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Purine derivatives with antituberculosis activity

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The review summarizes the data published over the last 10 – 15 years concerning the key groups of purine derivatives with antituberculosis activity. The structures of purines containing heteroatoms (S, O, N), fragments of heterocycles, amino acids and peptides, in the 6-position, as well as of purine nucleosides are presented. The possible targets for the action of such compounds and structure – activity relationship are discussed. Particular attention is paid to the most active compounds, which are of considerable interest as a basis for the development of efficient antituberculosis drugs.
The bibliography includes 99 references.

Contents

1. Introduction 604
2. Derivatives of 6-thio- and 6-alkoxypurines 605
3. 6-Hetarylpurines and related compounds 606
4. 6-Aminopurines 608
5. Purine nucleosides 611
6. Purine derivatives containing amino acid and peptide moieties 614
7. Conclusion 616

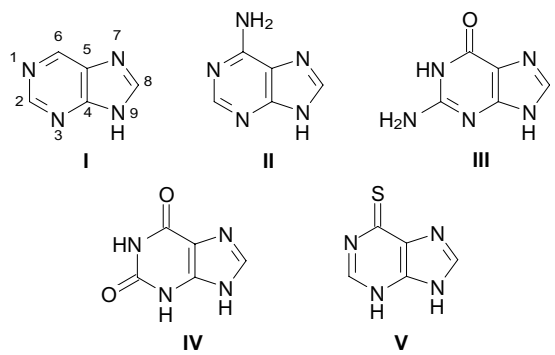
1. Introduction

Purine (imidazo[4,5-*d*]pyrimidine, **I**) and purine bases — adenine (**II**), guanine (**III**) and xanthine (**IV**) — play an important role in the metabolism of living organisms. Purine moieties are part of the most important biomolecules: DNA, RNA, ATP, nicotinamide adenine dinucleotide (NAD) coenzyme, alkaloids, *etc*. Therefore, the synthesis and study of purine derivatives are of great interest for creating related efficient drugs.[1 – 3]

To date, a large number of purine-based drugs have been introduced into clinical practice. In particular, 6-thiopurine (mercaptopurine, **V**) and its derivatives are used in therapy of cancer and inflammatory diseases,[4, 5] and efficient antitumour drugs have been created on the basis of purine nucleosides.[6 – 9] Major advances have been made using purine derivatives for the treatment of socially significant viral diseases such as herpes, pox, HIV, hepatitis B *etc*.[10 – 14] The mechanism of action of purine-based drugs is, as a rule, associated with impaired synthesis of nucleic acids or blocking of key enzymes involved in metabolism.

In recent years, among the purine derivatives, the search for compounds possessing antibacterial, including antituberculosis, activity has been extensively conducted. Tuberculosis is the most common infectious disease on the Earth.

Structures I – IV



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Annually, there are about 2 million deaths and about 10 million new cases of tuberculosis worldwide (see Refs 15, 16 and Global Tuberculosis Report 2016 released in May 2017 and posted on the website of the World Health Organization (http://www.who.int/tb/publications/global_report/ru/). One of the causes that hampers treatment of tuberculosis is the emergence of multiple drug resistance to both traditional first-line antituberculosis drugs, which include isoniazid, rifampicin, pyrazinamide, and ethambutol, and second-line drugs, such as cycloserine, ofloxacin, ciprofloxacin, and amikacin.[17,18] Recently, extensively or totally drug-resistant *Mycobacterium tuberculosis* strains, *i.e.*, strains resistant to most or all of the existing antituberculosis agents have spread.[19–21] The search for antituberculosis agents is conducted on a wide front and involves a wide variety of classes of compounds, primarily nitrogen heterocycles.[22–24] Recently, the arsenal of antituberculosis drugs has been augmented with several new drugs, such as bedaquiline[25] and perchlozone.[26] Because of the wide spread of tuberculosis and the increasing resistance of *M. tuberculosis* to the existing drugs, the creation of new efficient antituberculosis drugs is a particularly urgent task.

The purine moiety is not incorporated into the molecules of currently used antibacterial drugs, in particular, antituberculosis agents. It is not impossible that compounds differing in the mechanism of action from existing drugs and, as a consequence, efficient against multidrug-resistant tuberculosis strains, can be found among the purine derivatives.[27,28] This circumstance fuels the interest in synthesis and research of purine derivatives as promising antituberculosis agents.

It should be noted that reviews devoted to the synthesis and biological activity of purine bases and nucleosides were published in the early 2000s (see, for example, Refs 1 and 2), but they contained only fragmentary information on the antimycobacterial activity of such compounds. In the present work, literature data on the antitubercular (tuberculostatic) activity of purine derivatives have been systematized for the first time.

There are two general approaches to the search for potential antituberculosis drugs. In the case where the structure of the target within the mycobacterial cell, for example, of some important enzyme, is known, the modelling of the location of inhibitor molecules in the active site of the enzyme is carried out by molecular docking. Then, the chemical synthesis of priority compounds selected on the basis of molecular modelling results is carried out, and the structure of inhibitors is 'refined' according to the results of *in vitro* tests. The main drawback of this approach is that, for various reasons, the inhibitor compound does not always reach the target and does not provide the desired therapeutic effect.

The other approach is to synthesize and screen a significant number of compounds in order to identify among them substances that possess *in vitro* tuberculostatic activity. Due to the variety of biochemical processes involving purine and its derivatives, the latter approach makes it possible to reveal compounds with tuberculostatic activity and, through further targeted modification, to create efficient antituberculosis agents for which drug resistance is absent. A disadvantage of this method is the difficulty of establishing the mechanism of tuberculostatic action of purine derivatives, which is also due to the variety of biochemical processes involving these compounds.

The aim of this review is to summarize the information on the antitubercular activity of purine derivatives established on the basis of *in vitro* tests. The authors have systematized data on the activity of such compounds of various structures against mycobacteria, including data on the dependence of antimycobacterial activity on the structure and position of substituents in the purine system. Data on known targets and mechanisms of action of purine derivatives with antituberculosis activity have been summarized.

The basic approaches to obtain the selectively substituted purine derivatives have been well covered in the literature (see, for example, reviews[2,29,30]). The purine molecule has several positions available for modification. In this review, we consider compounds belonging to several groups which differ in the structure of substituents in the purine nucleus. Methods for the synthesis of specific purine derivatives with antimycobacterial activity were described in the original works cited in the relevant sections.

As a model for assaying *in vitro* tuberculostatic activity of purine derivatives, a standard laboratory strain of *M. tuberculosis* H37Rv, which is close to the mycobacteria found in tuberculosis patients, is usually used.[31] Although in recent years, differences in the genotypes of the H37Rv strain and strains of *M. tuberculosis* isolated in modern patients have been reported,[32–34] this model continues to be the world standard for laboratory testing of new compounds.

Studies of the metabolism and mechanism of action of tuberculostatic agents are often performed on the avirulent form of *M. smegmatis* bacteria related to *M. tuberculosis* and characterized by rapid growth during cultivation; in some cases, gene-modified strains of *M. smegmatis* are used.[35–37]

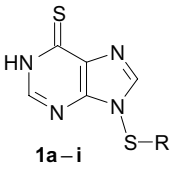
In connection with the problem of drug resistance of tuberculosis mycobacteria, especially relevant in recent times, it is necessary to search for antimycobacterial agents that are active against strains resistant to first-line drugs. For this reason, purine derivatives most active against the standard strain H37Rv are tested against strains of *M. tuberculosis* resistant to isoniazid, rifampicin, ethambutol and other drugs. In many cases, purine derivatives exhibit no cross-resistance with the drugs used in the clinic, which, along with their low toxicity, makes such compounds promising candidates for creating new antituberculosis drugs.

2. Derivatives of 6-thio- and 6-alkoxypurines

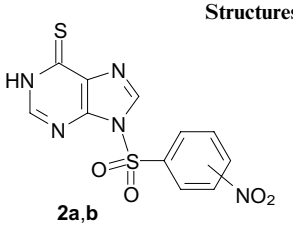
The first examples of purine-based antimycobacterial agents are 9-sulfenyl and 9-sulfonyl derivatives of 6-thiopurine **1a–i** and **2a,b**.[38]

Compounds **1** (MIC = 0.39–3.39 μg ml^{-1}) and **2** (MIC = 0.78 μg ml^{-1}) exhibited high activity against laboratory strain of *M. tuberculosis* H37Rv; dimethylaminosulfenyl derivative **1a** (R = NMe_2) turned out to be the most efficient inhibitor. 9-Arylsulfenyl- and 9-arylsulfonyl-6-thiopurines **1b–i** and **2a,b** exhibited lower inhibitory activity against this strain, although they were superior to compound **1a** in the activity against the opportunistic *M. avium* strain. Compound **2b** retained high activity against *M. tuberculosis* strains resistant to rifampicin, ethambutol and kanamycin (MIC = 0.78–1.56 μg ml^{-1}). The parent

Structures 1, 2



1a–i



2a,b

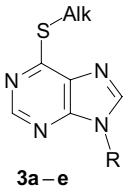
Isomers: (**a**) *ortho*, (**b**) *para*

Compound **1**	R	MIC†/μg ml^{-1}
a	Me_2N	0.39
b	4-MeC_6H_4	1.60
c	4-FC_6H_4	3.39
d	4-ClC_6H_4	3.13
e	4-BrC_6H_4	0.78
f	4-$H_2NC_6H_4$	0.78
g	3-$H_2NC_6H_4$	3.13
h	2-$O_2NC_6H_4$	1.56
i	4-$AcNHC_6H_4$	0.78

6-thiopurine, which is a well-known antimetabolite, showed no antimycobacterial activity.

Compounds with significant antimycobacterial activity were found in a series of purines containing sulfur and oxygen atoms in the 6-position.[39,40] Among 6-alkylthio- and 6-arylthiopurines, derivative **3a** with a hydrophobic alkyl substituent was the most efficient inhibitor of *M. tuberculosis* H37Rv growth (MIC = 3.13 μg ml^{-1}). 6-Alkylthiopurine derivatives **3b–e** with substituents in the 9-position had an even higher activity against the standard strain (MIC up to 0.78 μg ml^{-1}).[39] Ethyl esters **3b**,**c** showed lower toxicity for the mammalian cells in comparison with *tert*-butyl ester **3d** and N(9)-unsubstituted analogue **3a**. Compounds **3a**,**b** were able to suppress the activity of mycobacteria inside macrophages.[39] 6-Dodecylthiopurine **3c** exhibited high *in vitro* activity against strains resistant to the action of known antituberculosis drugs.

Structures 3



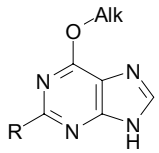
3a–e

Compound **3**	R	Alk	MIC/μg ml^{-1}
a	H	n-$C_{10}H_{21}$	3.13
b	CH_2CO_2Et	n-$C_{10}H_{21}$	1.56
c	CH_2CO_2Et	n-$C_{12}H_{25}$	0.78
d	$CH_2CO_2Bu^t$	n-$C_{10}H_{21}$	3.13
e	CH_2CN	n-$C_{10}H_{21}$	1.56

† Here and below, unless otherwise specified, the minimum inhibitory concentrations that cause complete (MIC), 99% (MIC_{99}) or 90% (MIC_{90}) inhibition of growth of *Mycobacterium tuberculosis* H37Rv are given.

High antimycobacterial activity was found for some *O*-decyl and *O*-dodecyl derivatives of guanine (**4a**,**b**) and hypoxanthine (**4c**,**d**).[40] However, the introduction of substituents into the 9-position of purine in these compounds led to the loss of activity.

Structures 4



4a–d

Compound **4**	R	Alk	MIC/μg ml^{-1}
a	NH_2	n-$C_{10}H_{21}$	3.13
b	NH_2	n-$C_{12}H_{25}$	0.78
c	H	n-$C_{10}H_{21}$	1.56
d	H	n-$C_{12}H_{25}$	0.78

Studying purines **3c** and **4b** on *in vivo* models have shown that these derivatives are nontoxic in concentrations up to 500 μg kg^{-1}, but they do not exert tuberculostatic effect in mice with the 'turned off' interferon-γ gene.[40] The authors could not reveal a clear structure–activity relationship for compounds **3**, **4** and their analogues, and also could not identify the mechanism of antimicrobial action for them.

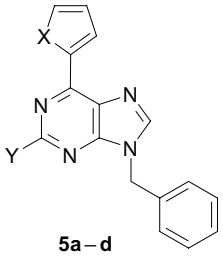
3. 6-Hetarylpurines and related compounds

In 2000, Gundersen and co-workers[41] synthesized a large number of 6-(het)aryl-substituted purines and studied their *in vitro* antimycobacterial activity. The greatest inhibitory activity against *M. tuberculosis* H37Rv was exhibited by the 6-furyl- and 6-thienyl-9-benzyl derivatives **5a–d**.

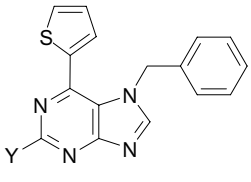
Position of benzyl substituent played an important role in the biological activity of synthesized compounds. In particular, 7-benzyl-6-thienylpurines **5e**,**f** did not show activity against *M. tuberculosis*. 8-Halogen-substituted analogues **5g–i** were also inactive.[41] 1,9-Dibenzyl derivatives of 2-oxopurine **5j–m** also did not show *in vitro* tuberculostatic activity.[42] The presence of a chlorine atom in the 2-position of purine enhanced the antimycobacterial activity of 6-furyl and 6-thienyl derivatives; the highest antimycobacterial activity was shown by 9-benzyl-6-(2-furyl)-2-chloropurine (**5b**, MIC = 0.78 μg ml^{-1}), which also had low cytotoxicity in the MTT assay.[41] This compound showed high activity against *M. tuberculosis* strains resistant to individual first-line drugs (rifampin, isoniazid, ethambutol, kanamycin and ciprofloxacin) (MIC < 0.39 μg ml^{-1}) and was also able to kill mycobacteria inside macrophages in *in vitro* experiments.[43]

The relationship between the antimycobacterial action and the structure of substituents at the 6- and 9-positions for compounds **5** and their analogues **6** has been systematically studied.[43–45] Variation of the substituents in the benzyl moiety made it possible to identify compounds **6a–e** exhibiting high tuberculostatic activity (MIC up to 0.39 μg ml^{-1}) and lower toxicity compared to 9-benzyl-6-(2-furyl)-2-chloropurine (**5b**).[45]

Structures 5



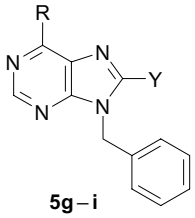
5a–d



5e,f

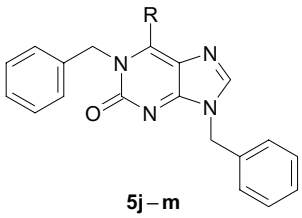
Y = H (**e**), Cl (**f**)

Compound **5**	X	Y	MIC /μg ml^{-1}
a	O	H	3.13
b	O	Cl	0.78
c	S	H	6.25
d	S	Cl	1.56



5g–i

Y = Cl: R = Ph (**g**), 2-Th (**h**);
Y = I, R = H (**i**); Th is thienyl



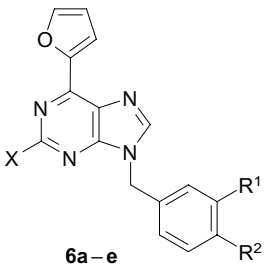
5j–m

R = C≡CPh (**j**), Ph (**k**), 2-Fu (**l**),
2-Th (**m**); Fu is furyl

6-Thienyl and 6-furylpurines not substituted at 9-position (**6f**), as well as 9-methyl- (**6g**) and 9-allyl derivatives (**6h**) did not show high tuberculostatic activity. An increase in the length of the spacer between the phenyl ring and the purine moiety (compound **6i**), as well as the introduction of the methyl substituent [compounds (*S*)-**6j** and (*R*)-**6j**)] led to a decrease in the antimycobacterial effect. 9-Phenyl-6-furylpurines **6k**,**l**, THP-substituted analogues **6m**,**n** (THP is tetrahydropyran-2-yl), ribosides **6o**,**p** and sulfonyl derivative **6q** were also inactive.[43,45]

In general, the most efficient *in vitro* growth inhibitors of *M. tuberculosis* H37Rv were 9-benzylpurines containing the 2-furyl moiety at the 6-position. At the same time, 6-(2-thienyl)- and 6-phenyl-9-benzylpurines, as well as 9-benzylpurines substituted in the 6-position with nitrogen-containing heterocycles (compounds **6r–w**), had lower activity. The change in the position of the heteroatom in the furan ring (derivative **6x**) led to the loss of antimycobacterial activity.[44]

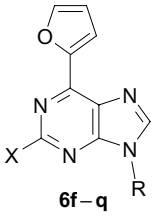
Structures 6a–e



6a–e

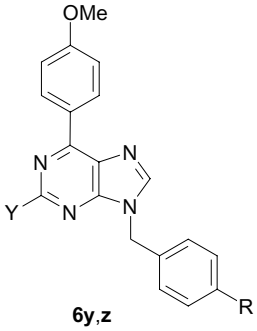
Compound **6**	X	R^1	R^2	MIC /μg ml^{-1}
a	H	H	OMe	1.56
b	H	Me	OMe	0.78
c	Cl	H	Me	0.78
d	Cl	H	OMe	0.39
e	Cl	Me	OMe	0.78

Structures 6f–z



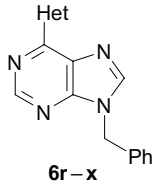
6f–q

Compound **6**	X	R
f	H	H
g	H	Me
h	H	All
i	H	CH_2Bn
j	H	CH(Me)Ph
k	H	Ph
l	Cl	Ph
m	H	THP
n	Cl	THP
o	H	Ribosyl
p	Cl	Ribosyl
q	H	SO_2Ph



6y,z

6y,**z**: Y = R = H
(**y**, MIC = 6.25 μg ml^{-1});
Y = Cl, R = OMe
(**z**, MIC = 6.25 μg ml^{-1});



6r–x

6r–x: Het is thiazol-2-yl (**r**),
oxazol-2-yl (**s**), pyrrol-1-yl (**t**),
imidazol-2-yl (**u**), 2-Py (**v**),
3-Py (**w**), 3-Fu (**x**); Py is pyridyl

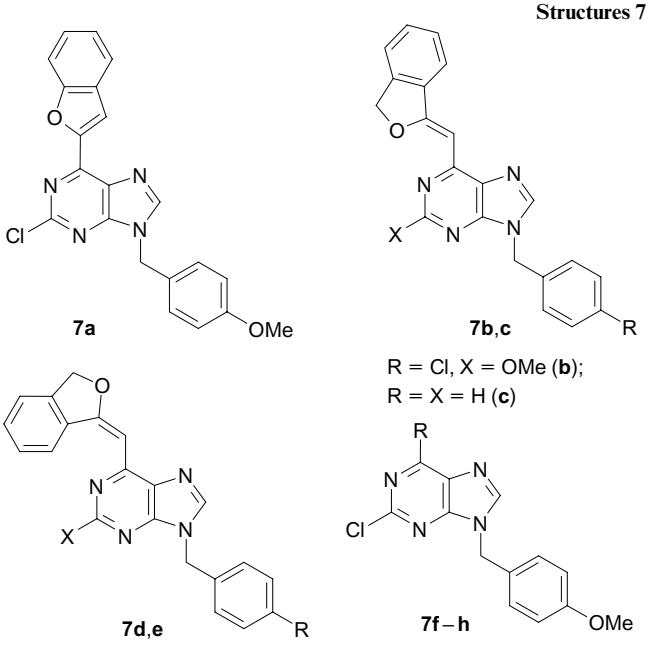
Compound **7a** with a benzofuran moiety showed activity comparable with that for compound **6d** of similar structure.[46] 6-(Isobenzofuran-1-ylidenemethyl)purines **7b–e**, as well as 9-(4-methoxybenzyl)-2-chloropurines containing styryl (**7f**), benzyl (**7g**) and furfuryl (**7h**) substituents in the 6-position, exhibited lower activity as compared with the 6-furyl-substituted analogues.[46,47]

Varying the substituent in the 2-position of the purine moiety made it possible to synthesize analogues of antimycobacterial agent **7d** — compounds **8a–i** the exhibiting high activity against the *M. tuberculosis* H37Rv strain.[48] The replacement of the chlorine atom in compound **7d** by the fluorine atom did not alter the antimycobacterial effect: for compound **8a**, MIC was 0.39 μg ml^{-1}. Derivatives **8b**,**c**, with the methylthio- or methoxy group in the 2-position, showed somewhat lower activity (MIC = 0.78 μg ml^{-1}); at the same time, compound **8b** was considerably toxic. The largest tuberculostatic effect was exhibited by 2-methyl derivative **8d** (MIC = 0.20 μg ml^{-1}).

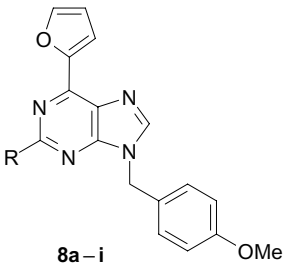
Based on the results of screening of 6-aryl- and 6-hetaryl purine derivatives as antimycobacterial drugs, Brændvang and Gundersen[48] have formulated structural requirements for efficient agents belonging to this group (Fig. 1):

(1) the 2-furyl substituent is preferred in the 6-position of purine;

Structures 7



Structures 8



Compound **8**	R	MIC/μg ml^{-1}
a	F	0.39
b	SMe	0.78
c	OMe	0.78
d	Me	0.20
e	Et	0.56
f	CH=CH$_2$	3.13
g	Ph	6.25
h	Ac	6.25
i	C≡CH	6.25

(2) a hydrophobic and small substituent should be in the 2-position;

(3) the benzyl moiety should not contain substituents at the methylene group and in the *ortho* position of the benzene ring;

(4) the presence of small donor groups in the *meta* and *para* positions is desirable;

(5) the 8-position should remain unsubstituted not to interfere with the orientation of the benzyl substituent in the active conformation.

Despite the discovery of a wide range of highly active tuberculostatic agents among 6-(het)aryl-9-benzylpurines, specific biotargets and the exact mechanism of their tuberculostatic action remain unclear.

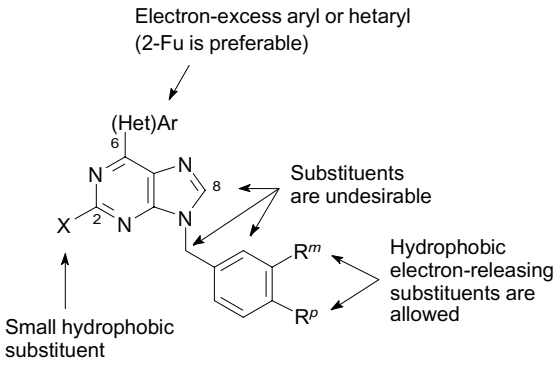


Figure 1. Structural requirements for antimycobacterial agents based on 9-benzyl-6-(het)arylpurines (according to Ref. 48).

4. 6-Aminopurines

In 2000, a significant antimycobacterial activity of alkaloid agelasine F (**9a**) isolated from sea sponges of the genus *Agelas* was reported.[49] Alkaloid **9a** was equally active against both the standard strain of *M. tuberculosis* H37Rv and strains resistant to the action of isoniazid, rifampicin, ethambutol, and ethionamide (MIC = 3.13–6.25 μg ml^{-1}).

Later, Gundersen an co-workers[50–55] have developed approaches to the synthesis of agelasine F and related compounds, including natural agelasines E and D. Compounds of this group contain a positively charged quaternary nitrogen atom located in the imidazole moiety of the purine system.

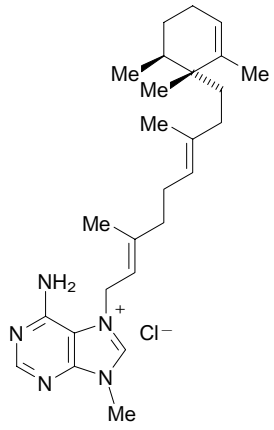
Systematic study of the antimycobacterial activity of agelasines, agelasimines and structurally similar compounds made it possible to reveal highly efficient antitubercular agents.

It has been demonstrated that agelasine F analogues with a free NH_2 group in the 6-position of purine [for example, agelasines E (**9b**) and D (**9c**) and related compounds **10a**,**b** and *ent*-**9b**] exhibit low antimycobacterial effect in *in vitro* experiments.[50, 52]

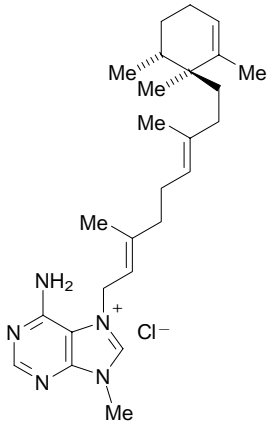
At the same time, derivatives **11a–c** containing a methoxy group at the nitrogen atom showed noticeable activity (MIC = 3.13 μg ml^{-1}), while the MIC of compounds **11d–g** with a smaller substituent at the N(7) atom, as well as of 7-unsubstituted 9-methyladenine, did not exceed 6.25 μg ml^{-1}. The authors considered the amphiphilic nature of compounds **9–11** and arrived at the conclusion that a bulky substituent of terpenoid nature at the N(7) atom of adenine is responsible for their hydrophobic properties, while the adenine moiety is responsible for the hydrophilic properties of the molecule.[56] Therefore, the molecules are able to efficiently penetrate through the cell wall of mycobacteria, which is characterized by significant thickness and lipophilicity. The higher activity of N-methoxy derivatives **11a–c** as compared with adenine derivatives **9b**,**c** and **10a**,**b** is presumably also due to the differences in polarity of molecules and their ability to penetrate through the cell wall of mycobacteria.

Systematic study of the antimycobacterial activity of agelasines and compounds with similar structure has

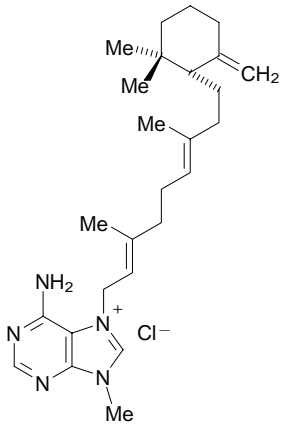
Structures 9



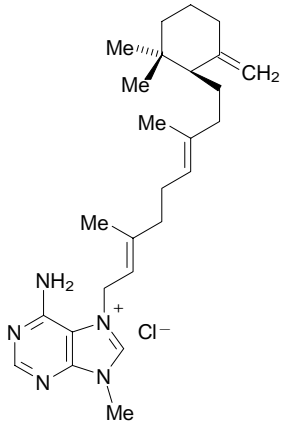
9a (agelasine F)



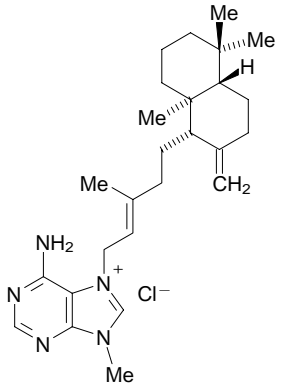
ent-**9a** (*ent*-agelasine F)



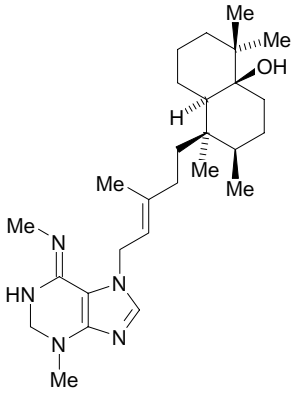
9b (agelasine E)



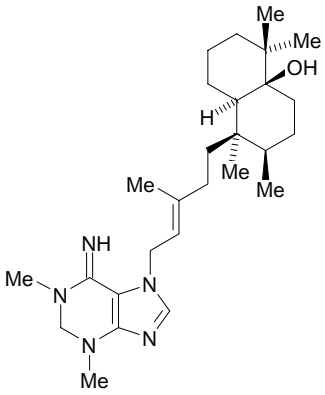
ent-**9b** (*ent*-agelasine E)



9c (agelasine D)

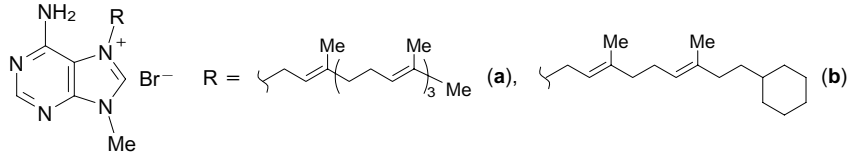


9d (agelasimine A)

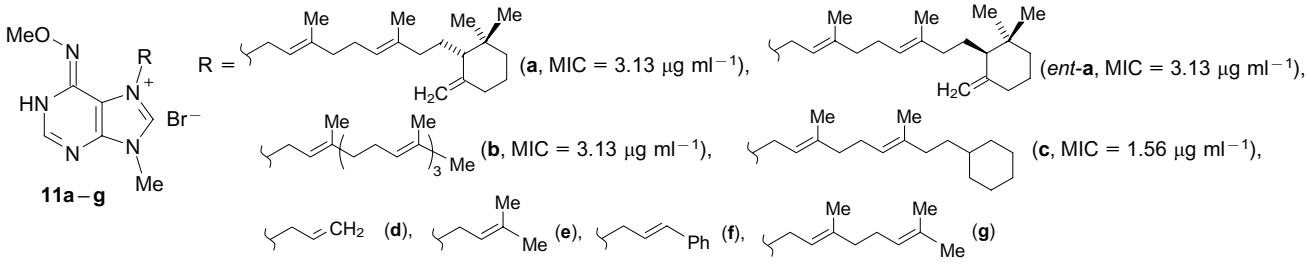


9e (agelasimine B)

Structures 10, 11a–g



10a,**b**



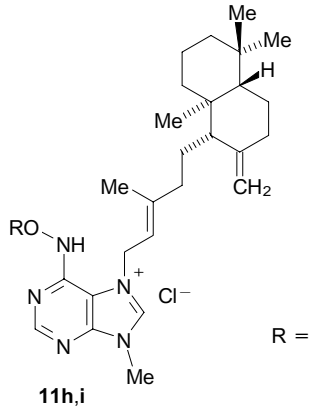
11a–g

revealed efficient antitubercular agents, in particular, N-alkoxy-substituted salts **11a–c** and **12a–l** (the dash means that MIC was not determined), as well as compounds **13a–e** — analogues of agelasimines A and B (the MIC against *M. tuberculosis* H37Rv was a high as 1.56 μg ml^{-1}).[52, 53, 56]

It has been demonstrated that the type of configuration of double bonds (*cis* or *trans*) in the terpenoid chain has no significant effect on the antimycobacterial activity of compounds **12** (in particular, as follows from comparison of the MICs of isomers **12a**,**b**).[56]

7-Geranylgeranyladenine (**14a**) also exhibited high activity, as distinct from its N-alkoxy-substituted analogues **14b**,**c**. It has been suggested that, along with the presence of a long-chain lipophilic substituent at the N(7) atom, a key factor responsible for the antimycobacterial effect is a positive charge at the nitrogen atom in the imidazole moiety of purines. In particular, the basicity of compound **14a** is sufficiently high for protonation during mycobacterium

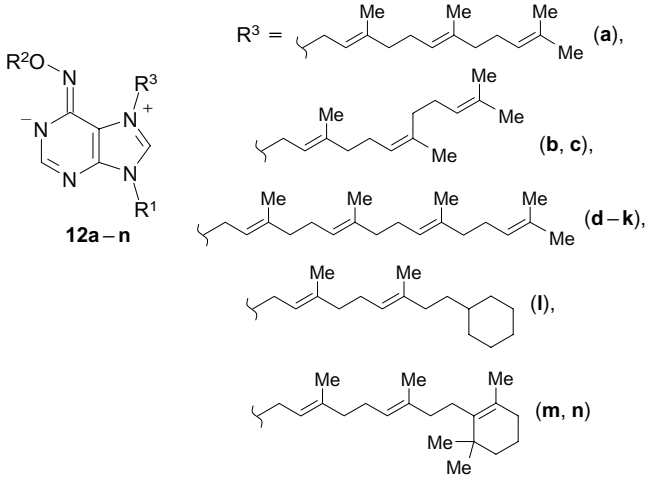
Structures 11h,i



11h,**i**

R = Me (**h**, MIC > 6.25 μg ml^{-1}), Bu^t (**i**, MIC = 3.13 μg ml^{-1})

Structures 12



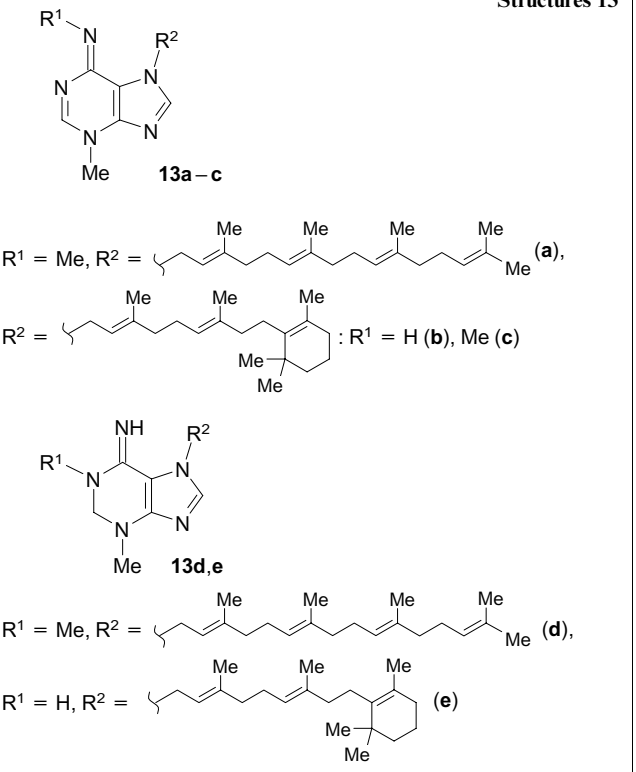
12a–n

Compound **12**	R^1	R^2	MIC/μg ml^{-1}
a	Me	Me	3.13
b	Me	Me	3.13
c	Me	Bn	3.13
d	Me	Me	3.13
e	Me	Bn	3.13
f	Me	Bu^t	3.13
g	Pr^i	Me	1.56
h	All	Me	3.13
i	$(CH_2)_2CN$	Me	> 6.25
j	Bn	Me	1.56
k	$CHPh_2$	Me	3.13
l	Me	Me	1.56
m	Me	Me	–
n	Me	Bu^t	–

cultivation, while less basic derivatives **14b**,**c** are in the culture medium in the nonprotonated form.[56]

A distinctive feature of compounds **12**–**14**, active against *M. Tuberculosis* strains is the absence of chiral centres in the molecule and a simpler structure as compared with natural alkaloids **9a**–**e**. This significantly simplifies their synthesis and, hence, makes them attractive for use as therapeutic agents.

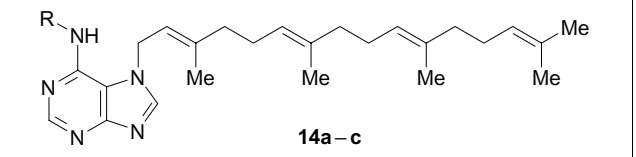
Structures 13



13a–c

13d,**e**

Structures 14

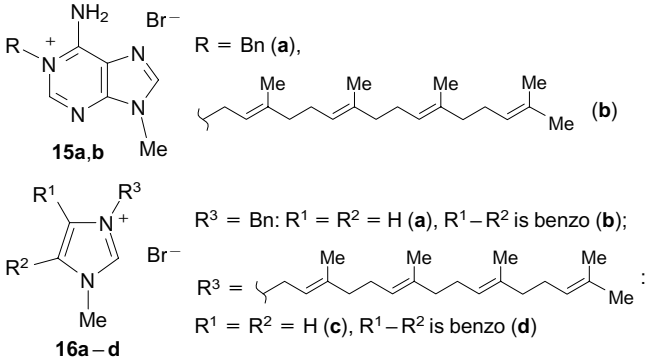


14a–c

R = H (**a**, MIC = 1.56 μg ml^{-1}), OMe (**b**), OBn (**c**)

Tests for antimycobacterial activity of 1,9-dialkyladenines **15a**,**b** and imidazo derivatives **16a–d** have shown that such compounds are weak mycobacterium growth inhibitors.[56]

Structures 15, 16

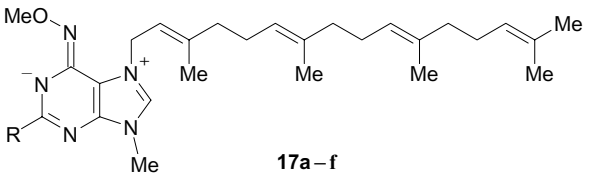


15a,**b**

16a–d

Zwitterionic purines **17a–f** — 2-substituted analogues of geranylgeranyl derivative **12d** — were studied.[57] It turned out that methyl derivative **17a** was essentially more active than initial substrate **12d**, while the inhibitory effect of the other compounds was moderate. This fact allowed the

Structures 17



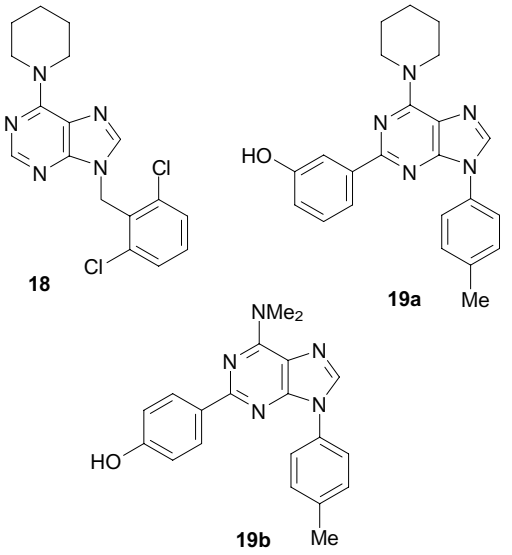
17a–f

Compound **17**	R	MIC/μg ml^{-1}
a	Me	< 0.2
b	Cl	2.6
c	OH	3.0
d	OEt	3.0
e	NHMe	3.0
f	NMe_2	3.0

authors to conclude that, for agelasine analogues to exhibit activity against *M. tuberculosis*, the presence of a small substituent similar in electronic properties to the hydrogen atom in the 2-position is favourable.[58]

Among purine derivatives containing secondary amine residues in the 6-position, 9-(2,6-dichlorobenzyl)- (**18**) and 2-hydroxyphenyl-9-*p*-tolyl derivatives (**19a**,**b**) showed a moderate *in vitro* tuberculostatic effect.[59, 60]

Structures 18, 19

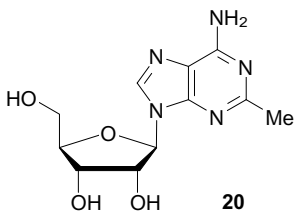


18 **19a** **19b**

5. Purine nucleosides

The results of studying the antimycobacterial activity of 2-methyladenosine (**20**) were reported in 2003.[61]

Structure 20



20

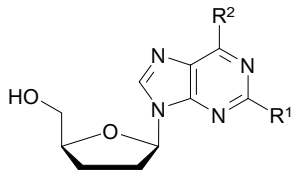
This nucleoside is a close analogue of natural adenosine, which is a very important structural moiety of RNA, DNA, ATP, cAMP and other biomolecules. For compound **20**, the MIC against the laboratory *M. tuberculosis* strain H37Rv was 3.1 mg litre^{-1}. 2-Methyladenosine exhibited good activity against mycobacterium strains resistant to the action of the known antituberculosis drugs (MIC < 1.56 mg litre^{-1}), as well as against avirulent H37Ra strain (MIC = 8 mg litre^{-1}). In addition, it has been demonstrated that compound **20** administered to mice at a dose of 25 mg kg^{-1} daily for 45 days is nontoxic.

Inside mycobacteria, 2-methyladenosine (**20**) is phosphorylated by adenosine kinase to methyl-AMP, which is further converted to methyl-ATP and incorporated into nucleic acids.[62, 63] The authors have suggested that the mechanism of the suppressive action of nucleoside **20** on *M. tuberculosis* involves the inhibition of early stages of protein synthesis and (to a lesser extent) the synthesis of DNA, but not the inhibition of the synthesis of RNA. At the same time, a study of the metabolism of compound **20** in *M. smegmatis* has demonstrated that the incorporation of 2-methyladenosine into the RNA structure plays an important role in the antimycobacterial action.[62]

Because adenosine kinase is a key enzyme in the metabolism of mycobacteria, it can be thought of as one of the priority targets for the action of antimycobacterial agents.[64, 65]

The activity of 2′,3′-dideoxynucleosides **21a–e** based on purine derivatives against the *M. tuberculosis* H37Ra, *M. bovis* and *M. avium* strains was assayed.[66] Among these compounds, only 2-amino-9-(2,3-dideoxy-β-D-glyceropentofuranosyl)-6-ethylthiopurine (**21e**) showed a noticeable inhibitory effect against *M. bovis* and *M. tuberculosis* H37Ra (MIC_{90} was 10–50 μg ml^{-1}). It has been concluded that, for better antimycobacterial activity in the case of dideoxynucleosides, the alkylthio group is a more preferable substituent in the 6-position of the purine nucleus than amino, hydroxy or methoxy group.

Structures 21



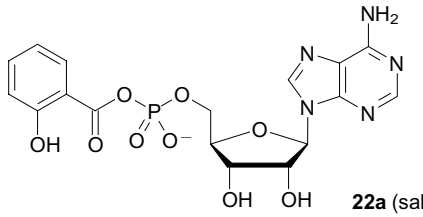
21

Compound **21**	R^1	R^2
a	H	NH_2
b	NH_2	OH
c	NH_2	NH_2
d	NH_2	OMe
e	NH_2	SEt

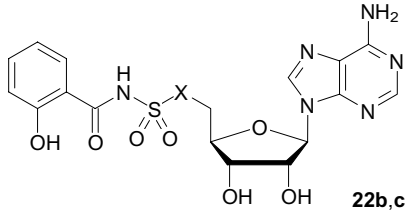
One of the important targets for new antitubercular agents is the biosynthesis of siderophores — low-molecular-weight compounds selectively transporting iron into microbial cells.[67–69] In mycobacteria, the role of such carriers is performed by mycobactins — peptide/polyketide hybrid molecules containing the salicylic acid moiety. The key intermediate compound in the biosynthesis of myco-

bactins is salicyl-AMP (**22a**), which is readily hydrolysed in the active site of the enzyme that transfers the salicylic acid residue to the polyketide fragment. The target for mycobactin biosynthesis inhibitors is enzyme MbtA, which converts salicylic acid and ATP to salicyl-AMP.

Structures 22



22a (salicyl-AMP)



22b,**c**

X = O (**b**, MIC = 0.29 μmol litre^{-1}),
NH (**c**, MIC = 0.19 μmol litre^{-1})

At first, a nonhydrolysable salicylic derivative of sulfamoyladenosine, compound **22b** was proposed as an inhibitor of mycobactin biosynthesis.[70] It inhibited the biosynthesis of mycobactins in a nanomolar concentration and showed high inhibitory activity against *M. tuberculosis* H37Rv cultured under iron-deficient conditions [the half-maximal inhibitory concentration (IC_{50}) = 2.2 ± 0.3 μmol litre^{-1}]. The *in vivo* experiments (in mice) have revealed its disadvantages consisting of a short half-life and low bioavailability after oral administration.[71]

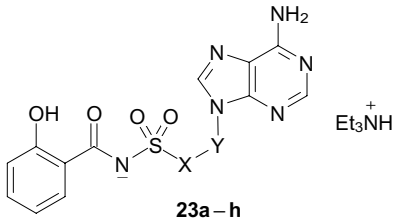
Replacement of the oxygen atom by the amino group led to compound **22c** — the inhibitor of *M. tuberculosis* growth not inferior in activity to isoniazid.[72] Further screening of inhibitors of siderophore biosynthesis in a series of structural analogues of salicyl-AMP revealed a series of highly active antimycobacterial agents **23a**–**h** (the MIC values are given in μmol litre^{-1}),‡ which suppress *M. tuberculosis* H37Rv growth both in iron-deficient and iron-rich media.[73–77]

Structural analogues of compound **22b**, containing deoxysugars, carbocyclic and linear ribose analogues, as a carbohydrate moiety had lower inhibitory activity than the parent compound; deoxy derivative **23a** and cyclopentyl derivative **23b** were the most active ones. The replacement of the ribose moiety by fluorine-containing carbohydrates of various configurations made it possible to obtain compounds **23c**–**h**; some of them showed high antimycobacterial activity[78,79] and had better bioavailability (in experiments on rats) compared to their analogue **22b**.[78]

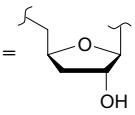
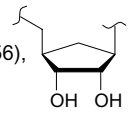
Nucleosides **24a**–**d**, which differ from compound **22b** by the presence of substituents in the acyl moiety, were synthesized using salicylic acid derivatives.[75]

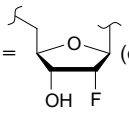
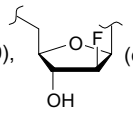
‡ For structures **23**–**25**, the minimal inhibitory concentrations against the *Mycobacterium tuberculosis* H37Rv strain in the iron-deficient culture medium are given.

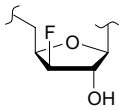
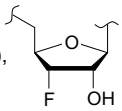
Structures 23

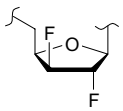
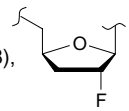


23a–**h**

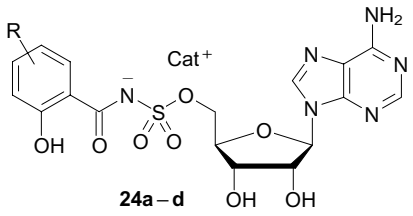
X = O: Y =  (**a**, MIC = 1.56),  (**b**, MIC = 1.56);

X = NH: Y =  (**c**, MIC = 0.19),  (**d**, MIC = 0.15),

 (**e**, MIC = 0.60),  (**f**, MIC = 2.30);

 (**g**, MIC = 0.78),  (**h**, MIC = 0.78)

Structures 24



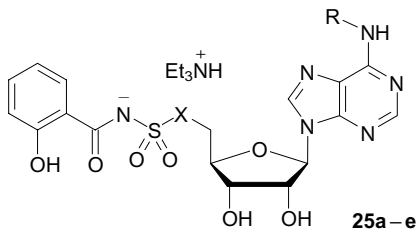
24a–**d**

Compound **24**	R	Cat	MIC_{99} /μmol litre^{-1}
a	4-F	Na	0.098
b	4-Me	Na	1.56
c	4-NH_2	Et_3NH	1.56
d	6-F	Et_3NH	0.78

Salts **24a**–**d** are nanomolar inhibitors of enzyme MbtA. Taken in concentrations 0.098–1.56 μmol litre^{-1}, they completely suppress the growth of *M. tuberculosis* H37Rv in an iron-poor medium. 4-Fluorosalicyl derivative **24a**, which exceeds in activity analogue **22b** containing the unsubstituted salicylic acid moiety, also retains its high activity in the presence of iron in a nutrient medium (MIC_{99} = 0.39 μmol litre^{-1}). This indicates the presence of an additional mechanism of antimycobacterial action, along with the inhibition of mycobactin synthesis.

In some cases, the introduction of substituents into the adenine moiety of structure **22b** led to an increase in inhibitory activity.[76,77,79] Compounds **25a**–**e**, containing small alkyl substituents at the adenine amino group, were almost not inferior in *in vitro* antimycobacterial activity to inhibitor **22b** with the unsubstituted NH_2 group.[76,79] However, derivative **25a** had much worse pharmacokinetic characteristics (bioavailability, half-life).[77]

Structures 25a–e

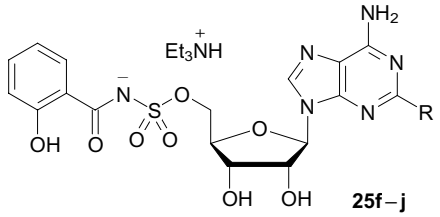


25a–e

Compound **25**	X	R	MIC_{99} /μmol litre^{-1}
a	O	Me	0.39
b	O	Et	0.39
c	O	Pr^n	0.39
d	O	cyclo-C_3H_5	0.098
e	NH	cyclo-C_3H_5	0.098

Molecular modelling has predicted that, for the closer binding of inhibitors **25f–i** to the Lys332 and Val448 residues of the MbtA enzyme, the presence of a bulky aromatic substituent in the 2-position of the adenine moiety is preferred.[76] Nucleosides **25g–i** containing aromatic moieties in substituents at the C(2) atom of adenine were synthesized according to this assumption and turned out to be efficient inhibitors of mycobactin synthesis; these compounds taken in a concentration of 0.049 and 0.39 μmol litre^{-1} (in the absence and presence of iron in the nutrient medium, respectively) suppressed the growth of mycobacteria. Thus, compounds **25g–i** are the most active inhibitors of *M. tuberculosis* growth known to date. Derivatives **25f**,**j**, containing the iodine atom or the azido group in the adenine moiety are somewhat less efficient.[76, 77]

Structures 25f–j



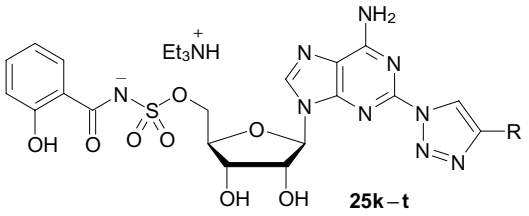
25f–j

Compound **25**	R	MIC_{99} /μmol litre^{-1}
f	I	0.19
g	NHPh	0.049
h	C≡CPh	0.049
i	Ph	0.049
j	N_3	0.39

Among substituted 2-triazolylnucleosides, compounds **25k–t** were found to have MIC_{99} = 0.78–1.56 μmol litre^{-1} under iron-deficient conditions[77] (for isoniazid, MIC_{99} is 0.18 μmol litre^{-1} regardless of the iron content).

In 2016, in order to improve the pharmacokinetic parameters (primarily bioavailability after oral administration), prodrugs **26a–h** were synthesized on the basis of compound **23c**.[80] They were distinguished by high stability under neutral and acid conditions and in human blood serum. However, their tuberculostatic activity was lower than that of parent compound **23c** because of their removal from the mycobacterial cells by the active transport mechanism.

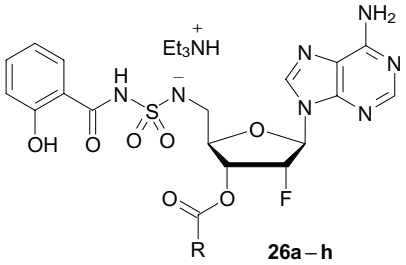
Structures 25k–t



25k–t

Compound **25**	R	MIC_{99} /μmol litre^{-1}
k	cyclo-C_5H_9	1.56
l	2-$H_2NC_6H_4$	0.78
m	4-$H_2NC_6H_4$	0.78
n	2-Py	0.78
o	3-Py	0.78
p	4-Py	0.78
q	2-HOC_6H_4	1.56
r	3-HOC_6H_4	1.56
s	4-HOC_6H_4	1.56
t	Pr^n	1.56

Structures 26

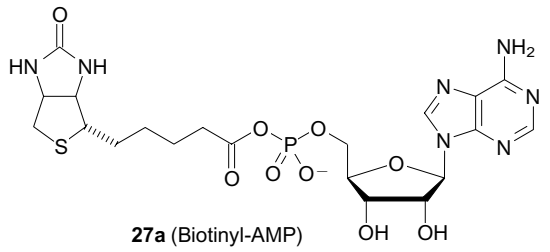


26a–h

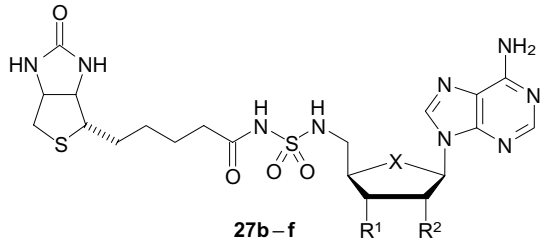
R = Me (**a**), Et (**b**), Pr^n (**c**), Bu^n (**d**), n-C_7H_{15} (**e**), n-$C_{11}H_{23}$ (**f**), Pr^i (**g**), pent-3-yl (**h**)

The synthesis of nucleosides **27b–f** — analogues of natural substrate biotinyl-AMP (**27a**) was reported.[81, 82] The structure of these compounds differs from structures **22–25** by the presence of the biotinyl moiety instead of the salicylic acid residue. Compounds **27b–f** exhibited high activity against *M. tuberculosis* H37Rv (MIC_{99} = 0.78–1.56 μmol litre^{-1}).[81, 82] The mechanism of their action involves inhibition of biotin protein ligase, which plays a crucial role in the biosynthesis of coenzyme malonyl-CoA, necessary for the building of lipids of the cell wall of mycobacteria. Compounds **27b–f** block the active site of the enzyme in nanomolar concentrations and have low toxicity (for the hepatocyte HepG2 model).

Structures 27



27a (Biotinyl-AMP)



27b–f

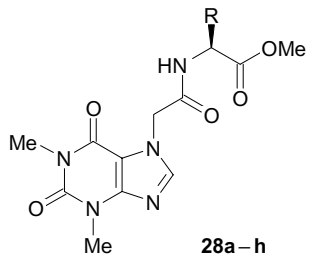
Compound **27**	X	R^1	R^2	MIC_{99} /μg mlitre^{-1}
b	O	OH	OH	0.78
c	CH_2	H	H	1.56
d	O	OH	NH_2	1.25
e	O	OH	F	1.25
f	O	H	OH	0.78

6. Purine derivatives containing amino acid and peptide moieties

Derivatives containing amino acid residues and short peptides constitute a separate group of purine-based antimycobacterial agents. Biologically active compounds with moieties of natural amino acids are often characterized by better bioavailability and lower toxicity than other xenobiotics.[83–86]

The synthesis of theophylline-7-acetic acid derivatives containing moieties of eight natural amino acids and their *in vitro* antitubercular activity were reported in 2014.[87] Among such compounds, derivatives of methyl esters of glycine (**28a**), alanine (**28b**), valine (**28c**), tryptophan (**28d**) and methionine (**28e**) showed high tuberculostatic activity (MIC from 0.26 to 0.65 μmol litre^{-1}) and very low cytotoxicity for human embryo kidney cells. The activity of compounds **28a–e** against the *M. tuberculosis* H37Rv strain exceeded 10–25-times the activity of the antituberculosis drug ethambutol used as a reference agent. Alkaline hydrolysis of the ester groups of compounds **28a–e** led to the corresponding acids, and their tuberculostatic activity was comparable with the activity of methyl esters, except theophylline-7-acetic acid derivatives incorporating glycine and valine moieties.

Structures 28



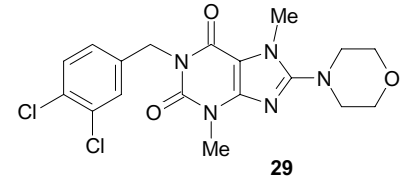
28a–h

Compound **28**	R	MIC /μg mlitre^{-1}
a	H	0.65
b	Me	0.62
c	Pr^i	0.57
d	Indol-3-ylmethyl	0.46
e	$MeS(CH_2)_2$	0.26
f	Imidazol-4-ylmethyl	0.128
g	Bn	0.125
h	4-$HOC_6H_4CH_2$	0.120

Based on the structure and antitubercular activity of amino acid derivatives **28a–e**, the same group of researchers suggested a computational model for establishing the structure–activity relationship.[88] A series of 14 different *N*-(theophylline-7-acetyl) amino acids and their methyl esters. The highest activity was predicted for methyl esters of histidine (**28f**), phenylalanine (**28g**) and tyrosine (**28h**). These compounds were synthesized and corresponding *in vitro* antitubercular activity was assayed against the *M. tuberculosis* H37Rv strain. The results confirmed the computational data: the MIC for compounds **28f–h** was 0.120–0.128 μmol litre^{-1}; *i.e.*, their activity was 60 times higher than that of ethambutol. From the experimental and computational data for this series of compounds, the authors made a conclusion that theophylline-7-acetic acid derivatives containing moieties of methyl esters of amino acids with aromatic substituents in the side chain (histidine, phenylalanine, tyrosine and tryptophan) are the most efficient inhibitors of tuberculosis mycobacterium growth.

Previously, xanthine derivatives that have no amino acid moieties in their structure have been suggested as inhibitors of some enzymes of mycobacteria.[89,90] An important target for antitubercular agents is mycobacterial glutamine synthetase.[91,92] High-throughput screening of nitrogen-containing heterocyclic derivatives as inhibitors of this enzyme has revealed xanthine derivative **29**, which is able to selectively block the ATP-binding domain of *M. tuberculosis* glutamine synthetase but is inactive against human glutamine synthetase.[89] This compound opens the way to the design, on its basis, of a new group of glutamine synthetase inhibitors that are not analogues of glutamate.

Structure 29

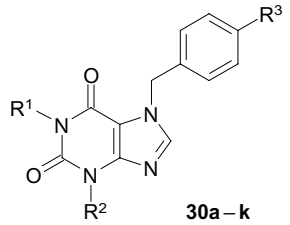


29

The screening results for *M. tuberculosis* dihydrofolate reductase have been reported.[90] Despite the encouraging results of molecular docking, 7-benzyl derivatives of xanthine **30a–k** did not show high *in vitro* antimycobacterial activity (MIC not lower than 31.5 μg ml^{-1}).

The authors of this review have recently synthesized purine and 2-aminopurine conjugates with natural amino acids (glycine, alanine, valine, phenylalanine, methionine, proline, aspartic and glutamic acids) and short peptides and have studied their *in vitro* antitubercular activity.[93–98] Among the synthesized purine derivatives, compounds with noticeable antimycobacterial effect against the

Structures 30

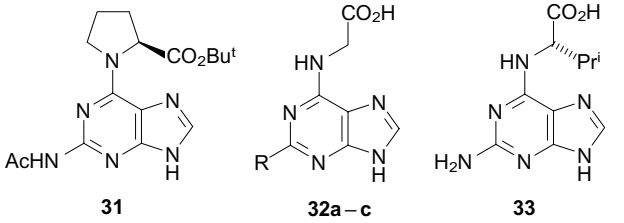


30a–k

Compound **30**	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	H	Me	Me
d	H	Me	Cl
e	H	Me	F
f	H	Me	OMe
g	Me	Me	H
h	Me	Me	Me
i	Me	Me	F
j	Me	Me	OMe
k	Me	Me	Cl

M. tuberculosis H37Rv strain have been identified. In particular, 2-acetamidopurine containing the *tert*-butyl L-prolinate moiety (compound **31**) exhibited moderate activity (MIC = 6.25 μg ml^{-1}). Among the synthesized *N*-(purin-6-yl)amino acids, moderate activity was observed for glycine (compounds **32b**,**c**) and L-valine (**33**) derivatives (MIC = 6.25 μg ml^{-1}). *N*-(2-Acetamidopurin-6-yl)glycine (**32a**) showed high inhibitory activity against both the laboratory *M. tuberculosis* H37Rv strain and a multidrug resistant strain.[95,96]

Structures 31–33

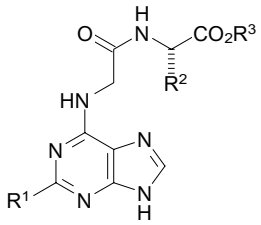


31 **32a–c** **33**

32: R = NHAc (**a**, MIC = 0.7 μg ml^{-1}), NH_2 (**b**, MIC = 6.25 μg ml^{-1}), H (**c**, MIC = 6.25 μg ml^{-1})

N-(2-Acetamidopurin-6-yl)glycine (**32a**) and *N*-(purin-6-yl)glycine (**32c**) were used as starting compounds in the synthesis of purine and 2-aminopurine conjugates with glycyl dipeptides.[95] Among the compounds obtained, *N*-(2-aminopurin-6-yl) (**34c**) and *N*-(purin-6-yl) (**34f**) L-glutamic acid derivatives were found to be most active against mycobacterium strains, including multidrug-resistant strains: for them, MIC = 0.7 μg ml^{-1} (Refs 95 and 97). Apparently, the high tuberculostatic activity of these compounds is due to their possible participation in the processes associated with glutamine transformation in the metabolism of mycobacteria. The derivatives of L-methionine (**34a**,**b**) and L-phenylalanine (**34d**,**e**) also demonstrated rather high antitubercular activity. The synthesized purine, 2-aminopurine and 2-acetamidopurine conjugates with amino acids were nontoxic for human embryonic fibroblasts,[95] which makes them attractive targets for testing antituberculosis effect on living organisms.

Structures 34

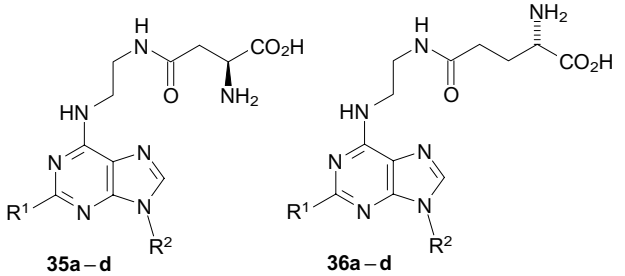


34a–f

Compound **34**	R^1	R^2	R^3	MIC /μg ml^{-1}
a	NHAc	$(CH_2)_2SMe$	Me	3.1
b	NH_2	$(CH_2)_2SMe$	H	3.1
c	NH_2	$(CH_2)_2CO_2H$	H	0.7
d	H	Bn	Me	1.5
e	H	Bn	H	3.1
f	H	$(CH_2)_2CO_2H$	H	0.7

Recently, purin-6-yl derivatives of (*S*)-asparagine (**35a–d**) and (*S*)-glutamine (**36a–d**) containing free functional groups in the α-position and the ethylenediamine spacer have been assayed as antimycobacterial agents.[98] Asparagine conjugates **35a**,**b** showed high *in vitro* tuberculostatic activity against mycobacteria, including a multidrug-resistant *M. tuberculosis* strain (MIC = 0.7 and 1.5 μg ml^{-1}). The activity of glutamine derivatives, as well as of compounds with a linear sugar analogue in the 9-position of the purine moiety, was significantly lower (MIC = 12.5 μg ml^{-1}).

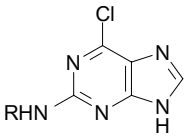
Structures 35, 36



35a–d **36a–d**

Compounds **35**, **36**	R^1	R^2	MIC /μg ml^{-1}	
			35	**36**
a	H	H	0.7	12.5
b	NH_2	H	1.5	1.5
c	H	$O(CH_2)_2OH$	12.5	12.5
d	NH_2	$O(CH_2)_2OH$	12.5	12.5

Structures 37



37a – d

Compound **30**	R^1	MIC /μg ml^{-1}
a	H	0.7
b	Ac	1.5
c	HC(O)	1.5
d	$CF_3C(O)$	6.1

It should be noted that structurally simple 2-amino derivatives of 6-chloropurine **37a – d**, starting compounds in the synthesis of conjugates **31 – 36**, exhibited a significant antimycobacterial activity against *M. tuberculosis* H37Rv.[99] Starting 2-amino-6-chloropurine (**37a**) taken at the lowest concentration (MIC = 0.7 μg ml^{-1}) inhibited mycobacterium growth. Compounds **37a – c** retained high activity against *M. tuberculosis* strain resistant to first-line antitubercular drugs.

7. Conclusion

The data presented in this review indicate that purine derivatives represent a very promising group in which compounds with significant antituberculosis activity have been identified. For some purines (predominantly adenosine derivatives), exact mechanisms of antimycobacterial action are known, while the mechanism of action of the majority of non-nucleoside agents remains unclear to date. The search for antitubercular agents among the purine derivatives by molecular modelling or high-throughput screening has made it possible to identify the most efficient antitubercular agents and, in some cases, to find structure – activity relationships. Apparently, the current stage of studies of the compounds of this group can be characterized as a period of information accumulation, which in the future can lead to the creation of new efficient purine-based drugs for the treatment of tuberculosis.

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