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PROSPECTS OF USING PHARMACOLOGICALLY ACTIVE COMPOUNDS FOR THE CREATION OF ANTIMYCOBACTERIAL DRUGS

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The growth of resistance to antimycobacterial drugs dictates the need to develop new agents with high therapeutic efficacy and low toxicity. The present review analyzes and summarizes literature data over the past decade on the synthesis and study of antimycobacterial agents using both an empirical approach and molecular docking. Pyrimidines, amides, coumarins, chalcones, furans, azomethines, salicylanilides, oxazolidines, nitroimidazoles, benzothiazinones, diarylquinolines, azaindoles, imidazopyridines, benzimidazoles, and riminophenazines, some of which are in various stages of clinical trials, are of most interest to researchers. Special attention is paid to identifying the targets of new compounds and studying their mechanisms of action when creating antimycobacterial agents.

Keywords: antituberculosis activity, antileprosy activity, targets, molecular docking, minimum inhibitory concentration, lipophilicity.

Tuberculosis and leprosy are the most dangerous mycobacterial diseases for man. Their treatment involves long-term courses of antibacterial therapy. Paleontological discoveries with signatures of these pathologies are geographically widespread and date to various periods starting from the Bronze and Iron Ages to the present, demonstrating a striking example of the coevolution of a pathogen and host [1]. Mycobacterial infections continue to present a global hazard because of the specifics of the genome and the resistance of mycobacteria to most antimicrobial drugs [1 – 3]. Therefore, research directed toward the discovery of compounds with antimycobacterial activity to create medicines based on them is undoubtedly critical [4 – 6]. In particular, compounds known to be biologically active can provide platforms for designing them [7, 8].

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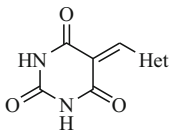
Heterocyclic compounds in general and pyrimidines in particular are natural compounds with significant potential biological activity [9, 10].

Pyrimidines

Pyrimidines are currently the leaders among N-containing heterocyclic compounds and exhibit broad spectra of antiviral, antibacterial, and antimycobacterial activity [11 – 13]. Many scientific groups are searching for new synthetic pathways to them [14 – 19]. According to Verbitskii, et al. [20], mono- and disubstituted pyrimidines are active against mycobacteria strains *Mycobacterium tuberculosis* H_{37}Rv, *M. avium*, and *M. terrae* because of the presence of several styryl- and (het)aryl-substitutions on pyrimidine C(4)–C(5) atoms.

The antimycobacterial activity and acute toxicity of synthetic 5-(hetarylmethylidene)-2,4,6-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (**1 – 5**) and 5-(2-chloropropylidene)-2,4,6-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (**6** and **7**) [21] and 5-(arylmethylidene)-2,4,6-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (**8 – 13**) [22] against *M. lufu* were studied at the Leprosy Research Institute, Ministry of Health of Russia.



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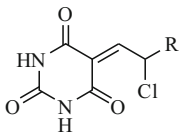

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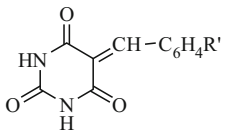
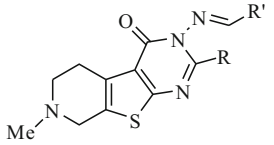


8-13

Het: 1-benzofuran-2-yl (**1**), 1,3-benzothizaol-2-yl (**2**), 2,1,3-benzooxadiazol-5-yl (**3**), 1,3-dimethyl-5-morpholinopyrazol-4-yl (**4**), 5-acetoxymethylfuran-2-yl (**5**);
R: acetyl (**6**), 2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione-5-ethyliden-5-yl (**7**);
R′: H (**8**), 4-OMe (**9**), 4-NMe_2 (**10**), 4-Cl (**11**), 3-NO_2 (**12**), 4-OH (**13**)

The WHO recommends using *M. lufu*, which has a sensitivity comparable to that of *M. leprae* to the main antileprosy drug dapsone, for primary selection of compounds with potential antileprosy activity *in vitro* because the leprosy vector is not cultivated in artificial growth media [23]. These compounds were shown to possess low toxicity and antimycobacterial activity of different strengths as compared to dapsone.

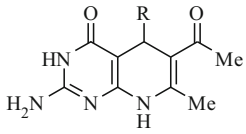
It was found that 7-methyl-5,6,7,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-4(3*H*)-triones (**14 – 23**) possessed potential antimicrobial and antimycobacterial properties against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *M. tuberculosis* $H_{37}Rv$ [24].



14-23

R = H, R′ = 4-ClC_6H_4 (**14**); R = H, R′ = 4-FC_6H_4 (**15**); R = H, R′ = 4-CNC_6H_4 (**16**); R = H, R′ = 2,6-$Cl_2C_6H_3$ (**17**); R = Me, R′ = 4-ClC_6H_4 (**18**); R = Me, R′ = 4-FC_6H_4 (**19**); R = Me, R′ = 4-CNC_6H_4 (**20**); R = Me, R′ = 4-$OMeC_6H_4$ (**21**); R = Me, R′ = thiophen-2-yl (**22**); R = Me, R′ = 2,6-$Cl_2C_6H_3$ (**23**)

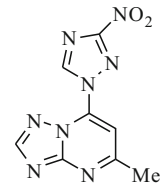
Other researchers established that 5-substituted 6-acetyl-2-amino-7-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-4(3*H*)-trione derivatives (**24**) inhibited growth of *M. tuberculosis* strain $H_{37}Rv$ but were inactive against *M. aurum*, *E. coli*, and *S. aureus*, which indicated their action was specific for slow-growing mycobacteria [25].



24

R = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-FC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeSC_6H_4$, 4-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_3$, 3,4,5-$(OMe)_3C_6H_2$, 4-OHC_6H_4, 3-$OMeC_6H_4$, 3-OHC_6H_4, 3,5-$(OMe)_2$-4-OHC_6H_2, 2-SHC_6H_4, (1,3-benzodioxol)-5-yl

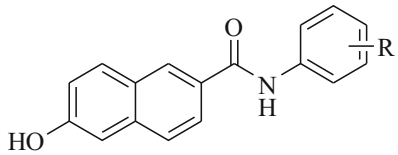
5-Methyl-7-(3-nitro-[1,2,4]-triazol-1-yl)-[1,2,4]triazolo-[1, 5-*a*]pyrimidine (**25**) with antituberculosis activity against a *M. tuberculosis* strain with multiple drug resistance was synthesized [26].



25

Amides

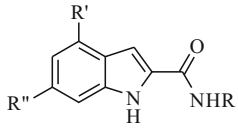
Antimycobacterial activity due to the ability of an amide bonded to a hydrophobic moiety to inhibit enzyme systems of bacteria was also shown for compounds based on carboxamides. For example, *in vitro* experiments with *N*-(alkoxyphenyl)-2-hydroxynaphthalene-1-carboxamide (**26**) demonstrated that the tested compounds were effective against *M. tuberculosis* $H_{37}Ra$, *M. kansasii*, and *M. smegmatis* [27, 28]; 6-hydroxynaphthalene-2-carboxanilides, against *M. tuberculosis* $H_{37}Ra$ and *M. avium*. They were more active against the main antituberculosis drugs isoniazid (2 times) and rifampicin (4.5 times) [29].



26

R = H, 2-OMe, 3-OMe, 4-OMe, 2-Me, 3-Me, 4-Me, 2-F, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-CF_3, 3-CF_3, 4-CF_3, 2-NO_2, 3-NO_2, 4-NO_2

Research on indole-2-carboxamides (**27** and **28**) revealed they were effective against a whole range of mycobacterial strains: *M. abscessus*, *M. massiliense*, *M. bolletii*, *M. chelonae*, *M. tuberculosis*, *M. avium*, *M. xenopi*, and *M. smegmatis* [30]. The researchers found that the minimum inhibitory concentration (MIC) for each tested strain was different and depended directly on the compound structural features. For example, the antimycobacterial activity increased with increasing number of methylenes and size of the aliphatic rings.



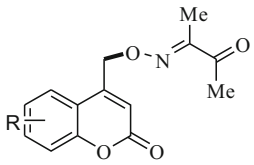
27

R′ = R″ = H, R′ = R″ = Me, R = adamantan-1-yl, 1-ethyladamantan-3-yl, 1-ethyladamantan-2-yl, cyclooctan-1-yl, cycloheptan-1-yl, cyclohexan-1-yl, cyclopentan-1-yl, *trans*-4-methylcyclohexan-1-yl, *cis*-4-methylcyclohexan-1-yl, *n*-heptan-1-yl, *n*-octan-1-yl, (1*S*,2*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl, 3-ClC_6H_4.

Coumarins

Coumarins are an expansive class of natural heterocyclic compounds contained in large quantities in various plant parts and possessing anti-inflammatory, antitumor, antimicrobial, and antituberculosis properties [31 – 37].

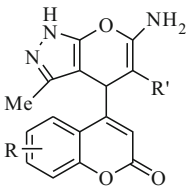
The biochemical potential and broad pharmacological applications of coumarins make them convenient synthetic scaffolds [38 – 42]. For example, the presence of the benzene ring of the 2-phenyl-2*H*-chromene in synthetic coumarin derivatives **28** showed clearly pronounced antimycobacterial effects against *M. tuberculosis* $H_{37}Rv$ [43, 44].



28

R = 5-Me, 5-Cl, 5-OMe, 7,8-Me_2, 7-Cl, 7-Me, 5,7-Me_2, 6-Br, 5,6-benzo, 7,8-benzo

Also, an attempt was made to produce new coumarin oxime ether analogs with high biological activity by adding carbonyl groups and N atoms to the molecular design of synthesized isomers. A series of experiments established pronounced antimycobacterial activity of methyl-substituted coumarin analogs for *M. tuberculosis* strain $H_{37}Rv$. Dimethyl-substituted coumarins were characterized with the highest antituberculosis activity (MIC 0.04 and 0.09 μg/mL) that was comparable to that of isoniazid (MIC = 0.02 μg/mL) [43]. Other coumarin derivatives such as pyrano[3,2-*c*]-chromenes (**29 – 31**) showed antimicrobial activity against Gram-positive (*S. aureus*, *E. faecalis*, and *B. cereus*) and Gram-negative bacterial strains (*E. coli*, *Pseudomonas aeruginosa*, and *P. intermedia*). The best results were found for the tested compounds against *E. faecalis* and *E. coli* [44].



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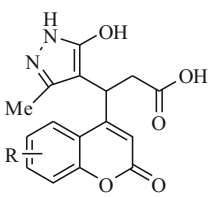

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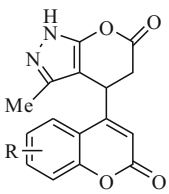
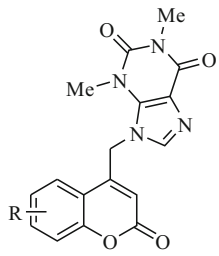


31

29, 30: R = 6-Me, 6-OMe, 6-Cl, 7-Me, 7,8-benzo; R′ = CN,CO_2Et
31: R = 6-Me, 6-OMe, 6-Cl, 7-Me, 7,8-benzo

Theophylline-type coumarin derivatives (**32**) were synthesized and found to be active against *M. tuberculosis* $H_{37}Rv$, Gram-negative and Gram-positive bacteria, and yeast-like fungi [45, 46]. We found that the tested compounds inhibited growth in 96% of mycobacterial cells with 100% growth suppression of the reference drug isoniazid.

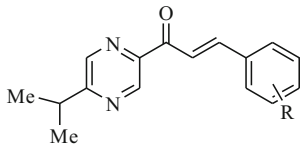


32

R = 6-Me, 7-Me, 5,6-benzo, 7,8-benzo, 5,7-Me_2, 6-OMe, 6-Cl, 6-Br, 6-*t*-Bu

Chalcones

Chalcones are other potential motifs for development of new antimycobacterial drugs. They are flavonoid compounds with an open pyran ring that demonstrate high levels of biological activity [47, 48]. Natural chalcones such as isoliquiritigenin, flavokawain, and xanthohumol, which are present in the families Fabaceae, Piperaceae, Cannabaceae, and Moraceae, possess antitumor and chemopreventive properties [49, 50]. Antimycobacterial and antifungal activities of nitro-substituted chalcones **33** against *M. tuberculosis* $H_{37}Rv$ and *Trichophyton mentagrophytes* were observed and were comparable to that of isoniazid, rifampicin, and fluconazole [51].



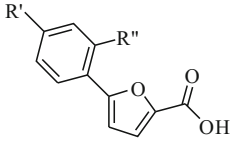
33

R = 2-OH, 3-OH, 3-OMe, 4-OH, 2-OMe, 4-OMe, 2-NO_2, 3-NO_2, 4-NO_2, 4-Cl

Spanish researchers showed that substituted chalcones with pyrimidine rings that were synthesized by them were active antituberculosis agents against several mycobacterial strains, i.e., *M. tuberculosis* $H_{37}Rv$ and *M. bovis* and a highly virulent clinical isolate of *M. tuberculosis*. The antimycobacterial activities of the tested compounds were characterized by different potencies as compared to the standard antituberculosis drug rifampicin [52].

Furans

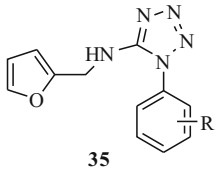
Natural and synthetic furans could become potential sources of components for constructing new antimycobacterial drugs [53, 54]. Synthetic 5-arylfuran-2-carboxylic acids **34** were found to be capable of inhibiting the biosynthesis of tuberculosis mycobacteria [55].



34

R′ = CF_3, NO_2, R″ = Cl, F, Br, OH, Me, NH_2, CN, CF_3

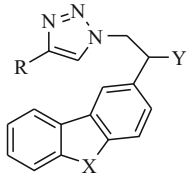
According to the researchers [56], *N*-(furan-2-ylmethyl)-1*H*-tetrazole-5-amines (**35**), which possessed antitumor activity, could be promising antituberculosis agents without the toxic effect of the tested compounds on healthy cells *in vivo*.



35

R = 4-F, 5-Cl, 2-Me, 4-I, 3-Cl, 3,4-Cl_2, 2-F, 3-Br, 4-Cl, 3-F, 4-Br, 2-Cl, 2-Br

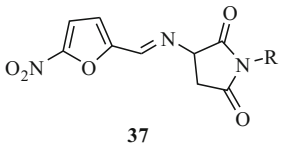
Research on 1,4-disubstituted 1,2,3-triazole derivatives of 9-ethyl-9*H*-carbazole and dibenzo[*b, d*]furan (**36**) revealed antimycobacterial properties against *M. smegmatis* and immunomodulatory activity [57].



36

X = NEt, O; Y = Me, Ph

Microbiological screening of the series of nitrofuran analogs **37** found high antimycobacterial activity against a laboratory strain of *M. tuberculosis* that was comparable to that of the control drug isoniazid [58].



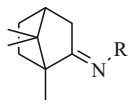
37

R = Me, Et, Pr, Bu, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_8H_{17}, *n*-C_9H_{19}, *n*-$C_{10}H_{21}$, *n*-$C_{11}H_{23}$, *n*-$C_{12}H_{25}$, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-MeC_6H_4, Ph, 4-$OMeC_6H_4$, 4-BrC_6H_4, $C_6H_5CH_2CH_2$

Azomethines

Schiff bases are nitrogen analogs of aldehydes or ketones, contain an imine or azomethine group, and can exemplify effective antimycobacterial, antimalarial, antiviral, and antifungal agents [59 – 61].

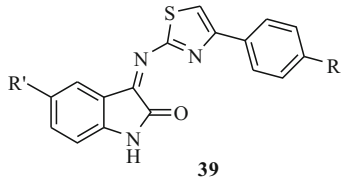
Antimycobacterial activity was found for synthetic imine derivatives **38** against *M. tuberculosis* and was comparable to that of the antituberculosis drug ethambutol [60].



38

R = $PhCH_2$, Bu, cyclopropyl, cyclohexyl, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-OH, 4-OMe, 2-OH, pyridin-4-yl, pyridin-2-yl, 2,5-$(OMe)_2C_6H_3$, 1,3-thiazol-2-yl

Experimental investigations found antituberculosis activity for 3-{[4-(4-hydroxyphenyl)-1,3-thiazol-2-yl]imino}-1,3-dihydro-2*H*-indol-2-one (**39**) on the strain *M. tuberculosis* $H_{37}Rv$ [62].

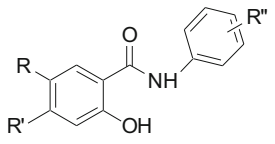


39

R = H, OH, OMe, NO_2; R″=H, Cl

Salicylanilides

Salicylanilides **40 – 42** are organic compounds known for their anthelmintic, antimicrobial, and antituberculosis activity [63 – 65].



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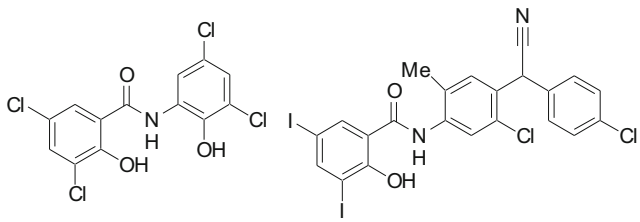
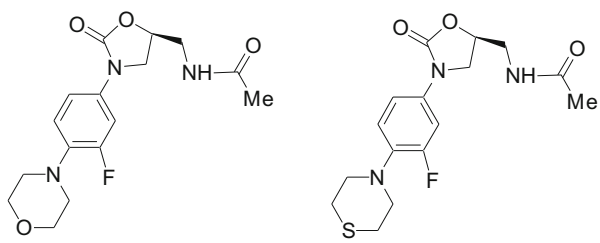


41 **42**

40: R = Cl, R′ = Br; R = Br, R′ = Cl; R = R′ = Br; R = R′ = Cl; R″ = 4-Br, 3,4-Cl_2, 4-CF_3, 3,5-$(CF_3)_2$

Oxazolidines and nitroimidazoles

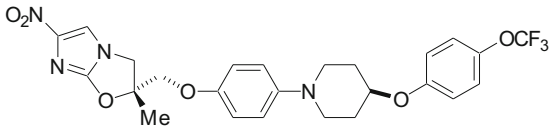
Promising antituberculosis agents include derivatives with oxazolidinone and nitroimidazole moieties. Oxazolidinone derivatives, in particular linezolid (**43**) and sutezolid (**44**), were highly active against Gram-positive lung pathogens, including those with multi-drug resistance, e.g., *M. tuberculosis*. Linezolid (**43**) blocked the synthesis of ribosomal protein in the early stage [66].



43 **44**

Nitroimidazoles inhibited cell growth by releasing reactive nitrogen species and blocking the synthesis of mycolic acid. It was established that delamanid (**45**) affected myco-

bacterial cell-wall components by inhibiting the synthesis of mycolic and ketomycolic acids [67].



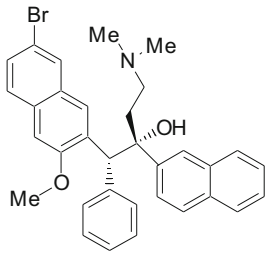
45

Delamanid was active against aerobic and anaerobic organisms.

Benzothiazinones, diarylquinolines, azaindoles, imidazopyridines, benzimidazoles

Heterocyclic compounds with benzothiazinone, diarylquinoline, azaindole, imidazopyridine, and benzimidazole fragments are promising antimycobacterial drugs and are active against various targets [66, 68].

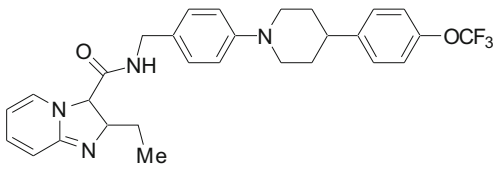
ATP-synthase is the target of a heterocyclic compound with a diarylquinoline fragment, i.e., bedaquiline (**46**).



46

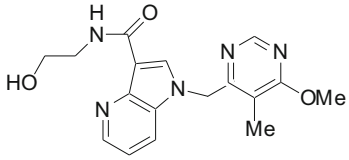
This drug suppressed cellular energy metabolism [69].

A study of a compound with an imidazopyridine moiety (**47**) showed that its target was the *bc*1 cytochrome complex. The compound inhibited ATP synthesis [70].



47

An azoindole (**48**) was an inhibitor of the enzyme $DprE_1$ and a moderate inhibitor of the enzyme PDE_6. It was rather highly active against *M. tuberculosis* (MIC 0.78 – 3.12 μg/mL).



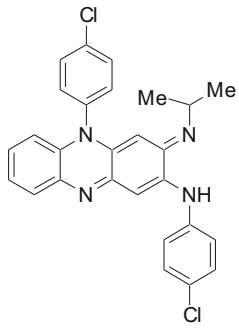
48

Strains of *M. tuberculosis* that were resistant to **48** had mutations in dprE1 (Rv3790) where tyrosine 314 was replaced by histidine. A second mutation in Rv1937 (Phe426Cys) was observed in these strains although its role in the resistance to this drug remains obscure.

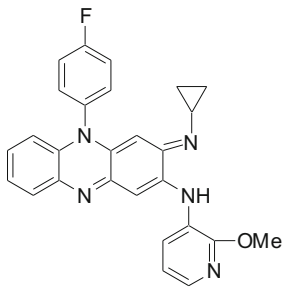
Riminophenazines

A brief historical description of riminophenazines, their total synthesis, mechanisms of action, physicochemical properties, and antituberculosis activities were discussed in a review [71]. Clofazimine (**49**) is a representative riminophenazine that has been used to treat leprosy since 1969 and is today considered a repurposed drug for tuberculosis [72, 73].

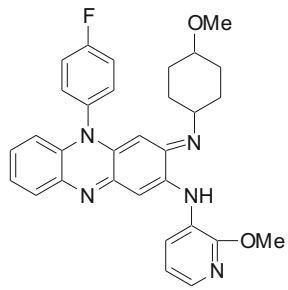
The antimycobacterial activity of **49** is probably associated with its high lipophilicity (C log P = 7.50) and high redox potential at pH 7.0 (0.18 V). In addition to antimycobacterial activity, riminophenazines exhibit prooxidant activity [71]. The synthesis of new representative riminophenazines, e.g. **50** and **51**, is a promising direction for the discovery of new candidate antileprosy and antituberculosis agents [74, 75].



49



50



51

The emergence of drug resistance in mycobacteria requires constant vigilance and studies of various pyrazoline, oxadiazole, triazole, and other derivatives of isoniazid, the first-line drug used for chemotherapy of tuberculosis [76 – 78].

Starch nanocrystals functionalized with polyurethane are being studied as a drug delivery system to minimize side effects from first-line antituberculosis drugs used in the clinic, e.g., isoniazid, rifampicin, pyrazinamide, and streptomycin [79].

CONCLUSION

The currently observed increased incidence of resistance to antimicrobial drugs dictates the necessity to develop new

drugs with high therapeutic efficacy and low toxicity. Several existing approaches should be monitored by scientists interested in developing antimycobacterial drugs. An empirical approach based on the use of known chemical compounds with a combination of various functional groups in their structures to produce new compounds that are more effective than the starting ones could be one possible solution to this problem. Such an approach enables nontoxic compounds with broad spectra of activity to be produced, including those with pronounced antimycobacterial activity. Targeted screening based on molecular docking using defined targets is now becoming more significant. The combination of these two approaches increases the chances of identifying new candidates during development of antimycobacterial drugs.

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