Natural and Synthetic Compounds with an Antimycobacterial Activity

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Abstract: This review discusses the most active natural and synthetic compounds demonstrating the antimycobacterial activity at minimum inhibiting concentrations (MIC) of 5 μg/ml or less. For better insight into the "structure-activity" relationships, we occasionally considered compounds with high values of MIC. The review covers the period from 2001 to 2007. The data are grouped according to chemical structures, namely, nitrogen-, oxygen-, and sulfur-containing heterocyclic compounds, peptide, alkaloids, terpenoids, and others.

Keywords: Tuberculosis, multidrug-resistance tuberculosis, *M. tuberculosis*, antimycobacterial activity, antituberculosis activity, cytotoxicity, "structure-activity" relationships.

1. INTRODUCTION

Tuberculosis is a chronic infectious disease, one of the major enemies of the humanity from times immemorial. Today it still remains one of the most serious medical and social problems. It is responsible for 3 million deaths per year and around 8 million cases of first-recorded disease. The advances in the chemotherapy of tuberculosis in the mid-20th century have recently given way to anxiety over the evolution of drug resistance based on the genetically fixed mutations of *M. tuberculosis*. Moreover, nearly all drugs used for the treatment of tuberculosis and possessing different mechanisms of activity are able to cause adverse side effects on the human organism. Therefore, it is extremely important to search for new, low-toxic substances superior to the available drugs in their activity and efficiency. This primarily concerns the agents possessing activity against *M. tuberculosis* strains with multidrug resistance.

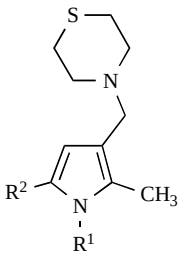
Modern tuberculosis is generally associated with *M. tuberculosis* and *M. bovis*, mycobacteria that are pathogenic to the human organism. Because of slow growth and pathogenicity of *M. tuberculosis* H37Rv, many research groups used fast-growing and/or nonpathogenic mycobacteria including *M. tuberculosis* H37Ra, *M. smegmatis*, *M. aurum*, and others as organisms to be tested. The antimycobacterial activity was also investigated on *M. avium* and *M. intracellulare*, which cause bird tuberculosis and are associated with human diseases in advanced countries (AIDS patients and immunocompromised individuals), to find compounds with a wide range of activity. A special group of research works includes investigations on *M. tuberculosis* clinical isolates and strains possessing multidrug resistance. Multidrug-resistant tuberculosis (MDRTB) is strictly defined as *M. tuberculosis* strains showing resistance simultaneously against isoniazid and rifampicin [1, 2]. Tuberculosis with a different drug resistance (DDRTB) involves *M. tuberculosis* strains displaying mono- or polyresistance not including associated resistance against isoniazid and rifampicin [3]. *M. tuberculosis* strains may be sensitive (inhibited by first series drugs such as isoniazid) or resistant (not inhibited by isoniazid). Since researchers use different analytical procedures and/or organisms under test, care should be taken in comparing the biological activities obtained by different authors.

The review covers publications from 2001 to 2007; the selected structures have minimum inhibiting concentrations (MIC) of 5 μg/ml or less. Due to this limitation, the most effective compounds were analyzed within one review. For better insight into the "structure-property" relationship, we occasionally gave structures with higher MIC values. The review includes the introduction section, two chapters on synthetic and natural compounds with an antimycobacterial activity, and the conclusions section. To reveal possible "structure-activity" relationships, we grouped the data according to chemical structures.

2. SYNTHETIC COMPOUNDS WITH AN ANTIMYCOBACTERIAL ACTIVITY

a. Nitrogen-Containing Heterocycles

The (thiomorpholin-4-yl)methyl fragment at the C-3 atom of the pyrrole ring is the key feature that is essential to the antituberculosis activity of new 1,5-diarylpyrroles against *M. tuberculosis* 103471 and atypical mycobacteria since the N-methylpiperazinomethyl derivatives are more toxic and less active than the corresponding thiomorpholinomethyl compounds. The antituberculosis activity of the thiomorpholinomethyl derivatives can be improved by introducing a second halophenyl substituent in the molecule (a strong effect is produced by the nature of the halogen atom) and a methyl group, which is more lypophilic than the halogen atom, in the second phenyl ring. New compounds **(1)**, **(2),** and **(3)** (MIC 1, 0.4, and 0.5 μg/ml, respectively) were found, whose activity with respect to *M. tuberculosis* was comparable to that of isoniazid, streptomycin, and rifampicin. The cytotoxicity of these compounds is lower than that of isoniazid and streptomycin and comparable to that of rifampicin. Remarkably, compounds **(1)**, **(2)**, and **(3)** are active against the intracellular (intramacrophage) *M. tuberculosis*; in this case, the MIC of **(1)** (1 μg/ml) is three times lower than that of rifampin (3 μg/ml). Moreover, compounds **(1)**, **(2)**, and **(3)** are active against different strains and clinical isolates of *M. tuberculosis* resistant to one or more drugs. Note that the pyrroles presented here show high selectivity with respect to *M. tuberculosis* and are inactive against the atypical mycobacteria *M. gordonae* 6427, *M. smegmatis* 103599, *M. marinum* 6423, and *M. avium* 103317 (generally, MIC > 16 μg/ml) [4, 5].



(1) R^1 = 2-F-Ph R^2 = 2-F-Ph
(2) R^1 = 4-F-Ph R^2 = 4-CH_3-Ph
(3) R^1 = 2-F-Ph R^2 = 4-F-Ph

Oxazolidinones, a new class of synthetic antimicrobial drugs, have no cross resistance to other types of antibiotic because of the different mechanism of activity. Among these are linezolide **(4)** (MIC 0.25-2 μg/ml for *M. tuberculosis* H37Rv, sensitive and resistant clinical isolates) and its thiomorpholine analog PNU-100480 **(5)**, exhibiting an interesting antituberculosis activity. In continua-

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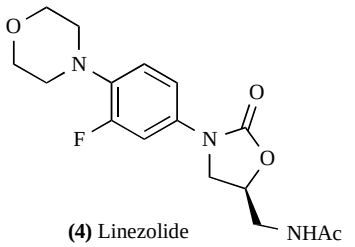
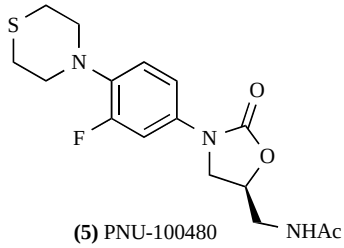
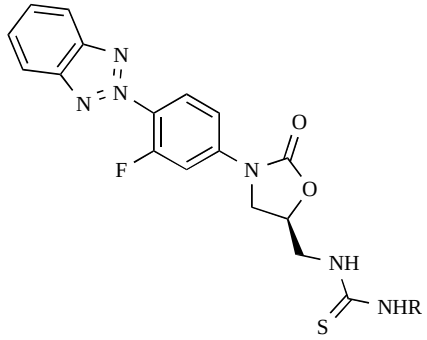


(4) Linezolide



(5) PNU-100480

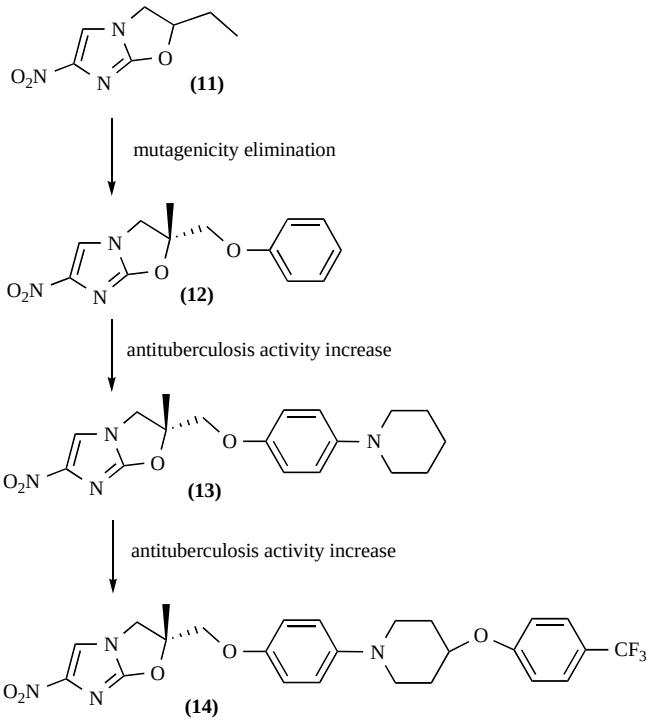


R = NH_2, NHCO-4-pyridyl, $CH(Et)CH_2OH$, $CH_2CH(OEt)_2$, $CH_2CH_2NH_2$ (**6**), CH_2CH_2-2-pyridyl (**7**), cyclopropyl (**8**), CH_2CH_2-pyrrolidine (**9**), CH_2CH_2-piperidine (**10**), CH_2CH_2-morpholine

tion of the work on the creation of antituberculosis drugs, a new series of 1-[3-(4-benzotriazol-1/2-yl-3-fluorophenyl)-2-oxo-oxazolizin-5-ylmethyl]-3 derivatives of thiourea were synthesized. The activity of these compounds was completely lost when the hydrogen atom in the terminal ethyl group of thiourea was replaced with a morpholine fragment. A considerable activity against various types of mycobacteria (*M. tuberculosis* H37Rv, sensitive and resistant clinical isolates) was exhibited by compounds **(6)-(9)** (MIC 0.5-8 μg/ml) having the amino, 2-pyridyl, 1-pyrrolidinyl, and 1-piperidinyl groups ethyl-bridged with thiourea. The replacement of ethyl with cyclopropyl led to the formation of compound **(10)**, possessing an excellent antituberculosis activity (MIC 0.06-2 μg/ml) comparable to that of linezolide and exceeding that of isoniazid for all tested strains [6].

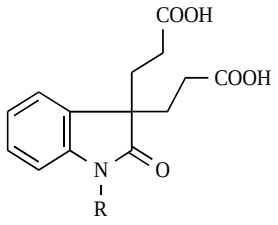
Stepwise modification of long-known bicyclic nitroimidazooxazole **(11)**, possessing not only *in vitro* antituberculosis activity and *in vivo* efficiency but also mutagenicity, was carried out effectively. Compounds not possessing mutagenicity were found among structures with heteroatomic substituents in the 2nd position of 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole; the (*R*) form **(12)** proved more active (MIC 0.05 μg/ml against *M. tuberculosis* H37Rv). The antituberculosis activity was improved by sequentially introducing a hydrophilic (compound **(13)**, 0.39-0.78 μg/ml against resistant *M. tuberculosis* H37Rv and *M. tuberculosis* H37Rv) and lypophilic (compound **(14)**, MIC 0.006 μg/ml against resistant *M. tuberculosis* H37Rv and *M. tuberculosis* H37Rv) substituents in the molecule. Based on its excellent *in vitro* antituberculosis activity against drug-susceptible and drug-resistant strains of *M. tuberculosis* H37Rv and *in vivo* efficacy in mice infected with *M. tuberculosis* Kurono, compound **(14)** was selected as an active candidate (administered orally) for the treatment of tuberculosis. Remarkably, compound **(14)** shows as high *in vivo* efficiency as that of rifampicin when used at lower doses for oral administration (0.313 mg/kg and 5 mg/kg, respectively) [7].

The spiro derivatives of oxyindole **(15), (17) (**MIC 0.1 μg/ml for each), and **(16) (**MIC 0.05 μg/ml) possess an antituberculosis activity against *M. tuberculosis* H37Rv comparable to that of isoniazide (MIC 0.025–0.2 μg/ml) and refampin (MIC 0.06–0.5 μg/ml) [8].

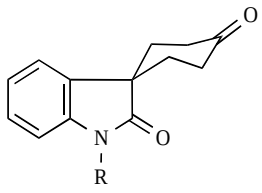


Compounds **(18)** and **(19)** (MIC <0.25 and 0.5 μg/ml, respectively), which are most active against *M. tuberculosis* H37Ra among pyrazine and quinoxaline acid esters tested, have a 4-acetoxybenzyl substituent in the phenyl ring. Curiously, the 2-nitro- and 4-nitrobenzyl analogs possess much lower activity. This indicates that under the given conditions (pH 6.6), the nitro group does not undergo bioreduction to the amino group; instead, the 4-acetoxy group undergoes enzymatic deacylation [9].

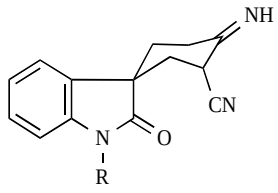
The analogs of the first-line drug pyrazineamide, having aryl substituents in the piperazine ring, possess antituberculosis activity *in vitro* and *in vivo* against the *M. tuberculosis* H37Rv and MDR strains resistant to isoniazid, rifampicin, pyrazineamide, and oflox-



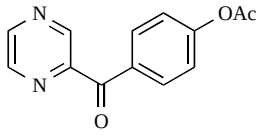
(15) R = Me, Et



(16) R = Me, Et



(17) R = Me, Et



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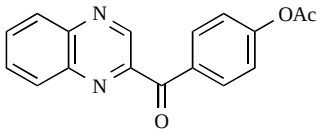

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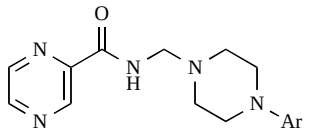
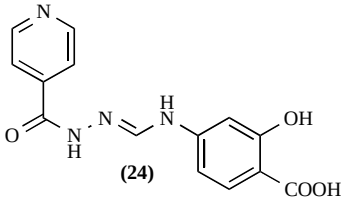


Ar = Bz, Ph, 4-ClPh **(20)**, 3-ClPh **(21)**, 4-ClPh **(22)**, 4-CF_3Ph **(23)**



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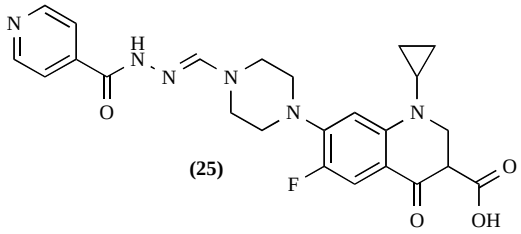

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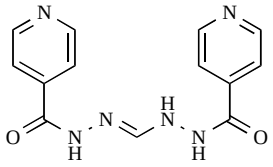

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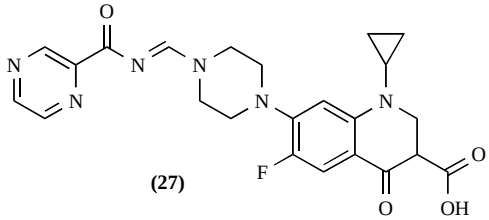

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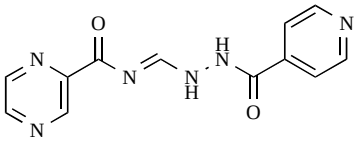

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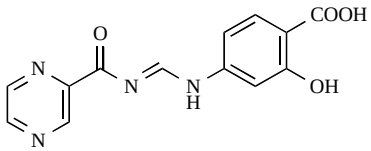


(29)

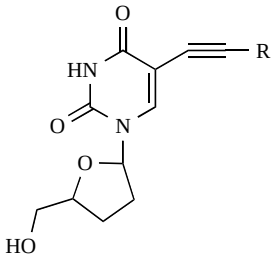
acin; these are compounds **(20)** (MIC 3.12 and 12.5 μg/ml), **(21)** (MIC 3.12 and 6.25 μg/ml)**, (22)** (MIC 1.76 and 1.76 μg/ml)**,** and **(23)** (MIC 0.78 and 1.76 μg/ml). Their activity is enhanced by the halogen-containing substituents (Cl, F) of the aryl ring [10].

Isoniazid and pyrazineamide are widely used, generally in combination with other pharmaceuticals, as first-line drugs for the treatment of tuberculosis. Antituberculosis compounds of a new type were developed and synthesized, which could be regarded as "double active" molecules because isoniazid or pyrazineamide in them were linked via the CH group to another standard antituberculosis drug (ciprofloxacin, *para*-aminosalicylic acid). The resulting compounds **(24)** (MIC 0.39 μg/ml), **(25)** (MIC 3.13 μg/ml), **(26)** (MIC 0.39 μg/ml), **(27)** (MIC 0.78 μg/ml), **(28)** (MIC 3.13 μg/ml), and **(29)** (MIC 0.1 μg/ml) possess a very high antituberculosis activity against *M. tuberculosis* H37Rv (MIC is 0.025-0.2 μg/ml for isoniazid, 6-60 μg/ml for pyrazineamide, and 2.00 μg/ml for ciprofloxacin); this is attributed to the synergetic action of the components and high lypophilicity of the products, facilitating effective transport of molecules across cell membranes [11].

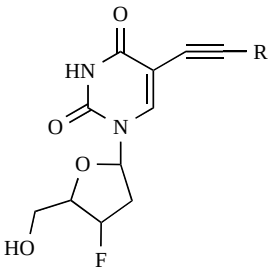
New inhibitors with effective and selective antituberculosis activity against *M. bovis*, *M. tuberculosis*, and *M. avium* were found, namely, the acetylene derivatives of 2′,3′-dideoxyuridine and 3′-fluoro-2′,3′-dideoxyuridine. Compounds **(30**) and **(31**) are the most promising members of this class; they effectively inhibit growth of *M. bovis*, *M. tuberculosis* (MIC_{90} 1-2 μg/ml), and drug-resistant strains of *M. tuberculosis* [12].

The activity against *M. tuberculosis*, *M. bovis*, and *M. avium* was investigated in the series of 1-*β*-D-2′-arabinofuranosyl- and 1-(2′-deoxy-2′-fluoro-*β*-D-ribofuranosyl)pyrimidine nucleosides with different substituents at the C-5 atom of uracil (alkynyl, alkenyl, alkyl, and halogen). High antituberculosis activity against *M. tuberculosis* and *M. bovis* was found for nucleosides **(32)** (MIC_{90} 1-5 μg/ml), **(33)** (MIC_{90} 1-5 μg/ml), and **(34)** (MIC_{90} 1 μg/ml). The MIC_{90} of these compounds were comparable to the corresponding characteristic of rifampicin (MIC_{90} 0.5-1 μg/ml). However, these compounds in the same concentrations also actively inhibit growth of the rifampicin-resistant strain of *M. tuberculosis* H37Rv [13].

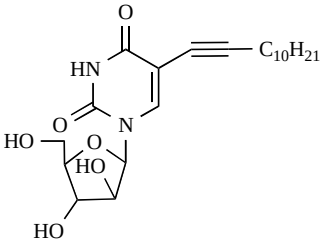
The new quinoxaline derivatives show high efficiency, selectivity, and low cytotoxicity. Their antituberculosis activity depends on the nature of the R^1 substituent in the quinoxaline ring; the chloro, methyl, and methoxy groups in the 7th position of the benzene ring decrease the minimum inhibiting concentration. The activity of



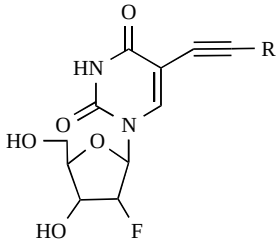
R = $(CH_2)CH_3$, $(CH_2)_7CH_3$, $(CH_2)_9CH_3$ (**30**), $(CH_2)_{10}CH_3$, $(CH_2)_{11}CH_3$, C_6H_5



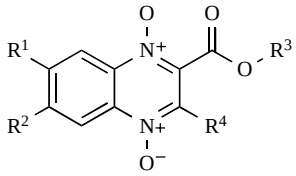
R = $(CH_2)_4CH_3$, $(CH_2)_7CH_3$, $(CH_2)_9CH_3$, $(CH_2)_{10}CH_3$, $(CH_2)_{11}CH_3$ (**31**), 4-Pr-C_6H_4



(**32**)



R = $C_{10}H_{21}$ (**33**), $C_{11}H_{23}$ (**34**)



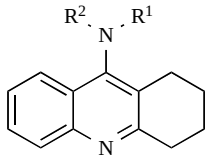
R^1 = H, Me, OMe, Cl, F;
R^2 = H, Me, Cl, F;
R^3 = Me, CH_2COOEt
R^4 = Me, Et, *tert*-Bu, $CH_3CH_2OCH_3$, $CH_2CH{=}CH_2$, CH_2Ph

(35), $R^1 = R^2$ = H, R^3 = Me, R^4 = Et
(36), R^1 = Cl, R^2 = H, R^3 = Me, R^4 = Et
(37), $R^1 = R^2$ = H, R^3 = Me, R^4 = CH_2Ph
(38), R^1 = Cl, R^2 = H, R^3 = Me, R^4 = CH_2Ph
(39), $R^1 = R^2 = R^3$ = Me, R^4 = Et

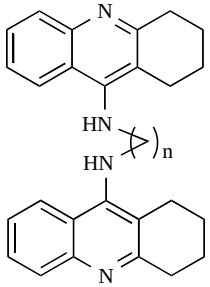
these compounds, however, also depends on the R^4 substituent, decreasing in the series benzyl > ethyl > 2-methoxyethyl > allyl > *tert*-butyl. Studies on tuberculosis-infected macrophages led to the discovery of compounds (**35**)-(**38**) with a good antituberculosis activity (MIC 1.56, 0.20, 0.10, and 0.10 μg/ml, respectively). Compound (**39**) was active against seven different monoresistant strains (MIC 0.39-1.56 μg/ml) [14].

While phenoxazines, phenothiazines, and acridines are well-known pharmacophores for antituberculosis activity, the antituberculosis profile of 1,2,3,4-tetrahydroacridines having different substituents at the C-9 atom was reported for the first time. Among 9-aminoalkyl-tetrahydroacridines, compound **(40)** (MIC 1.56 μg/ml) is more specific for the avirulent strain H37Ra, while **(41)** is more specific for the virulent strain H37Rv (MIC 0.78 μg/ml). Replacement of the aminoalkyl group at the C-9 atom by the phenoxy- or thiophenyl group leads to a loss of activity, indicating that a nitrogen atom is required. Of the five *bis*-acridine derivatives, only one compound, **(42)** (MIC 3.12 μg/ml), is active against the avirulent strain, which means that the introduction of more than one acridine unit in the molecule does not confer any advantages on the compound [15].

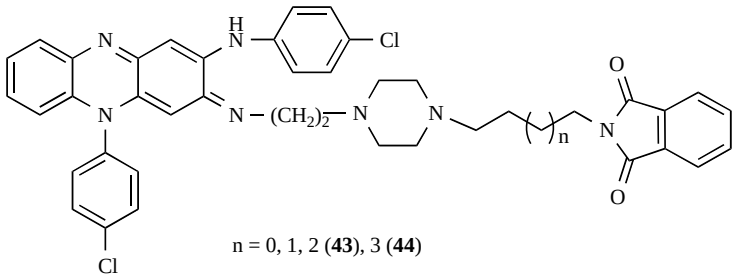
Two phenazines, **(43)** and **(44)** (MIC 1-4 μg/ml), actively inhibit growth of drug-susceptible and drug-resistant strains of *M. tuberculosis*. For drug-resistant clinical isolates, these two com-



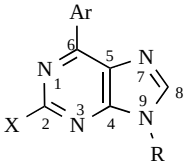
R^1R^2NH- = *n*-hexyl-NH-, *n*-octyl-NH- (**40**), *n*-dodecyl-NH- (**41**), morpholinyl, phenylmethylNH-, 3-chlorophenylethylNH-, 4-methoxyphenylNH-, 2-hydroxyethylNH-



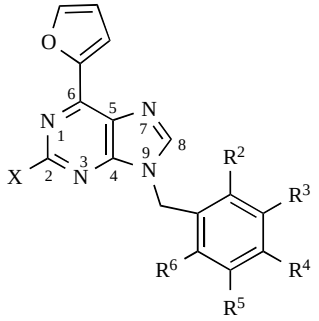
n = 3-5, 7, 10 (**42**)



n = 0, 1, 2 (**43**), 3 (**44**)

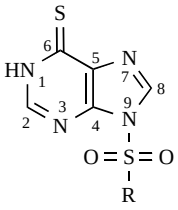


X = H, Cl;
Ar = 2-thienyl, 2-furyl, Ph;
R = H, CH_3, $CH_2CH{=}CH_2$, CH_2Ph, CH_2-cyclohexyl, CH_2CH_2Ph, THP;

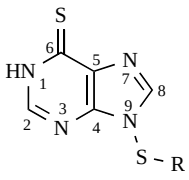


X = H
R^2 = H, OCH_3, Cl, F; R^3 = H, CH_3, OCH_3, Cl;
R^4 = H, CH_3, $C(CH_3)_3$, CF_3, NH_2, $NHCOCH_3$, $N(CH_3)_2$, NO_2; SCH_3, SO_2CH_3; OH, OCH_3, OCH_2CH_3, OCH_2Ph, $OCOCH_3$; Cl, F;
R^5 = H, OCH_3; R^6 = H, Cl, F;

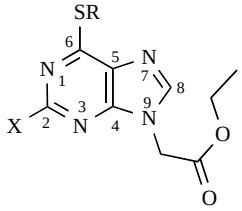
X = Cl
R^2 = H, OCH_3; R^3 = H, CH_3, OCH_3, Cl;
R^4 = H, CH_3, OCH_3, Cl, F;
R^5 = R^6 = H;
(45) R^2 = R^3 = R^4 = R^5 = R^6 = H;
(46) R^2 = R^3 = H, R^4 = OCH_3, R^5 = R^6 = H



R = $N(CH_3)_2$, X-C_6H_4
X = 4-CH_3, 4-NH_2, 4-NHAc, 4-Cl, 4-Br, 4-F, 3-NH_2, 2-NO_2



R = 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$ (**47**)



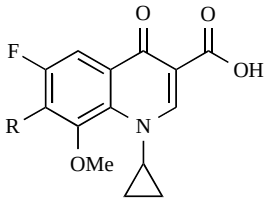
X = H, OH
R = $C_{10}H_{21}$, $C_{12}H_{25}$, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-naphthyl, $CH_2C_6H_5$, $CH_2C_6H_3$-3-Cl-6-F, $CH_2C_6H_3$-2-Me-3-NO_2, $CH_2C_6H_4$-2-F
(48) X = H, R = $C_{10}H_{21}$; **(49)** X = H, R = $C_{12}H_{25}$

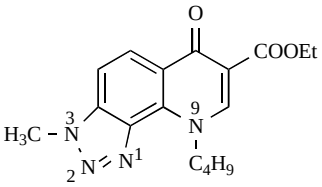
pounds showed better results than isoniazid. As shown by investigations, the antituberculosis activity of compounds of this type depends on the length of the alkyl chain between piperazine and phthalimide fragments, the optimum length of the carbon chain being five or six atoms [16].

Among the aryl- and heteroarylpurines studied, 6-(2-furyl)purines proved most effective. The presence of a substituent in the 9th position was a critical factor for activity against *M. tuberculosis*. Compounds with small alkyl groups or without a substituent in the 9th position were inactive; 9-aryl- and 9-sulfonylarypurines possessed low activity against mycobacteria, and 9-benzylpurines were good inhibitors, especially those that had electron donor substituents in the phenyl ring. However, lower activity was observed for compounds with a slightly longer distance between the purine and phenyl (CH_2CH_2Ph) rings. The chlorine atom in the 2nd position of purine increased the activity of these compounds. The basic structures of this class are 2-chloro-6-(2-furyl)-9-benzylpurine **(45)** (MIC 0.78 μg/ml) and 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **(46)** (MIC 0.39 μg/ml versus MIC 0.25 μg/ml for rifampicin). Compound **(45)** has low toxicity and is highly active against several monoresistant strains of *M. tuberculosis*. The high antituberculosis activity of compound **(46)** against *M. tuberculosis* H37Rv, its low toxicity for human cells, and activity inside macrophages indicate that the compound is useful as an antituberculosis drug [17, 18].

A very interesting activity against *M. tuberculosis* H37Rv have 9-sulfenyl/sulfonyl-6-mercaptopurines (MIC 0.39-3.39 μg/ml). Therefore, these compounds were chosen as basic structures for the synthesis of more effective antituberculosis drugs. In addition, compound **(47)** is active against several drug-resistant strains of *M. tuberculosis* (MIC < 1 μg/ml) [19].

Among the thio derivatives of purine, pyrimidine, and pyridine tested for activity against the *M. tuberculosis* H37Rv and H37Ra strains, pyrimidines and pyridines proved inactive. Thiopurines with a substituent in the 6th position were less active than their 6,9-substituted analogs, among which 9-(ethylcarboxymethyl)-6-(decylthio)-9*H*-purine (**48**, MIC 1.56 μg/ml) and 9-(ethylcarboxymethyl)-6-(dodecylthio)-9*H*-purine (**49**, MIC 0.78 μg/ml) were especially active. Substitution in the 9th position of the purine ring obviously enhances the antituberculosis activity of these compounds [20].





(53)

R = Me (**50**)
R = $NH(CH_2)_2NHC_{10}H_{21}$ (**51**)
R = $NH(CH_2)_3NHC_{10}H_{21}$ (**52**)

The oxoquinoline analog of quinolones of third and fourth generation (**50**, MIC 0.2 μg/ml) is seven times more active against multidrug-resistant *M. tuberculosis* than isoniazid (MIC 1.56 μg/ml) [21]. The antituberculosis activity of the new lypophilic derivatives of fluoroquinolones obtained by replacement of the 1,2-diamine fragment by *N*-alkylated 1,2-ethanediamine or 1,3-propanediamine depends on the length and degree of branching of the alkyl chain. An ideal carbon chain contains 10 atoms, as in compounds **(51)** (MIC *M. tuberculosis* H37Rv 0.62 μg/ml) and **(52)** (MIC 0.31 μg/ml). All 1,3-propanediamine derivatives are more active than the 1,2-ethanediamine derivatives with similar alkyl chains [22].

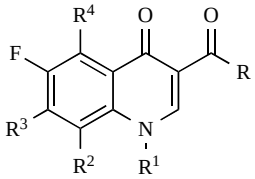
6-Oxo-6,9-dihydro-3H-[1,2,3]-triazole[4,5-h]quinoline-7-carboxylic acids and their ethers is a class of compound structurally related to fluoroquinolines except that their molecules contain a triazole ring, which can affect either the lypophilicity or the activity of the molecule in general. Indeed, some of these compounds possess an antituberculosis activity that correlates with the length of the substituent and its position in the triazole ring and also depends on the type of substituent at the quinolone nitrogen atom. Methyl at the N-3 atom of the triazole ring proved an optimum substituent. The activity is drastically lowered (MIC_{90} from 1.6 to >32 μg/ml) if the methyl group is replaced by ethyl and vanishes if the methyl group is transferred from the N-3 atom to the N-2 or N-1 atoms. An alkyl substituent at the N-9 atom was preferable to the propenyl or benzyl group, while the phenylethyl group was tolerable. Compound **(53)** was the most effective derivative possessing high antituberculosis activity and no cytotoxicity (MIC_{90} 0.5 μg/ml for 11 clinical isolates of *M. tuberculosis* and human infectious macrophages (J774-A1)) [23].

The new derivatives of fluoroquinolonecarboxylic acids (**54**-**56**) exhibit pronounced antituberculosis activity, making them promising for further search for antituberculosis drugs. Fluoroquinolones **(54**, MIC 0.2-1.6 μg/ml) showed higher antituberculosis activity than perfloxacin (MIC 4 μg/ml).

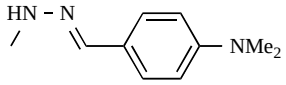
In the series of thiadiazinoquinolones **(55**, MIC 0.2-1.6 μg/ml), the activity decreases considerably when R^3 = H is replaced with a fluorine atom. Among oxadiazinoquinolones **(56**, MIC 0.2-0.6 μg/ml), the compound with a nitrophenyl residue for R^1 showed a slightly greater activity than pyridyl-4-yl-substituted derivatives [24].

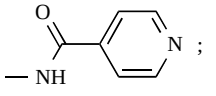
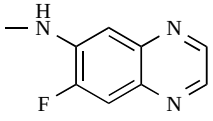
b. Oxygen-Containing Heterocycles

The basic structure for the synthesis of nitrofuranylamides of the second generation was 5-nitrofuran-2-carboxyl-3,4-dimethoxybenzylamide **(57)**, possessing a considerable antituberculosis activ-



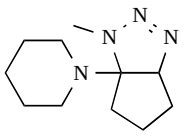
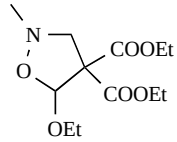
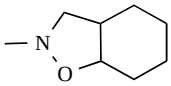
(54)

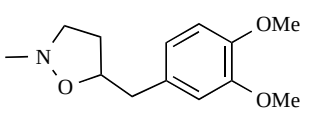
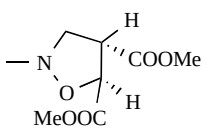
R = $NHNH_2$; OH; OEt; 

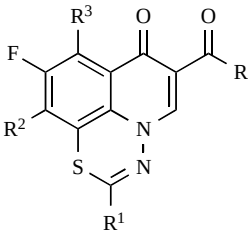
R^1 = Et; $NHC(O)CH_2CN$; 2-Cl-4-CF_3-Ph;  ; 

R^2 = H; F; R^4 = H; F; pyrrolidin-1-yl;

R^3 = morpholin-4-yl; 2,6-morpholin-4-yl; pyrrolidin-1-yl; 4-methylpiperidin-1-yl;

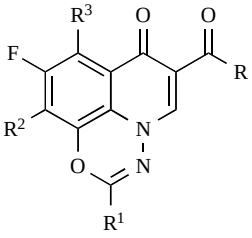
 ;  ;  ;

 ; 



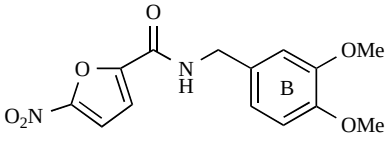
(55)

R = OH;
R^1 = pyrrolidin-1-yl;
R^2 = F; 4-ethoxycarbonyl; pyrrolidin-1-yl; morpholin-4-yl; piperazin-1-yl;
R^3 = H; F; 4-ethoxycarbonyl; morpholin-4-yl; piperazin-1-yl; 4-methylpiperidin-1-yl

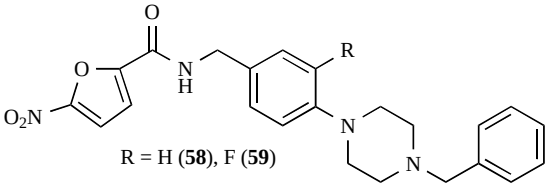


(56)

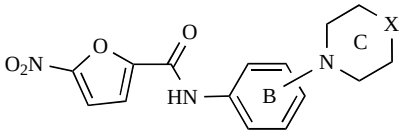
R = OH; OEt;
R^1 = 3-nitrophenyl; pyridin-1-yl;
R^2 = F; pyrrolidin-1-yl;
R^3 = H; F



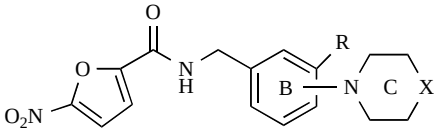
(**57**)



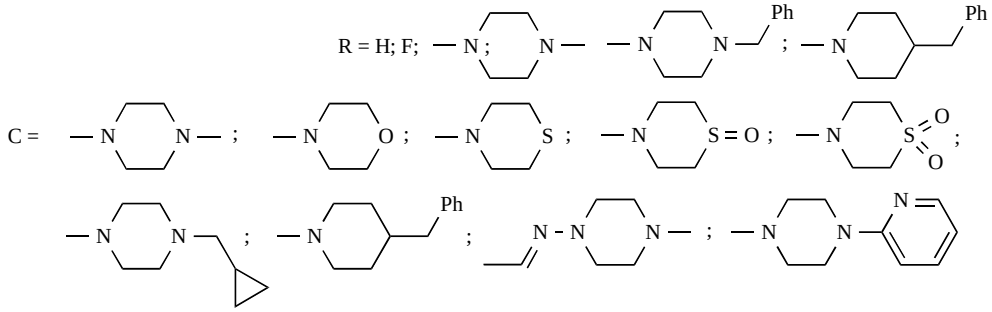
R = H (**58**), F (**59**)



Phenyl amides

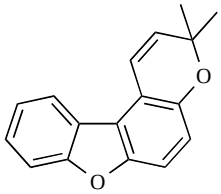


Benzyl amides

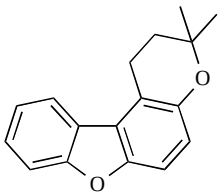


ity (MIC 0.2 μg/ml) but low solubility. The aim was to improve the solubility and biological accessibility of the new compounds by introducing hydrophilic cyclic fragments C in the benzyl or phenyl ring B. It appeared that substituted benzyl compounds (MIC 0.0125-3.13 μg/ml) showed an antituberculosis activity higher than that of substituted phenyl compounds (MIC 0.4-12.5 μg/ml). In both cases, the antituberculosis activity was improved by substitution in the *para*-position. Compounds from the benzyl series were highly effective, especially compound **(58)** with the *para*-benzylpiperazine substituent (MIC of *M. tuberculosis* H37Rv is 0.0125 μg/ml) and its analog **(59)** with the *meta*-fluorine atom in the benzene ring (MIC 0.025 μg/ml) [25].

The authors of [26] synthesized potential antituberculosis compounds whose structure contained a dibenzofuran framework and a dimethylpyrane ring fused with it. Compound **(60)** (MIC 5 μg/ml) and its reduced analog **(61)** (MIC 1-5 μg/ml), along with isoniazid, actively inhibited growth of various strains of *M. tuberculosis*. In addition, the products possessed low cytotoxicity. It was assumed that the double bond in the pyrane ring could provide some extra possibilities for modification. However, functionalization of these compounds for improving their solubility in biocompatible solvents, namely, dihydroxylation of the dimethylpyrane ring and further transformation into ethers led to a complete loss of activity.



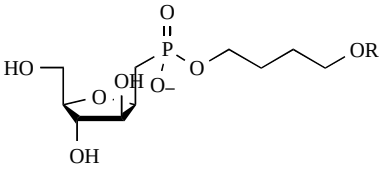
(60)



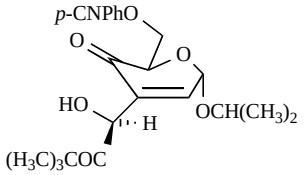
(61)

The next group of compounds includes the synthetic derivatives of saccharides.

Among the *C*-phosphonate analogs of decaprenolphosphoarabinose and the key intermediates in biosynthesis of mycobacterial arabinogalactane and lypoarabinomannane, only compound **(62)** (MIC 3.13 μg/ml) with a hexadecyl substituent has the required activity against *M. tuberculosis* H37Rv ATCC 27294. This clearly



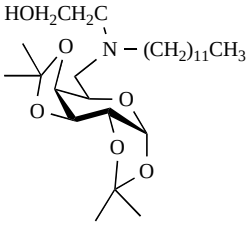
R = $(CH_2)_6CH_3$, $(CH_2)_7CH_3$, $(CH_2)_8CH_3$, $(CH_2)_9CH_3$, $(CH_2)_{11}CH_3$, $(CH_2)_{15}CH_3$ **(62)**

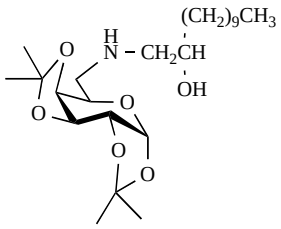


(63)

$CH_3(CH_2)_nNHCH_2CH_2OH$

n = 7, 9, 11 (**64**), 13, 15





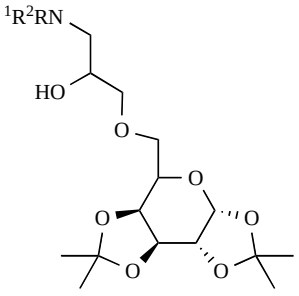
$CH_3(CH_2)_9CH(H)CH_2NH_2$

(65) **(66)** **(67)**

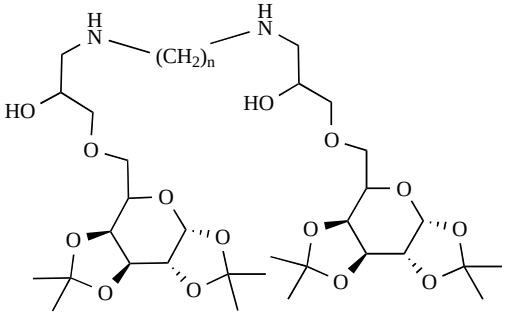
indicates that the length of the alkyl chain determines the antituberculosis activity of compounds of this type [27]. The new class of compounds, namely, the derivatives of 2,3-dideoxyhex-2-enepyranoside with alkyl and arylalkyl substituents at the C-3 atom of hexenepyranoside, were studied *in vitro* for full inhibition of growth of *M. tuberculosis* H37Rv. Compound **(63)** (MIC 3.12 μg/ml), which shows the highest activity combined with the absence of cytotoxicity was chosen for further investigation [28]. The antituberculosis activity was investigated for a series of N- and C-alkylated aminoalcohols and their galactopyranosyl derivatives. It was shown that the activity of free amino alcohols depended on the length of the alkyl chain; the best results were obtained for **(64)** and **(65)**, and the C-alkylated compound **(65)** (MIC 3.12 μg/ml for *M. tuberculosis* H37Rv) was twice more active than its *N*-alkylated analog **(64)** (MIC 6.25 μg/ml). Compounds with a longer alkyl chain proved half as active as **(64)**, yet more active than compounds with a short alkyl chain. A similar effect was also observed for galactopyranosyl derivatives of these aminoalcohols, but in this case, the N-alkylated galacoso derivative **(66)** (MIC 3.12 μg/ml) was four times more active than its *C*-alkylated analog **(67)** (MIC 12.5 μg/ml). Glycosylation of *N*-alkylated aminoalcohols generally increased their activity, indicating that the carbon fragment was important for the antituberculosis activity of these compounds. A linear carbon chain is another important factor that affects the activity; compounds with a branched alkyl chain have no antituberculosis activity in tested concentrations [29].

Glycosylated aminoalcohols having alkyl chains of varying length were suggested as a new class of antituberculosis compounds [30]. The antituberculosis activity of these compounds depends on the nature of the hydroxyaminoalkyl chain. Thus, compounds with a simple straight aminoalkyl chain were more active than their analogs with furfuryl, benzyl, or cyclic amine fragments. In an effort to find more effective analogs, the authors chose compound **(68)** (MIC 1.56 μg/ml), which was more active than the available antituberculosis drugs such as the aminoalcohol ethambutol (MIC 3.25 μg/ml) against *M. tuberculosis* H37Rv and against five clinical MDR isolates at a concentration (50 μg/ml) at which the existing antituberculosis drugs were ineffective. A 12-membered carbon chain and two galactopyranosyl units were essential for a compound to exhibit an activity as high as this.

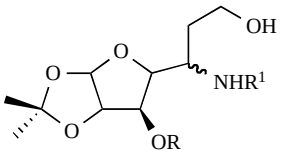
A series of aminosaccharides were tested for an antituberculosis activity against *M. tuberculosis* H37Ra and H37Rv. It was estab-



NR^1R^2 = $PhCH_2NH$-; furfurylNH-; $CH_3(CH_2)_{11}NH$-; $H_3(CH_2)_{15}NH$-; $CH_3(CH_2)_7CH{=}CH(CH_2)_8NH$-; 1- pyrrolidinyl; 1-piperidinyl; 1-morpholinyl; 4-(6-chloro-2-pyridyl)piperazinyl



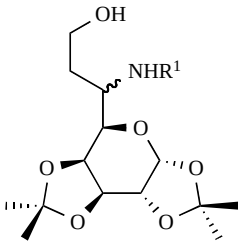
n = 3, 7, 9, 10, 12 **(68)**



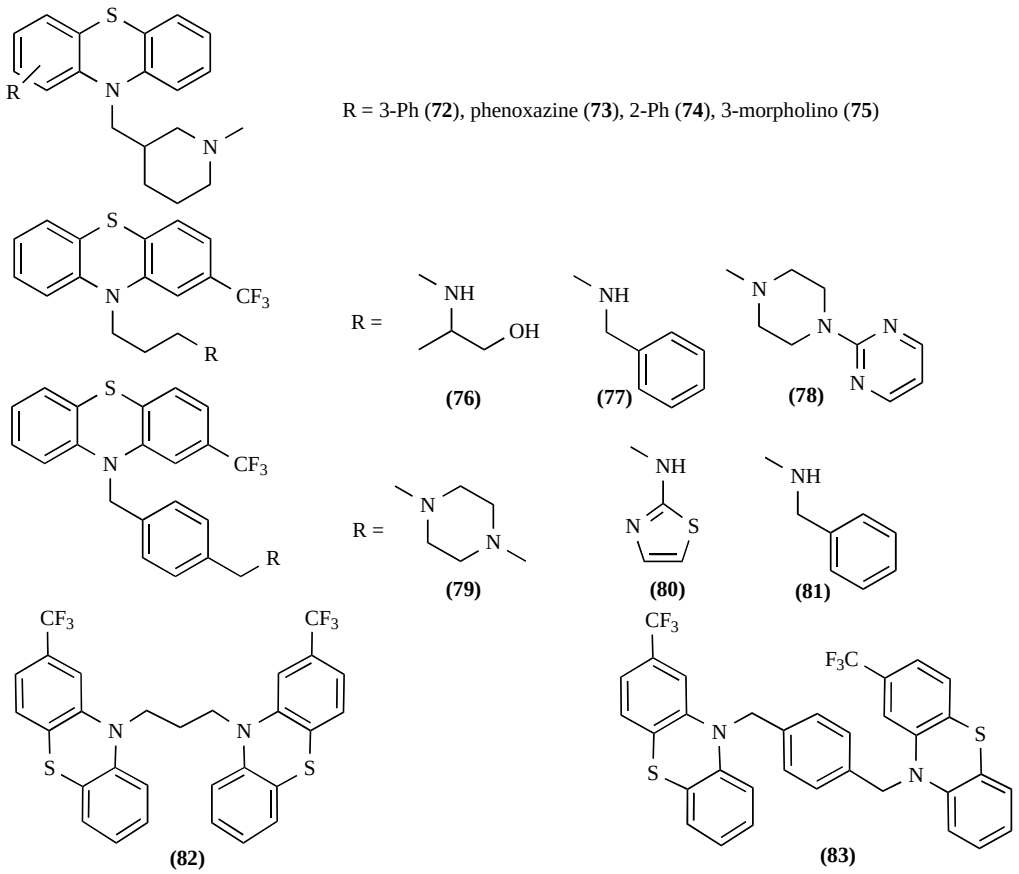
R = Me; CH_2Ph

NHR^1 = HN-cyclopripyl;HN-cyclohexyl; $HN(CH_2)_6CH_3$; $HN(CH_2)_{11}CH_3$; $HN(CH_2)_{15}CH_3$; oleyl amine

(69) R = CH_2Ph; NHR^1 = $HN(CH_2)_{11}CH_3$



NHR^1 = HN-cyclopripyl;HN-cyclohexyl; $HN(CH_2)_6CH_3$; $HN(CH_2)_{11}CH_3$; $HN(CH_2)_{15}CH_3$ **(70)**; oleyl amine **(71)**



lished that compound **(69)** (MIC 3.12 μg/ml) with N-dodecyl and 3-O-benzyl substituents showed the highest antituberculosis activity among the compounds of its series. Galactopyranosylylated aminoalcohol **(70)** (MIC 3.125 μg/ml) with a hexadecyl substituent proved most active against the *M. tuberculosis* H37Rv strain, while compound **(71)** (MIC 3.12 μg/ml**)** with an oleyl fragment was most active against *M. tuberculosis* H37Ra. Further optimization is required for the synthesis of compounds with lower MIC values [31].

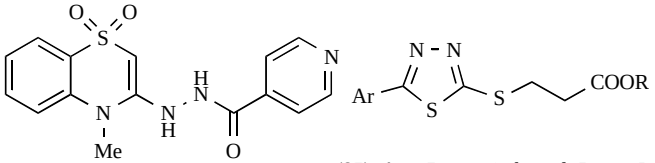
c. Sulfur-Containing Heterocycles

It has long been known that phenothiazines had an antituberculosis activity, but were mainly used as psychotropic drugs (chlorpromazine, thioridazine, trifluoperazine) because of the binding of these compounds with a number of dopamine and serotonin receptors. Therefore, analogs of phenothiazine were synthesized to examine their modification leading to growth of their antituberculosis activity and selectivity. All the existing phenothiazine drugs have various side chains in the 10th position of the phenothiazine ring in their structure, as well as substituents in the aromatic ring. Moreover, for several classes of compounds, it is known that biological activity is enhanced by the binding of the minimum active units into dimers or bis-compounds.

In a series of compounds with a fixed methylpiperidine side chain, compounds **(72)** and **(73)** with phenyl substituents (MIC 4.5 and 2.1 μg/ml) were most active against *M. tuberculosis* H37Rv; these compounds show a weak tendency toward the binding with serotonine receptors and only moderately decreased tendency toward the binding with dopamine receptors. The weakest tendency is inherent in analogs **(74)** and **(75)**, which are inactive against *M. tuberculosis*. Of all compounds with a fixed CF_3 substituent in the aromatic moiety and varied side chain, the most active compounds are **(76)** and **(77)** (MIC 4.6 and 4.2 μg/ml). Due to the increased steric size of the side chain in **(78)-(81)** (MIC 10-20 μg/ml), the binding with all subtypes of receptors decreases. However, two bis-phenothiazines, **(82)** and **(83)**, (MIC 2.3 and 2.0 μg/ml) demonstrated simultaneously increased antituberculosis activity and considerably decreased binding with receptors [32].

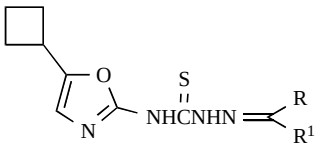
Unification of the ring of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides and the pyridine fragment, separately possessing the antimicrobial and antituberculosis effects, afforded a new type of structure with an antituberculosis activity. Compound **(84)** demonstrated an excellent activity against *M. tuberculosis* H37Rv ATCC 27294 and drug-resistant and drug-susceptible clinical isolates of *M. tuberculosis* (MIC 0.5-2.0 μg/ml), and moderate activity against *M. avium* ATCC 49601 and *M. intracellulare* ATCC 13950 (MIC 2.0 μg/ml). However, this compound did not show equal activity when tested *in vivo* in mice, probably because of poor biological accessibility [33].

To optimize the structure-antituberculosis activity relationships, various alkyl 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl, and sulfonyl] acetates and propionates were synthesized; the variable characteristics were the type of the aryl substituent (5-nitroheterocycle), the degree of oxidation of the sulfur atom (n = 0−2), the presence of a methyl and methylene groups at the α-carbon atom of the ether fragment, and the structure of the ester group. This resulted in compound **(85)** characterized by high antituberculosis activity against *M. tuberculosis* H37Rv (MIC 1.56 μg/ml) and suitable for further *in vitro* and *in vivo* evaluation [34].



(84)

(85), Ar = 5-nitro-2-thienyl; R = *n*-Pr



R = H, Me, Ph

R^1 = 2-NO_2-Ph, 3-NO_2-Ph, 4-NO_2-Ph, 4-CH_3-Ph, 4-Cl-Ph, 4-Me_2N-Ph, 4-H_2N-Ph, 2-OH-Ph, 4-OH-Ph, 4-Br-Ph, Ph

(86), R = Ph; R^1 = 4-Br-Ph

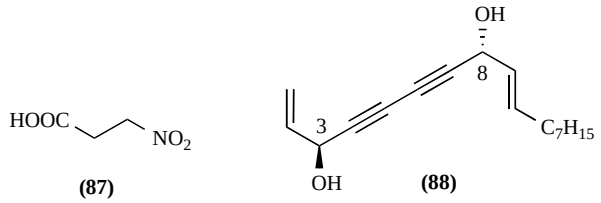
d. Other Compounds

High efficiency against *M. tuberculosis* H37Rv and MDR clinical isolates of *M. tuberculosis*, selectivity, and low cytotoxicity are also inherent in 4-(5-cyclobutyloxazol-2-yl)thiosemicarbazones. Thus, the action of **(86)** against *M. tuberculosis* H37Rv was equivalent to that of isoniazid (MIC 0.05 μg/ml for both compounds), and eight compounds were more effective (MIC 0.05-0.78 μg/ml) than ethambutol (MIC 1.56 μg/ml). Eight compounds inhibited growth of MDR *M. tuberculosis* more effectively (MIC 0.05-0.78 μg/ml) than isoniazid (MIC 1.56 μg/ml), and nine compounds were more effective than rifampicin (MIC 3.12 μg/ml); all compounds under study were more effective than ethambutol (MIC 25 μg/ml). The antituberculosis activity of the compounds depends on the presence and nature of the R and R^1 substituents. For R = R^1 = H, growth of mycobacteria was not inhibited. The R^1(NO_2, Cl) electron donor substituents enhanced the activity. In the series of the R substituents, the activity increases in the order phenyl > methyl > H [35].

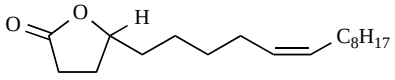
3. NATURAL COMPOUNDS WITH AN ANTIMYCOBACTERIAL ACTIVITY

a. Alkynes and Heterocyclic Compounds

The metabolite of several strains of the endophytic fungus of the genus *Phomopsis*, 3-nitropropionic acid **(87),** actively inhibited growth of *M. tuberculosis* H37Ra (MIC 0.4 μg/ml). Although the high neurotoxicity of this compound was a hindrance to its use as a pharmaceutical, it could be used as a model for the synthesis of new inhibitors of isocitratelyase, an enzyme essential to the catabolism of fatty acids and virulence of *M. tuberculosis* [36]. An example of polyacetylene compounds is 3*S*,8*R* stereoisomer **(88)** isolated from *Anethum graveolens* and having MIC 2–4 μg/ml when tested on a group of fast growing mycobacteria (*M. fortuitum* ATCC 6841, *M smegmatis* ATCC 14468, *M. phlei* ATCC 11758, *M. aurum* Pasteur Institute 104482, and *M. abscessus* ATCC 19977; for ethambutol, MIC 0.5-4 μg/ml) [37]. However, cytotoxicity of this class of polyacetylene compounds can lower the interest in their biological activity [38]. Micromolide **(89)**, which is a γ-lactone derivative of oleic acid, was isolated from the stem bark of *Micromelum hirsutum* and has MIC 1.5 μg/ml against *M. tuberculosis* (H37Rv). Further evaluation of activity on J774 mice cells infected with a more virulent strain of *M. tuberculosis* Erdman gave MIC 5.6 μg/ml [39]. Compounds **(90)** and **(91)**, the synthetic analogs of the natural antibiotic thiolactomycin, inhibit growth of *M. tuberculosis* with MIC 1–16 μg/ml, including drug-resistant strains [40]. Investigation of the components of the plant *Cinnamomum kotoense* led to the isolation of a number of compounds, of which lincomolide B **(92)** with MIC 2.8 μg/ml had the highest antituberculosis activity [41]. 2-Substituted furans **(93**) and **(94)** isolated from the roots of *Polyalthia evecta* possess activity against *M. tuberculosis* (MIC 3.1 and 6.25 μg/ml, respectively) [42]. The synthesized natural compound pamamycin-607 **(95)** inhibits growth of *M. bovis* BCG, *M. smegma-*



(87) **(88)**



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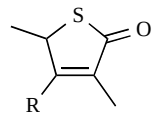
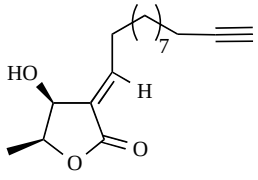
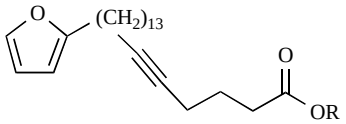


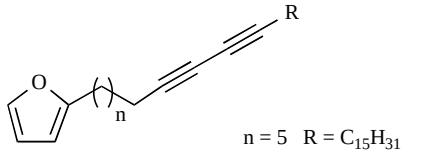


(92)

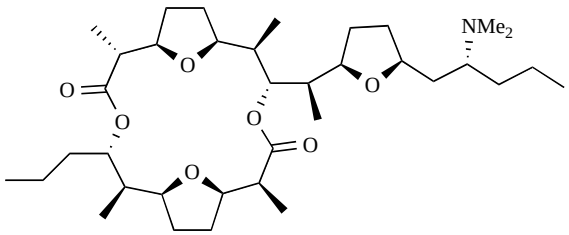
(90), R = $O(CH_2)_{10}Br$
(91), R = $O(CH_2)_8SCH_2COOMe$



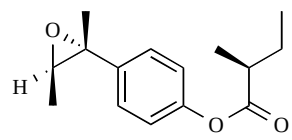
R = H, Me (**93**)



n = 5 R = $C_{15}H_{31}$
(**94**), n = 3 R = $(CH_2)_{13}OH$



(95)



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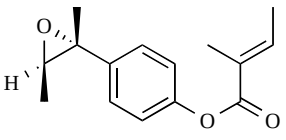

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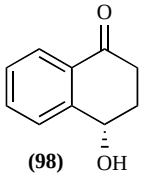

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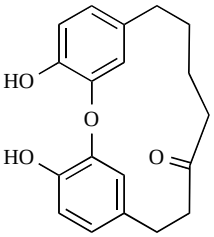

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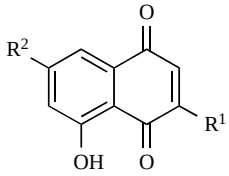
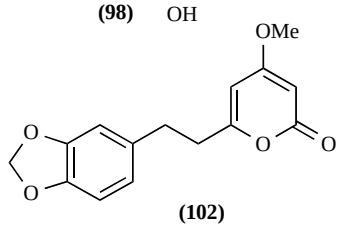
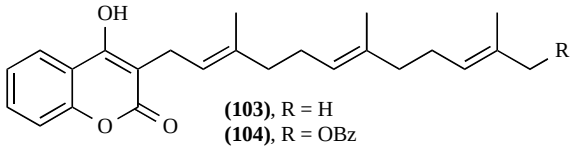


(100) R^1 = OMe; R^2 = H
(101) R^1 = H ; R^2 = Me



(102)

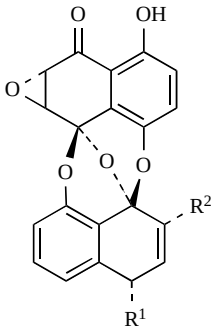


(103), R = H
(104), R = OBz
(105), R = OH
(106), R = OAc

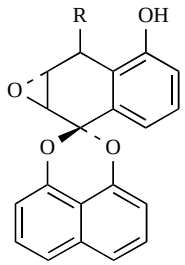
tis, and *M. tuberculosis* (MIC 0.5-4.7 μg/ml). It does not show cross resistance to isoniazid and rifampicin [43].

b. Phenols and Quinones

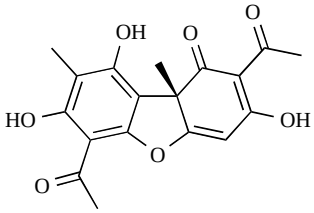
Phenylpropanoids (**96)** and **(97)**, metabolites of *Pimpinella* sp., inhibit growth of a number of mycobacteria, including *M. intracellulare*, *M. smegmatis*, *M. aurum*, and *M. phlei* (MIC 1.25–10 μg/ml) [44]. (−)-4-Hydroxy-1-tetralone (**98**, MIC 4.0 μg/ml) was isolated as an antituberculosis component of the extract from the roots of *Engelhardia roxburghiana* [45]. The tricyclic diphenol ether engelhardion **(99)** and 3-methoxyjuglon **(100)** isolated from *Engelhardia roxburghiana* are very active against *M. tuberculosis* H37Rv (MIC 0.2 μg/ml) [45]. As is known, the level of the intra- and extracellular inhibition of *M. tuberculosis* by 7-methyljuglon **(101)** (MIC 0.5 μg/ml) extracted from the plant *E. natalenis*, is comparable to that of streptomycin and ethambutol (MIC 1 and 2 μg/ml, respectively). Its derivatives, namely, 5-hydroxy-, 5-alkoxy-, and 5-acetoxy-8-substituted naphthoquinones, are less active (MIC 2.5- >20 μg/ml) and possess low antituberculosis selectivity, probably because of their nonspecific activity with various disulfide reductases found in mammal cells. Optimization of the specificity of these compounds for mycothiol disulfide reductase, which is one of the several biological targets for the antituberculosis activity of naphthoquinones of this structure, is required [46]. Pyrone **(102**, MIC 4 μg/ml) is a component of *Piper sanctum* that is active against *M. tuberculosis* H37Rv [47]. Ferulenol **(103)** isolated from the Sardinian giant fennel *Ferula communis* is effective against *M. smegmatis* (MIC 0.5 μg/ml), as well as *M. fortuitum*, *M. phlei*, and *M. aurum* (MIC 2 μg/ml). The analogs of this compound, **(104)-(106)**, were isolated from the same plant; compound **(104)** with a benzyloxy group retained its activity against *M. smegmatis* and *M. phlei*, and, to a lesser extent, against *M. fortuitum* and *M. aurum*, while the activity of **(105)** and **(106)** with the hydroxy and acetoxy groups is considerably lower [48]. Compounds (**107)**–(**114)**, isolated from the lichen fungus *Microsphaeropsis* sp., show different activities against *M. tuberculosis* H37Ra (MIC 25, 3.12, 3.12–6.25, 6.25, 12.5, 25, 1.56–3.12, 50 μg/ml, respectively), but are also characterized by cytotoxicity [49]. The dibenzofuran derivative, usnic acid (**115**), which is a secondary metabolite of lichen, inhibits growth of *M. tuberculosis* (MIC 2.5–5 μg/ml) [50]. One of the xanthone dimers isolated from the endophytic fungus of the genus *Phomopsis*, phomoxanthone A (**116**), is very active against *M. tuberculosis* H37Ra (0.5 μg/ml), while its deacetylated derivative (**117**) is inactive. Phomoxanthone B (**118**) is less active (MIC 6.25



(**107**) R^1 = OH, R^2 = H
(**108**) R^1 = OH, R^2 = H, Δ saturated
(**109**) R^1 = O, R^2 = H
(**110**) R^1 = O, R^2 = H, Δ saturated
(**111**) R^1 = O, R^2 = OMe, Δ saturated
(**112**) R^1 = O, R^2 = OH, Δ saturated



(**113**) R = O
(**114**) R = OH



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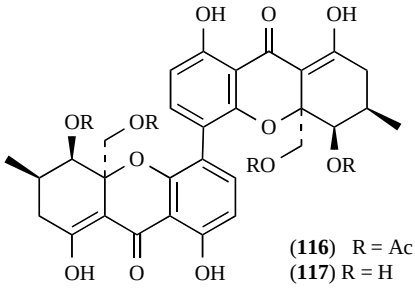
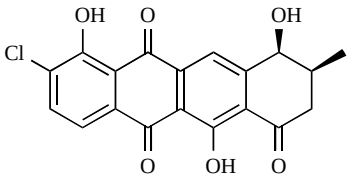


(**116**) R = Ac
(**117**) R = H



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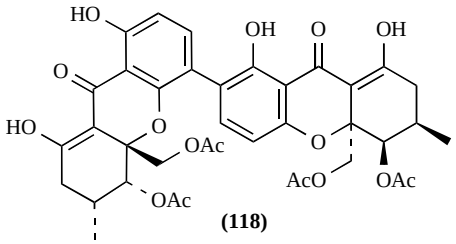

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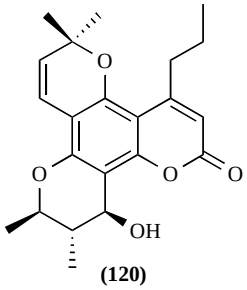
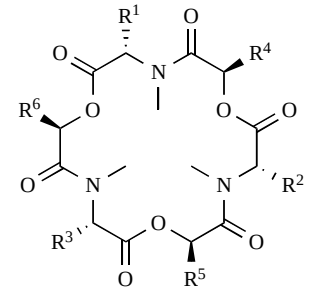


(120)

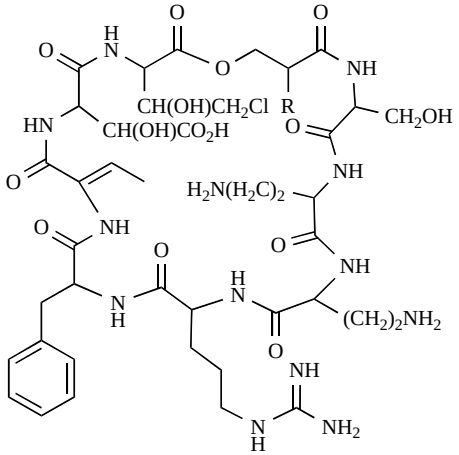
μg/ml). Both active compounds are cytotoxic [51]. The anthraquinone celastramycin B (**119**), isolated from the unknown species *Streptomyces*, is active against *M. Vaccae* (MIC 3.1 μg/ml) [52]. The anti-HIV agent (+)-calanolide A **(120)** was tested for the antituberculosis activity; a combination of the anti-HIV and antituberculosis activities in one agent is very attractive in view of the concurrence of these diseases. This compound, isolated from the tropical tree *Calophyllum lanigerum*, also has an antituberculosis activity against *M. tuberculosis* (MIC 3.13 μg/ml) and a number of drug resistant strains (MIC 8–16 μg/ml) [53].

c. Peptides

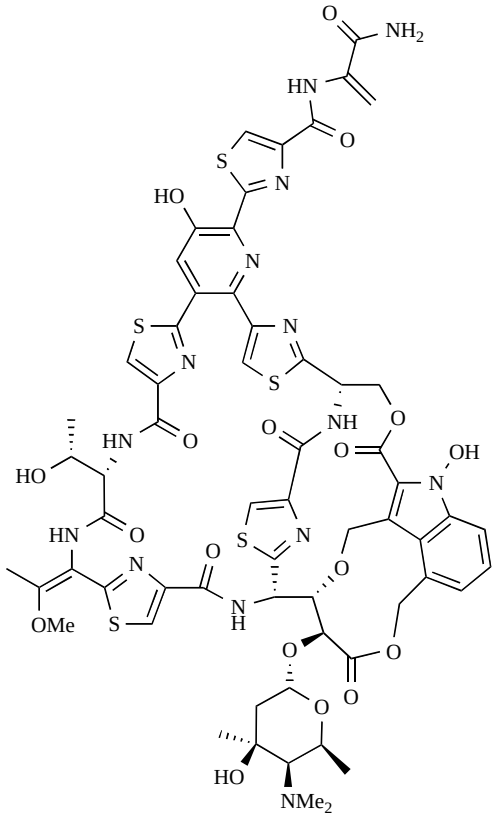
Four cyclic peptides, namely, enniatins H **(121),** I **(122)**, B **(123),** and B4 **(124)**, which are the components of the pathogenic fungus *Verticillium hemipterigenum*, inhibit growth of *M. tuberculosis* H37Ra (MIC 3.12–6.25 μg/ml) [54]. Syringomycin E (**125**), isolated from *Pseudomonas syringae* pv. *Syringae*, is active against *M. smegmatis* (MIC 1.5 μg/ml) [55]. The metabolite of *Nocardia* sp. (ATCC 202099), namely, the thiazole peptide nocathiacin **(126)** shows activity against *M. tuberculosis* ATCC 35828, *M. avium* A26778, and *M. avium* A26640 (MIC ≤0.008, 0.06, and 0.25 μg/ml,



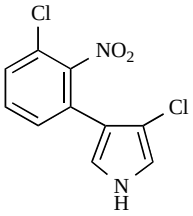
(**121**) $R^1 = R^2 = R^3 = R^5 = R^6$ = i-Pr; R^4 = s-Bu;
(**122**) $R^1 = R^2 = R^3 = R^6$ = i-Pr; $R^4 = R^5$ = s-Bu;
(**123**) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6$ = i-Pr;
(**124**) R^1 = i-Bu; $R^2 = R^3 = R^4 = R^5 = R^6$ = i-Pr



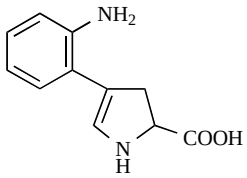
(**125**), R = $NHCOCH_2CH(OH)(CH_2)_8CH_3$



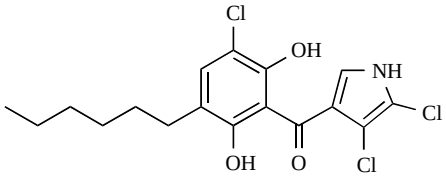
(**126**)



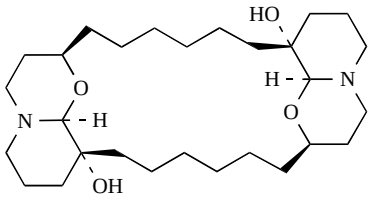
(127)



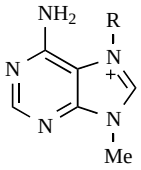
(128)



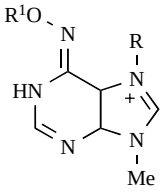
(129)



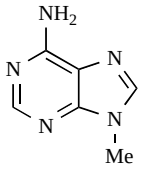
(130)



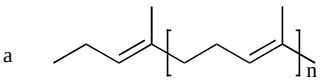
(131) R = c
(132) R = d

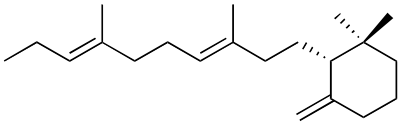


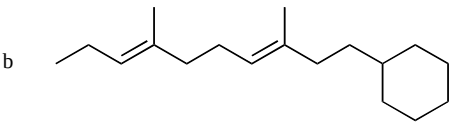
(133) R = a, R^1 = Me
(134) R = b, R^1 = Me
(135) R = c, R^1 = Me
(136) R = d, R^1 = Me
(137) R = d, R^1 = *t*-Bu

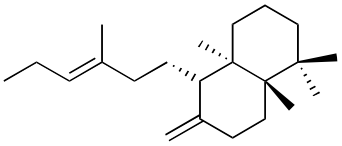


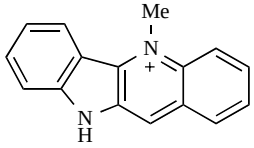
(138)











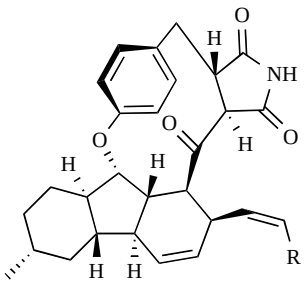
(139)

respectively). Unfortunately, compounds from this class typically show poor pharmacokinetics and solubility (the latter problem can be solved by synthesizing analogs with higher solubility in water) [56].

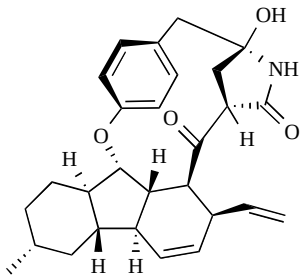
d. Alkaloids

wo compounds, namely, the known antibiotic pyrrolnitrin (**127**) and banegasine **(128)**, isolated from the zoobacterium *Aristabacter necator*, act synergetically against *M. smegmatis* (MIC **(128)** >0.5 μg/ml, (**127**) 0.3 μg/ml, **(128)** + (**127**) 0.075 μg/ml) [57]. Their analog celastramycin A (**129**), which is a dichloropyrrole metabolite of the *Streptomyces* strain, has a broad spectrum of antimycobacterial activity (MIC 0.05–3.1 μg/ml against *M. smegmatis*, *M. aurum*, *M. vaccae*, and *M. fortuitum*) [58]. The bis-1-oxaquinolizidine alkaloid (−)-araguspongine C (**130**), isolated from the sea sponge *Xestospongia exigua*, inhibits growth of *M. tuberculosis* H37Rv (MIC 1.9 μg/ml) [59]. Agelasine E (**131**) and agelasine D (**132**) were previously isolated from the sea sponge *Agelas nakamurai*. While agelasine E is inactive, its methoxy analogs **(133)–(135)**, having different terpenoid side chains, demonstrate high activity against *M. tuberculosis* H37Rv (MIC 3.13, 1.56, and 3.13 μg/ml respectively). Possibly, the presence of an alkoxy group at the terminal nitrogen atom is a very important factor for the antimycobacterial activity of these compounds. However, there is only slight difference between the activities of agelasine Д (**132**) and its alkoxy derivatives (**136)** and **(137)** [60]. It is interesting that the simpler analog of the compounds, 9-methyladenine **(138)**, has MIC of 6.25 μg/ml [61]. The tetracyclic alkaloid cryptolepine **(139)**, isolated from *Cryptolepis sanguinolenta*, is active against a number of fast-growing mycobacteria, including *M. aurum* (MIC 2 μg/ml), *M. phlei* (MIC 4 μg/ml), and *M. fortuitum* (MIC 16 μg/ml) [62].

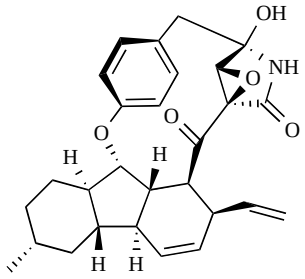
The metabolites of the Thailand pathogenic fungus *Hirsutella nivea* BCC 2594 hirsutellones A–D **(140)-(143)** inhibit growth of *M. tuberculosis* H37Ra (MIC 0.78, 0.78, 0.78, and 3.125 μg/ml, respectively). Compound **(142)** exhibits moderate *in vitro* cytotoxicity, while other compounds are less cytotoxic [63]. Hirsutellone F **(144)**, which is a new dimer alkaloid isolated, together with known hirsutellones A, B, and C, from the seeds of the fungus Tricho-



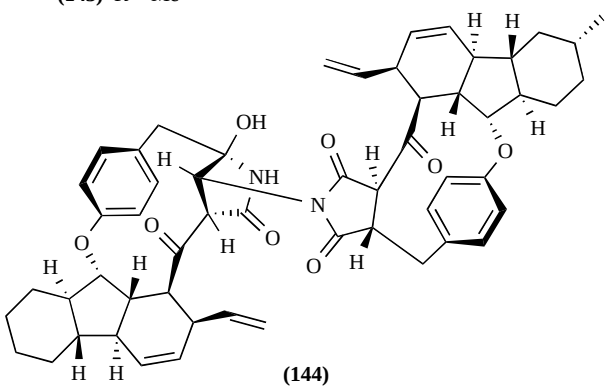
(140) R = H
(143) R = Me



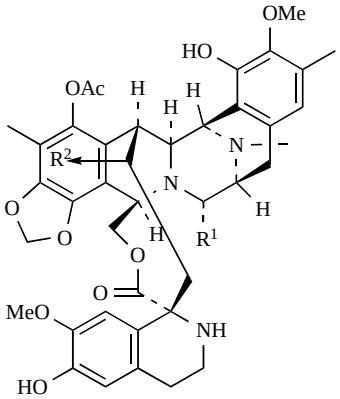
(141)



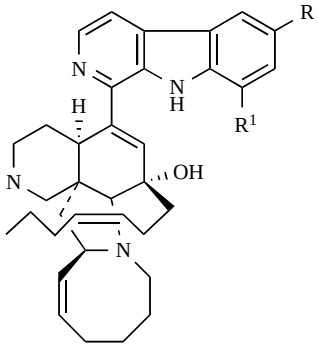
(142)



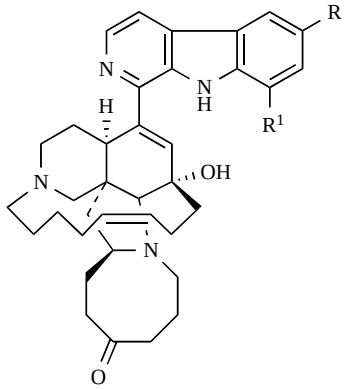
(144)



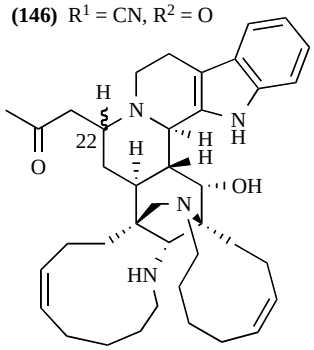
(145) R^1 = CN, R^2 = none
(146) R^1 = CN, R^2 = O



(147), R = R^1 = H
(151), R = H, R^1 = OH



(148), R = R^1 = H
(149), R = H, R^1 = OH
(150), R = OH, R^1 = H

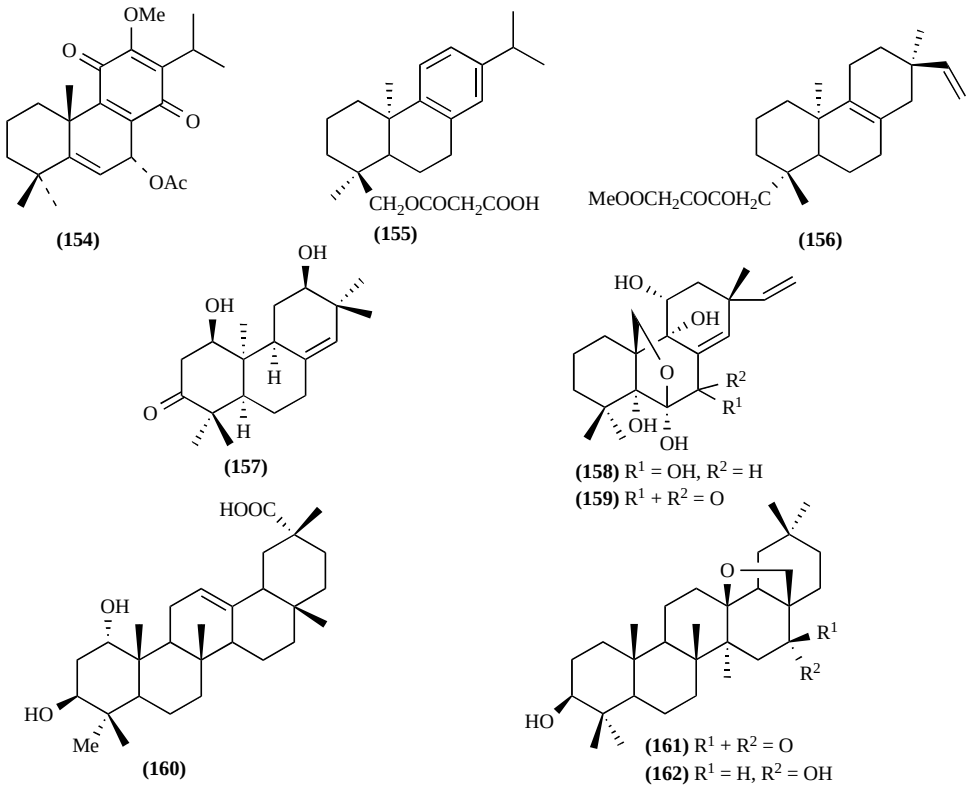


(152), 22βH
(153), 22αH

derma sp. BCC 7579 shows a weaker antituberculosis activity against *M. tuberculosis* H37Ra (MIC 3.12 μg/ml) than hirsutellones A, B, and C [64]. The known alkaloid ecteinascidin 770 (**145**) and the new one, ecteinascidin 786 (**146**), both isolated from *Ecteinascidia thurstoni*, inhibit growth of *M. tuberculosis* H37Ra (MIC 0.1 and 1.6 μg/ml, respectively) [65]. Manzamine alkaloids isolated from sea sponges are promising from the viewpoint of their antituberculosis activity. Manzamines A **(147)**, E **(148)**, and F **(149)** and their hydroxyl derivatives 6-hydroxymanzamine E **(150)** and **(+)**-8-hydroxymanzamine A **(151)** show activity against *M. tuberculosis* H37Rv (MIC 1.5, 3.8, 2.6, 0.4, and 0.9 μg/ml, respectively) [66]. Manadomanzamines A **(152)** and B **(153)** inhibit growth of *M. tuberculosis* H37Rv (MIC 1.9 and 1.5 μg/ml, respectively) [67].

e. Terpenes

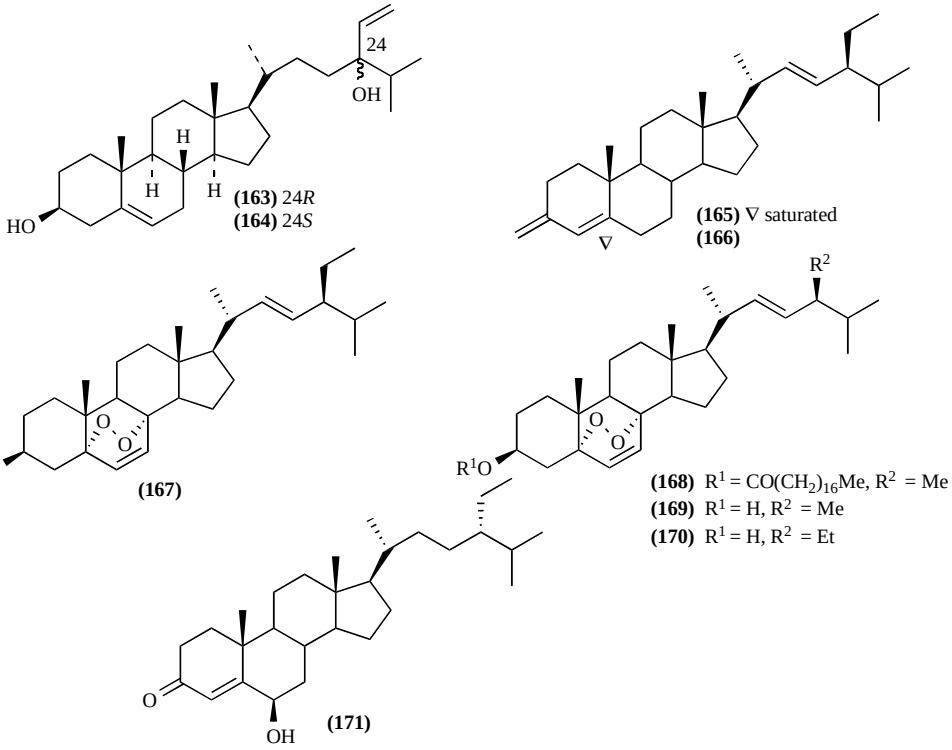
Compound **(154)**, isolated from *Indigofera longeracemosa*, is active against *M. tuberculosis* (MIC 0.38 μg/ml) [68]. Diterpenes **(155)** and **(156)** from *Calceolaria pinnifolia* [69] and the structurally related lecheronol A **(157)**, isolated from *Sapium haematospermum* (MIC 4 μg/ml), have the same value of MIC against *M. tuberculosis* H37Rv [70]. The diterpenes diaportheines A **(158)** and B **(159)** were isolated from the fungus *Diaporthe* sp. Compound **(159)** has antituberculosis activity against *M. tuberculosis* H37Ra (MIC 3.1 μg/ml) and cytotoxicity, while compound **(158)** is much less active and cytotoxic (MIC 200 μg/ml) [71]. These data indicate that the presence of a carbonyl group is important for the antituberculosis activity. A metabolite of the African tree *Combretum imberbe*, traditionally used in folk medicine is imberbic acid **(160)**, which shows activity against *M. fortuitum* (MIC 1.56 μg/ml) [72]. Aegicerin **(161)** and protoprimulagenin A **(162)** were isolated from *Aegiceras* spp., *Embelia Schimperi*, and the Peruvian plant *Clavija procera*. Aegicerin **(161)** was tested on 37 different strains of tuberculosis (MIC 1.6-3.1 μg/ml against one strain of H37Rv, 21 sensitive clinical strains, two clinical isolates resistant to isoniazid, and 13 MDR clinical strains). The inactivity of protoprimulagenin A **(162)** (MIC 200 μg/ml) demonstrates that as in the case of **(158)** and **(159)**, the presence of a carbonyl group is critical for the antituberculosis activity. For the first time, an oleane type triterpene shows uniformly high activity against a wide range of both sensi-



tive and resistant strains. Regretfully, for many MDR strains, its excellent antituberculosis activity (for comparison, MIC is 4-32 μg/ml for isoniazid and 2-16 μg/ml for rifampicin) has not yet been effected [73].

f. Steroids

Saringosterol, isolated from brown seaweeds *Sargassum ringgoldianum* and *Lessonia nigrescens* in the form of a 1 : 1 mixture of the 24*R* isomer (**163**) and 24*S* isomer (**164**), inhibits growth of *M. tuberculosis* H37Rv (MIC 0.25 μg/ml) and has low cytotoxicity. In pure form these isomers possess different levels of activity (MIC is 0.125 μg/ml for the 24*R* isomer and 1 μg/ml for the 24*S* isomer) [74]. Lipids that inhibit growth of *M. tuberculosis* H37Rv were isolated from an extract from *Morinda citrifolia* (Rubiaceae), traditionally used in folk medicine in the Philippines for the treatment of tuberculosis and respiratory diseases. The highest activity was found for a mixture of (**165**) and (**166**) (MIC <2.0 μg/ml for the 2 : 1 mixture) and endoperoxide (**167**) (MIC 2.5 μg/ml) [75]. Sterines



(**168**)-(**171**), isolated from an extract from the Argentinian plant *Ruprechtia triflora*, are active against *M. tuberculosis* (MIC 2–4 μg/ml) [69].

CONCLUSIONS

Analysis of the reviewed material shows that there are no publications on the synthesis of substances that are complexes of the structures of natural metabolites with an antituberculosis activity and synthetic mycostatics.

Meanwhile, studies in the fields of the design and synthesis of agents of this type are underway to develop drugs with various medical applications.

Synthesis of the potential mycostatic agents of mixed structural types will hopefully lead to the anticipated results and the isolation of highly promising substances.

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