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Antituberculosis Activity of Natural and Synthetic Compounds

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Abstract

The review presents the most active natural and synthetic compounds those exhibit antimycobacterial activity providing the minimum inhibiting concentration (MIC) ≤ 5 μg/mL. For better understanding the structure–activity relationship, compounds with a high value of MIC are considered in some cases. The review covers the papers published within the range of 2001–first half of 2009. The information in the review is systematized with respect to chemical structures (the nitrogen-, oxygen-, sulphur-containing heterocyclic compounds, peptides, alkaloids, terpenoids and others.).

Key words: tuberculosis, tuberculosis with plural drug resistance, *M. tuberculosis*, antimycobacterial activity, antituberculosis activity, cytotoxicity, structure–property relationship

Contents

INTRODUCTION

Tuberculosis represents a chronic infectious disease, it is known since extreme antiquity. This disease remains the most large-scale problem not only from medical, but also from social viewpoint for the present day, too. Annually, owing to tuberculosis about 3 million people dies all over the world and approximately 8 million events of first registered tuberculosis are observed every year. The progress in tuberculosis chemotherapy in the middle of 20th century was in the recent time changed into solicitude about the evolution of drug resistance on the base of genetically fixed mutation of *M. tuberculosis*.

Besides, almost all medicinal preparations used for the treatment of tuberculosis those exhibit different mechanisms of the action, are capable of exerting negative side effects on a human organism. In this connection, the problem of searching for new, low toxic medicinal agents, exceeding the existing preparations in the activity and efficiency is extremely urgent. First of all, all this concerns the agents efficient in combating against strains of *M. tuber-*

culosis with plural resistance with respect to pharmaceutical preparations.

Contemporary tuberculosis is usually connected with *M. tuberculosis* and *M. bovis*, the mycobacteria pathogenic for human beings. Owing to slow growing and high pathogenicity of *M. tuberculosis* H37Rv many research groups are using fast-growing and/or nonpathogenic mycobacteria, including *M. tuberculosis* H37Ra, *M. smegmatis*, *M. aurum* and others as an organism under testing. Besides, antimycobacterial activity is studied also using such strains as *M. avium* and *M. intracellular* those cause bird tuberculosis associating with human diseases in developed countries (AIDS patients and immunocompromised individuals), for the purpose of finding the compounds those exhibit a broad spectrum of activity. Studies should be especially noted performed with clinical isolates and strains of *M. tuberculosis* those exhibit plural resistance with respect to pharmaceutical preparations. Tuberculosis with plural medicinal resistivity (multidrug resistant TB, MDRTB) is unequivocally determined as the strain of *M. tuberculosis* resistant simultaneously against both isoniazid and rifampicin [1, 2]. Tuberculosis with other drug resistance (ODRTB) corresponds to the strains of *M. tuberculosis* those exhibit mono- or poly-resistance which includes combined resistance with respect to isoniazid and rifampicin [3]. Researchers distinguish susceptible *M. tuberculosis* strains (those can be inhibited by the preparations of the first series, for instance, by isoniazid) and resistant *M. tuberculosis* strains (those are not inhibited by isoniazid). For the work, and/or organisms under testing are used different methods of analysis, which is necessary for taking into account in comparing biological activity values obtained from different studies.

As reference preparations when testing the compounds, researchers often use preparations applied in the modern medicinal therapy of tuberculosis. There are several categorizations of antituberculosis medicinal preparations. So, medicinal preparations are divided into basic remedies (isoniazid, rifampicin, pyrazinamide, and ethambutol) and reserve remedies (cycloserine, kanamycin, ethionamide). The other way to divide into groups the medicinal preparations consists in taking into account the efficiency. The I group/series (the most efficient medicinal preparations) includes isoniazid and rifampicin, the II group (the preparations of medium efficiency) includes ethambutol, streptomycin, ethionamide, pyrazinamide, kanamycin, cycloserine), the III group (the preparations with moderate activity) includes PASA (*para*-aminosalicylic acid), thioacetazone [4].

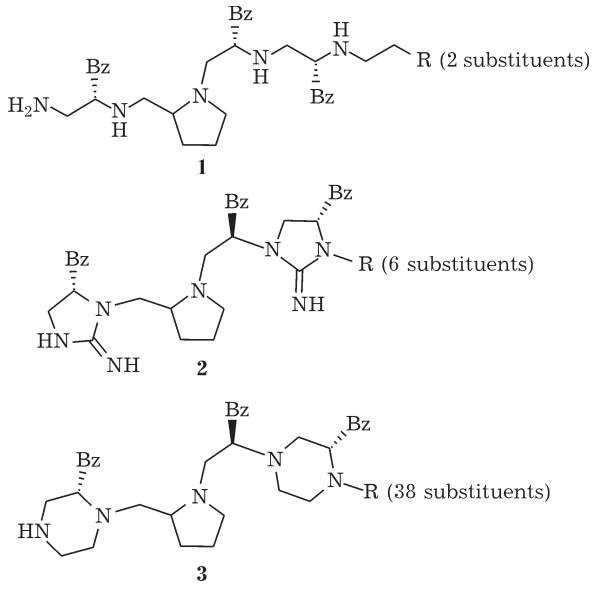
The presented review covers the papers within the period since 2001 up to the first half of 2009, whereas the selected structures are characterized by values of minimal inhibition concentration (MIC) ≤ 5 μg/mL. Such a restriction allowed the authors to gather and analyze the most efficient compounds in one review. In some cases, for better understanding the structure–property relationship, structures with higher MIC values are presented. In order to separate any possible structure–activity relations, the information in the review is systematized taking into account chemical structure.

SYNTHETIC COMPOUNDS WITH ANTIMYCOBACTERIAL ACTIVITY

Nitrogen-containing heterocycles

Chiral pentaamines **1** (MIC = 3.13 μg/mL), bicyclic guanidines **2** (MIC = 3.9 μg/mL) and piperazines **3** (MIC = 2–3.9 μg/mL) inhibit the growing of *M. tuberculosis* H37Rv (ATCC 27294) more efficiently by contrast with ethambutol (MIC = 10 μg/mL) [5] (Scheme 1).

For the present day, 1,5-diarylpyrroles are well studied those represent the analogues of compound BM 212 (MIC 1 μg/mL), the leader structure of this class of compounds and one of the most promising antimycobacterial preparations [6]. Pharmacophore ligands were determined for them; the chemical groups in the pyrrole inhibit the growing ring determining a high level of activity. The key moment for the occurrence of antituberculosis activity of 1,5-diarylpyrroles consists in the presence of (thiomorpholine-4-yl)methyl fragment at C-3 atom of the pyrrole ring, since N-methylpiperazine methyl derivatives are much more toxic and much more active than corresponding methyl thiomorpholine compounds. The improvement of antituberculosis activity thiomorpholine methyl derivatives is promoted by the introduc-



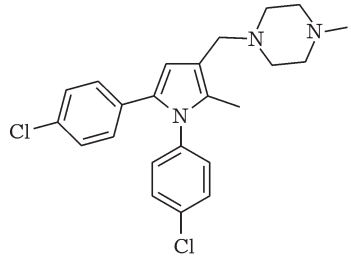
Scheme 1.

tion of a halophenyl substituent into the molecule (in this case, a strong effect is exerted by the nature of halogen atom), as well as the presence of methyl group in the second phenyl ring much more lipophilic, than the atom of halogen.

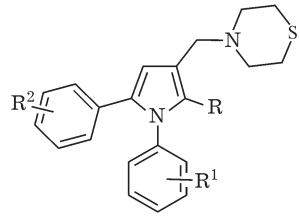
Several novel compounds (**4a–c**), MIC = 1, 0.4 and 0.5 μg/mL, respectively) were found, whose activity with respect to *M. tuberculosis* is comparable with isoniazid, streptomycin and rifampicin. Additionally, they exhibit much more low cytotoxicity by the contrast with isoniazid and streptomycin comparable with the cytotoxicity value observed for rifampicin. It should be noted that compound **4a–c** are active against intracellular (intramacrophage) *M. tuberculosis*, herewith the MIC value of compound **4a** is three times lower comparing to the MIC value of rifampicin (1 and 3 μg/mL, respectively). In addition, compounds **4a–c** are active against different strains and clinical isolates of *M. tuberculosis* resistant with respect to one or simultaneously against several medicinal preparations [7, 8] (Scheme 2).

The influence of different substituents in aromatic rings of 1,5-diarylpyrroles was studied concerning the activity against *M. tuberculosis*, atypical mycobacteria and resistant strains. As the *M. tuberculosis* 103471 is concerned, compounds **4d–t** are active alongside with isoniazid, streptomycin and rifampicin, except for compound **4i** (MIC = 16 μg/mL). So, for compound **4o** and isoniazid MIC = 0.125 μg/mL, for compounds **4d,g,l,m,r,s,** and rifampicin MIC = 0.25 μg/mL, whereas for compounds **4k,o,p** and streptomycin MIC = 0.5 μg/L. In the case of rifampicin-resistant strain (the MIC value for rifampicin is higher than 64 μg/mL) the order changes: compounds **4m,n** exhibit the MIC value amounting to 0.125 μg/mL, for compounds **3 g,l,p,r** and isoniazid MIC= 0.25 μg/mL, for compounds **3d,k,o,p** MIC= 0.5 μg/mL, whereas for streptomycin MIC= 4 μg/mL [6].

As the result of the further structural optimization of this class of compounds researchers found the compound **4t** (MIC = 0.25 μg/mL for *M. tuberculosis* CIP 103471, *M. tuberculosis* H37Rv ATCC 27294 and the rifampicin-resistant *M. tuberculosis* ATCC 35838; very low cytotoxicity) which compound exhibits a better biological profile than its 2-methyl analogue **4b** and reference preparations such as streptomy-



BM 212



4a R = Me, R^1 = 2-F, R^2 = 2-F
4b R = Me, R^1 = 4-F, R^2 = 4-CH_3
4c R = Me, R^1 = 2-F, R^2 = 4-F
4d R = Me, R^1 = 4-F, R^2 = 4-Me
4e R = Me, R^1 = 4-F, R^2 = 4-Et
4f R = Me, R^1 = 4-F, R^2 = 4-Pr
4g R = Me, R^1 = 4-F, R^2 = 4-Pr^i
4h R = Me, R^1 = 4-Et, R^2 = 4-F
4i R = Me, R^1 = 4-Pr, R^2 = 4-F
4j R = Me, R^1 = 4-Pr^i, R^2 = 4-F
4k R = Me, R^1 = 4-Cl, R^2 = 4-Me
4l R = Me, R^1 = 4-Cl, R^2 = 4-Et
4m R = Me, R^1 = 4-Cl, R^2 = 4-Pr
4n R = Me, R^1 = 4-Cl, R^2 = 4-Pr^i
4o R = Me, R^1 = 4-Me, R^2 = 4-Cl
4p R = Me, R^1 = 4-Et, R^2 = 4-Cl
4r R = Me, R^1 = 4-Pr, R^2 =4-Cl
4s R = Me, R^1 = 4-Pr^i, R^2 = 4-Cl
4t R = Et, R^1 = 4-F, R^2 = 4-CH_3

Scheme 2.

cin (MIC = 0.5 μg/mL for three strains) and rifampicin (MIC= 0.25 μg/mL for two strains). Other 1,5-diaryl-2-ethyl-pyrroles were active, too (MIC = 1–4 μg/mL) being more efficient than 2-methyl analogues of their own [9].

It should be noted that the derivatives of pyrrole presented here exhibit a high selectivity with respect to *M. tuberculosis* being inactive against atypical mycobacteria *M. gordonae* 6427, *M. smegmatis* 103599, *M. marinum* 6423 and *M. avium* 103317 (mainly, MIC > 16 μg/mL).

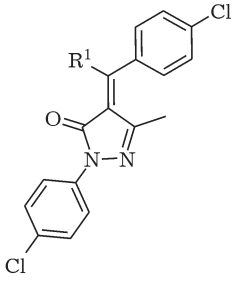
The best results concerning the inhibition of growing *M. tuberculosis* H37Rv have demonstrated only two compounds (**5a,b**, MIC = 4 μg/mL) from two series of novel pyrozolone derivatives. However basing on structure–activity correlation studied the authors of [10] have drawn an important conclusion: for the antituberculosis activity of a compound, the presence of *para*-chlorobenzene fragment at C-4 atom of the pyrazole ring is required. Six derivatives of imidazole **5c** well inhibit the growing of *M. tuberculosis* H37Rv (MIC = 4 μg/mL, for the comparison (the MIC value for isoniazid amounts to 0.5 μg/mL. The presence of phenyl or 4-fluorophenyl substituent at N-1 atom of the pyrazole ring appeared much more preferable than the methyl group or hydrogen atom in this position [11] (Scheme 3).

Oxazolidinones represent a novel class of synthetic antimicrobial remedies those exhibit no cross-resistance with respect to the other types antibiotics, since a new mechanism of action is inherent in them. Amongst them there is linezolid (MIC = 0.25–2 μg/mL for *M. tuberculosis* H37Rv, of susceptible and resistant clinical isolates), and its thiomorpholine analogue PNU-100480 **6a** exhibiting an interesting antituberculosis activity. Continuing the work concerning the development of antituberculosis preparations a new series of 1-[3-(4-benzotriazole -1/2-yl-3-fluorophenyl)-2-oxo-oxazolidine-5-yl-methyl]-3 derivatives of thiourea was created. A complete activity loss was caused by the substitution of the hydrogen atom in the terminal ethyl group of thiourea by the morpholine fragment. A significant activity against different mycobacterial species (*M. tuberculosis* H37Rv, susceptible and resistant clinical isolates) is exhibited by compound **6b–f** (MIC = 0.5–8 μg/mL), having amino-, 2-pyridyl-, 1-pyrrolidinyl- and 1-piperidinyl groups bound by ethyl bridge with thiourea. Substituting the whole ethyl group by the cyclopropyl one results in the forming the compound **6d** which exhibits an excellent antituberculosis activity (MIC = 0.06–2 μg/mL), comparable with the activity of linezolid with exceeding the activity of isoniazid for all the tested strains [12]. Amongst different C-5 triazole substituted oxazolidinones there is 3-(4-acetylphenyl)-5-(1*H*-1,2,3-triazole-1-yl)methyl)-oxazolidinone **6g** (MIC = 1 μg/mL with respect to *M. smegmatis* ATCC 14468), fourfold exceeding the activity of isoniazid [13].

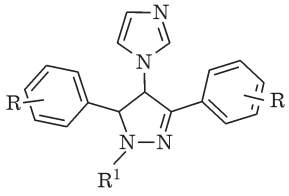
A high inhibiting activity of peptide deformylase for mono- and poly-resistant strains of *M. tuberculosis* was demonstrated by compound **7a–e** (MIC = 0.03–0.6 μg/mL) [14] (Scheme 4).

A stage-by-stage modification was successfully performed for well known bicyclic nitroimidazooxazole **8** which exhibit not only satisfactory *in vitro* antituberculosis activity and *in vivo* efficiency, but also mutagenicity. Compounds those exhibit no mutagenicity were revealed among the structures containing heteroatomic substituents at the 2nd position of 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole, herewith (*R*)-form **8a** appeared much more active (MIC = 0.05 μg/mL with respect to *M. tuberculosis* H37Rv).

The improvement of antituberculosis activity was attained by means of consequent introducing the molecule with a hydrophilic substituent (compound **8b**, MIC = 0.78 μg/mL with

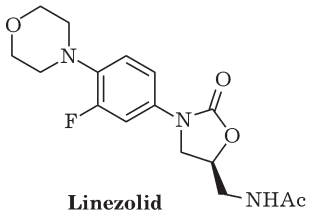


5a,b R = *N*-Me-piperazine, morpholine

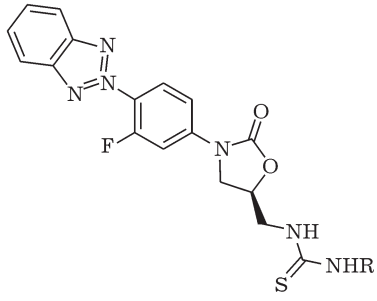


5c R = 4-Br, 4-Cl, 2,4(Cl)$_2$, 4-Me
R^1 = Ph, 4-F-Ph

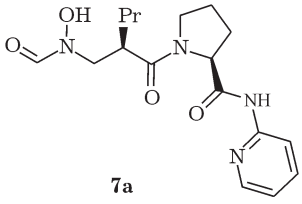
Scheme 3.



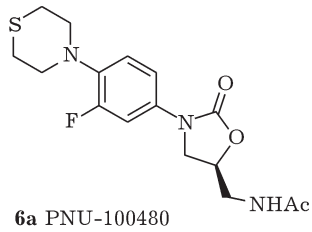
Linezolid



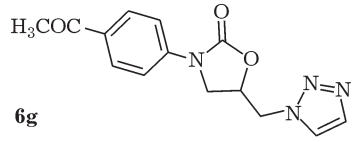
R = NH_2, NHCO-4-pyridyl, $CH(Et)CH_2OH$, $CH_2CH(OEt)_2$, $CH_2CH_2NH_2$ **(6b)**, CH_2CH_2-2-pyridyl **(6c)**, cyclopropyl **(6d)**, CH_2CH_2-pyrrolidine **(6e)**, CH_2CH_2-piperidine **(6f)**, CH_2CH_2-morpholine **(6g)**



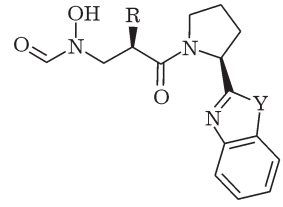
7a



6a PNU-100480



6g

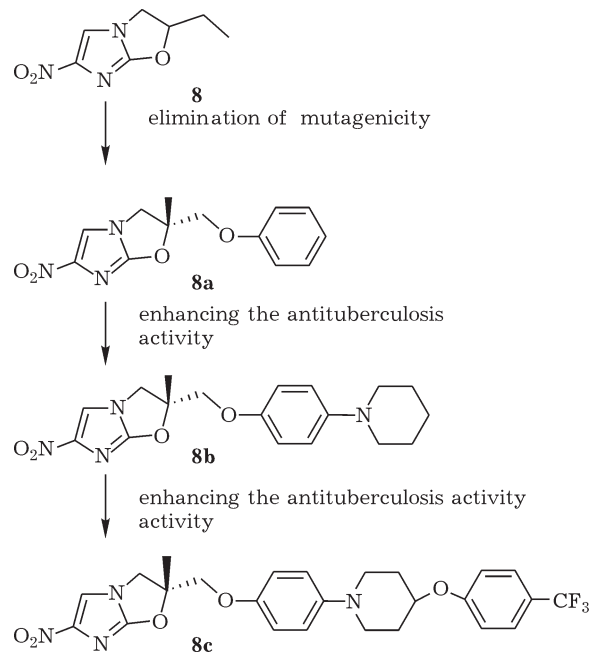


7b R = Bu, Y = NH
7c R = Cpm, Y = NH
7d R = Bu, Y = O
7e R = Cpm, Y = NH

Scheme 4.

respect to *M. tuberculosis* H37Ra and MIC = 0.39 μg/mL with respect to each of two mono-resistant strains of *M. tuberculosis* H37Rv (mono-resistance against isoniazid and against rifampicin, respectively) and with a lipophilic substituent (compound **8c**, MIC = 0.006 μg/mL with respect to each of two mono-resistant strains of *M. tuberculosis* H37Rv (mono-resistance against isoniazid and rifampicin, respectively). Basing on the excellent *in vitro* antituberculosis activity with respect to drug-susceptible and drug-resistant strains of *M. tuberculosis* H37Rv as well as *in vivo* efficiency in mice infected by *M. tuberculosis* Kurono, compound **8c** was chosen as an active remedy nominated for oral introduction in tuberculosis treatment. Particularly significant is the fact that compound **8c** *in vivo* is highly competitive in the efficiency with rifampicin at a much lower dose for oral introduction (0.313 and 5 mg/kg, respectively) [15] (Scheme 5).

The oxyindole derivatives **9a, 9c** (MIC = 0.1 μg/mL for each) and **9b** (MIC = 0.05 μg/mL)



Scheme 5.

exhibit the antituberculosis activity with respect to *M. tuberculosis* H37Rv, comparable with the effect of isoniazid (MIC = 0.025–0.2 μg/mL) and rifampicin (MIC 0.06–0.5 μg/mL) [16].

For the ability to inhibit *M. tuberculosis* H37Rv (ATTC 27294) a series of phthalimide derivatives was tested. Among the compounds studied, a good antituberculosis activity was demonstrated by compound **10a,b** (MIC = 3.9 and 5 μg/mL, respectively), which alongside with the absence of cytotoxicity allows one to choose these compound as leading structures for obtaining more efficient antituberculosis remedies [17].

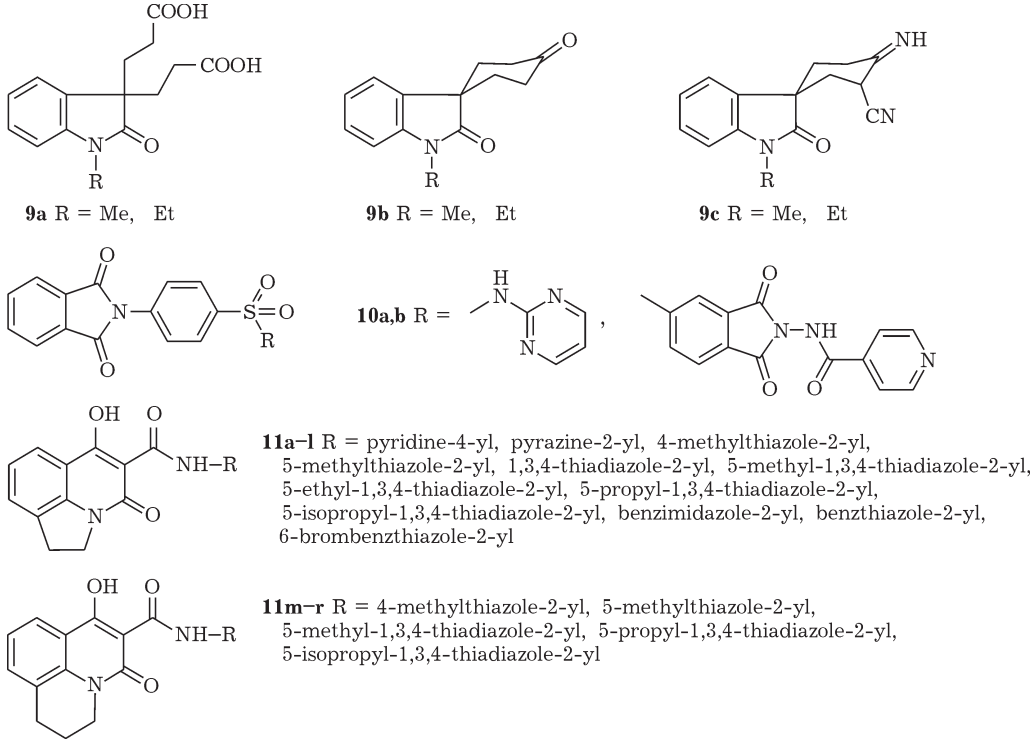
Studies were performed concerning the antituberculosis activity for the series of hetarylamides of 1-hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic and 1-hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acids, basing on which some regularities in biological structures were revealed. A pronounced antituberculosis effect with respect to *M. tuberculosis* H37Rv ATCC 27294 is exhibited by compound (**11a–l**, MIC < 3.13 μg/mL), from those the five of the most promising compounds were chosen (**11g–k**, MIC = 0.39–0.78 μg/mL) [18], and compounds (**11m–o,s**, with MIC = 3.13 μg/mL) and (**11p,r**, with MIC= 0.78 and 1.56 μg/mL, respectively) [19] (Scheme 6).

The studies on 3,5-bis(benzylidene)-4-piperidones* and their *N*-4-(2-aminoethoxy)phenyl carbonyl analogues **12a** has allowed researchers to reveal a number of substituents determining not only high antituberculosis characteristics (MIC = 1.56–3.13 μg/mL), but also the absence of neurotoxicity. The leading structures of this class of compounds are presented by compound **12b,c** (MIC = 0.2 and 0.78 μg/mL, respectively) [20].

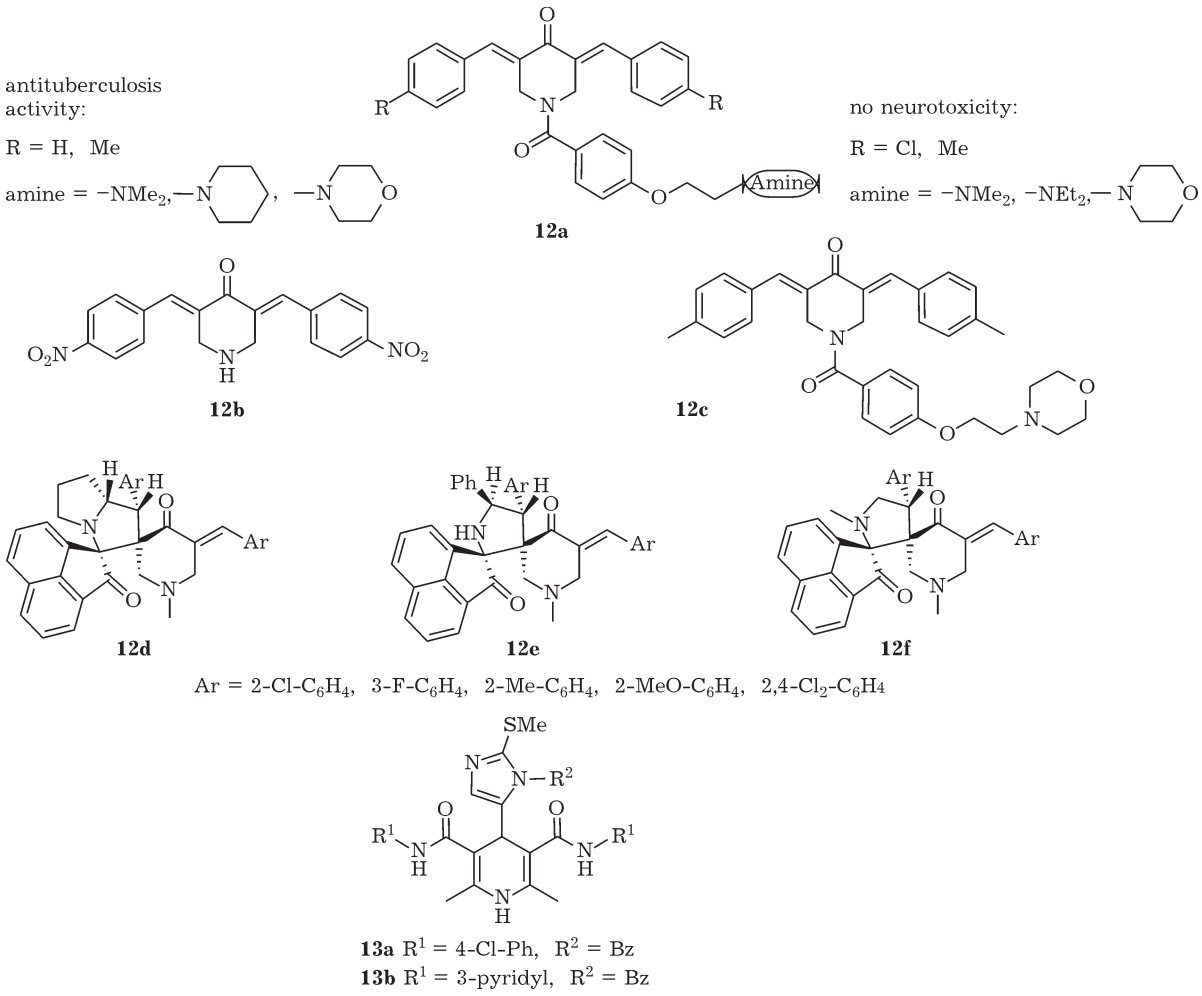
Novel spiroheterocycles **12d–f** (MIC = 0.4–3.13 μg/mL) obtained on the base of 1-methyl-3,5-bis(benzylidene)-4(1*H*)-piperidone, highly active not only against *M. tuberculosis* H37Rv, but also against clinical isolates with MDRTB resistant with respect to isoniazid, rifampicin, ethambutol and ciprofloxacin [21].

Among 4-substituted imidazolyl-2,6-dimethyl-N^3,N^5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides, the most pronounced activity is

*In the Schemes 7–38 the imaging of substituents near the frame under discussion without labelling the particular number of a compound means that for the structure presented MIC > 5 μg/mL.



Scheme 6.

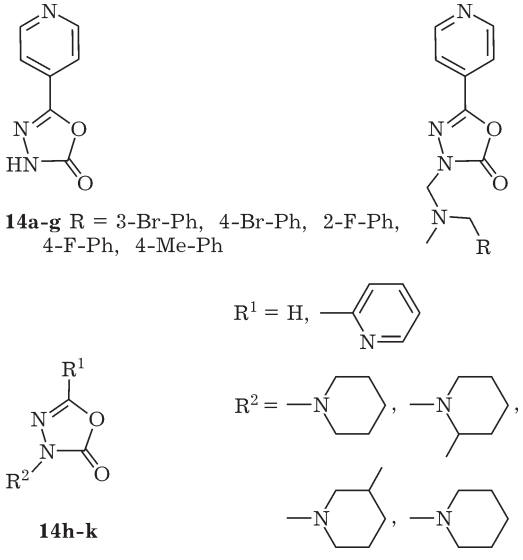


Scheme 7.

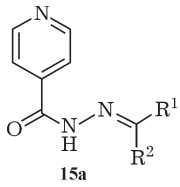
exhibited compound **13a** (MIC = 1 μg/mL for *M. tuberculosis* H37Rv ATCC 27294) which is an equivalent with respect to the action of reference preparation rifampicin. A good inhibiting ability is exhibited also by analogue **13b** (MIC = 2 μg/mL for *M. tuberculosis* H37Rv ATCC 27294). Compounds with other substituent (R^1= 2-Cl−Ph, 3-Cl−Ph, 4-Br−Ph, 2-pyridyl; R^2 = NHPh) represent much more weak inhibitors [22] (Scheme 7).

Novel efficient inhibitors for P450 **14α**-sterol demethylase of *M. tuberculosis* were revealed such as 3.5-disubstituted derivatives 1,3,4-oxadiazole-2(3*H*)-one **14a–k** (MIC = 4 μg/mL) [23] (Scheme 8).

Compounds **15a** obtained by means of isoniazid structure modification at N-2 atom exhibit a high level of antituberculosis activity (*M. tuberculosis* H37Rv and *M. tuberculosis* Erdman *in vitro* and *in vivo* in experimental ani-



Scheme 8.



15a

R^1 = $(CH_2)_4CH_3$, H, CH_2Ph; R^2 = Ph, 4-Cl-C_6H_4, 3,4-Cl_2-C_6H_3, 2,6-F_2-C_6H_3, 4-Cl-3-NO_2-C_6H_3, $CH_2CO_2CH_2CH_3$

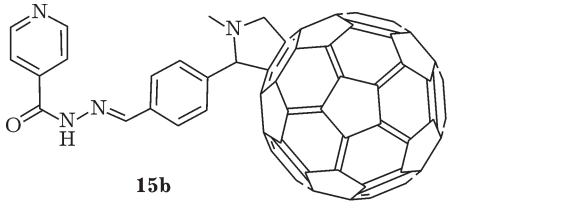
R^1R^2 = $CCH_2CH(CH_3)CH_2C(CH_3)_2CH_2$, $C(CH_2CH_2)_2CH_2$

Scheme 9.

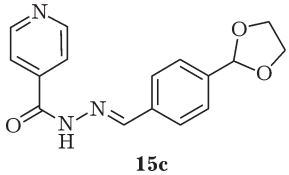
mals) as well as a low level of toxicity. Among 44 compounds, for 34 ones the typical MIC values are amounting to 0.025–0.5 μg/mL (for isoniazid MIC = 0.06 μg/mL). Eleven compounds tested for infected macrophages exhibit bacteriostatic and bactericidal activity equivalent or even greater than those for isoniazid (EC_{90} = 0.028–0.106 μg/mL, EC_{99} = 0.121–0.5 9 6 μg/mL, respectively; for isoniazid EC_{90} =0.03 μg/mL, EC_{99} = 0.42 μg/mL) [24] (Scheme 9).

Excellent antituberculosis characteristics studied *in vivo*, alongside with low cytotoxicity is exhibited by fullerene-isoniazid conjugate **15b** (MIC = 0.5, 2.5 and 5 μg/mL for *M. tuberculosis* H37Rv ATCC 27294, *M. tuberculosis* H6/99 and *M. avium* ATCC 27291, respectively, the MIC value of isoniazid is 0.25 μg/mL for *M. tuberculosis* H37Rv ATCC 27294, in the other cases isoniazid is resistant). Arabinoses for obtaining this compound **15c,d** (MIC = 5 μg/mL for *M. tuberculosis* H37Rv ATCC 27294) also exhibit the antituberculosis activity [25] (Scheme 10).

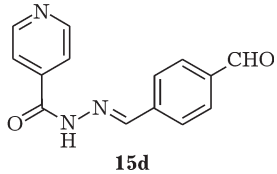
Isoniazid and pyrazinamide are widely used as basic medicinal preparations for the treatment of tuberculosis, usually together with other drugs. The authors have designed and synthesized a new type antituberculosis compounds those could be considered as «double active» molecules since isoniazid or pyrazinamide are linked therein with another standard antituberculosis drug (ciprofloxacin, *para*-aminosalicylic acid) by means of C–H group. The compounds were obtained **15e** (MIC = 0.39 μg/mL), **15f** (MIC = 3.13 μg/mL), **15g** (MIC = 0.39 μg/mL), **16a** (MIC = 0.78 μg/mL), **16b** (MIC = 3.13 μg/mL), **16c** (MIC = 0.1 μg/mL) exhibit a very high antituberculosis activity with respect to *M. tuberculosis* H37Rv (the MIC for isoniazid amounting to 0.025–0.2 μg/mL, the MIC for pyrazinamide being equal to 6–60 μg/mL, the MIC for ciprofloxacin is of 2.00 μg/mL), which could be connected with the synergetic action of components and a high lipophilicity of compounds obtained that corresponds to the efficient transport of molecules through cellular membrane [26]. Antituberculosis activity *in vitro* and *in vivo* with respect to *M. tuberculosis* H37Rv and MDRTB strains resistant with respect to isoniazid, rifampicin, pyrazinamide and ofloxacin is exhibited by the aminomethylene amide analogues of the first series pyrazinamide preparation having aryl substituents in the piperazine ring such as compounds **16d** (MIC= 3.12 and 12.5 μg/mL, respectively), **16e** (MIC = 3.12 and 6.25 μg/ mL), **16f** (MIC =1.76 and 1.76 μg/mL), **16g** (MIC= 0.78 and 1.76 μg/mL). Halogen-containing (Cl, F) substituents in the aryl ring cause the activity to enhance [27] (Scheme 11).



15b



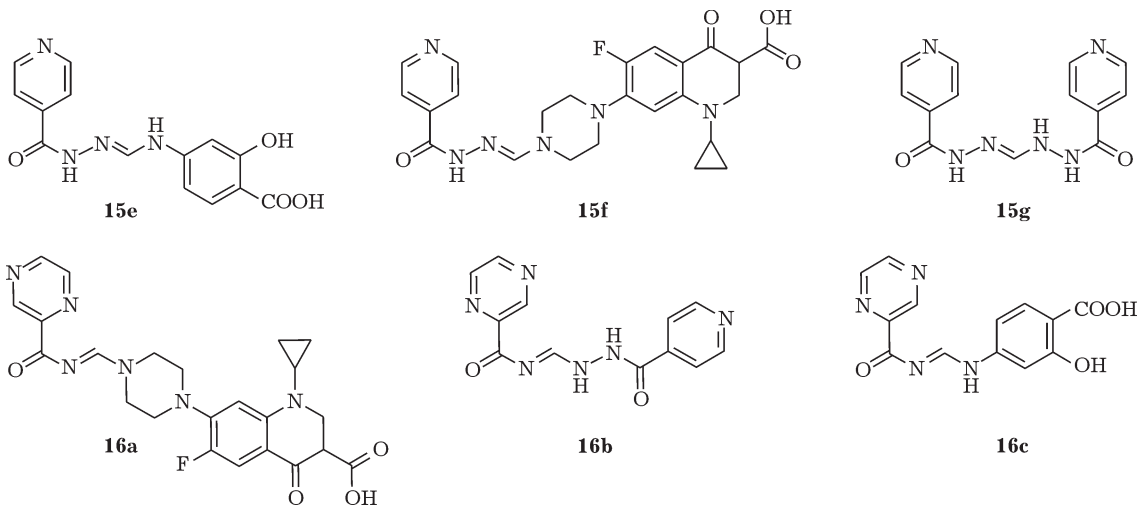
15c



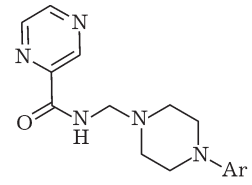
15d

Scheme 10.

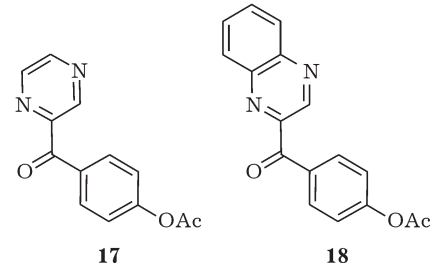
Compounds **17** and **18** (MIC < 0.25 and 0.5 μg/mL, respectively) the most active with respect to *M. tuberculosis* H37Ra resulted from tested esters of pyrazinoic and quinoxalinic acids, have the 4-acetoxy group in the phenyl ring. It is interesting that comparing to them 2-nitro- and 4-nitrobenzyl analogues exhibit much lower activity. This indicates the fact that under those conditions (pH 6.6), to all appearance, the reduction of the nitro group into amino group does not occur, whereas enzymatic deacylation of 4-acetoxy group can proceed [28].



Scheme 11.



Ar = Bz, Ph, 4-ClPh **(16g)**, 3-ClPh **(16e)**, 4-ClPh **(16f)**, 4-CF_3Ph **(16g)**

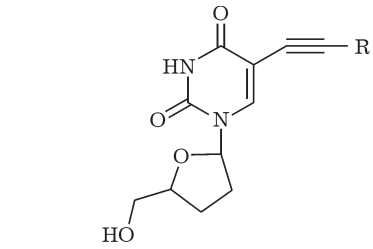


Novel inhibitors were found with efficient and selective antituberculosis characteristics with respect to *M. bovis*, *M. tuberculosis* and *M. avium* such as acetylene derivatives of 2′,3′-dideoxyuridine and 3′-fluoro-2′,3′-dideoxyuridine. The most promising representatives of this class of compounds are presented by compounds **19** and **19b**, successfully inhibiting the growth of *M. bovis*, *M. tuberculosis* (MIC_{90} = 1−2 μg/mL) and drug-resistant strains of *M. tuberculosis* [29].

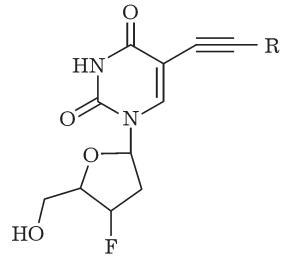
The activity with respect to *M. tuberculosis*, *M. bovis* and *M. avium* was studied for a number of 1-β-*D*-2′-arabinofuranosyl- and 1-(2′-deoxy-2'-fluoro-β-*D*-ibofuranosyl)pyrimidine nucleosides with different substituents at C-5 carbon atom of uracyl (alkinyl, alkenyl, alkyl and halogen). A high antituberculosis activity among the compounds studied with respect to *M. tuberculosis* and *M. bovis* was demonstrated by nucleosides **19c** (MIC_{90} = 1−5 μg/mL), **19d** (MIC_{90} = 1−5 μg/mL) and **19e** (MIC_{90} = 1 μg/ mL). The values of MIC_{90} for these compounds are comparable with those for rifampicin (MIC_{90} = 0.5−1 μg/mL). However, being of the same concentration, these compounds actively inhibit also the growth of a rifampicin-resistant *M. tuberculosis* H37Rv strain [30] (Scheme 12).

On the base of imidazooxazine PA-824 (MIC = 0.015−0.25 μg/mL), the most modern antimycobacterial agent under clinical trials, novel imidazo[1,2-*c*]pyrimidines **20a–g** (MIC = 2−5 μg/mL with respect to *M. tuberculosis* H37Rv) were designed. The most low MIC parameter is exhibited by compound **20b** (2 μg/ mL), which comparable with the MIC value for reference preparation amikacin (2 μg/mL), however higher comparing to the MIC value for reference preparation rifabutine (0.05 μg/mL). The results of the present investigation indicate the fact that one could obtain compound with a good antimycobacterial potential *via* bioizosteric substitution of imidazooxazine ring in PA-824 by condensed imidazopyrimidine ring [31] (Scheme 13).

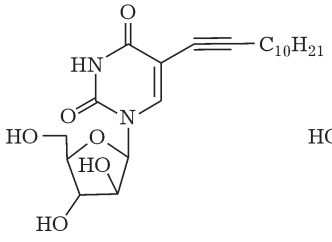
High efficiency, selectivity and low cytotoxicity are inherent in novel quinoxaline derivatives. Their antituberculosis activity depends on the nature of substituent R^1 in the quinoxaline nucleus: the presence of chloro, methyl and methoxy group at the position 7 of the



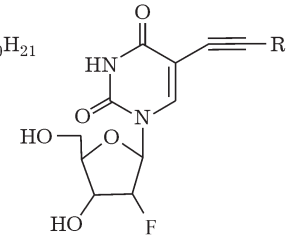
R = $(CH_2)CH_3$, $(CH_2)_7CH_3$, $(CH_2)_9CH_3$ **(19a)**, $(CH_2)_{10}CH_3$, $(CH_2)_{11}CH_3$, C_6H_5



R = $(CH_2)_4CH_3$, $(CH_2)_7CH_3$, $(CH_2)_9CH_3$, $(CH_2)_{10}CH_3$, $(CH_2)_{11}CH_3$ **(19b)**, 4-Pr-C_6H_4

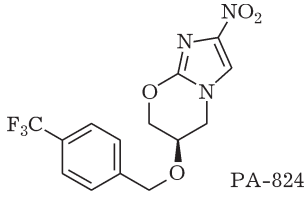


19c

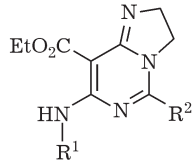


R = $C_{10}H_{21}$ **(19d)**, $C_{11}H_{23}$ **(19e)**

Scheme 12.



PA-824



20a-g R^1 = 4-Me-C_6H_4, 2-F-C_6H_4, 4-F-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4
R^2 = H, Ph

20b R^1 = 4-MeO-C_6H_4
R^2 = H

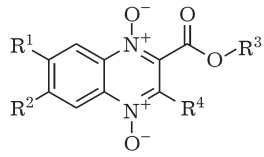
Scheme 13.

benzene ring causes the minimum inhibiting concentration to decrease. However, the activity of these compounds depends also on the substituent R^4 in the following order: benzyl > ethyl > 2-methoxyethyl > allyl > *tert*-butyl. The studies concerning macrophages infected with tuberculosis, allowed revealing compounds **21a–d** with a good antituberculosis by activity (MIC =1.56, 0.20, 0.10, 0.10 μg/mL, respectively). Compound **21e** is active with respect to seven different monoresistant strains (MIC = 0.39–1.56 μg/mL) [32].

For 34 compounds with general formula **21f**, among 70 tested 3-phenylquinoxaline-1,4-di-*N*-oxides the MIC value is less than 2 μg/mL, which is comparable with the activity of rifampicin (MIC = 0.125 μg/mL) [33].

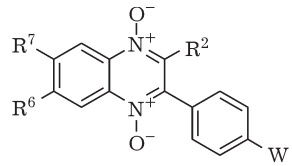
More efficiently comparing to rifampicin (reference substance, MIC = 1.00 μg/mL), *M. tuberculosis* H37Rv (ATCC 27294) is inhibited by and macrolactone **21g** (MIC = 0.62 μg/mL) [34] (Scheme 14).

Though phenoxazines, phenothiazines and acridines are well known pharmacophores connected with antituberculosis activity, the antituberculosis profile was for the first time reported concerning 1,2,3,4-tetrahydroacridines those have different substituents at C-9 atom. Among 9-aminoalkyltetrahydroacridines, compound **22a** (MIC = 1.56 μg/mL) is much more specific with respect to an avirulent strain H37Ra, whereas compound **22b** is more specific with respect to virulent strain H37Rv (MIC = 0.78 μg/mL). Substituting the aminoalkyl group at C-9 atom by phenoxy or thiophenyl group results in the loss of activity, which indicates that nitrogen atom is required for the activity to be exhibited. Only one compound (**22c**, MIC = 3.12 μg/mL) among five bisacridine derivatives appeared active against an avirulent strain. This fact indicates that introducing more than one acridine unit into the molecule does not result in any advantage [35]. Two derivatives of phenazine (**23a** and **23b**, MIC = 1–4 μg/mL) actively inhibit the growth of drug-susceptible and drug-resistant strains of *M. tuberculosis*. As clinical isolates with drug resistance are concerned, these two compounds demonstrated much better results than isoniazid. The studies demonstrated that the antituberculosis activity of this type of compounds depends on the lengths of the alkyl chain be-

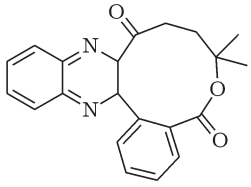


R^1 = H, Me, OMe, Cl, F;
R^2 = H, Me, Cl, F;
R^3 = Me, CH_2COOEt
R^4 = Me, Et, *tert*-Bu, $CH_3CH_2OCH_3$, $CH_2CH{=}CH_2$, CH_2Ph

21a $R^1 = R^2 = H$, R^3 = Me, R^4 = Et
21b R^1 = Cl, $R^2 = H$, R^3 = Me, R^4 = Et
21c $R^1 = R^2 = H$, R^3 = Me, $R^4 = CH_2Ph$
21d R^1 = Cl, $R^2 = H$, R^3 = Me, $R^4 = CH_2Ph$
21e $R^1 = R^2 = R^3$ = Me, $R^4 = Et^2$



21f R^2 = CN, CO_2Et;
W = H, Me, OMe, CO_2Me, F, Cl, Br, NO_2;
R^6 = H, Me, Cl
R^7 = H, Me, OMe, F, Cl, Br;

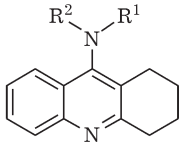


21g

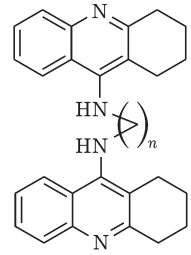
Scheme 14.

tween piperazine and phthalimide fragments, however the optimum carbon chain contains 5–6 atoms [36] (Scheme 15).

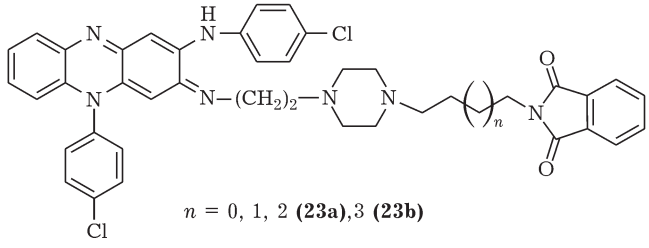
Among the studied aryl or hetepoarylpurines, 6-(2-furyl)purines are most efficient. Furthermore, the presence of a substituent at the position 9 was a crucial factor concerning the activity against *M. tuberculosis*. Compounds with small alkyl groups or with no substituent at position 9 are inactive, 9-aryl- and 9-sulphonylarylpurines exhibit a low activity against mycobacteria, however 9-benzylpurines represent good inhibitors, particularly those of them which have electron donating substituents in the phenyl ring. However, an insignificant increase in the distance between purine and phenyl rings (CH_2CH_2Ph) resulted in the reduction of the activity. The growth of the activity is promoted also by chlorine atom at the position 2 of purine. The leading structures of this class of compounds are presented by 2-chloro-6-(2-furyl)-9-benzylpurine **24a** (MIC = 0.78 μg/mL) and 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-9*H*-purine **24b** (MIC = 0.39 μg/mL in contrast with as compared to the MIC value for rifampicin equal 0.25 μg/mL). Compound **24a** exhibits low toxicity and high activity with respect to several monoresistant strains of *M.*



R^1R^2NH- = *n*-hexyl-NH–, *n*-octyl-NH– **(22a)**, *n*-dodecyl-NH– **(22b)**, morpholinyl, phenylmethyl-NH–, 3-chlorophenylethyl-NH–, 4-methoxyphenyl-NH–, 2-hydroxyethyl-NH–



n = 3–5, 7, 10 **(22c)**



n = 0, 1, 2 **(23a)**,3 **(23b)**

Scheme 15.

tuberculosis. A high antituberculosis activity with respect to *M. tuberculosis* H37Rv, low toxicity for human cells and the activity inside macrophages inherent in the compound **24b** indicate the compound is possible to use as an antituberculosis remedy [37, 38] (Scheme 16).

A rather interesting activity with respect to *M. tuberculosis* H37Rv is exhibited by 9-sulphenyl /sulfonyl-6-mercaptopurines (MIC = 0.39–3.39 μg/mL). In this connection, these compounds were chosen as leading structures for obtaining much more efficient antituberculosis remedies. Compound **24c** exhibits the activity against several drug-resistant strains of *M. tuberculosis* (MIC < 1 μg/mL) [39].

Amongst thio derivatives of purine, pyrimidine and pyridine tested for the activity with respect to *M. tuberculosis* strains H37Rv and H37Ra, the compounds of pyrimidine and pyridine appeared inactive. Thio compounds of purine with a substituent at the position 6 are much more active than their 6,9-substituted analogues among those 9-(ethylcarboxymethyl)-6-(decylthio)-9*H*-purine **24d** (MIC = 1.56 μg/mL) and 9-(ethylcarboxymethyl)-6-(dodecylthio)-9*H*-purine **24e** (MIC = 0.78 μg/mL) are most remarkable. It is obvious that substitution at the position 9 of the purine ring a intensifies the antituberculosis activity of these compounds [40].

A good inhibiting ability with respect to *M. tuberculosis* H37Rv is exhibited pyrazolo[3,4-*d*]pyrimidines **24g–i,l** and **24f,j,k,m** (MIC = 1.2 and 3.25 μg/mL, respectively) [41] (Scheme 17).

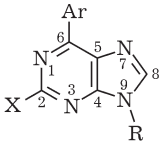
The authors of [43] synthesized and tested for antituberculosis activity (against *M. tuberculosis* H37Rv) different 7-chloroquinolone derivatives, designed *via* joining together the two pharmacophore fragments of into one molecule antimalarial preparations and ethambutol. The important property of these compounds is presented by the absence of cytotoxicity at the concentration efficient for the inhibition of *M. tuberculosis*. The most active among the compounds studied were 7-chloro-4-diaminoquinoline derivatives **25a–c** , wherein an increase in the length of the alkyl chain between nitrogen atoms results in improving the activity (n = 6, 8, 10, MIC = 25.00, 6.25, 3.12 μg/mL, respectively).

A similar approach was used by the authors of [44]. The derivatives designed on the base of isoniazid (MIC = 0.2 μg/mL) and *trans*-cinnamic or benzoic acids exhibit antituberculosis activity being herewith not cytotoxic. All the compounds of benzoic acid are sufficiently more active than their own cinnamic analogues **25d–g** (MIC = 3.12 μg/mL).

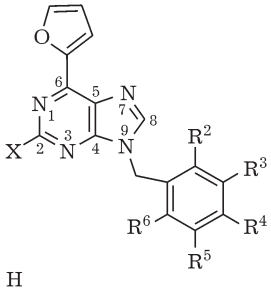
The presence of the cinnamic acid fragment is very important for the antituberculosis activity of its linear thioesters and amides containing substituents at the position 4 of the benzene ring **25h–k** (MIC = 0.6, 0.6, 0.1, 1 μg/mL with respect to *M. tuberculosis* H37Rv) [44] (Scheme 18).

Among 20 quinoline derivatives containing different substituents (triazole, urea, thiourea), the three compounds **25l–n** were chosen with functional groups required for the presence of the antituberculosis to activity (MIC = 3.125, 6.25, 3.125 μg/mL, respectively, against *M. tuberculosis* H37Rv) [45] (Scheme 19).

The structural optimization of 4-(adamantane-1-yl)-2-quinolinecarbohydrazide and 4-(adamantane-1-yl)-2-quinolinecarboxamide studied earlier, allowed researchers to reveal compounds **25o–t** (MIC = 3.125 μg/mL against a



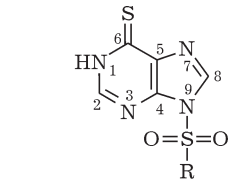
X = H, Cl;
Ar = 2-thienyl, 2-furyl, Ph;
R = H, CH_3, $CH_2CH{=}CH_2$, CH_2Ph, CH_2-cyclohexyl, CH_2CH_2Ph, THP;



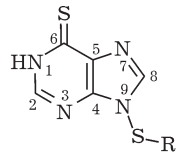
X = H
R^2 = H, OCH_3, Cl, F; R^3 = H, CH_3, OCH_3, Cl;
R^4 = H, CH_3, $C(CH_3)_3$, CF_3, NH_2, $NHCOCH_3$, $N(CH_3)_2$, NO_2; SCH_3, SO_2CH_3; OH, OCH_3, OCH_2CH_3, OCH_2Ph, $OCOCH_3$; Cl, F;
R^5 = H, OCH_3; R^6 = H, Cl, F;

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;
24a R^2 = R^3 = R^4 = R^5 = R^6 = H;
24b R^2 = R^3 = H, R^4 = OCH_3, R^5 = R^6 = H

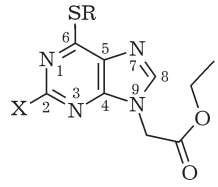
Scheme 16.



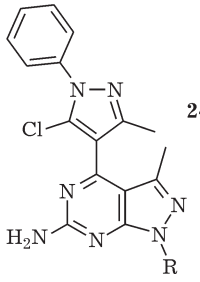
R = $N(CH_3)_2$, X-C_6H_4
X = 4-CH_3, 4-NH_2, 4-NHAc, 4-Cl, 4-Br, 4-F, 3-NH_2, 2-NO_2



R = 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$ **(24c)**

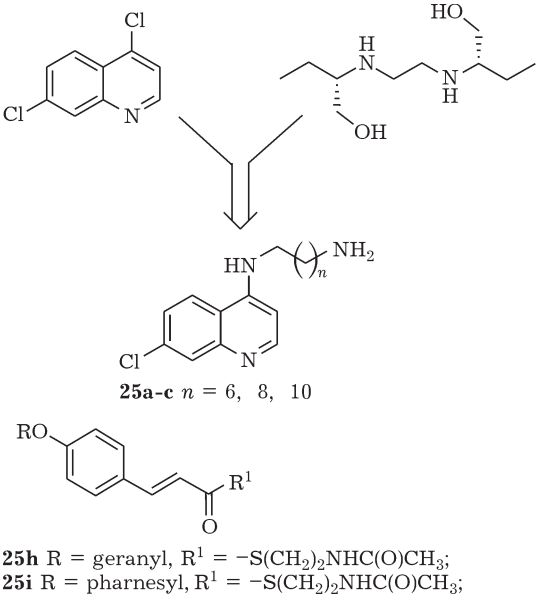


X = H, OH
R = $C_{10}H_{21}$, $C_{12}H_{25}$, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-naphthyl, $CH_2C_6H_5$, $CH_2C_6H_3$-3-Cl-6-F, $CH_2C_6H_3$-2-Me-3-NO_2, $CH_2C_6H_4$-2-F
24d X = H, R = $C_{10}H_{21}$;
24e X = H, R = $C_{12}H_{25}$



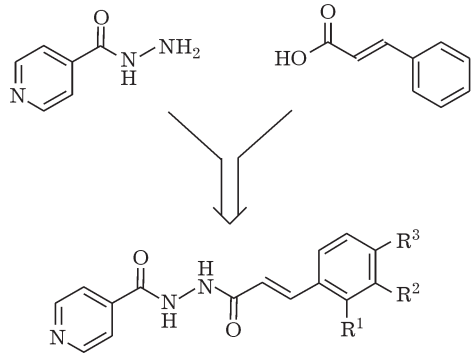
24f-m R = Ph, 2-Cl-phenyl, 3-Cl-phenyl, 4-Me-phenyl, 3-sulfophenyl, 4-sulfophenyl, 2-Cl-5-sulfophenyl, 2,5-Cl-4-sulfophenyl

Scheme 17.



25a-c n = 6, 8, 10

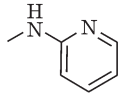
25h R = geranyl, $R^1 = -S(CH_2)_2NHC(O)CH_3$;
25i R = pharnesyl, $R^1 = -S(CH_2)_2NHC(O)CH_3$;



25d $R^1 = R^2 = R^3 = H$; **25e** $R^1 = R^2 = H$, $R^3 = NO_2$
25f $R^1 = R^2 = H$, R^3 = OMe; **25g** $R^1 = H$, $R^2 + R^3 = OCH_2O$

25j R = geranyl, $R^1 = -NH(CH_2)_2NHC(O)CH_3$;

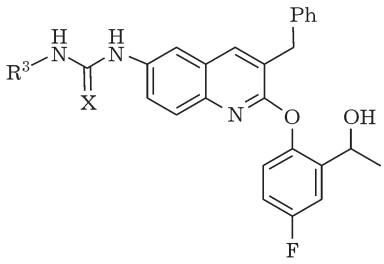
25k R = geranyl, R^1 =



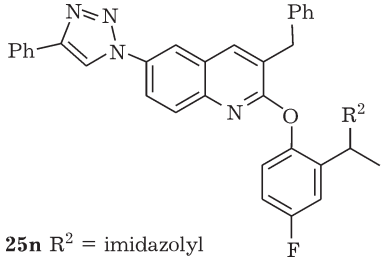
Scheme 18.

susceptible strain of *M. tuberculosis* H37Rv) and compound **25u** (MIC = 1.00 μg/mL with respect to a drug-susceptible strain of *M. tuberculosis* H37Rv and 3.125 μg/ mL with respect to an isoniazid-resistant strain of *M. tuberculosis* H37Rv) [46] (Scheme 20).

The analogue of new-generation fluoroquinolones such as oxoquinoline **26a** (MIC = 0.2 μg/mL) is sevenfold more active against *M. tuberculosis* with MDRTB than isoniazid (MIC = 1.56 μg/mL) [47]. The antituberculosis activity of novel lipophilic fluoroquinolone derivatives obtained *via* the substitution of the 1,2-diamine fragment by *N*-alkylated 1,2-ethanediamine or 1,3-propanediamine depends on the lengths and brunching level of the alkyl chain. The ideal carbon chain contains 10 atoms, as it is for compounds **26b** (MIC = 0.62 μg/mL with respect to *M. tuberculosis* H37Rv) and **26c** (MIC = 0.3 μg/mL). All the 1.3-propanediamine derivatives are much more active comparing to 1,2-ethanediamine derivatives with similar alkyl chains [48].

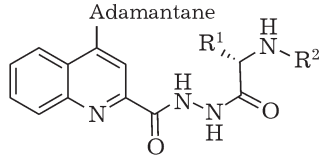


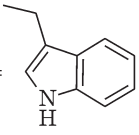
25l R^3 = 3-OMe-Ph, X = O
25m R^3 = 3-NO_2-Ph, X = O

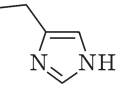


25n R^2 = imidazolyl

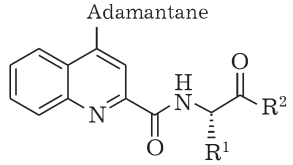
Scheme 19.

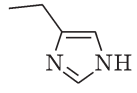


25o R^1 =  $R^2 = CO_2C(CH_3)_3$

25p R^1 =  $R^2 = CO_2C(CH_3)_3$

25q $R^1 = (CH_2)_3NHC(=NH)NH_2$
$R^2 = CO_2C(CH_3)_3$



25r R^1 =  $R^2 = OCH_3$

25s $R^1 = (CH_2)_3NHC(=NH)NH_2$, $R_2 = OCH_3$
25t $R^1 = (CH_2)_3NHC(=NH)NH_2$, $R_2 = NHNH_2$

Scheme 20.

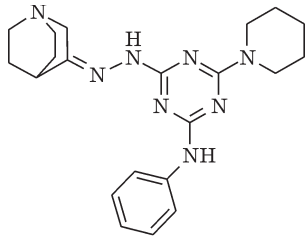
The class of 6-oxo-6,9-dihydro-3*H*-[1,2,3]-triazole[4,5-*h*]quinoline-7-carboxylic acids and their esters is structurally close to fluoroquinolones, however they contain the triazole ring, which could affect on the lipophilic properties or the activity of the molecule as a whole. Indeed, some of these compounds exhibit the antituberculosis activity that correlates with the length and position of the substituent in the triazole ring, as well as depends on the type of the substituent at the quinolone nitrogen atom. A methyl substituent at the N-3 atom of the triazole ring appeared to exhibit optimum properties. Its substitution by the ethyl group sharply reduces the activity (MIC_{90} from 1.6 to >32 μg/mL), however when transferring the methyl groups from N-3 atom towards N-2 or N-1 atom the activity disappears. The presence of the alkyl substituent at N-9 atom appeared to be much more preferred for high antituberculosis activity than the presence of propenyl or benzyl groups, whereas the phenylethyl group is tolerant one. The most efficient derivative possessing a high antituberculosis activity associated with the absence of cytotoxicity, appeared to be presented by compound **26d** (MIC_{90} = 0.5 μg/mL with respect to 11 clinical isolates of *M. tuberculosis* and human infectious macrophages (J774-A1) [49].

Novel derivatives of fluoroquinolone carboxylic acids **26e–g** exhibit a pronounced antituberculosis activity, which determines their prospectivity in the further searching for antituberculosis remedies. Fluoroquinolones **26e** (MIC = 0.2–1.6 μg/mL) exhibit a much more high antituberculosis activity than perfloxacin (MIC = 4 μg/mL).

In the series of thiadiazinoquinolones **26f** (MIC = 0.2–1.6 μg/mL), the activity decreases to a considerable extent when substituting R^3 = H by fluorine atom. Among oxadiazinoquinolones **26g** (MIC = 0.2–0.6 μg/mL), the compound having nitrophenyl remainder as R^1 has demonstrated somewhat greater activity as compared to pyridine-4-yl-substituted derivatives [50] (Scheme 21).

A highly efficient inhibitor of indole-3-glycerol phosphate synthase (IGPS) of *M. tuberculosis* is presented by compound **27** (ATB107) that is rather active both with respect to the laboratory strains of *M. tuberculosis* H37Rv, *M. tuberculosis* H37Ra and *M. bovis* BCG (MIC

0.1 μg/mL), and with respect to clinical isolates such as drug-susceptible strains (50 strains, MIC = 0.1–1.0 μg/mL) and strains with MDRTB (80 strains, MIC = 1.0 μg/mL). The further studies concerning the toxicity, pharmacology and activity *in vivo* in model animals are under planning [51] (Scheme 22).

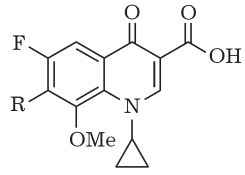


27

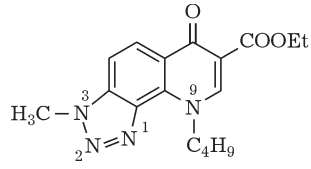
Scheme 22.

Oxygen-containing heterocycles

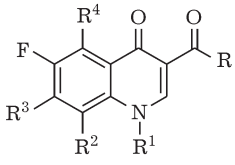
As a base structure for synthesizing the second nitrofuranylamide generation, 3,4-dimethoxybenzylamide of 5-nitrofuran-2-carboxylic acid **28a** found earlier exhibiting a significant antituberculosis activity (MIC = 0.2 μg/mL), but having a low solubility, was chosen. The authors put the problem to improve the solubility and bioavailability of novel compounds due to the introducing hydrophilic cyclic fragment C to the benzyl or phenyl ring B. It appeared that substituted benzyl compounds (MIC = 0.0125–3.13 μg/mL) exhibit a more high antituberculosis activity, than substituted phenyl compounds (MIC = 0.4–12.5 μg/mL). In both cases,



26a-c R = Me, $NH(CH_2)_2NHC_{10}H_{21}$, $NH(CH_2)_3NHC_{10}H_{21}$

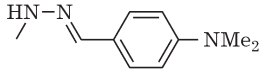


26d

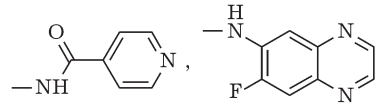


26e

R = $NHNH_2$, OH, OEt

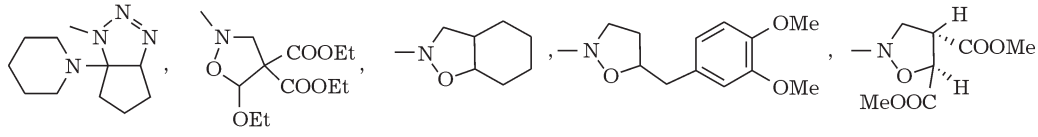


R^1 = Et, $NHC(O)CH_2CN$, 2-Cl-4-CF_3-Ph

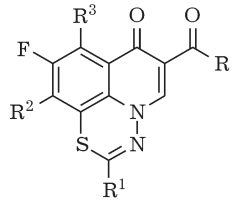


R^2 = H, F

R^3 = morpholine-4-yl, 2,6-morpholine-4-yl, pyrrolidine-1-yl, 4-methylpiperidine-1-yl



R^4 = H, F, pyrrolidine-1-yl



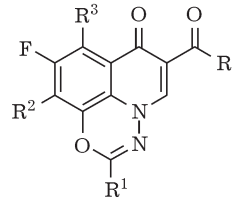
26f

R = OH

R^1 = pyrrolidine-1-yl

R^2 = F, 4-ethoxycarbonyl, pyrrolidine-1-yl, morpholine-4-yl, piperazine-1-yl

R^3 = H, F, 4-ethoxycarbonyl, morphline-4-yl, morpholine-4-yl, piperazine-1-yl



26g

R = OH, OEt

R^1 = 3-nitrophenyl, pyrrolidine-1-yl

R^2 = F, pyrrolidine-1-yl

R^3 = H, F

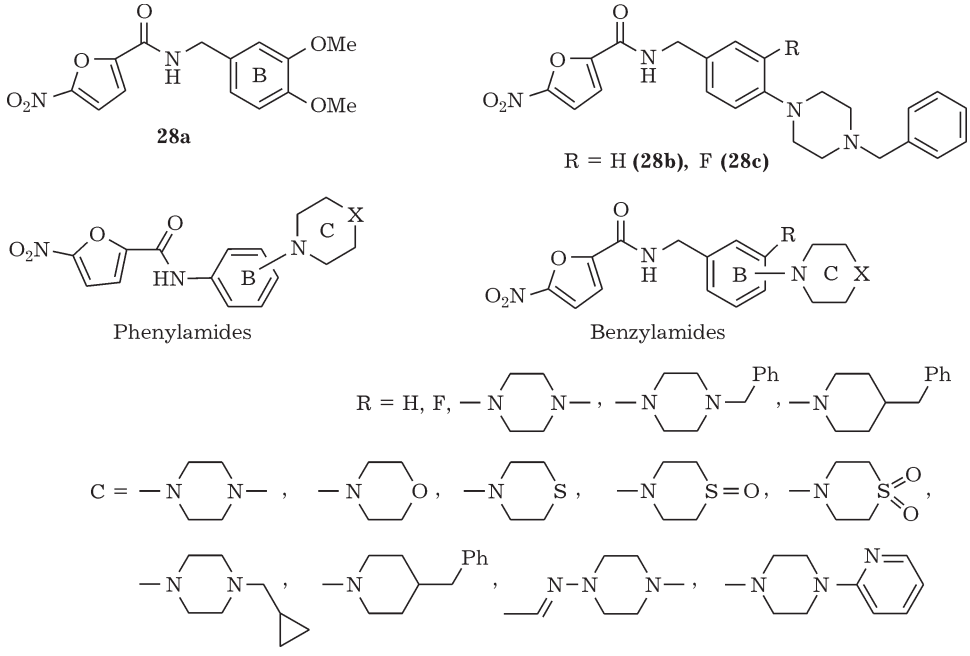
Scheme 21.

substitution at *para* position caused the antituberculosis activity to be improved. The compound from the benzyl series are extremely efficient, in particular compound **28b** with a *para*-benzylpiperazine substituent (MIC = 0.0125 μg/mL against *M. tuberculosis* H37Rv) and compound **28c** similar to the mentioned one with *meta*-fluorine atom in the benzene ring (MIC = 0.025 μg/mL) [52] (Scheme 23).

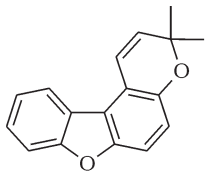
The authors of [53] synthesized potential antituberculosis compounds having in the structure the dibenzofuran skeleton and dimethylpyrane ring condensed together with it. Compound **29a** (MIC = 5 μg/mL) and its reduced analogue **29b** (MIC = 1–5 μg/mL) actively inhibit the growth of different strains of *M. tuberculosis* alongside with isoniazid. Furthermore, compounds obtained exhibit a low cytotoxicity level. It was expected that the double bond in the pyrane cycle would allow additional potentialities for the modification. However, the functionalization of these compounds aimed at improving the solubility in biocompatible solvents, namely the dihydroxylation of the dimethylpyrane ring and the further conversion into esters resulted in a complete loss of the activity. As the result of studies concerning the optimization of structure–antituberculosis activity relations, compounds **29c** and **29d** were found inhibiting well *M. tuberculosis* (MIC = 2.5 and 3 μg/mL, respectively) and *M. smegmatis* (MIC = 3 and 6.2 μg/mL, respectively) [54], as well as furo[3,2-*f*]-chromanes **29e** (MIC_{95} = 0.6–5 μg/mL for *M. bovis* BCG and *M. tuberculosis* H37Rv) [55]. Unfortunately, the majority of compounds **29e** at these concentration values are cytotoxic (Scheme 24).

The following group of compounds is presented by synthetic derivatives of saccharides.

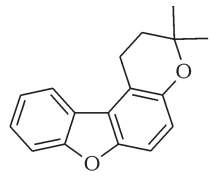
Among the compounds those represent the C-phosphonate analogues of decaprenolphosphoarabinose being key intermediates in the biosynthesis of mycobacterial arabinogalactan and lipoarabinomannan, only compound **30** (MIC = 3.13 μg/mL) with a hexadecyl substituent exhibits the required activity with respect to *M. tuberculosis* H37Rv ATCC 27294. This fact clearly indicates that the length of the alkyl chain determines the antituberculosis activity of this type of compounds [56]. A novel class of compounds such as derivatives of 2,3-dideoxy-hex-2-en-pyronazide with alkyl and arylalkyl substituents at C-3 atom of hexenpyranoside was studied in vitro aimed at com-



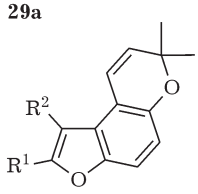
Scheme 23.



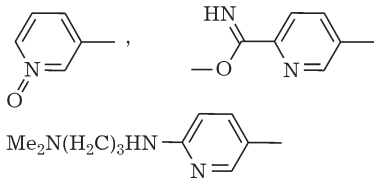
29a



29b



29c R^1 = 4-pyridyl, R^2 = H
29d R^1 = 4-pyridyl, R^2 = Me
29e R^1 = 4-pyridyl, 3-pyridyl, 3-CH_2-pyridyl, 3-pyridyl-CH=CH−, 3-pyridyl-$(CH_2)_2$−, R^2 = H, $(CH_2)_3OAc$,



Scheme 24.

plete inhibiting the growth of *M. tuberculosis* H37Rv. For the further studying, compound **31** (MIC = 3.12 μg/mL) was chosen which is characterized by a maximal activity combined with the absence of cytotoxicity [57].

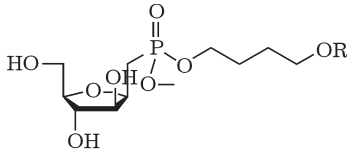
The antituberculosis activity was studied for the series of N- and C-alkylated amino alcohols and their galactopyranozyl derivatives **32a–i**. It was demonstrated that the activity free amino alcohols depends on the length of the alkyl chain: the best results were obtained for compounds **32a** and **32b**. Herewith the C-alkylated compound **32b** (MIC = 3.12 μg/mL with respect to *M. tuberculosis* H37Rv) is two times more active than its N-alkylated analogue **32a** (MIC = 6.25 μg/mL). Compounds with a longer alkyl chain appeared two times less active comparing to compound **32a**, but more active than compounds with a shortened alkyl chain. A similar effect was observed also for galactopyranozyl derivatives of these amino alcohols, but in this case N-alkylated galactoso derivative **32c** (MIC = 3.12 μg/mL) is four times more active than C-alkylated analogue **32d** (MIC = 12.5 μg/mL). As a whole, the glycosylation of N-alkylated amino alcohols enhanced their activity indicating that the carbohydrate fragment is important for antituberculosis activity of these compounds. One more important factor determining the activity, is presented by the linearity of the hydrocarbon chain, since the compound those have a brunched alkyl chain do not exhibit antituberculosis activity at the concentration under testing [58].

The authors of [59] noted that the antituberculosis activity of glycosylated amino alcohols **32e** having different length alkyl chain depends on the nature of the hydroxyaminoalkyl chain. So, compounds with simple linear aminoalkyl chain more active than their analogues with furfuryl, benzyl or cyclic amine fragment. Compound **32f** (MIC = 1.56 μg/mL) chosen as a leader in order to search for much more efficient analogues surpasses in the action the existing antituberculosis preparations such as amino alcohol ethambutol with respect to *M. tuberculosis* H37Rv (MIC = 3.25 μg/mL) and with respect to five clinical isolates with MDRTB at the concentrations of 50 μg/mL wherewith the existing antituberculosis preparations are inefficient. Such an activity requires for 12-membered carbon chain and the presence of two galactopyranozyl units.

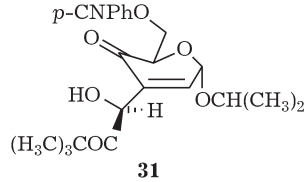
A novel series of amino sugar derivatives was tested for antituberculosis activity against *M. tuberculosis* H37Ra and H37Rv. It was established that compound **32g** (MIC = 3.12 μg/ mL) with *N*-dodecyl and 3-*O*-benzyl substituents exhibits the best antituberculosis activity amongst the compounds this series. Galactopyranosylated amino alcohol **32h** (MIC = 3.125 μg/ mL) with a hexadecyl substituent appeared the most active against the strain of *M. tuberculosis* H37Rv, whereas compound **32i** (MIC = 3.12 μg/mL) with oleyl fragment was most active with respect to *M. tuberculosis* H37Ra. For obtaining compounds with lower values of MIC, further optimization is necessary [60] (Scheme 25).

Sulphur-containing heterocycles

A novel type of compounds with antimycobacterial activity is presented by the derivatives of triarylmethane **33a–f** (MIC = 3.12 μg/mL with respect to *M. tuberculosis* H37Rv), wherein one aryl group is substituted by the thiophene fragment, that exhibits aromatic properties, too [61].



R = $(CH_2)_6CH_3$, $(CH_2)_7CH_3$, $(CH_2)_8CH_3$, $(CH_2)_9CH_3$, $(CH_2)_{11}CH_3$, $(CH_2)_{15}CH_3$ **(30)**



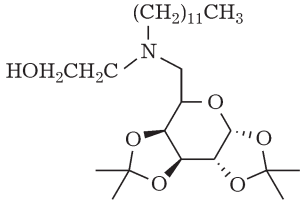
31

$CH_3(CH_2)_nNHCH_2CH_2OH$

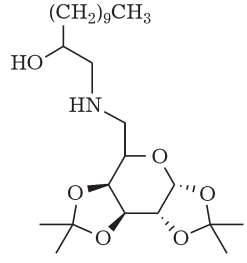
n = 7, 9, 11 **(32a)**, 13, 15

$CH_3(CH_2)_9CH(OH)CH_2NH_2$

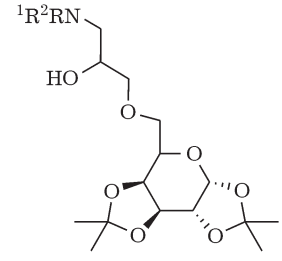
32b



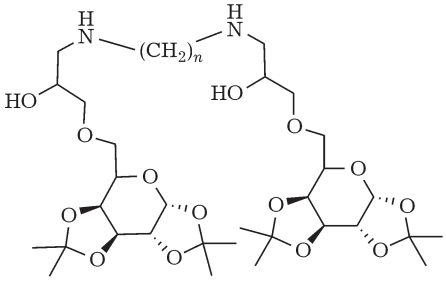
32c



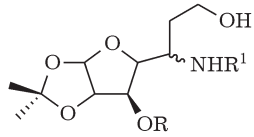
32d



32e NR^1R^2 = $PhCH_2NH-$, furfuryl NH–, $CH_3(CH_2)_{11}NH-$, $H_3(CH_2)_{15}NH-$, $CH_3(CH_2)_7CH{=}CH(CH_2)_8NH-$, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, 4-(6-chloro-2-pyridyl)piperazinyl



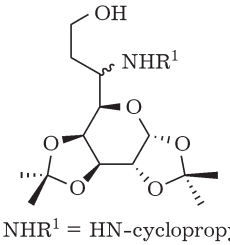
n = 3, 7, 9, 10, 12 **(32f)**



R = Me, CH_2Ph

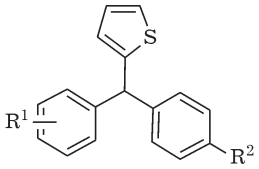
NHR^1 = HN-cyclopropyl, HN-cyclohexyl, $HN(CH_2)_6CH_3$, $HN(CH_2)_{11}CH_3$, $HN(CH_2)_{15}CH_3$, oleylamine

32g R = $(CH_2)Ph$, NHR^1 = $HN(CH_2)_{11}CH_3$



NHR^1 = HN-cyclopropyl, HN-cyclohexyl, $HN(CH_2)_6CH_3$, $HN(CH_2)_{11}CH_3$, $HN(CH_2)_{15}CH_3$ **(32h)**, oleylamine **(32i)**

Scheme 25.



33a-f R^1 = 4-OMe, 3-OMe, 4-SMe, 4-Cl
R^2 = OH, NEt_2, heptamethyleneimine

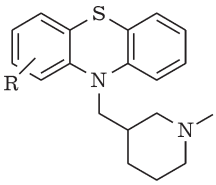
It is known for long that phenothiazines exhibit the antituberculosis activity, but their using is limited by psychotropic effects (medicinal preparations chlorpromazine, tirioridazine, trifluoperazine), which could be caused by binding these compounds with dopamine and serotonin receptors. In connection with these circumstances, the synthesis of phenothiazine analogues was realized for the purpose of clarifying of the types of their modification those result in increasing the antituberculosis activity and action selectivity. All the existing phenothiazine preparations possess different lateral chains in the structure, at the position 10 of phenothiazine ring, as well as substituents in the aromatic ring. Furthermore, for some classes of the compounds, the events are known connected with increasing the biological activity, when minimal active units are bound between each other with the formation of dimers or bis-compounds.

For a series of compounds with a fixed by methylpiperidine lateral chain, the most active compounds with respect to *M. tuberculosis* H37Rv are presented by the compounds with phenyl substituents **34a** and **34b** (MIC = 4.5 and 2.1 μg/mL, respectively) those exhibit a weak tendency towards binding with serotonin receptors and only moderate tendency towards binding with dopamine receptors. The most considerable tendency towards binding with these receptors is inherent in analogues **34c** and **34d**, inactive with respect to *M. tuberculosis*. Among all the compounds with fixed by CF_3 substituent in the aromatic part of the molecule and varied lateral chain, one could indicate only two compounds (**34e** and **34f**, MIC = 4.6 and 4.2 μg/mL, respectively). An increase in the steric volume of the lateral chain in the compound **34g–j** (MIC = 10–20 μg/mL) causes the binding level with all the subtypes of receptors to decrease. Only both bisphenothiazine compounds **34k** and **34l** (MIC = 2.3 and 2.0 μg/mL, respectively) simultaneously demonstrate both the most significant increase in the antituberculosis activity, and a considerable reduction of binding with a receptor [62] (Scheme 26).

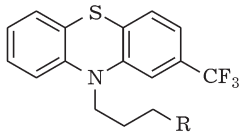
Joining together the cycle of 4*H*-1,2,4-benzothiadiazine-1,1-dioxide with the pyridine fragment those separately exhibit antimicrobial and antituberculosis effect, allowed researchers to obtain a novel type of a structure with antituberculosis activity. Compound **35** demonstrates the best activity with respect to *M. tuberculosis* H37Rv ATCC 27294, drug-resistant and drug-susceptible clinical isolates of *M. tuberculosis* (MIC = 0.5–2.0 μg/mL), as well as a moderate activity with respect to *M. avium* ATCC 49601 and *M. intracellulare* ATCC 13950 (MIC = 2.0 μg/mL). However, this compound has not demonstrated such an activity when *in vivo* testing in mice, to all appearance, due to bad bioavailability [63].

In order to optimize the structure–antituberculosis activity relationship, different alkyl esters of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-yl-thiosulfinyl- and sulfonyl]acetic and propionic acids were synthesized, in this case the type of aryl substituent (5-nitroheterocycle), the oxidation degree of sulphur atom (n = 0–2), the presence of methyl and methylene groups at α-carbon atom of the estereal fragment, the structure ester groups were varied. As a result, compound **36** was found with a high antituberculosis activity against *M. tuberculosis* H37Rv (MIC = 1.56 μg/mL), which suits for the further *in vitro* and *in vivo* estimation [64] (Scheme 27).

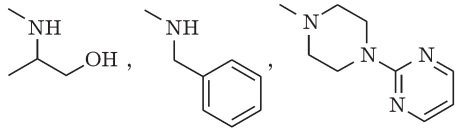
The activity with respect to *M. tuberculosis* H37Rv and the strains of *M. tuberculosis* with MDRTB was studied for 22 novel 2-aryl-3,4-dihydro-2*H*-thieno-[3,2-*b*]indoles. Among the compounds of 13 indoles tested, compounds **37a–n** inhibit the growth of *M. tuberculosis* much more efficiently than the applied medicinal preparations. So, compounds **37e,f,h,l,n** (MIC = 0.78, 078, 0.78, 0.4, 0.78 μg/mL, respectively, with respect to *M. tuberculosis* H37Rv) are more active, than ethambutol (MIC = 1.56 μg/mL) and pyrazinamide (MIC = 6.25 μg/mL), but compounds **37a,b,h,i** and **37e,f,l,o** (MIC with respect to *M. tuberculosis* with MDRTB being equal to 0.78 and 0.4 μg/mL, respectively) are more efficient than isoniazid (MIC = 1.56 μg/mL) and pyrazinamide (MIC = 3.13 μg/mL). The results obtained demonstrate that the increase in the

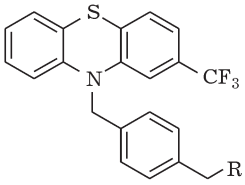


34a-d R = 3-Ph, phenoxazine, 2-Ph, 3-morpholino

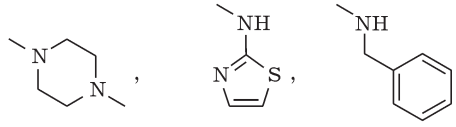


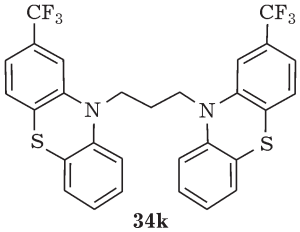
34e-g R =



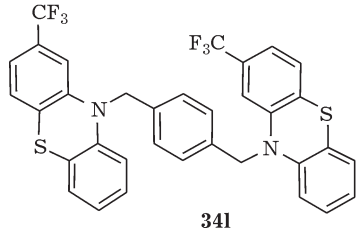


34h-j R =



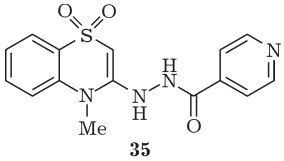


34k

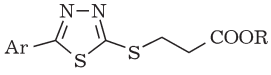


34l

Scheme 26.

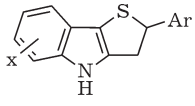


35



36 Ar = 5-nitro-2-thienyl; R = *n*-Pr

Scheme 27.



37a Ar = 2,4-$Cl_2C_6H_3$; X = H
37b Ar = 3-$NO_2C_6H_4$; X = H
37c Ar = 2-BrC_6H_4; X = H
37d Ar = 3-FC_6H_4; X = H
37e Ar = 4-$Pr^iC_6H_4$; X = H
37f Ar = 2,4-$Cl_2C_6H_3$; X = 7-Cl
37g Ar = 2-ClC_6H_4; X = 7-Cl
37h Ar = 4-$Pr^iC_6H_4$; X = 7-Cl
37i Ar = 4-FC_6H_4; X = 7-Cl
37j Ar = 4-ClC_6H_4; X = 7-F
37k Ar = 4-MeC_6H_4; X = 7-F
37l Ar = 2,4-$Cl_2C_6H_3$; X = 7-F
37m Ar = 2-ClC_6H_4; X = 7-F
37n Ar = 4-$Pr^iC_6H_4$; X = 7-F

Scheme 28.

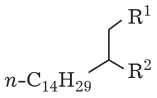
activity is promoted by the presence of a halogen atom in the ring, in this case fluorinated derivatives are more active, than chlorine-containing compounds [65] (Scheme 28).

Other compounds

A very good antituberculosis activity comparable with the activity of ethambutol (MIC = 3.12 μg/mL) is exhibited by α,ω-diaminoalkanes $H_2N(CH_2)_nNH_2$ **38a–c** (n = 9–12, MIC = 2.5–3.12 μg/mL with respect to *M. tuberculosis* H37Rv). Moreover, these compounds are not cytotoxic at the concentration efficient for the inhibition of *M. tuberculosis*. It was established that for the activity to exhibit, both certain length of alkyl chain, and two amino groups in free state are required [66].

The derivatives of dihydrocsphingosine **39a–c** (MIC = 1.25 μg/mL) exhibit a high antimycobacterial activity with respect to strain *M. tuberculosis* H37Rv and clinical isolates, resistant against five medicinal antituberculosis preparations belonging to the first line, as well as 11 different strains with MDRTB. One should especially note compound **39b** which inhibits the

growth of strain 332 resistant with respect to all the medicinal antituberculosis preparations belonging to the first line, with a much lower MIC value (0.78 μg/mL) [67].



39a R^1 = OBn, R^2 = NH_2
39b R^1 = OBn, R^2 = NEt_2
39c R^1 = NEt_2, R^2 = NH_2

It is known that 5-hexyl-2-phenoxyphenol **40a** (MIC_{90} = (2.1±0.9) μg/mL) inhibits well the growth of *M. tuberculosis* strains both drug-susceptible, and drug-resistant with respect to isoniazid, however it has a considerable disadvantage: pronounced lipophilic properties of this compound cause the bioavailability to be reduced. The analogue of this compound **40b–d** (MIC_{90} = 3.13 μg/mL) obtained by modification of the ring B, the level of lipophilic properties was succeeded to reduce with the level of antituberculosis activity being conserved [68].

Ortho-, *meta*- and *para*-substituted diphenyl esters **40e–n** (MIC = 1 μg/mL) are also highly active with respect to *M. tuberculosis* H37Rv [69].

Optimizing the structure of triclosan (MIC = 40 μg/mL for *M. tuberculosis* H37Rv) was performed. The compounds obtained exhibit an improved antituberculosis activity, too, herewith the inhibitors those have hydrophobic substituents such as alky groups, appeared much more efficient. The derivatives of triclosan **40o,p** (MIC = 4.7 μg/ mL) demonstrate a good activity only with respect to clinical isolate 5071 (resistant against isoniazid and streptomycin), whereas compound **40q** is efficiently both against widespread *M. tuberculosis* H37Rv, and against clinical isolate 5071 with similar MIC values (4.7 μg/mL) [70].

Very important parameters for a good antituberculosis activity of salicylanilides **40r,s** (MIC = 3.13 μg/mL, for isoniazid MIC = 0.025–0.2 μg/mL) with respect to *M. tuberculosis* H37Rv (ATCC 27294) are presented by the substituent R^1 (CF_3 group and atom Cl at certain of the aromatic ring), small size and the stereochemistry of substituent R^2 (*S*-methyl group). In order to determine an exact difference in the antituberculosis activity between individual *R*/*S* enantiomers, additional studies are required [71] (Scheme 29).

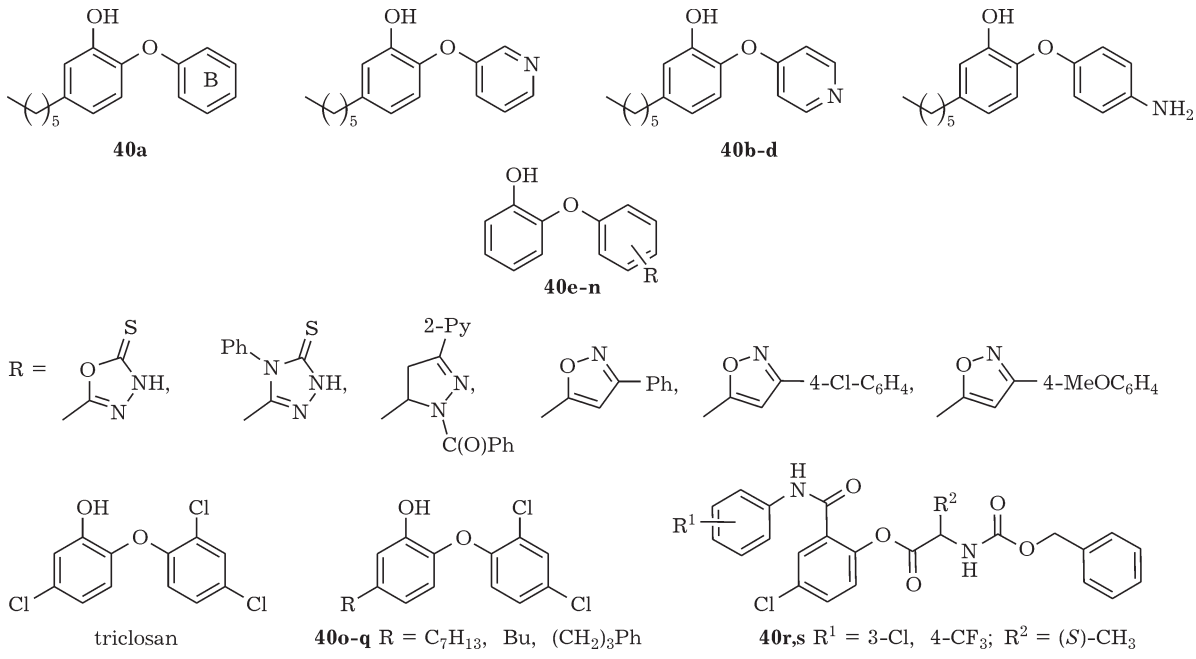
Active inhibitors of growing *M. tuberculosis* H37Rv such as **41a–d** (MIC = 0.79–3.57 μg/mL, for rifampicin MIC = 0.125 μg/mL) were revealed among 5-methyl/trifluoromethoxy-1*H*-indole-2,3-dione-3-thiosemicarbazones [72].

A high efficiency with respect to *M. tuberculosis* H37Rv and clinical isolates of *M. tuberculosis* with MDRTB, selectivity of actions and low cytotoxicity are inherent in 4-(5-cyclobutyloxazole-2-yl)thiosemicarbazones. So, with respect to *M. tuberculosis* H37Rv, the action of compound **42** equivalent to isoniazid (MIC = 0.05 μg/mL for both compounds), whereas eight compounds are much more efficient (MIC = 0.05–0.78 μg/mL) than ethambutol (MIC = 1.56 μg/mL). Eight compounds inhibit the growth of *M. tuberculosis* with MDRTB more efficiently (MIC = 0.05–0.78 μg/mL) than isoniazid (MIC = 1.56 μg/mL), nine compounds inhibit this process more efficiently, than rifampicin (MIC = 3.12 μg/mL), however all the compounds studied are much more efficient, than ethambutol (MIC = 25 μg/mL). The antituberculosis activity the compounds under investigation depends on the presence and nature of substituents R and R^1. When R = R^1 = H the absence of inhibition mycobacteria growth was observed. Electron donating substituents R^1(NO_2, Cl) cause the activity to increase. Substituent R influences the activity according the following order: phenyl > methyl > H [73] (Scheme 30).

NATURALLY OCCURRING COMPOUNDS WITH ANTIMYCOBACTERIAL ACTIVITY

Alkines and heterocyclic compounds

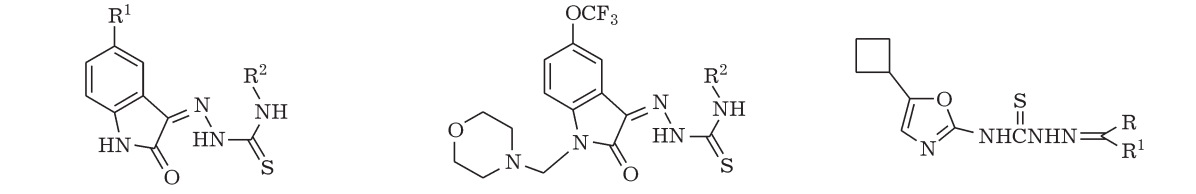
The metabolite of several strains of an endophytic fungus belonging to genus *Phomopsis*, 3-nitropropionic acid **43**, actively inhibits the growth of *M. tuberculosis* H37Ra (MIC = 0.4 μg/mL). Though the strong neurotoxicity of this compound prevents it from using as a medicinal preparation, one could apply it as a useful model for the synthesis of a novel inhibitor of isocitrate lyase, an enzyme required for the catabolism of fatty acids and



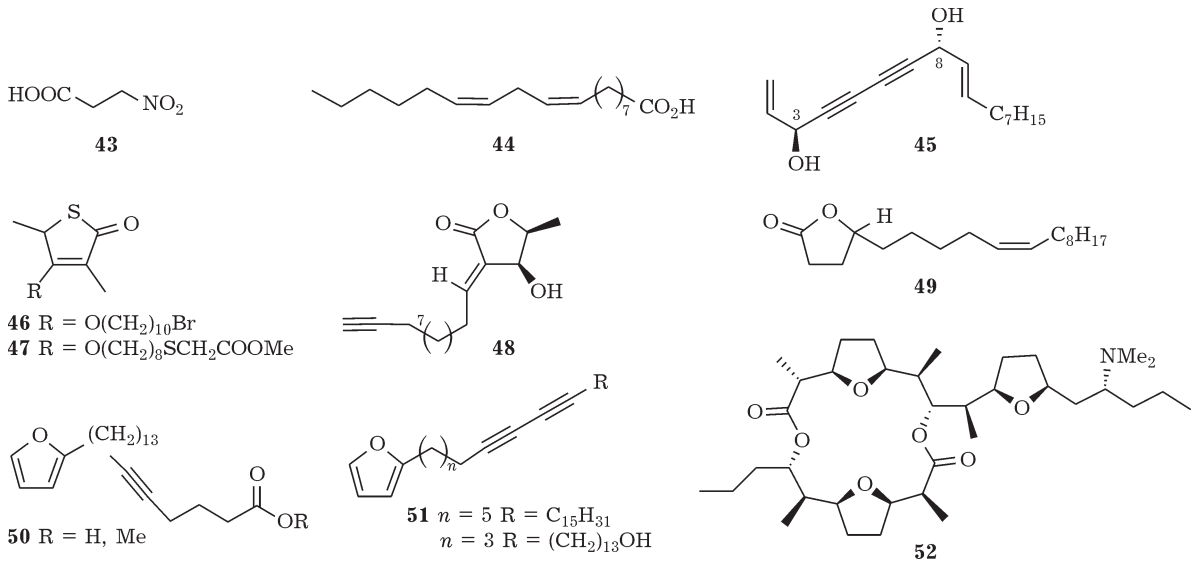
Scheme 29.

the virulence of *M. tuberculosis* [74]. From a hexane extract of all the parts of plant *Humulus lupulus*, linoleic acid **44** was isolated inhibiting the growth of *M. phlei* (MIC = 2 μg/mL) [75]. The polyacetylene compounds are exemplified by falcarindiol **45**, isolated from *Anethum graveolens* ((MIC = 2–4 μg/mL when testing on the 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) [76]. However, the cytotoxicity of this class of polyacetylene compounds could restrict the interest in their biological activity [77].

Compounds **46** and **47**, synthetic analogues of natural antibiotic thiolactomicin, inhibit the growth of *M. tuberculosis* with the value of MIC = 1–16 μg/mL including strains with drug resistance, too [78]. The study on the components of plant *Cinnamomum kotoense* resulted in the isolation of a number of compounds among those the most pronounced antituberculosis activity is exhibited by lincomolide B **48** (MIC = 2.8 μg/mL) [79]. Micromolide **49**, γ-lacton derivative of oleic acid was isolated from the stalk rind of *Micromelum hirsutum*, it is characterized by MIC = 1.5 μg/mL with respect to *M. tuberculosis* (H37Rv). Further testing the activity with respect to the cells of mice J774,



Scheme 30.



Scheme 31.

infected with a much more virulent strain *M. tuberculosis* Erdman has demonstrated that value of MIC is equal to 5.6 μg/mL [80]. The 2-substituted furans **50** and **51** isolated from the root of *Polyalthia evecta* exhibit the activity against *M. tuberculosis* (MIC = 3.1 and 6.25 μg/mL, respectively) [81]. Natural compound pamamycine-607 synthesized **52** inhibits the growth of *M. bovis* BCG, *M. smegmatis* and *M. tuberculosis* (MIC = 0.5–4.7 μg/mL). It was established that there is the absence of cross resistance against isoniazid and rifampicin [82] (Scheme 31).

Phenols and quinones

Phenylpropanoids **53** and **54**, the metabolites of *Pimpinella* sp., inhibit the growth of a number of mycobacteria, including *M. intracellulare*, *M. smegmatis*, *M. aurum* and *M. phlei* (MIC 1.25–10 μg/mL) [83]. Engelhardione **54** is very active with respect to *M. tuberculosis* H37Rv (MIC 0.2 μg/mL) [84]. As antituberculosis components, from *Engelhardia roxburghiana*, (−)-4-hydroxy-1-tetralone **55** (MIC = 4.0 μg/mL), 3-methoxyjuglone **56a** (MIC = 0.2 μg/mL) and 3-methoxycarbonyl-1,5-dihydroxyanthraquinone **57** (MIC = 3.125 μg/mL) were isolated [84]. It is known that the level of intracellular and extracellular *M. tuberculosis* inhibition by 7-methyljuglone **56b** (MIC = 0.5 μg/mL) isolated from plant *Euclea natalensis*, is comparable with streptomycin and ethambutol (MIC = 1 and 2 μg/mL, respectively). Its derivatives such as 5-hydroxy-, 5-alkoxy- and 5-acetoxy-8-substituted naphthoquinones are much more active (MIC ranging from 2.5 up to and more than 20 μg/mL) and, moreover, exhibit a low antituberculosis selectivity, which, to all appearance, could be caused by their non-specific activity with respect to different disulphide reductases, found in the cells of mammals.

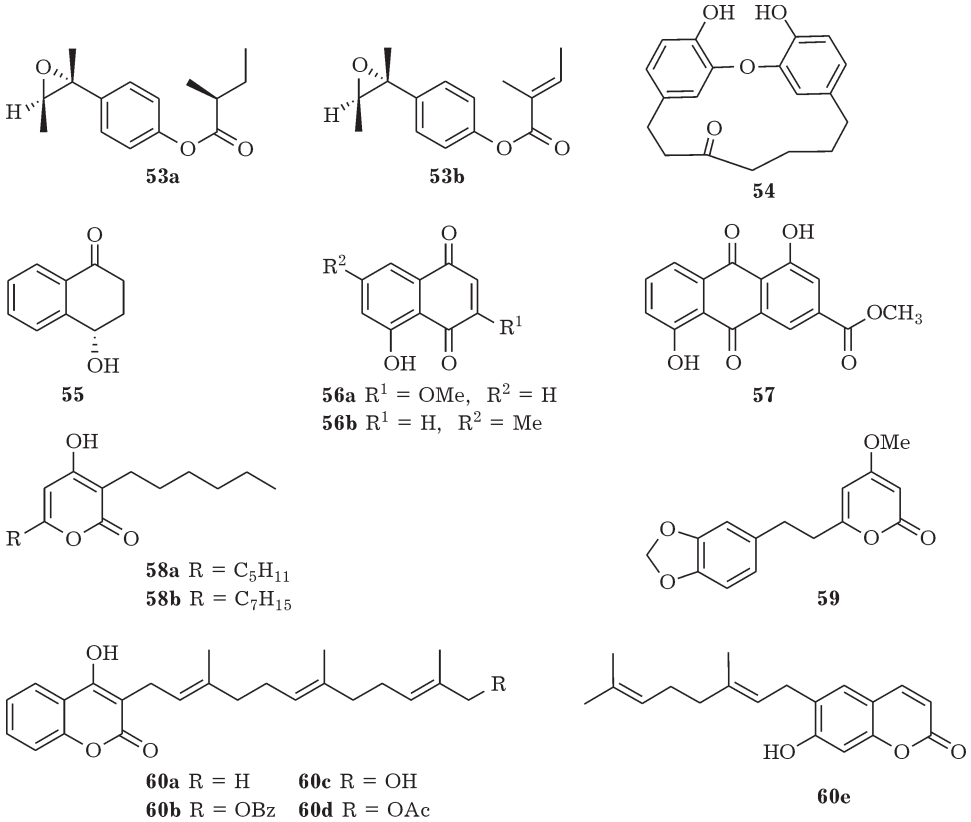
Optimization is required concerning the specificity of these compounds with respect to micothiol disulphide reductase, of several biological targets for antituberculosis activity of naphthoquinones with such type of structure [85]. Maritime metabolites pseudopyronines A and B **58a,b** (MIC = 0.78–3.125 μg/mL) well inhibit the growth of *M. tuberculosis* H37Rv [86]. The component of *Piper sanctum* active with respect to *M. tuberculosis* H37Rv is presented by pyrone **59** (MIC = 4 μg/mL) [87]. Ferulenol **60a** isolated from the Sardinian giant fennel *Ferula communis* is efficient against *M. smegmatis* (MIC = 0.5 μg/mL) as well as with respect to *M. fortuitum*, *M. phlei* and *M. aurum* (MIC = 2 μg/mL). From the same plant, its analogues **60b–d** were isolated, among those the compound **60b** with the benzyloxy group remains active with respect to *M. smegmatis* and *M. phlei* as well as against *M. fortuitum* and M. aurum to a lesser extent, however the activity of compounds **60c,d** with hydroxy and

acetoxy groups is reduced to a considerable extent [88]. Ostruthin **60e**, the etabolite of *Peucedanum ostruthin* Koch, also inhibits the growth of *M. aurum* (MIC = 3.4 μg/ mL) [75] (Scheme 32).

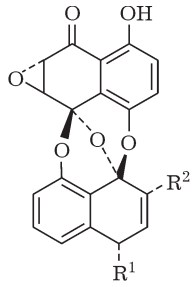
Compound **61a–h**, isolated from the lichen fungus *Microsphaeropsis* sp., to a different level exhibit the activity against *M. tuberculosis* H37Ra (MIC = 25, 3.12, 3.126.25, 6.25, 12.5, 25, 1.56–3.12, 50 μg/mL, respectively), however cytotoxicity is inherent in them [89]. A dibenzofuran derivative such as usnic acid **62**, a secondary metabolite of lichens, inhibits the growth of *M. tuberculosis* (MIC = 2.5–5 μg/mL) [90]. One of xanthone dimers phomoxanthone A **63a** isolated from an endophyt fungus belonging to genus *Phomopsis*, is very active with respect to *M. tuberculosis* H37Ra (MIC = 0.5 μg/mL), whereas its deacetylated derivatives **63b** is inactive. Phomoxanthone B **63c** is less efficient (MIC = 6.25 μg/mL). Both active compounds are cytotoxic [91]. Anthraquinone celastramycin B **64** isolated from an unknown *Streptomyces* sp., is active with respect to *M. vaccae* (MIC = 3.1 μg/mL) [92]. An anti-HIV agent (+)-calanolide A **65** was tested for the antituberculosis activity, since the existence of the same agent with anti-HIV and antituberculosis activity is very attractive, particularly taking into consideration simultaneous clinical course for the two diseases. This compound isolated from tropical tree *Calophyllum lanigerum*, exhibits also antituberculosis activity against *M. tuberculosis* (MIC = 3.13 μg/mL) as well as against a number of drug-resistant strains (MIC = 8–16 μg/mL) [93] (Scheme 33).

Peptides

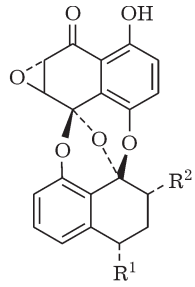
Four cyclic peptides such as enniatin H **66a**, I **66b**, B **66c** and B4 66d, the components pathogenic fungus *Verticillium hemipterigenum*, inhibit the growth of *M. tuberculosis* H37Ra (MIC = 3.12–6.25 μg/mL) [94]. Syringomycin E **67** isolated from *Pseudomonas syringae* pv. *Syringae*, is active with respect to *M. smegmatis* (MIC = 1.5 μg/mL) [95]. The metabolite of *Nocardia* sp. (ATCC 202099), the thiazole peptide nocathiacin I **68**, exhibits an ac-



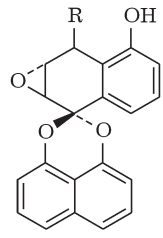
Scheme 32.



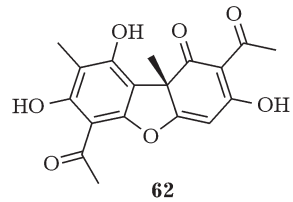
61a R^1 = OH, R^2 = H
61c R^1 = O, R^2 = H



61b R^1 = OH, R^2 = H
61d R^1 = O, R^2 = H
61e R^1 = O, R^2 = OMe
61f R^1 = O, R^2 = OH



61g R = O
61h R = OH



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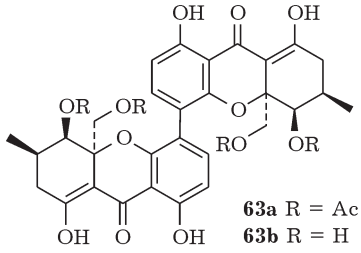
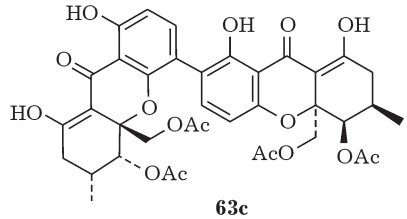
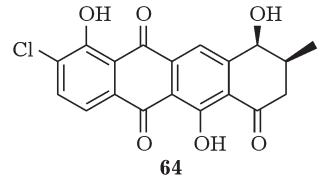


63a R = Ac
63b R = H



63c



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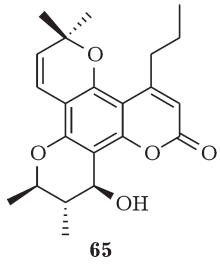

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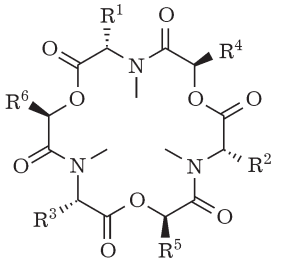
Scheme 33.

tivity with respect to *M. tuberculosis* ATCC 35828, *M. avium* A26778 and *M. avium* A26640 (MIC = 0.008, 0.06 and 0.25 μg/mL, respectively). Unfortunately, bad pharmacokinetics and solubility problem are inherent in this class of compounds, which could be overcome *via* synthesizing water-soluble analogues [96] (Scheme 34).

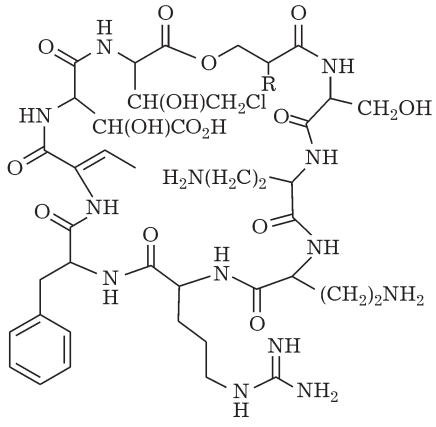
Alkaloids

The two compounds such as well-known antibiotic pyrrolnitrine **69a** and banegazine **69b**, isolated from zoobacteria Aristabacter necator, exhibit a synergic action against *M. smegmatis* (MIC > 0.5 μg/mL for **69b**, 0.3 μg/mL for **69a**, and 0.075 μg/mL for (**69b** + **69a**) [97]. A similar celastramycin A **70**, a dichloropyrrol metabolite of strain *Streptomyces* exhibits a broad spectrum of antimycobacterial activity (MIC = 0.05–3.1 μg/mL with respect to *M. smegmatis*, *M. aurum*, *M. vaccae* and *M. fortuitum*) [98]. Quinolone alkaloids **71a–d** isolated from dried unripe fruits *Evodia rutaecarpa* having unsaturated aliphatic chain at the position 2 of the quinolone ring, exhibit the best antimycobacterial activity in contrast with their own analogues with a saturated lateral chain (MIC = 2–4 μg/mL with respect to *M. fortuitum* ATCC 6841, *M. smegmatis* ATCC 19429, *M. phlei* ATCC 19249) [75]. Bis-1-oxaquinolizidine alkaloid (−)-araguspongine C **72** isolated from maritime sponge *Xestospongia exigua*, inhibits the growth of *M. tuberculosis* H37Rv (MIC = 1.9 μg/mL) [99]. Agelazine E **73a** and agelazine D **73b** were earlier isolated maritime sponge *Agelas nakamurai*.

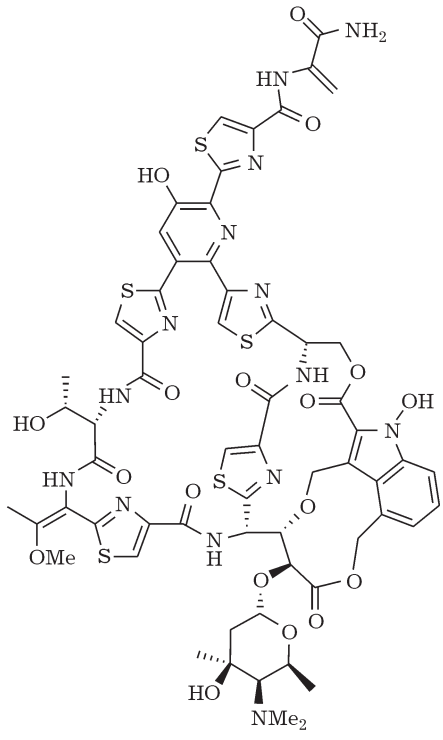
Whereas agelazine E is inactive, its methoxy analogues **73c–e** having different terpenoid lateral chains demonstrate a high activity with respect to *M. tuberculosis* H37Rv (MIC = 3.13, 1.56 and 3.13 μg/mL, respectively). To all



66a $R^1 = R^2 = R^3 = R^5 = R^6 = i\text{-Pr}$; $R^4 = s\text{-Bu}$;
66b $R^1 = R^2 = R^3 = R^6 = i\text{-Pr}$; $R^4 = R^5 = s\text{-Bu}$;
66c $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = i\text{-Pr}$;
66d $R^1 = i\text{-Bu}$; $R^2 = R^3 = R^4 = R^5 = R^6 = i\text{-Pr}$



67 R = $NHCOCH_2CH(OH)(CH_2)_8CH_3$



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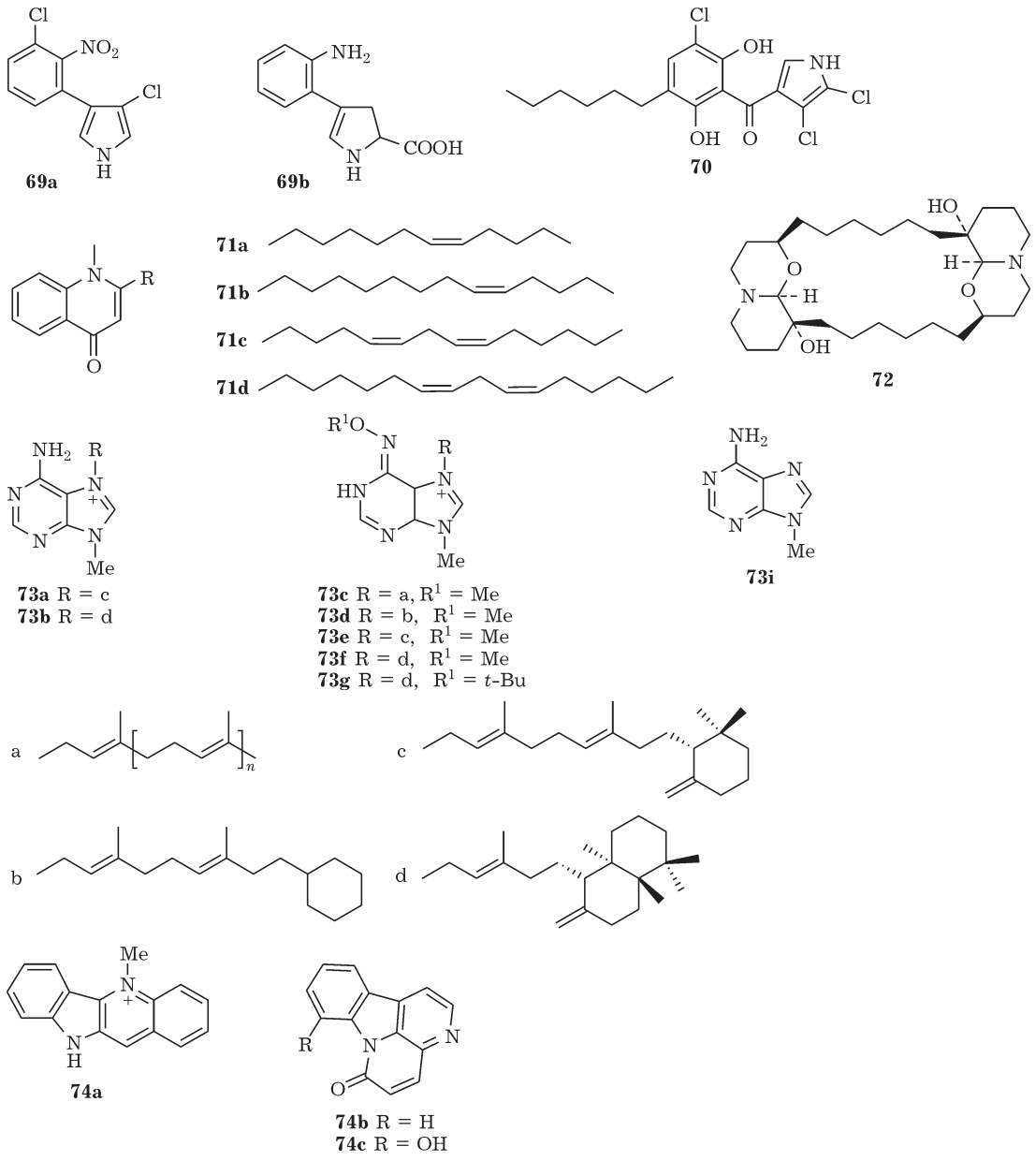
Scheme 34.

appearance, the presence of the alkoxy group at the terminal nitrogen atom is very important factor for the antimycobacterial activity of these compounds. At the same time, only small difference was found between the activity values of agelazine D **73b** and its alkoxy derivatives **73f,g** [100]. It is quite interesting that a simpler analogue of compounds under discussion such as 9-methyladenine **73h** exhibits the MIC value, equal to 6.25 μg/mL [101]. Tetracyclic alkaloid cryptolepine **74a** isolated from *Cryptolepis sanguinolenta* exhibits an activity 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) [102]. The metabolite of *Allium neapolitanum* **74c** exhibits an increased activity with respect strain *M. smegmatis* ($mc^2$2700) in contrast with its unsubstituted analogue cantine-6-one **74b** (MIC = 2 and 8 μg/mL, respectively). It was established that the activity compound 74c against the strain *M. smegmatis* ($mc^2$2700) is much higher than the activity with respect to strain *M. smegmatis* (ATCC 14468) (for **74c** and **74b** MIC = 16 and 8 μg/mL, respectively) [103] (Scheme 35).

The metabolites of the Thailand pathogenic fungus *Hirsutella nivea* BCC 2594 hirsutellones A–D **75a–d** inhibit the growth of *M. tuberculosis* H37Ra (MIC = 0.78, 3.125, 0.78, and 0.78 μg/mL, respectively). Compound **75d** demonstrates moderate *in vitro* cytotoxicity, whereas the rest compounds are less cytotoxic [104]. Hirsutellone F **75e** isolated jointly together with already known hirsutellones A, B and C from the seeds of fungus *Trichoderma* sp. BCC 7579, a new dimeric alkaloid, exhibits a more weak anti-tuberculosis activity with respect to *M. tuberculosis* H37Ra (MIC = 3.12 μg/mL) in contrast with hirsutellones A, B and C [105]. Already known alkaloid esteinascidin 770 **76a** and a new esteinascidin 786 **76b** isolated from *Ecteinascidia thurstoni*, inhibit the growth of *M. tuberculosis* H37Ra (MIC = 0.1 and 1.6 μg/mL,

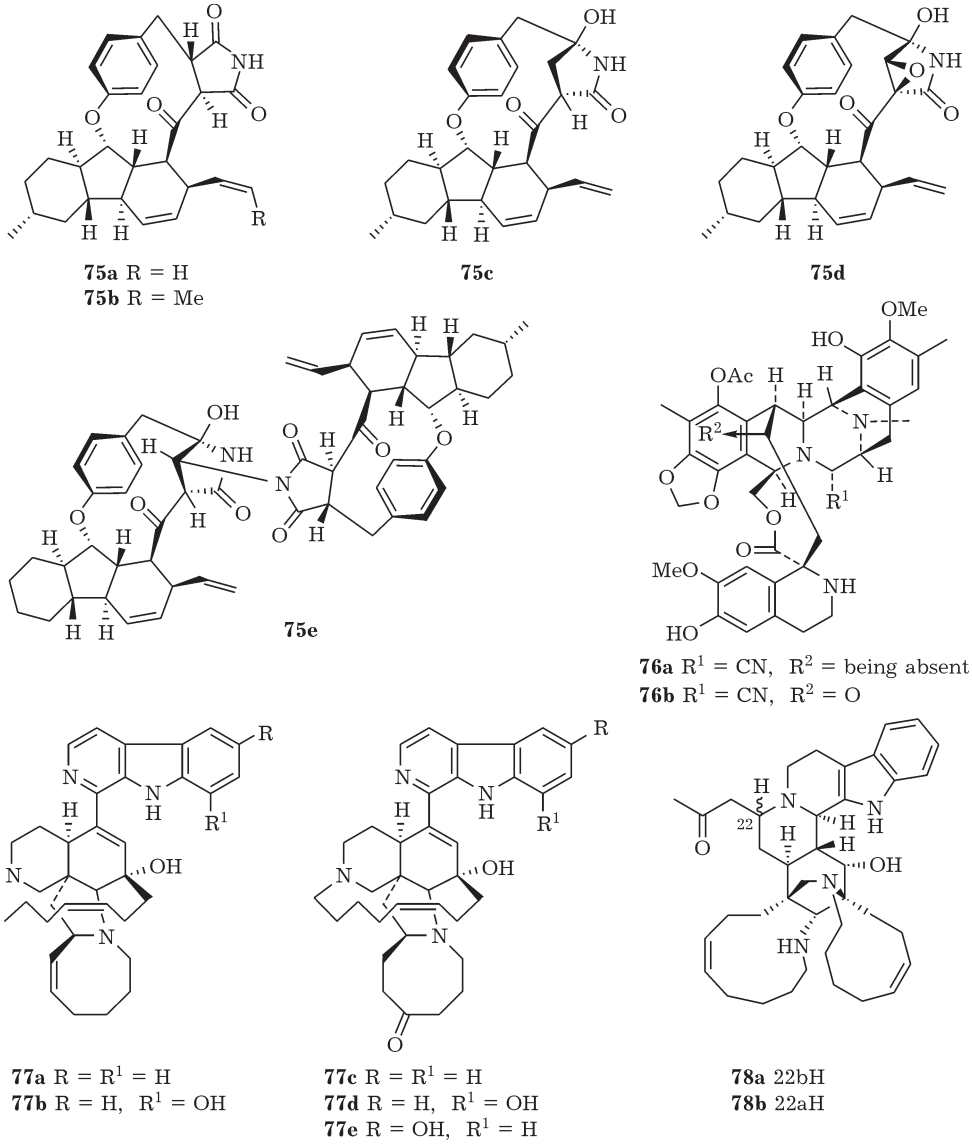


Scheme 35.

respectively) [106]. A promising antituberculosis activity is exhibited by manzamine alkaloids isolated from maritime sponges. Manzamines A **77a**, E **77c**, F **77d** and their hydroxyl derivatives, 6-hydroxymanzamine E **77e** and (+)-8-hydroxymanzamine A **77b**, exhibit an activity with respect to *M. Tuberculosis* H37Rv (MIC = 1.5, 3.8, 2,6, 0.4 and 0.9 μg/mL, respectively) [107]. Manadomanzamines A **78a** and B **78b** inhibit the growth of *M. tuberculosis* H37Rv (MIC = 1.9 and 1.5 μg/mL, respectively) [108] (Scheme 36).

Terpenoids

Compound **79** isolated from *Indigofera longeracemosa* is active with respect to *M. tuberculosis* (MIC = 0.38 μg/mL) [109]. Identical MIC values with respect to *M. tuberculosis* H37Rv are demonstrated by diterpenoids **80** and **81** isolated *Calceolaria pinnifolia* [110] and structurally close lecheronol A **82** isolated from *Sapium haematospermum*) [111], as well as by 6-hydroxyculactone **83**, the metabolite of



Scheme 36.

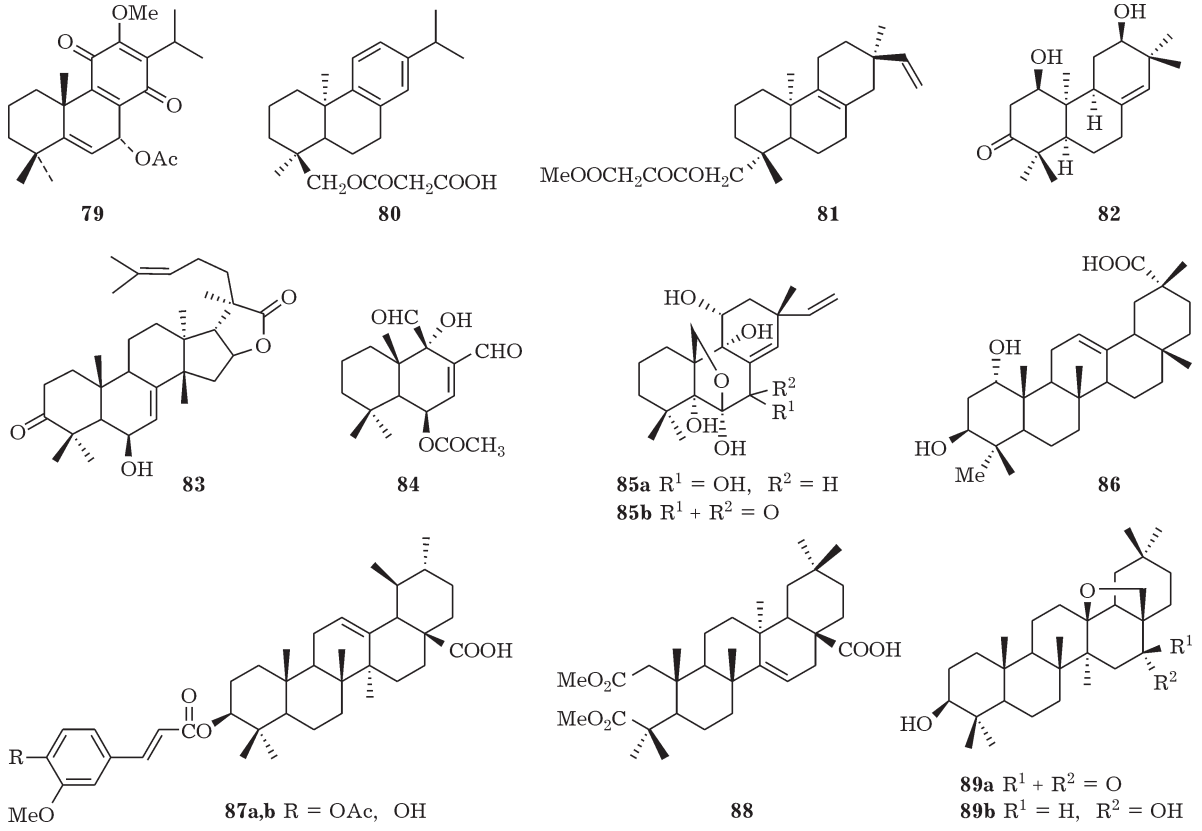
Melica volkensii [75] (MIC = 4 μg/mL). With the same value of MIC, ugandensidial **84** (from *Warbugia ugandensis*) inhibits the growth of *M. aurum* and *M. phlei* [75]. Diterpenes diaportheines A **85a** and B **85b** were isolated from fungus *Diaporthe* sp. Compound **85b** exhibits the antituberculosis activity with respect to *M. tuberculosis* H37Ra (MIC = 3.1 μg/mL) being cytotoxic, whereas compound **85a** is much less active and cytotoxic (MIC = 200 μg/mL) [112]. These data indicate an important role of the carbonyl group in the antituberculosis activity. A metabolite of African tree *Combretum imberbe*, traditionally used in folk medicine, is imberbic acid **86** which exhibits the activity with respect to *M. fortuitum* (MIC = 1.56 μg/mL) [113].

Chemical modifying the ursolic acid (*via* entering the fragment of substituted cinnamic acid into the position C-3) causes a four-fold increase in antituberculosis activity of this type of compounds **87a,b** (MIC = 3.13 μg/mL with respect to *M. tuberculosis* H37Ra, for the ursolic acid MIC = 12.5 μg/mL) [114]. Triterpene **88** isolated from the leaves of *Elateriospermum tapos* is active with respect to M. tuberculosis H37Ra (MIC = 3.13 μg/mL, for isoniazid and kanamycin the MIC value amounts to 0.5 and 1.25 μg/mL, respectively) [115]. Aegicerin **89a**

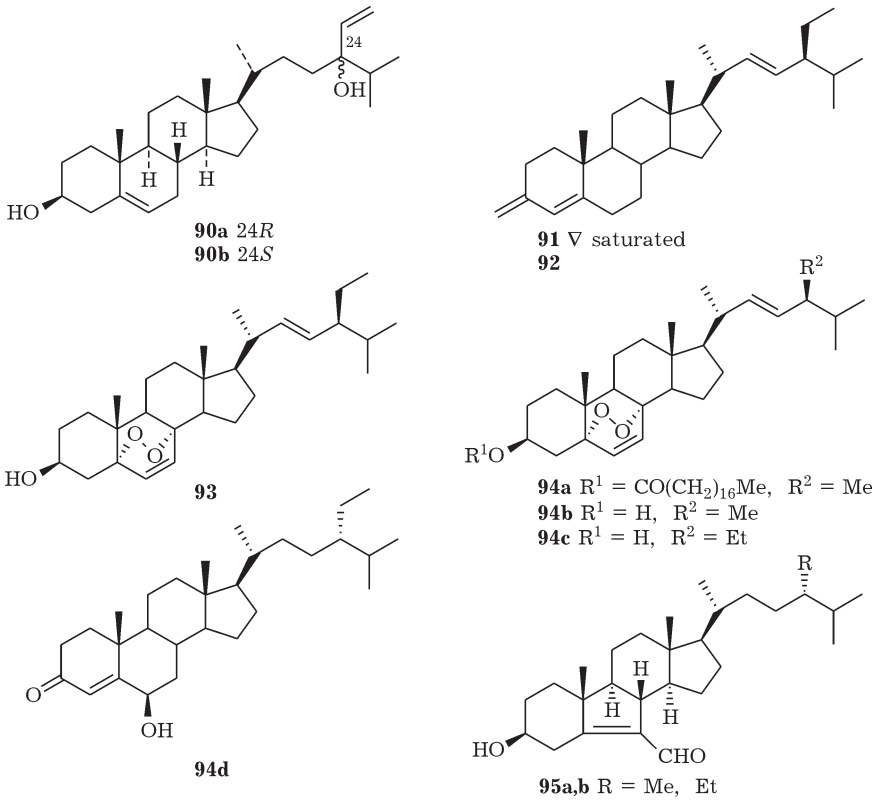
and protoprimulagenin A **89b** were isolated from *Aegiceras* spp., *Embelia schimperi* and Peruvian plant *Clavija procera*. Aegicerin **89a** was tested in 37 different tuberculosis strains (MIC = 1.6–3.1 μg/mL with respect to one strain H37Rv, 21 drug-susceptible clinical strains, two clinical isolates drug-resistant with respect to isoniazid and 13 clinical strains with MDRTB). The absence of the activity inherent in protoprimulagenin A **89b** (MIC 200 μg/mL) confirms the hypothesis that the presence of the carbonyl groups, as in the case of compound **85a** and **85b** represents a determining factor for the antituberculosis activity. For the first time the triterpene of the oleane type demonstrates such a uniformly high activity with respect to a wide range of either drug-susceptible, and drug-resistant strains. Unfortunately, its excellent antituberculosis activity concerning a large number of strains with MDRTB (for the comparison: MIC values for isoniazid range within 4–32 μg/mL, MIC values for rifampicin ranging within 2–16 μg/mL) has not found any practical application until now [116] (Scheme 37).

Steroids

Saringosterol isolated from brown seaweed *Sargassum ringgoldianum* and *Lessonia nigrescens* in the form of mixture (1 : 1) of 24*R* isomer **90a** and 24*S* isomer **90b**, inhibits the growth of *M. tuberculosis* H37Rv (MIC = 0.25 μg/mL) exhibiting, in addition, a low cytotoxicity level. These pure isomers exhibit a different activity level (the MIC value for 24*R* isomer is equal to 0.125 μg/mL, the MIC value for 24*S* isomer being equal to 1 μg/mL) [117]. From the extract of *Morinda citrifolia* (Rubiaceae) traditionally used in the Philippine folk medicine for treating various tuberculosis and respiratory diseases, lipids were isolated those inhibit the growth of *M. tuberculosis* H37Rv. The most intense activity is exhibited by the mixture of compounds **91** and **92** (MIC < 2.0 μg/mL



Scheme 37.



Scheme 38.

in the ratio of 2 : 1) as well as endoperoxide **93** (MIC = 2.5 μg/mL) [118]. The derivatives of sterine **94a–e** isolated from the extract of Argentinean plant *Ruprechtia triflora* are active with respect to *M. tuberculosis* (MIC = 2–4 μg/mL) [110]. Synthetic analogues of 5(6→7)abeo-sterol, the metabolite of Caribbean marine sponge *Svenzea zeai*, compound **95a,b**, well inhibits the growth of *M. tuberculosis* H37Rv ATCC 27294 (MIC = 3.8 and 3.95 μg/mL, respectively), but exhibit moderate cytotoxicity [119] (Scheme 38).

CONCLUSION

The analysis of the material of the review allows one to draw a conclusion concerning the fact that are there are no papers available from the literature devoted to the synthesis of substances those represent the structures of naturally occurring metabolite of antituberculosis action linked together with synthetic mycostatics.

Meanwhile, the studies in the field of design and synthesis of such agents are performed in the course of the development of medicinal preparations with the most different scopes of medical use.

One could hope that the synthesis of potential mycostatic agents with mixed structure types would result in expected success and would allow one to reveal highly promising substances.

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