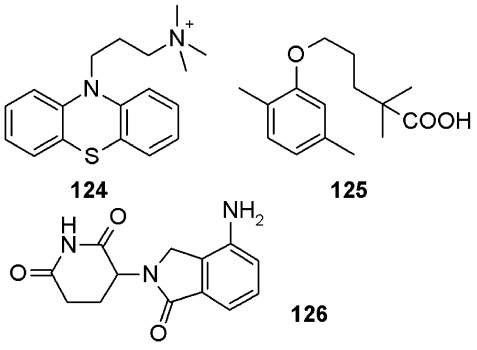


Figure 43.

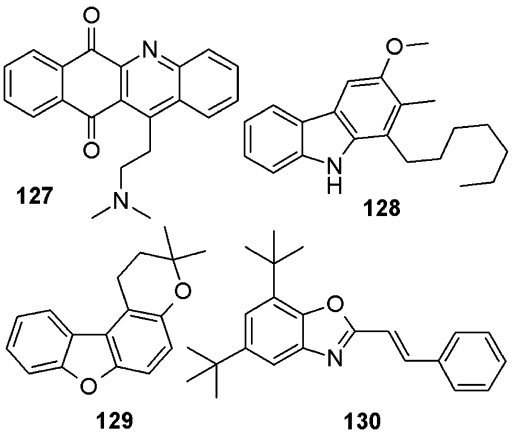


Figure 44.

the same for many carbazoles such as **128**[627] which are reminiscent of dibenzofurans reported some time ago.[628–630] Antimycobacterial benzofurobenzopyrans such as **129** have a notable selectivity for mycobacteria.[631] This type of compound is actually currently keeping us busy.[632,633] Highly lipophilic benzoxazoles such as **130** are even more selective as this compound is only effective on *M. tuberculosis* and on none of the other mycobacteria tested.[634] Further works were recently reported on a series of indolizines bearing very lipophilic substituents[635] (Fig. 44).

Extensive structure–activity relationship was reported for a series of 6-substitued purines such as **131**.[636,637] Again, a specificity of action against mycobacteria was noted. Remotely related purines such as **132** were also reported.[638] Two types of arylketones such as **133**[639] or **134**[640] were found to be inhibitors of mycobacterial growth (Fig. 45).

Last but not least, four different natural product series were reported for their antimycobacterial properties. The basiliskamide A **135**[641] and quinolones such as **136**[642] only share a lipophilic character and the pamamycin-607[643] **137** or the lydiamycin A[644] **138** a macrocyclic structure (Fig. 46).

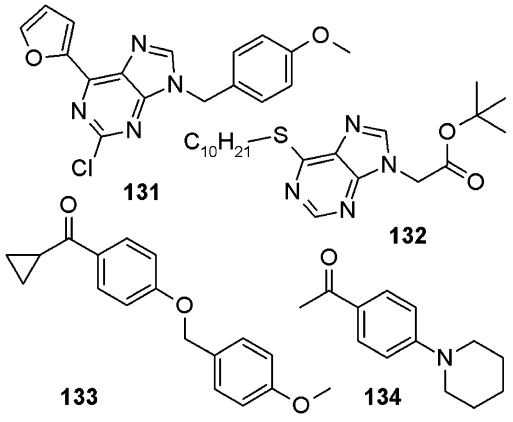


Figure 45.

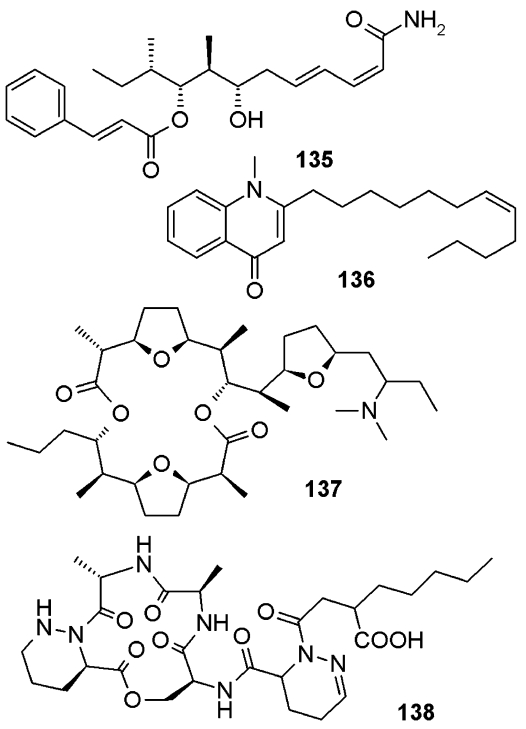


Figure 46.

4. Conclusion

Although not all the results were reported, it is likely that a fair proportion of the organic compounds synthesized or isolated in the last 100 years have been assayed for their eventual inhibition of *M. tuberculosis* growth, either in vitro or in vivo, in the past 60 years. From this, came out many antituberculosis drugs with, in a number of cases, remarkably simple structures as well as even more remarkable mechanisms of action. The problem of resistant strains was identified quickly after the introduction of the first drug and antituberculosis polychemotherapy became the norm decades before it had to be implemented for AIDS therapy. This, along with improved sanitary precautions, provided the world a respite from this ancient human disease. However, the multiresistant strains recurrently isolated from patient's sputum darken the future. If today this happens mostly in places not usually targeted by the market research department of the pharmaceutical industry, its incidence will be increasing everywhere in the future.

Due to this concern, the mid 1990s saw renewed in vitro 'blind' screening programmes as well (quite 'blind') structure–activity relationship studies. It is this strategy that provided the five classes of compounds under clinical studies listed above. Unfortunately, it may well be that none of these antimycobacterials are suitable for tuberculosis treatment and thus the research efforts must be continued. The rational approaches involving the determination and biological validation of a biochemical process as a good antituberculosis target, which would provide a better 'vision', were also initiated at that time. This is resulting today in vast amount of screenings of available chemical libraries on many identified targets.[17,19] This fairly often led to original series of compounds that have yet to go into clinical studies. In any case, whatever the strategy used for a hit identification, some new compounds will hopefully pass throughout the pharmaceutical pipeline process leading to new antituberculosis drugs although money and pharmaceutical industry investment policies are crucial issues at that stage.[645]

At the bench level, many *M. tuberculosis* biochemical transformations have been identified as potential targets for original antituberculosis treatment today.[17,19] In view of this wealth, it seems, to our probably biased chemist point of view, that the current limiting factor at our level is not anymore the availability of new biochemical targets but may well be the access to original (i.e., untested) chemical compounds. There are two sources of new chemical entities. The first is the extraordinary diversity provided by natural product extraction, biological evaluation and characterization. The second results from original compounds made more accessible by the design of new, or the modernisation of, synthetic transformations. That is: how many more original compounds can be made if a six-step synthetic pathway to a series of potential interest is shrunk to three steps? To improve the chances of success of this second approach, chemist should also aim at enlarging the chemical pool with new entities featuring reasonably 'druggable' structures. This last term is fairly difficult to define, it is also outside of the scope of this review, although Lipinski rule of five is probably a good starting point.[646]

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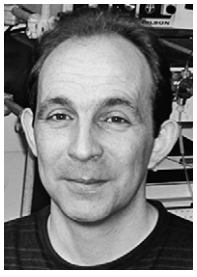

Yves Janin obtained his PhD in organic chemistry in 1993, from the University of Paris VI, under the guidance of Dr. Emile Bisagni at the Institut Curie. Following a year without any employment in science, he joined, for a two year long post-doc, Dr. David S. Grierson at the ICSN, Gif/Yvette, France. He then enjoyed a postdoctoral year in Prof. Povl Krogsgaard-Larsen research laboratory at the Danish School of Pharmacy in Copenhagen. Following six years in the Institut Curie as a junior CNRS scientist, he went on a sabbatical year in Vitry/Seine Aventis research facilities before joining the Institut Pasteur in 2004. Throughout 15 years he worked on various medicinal chemistry-driven syntheses of heterocyclic derivatives concerning oncology, virology, neurobiology and now infectious diseases.