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Antituberculosis activity of α-aminoacyl amide derivatives

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The preparation and evaluation of *α*-aminoacyl amide derivatives against *M. tuberculosis* H37Rv is reported. The systematic modifications of hit compounds have been carried out. Compounds **19b** and **19c** are identified as potent and selective inhibitors of *M. tuberculosis* H37Rv with MIC 2.5 µM and 2.6 µM, respectively. Compounds **19b** and **19c** hold a promise for further development to discover new potent antituberculosis leads.

Keywords: Antituberculosis agents, Amides, Tuberculosis, α-Aminoacyl amide

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. According to WHO statistics for 2023 (Global TB report 2024), 10.8 million people fell ill with tuberculosis (TB), and 1.25 million people died from TB[1]. The WHO's "end the global TB epidemic" aims to reduce TB incidence and deaths by 17% per year between 2025 and 2035. A multidrug-resistant TB (MDR-TB) is on rise from the last two decades. Hence, there is an unmet medical need to develop a drug for tuberculosis. Efforts to develop leads and drugs effective against tuberculosis afforded various heterocyclic compounds with potent antituberculosis activity[2]. These inhibitors include adamantyl ureas[3], azaindole (**1**) with MIC range from 0.78-3.12 µM (Fig. 1)[4]. The azetidin-2-ones[5] and benzimidazole[6] are highly effective against *M. tuberculosis*. Ethionamide (**2**) is antimycobacterial drug with the MIC 0.25 µg/mL[7]. To tackle drug-resistant tuberculosis, in last decade, several antimycobacterial drugs have been discovered with potent activity. The three prominent examples are Bedaquiline (**3**), Pretomanid (**4**) and Delamanid (**5**) (Fig. 1). These drugs have been approved for the treatment of MDR-TB[8,9]. The MIC value for Bedaquiline (**3**) is 0.030 µg/mL[10]. Pretomanid (**4**) showed MIC of 0.1 µg/mL[11]. Delamanid (**5**, OPC-67683) is closely related to pretomanid (**5**)**.** It is a nitroimidazole analog which is recommended for the patients suffering from MDR-TB[12]. The compound **5** showed MIC 0.012 µg/mL against *M. tuberculosis* H37Rv[13].

Over the last three decades, a large number of inhibitors active against *M. tuberculosis* H37Rv were reported[14,15]. These are shown in Fig. 2. Adamantane based compound **6** was discovered by Grzegorzewicz *et al*. which has MIC 0.01 µg/mL against *M. tuberculosis*[16]. Compound **7** is a hydroxylamine derivative with MIC 0.25 µg/mL[17]. Rao *et al*. revealed that indole carboxamide derivatives **8** had MIC values of 0.02–0.04 µM against drug-sensitive *Mtb* H37Rv[18]. Compounds **9** (BTZ043) with MIC 0.001 µg/mL and 0.004 µg/mL against *Mtb* H37Rv and *M. smegmatis*, respectively, have been reported. The SAR study suggested that, the nitro group and sulfur atom of compound **9** are essential for the antibacterial

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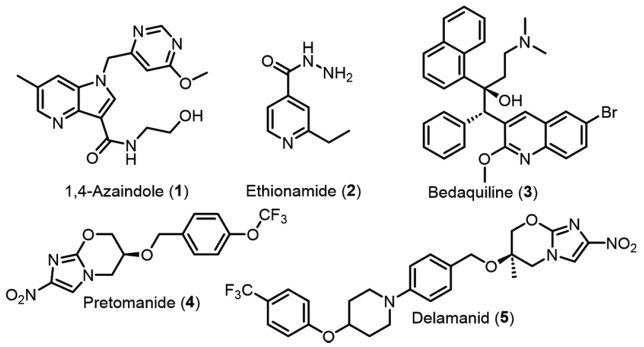


Fig. 1 — Structure of antituberculosis agent and drugs

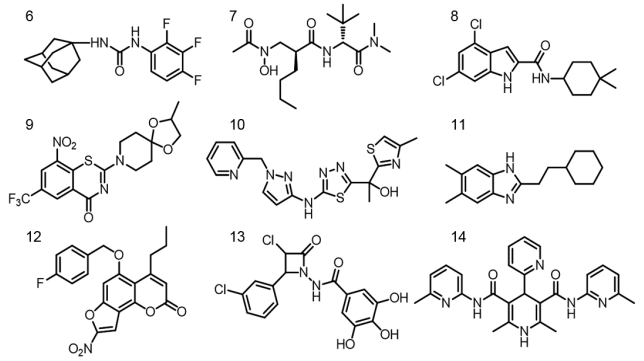


Fig. 2 — Structure of antituberculosis compounds

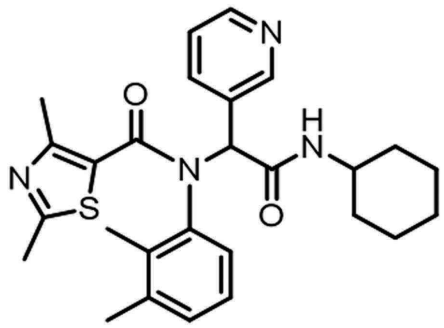
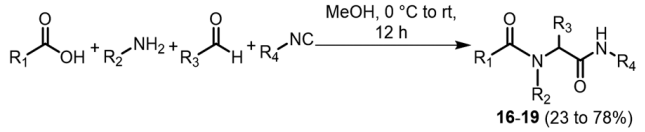


Fig. 3 —Structure of **15**

activity[19,20]. Castro and co-workers synthesized inhibitor **10** with MIC ≤1 μM[21]. Compound **11** showed MIC value 0.75 μg/mL against *M. tuberculosis*[22] whereas compound **12** has MIC 0.6 μg/mL against replicating, and 3.0 μg/mL against nonreplicating *Mtb*, respectively. The compound **13** showed antituberculosis activity with MIC 0.57 μg/mL which was more or less similar to INH (MIC= 0.56 μg/mL)[23]. Pyridine containing compound **14** (MIC = 12.5 μg/mL) showed moderate inhibition of Mtb[24]. Further to our efforts towards identifying antituberculosis agent, herein, we report the development of α-aminoacyl amide derivatives with moderate antituberculosis activity.



Scheme 1 — Preparation of α-aminoacyl amide derivatives **16-19**

Results and Discussion

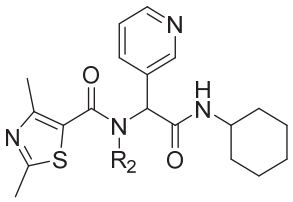
In our earlier report, we described the development of compound **15**, with MIC 0.78 μM against *Mtb* H37Rv[25]. Herein, we are reporting further modifications on this series of compounds with antituberculosis activity (Fig. 3).

Synthesis of α-aminoacyl amide derivatives **16-19** was carried out using multicomponent Ugi reaction involving aldehyde, an amine, isocyanide, and carboxylic acid in methanol at RT (Scheme 1).

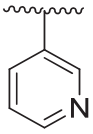
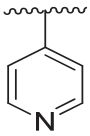
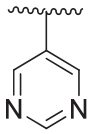
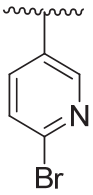
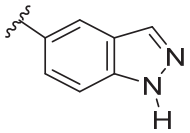
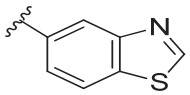
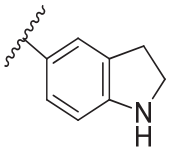
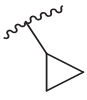
The Ugi reaction was carried out using acids including 2,4-dimethylthiazole-5-carboxylic acid, pyrazine-2-carboxylic acid, *1H*-indole-2-carboxylic acid, (*E*)-3-(furan-2-yl)acrylic acid, 2-bromonicotinic acid, 2-(1*H*-indol-3-yl)acetic acid, 5-nitrofuran-2-carboxylic acid, and 5-chlorofuran-2-carboxylic acid whereas cyclohexyl isocyanides and adamantly isocyanides were employed as isocyanides in this reaction. Various aromatic, heteroaromatic and cyclic amines were employed as amine component whereas aldehydes such as substituted isoxazole-4-carbaldehyde, 5-(2-(trifluoromethyl)phenyl)furan-2-carbaldehyde, *1H*-indazole-3-carbaldehyde and 2,3-dihydrobenzofuran-6-carbaldehyde were employed as aldehyde components. The compounds with MIC ≥100 μM are termed as inactive. Isoniazid was used as positive control (MIC of 0.4 μM) against *M. tuberculosis* H37Rv. We studied various substituents on *α*-aminoacyl amide linker (Table 1, Table 2, Table 3 and Table 4) in order to obtain potent analogues. Initially, the effect of R_2 substituents on the antituberculosis activity was assessed (Table 1). Compound **16g**, which has indoline as R_2 substituent, showed potent antituberculosis activity with MIC 3.12 μM against *M. tuberculosis* H37Rv. Compound **16f**, which has benzo[*d*]thiazole as R_2 substituent, showed moderate activity whereas compounds **16a, 16b, 16c, 16d, 16e, 16h, 16i, 16j,** and **16k** which have 3-pyridinyl, 4-pyridinyl, pyrimidinyl, 6-bromo-3-pyridinyl, 1*H*-benzo[*d*]imidazole, cyclopropyl, cyclobutyl, cyclopentyl cyclohexyl at R_2 substituents were inactive. This indicates that compound **16g** which has indoline as R_2 is required substituent for the activity.

We explored the requirement of R_3 subunit on the antimycobacterial activity. The results are

Table 1 — Effect of R_2 substitution on antituberculosis activity of compounds

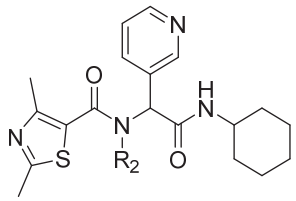


16a-16k

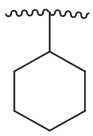
Compd	R_2	Mol. Wt.	cLogP	MIC (μM)
16a		449.5	3.4	>100
16b		449.6	3.4	>100
16c		450.0	2.8	>100
16d		528.0	4.1	>100
16e		505.0	4.5	>100
16f		448.6	3.7	12.5
16g		489.1	3.9	3.12
16h		412.5	3.6	>100
16i		426.1	3.6	>100
16j		440.0	3.9	>100

(*Contd.*)

Table 1 — Effect of R_2 substitution on antituberculosis activity of compounds (*Contd.*)

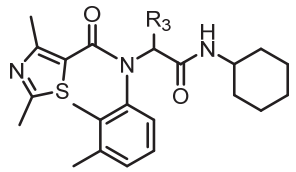


16a-16k

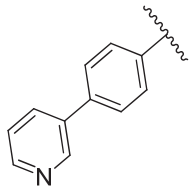
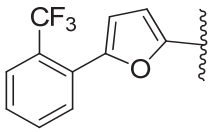
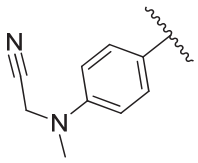
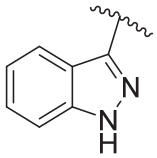
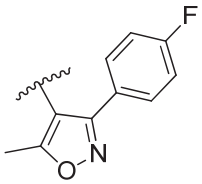
Compd	R_2	Mol. Wt.	cLogP	MIC (μM)
16k		454.0	4.1	>100

Minimum inhibitory concentration (MIC) of compounds against *M. tuberculosis* H37Rv. MW = Molecular weight. cLogP = Partition coefficient. The wavy bond indicates the point of attachment to the *α*-aminoacyl amide.

Table 2 — Effect of R_3 substitution on antituberculosis activity of compounds

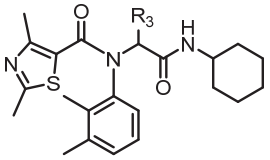


17a-17j

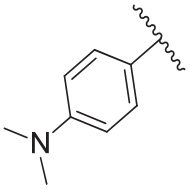
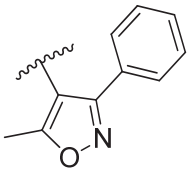
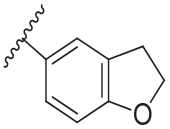
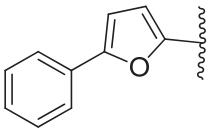
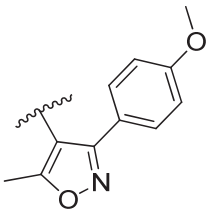
Compd	R_3	Mol. Wt.	cLogP	MIC (μM)
17a		552.7	5.9	12.5
17b		4624.0	6.8	>100
17c		542.0	5.6	25
17d		515.1	4.9	6.25
17e		574.0	6.1	>100

(*Contd.*)

Table 2 — Effect of R_3 substitution on antituberculosis activity of compounds (*Contd.*)

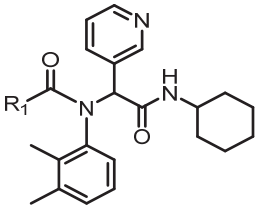


17a-17j

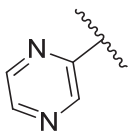
Compd	R_3	Mol. Wt.	cLogP	MIC (μM)
17f		518.0	5.3	>100
17g		556.0	5.8	>100
17h		533.0	4.9	>100
17i		541.0	5.9	>100
17j		586.0	5.8	>100

Minimum inhibitory concentration (MIC) of compounds against *M. tuberculosis* H37Rv. MW = Molecular weight. cLogP = Partition coefficient calculated using SwissADME. The wavy bond indicates the point of attachment to the *α*-aminoacyl amide.

Table 3 — Effect of R_1 substitution on the antituberculosis activity of compounds

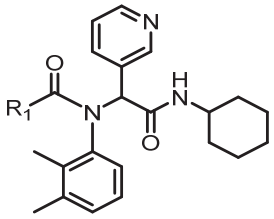


18a-18h

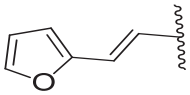
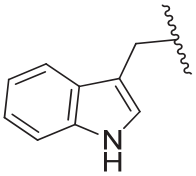
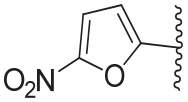
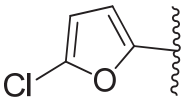
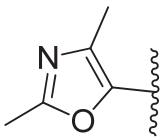
Compd	R_1	Mol. Wt.	cLogP	MIC (μM)
18a		443.5	3.2	>100

(*Contd.*)

Table 3 — Effect of R1 substitution on the antituberculosis activity of compounds (*Contd.*)

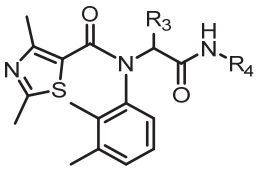


18a-18h

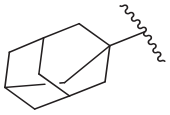
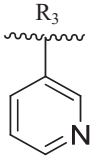
Compd	R_1	Mol. Wt.	cLogP	MIC (μM)
18c		457.6	4.2	>100
18d		521.5	4.5	6.2
18e		480.6	4.2	25
18f		476.5	3.6	12.5
18g		465.9	4.5	>100
18h		460.0	4.0	12.5

Minimum inhibitory concentration (MIC) of compounds against *M. tuberculosis* H37Rv. MW = Molecular weight. cLogP = Partition coefficient calculated using SwissADME. The wavy bond indicates the point of attachment to the *α*-aminoacyl amide.

Table 4 — Effect of R_1 substitution and extended substitution pattern at R_3 on the antituberculosis activity of compounds

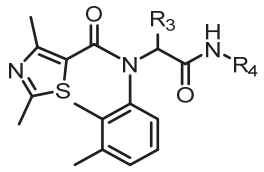


19a-19c

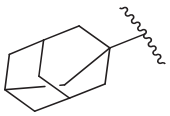
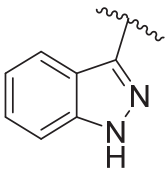
Compd	R_4	R_3	Mol. Wt.	cLogP	MIC (μM)
19a			528.7	3.2	12.5

(*Contd.*)

Table 4 — Effect of R_1 substitution and extended substitution pattern at R_3 on the antituberculosis activity of compounds (*Contd.*)



19a-19c

Compd	R_4	R_3	Mol. Wt.	cLogP	MIC (μM)
19c			567.7	5.7	2.6

Minimum inhibitory concentration (MIC) of compounds against *M. tuberculosis* H37Rv. MW = Molecular weight. cLogP = Partition coefficient calculated using SwissADME. The wavy bond indicates the point of attachment to the *α*-aminoacyl amide.

summarized in Table 2. Compound **17d** showed potent activity with MIC 6.25 μM against *M. tuberculosis* H37Rv whereas compound **17a** which has 4-(3-pyridinyl)phenyl as R_3 substituent showed moderate antituberculosis activity with MIC 12.5 μM against *M. tuberculosis* H37Rv. The compound **17c** which has *N*-(1-(4-((2-cyanoethyl)(methyl)amino) phenyl as R_3 substituent, showed weak antituberculosis activity with MIC 25 μM against *M. tuberculosis* H37Rv, whereas compounds **17b, 17e, 17f, 17g, 17h, 17i** and **17j** which have 5-(2-(trifluoromethyl)phenyl)furanyl, 4-fluorophenyl-5-methylisoxazole, 4-*N,N*-dimethylphenyl, phenyl-5-methylisoxazole, 2,3-dihydrobenzofuran, 5-phenyl furanyl and 4-methoxyphenyl-5-methylisoxazole as R_3 substituents, respectively, did not show activity against *M. tuberculosis* H37Rv.

Next, the effect of R_1 substituents on the antimycobacterial activity of *α*-aminoacyl amide was studied (Table 3). The compounds **18d, 18f,** and **18h** showed activity against *Mtb.* Compound **18d** showed potent activity with MIC 6.2 μM, against *M. tuberculosis* H37Rv, which has 3-3(2-bromo) pyridyl as R_1 substituent. Compound **18e** has 3-methylene-*1H*-indole and showed moderate activity against *M. tuberculosis*. Compounds **18a, 18b, 18c**, and **18g** which are having pyrazinyl, 2-substited-*1H*-indole, (*E*)-2-(prop-1-en-1-yl) furan and 2-chlorofuronyl as R_1 substituents did not show any activity.

Finally, the effect of R_4 substitution of *α*-aminoacyl amide on the antitubercular activity was studied (Table 4). Compound **19a** showed moderate activity against *M. tuberculosis* H37Rv indicating adamantyl is well tolerated as R_4 substituent. Compounds **19b** and **19c** also showed potent activity, where R_3 substitution is different as compared to compound **19a.** In compound **19a**, R_3 substituent is pyridyl while in compounds **19b** and **19c** respectively[9].

All the compounds were tested against a panel of ESKAPE pathogens. None of them showed inhibition of these bacteria (Table 5) indicating selective killing of *M. tuberculosis* by these compounds.

Experimental Section

Chemistry

Synthesis of compounds

Aldehyde (0.8 equivalents) and amine (0.7 equivalent) were dissolved in methanol (2.0 mL) and stirred for three hours. The acid (100 mg, 1 equivalent) and isocyanide (0.7 equivalent) were added in the reaction mixture and further stirred. The reaction mixture was monitored using TLC analysis. Water (4 mL) was added upon completion of the reaction. The resulted solid was filtered off and dissolved in ethyl acetate (10 mL), washed with water (2 × 3 mL) and dried over sodium sulphate. The crude product was purified using silica gel column chromatography. The ethyl acetate:hexane (6:4) solvent system was used for the purification of these compounds.

Table 5 — MICs (μM) of compounds against a panel of ESKAPE pathogens

Compd	*E. coli* ATCC 25922	*S. aureus* ATCC 29213	*K. pneumoniae* BAA 1705	*A. baumannii* BAA 1605	*P. aeruginosa* ATCC 27853
16a	>50	>50	>50	>50	>50
16b	>50	>50	>50	>50	>50
16c	>50	>50	>50	>50	>50
16d	>50	>50	>50	>50	>50
16e	>50	>50	>50	>50	>50
16f	>50	>50	>50	>50	>50
16g	>50	>50	>50	>50	>50
16h	>50	>50	>50	>50	>50
16i	>50	>50	>50	>50	>50
16j	>50	>50	>50	>50	>50
16k	>50	>50	>50	>50	>50
17a	>50	>50	>50	>50	>50
17b	>50	>50	>50	>50	>50
17c	>50	>50	>50	>50	>50
17d	>50	>50	>50	>50	>50
17e	>50	>50	>50	>50	>50
17f	>50	>50	>50	>50	>50
17g	>50	>50	>50	>50	>50
17h	>50	>50	>50	>50	>50
17i	>50	>50	>50	>50	>50
17j	>50	>50	>50	>50	>50
18a-18h	>50	>50	>50	>50	>50
19a-19c	>50	>50	>50	>50	>50

The compounds (**17a-17j**, **18a-18h** and **19a-19c**) have *ortho* substituent as R_2. These compounds appear to be a mixture of rotamers. Hence, NMR spectra of these compounds are not characteristics. Such a complexity in NMR pattern for these types of compounds is mentioned in the literature[26-29].

Analytical data of the compounds

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethyl-*N*-(pyridin-3-yl)thiazole-5-carboxamide, 16a**: White solid. Yield 35 mg (32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (dd, *J* = 4.7, 1.6 Hz, 2H), 8.40 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.09 (bs, 1H), 7.61 (bs, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 7.9, 4.9 Hz, 2H), 6.25 (s, 1H), 5.73 (d, *J* = 7.9 Hz, 1H), 3.92 – 3.78 (m, 1H), 2.54 (s, 3H), 2.46 (s, 3H), 2.06 – 1.96 (m, 1H), 1.92 – 1.84 (m, 1H), 1.79 – 1.71 (m, 3H), 1.40 – 1.32 (m, 2H), 1.20 – 1.03 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 167.54, 164.33, 157.91, 151.90, 151.44, 150.38, 149.49, 138.78, 137.89, 136.05, 130.20, 123.64, 123.57, 122.70, 62.85, 49.31, 32.93, 25.54, 24.93, 24.84, 18.95, 17.64, 15.52; EIMS: *m/z* 450.10 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethyl-*N*-(pyridin-4-yl)thiazole-5-carboxamide, 16b**: White solid. Yield 100 mg (34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 – 8.56 (m, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.26 (s, 5H), 6.23 (s, 1H), 6.12 (d, *J* = 7.5 Hz, 1H), 3.90 – 3.74 (m, 1H), 2.72 (d, *J* = 3.9 Hz, 7H), 1.99 – 1.89 (m, 2H), 1.80 – 1.72 (m, 3H), 1.44 – 1.32 (m, 3H), 1.24 – 1.10 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 167.54, 164.33, 157.91, 151.90, 151.44, 150.38, 149.49, 138.78, 137.91, 136.05, 130.20, 123.64, 123.57, 122.70, 62.9, 49.31, 32.93, 25.54, 24.93, 24.84, 19.00, 17.64, 15.53; EIMS: *m/z* 450.10 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-2,4-dimethyl-*N*-(pyrimidin-5-yl)thiazole-5-carboxamide, 16c**: White solid. Yield 115 mg (38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.65 (s, 1H), 8.56 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.21 (s, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.29 (s, 1H), 5.64 (d, *J* = 7.9 Hz, 1H), 3.89 – 3.79 (m, 1H), 2.52 (s, 3H), 2.48 (s, 3H), 2.06 – 1.99 (m, 1H), 1.90 – 1.83 (m, 1H), 1.78 – 1.64 (m, 3H), 1.41 – 1.32 (m, 2H), 1.23 – 1.00 (m,

3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.10, 167.31, 164.17, 158.79, 157.61, 151.53, 150.92, 149.92, 143.11, 140.54, 137.71, 134.95, 129.88, 123.86, 62.12, 49.44, 32.94, 29.86, 25.51, 24.93, 24.83, 19.06, 17.55; EIMS: *m/z* 451.00$[M+H]^+$.

***N*-(6-Bromopyridin-3-yl)-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethylthiazole-5-carboxamide, 16d**: White solid. Yield 35 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 7.82 (s, 1H), 7.48 (s, 1H), 7.45 – 7.41 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.26 (s, 1H), 5.69 (d, *J* = 7.9 Hz, 1H), 3.88 – 3.77 (m, 1H), 2.52 (s, 3H), 2.50 (s, 3H), 2.03 – 1.95 (m, 1H), 1.92 – 1.83 (m, 1H), 1.79 – 1.62 (m, 3H), 1.42 – 1.30 (m, 2H), 1.23 – 0.99 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.92, 167.43, 164.20, 157.93, 152.09, 151.44, 150.69, 141.71, 141.18, 137.76, 135.56, 129.98, 128.27, 123.79, 122.42, 62.49, 49.40, 32.92, 25.52, 24.93, 24.83, 19.11, 17.59; EIMS: *m/z* 528.00 $[M]^+$.

***N*-(1*H*-Benzo[d]imidazol-5-yl)-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethylthiazole-5-carboxamide, 16e**: Brown solid. Yield 35 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, *J* = 2.1 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.98 (s, 1H), 7.46 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.31 – 7.17 (m, 5H), 7.04 (dd, *J* = 7.7, 4.6 Hz, 1H), 6.26 (s, 1H), 5.95 (d, *J* = 7.4 Hz, 1H), 3.93 – 3.81 (m, 1H), 2.62 (s, 3H), 2.37 (s, 3H), 2.06 – 2.00 (m, 1H), 1.92 – 1.86 (m, 1H), 1.79 – 1.66 (m, 3H), 1.39 – 1.31 (m, 2H), 1.22 – 1.05 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.88, 167.50, 164.53, 158.35, 151.31, 149.69, 139.21, 138.04, 135.54, 132.23, 130.57, 129.93, 124.25, 123.22, 122.76, 110.17, 63.39, 49.07, 32.83, 29.72, 25.47, 24.82, 24.73, 18.71, 17.87; EIMS: *m/z* 489.10 $[M+H]^+$.

***N*-(Benzo[d]thiazol-5-yl)-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethylthiazole-5-carboxamid, 16f**: White solid. Yield 66 mg (25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.51 (d, *J* = 2.1 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.44 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.26 (s, 2H), 7.05 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.25 (s, 1H), 5.83 (d, *J* = 7.9 Hz, 1H), 3.92 – 3.81 (m, 1H), 2.59 (s, 3H), 2.38 (s, 3H), 2.01 (s, 1H), 1.94 – 1.85 (m, 1H), 1.77 – 1.64 (m, 3H), 1.42 – 1.33 (m, 2H), 1.22 – 1.02 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.80, 167.60, 164.36, 158.31, 156.19, 153.00, 151.47, 150.15, 137.83, 136.76, 134.17, 130.41, 129.63, 125.10, 123.72, 122.89, 63.65, 60.55, 49.29, 32.97, 25.57, 24.95, 24.86, 18.93, 17.88; EIMS: *m/z* 506.2 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-*N*-(indolin-5-yl)-2,4-dimethylthiazole-5-carboxamide, 16g**: White solid. Yield 130 mg (41%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (d, *J* = 1.9 Hz, 1H), 8.43 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.38 – 8.32 (m, 1H), 7.51 – 7.47 (m, 1H), 7.22 – 7.20 (m, 1H), 7.07 – 7.02 (m, 1H), 6.45 (s, 1H), 6.21 (s, 1H), 6.17 (s, 1H), 3.93 – 3.83 (m, 1H), 2.62 (s, 3H), 2.35 (s, 3H), 2.04 – 1.99 (m, 1H), 1.93 – 1.88 (m, 1H), 1.81 – 1.73 (m, 3H), 1.68 – 1.64 (m, 2H), 1.63 – 1.57 (m, 2H), 1.40 – 1.33 (m, 2H), 1.23 – 1.09 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.88, 167.50, 164.53, 158.35, 151.31, 149.69, 139.21, 138.04, 135.54, 132.23, 130.57, 129.93, 124.25, 123.22, 122.76, 110.17, 63.39, 49.07, 32.83, 29.72, 25.47, 46.60, 30.31, 24.82, 24.73, 18.71, 17.87; EIMS: *m/z* 489.6 $[M+]^+$.

***N*-Cylopropyl-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethylthiazole-5-carboxamide, 16h**: White solid. Yield 100 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 – 8.65 (m, 1H), 8.60 (d, *J* = 3.7 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 5.68 (s, 1H), 3.88 – 3.77 (m, 1H), 2.71 – 2.66 (m, 3H), 2.62 – 2.55 (m, 1H), 2.50 – 2.43 (m, 3H), 1.96 – 1.86 (m, 2H), 1.77 – 1.66 (m, 3H), 1.62 – 1.53 (m, 2H), 1.41 – 1.32 (m, 2H), 1.21 – 1.11 (m, 3H), 0.90 – 0.84 (m, 1H), 0.63 – 0.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.13, 168.25, 166.86, 166.74, 155.01, 150.96, 149.75, 137.47, 124.68, 123.57, 64.81, 48.75, 48.56, 32.83, 32.78, 32.00, 25.60, 24.72, 19.27, 17.04, 11.35, 10.22; EIMS: *m/z* 413.2 $[M+H]^+$.

***N*-Cyclobutyl-*N*-(2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethylthiazole-5-carboxamide, 16i**: White solid. Yield 125 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.53 (d, *J* = 4.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 5.30 (s, 1H), 4.53 – 4.42 (m, 1H), 3.90 – 3.81 (m, 1H), 2.68 (s, 3H), 2.43 (s, 3H), 2.26 – 2.18 (m, 1H), 2.16 – 2.07 (m, 2H), 1.98 – 1.91 (m, 1H), 1.89 – 1.83 (m, 1H), 1.75 – 1.63 (m, 3H), 1.62 – 1.51 (m, 3H), 1.42 – 1.32 (m, 2H), 1.22 – 1.10 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.48, 166.60, 165.08, 153.98, 149.05, 148.76, 135.60, 132.14, 123.81, 123.68, 62.45, 55.32,

48.69, 32.75, 32.74, 29.54, 29.49, 25.58, 24.61, 19.27, 16.54, 14.53, 14.19; EIMS: *m/z* 427.20 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-cyclopentyl-2,4-dimethylthiazole-5-carboxamide, 16j**: White solid. Yield 115 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 – 8.51 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.30 (dt, *J* = 7.3, 3.7 Hz, 1H), 6.96 (bs, 1H), 4.96 (s, 1H), 4.34 – 4.20 (m, 1H), 3.92 – 3.81 (m, 1H), 2.69 (s, 3H), 2.45 (s, 3H), 2.08 – 1.99 (m, 1H), 1.97 – 1.85 (m, 3H), 1.83 – 1.73 (m, 3H), 1.71 – 1.63 (m, 3H), 1.61 – 1.48 (m, 4H), 1.43 – 1.32 (m, 2H), 1.23 – 1.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.71, 165.98, 165.29, 153.28, 149.24, 148.79, 135.16, 132.14, 123.65, 123.50, 62.70, 62.47, 48.70, 32.77, 32.72, 30.05, 30.03, 29.83, 25.60, 24.62, 24.09, 22.82, 19.24, 16.40; EIMS: *m/z* 441.22 $[M+H]^+$.

***N*-Cyclohexyl-*N*-*(*2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-2,4-dimethylthiazole-5-carboxamide, 16k**: White solid. Yield 90 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 2.0 Hz, 1H), 8.52 (d, *J* = 4.7 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.26 (m, 2H), 5.03 (s, 1H), 3.92 – 3.74 (m, 2H), 2.70 (s, 3H), 2.44 (s, 3H), 1.95 (dd, *J* = 12.4, 3.8 Hz, 1H), 1.90 – 1.76 (m, 6H), 1.71 – 1.61 (m, 3H), 1.60 – 1.53 (m, 2H), 1.44 – 1.33 (m, 2H), 1.29 – 1.21 (m, 3H), 1.19 – 1.04 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.12, 166.01, 165.23, 153.82, 149.05, 148.69, 135.09, 132.32, 123.55, 123.26, 62.59, 61.34, 48.58, 32.83, 32.74, 32.06, 31.99, 25.80, 25.62, 24.95, 24.62, 19.28, 16.44; EIMS: *m/z* 455.3 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(4-(pyridin-3-yl) phenyl)ethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17a**: White solid. Yield 110 mg (38%); EIMS: *m/z* 553.1 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(5-(2-(trifluoromethyl) phenyl)furan-2-yl)ethyl)-N-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17b**: White solid. Yield 91 mg (57%); EIMS: *m/z* 610.1 $[M+H]^+$.

***N*-(1-(4-((Cyanomethyl)(methyl)amino)phenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17c**: White solid. Yield 37 mg (33%); EIMS: *m/z* 558.1 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-1-(1*H*-indazol-3-yl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17d**: White solid. Yield 101 mg (36%); EIMS: *m/z* 516.1 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-1-(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17e**: White solid. Yield 99 mg (28%); EIMS: *m/z* 575.1 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-1-(4-(dimethylamino) phenyl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17f**: White solid. Yield 120 mg (43%); EIMS: *m/z* 519.2 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-1-(5-methyl-3-phenylisoxazol-4-yl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17g**: White solid. Yield 126 mg (36%); EIMS: *m/z* 556.2 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-1-(2,3-dihydrobenzofuran-5-yl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17h**: White solid. Yield 35 mg (32%); EIMS: *m/z* 518.10 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(5-phenylfuran-2-yl)ethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17i**: White solid. Yield 129 mg (41%); EIMS: *m/z* 542.00 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-1-(3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethylthiazole-5-carboxamide, 17j**: White solid. Yield 102 mg (66%); EIMS: *m/z* 586.2 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)pyrazine-2-carboxamide, 18a**: White solid. Yield 49 mg (34%); EIMS: *m/z* 443.2 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)-1*H*-indole-2-carboxamide, 18b**: White solid. Yield 116 mg (78%); EIMS: *m/z* 481.00 $[M+H]^+$.

(E)-*N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)-3-(furan-2-yl)acrylamide, 18c: White solid. Yield 89 mg (30%); EIMS: *m/z* 558.10 $[M+H]^+$.

2-bromo-*N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-*N*-(2,3-dimethylphenyl)nicotinamide, 18d: White solid. Yield 115 mg (78%); EIMS: *m/z* 520.00 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)-1*H*-indole-3-carboxamide, 18e**: Brown solid. Yield 90 mg (57%); EIMS: *m/z* 495.20 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)-5-nitrofuran-2-carboxamide, 18f**: White solid. Yield 150 mg (51%); EIMS: *m/z* 477.00 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)-5-chlorofuran-2-carboxamide, 18g**: White solid. Yield 126 mg (36%); EIMS: *m/z* 466.18 $[M+H]^+$.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyridin-3-yl) ethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethyloxazole-5-carboxamide, 18h**: White solid. Yield 76 mg (28%); EIMS: *m/z* 461.10 [M+H].

***N*-(2-(Adamantan-1-ylamino)-2-oxo-1-(pyridin-3-yl)ethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethyloxazole-5-carboxamide, 19a**: White solid. Yield90 mg (30%); EIMS: *m/z* 529.10 $[M+H]^+$.

***N*-(2-(Adamantan-1-ylamino)-2-oxo-1-(4-(pyridin-3-yl)phenyl)ethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethyloxazole-5-carboxamide, 19b**: White solid. Yield 66 mg (23%); EIMS: *m/z* 605.20 $[M+H]^+$.

***N*-(2-(Adamantan-1-ylamino)-1-(1*H*-indazol-3-yl)-2-oxoethyl)-*N*-(2,3-dimethylphenyl)-2,4-dimethyloxazole-5-carboxamide, 19c**: White solid. Yield 75 mg (23%); EIMS: *m/z* 567.74 [M+H].

Biology

Antituberculosis activity

This assay has been described in Supporting Information.

Antibacterial activity on ESKAPE pathogen

This assay has been described in the Supporting Information.

Conclusion

In summary, we reported the modification of *α*-aminoacyl amide derivatives against *M. tuberculosis* H37Rv. The 3(2-bromo)pyridyl, 2-nitrofuronyl and 2,4-dimethyloxazole as R_1 substituents of *α*-aminoacyl amide were well tolerated whereas indoline and benzo[*d*]thiazole as R_2 substituents were well tolerated. The 4-pyridinyl phenyl and *1H*-indazole as R_3 substituents of *α*-aminoacyl amide were required for the antituberculosis activity whereas adamantyl was found to be optimal R_4 substituent. Compounds **19b** and **19c** have been identified as potent and selective inhibitors of *M. tuberculosis* H37Rv with MIC 2.5 μM and 2.6 μM respectively. Compounds **19b** and **19c** hold a promise for further development to discover new potent antituberculosis lead.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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References

1 WHO TB report (https://www.who.int/teams/global-tuberculosis-programme/tb-reports).

2 a); Makane VB, Vamshi Krishna E, Karale UB, Babar DA, Kalari S, Rekha EM, Shukla M, Kaul G, Sriram D, Chopra S, Misra S, Rode HB, *Arch Pharm* (Weinheim) 353 (2020) e2000192; b) Kumar V, Patel S, Jain R, *Med Res Rev*, 34 (2017) 1; c) Fernandes G, Chin C M & Santos J L D, *Pharmaceuticals*, 10 (2017) 1; d) Karale UB, Shinde AU, Babar DA, Sangu KG, Vagolu SK, Eruva VK, Jadav SS, Misra S, Dharmarajan S, Rode HB, *Arch Pharm* (Weinheim) 354 (2021) e2000419.

3 Grzegorzewicz A E, Pham H, Gundi V A K B, Scherman M S, North E J, Hess T, Jones V, Gruppo V, Born S E M, Kordulakova J, Chavadi S S, Morisseau C, Lenaerts A J, Lee R E, McNeil M R & Jackson M, *Nat Chem Bio*, 8 (2012) 334.

4 Chatterji M, Shandil R, Manjunatha M R, Solapure S, Ramachandran V, Kumar N, Saralaya R, Panduga V, Reddy J, Prabhakar K R, Sharma S, Sadler C, Cooper C B, Mdluli K, Iyer P S, Narayanan S & Shirude P S, *Chemother*, 58 (2014) 5325.

5 K Ilango, S Arunkumar, *Trop J Pharm Res*, 10 (2011) 219.

6 Jadhav G R, Shaikh M U, Kale R P, Shiradkar M R, Gill C H, *Eur J Med Chem*, 44 (2009) 2930.

7 (a) Toit L C D, Pillay V & Danckwerts M P, *Respir Res*, 7 (2006) 1 ; (b) Panchagnula R, Agrawal S, Ashokraj Y, Varma M, Sateesh K, Bhardwaj V, Bedi S, Gulati I, Parmar J & Kaul C L, Blomberg B, Fourie B, Roscigno G, Wire R, Laing R, Evans P & Moore T, *Meth Find Exp Clin Pharm*, 26 (2004) 703 ; (c) Quy H, Lonnroth K, Lan N T N & Buu T N, *Int J Tuber Lung Dis*, 7 (2003) 1139.

8 Pym A S, Diacon A C, Tang S J, Conradie F, Danilovits M, Chuchottaworn C, Vasilyeva I, Andries K, Bakare N, Marez T D, Haxaire-Theeuwes M, Lounis N, Meyvisch P,

Baelen B Van, Heeswijk R P V & Dannemann B, *Eur Resp J,* 47, (2016) 564.
9 Gler M T, Skripconoka V, Sanchez-Garavito E, Xiao H P, Cabrera-Rivero J L, Vargas-Vasquez J D E, Gao M Q, Awad M, Park S K, Shim T S, Suh G Y, Danilovits M, Ogata H, Kurve A, Chang J, Suzuki K, Tupasi T, Koh W J, Seaworth B, Geiter L J & Wells C D, *N Engl J Med*, 366 (2012) 2151.
10 Andries K, Verhasselt P, Guillemont J, Göhlmann HW, Neefs JM, Winkler H, Van Gestel J, Timmerman P, Zhu M, Lee E, Williams P, de Chaffoy D, Huitric E, Hoffner S, Cambau E, Truffot-Pernot C, Lounis N, Jarlier V, *Science* 307 (2005) 223.
11 Stover C K, Warrener P, Van Devanter D R, Sherman D R, Arain T M, Langhorne M H, Anderson S W, Towell J A, Yuan Y, McMurray D N, Kreiswirth B N, Barry C E & Baker W R, *Nature*, 405 (2000) 962.
12 (a) Fischer J, *Successful Drug Discovery*, (John Wiley & Sons, Wiley-VCH), 2016, p 139.; (b) Gler M T, Skripconoka V, Sanchez-Garavito E, Xiao H P, Cabrera-Rivero J L, Vargas-Vasquez D E, Gao M Q, Awad M, Park S K, Shim T S, Suh G Y, Danilovits M, Ogata H, Kurve A, Chang J, Suzuki K, Tupasi T, Koh W J, Seaworth B, Geiter L J & Wells C D, *New Engl J Med*, 366 (2012) 2151.
13 Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, Shimokawa Y & Komatsu M, *PLoS Med,* 3 (2006) 2131.
14 Kumar V, Patel S & Jain R, *Med Res Rev*, 38 (2018) 684.
15 Lade D M, Krishna V S, Sriram D & Rode H B, *Chem Sel*, 2 (2017) 1250.
16 Grzegorzewicz A E, Pham V A K B & Gundi H, *Nat Chem Biol*, 8 (2012) 334.
17 Cynamon M H, Freites E A & Yeo A E T, *J Antimicro Chem*, 53 (2004) 403.
18 Rao S P S, Lakshminarayana S B, Kondreddi R R, Herve M, Camacho L R, Bifani P, Kalapala S K, Jiricek J, Ma N L, Tan B H, Ng S H, Nanjundappa M, Ravindran S, Seah P G, Thayalan P, Lim S H, Lee B H, Goh A, Barnes W S, Chen Z, Gagaring K, Chatterjee A K, Pethe K, Kuhen K, Walker J, Feng G, Babu S, Zhang L, Blasco F, Beer D, Weaver M, Dartois V, Glynne R, Dick T, Smith P W, Diagana T T & Manjunatha U H, *Sci Trans Med*, 5 (2013) 214.
19 Makarov V, Cole S T & Mollemam U, *WO 2007/134625 Al*, 2007.
20 Makarov V, Manina G & Mikusova K, *Science*, 324 (2009) 801.
21 Pichel C, Pilar E, Velando F & Gonzalez S, *US 2013/0203802 A1*, 2013.
22 Gobis K, Foks H, Serocki M, Augustynowicz-Kopeć E & Napiórkowska A, *Eur J Med Chem,* 89 (2015) 13.
23 Ilango K & Arunkumar S, *Trop J Pharm Res*, 10 (2011) 219.
24 Sirisha K, Achaiah G & Reddy V M, *Rch Pharm (Weinheim)*, 343 (2010) 342.
25 Makane V B, Krishna V S, Shukla M, Mahizhaveni B, Misra Sunil, Chopra S, Sriram D, Dusthackeer V N A & Rode H B, *Eur J Med Chem*, 164 (2019) 665.
26 Han W, Wu J & Dai W-M, *Synlett*, 25 (2014) 2019.
27 Harikrishna K, Balasubramaniam S, Rakshit A & Sing A I, *Indian J Chem Sec B*, 54 (2015) 77.
28 Butani H H, Vachhani D D, Bhoya U C, Shah A K & Eycken E V V D, *Eur J Org Chem*, 2014 (2014) 6634.
29 Modha S G, Kumar A, Vachhani D D, Sharma S K, Parmarb V S & Van Der E V, *Chem Comm*, 48 (2012) 10916.