INTERNATIONAL JOURNAL OF LATEST TECHNOLOGY IN ENGINEERING, MANAGEMENT & APPLIED SCIENCE (IJLTEMAS)

ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue XI, November 2025

Synthesis and Molecular Docking Studies of Pyrazolylpyrazoline-Clubbed Triazole and Tetrazoles.

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DOI: https://doi.org/10.51583/IJLTEMAS.2025.1411000025

Received: 21 November 2025; Accepted: 28 November 2025; Published: 03 December 2025

ABSTRACT:

To increase the antitubercular potency, we synthesized a series of novel pyrazolylpyrazoline derivatives (9a−n) using the one-pot multi component reaction of the substituted hetero aryl aldehyde (3a,b), 2-acetyl pyrrole/thiazole (4a,b),and substituted hydrazine hydrates(5−8) in the presence of base KOH as a catalyst in ethanol as the solvent at room temperature. Substituted hetero aryl aldehyde (3a,b) was synthesized from 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4 methyl-carbaldehyde by treatment with 4-amino triazole/5-amino tetrazole. 5-Chloro-4-(1,3-dioxolan-2-yl)-3-methyl-1-phenyl-1*H*-pyrazole (**1**) was reacted with 4*H*-1,2,4-triazol-4-amine (**a**) and 1*H*-tetrazol-5-amine (**b**) in the presence of K_2CO_3 in 1,4-dioxane at 80 °C for 13 h. Similarly, 5-((4*H*-1,2,4-triazol-4-yl)amino)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3a**) and 5-((1*H*-tetrazol-5-yl)amino)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3b**) were achieved further reacted with 2-acetyle thiophene (**4a**) and 2-acetyle furan (**4b**) and substituted hydrazide derivatives (**5**–**8**) in the presence of 50% ethanolic KOH solution at room temperature All of the compounds were tested against Mycobacteriumtuberculosis H37Rv, Theoretical results were in good accord with the observed experimental values. The docking score of the most active compound 9n was found good Glide energy .

Key Words: K_2CO_3 in 1,4-dioxane, Pyrazolylpyrazoline

INTRODUCTION:

According to the World Health Organization, 10 million new cases of tuberculosis were reported worldwide with 5.6 million men, 3.3 million women, and 1.1 million children.[1] Tuberculosis is the 13th leading cause of death and the second leading infectious killer. Tuberculosis predominantly triggered by *Mycobacterium tuberculosis* is one of the leading causes of human morbidity and mortality universally. Rifampicin, isoniazid, and ethambutol are the most effective drugs against tuberculosis that are available in the market, but bacteria have started developing resistance to these drugs, and it is a major public health concern in many countries for a couple of years. Nearly 6% of patients with tuberculosis have multidrug-resistant tuberculosis in the world, but in some areas, like Ukraine, Moldova, Kazakhstan, and Kyrgyzstan, this ratio increases up to 25%. Treatment for patients with multidrug-resistant tuberculosis is long, and patients with multidrug-resistant tuberculosis have less favorable outcomes than those treated for drug-susceptible tuberculosis. (2) The increasing occurrence of extensively drug-resistant (XDR)-TB coinfection with HIV and multidrug-resistant (MDR)-TB has driven the new tubercular drug discovery. Therefore it is an urgent need to develop antitubercular agents with a novel mechanism of action and potent biological activity against the drug-resistant tuberculosis strain.

In recent years, there has been endless interest in the exploration of novel pyrazole-clubbed pyrazoline moieties. A variety of modifications have been made to the pyrazole and pyrazoline moiety to boost its pharmacological effect because pyrazole–pyrazoline derivatives are widely studied for broad-spectrum biological activities. (3−12) The pyrazoline derivatives are widely used as anticancer, (13) antibacterial, antifungal, (14) antitubercular, (15) antimalarial, (16) anti-inflammatory, (17) etc. The chemistry of triazole- and tetrazole-fused heterocyclic derivatives has gathered a lot of attention in recent years due to their synthetic and biological importance. 1,2,4-Triazoles and their fused heterocyclic derivatives have been reported to possess a wide range of bioactivities such as

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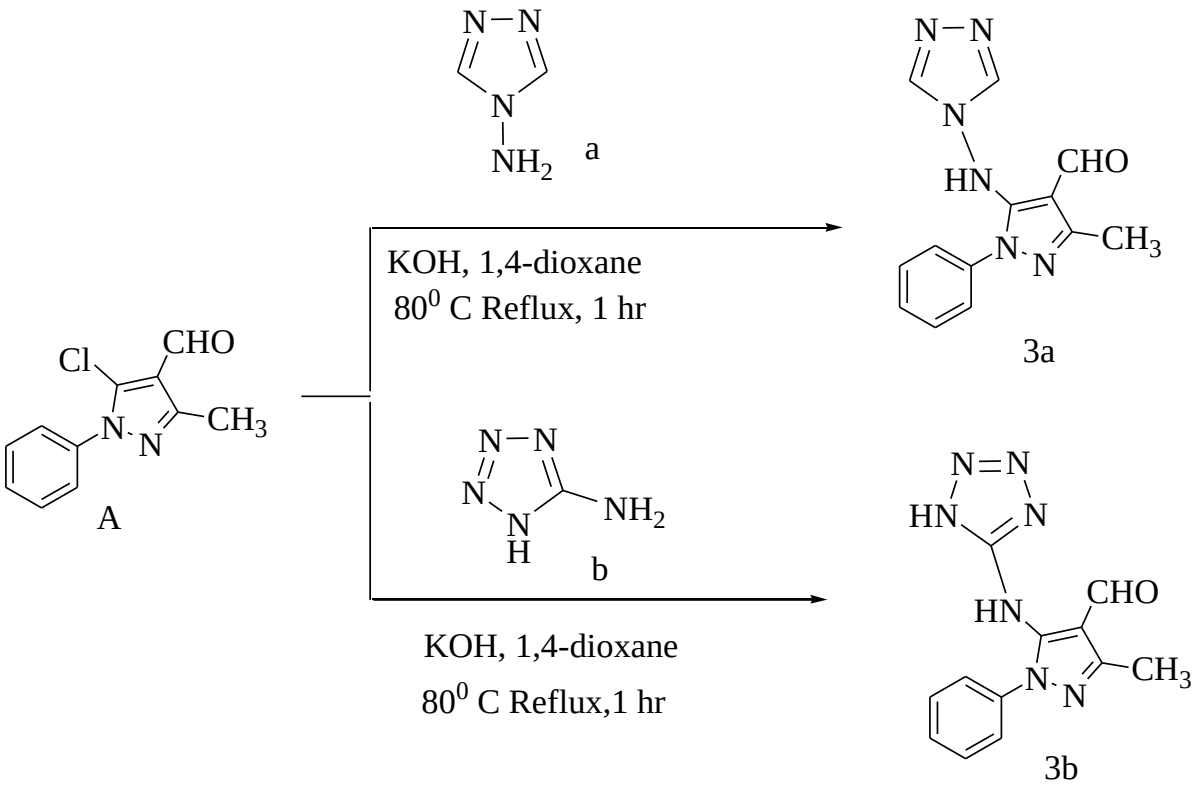
neuroprotectant, (18) antioxidant, (19) antimalarial, (20) antileishmanial, (21) antiurease, (22) anticonvulsant, (23) and antiviral. (24) Tetrazole is a carboxylic acid bio isostere that can be used to substitute the carboxyl group in therapeutic molecules to improve lipophilicity, bioavailability, and side effects. Tetrazole can interact noncovalently with a variety of enzymes and receptors in organisms, resulting in anticancer, (25) antifungal, (26) antitubercular, and antimalarial (27) effects. Figure 1 illustrates commercially available pharmaceuticals active ingratiates with pyrazole and pyrazoline analogues. To improve antitubercular activity, our research work focused on the synthesis of certain novel structural hybrids of pyrazole–pyrazoline clubbed with triazole and tetrazole pharmacophores in a single molecular framework. We synthesized scaffolds (**9a**–**n**) by incorporating the pharmacophores feature of isoniazid (antitubercular), fezolamine (antidepressant), and dipyrone (anti-inflammatory) in quest of novel heterocycles with good potency against drug-resistant tuberculosis. The structure–activity relationship (SAR) of the various pharmacophores was taken into account when designing the targeted compounds (**9a**–**p**; Figure 1). By altering the nitrogen atom and cyclization reaction of the side chain of the isoniazid drug, modification of the side chain of the dipyrone drug by adding the five-member heterocycles, and introducing the 1,3,4 substituents into the fezolamine drug, novel scaffolds (**9a**–**n**) were created and investigated for the in vitro antitubercular activity.

RESULT & DISCUSSSION:

The traditional synthesis pathways for novel pyrazolylpyrazoline-clubbed triazole and tetrazole derivatives (**9a**–**n**) are shown in scheme 1.

The starting compound 5-Chloro-4-(1,3-dioxolan-2-yl)-3-methyl-1-phenyl-1*H*-pyrazole (**1**) was reacted with 4*H*-1,2,4-triazol-4-amine (**a**) and 1*H*-tetrazol-5-amine (**b**) in the presence of K_2CO_3 in 1,4-dioxane at 80 °C for 13 h. Similarly, 5-((4*H*-1,2,4-triazol-4-yl)amino)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3a**) and 5-((1*H*-tetrazol-5-yl)amino)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3b**) were achieved further reacted with 2-acetyle thiophene (**4a**) and 2-acetyle furan (**4b**) and substituted hydrazide derivatives (**5**–**8**) in the presence of 50% ethanolic KOH solution at room temperature. The obtained solid precipitate was filtered, washed with ethanol, and dried in an oven. The products (**9a**–**n**) were received quantitatively in 80–90% yields with excellent purity (see Table 1).



Scheme 1. Synthesis of Triazole/Tetrazole Hybrid Pyrazole Derivatives (3a,b)

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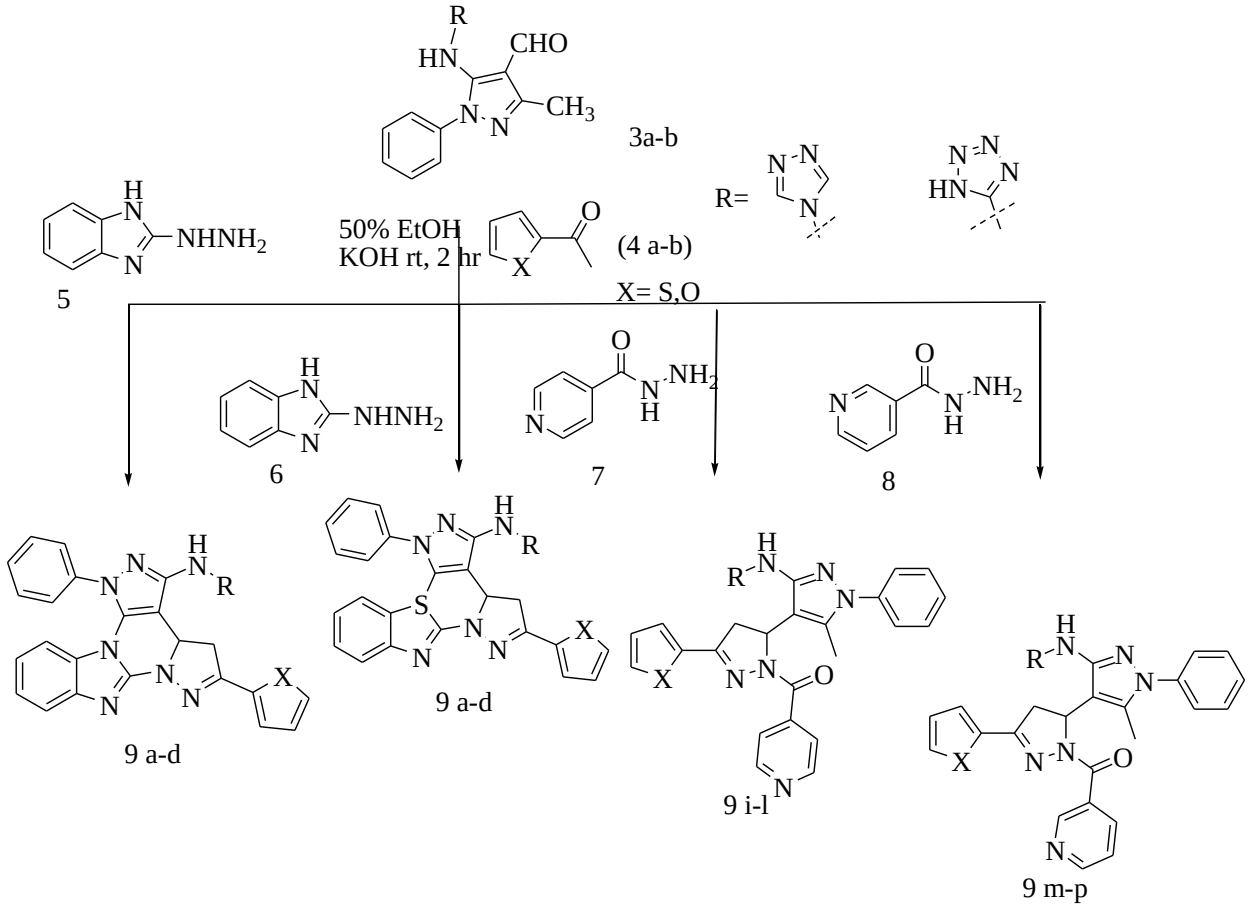
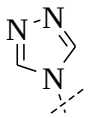
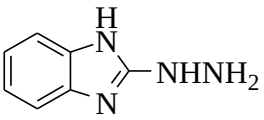
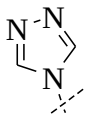
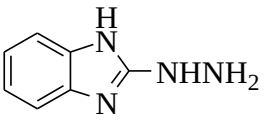
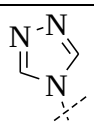
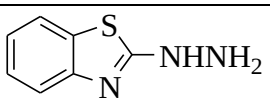
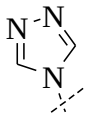
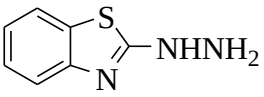
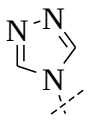
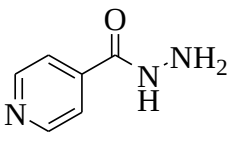


Scheme 2. Synthesis of Novel Pyrazolylpyrazoline-Clubbed Triazole and Tetrazole Derivatives (**9a**–**n**).

Sr	R	Hydrazine derivatives	Compound	Yield
1			9a	75
2			9b	77
3			9c	72
4			9d	78
5			9e	77

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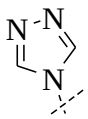
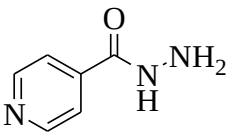
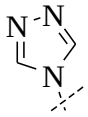
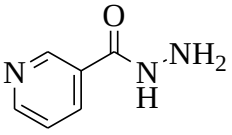
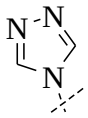
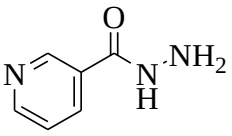
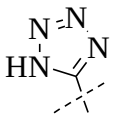
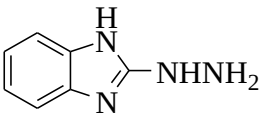
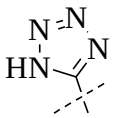
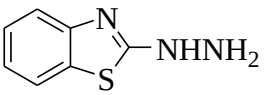
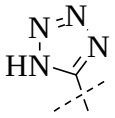
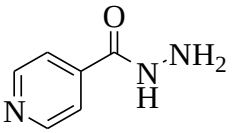
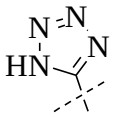
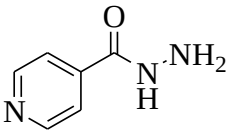
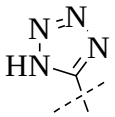
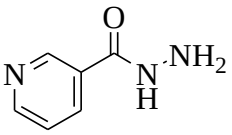
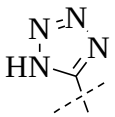
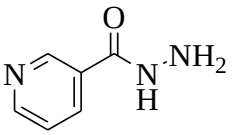
6			9f	80
7			9g	85
8			9h	83
9			9i	79
10			9j	80
11			9k	82
12			9l	86
13			9m	87
14			9n	90

Experimental Section:

Materials and Methods: All reactions were performed with analytical grade reagents (Sigma-Aldrich), which were used without further purification. The progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum plates coated with silica gel 60F 254 (layer thickness 0.25mm; Merck); components were detected by exposure to UV light or iodine vapor. The melting points were determined in open capillary tubes on an electro thermal melting point apparatus. The IR spectra were recorded in KBr on a Perkin Elmer FT-IR spectrophotometer (490−8500cm−1).The 1H NMR and 13CNMR spectra were recorded in DMSO-d6 on a Bruker Advance 400 spectrometer at 400 and 100MHz, respectively, using DMSO-d6 as a solvent and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Elemental analysis (% C,H,N) was performed using a Perkin Elmer 2400 Series II elemental analyzer. A mass spectrum was scanned on a Shimadzu

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LC−MS 2010 spectrophotometer. Preparation of 5-Chloro-4-(1,3-dioxolan-2-yl)-3-methyl-1 phenyl-1H-pyrazole(1). A mixture of the starting material 5 chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (A, 30 mmol), 1,4-dioxane (20 mL), in to a 100mL RBF. Preparation of N-(4-(1,3-Dioxolan-2-yl)-3-methyl-1-phe nyl-1H-pyrazol-5-yl)-4H-1,2,4-triazol-4-amine (2a) and N (4-(1,3-Dioxolan-2-yl)-3-methyl-1-phenyl-1H-pyrazol-5-yl) 1H-tetrazol-5-amine (2b). In a three-neck RBF, 0.1 mol of compound1 was added to dry acetone (60mL), followed by addition of 0.15mol of anhydrous K_2CO_3. After that, 0.11mol of 4H-1,2,4-triazol-4-amine(a) or 1H-tetrazol-5-amine(b) was added to the above reaction mass. The mixture was stirred at 90°C for 2−3h.The progress of the reaction was monitored by TLC. The product mass was added to cold water, followed by extraction with ethyl acetate.The organic layer was dried over sodium sulfate and evaporate under reduced pressure to achieve compounds 2a,b in good yields (84−87%). Preparationof5-((4H-1,2,4-Triazol-4-yl)amino)-3-methyl 1-phenyl-1H-pyrazole-4-carbaldehyde (3a) and 5-((1H Tetrazol-5-yl)amino)-3-methyl-1-phenyl-1H-pyrazole-4-car baldehyde (3b).

General Procedure for the Synthesis of Pyrazolylpyrazo line-Clubbed Triazole andTetrazole Derivatives(9a−n): In a 200mL RBF, derivatives 3a,b(2.5mmol) and derivatives 4a,b were added to a solution of substituted hydrazide derivatives (5−8,2.5mmol) in a 50% ethanolic KOH solution (25mL) and the reaction mass was stirred for 2−3h at Room T. Obtained sproduct were filtered, washed with ethanol, and dried.The final products (9a−p) werer eceived quantitatively in 70−90% yields with excellent purity. All synthesized compounds were well characterized through different spectroscopic techniques.

Molecular Docking Study: The in silico approach of molecular docking is one of the most frequently used strategies because of its ability to predict the conformation of small molecules with in the appropriate target binding site. Therefore, to rationalize the promising level of antitubercular activity demonstrated by pyrazolylpyrazoline derivatives (9d,9i,9k,9l, 9o,and 9n) and gain an insight in to their plausible mechanism of action, amolecular docking study was performed against mycobacterial enoyl reductase (InhA) (pdb code: 4TZK) using the GLIDE (Grid-Based Ligand Docking with Energetics) module of Schrödinger molecular modeling software (Schrödinger, LLC, NewYork, NY). InhA,30 the enoyl acyl carrier protein reductase (ENR) from M. tuberculosis, is one of the key enzymes contributing to mycolic acid biosynthesis,which is a major component of the bacterial cell wall. Inhibition of InhA disrupts the integrity of the mycobacterial cellwall and thus qualifies it as the promising target of novel antimycobacterial drugs.31 All of the six compounds (9d, 9i, 9k, 9l, 9o, and 9n) were docked in the binding site of InhA and displayed a good binding affinity with docking scores in the range from−8.884to−7.113(Table 3).

Table3.Molecular Docking of Novel Compounds in the Active Site of MTB Enoyl Reductase (InhA)

Comp.	Glide code	Glide energy (kcal/mol)	H-bonding (A^0)	Pi-Pi staking A’
9c	-6.812	-45.64	Tyr158(2.501)	Tyr158(2.31)
9k	-7.124	-46.23	Lys165(1.98)	Tyr158(2,12)
9l	-7.843	-48.54	Lys165(2.23)	Tyr158(1.92)
9m	-7.526	-51.74	Lys165(2.34)	Tyr158(1.91)
9n	-8.451	-56.23	Lys165(2.12)	Tyr158(1.82)

Characterization of 2-(1H-Benzo[d]imidazol-2-yl)-5′ methyl-1′-phenyl-5-(thiophen-2-yl)-N-(4H-1,2,4-triazol-4 yl)-3,4-dihydro-1′H,2H-[3,4′-bipyrazol]-3′-amine (9a). Yield 79%, mp 225−226°C; IR (KBr) λmax:3350 (N−H stretching), 3320(N−Hstretching), 3062(Ar−CHstretching), 2925(C− Haliphatic stretching), 1610(C-Cstretching), 1599(C- N),760(−S-linkage);

1HNMR(DMSO-d6,400MHz):1.81 (dd, 1H,CH_2), 1.86(dd, 1H,CH_2), 1.89(dd, 1H,CH),2.30(s,3H,−CH3),5.16(s,1H,−NH),6.04 (s,1H,NH),7.07−7.96(m,14H,Ar−H);

ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue XI, November 2025

13CNMR(DMSO d6, 100MHz): 21.3, 43.4, 56.0, 115.2, 115.4, 115.8, 120.2, 120.8, 121.6, 121.7, 122.2, 124.2, 125.9, 127.0, 127.2, 128.2, 128.3, 128.5, 130.4, 130.8, 131.9, 133.3, 135.0, 148.8, 150.0, 152.2;

LCMS:m/z=507.10(M+);anal.calcdforC26H22N10S: C, 61.64;H, 4.38;N, 27.65%; found:C, 61.96;H, 4.52;N, 27.68%.

Characterization of 2-(1H-Benzo[d]imidazol-2-yl)-5 (furan-2-yl)-5′-methyl-1′-phenyl-N-(4H-1,2,4-triazol-4-yl) 3,4-dihydro-1′H,2H-[3,4′-bipyrazol]-3′-amine (9b). Yield 84%, mp225−227°C; IR(KBr) λmax:3350(N−Hstretching), 3321(N−Hstretching), 3058(Ar−CHstretching),2950(C− stretching), 1605(C-Cstretching), 1599(C-N),759(−S-linkage); 1HNMR(DMSO-d6,400MHz):1.81 (dd, 1H,CH_2), 1.86(dd, 1H,CH_2), 1.88(dd, 1H,CH),2.30(s,3H,−CH3),5.14(s,1H,−NH),6.05 (s,1H,NH),7.07−8.10(m,14H,Ar−H);

13CNMR(DMSO d6, 100MHz): 21.4, 43.4, 56.0, 115.4, 115.6, 115.9, 120.2, 120.8, 121.6, 121.7, 122.2, 124.2, 125.9, 127.0, 128.0, 128.2, 128.3, 128.5, 130.4, 130.9, 131.9, 133.3, 135.0, 148.8, 150.0, 152.4;

LCMS:m/z=491.2(M+);anal.calcdfor$C_{26}H_{22}N_{10}O$: C, 63.66;H, 4.52;N, 28.55%; found:C, 63.26;H, 4.60;N, 28.52%.

Characterization of 2-(1H-Benzo[d]imidazol-2-yl)-5′ methyl-1′-phenyl-N-(1H-tetrazol-5-yl)-5-(thiophen-2-yl)-3,4 dihydro-1′H,2H-[3,4′-bipyrazol]-3′-amine (9c). Yield 79%, mp 226−230 °C; IR(KBr) λmax: 3345 (N−Hstretching), 3340(N−Hstretching), 3321(N−Hstretching), 3058(Ar−CHstretching),2950(C−Haliphaticstretching),1605(C- C stretching), 1599 (C-N), 759 (−S-linkage);

1HNMR (DMSO-d6,400MHz):1.83(dd,1H,CH2group),1.84(dd, 1H, CH2), 1.85 (dd, 1H, CH), 2.30 (s, 3H, −CH3),5.16(s,1H,−NH),5.18(s,1H,−NH),6.06(s,1H, NH),7.10−8.10(m,12H,Ar−H); 13CNMR(DMSO-d6,100 MHz): 20.3, 44.4, 56.0, 113.2, 115.4, 115.8, 120.2, 120.8, 121.6, 121.7, 122.2, 124.2, 125.9, 127.0, 127.2, 128.2, 128.3, 128.5,130.4,131.8,131.9,133.3,135.2,148.8,163.4;

CONCLUSIONS

Optimization of the titled compounds will be important in the development of new antitubercular drugs in the upcoming years. Conventional synthesis and the hybrid molecule idea were used to develop the active analogues. The salient features of this green protocol are the one-pot reaction, short reaction time, and straightforward workup procedure. The majority of the derivatives were produced in good yields with high purity. The inclusion of electron-withdrawing and-donating groups in compounds 9l, 9k, resulted in excellent antitubercular activity. The pyrazolylpyrazoline derivatives may fit well into the active site of InhA, forming significant bonded and nonbonded interactions, according to molecular docking studies. These in silico findings, which are validated by in vitro antitubercular outcomes, provide a foundation for continuing the structure-based drug design approach to uncover potent leads with better selectivity. The fact that compound 9n with isoniazid, thiol link, and 2-acetylfuran. The compound fused with the pyrazole andpyrazoline ring has outstanding antitubercular activity and a high docking score motivated us to develop new hybrids based on the core structure and explore their antitubercular activity.

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ISSN 2278-2540 | DOI: 10.51583/IJLTEMAS | Volume XIV, Issue XI, November 2025

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