SYNTHESIS, MOLECULAR DOCKING AND ANTITUBERCULAR ACTIVITY OF NEW BI HETEROCYCLIC COMPOUNDS ON BENZIMIDAZOLE MOIETY

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ABSTRACT

A series of new and efficient Benzo [*d*] imidazole-2-yl -3, 5 substituted diphenyl -3,3a,5,6 –Tetrahydro 2H-pyrazole thiazole derivatives (4a-j) were synthesized from Schiff base derivatives of thiazolidinediones (3a-j) using hydrazine hydrate. The synthesized compounds were screened for their antitubercular and molecular docking studies. The results of docking studies are supporting antitubercular activity showing high inhibition constant and binding energy. The structures of synthesized compounds were characterized by IR, ¹HNMR, Mass spectroscopic methods.

Keywords: Synthesis, Molecular Docking, Antitubercular Activity, Benzimidazole Derivatives

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INTRODUCTION

The quest for synthesis of novel materials for specific applications has become a great challenge for researchers aiming to address urgent real-world demands.¹⁻² To meet this target, significant attention has been paid to design and develop heterocyclic molecules owning desirable properties.³⁻⁴

Heterocyclic chemistry is highly challenging especially in the growing demand for higher efficiency and eco-friendly synthesis.⁵⁻⁶ It always attracts the attention of scientists working in the area of natural products and synthesis of heterocyclic compounds, especially with nitrogen-containing heterocyclic molecules that occupy the key position in the area of drugs and pharmaceuticals.⁷⁻⁹ Majority of the pharmaceutical products are heterocyclic molecules that meet the expectations of biological and industrial requirements.

The present study involves the synthesis of high bioactive compounds like benzimidazole, thiazole and pyrazole which exhibit various biological activities like antitumor¹⁰, analgesic¹¹, antimicrobial¹²⁻¹³, antibacterial¹⁴⁻¹⁵ and anti-inflammatory etc.¹⁶ Hence, in this direction, efforts have been undertaken to introduce most active and biologically versatile molecules containing nitrogen and sulphur triheterocyclic compounds like Benzo [*d*] imidazole-2-yl -3, 5 substituted diphenyl -3,3a, 5, 6 –Tetrahydro 2H-pyrazole thiazole derivatives which were synthesized from 2-amino-substituted benzimidazole.

EXPERIMENTAL

Materials and Methods

Progress of the reaction was observed by TLC plates. IR Spectra were recorded by Perkin Elmer BX series and ¹H NMR spectra were recorded by Bruker 400 MHz instrument using DMSO as solvent and TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. Mass spectra were measured on a GC/MS-QP1000EX (EI, 70 eV) mass spectrometer. Elemental analysis was performed on PerkinElmer 240 CHN analyzer.

Scheme-1

General Reaction Procedure for Compound 2

A mixture of Benzaldehyde (0.004 mol) and 2-amino benzimidazole (1) (0.004 mol) with few drops of glacial acetic acid was refluxed in ethanol for about 4 hours. Reaction progress was monitored by TLC. After the completion of the reaction, the product was cooled, filtered and dried then recrystallized with methanol to afford the compound Schiff base (2).

General Reaction Procedure for Compound 3:

An equimolar mixture of compound 2 (0.01), mercaptoacetic acid (0.01) and aromatic aldehyde (0.01) in 1,4-dioxane (30ml) containing a small amount of ZnCl₂ was refluxed for about 6 hours. The resulting product was filtered and cooled in an ice bath to attain room temperature. The solid product was filtered and washed with 10% sodium bicarbonate and recrystallized with alcohol.

The remaining compounds (3b-3h) were prepared by similar procedure with minor changes as per the reaction conditions.

(Z)-3-(1H-benzo [d] imidazole -2-yl)-5-benzylidene-2-phenylthiazolidin-4-one (3a)

IR (KBr, cm⁻¹): 3328 (N-H), 1548 (C=N), 1230 (C=S), ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 5.92 (s, 1HCH-Ar), 7.12-7.22 (m, 4H, Ar-H), 7.26-7.48 (m, 5H, Ar-H), 7.56-7.74 (m, 5H, Ar-H), 9.85 (br, 1H, NH). MS, m/z (%), 383 (M⁺); Anal. calcd for C₂₃H₁₇N₃OS : C, 72.08; H, 4.47; N, 10.97 %. Found C, 71.45; H, 4.24; N, 10.23%.

(Z)- 3-(1H-benzo [d]imidazole -2-yl)-5-(4-methylbenzylidene)-2-phenylthiazolidin-4-one (3b)

IR (KBr, cm⁻¹): 3337 (N-H), 2960 (C-H), 1561 (C=N), 1672 (C=O), 1249 (C=S); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 2.85 (s, 3H, CH₃), 5.86 (s, 1H, N-CH-Ar), 7.15-7.24 (m, 4H, Ar-H), 7.28-7.38 (m, 4H, Ar-H), 7.542-7.64 (m, 4H, Ar-H), 9.96 (br, 1H, NH). MS, m/z (%), 397 (M⁺); Anal. calcd for C₂₄H₁₉N₃OS : C, 72.52; H, 4.82; N, 10.57 %. Found C, 71.81; H, 4.63; N, 10.24%.

(Z)- 3-(1H-benzo [d]imidazole -2-yl)-5-(4-methoxybenzylidene)-2-phenylthiazolidin-4-one(3c)

IR (KBr, cm⁻¹): 3341 (N-H), 3046 (C-H), 1560 (C=N), 1678 (C=O), 1239 (C=S); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 3.45 (s, 3H, OCH₃), 5.72 (s, 1H, N-CH-Ar), 7.18-7.25 (m, 4H, Ar-H), 7.26-7.51 (m, 5H, Ar-H), 7.65-7.84 (m, 4H, Ar-H), 10.05 (br, 1H, NH). MS, m/z (%), 413 (M⁺); Anal. calcd for C₂₄H₁₉N₃O₂S : C, 69.71; H, 6.62; N, 10.16 %. Found C, 69.02; H, 4.36; N, 10.02%.

(Z)- 3-(1H-benzo [d]imidazole -2-yl)-5-(4-hydroxybenzylidene)-2-phenylthiazolidin-4-one (3d)

IR (KBr, cm⁻¹): 3514 (OH), 3346 (N-H), 1566 (C=N), 1235 (C=S), ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 5.88 (s, 1HCH-Ar), 7.14-7.28 (m, 4H, Ar-H), 7.30-7.48 (m, 5H, Ar-H), 7.58-7.72 (m, 5H, Ar-H),

10.01 (br, 1H, NH), 11.28(s, 1H, OH); MS, m/z (%), 428 (M^+); Anal. calcd for $C_{23}H_{16}N_4O_3S$: C, 64.47; H, 3.76; N, 13.08 %. Found C, 64.23; H, 3.84; N, 12.81%.

(Z)-3-(1H-benzo[d]imidazole-2-yl)-5-(4-nitrobenzylidene)-2-phenylthiazolidin-4-one (3e)

IR (KBr, cm^{-1}): 3340 (N-H), 1572 (C=N), 1522 (-NO₂), 1684 (C=O), 1236 (C=S), ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 5.85 (s, 1HCH-Ar), 7.13-7.27 (m, 4H, Ar-H), 7.30-7.48 (m, 5H, Ar-H), 8.12-8.34 (m, 4H, Ar-H), 10.18 (br, 1H, NH); MS, m/z (%), 399 (M^+); Anal. calcd for $C_{23}H_{17}N_3O_2S$: C, 69.15; H, 4.28; N, 10.52 %. Found C, 68.45; H, 4.04; N, 10.40%.

(Z)-3-(1H-benzo[d]imidazole-2-yl)-5-(4-(dimethylamino)benzylidene)-2-phenylthiazolidin-4-one (3f)

IR (KBr, cm^{-1}): 3328 (N-H), 1562 (C=N), 1675 (C=O), 1315 (3⁰amine) ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 3.22 (s, 3H, OCH₃), 5.72 (s, 1H, N-CH-Ar), 7.17-7.28 (m, 4H, Ar-H), 7.26-7.50 (m, 4H, Ar-H), 7.55-7.82 (m, 4H, Ar-H), 10.14 (br, 1H, NH). MS, m/z (%), 426 (M^+); Anal. calcd for $C_{25}H_{24}N_4OS$: C, 70.40; H, 5.20; N, 13.14 %. Found C, 69.82; H, 4.96; N, 12.62%.

(Z)-3-(1H-benzo[d]imidazol-2-yl)-5-(4-chlorobenzylidene)-2-phenylthiazolidin-4-one(3g)

IR (KBr, cm^{-1}): 3366 (N-H), 1561(C=N), 1694 (C=O), 875 (C-Cl); ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 5.84 (s, 1H, N-CH-Ar), 7.14-7.26 (m, 4H, Ar-H), 7.25-7.48 (m, 4H, Ar-H), 7.51-7.82 (m, 4H, Ar-H), 10.04 (br, 1H, NH). MS, m/z (%), 433 (M^+); Anal. calcd for $C_{23}H_{16}ClN_3OS$: C, 66.10; H, 3.85; N, 10.04 %. Found C, 65.82; H, 3.13; N, 9.82%.

(Z)-5-(4-aminobenzylidene)-3-(1H-benzo[d]imidazol-2-yl)-2-phenylthiazolidin-4-one (3h)

IR (KBr, cm^{-1}): 3365 (N-H), 1563(C=N), 1697(C=O); ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 5.85 (s, 1H, N-CH-Ar), 6.22 (s, 2H, NH₂), 7.15-7.26 (m, 4H, Ar-H), 7.31-7.49 (m, 5H, Ar-H), 7.58-7.82 (m, 4H, Ar-H), 10.08 (br, 1H, NH). MS, m/z (%), 398 (M^+); Anal. calcd for $C_{23}H_{18}N_4OS$: C, 69.32; H, 4.55; N, 10.04 %. Found C, 68.82; H, 4.13; N, 12.82%.

General Reaction Procedure for Compound 4a

Equimolar mixture of 3a (0.03 mol), hydrazine hydrate (0.03mol) and anhydrous CH₃COONa (0.001 mol) in glacial acetic acid (30ml) were heated under reflux for about 6.5 hours, the resulting compound was cooled at room temperature and poured in to crushed ice. The product was filtered, washed with water and recrystallized with ethanol to afford the pure compound. The remaining compound (4b-4h) was prepared by similar procedure with minor changes as per the reaction conditions.

6-(1H-benzo[d]imidazole-2-yl)-3,5-diphenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4a)

IR (KBr, cm^{-1}): 3348 (N-H), 3078 (C-H), 1564 (C=N), 1671 (C=O), 1238 (C=S), 1042 (N-N); ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 4.42(d, 1H, CH-S), 4.85 (d, 1H, CH-N), 5.90 (s, 1H, N-CH-Ar), 7.10-7.22 (m, 4H, Ar-H), 7.26-7.45 (m, 5H, Ar-H), 7.55-7.78 (m, 5H, Ar-H), 9.75 (br, 1H, NH); MS, m/z (%) 397 (M^+); Anal. Calcd for $C_{23}H_{19}N_5S$: C, 69.92; H, 4.87; N, 17.97%. Found: C, 69.50; H, 4.52; N, 17.62%.

6-(1H-benzo[d]imidazole-2-yl)-5-phenyl-3-(p-tolyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4b)

IR (KBr, cm^{-1}): 3342 (N-H), 3085 (C-H), 1567 (C=N), 1675 (C=O), 1245 (C=S), 1048 (N-N); ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 2.85 (s, 3H, CH₃), 4.60 (d, 1H, CH-S), 4.83 (d, 1H, N-CH-Ar), 7.18-7.26 (m, 4H, Ar-H), 7.28-7.38 (m, 4H, Ar-H), 7.45-7.68 (m, 4H, Ar-H), 9.95 (br, 1H, NH); MS, m/z (%) 411 (M^+); Anal. Calcd for $C_{24}H_{21}N_5S$: C, 70.15; H, 5.17; N, 17.07%. Found: C, 69.81; H, 4.92; N, 16.82%.

6-(1H-benzo[d]imidazole-2-yl)-3-(4-methoxyphenyl)-5-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo [3,4-d] thiazole (4c)

IR (KBr, cm^{-1}): 3343 (N-H), 3038 (C-H), 1560 (C=N), 1685 (C=O), 1241 (C=S), 1062 (N-N); ¹HNMR (DMSO- d_6 , 400MHz, δ in ppm): 3.48 (s, 3H, OCH₃), 4.62 (d, 1H, CH-S), 4.83 (d, 1H, N-CH-Ar), 5.74 (s, 1H, N-CH-Ar), 7.21-7.28 (m, 4H, Ar-H), 7.31-7.58 (m, 4H, Ar-H), 7.68-7.87 (m, 4H, Ar-H), 10.06

(br, 1H,NH); MS, m/z (%) 427 (M^+) ; Anal. Calcd for $C_{24}H_{21}N_5OS$: C, 67.45; H, 4.95; N, 16.64 %. Found: C, 67.02; H, 4.26; N, 16.02%.

4-(6-(1H-benzo[d]imidazole-2-yl)-5-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazol-3-yl)phenol(4d)

IR (KBr, cm⁻¹): 3516 (OH), 3353 (N-H) , 3038(C-H) , 1571 (C=N), 1685 (C=O), 1242 (C=S), 1042 (N-N); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 4.62 (d, 1H, CH-S), 4.78 (d, 1H, N-CH-Ar), 5.94(s, 1H, N-CH-Ar), 7.18-7.3 (m, 4H, Ar-H) , 7.28-7.54 (m, 5H, Ar-H), 7.61-7.74 (m, 4H, Ar-H), 10.16 (br, 1H, NH), 11.35(s, 1H, OH) ; MS, m/z (%) 413 (M^+) ; Anal. Calcd for $C_{24}H_{19}N_5OS$: C, 66.81; H, 4.66; N, 16.88 %. Found: C, 67.23; H, 3.96; N, 16.42%.

6-(1H-benzo[d]imidazol-2-yl)-3-(4-nitrophenyl)-5-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4e)

IR (KBr, cm⁻¹): 3346 (N-H) , 1574 (C=N), 1528(NO₂) , 1682 (C=O), 1235 (C=S), 1052 (N-N); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 4.75 (d, 1H, CH-S), 4.92 (d, 1H, N-CH-Ar), 5.94 (s, 1H, N-CH-Ar), 7.16-7.30 (m, 4H, Ar-H) , 7.28-7.52 (m, 5H, Ar-H), 8.18-8.41 (m, 4H, Ar-H), 10.22 (br, 1H, NH) ; MS, m/z (%) 442 (M^+) ; Anal. Calcd for $C_{23}H_{18}N_6O_2S$: C, 62.45; H, 4.19; N, 18.52 %. Found: C, 68.45; H, 4.03; N, 10.42%.

4-(1H-benzo[d]imidazol-2-yl)-5-phenyl-3, 3a, 5, 6-tetrahydro-2H-pyrazolo [3,4-d] thiazole -3-yl)-N,N dimethyl amine (4f)

IR (KBr, cm⁻¹): 3334 (N-H) , 1564 (C=N) , 1678 (C=O), 1235 (C=S), 1323 (3^oamine), 1052 (N-N); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 3.27(s, 6H-N(CH₃)₂), 4.75 (d, 1H, CH-S), 4.91 (d, 1H, N-CH-Ar), 5.74(s, 1H, N-CH-Ar), 7.21-7.30 (m, 4H, Ar-H) , 7.36-7.55 (m, 4H, Ar-H), 7.62-7.84 (m, 4H, Ar-H), 10.18 (br, 1H, NH) ; MS, m/z (%) 440 (M^+) ; Anal. Calcd for $C_{25}H_{24}N_6S$: C, 68.16; H, 5.48; N, 19.04 %. Found: C, 68.86; H, 4.93; N, 18.62%.

6-(1H-benzo[d]imidazol-2-yl)-3-(4-chlorophenyl)-5-phenyl-3, 3a, 5, 6-tetrahydro-2H-pyrazolo [3, 4-d] thiazole (4g)

IR (KBr, cm⁻¹): 3382 (N-H) , 1565 (C=N) , 1698 (C=O), 1235 (C=S), 872 (C-Cl), 1052 (N-N); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 4.73 (d, 1H, CH-S), 4.91 (d, 1H, N-CH-Ar), 5.84 (s, 1H, N-CH-Ar), 7.18-7.32 (m, 4H, Ar-H) , 7.36-7.52 (m, 4H, Ar-H), 7.60-7.85 (m, 4H, Ar-H), 10.16 (br, 1H, NH) ; MS, m/z (%) 431 (M^+) ; Anal. Calcd for $C_{23}H_{26}N_5S$: C, 66.96; H, 4.26; N, 16.25 %. Found: C, 66.24; H, 4.03; N, 15.82%.

4-(6-(1H-benzo[d]imidazol-2-yl)-5-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazol-3-yl)aniline (4h)

IR (KBr, cm⁻¹): 3375 (N-H) , 1565 (C=N) , 1695 (C=O), 1232(C=S), 1052 (N-N); ¹HNMR (DMSO-d₆, 400MHz, δ in ppm): 4.75 (d, 1H, CH-S), 4.94 (d, 1H, N-CH-Ar), 5.94 (s, 1H, N-CH-Ar), 6.22(s, 2H, NH₂), 7.18-7.32 (m, 4H, Ar-H) , 7.38-7.55 (m, 4H, Ar-H), 7.62-7.92 (m, 4H, Ar-H), 10.06 (br, 1H, NH) ; MS, m/z (%) 398 (M^+) ; Anal. Calcd for $C_{23}H_{20}N_6S$: C, 66.97; H, 4.86; N, 20.36 %. Found: C, 66.64; H, 4.43; N, 20.04%.

RESULTS AND DISCUSSION

The present study reports the synthesis of thiazolo-pyrazole derivatives linked with benzimidazole with an appreciable yield. The compound **2** (Schiff base) is synthesized using 2-aminobenzimidazole with Benzaldehyde under simple conditions. The compound **3** (Chalcone derivatives of thiazolidinone) is synthesized by one-pot three-component cyclization using compound **2**, mercaptoacetic acid and aromatic aldehyde using anhydrous ZnCl₂. Later, the Chalcone derivative of thiazolidinone (**3**) undergoes cyclization with hydrazine hydrate in the presence of anhydrous acetic acid to afford the compound **4**. The structures of synthesized compounds were established based on spectral and analytical data. The compounds showed IR absorption bands at 3366 cm⁻¹ (NH), 1568 cm⁻¹ (C=N), 1241 cm⁻¹ (C=S), 1680 cm⁻¹ (C=O) respectively. ¹HNMR spectra of test compounds displayed singlet signals at 5.58 for N-CH-Ar, doublet signals at 4.62 CH-S, 4.82 CH-N, and 9.82 ppm for NH protons and also phenylic protons as

multiplet in the range of 7.10-8.10 ppm. Mass spectra of synthesized compounds showed a molecular ion peak at m/z concerning their molecular weights.

Table-1: Physical Data of Synthesized Compounds (3a-3h) and (4a-4h)

Compounds	3a	3b	3c	3d	3e	3f	3g	3h
R	Ar	4-CH ₃ - Ar	4-OCH ₃ - Ar	4-OH- Ar	4-NO ₂ - Ar	4- N(CH ₃) ₂ -Ar	4-Cl-Ar	4-NH ₂ -Ar
M.P (°C)	208-12	215-17	220-22	213-14	221-23	225-28	215-17	210-12
Yield (%)	80	82	78	81	76	75	76	80
Compounds	4a	4b	4c	4d	4e	4f	4g	4h
R	Ar	4-CH ₃ - Ar	4-OCH ₃ - Ar	4-OH- Ar	4-NO ₂ - Ar	4- N(CH ₃) ₂ -Ar	4-Cl-Ar	4-NH ₂ -Ar
M.P(°C)	238-40	245-47	250-52	243-46	250-52	255-57	246-48	241-42
Yield (%)	82	80	75	72	74	76	73	72

In response to nitrate, *Mycobacterium* which causes tuberculosis produces nitrate reductase by NarL.¹⁷⁻¹⁹ NarL is a cytoplasmic response regulator that is involved in regulating gene expression of this bacterium. NarL has been identified as a potential drug target due to its role in nitrate respiration.²⁰ The Docking studies were conducted on NarL similar to that reported by Prashantha et al²¹ using docking server software.²²⁻²³ The protein structure was downloaded from the Protein data bank and was docked to the ligand. The estimated free energy of binding was found to be -7.16 kcal/mol while the inhibition constant was found to be 5.60 uM and ARG63 was involved in polar bond formation with the ligand (Tables-2, 3 and 4). The docking pose of the ligand with NarL is shown in Fig.-1.

Fig.-1: Docking Pose between the Ligand and the Protein

Table-2: Free Energy of Binding between the Ligand and the Protein

Estt. Free Energy Binding	Estt. Inhibition Constant, Ki	vdW + H Bond + Desolv. Energy	Electrostatic Energy	Total Intermolecular Energy	Frequency	Interact Surface
-7.16 kcal/mol	5.60 uM	-7.73 kcal/mol	-0.07 kcal/mol	-7.79 kcal/mol	50%	809.37

Table-3: Decomposed Interaction Energies in Kcal/mole

Polar	Hydrophobic	Other
ARG63 (0)	PRO65 (0)	ARG115 (0)
	VAL119 (0)	ASP68 (0)
		GLU117 (0)
		LYS120 (0)
		THR116 (0)

Table-4: Interaction Showing the Various Bonds between the Ligand and the Protein

Polar	Hydrophobic	Other
N4 (15) [3.06] – ARG63 (CZ, NE, NH2)	C17 (23) [3.01] – VAL119 (CB, CG2)	C16 (22) [3.38] – ARG115 (CG, NE)
N5 (16) [2.66] – ARG63 (CZ, NE, NH2)	C18 (24) [3.19] – VAL119 (CB, CG1, CG2)	C17 (23) [3.48] – ARG115 (CG)
H8 (37) [2.74] – ARG63 (CZ, NE, NH2)	C16 (22) [3.85] – VAL119 (CG2)	C9 (12) [3.24] – THR116 (CB, CG2)
	C10 (14) [3.40] – PRO65 (CB)	S1 (13) [3.16] – THR116 (CB, CG2)
		C19 (25) [2.93] – THR116 (CB, OG1)
		C20 (26) [3.13] – THR116 (CB, OG1)
		C18 (24) [3.33] – THR116 (CB, CG2)
		C13 (19) [3.52] – THR116 (CG2)
		C17 (23) [3.75] – THR116 (CG2)
		C20 (26) [3.74] – GLU117 (CG)
		H8 (37) [2.15] – VAL119 (CB, CG1, CG2)

		N4 (15) [3.54]	VAL119 (CG1)
		N5 (16) [3.11]	VAL119 (CG1)
		N3 (10) [3.89]	LYS120 (CB)
		C6 (6) [3.50]	LYS120 (CD, NZ)
		C7 (8) [3.86]	LYS120 (CD)
		N2 (9) [3.51]	LYS120 (CD)
		C12 (18) [3.79]	LYS120 (CD)
		C21 (27) [3.81]	LYS120 (CD)
		C22 (28) [3.32]	LYS120 (CD)
		C23 (29) [3.31]	LYS120 (CD)
		C1 (1) [3.21]	LYS120 (NZ)
		C2 (2) [3.63]	LYS120 (NZ)
		C14 (20) [3.33]	ARG63 (CD, NE)
		C11 (17) [3.17]	ARG63 (NE)
		C13 (19) [3.59]	ARG63 (NE)
		N2 (9) [3.87]	PRO65 (CB)
		C14 (20) [3.46]	ASP68 (CB, OD2)
		C15 (21) [2.78]	ASP68 (CB, CG, OD2)
		C16 (22) [3.24]	ASP68 (OD2)

CONCLUSION

The experimental results conclude that a new series of thiazolo –pyrazole containing benzimidazole nucleus and its derivatives are successfully synthesized. It has been reported in the present work that the title compounds (i.e., tri heterocyclic compounds) are exhibiting antitubercular activity based on In silico studies.

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