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Synthesis and Anti-Tubercular (Tb) Evaluation of Bis[4-Ethylidineamino[1,2,4]Triazole-3-Thiol] Tethered by 1,4-Dihydropyridine

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Abstract—A new series of 5,5'-(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis[4-(ethylideneamino)-4*H*-[1,2,4]-triazole-3-thiol) was synthesized via keto-imine condensation. The structural elucidation of the products was investigated by spectral and elemental techniques. Also, the newly synthesized compounds were evaluated for their in vitro anti-tubercular activity, the sensitive and resistant Mycobacterium tuberculosis. Among sixteen tested compounds, compound **(V)** is equipotent to the standard drug isoniazid against sensitive Mycobacterium tuberculosis, while compounds **(IXb)**, **(VIId)**, and **(IIIf)** have promising activity.

Keywords: 1,4-dihydropyridine, bis[1,2,4]triazole, Schiff base, condensation reaction, anti-tubercular activity

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* bacteria that often affect the lung. According to the World Health Organization (WHO), TB is considered one of the top ten causes of death [1]. One-third of the world's population has been exposed to the tuberculosis pathogen [2], and every 15 s, someone dies due to it [3]. In standard therapy, effective antituberculosis drugs are strongly limited to isoniazid, rifampicin, ethambutol, and pyrazinamide (first-line drugs). In the case of resistances, second-line antibiotics are used with low efficacy and tolerability. Therefore, there is an urgent need to develop novel antituberculosis drugs. The Global Alliance for Tuberculosis (GATB) drug development was established to develop more potent and fast-acting anti-TB drugs that will shorten chemotherapy duration from the current 6–8 months to two months or less [4]. The two primary routes to developing a new medication for TB are the synthesis of new derivatives of existing drugs and the searching of novel structures to treat multidrug-resistant TB [5]. To fulfill this goal, we rummaged about heterocyclic rings present in commonly used antituberculosis medications and found that pyridine derivatives are potent and commonly used in antituberculosis medication. It inhibits lipid and DNA synthesis of *M. tuberculosis* resulting in inhibition of cell wall synthesis and development [6]. This mode of action was suggested to be similar to that of isoniazid [7].

Also, many [1, 2, 4]triazole derivatives were found to have anti-tubercular activity [8–12]. Furthermore, the imine linker had played a pivotal role in exertion of the anti-TB activities [13–16]. Inspired by this information, and in continuation of our interests in synthesis of biologically active bis-heterocycles [17–30], we have aimed our research efforts to synthesize a new series of 1,4-dihydropyridine-[1,2,4]triazole hybrid derivatives, with imine linkers, and evaluate their activities against sensitive and resistant *M. tuberculosis*.

RESULTS AND DISCUSSION

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis[4-(ethylideneamino)-4*H*-[1,2,4]-triazole-

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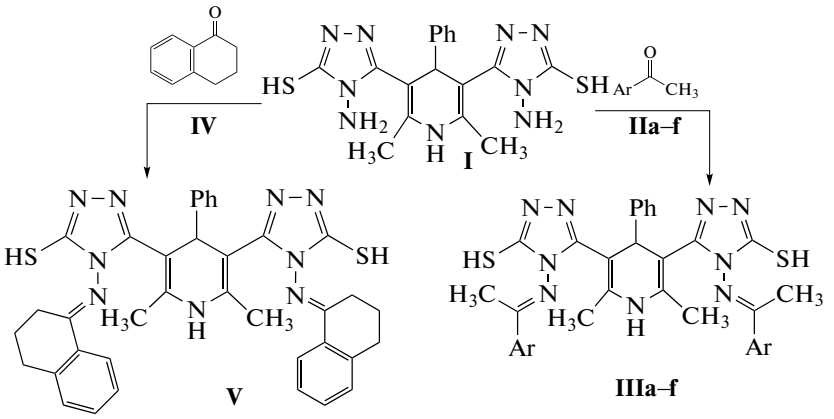
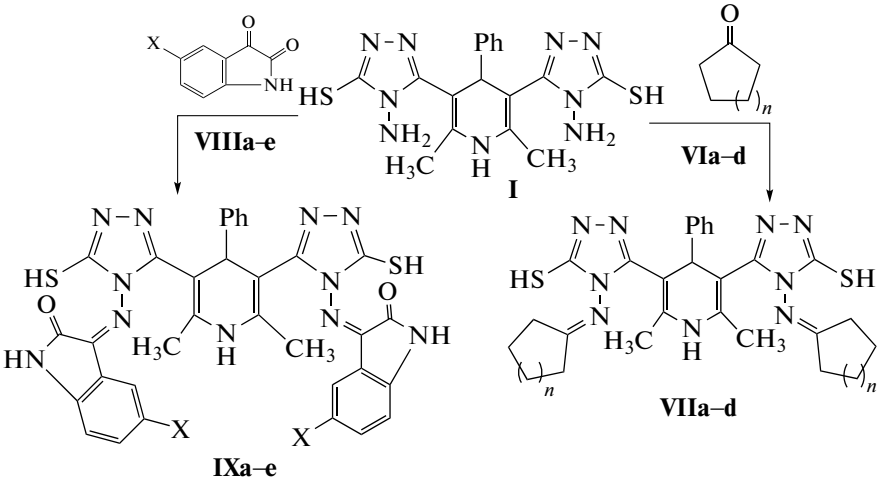
3-thiol) were prepared following the synthetic route described in Schemes 1 and 2. Condensation of 5,5'-(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-amino-4*H*-[1,2,4]triazole-3-thiol) (**I**) [31] with the substituted acetophenones (**IIa**–**f**), 3,4-dihydronaphthalen-1(2*H*)-one (**IV**), cycloalkanones (**VIa**–**d**) and substituted indoline-2,3-dione (**VIIIa**–**e**) (1 : 2 molar ratio) in acetic acid under refluxing condition (Schemes 1, 2) provided the respective bis-keto-imines (**IIIa**–**f**), (**V**), (**VIIa**–**d**) and (**IXa**–**e**).



No.	Ar
IIa, **IIIa**	C_6H_5
IIb, **IIIb**	4-ClC_6H_4
IIc, **IIIc**	4-BrC_6H_4
IId, **IIId**	4-$CH_3C_6H_4$
IIe, **IIIe**	4-$CH_3OC_6H_4$
IIf, **IIIf**	4-$NO_2C_6H_4$

Scheme 1. Synthesis of Schiff bases (**IIIa**–**f**) and (**V**).



No.	x
VIIIa, **IXa**	H
VIIIb, **IXb**	CH_3
VIIIc, **IXc**	OCH_3
VIIId, **IXd**	Cl
VIIIe, **IXe**	NO_2

VIa, **VIIa**	$n = 1$
VIb, **VIIb**	$n = 2$
VIc, **VIIc**	$n = 3$
VId, **VIId**	$n = 4$

Scheme 2. Synthesis of Schiff bases (**VIIa**–**d**) and (**IXa**–**e**).

The chemical structure of the target compounds was established based on IR, ^{1}H NMR, ^{13}C NMR, and MS spectra. For example, The IR spectra of Schiff bases showed the presence of (N–H) band near 3200 cm^{-1} and (C=N) functional groups at 1601–1580 cm^{-1}. Their ^{1}H NMR spectra indicated the presence of a broad singlet of pyridine (N–H) at δ = 8.57–8.99 ppm (exchangeable with D_2O) [32] and thiol protons at δ = 11.27–12.52 ppm [33]. The formation of the Schiff bases is also confirmed by the observed imine carbon (N=C) at δ = 161.6–163.8 ppm in the ^{13}C NMR spectra. The mass spectra showed their molecular ion peaks at the expected *m/z* values (see Experimental Section).

In-Vitro Anti-Mycobacterial Assay against Mycobacterium tuberculosis

In-vitro anti-tubercular activity of the synthesized compounds against *M. tuberculosis* strains (ATCC 27294 and ATCC 35823) was evaluated using the Microplate Alamar Blue Assay (MABA) [34]. Isoniazid (INH) was used as a reference drug and the results were presented in (Table 1, and Figs. 1, 2).

As illustrated in Table 1, Figs. 1 and 2 the majority of bis-[4-ethylidineamino [1, 2, 4] triazole-3-thioles] exhibited promising activity against *M. tuberculosis* strains. In particular, compound (**V**) showed comparable activities against ATCC 27294 strain similar to the first line anti-TB agent (isoniazid). Correlating the anti-TB activity with the structure of the tested compounds revealed the following findings.

Considering the MIC values of the tested samples (**IIIa–f**), with substituents (H, Cl, Br, Me, OMe, and NO_2) at the *para*-position of the phenyl ring, reveals that the compound (**IIIf**) (4-nitro group) was found to be the most active against two strains [MIC = 0.98 and 3.9]. These results indicated that, presence of strong electron-withdrawing group at para position increases the inhibition activity.

Comparison of the MIC of compound (**VIId**) (cyclooctyl) with (**VIIa**) (cyclopentyl), (**VIIb**) (cyclohexyl), and (**VIIc**) (cycloheptyl) indicates that the existence of the cyclooctyl ring is effective in increasing anti-tubercular activity [MIC = 0.48 and 1.95].

Analysis of MIC values of compounds (**IXa–e**) has revealed that, the compound (**IXb**) (containing methyl group at position 5 in the indole ring) has marked potency to inhibit in-vitro growth of Mycobacterium tuberculosis strains [MIC = 0.24 and 0.98].

Biological Activity

In vitro anti-mycobacterial evaluation. The in vitro anti-mycobacterial activity of the synthesized compounds was carried out against *M. tuberculosis* (ATCC 27294 and ATCC 35823) at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt. The details of this technique were described as reported methods [35, 36].

EXPERIMENTAL

All melting points were measured on the Electrothermal IA 9000 series digital melting point apparatus. The IR spectra were recorded in potassium bromide discs on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were measured in deuterated dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses and the biological evaluation of the products were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F254, Merck). 5,5'-(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiol) (**I**) [31] was prepared as reported in the literature.

Synthesis of 5,5'-(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis[4-(ethylidene amino)-4*H*-[1, 2, 4]-triazole-3-thiol) (IIIa–f, V, VIIa–d, and IXa–e). A mixture of compound **1** (0.413 g, 1 mmol) and substituted acetophenones (**IIa–f**), 3,4-dihydronaphthalen-1(2*H*)-one (**IV**), cycloalkanones (**VIa–d**) and substituted indoline-2,3-dione (**VIIIa–e**) (2 mmol) in glacial acetic acid (20 mL) was heated under reflux for 6 h. TLC monitored the completion of the reaction. Excess solvent was removed under reduced pressure and the reaction mixture was poured in a beaker containing crushed ice. The precipitated solid product that formed was filtered off, washed with water, dried, and recrystallized from ethanol to give the target compounds (**IIIa–f**), (**5**), (**VIIa–d**), and (**IXa–e**).

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis[(4-(1-phenylethylidene)amino)-4H-1,2,4-triazole-3-thiol)] (IIIa). Yellow crystal, (63%), mp: 153–155°C; IR (KBr) ν = 3341 (2 SH), 3238 (NH), 3089, 3062, 2976 (CH), 1601 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.84 (s, 6H, 2 CH_3), 2.26 (s, 6H, 2 CH_3), 4.87 (s, 1H, pyridine–H), 7.08–7.23 (m, 15H, Ar–H), 8.79 (s, 1H, NH), 12.28 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3 (imine-CH3), 16,4 (pyridine–CH_3), 62.0 (pyridine–CH), 110.8, 115.3, 118.5, 120.3, 122.5, 126.9, 129.2, 131.8, 135.5, 142.3, 146.2, 157.2 (Ar–C), 161.7 (N=C) ppm; MS, *m/z* (%) 618 (M^+, 37), 523 (55), 423 (11), 395 (17), 367 (19), 317 (29), 252 (51), 171 (22), 129 (22), 105 (23), 83 (45), 71 (54), 57 (100); Anal. calcd. for $C_{33}H_{31}N_9S_2$ (617.21), %: C, 64.16; H, 5.06; N, 20.41; S, 10.38. Found, %: C, 64.45; H, 4.76; N, 20.11; S, 10.27.

Table 1. The anti-tubercular activity as MICS (μg/mL) of tested samples against sensitive *Mycobacterium tuberculosis*

Compounds	MIC (μg/mL) against ATCC 27294	MIC (μg/mL) against ATCC 35823
Isoniazid (INH)	0.12	0.12
(IIIa)	31.25	NA
(IIIb)	62.5	NA
(IIIc)	3.9	15.63
(IIId)	7.81	31.25
(IIIe)	125	NA
(IIIf)	0.98	3.9
(V)	0.12	0.98
(VIIa)	NA	NA
(VIIb)	1.95	7.81
(VIIc)	31.25	125
(VIId)	0.48	1.95
(IXa)	125	NA
(IXb)	0.24	0.98
(IXc)	15.63	125
(IXd)	7.81	31.25
(IXe)	31.25	62.5

ATCC: American Type Culture Collection.
NA: No activity.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(1-(4-chlorophenyl) ethylidene)amino)-4*H*-1,2,4-triazole-3-thiol) (IIIb). Orang bowder, (70%), mp: 171–172°C; IR (KBr) ν = 3341 (2 SH), 3240 (NH), 3090, 3063, 2976 (CH), 1598 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.80 (s, 6H, 2 CH3), 2.27 (s, 6H, 2 CH_3), 4.87 (s, 1H, pyridine–H), 7.07–7.22 (m, 13H, Ar–H), 8.79 (s, 1H, NH), 12.22 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1 (imine–CH_3), 16,7 (pyridine–CH_3), 61.8 (pyridine–CH), 110.7, 118.5, 120.1, 122.5, 127.3, 129.1, 131.8, 134.5, 135.5, 142.2, 146.9, 157.7 (Ar–C), 161.6 (N=C) ppm; MS, *m/z* (%) 686 (M^+, 17), 577 (72), 545 (25), 509 (44), 492 (26), 437 (78), 398 (51), 368 (66), 339 (49)291 (85), 267 (34), 252 (38), 185 (32), 137 (34), 97 (34), 73 (37), 60 (34), 57 (100); Anal. calcd. for $C_{33}H_{29}Cl_2N_9S_2$ (685.14), %: C, 57.72; H, 4.26; N, 18.36; S, 9.34. Found, %: C, 57.99; H, 3.96; N, 18.04, S, 9.12.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(1-(4-bromophenyl) ethylideneamino)-4*H*-1,2,4-triazole-3-thiol) (IIIc). Orang crystal, (66%), mp: 165–166°C; IR (KBr) ν = 3342 (2 SH), 3242 (NH), 3088, 2977 (CH), 1599 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.90 (s, 6H, 2 CH_3), 2.28 (s, 6H, 2 CH_3), 4.86 (s, 1H, pyridine–H), 7.08–8.00 (m, 13H, Ar–H), 8.79 (s, 1H, NH), 11.92 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1 (imine–CH_3), 16,2 (pyridine–CH_3), 60.9 (pyridine–CH), 115.2, 118.5, 121.3, 122.5, 126.9, 129.1, 131.6, 133.9, 135.5, 142.3, 146.2, 157.1 (Ar–C), 162.4 (N=C) ppm; MS, *m/z* (%) 775 (M^+, 30), 734 (73), 684 (100), 617 (85), 599 (56), 518 (66), 482 (55), 422 (64), 340 (71), 71 (60); Anal. calcd. for $C_{33}H_{29}Br_2N_9S_2$ (773.04), %: C, 51.10; H, 3.77; N, 16.25; S, 8.27. Found, %: C, 51.31; H, 3.65; N, 16.00; S, 7.99.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(1-(4-methylphenyl) ethylideneamino)-

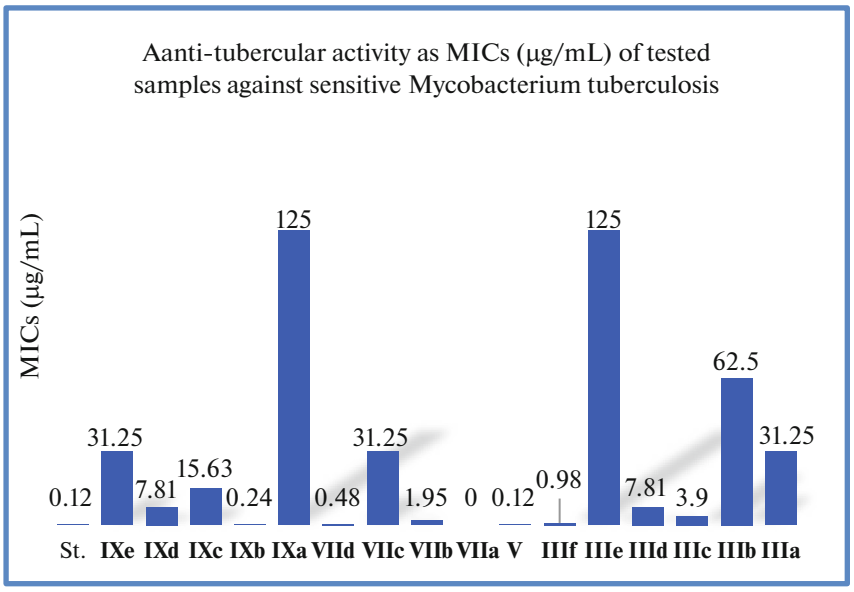


Fig. 1. The anti-tubercular activity of tested samples against sensitive *Mycobacterium tuberculosis* (ATCC 27294).

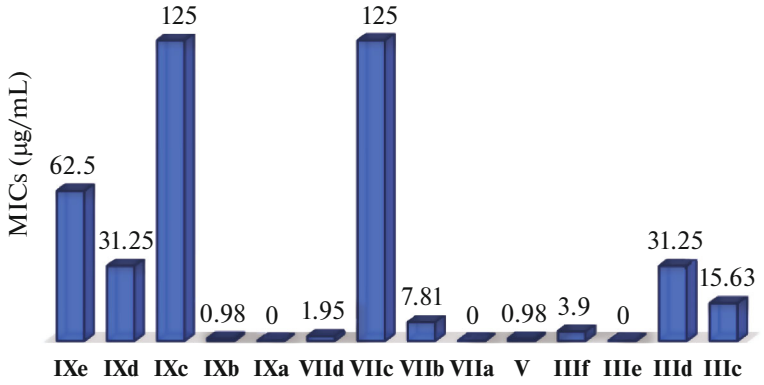


Fig. 2. The anti-tubercular activity of tested samples against resistance *Mycobacterium tuberculosis* (ATCC 35823).

4*H*-1,2,4-triazole-3-thiol) (IIId). Yellow crystal, (65%), mp: 159–160°C; IR (KBr) ν = 3341 (2 SH), 3238 (NH), 3088, 3062, 2976 (CH), 1599 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.92 (s, 6H, 2 CH_3), 2.29 (s, 6H, 2 CH_3), 2.43 (s, 6H, 2 CH_3), 4.86 (s, 1H, pyridine–H), 7.08–7.29 (m, 13H, Ar–H), 8.80 (s, 1H, NH), 12.52 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.2 (imine–CH_3), 16.1 (pyridine–CH_3), 24.7 (Ar–CH_3), 66.4 (pyridine–CH), 116.3, 118.4, 121.3, 122.5, 125.9, 128.8, 130.8, 131.5, 134.5, 142.3, 146.2, 157.6 (Ar–C), 163.4 (N=C) ppm; MS, *m/z* (%) 645 (M^+, 31), 520 (30), 455 (29), 367 (50), 284 (80), 252 (100), 224 (20), 167 (40), 105 (35), 67 (44); Anal. calcd. for $C_{35}H_{35}N_9S_2$ (645.25), %: C, 65.09; H, 5.46; N, 19.52; S, 9.93. Found, %: C, 65.25; H, 5.25; N, 19.31; S, 10.01.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(1-(4-methoxyphenyl) ethylideneamino)-4*H*-1,2,4-triazole-3-thiol) (IIIe). Reddish yellow crystal, (69%), mp: 148–150°C; IR (KBr) ν = 3343 (2 SH), 3240 (NH), 3090, 3063, 2977 (CH), 1600 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.87 (s, 6H, 2 CH_3), 2.32 (s, 6H, 2 CH_3), 3.33 (s, 6H, 2 OCH_3), 4.86 (s, 1H, pyridine–H), 7.09–8.11 (m, 13H, Ar–H), 8.79 (s, 1H, NH) 11.55 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.2 (imine–CH_3), 16,3 (pyridine–CH_3), 59.4 (Ar–OCH_3), 66.3 (pyridine–CH), 115.3, 119.4, 121.3, 122.5, 125.9, 127.8, 130.8, 131.4, 133.5, 142.3, 146.2, 157.6 (Ar–C), 163.8 (N=C) ppm; MS, *m/z* (%) 677 (M^+, 21), 591 (27), 522 (44), 493 (56), 424 (56), 387 (43), 343 (65), 317 (58), 291 (40), 222 (48), 185 (91), 105 (95), 57 (100); Anal. calcd. for $C_{35}H_{35}N_9O_2S_2$ (677.24), %: C, 62.02; H, 5.20; N, 18.60; S, 9.46. Found, % C, 62.24; H, 4.98; N, 18.40; S, 9.60.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(1-(4-nitrophenyl) ethylideneamino)-4*H*-1,2,4-triazole-3-thiol) (IIIf). Yellow powder, (78%), mp: 175–176°C; IR (KBr) ν = 3344 (2 SH), 3241 (NH), 3088, 2977 (CH), 1603 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.93 (s, 6H, 2 CH_3), 2.33 (s, 6H, 2 CH_3), 4.88 (s, 1H, pyridine–H), 7.13–7.89 (m, 13H, Ar–H), 8.90 (s, 1H, NH), 12.44 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1 (imine–CH_3), 16,7 (pyridine–CH_3), 61.9 (pyridine–CH), 119.5, 120.1, 122.5, 127.3, 129.1, 131.8, 134.5, 135.5, 136.8, 142.7, 146.9, 158.1 (Ar–C), 162.6 (N=C) ppm; MS, *m/z* (%) 708 (M^+, 36), 649 (31), 593 (50), 468 (38), 387 (100), 267 (33), 178 (47), 122 (42), 73 (66); Anal. calcd. for $C_{33}H_{29}N_{11}O_4S_2$ (707.18), %: C, 56.00; H, 4.13; N, 21.77; S, 9.06. Found, %: C, 56.18; H, 3.97; N, 21.59; S, 8.89.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-((-3,4-dihydronaphthalen-1(2*H*)-ylidene)-amino)-4*H*-1,2,4-triazole-3-thiol) (V). Umber crystal, (70%), mp: 200–201°C; IR (KBr) ν = 3340 (2 SH), 3239 (NH), 3063, 2977 (CH), 1598 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.51 (m, 4H, 2 CH_2), 2.11 (s, 6H, 2 CH_3), 2.44 (t, 4H, 2 CH_2), 3.34 (t, 4H, 2 CH_2), 4.87 (s, 1H, pyridine–H), 7.09–7.22 (m, 13H, Ar–H), 8.79 (s, 1H, NH), 12.43 (s,2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.2 (pyridine–CH_3), 22.4, 25.3, 27.1 (CH_2), 66.8 (pyridine–CH), 114.6, 120.8, 124.6, 125.9, 127.2, 129.7, 130.0, 131.0, 132.7, 133.6, 135.9, 139.4, 142.5 146.8 (Ar–C), 162.8 (C=N) ppm; MS, *m/z* (%) 670 (M+, 37), 590 (35), 519 (34), 443 (46), 390 (66), 314 (27), 272 (46), 252 (88), 190 (55), 97 (36), 85 (42), 57 (100); Anal. calcd. for $C_{37}H_{35}N_9S_2$ (669.25), %: C, 66.34; H, 5.27; N, 18.82; S, 9.57. Found, %: C, 66.55; H, 5.09; N, 18.65; S, 9.45.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(cyclopentylideneamino)-4*H*-1,2,4-triazole-3-thiol) (VIIa). Yellow crystal, (74%), mp: 184–185°C; IR (KBr) ν = 3342 (2 SH), 3230 (NH), 3087, 2978 (CH), 1599 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.11–1.15 (m, 8H, 4 CH_2), 2.11–2.43 (m, 8H, 4 CH_2), 2.33 (s, 6H, 2 CH_3), 4.88 (s, 1H, pyridine–H), 7.21–8.17 (m, 5H, Ar–H), 8.79 (s, 1H,

NH), 11.61 (s, 2H, 2 SH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.5 (pyridine–CH_3), 25.9, 32.1 (CH_2), 66.7 (pyridine–CH), 110.4, 117.4, 126.6, 128.3, 130.3, 132.5, 139.0, 143.5 (Ar–C), 163.4 (C=N) ppm; MS, *m/z* (%) 545 (M^+, 41), 506 (53), 470 (31), 402 (54), 390 (44), 322 (66), 282 (77), 184 (68), 105 (55), 71 (66), 57 (100); Anal. calcd for $C_{27}H_{31}N_9S_2$ (545.21), %: C, 59.42; H, 5.73; N, 23.10; S, 11.75. Found, %: C, 59.65; H, 5.58; N, 22.91; S, 11.64.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(cyclohexylideneamino)-4*H*-1,2,4-triazole-3-thiol) (VIIb). Yellow solid, (72%), mp: 189–190°C; IR (KBr) ν = 3341 (2 SH), 3241 (NH), 3088, 2978 (CH), 1601 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.42–1.68 (m, 12H, 6 CH_2), 2.23–2.26 (m, 8H, 4 CH_2), 2.31 (s, 6H, 2 CH_3), 4.80 (s, 1H, pyridine–H), 7.23–8.12 (m, 5H, Ar–H), 8.70 (s, 1H, NH), 11.57 (s, 2H, 2 SH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.3 (pyridine–CH_3), 25.9, 28.9, 32.1 (CH_2), 65.7 (pyridine–CH), 114.4, 117.4, 126.7, 128.3, 130.4, 132.5, 139.2, 142.9 (Ar–C), 162.9 (C=N) ppm; MS, *m/z* (%) 573 (M^+, 56), 445 (42), 390 (47), 259 (27), 185 (38), 97 (38), 69 (60), 57 (100); Anal. calcd. for $C_{29}H_{35}N_9S_2$ (573.25), %: C, 60.71; H, 6.15; N, 21.97; S, 11.17. Found, %: C, 60.58; H, 5.94; N, 21.76; S, 11.03.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(cycloheptylideneamino)-4*H*-1,2,4-triazole-3-thiol) (VIIc). Orange crystal, (74%), mp: 160–161°C; IR (KBr) ν = 3339 (2 SH), 3240 (NH), 3089, 2977 (CH), 1600 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.60–1.66 (m, 8H, 4 CH_2), 1.70–1.75 (m, 8H, 4 CH_2), 2.17–2.22 (m, 8H, 4 CH_2), 2.26 (s, 6H, 2 CH_3), 4.86 (s, 1H, pyridine–H), 7.11–8.17 (m, 5H, Ar–H), 8.99 (s, 1H, NH), 12.00 (s, 2H, 2 SH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.6 (pyridine–CH3), 25.7, 28.9, 32.1 (CH2), 66.7 (pyridine–CH), 115.4, 118.4, 120.5, 125.7, 128.3, 130.4, 132.5, 139.2, 142.8 (Ar–C), 163.6 (C=N) ppm; MS, *m/z* (%) 602 (M+, 28), 530 (100), 422 (27), 310 (26), 208 (36), 182 (64), 138 (37); Anal. calcd. for $C_{31}H_{39}N_9S_2$ (601.28), %: C, 61.87; H, 6.53; N, 20.95; S, 10.65. Found, %: C, 62.01; H, 6.32; N, 20.76; S, 10.48.

5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(4-(cyclooctylideneamino)-4*H*-1,2,4-triazole-3-thiol) (VIId). Yellow powder (81%), mp: 195–196°C; IR (KBr) ν = 3344 (2 SH), 3242 (NH), 3064, 2977 (CH), 1601 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.32–1.38 (m, 12H, 6 CH_2), 1.50–1.58 (m, 8H, 4 CH_2), 2.11–2.22 (m, 8H, 4 CH_2), 2.34 (s, 6H, 2 CH_3), 4.86 (s, 1H, pyridine–H), 7.21–8.17 (m, 5H, Ar–H), 8.90 (s, 1H, NH), 11.89 (s, 2H, 2 SH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.4 (pyridine–CH_3), 25.9, 26.3, 28.9, 32.1 (CH2), 66.7 (pyridine–CH), 110.4, 114.4, 119.4, 126.7, 128.3, 130.4, 132.5, 139.2, 142.9 (Ar–C), 162.8 (C=N) ppm; MS, *m/z* (%) 630 (M+, 33), 589 (33), 522 (47), 451 (76), 368 (88), 290 (39), 171 (32), 97 (36), 73 (48), 57 (100); Anal. calcd. for $C_{33}H_{43}N_9S_2$ (629.31), %: C, 62.93; H, 6.88; N, 20.01; S, 10.18. Found, %: C, 63.15; H, 6.68; N, 19.88; S, 10.05.

3,3'-(((2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(5-mercapto-4*H*-1,2,4-triazole-3,4-diyl))-bis(azanylylidene))bis(indolin-2-one) (IXa). Red crystal, (61%), mp: 130–131°C; IR (KBr) ν = 3481 (2 SH), 3343 (2 NH), 3210 (NH), 3066, 2970 (CH), 1648 (2 C=O), 1599 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.20 (s, 6H, 2 CH_3), 3.70 (s, 1H, pyridine–H), 7.03–7.93 (m, 13H, Ar–H), 8.57 (s, 1H, NH), 11.83 (s, 2H, 2 NH), 12.07 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.8 (pyridine–CH_3), 48.4 (pyridine–CH), 103.7, 112.5, 121.3, 132.7, 132.8, 133.9, 134.3, 136.9, 137.5, 139.6, 140.8, 141.9, 142.0, 146.9 (Ar–C), 162.8 (C=N), 179.4 (2 C=O) ppm; MS, *m/z* (%) 671 (M^+, 64), 249 (44), 64 (100); Anal. calcd. for $C_{33}H_{25}N_{11}O_2S_2$ (671.16), %: C, 59.00; H, 3.75; N, 22.94; S, 9.55. Found, %: C, 59.12; H, 3.63; N, 22.72; S, 9.36.

3,3'-(((2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(5-mercapto-4*H*-1,2,4-triazole-3,4-diyl))-bis(azanylylidene))bis(5-methylindolin-2-one) (IXb). Red powder, (75%), mp: 140–142°C; IR (KBr) ν = 3431 (2 SH), 3345 (2 NH), 3220 (NH), 3099, 2976 (CH), 1685 (C=O), 1598 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.28 (s, 6H, 2 CH_3), 2.36 (s, 6H, 2 CH_3), 4.86 (s, 1H, pyridine–H), 6.78–7.29 (m, 11H, Ar–H), 8.79 (s, 1H, NH), 11.02 (s, 2H, 2 NH), 11.27 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.7 (pyridine–CH_3), 32.2 (Ar–CH_3), 49.1 (pyridine–CH), 108.7, 112.4, 125.3, 132.7, 132.8, 133.9, 134.2, 136.9, 137.7, 139.6, 140.8, 141.8, 142.0, 146.9 (Ar–C), 162.7 (C=N), 179.4 (2 C=O) ppm; MS, *m/z* (%) 700 (M+, 47), 681 (38), 581 (39), 466 (52), 392 (31), 292 (73), 155 (68), 97 (26), 60 (38), 57 (100); Anal. calcd. for $C_{35}H_{29}N_{11}O_2S_2$ (699.19), %: C, 60.07; H, 4.18; N, 22.02; S, 9.16. Found, %: C, 60.25; H, 4.35; N, 21.94; S, 8.99.

3,3'-(((2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(5-mercapto-4*H*-1,2,4-triazole-3,4-diyl))-bis(azanylylidene))bis(5-methoxyindolin-2-one) (IXc). Browen crystal, (65%), mp: 139–140°C; IR (KBr) ν = 3428 (2 SH), 3343 (2 NH), 3221 (NH), 3069, 2975 (CH), 1686 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.29 (s, 6H, 2 CH_3), 3.33 (s, 6H, 2 OCH_3), 4.89 (s, 1H, pyridine–H), 6.72–7.30 (m, 11H, Ar–H), 8.80 (s, 1H, NH), 11.01 (s, 2H, 2 NH), 11.30 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.7 (pyridine–CH_3), 49.8 (pyridine–CH), 62.2 (Ar–OCH_3), 110.7, 114.4, 124.3, 128.7, 130.8, 132.9, 134.2, 136.9, 138.7, 139.6, 140.8, 142.8, 144.1, 146.9 (Ar–C), 162.6 (C=N), 179.8 (2 C=O) ppm; MS, *m/z* (%) 732 (M^+, 29), 674 (54), 638

(100), 580 (77), 551 (56), 436 (52), 371 (56), 215 (65), 169 (65); Anal. calcd. for $C_{35}H_{29}N_{11}O_4S_2$ (731.18), %: C, 57.44; H, 3.99; N, 21.05; S, 8.76. Found, %: C, 57.65; H, 3.74; N, 20.96; S, 8.59.

3,3'-(5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(3-mercapto-4H-1,2,4-triazole-5,4-diyl))bis(azanylylidene)bis(5-chloroindolin-2-one) (IXd). Light brown crystal, (63%), mp: 148–150°C; IR (KBr) ν = 3483 (2 SH), 3345 (2 NH), 3225 (NH), 3077, 2974 (CH), 1689 (C=O), 1598 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.13 (s, 6H, 2 CH_3), 4.50 (s, 1H, pyridine–H), 7.15–7.35 (m, 11H, Ar–H), 8.74 (s, 1H, NH), 11.11 (s, 2H, 2 NH), 12.20 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.9 (pyridine–CH_3), 51.4 (pyridine–CH), 108.7, 118.5, 122.3, 128.7, 130.8, 132.9, 134.3, 136.8, 137.5, 138.8, 140.2, 141.6, 142.6, 146.8 (Ar–C), 162.7 (C=N), 179.2 (2 C=O) ppm; MS, *m/z* (%) 740 (M^+, 22), 610 (38), 571 (31), 536 (25), 475 (100), 385 (40), 360 (43), 256 (88), 231 (77), 160 (56), 78 (49); Anal. calcd. for $C_{33}H_{23}C_{l2}N_{11}O_2S_2$ (739.09), %: C, 53.52; H, 3.13; N, 20.80; S, 8.66. Found, %: C, 53.70; H, 2.97; N, 20.72; S, 8.45.

3,3'-(5,5'-(2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(3-mercapto-4*H*-1,2,4-triazole-5,4-diyl))bis(azanylylidene)bis(5-nitroindolin-2-one) (IXe). Red crystal, (68%), mp: 135–137°C; IR (KBr) ν = 3483 (2 SH), 3367, 3343 (2 NH), 3226 (NH), 3068, 2975 (CH), 1688 (C=O), 1601 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.26 (s, 6H, 2 CH_3), 4.48 (s, 1H, pyridine–H), 6.99–8.20 (m, 11H, Ar–H), 8.80 (s, 1H, NH), 11.07 (s, 2H, 2 NH), 11.33 (s, 2H, 2 SH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.2 (pyridine–CH_3), 52.4 (pyridine–CH), 110.7, 118.5, 122.3, 125.7, 129.8, 131.9, 133.8, 136.7, 137.6, 138.8, 140.8, 142.6, 144.6, 146.9 (Ar–C), 162.8 (C=N), 178.2 (2 C=O) ppm; MS, *m/z* (%) 762 (M^+, 29), 636 (32), 550 (43), 480 (49), 393 (41), 279 (72), 198 (58), 83 (50), 69 (64), 57 (100); Anal. calcd. for $C_{33}H_{23}N_{13}O_6S_2$ (761.13), %: C, 52.03; H, 3.04; N, 23.90; S, 8.42. Found, %: C, 52.15; H, 2.87; N, 23.80; S, 8.64.

CONCLUSIONS

In this research, a new series of 1,4-dihydropyridine-1,2,4-triazole hybrid derivatives were prepared, characterized, and evaluated as potential anti-tubercular agents against Mycobacterium tuberculosis strains. Two dihydropyridine-triazole hybrids, (**V**) and (**IXb**), were identified as the most active of this series against the two tested strains. Especially, compound 5 displays equal activity to isoniazid.

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COMPLIANCE WITH ETHICAL STANDARDS

This article doesnot contain any studies involving human participants performed by any of the authors and doesnot contain any studies involving animals performed by any of the author.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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