Asian Journal of Chemistry; Vol. 36, No. 4 (2024), 969-973

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2024.31314

Design, Synthesis, Characterization and Antitubercular Activity of Novel Benzimidazole Mannich Base Derivatives

CHANDRAVADIVELU GOPI[1,*], MAGHARLA DASARATHA DHANARAJU[2], KONATHAM PRANUSHA[1], THIYAGARAJAN DEEPAN[3], AR MAGESH[3] and DHANARAJU KAVITHA[1]

[1]Department of Pharmaceutical Chemistry, GIET School of Pharmacy, Rajamahendravaram-533296, India
[2]Research Lab, GIET School of Pharmacy, Rajamahendravaram-533296, India
[3]Department of Pharmaceutical Analysis, GIET School of Pharmacy, Rajamahendravaram-533296, India

*Corresponding author: Fax: +91 883 2484444; E-mail: gopi@giet.ac.in

Received: 1 February 2024; *Accepted*: 9 March 2024; *Published online*: 30 March 2024; AJC-21599

In present work, the newly synthesized benzimidazole Mannich base derivatives were design, synthesized and evaluated the *in silico* and *in vitro* antitubercular activity. These compounds were synthesized by condensation reaction between 1-(1*H*-benzo[*d*]imidazol-1-yl)ethanone and aliphatic/aromatic amines. The synthesized compound structures were identified by FTIR, ^{13}C NMR, ^{1}H NMR and mass spectroscopies. The results indicated that these derivatives have significant antitubercular activity against *Mycobacterium tuberculosis* (M.tb) cell wall enzyme enoyl acyl carrier protein reductase (InhA), EthR regulatory protein in H73Rv strain. The results found in the *in vitro* study are firmly similar to the *in silico* study. Among the synthesized compounds, **3d** and **3e** exhibited the highest activity due to the connection of the electron-donating group to the Mannich base. Therefore, these compounds deserve the development of new antitubercular agents.

Keywords: Benzimidazole, Mannich base, Aliphatic/aromatic amines, Antitubercular activity.

INTRODUCTION

According to the literature study, benzimidazole and its derivatives have an enormous role in the preparation of novel pharmaceuticals [1-3]. The parent component of the series is commonly referred to as benzimidazole, however benzoglyoxaline is frequently used as an alternative term [4]. This moiety plays a critical role in diverse pharmacological benefits such as antitumour [5], antiviral [6], antimicrobial [7], antifungal [8], antihelminthic [9], anti-inflammatory [10], antihistaminic [11], proton pump inhibitor [12], antioxidant [13], antitubercular activity [14]. In the same way, Mannich bases have an excellent therapeutic profiles, relatively safe and well-tolerated molecules [15,16]. Ketone, aldehyde and a primary and secondary amine form a complex molecule called Mannich base [17,18].

Mannich bases also act as vital pharmacophores which are employed for the preparation of different therapeutic agents holding the group of aminoalkyl chains [19]. They offered various pharmacological benefits, such as anti-inflammatory [20], anticancer [21], antipyretic [22], antibacterial [23], antifungal [24], anthelmintic [25], anticonvulsant [26], analgesic [27], antitubercular [28], anti-HIV [29], antimalaria [30], antiviral agent [31], antipsychotic [32], *etc*. Some of the medicinal compounds having Mannich base are fluoxetine, atropine and ranitidine, *etc*. The above benefits and our interest in the synthesized compounds containing benzimidazole and Mannich base encourage us to synthesize a series of the novel benzimidazole Mannich base derivatives. These compounds were produced from needed materials and the construction of the structures was recognized by different spectral studies and screened for tuberculosis by using *in vitro* and *in silico* methods. The experimental outcome recommended that all Mannich base derivatives showed excellent antitubercular activity against *Mycobacterium tuberculosis*. The therapeutic activity of the synthesized Mannich base derivatives (**3a-e**) is similar to standard drugs.

EXPERIMENTAL

The chemicals and solvents were acquired from leading pharma companies like Sigma, Alrich, Ranbaxy and Dr. Reddy.

Functional groups present in the compounds were identified from Perkin-Elmer FT-IR spectrophotometer, ranges 4000-400 cm^{-1}. Using Bruker Avance III™ instrument, ^1H NMR spectra (400 MHz) were used to analyze the protons that exist in the synthesized Mannich bases from chemical shift using deuterated chloroform as solvent. Shimadzu mass spectrometer was used to analyzed the molecular weight of the synthesized compounds, whereas Perkin-Elmer analyzer (2400 CHN) was employed to identify the elements (CHN) present in the synthesized Mannich base derivatives.

Synthesis of 1*H*-benzo[*d*]imidazole: *O*-Phenylene diamine 0.5 mol (54 g) taken in a 250 mL round bottom flask was added to 90% formic acid (0.75 mol, 34.6 g) gradually and then the mixture was warmed in a water bath for 2 h. After cooling, 10% NaOH was added slowly to turn the mixture alkaline. The precipitated solid was isolated by vacuum filter, rinsed with little water and recrystallized from ethyl alcohol [33-36].

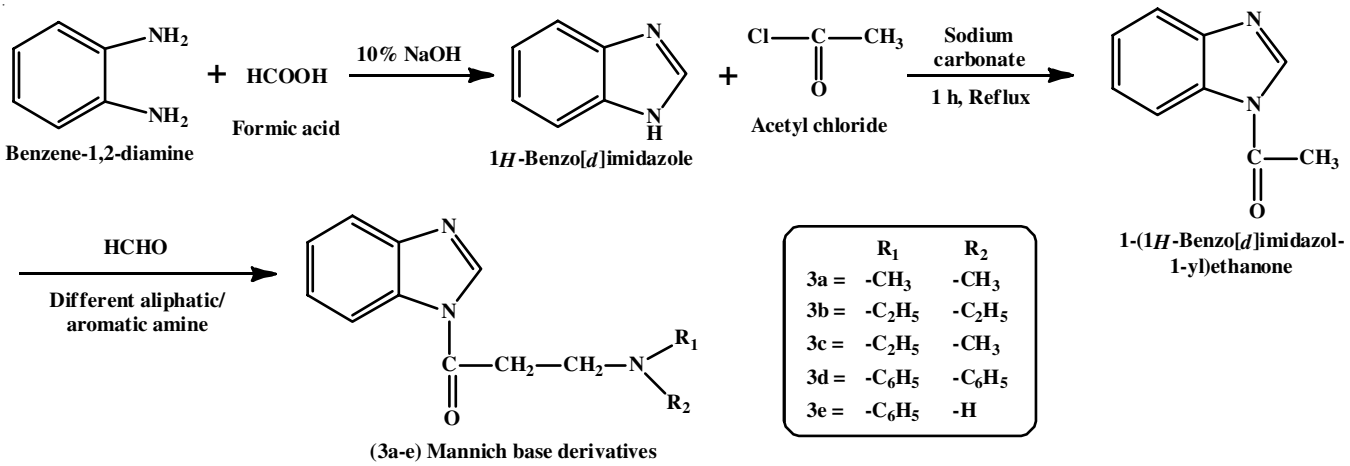
Synthesis of 1-(*H*-benzo[*d*]imidazole-1-yl)ethenone: Benzimidazole (1 mmol), acetyl chloride (0.5 mmol) and sodium carbonate (1 mmol) were mixed in a round bottom flask followed by the addition of 3 mL of DMSO solvent. The content was agitated for 10 min and connected through a reflux condenser and heated for 1 h followed by the addition of 10 mL of water and extracted with ethyl acetate. The hot solution was cooled to 28 ºC and the oil layer on the solid surface was eliminated by rinsing with water. The separated 1-(*H*-benzo[*d*]imidazole-1-yl)ethenone was rinsed with water and recrystallized from ethyl alcohol [37].

Synthesis of 3-amino-1-(1*H*-benzo[*d*]imidazol-1-yl)-propan-1-one Mannich base derivatives (3a-e): The above synthesized 3-amino-1-(1*H*-benzo[*d*]imidazol-1-yl)-propan-1-one (0.1 mol), formaldehyde (0.1 mol) and aliphatic/aromatic amines (0.1 mol) were mixed in 30 mL of ethyl alcohol and refluxed for 4 h and left overnight untouched. The solid obtained was rinsed with aqueous solvent and recrystallized from acetone [38] (**Scheme-I**).

1-(1*H*-Benzo[*d*]imidazol-1-yl)-3-(dimethylamino)propan-1-one (3a): Yield: 79%; m.p.: 202-204 ºC; colour: light yellow; FTIR (ν_{max}, cm^{-1}): 3063 (*str.*, Ar-proton), 1587 (*str.*, Ar-carbon), 1680 (C=O); ^1H NMR ($CDCl_3$, δ ppm): 2.54 (t, 2H, *J* = 9.6 Hz, CH_2-proton), 2.92 (s, 6H, CH_3-proton), 3.84 (t, 2H, *J* = 8 Hz, CH_2-proton), 7.42-7.54 (m, 2H, Ar-proton), 7.85-7.94 (m, 2H, Ar-proton), 8.11 (s, 1H, CH-proton); ^{13}C NMR (DMSO-d_6, δ ppm): 30.5 (C-1), 46.7 (C-2), 46.7 (C-3), 58.4 (C-4), 170.42 (C-5), 123.25 (C-6), 123.25 (C-7), 114.12 (C-8), 120.46 (C-9), 137.25 (C-10), 137.25 (C-11), 142.23 (C-12); MS (*m/z*, %): 217 (49) [M^+], 202 (32), 173 (100), 145 (22), 117 (33), 90 (46), 51 (63), 39 (28); Anal. calcd. (found) % for $C_{12}H_{15}N_3O$, (*m.w.* 320): C, 66.34 (66.49); H, 6.96 (7.18); O, 7.36 (7.35); N, 19.34 (19.32).

1-(1*H*-Benzo[*d*]imidazol-1yl)-3-(diethylamino)propan-1-one (3b): Yield: 75%; m.p.: 224-226 ºC; colour: white; FTIR (ν_{max}, cm^{-1}): 3055 (*str.*, Ar-proton), 1537 (*str.*, Ar-carbon), 1678 (C=O); ^1H NMR ($CDCl_3$, δ ppm): 1.06 (t, 6H, *J* = 9.2 Hz, CH_3-proton), 2.72 (t, 2H, *J* = 6.4 Hz, CH_2-proton), 3.04 (q, 4H, *J* = 6.8 Hz, CH_2-proton), 3.73 (t, 2H, *J* = 6.8 Hz, CH_2-proton), 7.35-7.42 (m, 2H, Ar-proton), 7.61-7.74 (m, 2H, Ar-proton), 8.12 (s, 1H, CH-proton); ^{13}C NMR (DMSO-d_6, δ ppm): 13.5 (C-1), 13.5 (C-2), 31.3 (C-3), 49.52 (C-4), 49.52 (C-5), 53.54 (C-6), 170.37 (C-7), 123.36 (C-8), 123.36 (C-9), 114.35 (C-10), 120.15 (C-11), 137.46 (C-12), 137.46 (C-13), 142.51 (C-14); MS (*m/z*, %): 245 (36) [M^+], 173 (43), 159 (100), 117 (38), 90 (31), 76 (26), 50 (42); Anal. calcd. (found) % for $C_{14}H_{19}N_3O$, (*m.w.* 320): C, 68.54 (68.42); H, 7.81 (7.56); O, 6.92 (6.91); N, 17.13 (17.37).

1-(1*H*-Benzo[*d*]imidazol-1-yl)-3-(ethyl(methyl)amino)-propan-1-one (3c): Yield: 85%; m.p.: 213-215 ºC; colour: white; FTIR (ν_{max}, cm^{-1}): 3043 (*str.*, Ar-proton), 1508 (*str.*, carbon), 1658 (C=O); ^1H NMR ($CDCl_3$, δ ppm): 1.05 (t, 3H, *J* = 9.2 Hz, CH_3-proton), 2.32 (s, 3H, CH_3-proton), 2.62 (t, 2H, *J* = 11.2 Hz, CH_2-proton), 2.83 (q, 2H, *J* = 9.2 Hz, CH_2-proton), 3.85 (t, 2H, *J* = 11.2 Hz, CH_2-proton), 7.19-7.25 (m, 2H, Ar-proton), 7.89-7.98 (m, 2H, Ar-proton), 8.15 (s, 1H, CH-H); ^{13}C NMR (DMSO-d_6, δ ppm): 13.2 (C-1), 30.7 (C-2), 46.36 (C-3), 53.76 (C-4), 55.3 (C-5), 170.24 (C-6), 123.21 (C-7), 123.21 (C-8), 114.34 (C-9), 120.42 (C-10), 137.53 (C-11), 137.53 (C-12), 142.76 (C-13); MS (*m/z*, %): 231 (391) [M^+], 173 (100), 159 (49), 117 (32), 76 (44), 51 (34); Anal. calcd. (found) % for $C_{13}H_{17}N_3O$ (*m.w.* 320): C, 67.51 (67.24); H, 7.41 (7.32); O, 6.92 (6.90); N, 18.17 (18.36).



Scheme-I: Synthetic protocol for various potent Mannich base derivatives (**3a-e**)

1-(1*H*-Benzo[*d*]imidazol-1-yl)-3-(diphenhlamino)propan-1-one (3d): Yield: 75%; m.p.: 367-369 ºC; colour: white; FTIR (ν_{max}, cm^{-1}): 3273 (*str.*, Ar-proton), 1534 (*str.*, Ar-carbon), 1685 (C=O); ^{1}H NMR ($CDCl_3$, δ ppm): 2.70 (t, 2H, *J* = 10.4 Hz, CH_2-proton), 3.58 (t, 2H, *J* = 8.4 Hz, CH_2-proton), 6.78 (q, 2H, *J* = 7.6 Hz, Ar-proton), 7.14-7.24 (m, 6H, Ar-proton), 7.34-7.43 (m, 4H, Ar-proton), 7.62-7.77 (m, 2H, Ar-proton), 8.10 (s, 1H, CH-proton); ^{13}C NMR (DMSO-d_6, δ ppm): 30.6 (C-1), 55.8 (C-2), 39.56 (C-3), 121.83 (C-4), 121.83 (C-5), 129.54 (C-6), 129.54 (C-7), 129.54 (C-8), 129.54 (C-9), 123.12 (C-10), 123.12 (C-11), 119.25 (C-12), 119.25 (C-13), 114.63 (C-14), 120.14 (C-15), 146.54 (C-16), 146.54 (C-17), 137.43 (C-18), 137.43 (C-19), 137.43 (C-20), 142.06 (C-21), 142.06 (C-22); MS (*m/z*, %): 341 (30) [M^+], 264 (58), 159 (100), 105 (40), 94 (76), 65 (32); Anal. calcd. (found) % for $C_{22}H_{19}N_3O$ (*m.w.* 320): C, 77.40 (77.16); H, 5.61 (5.72); O, 4.69 (4.65); N, 12.31 (12.42).

1-(1*H*-Benzo[*d*]imidazol-1-yl)-3-(phenylamino)propan-1-one (3e): Yield: 84%; m.p.: 295-297 ºC; colour: cream yellow; FTIR (ν_{max}, cm^{-1}): 3156 (*str.*, Ar-proton), 1525 (*str.*, Ar-carbon), 1642 (C=O); ^{1}H NMR ($CDCl_3$, δ ppm): 2.75 (t, 2H, *J* = 10.4 Hz, CH_2-proton), 3.55 (t, 2H, *J* = 8.8 Hz, CH_2-proton), 4.02 (s, 1H, NH-proton), 6.62 (d, 2H, *J* = 5.2 Hz, Ar-proton), 6.84 (q, 1H, *J* = 7.2 Hz, Ar-proton), 7.31-7.38 (m, 2H, Ar-proton), 7.78-7.83 (m, 2H, Ar-proton), 7.90-8.01 (m, 2H, Ar-proton), 8.10 (s, 1H, CH-proton); ^{13}C NMR (DMSO-d_6, δ ppm): 12.1 (C-1), 12.76 (C-2), 39.56 (C-3), 39.56 (C-4), 39.98 (C-5), 40.19 (C-6,7,8), 44.90 (C-9), 74.28 (C-10), 111.34 (C-11), 119.84 (C-12), 121.93 (C-13), 122.90 (C-14), 142.33 (C-15), 143.48 (C-16); MS (*m/z*, %): 265 (29) [M^+], 173 (57), 146 (46), 107 (100), 92 (44), 39 (30); Anal. calcd. (found) % for $C_{16}H_{15}N_3O$, (*m.w.* 320): C, 72.43 (72.26); H, 5.70 (5.83); O, 6.03 (5.99); N, 15.84 (15.02).

***In silico* docking method:** In this work, a docking study was performed by using iGEMDOCK software [39]. The crystal structures of InhA in complex with a DNA encoded library (PDB ID: 5G0V) and EthR complex (PDB ID: 5NIO) were acquired from the protein data bank. A set of 5 different ligands 2D structures was built in ChemDraw and later converted to the 3D structure. The best conformation of the ligand was preferred and employed to calculate the strength of the bond between the ligand and InhA/EthR. *Mycobacterium tuberculosis* (M.tb) cell wall enzyme enoyl acyl carrier protein reductase (InhA) and EthR play a chief role in mycolic acid formation.

Microplate alamar blue assay (MABA): *In vitro* antitubercular activity of newly synthesized Mannich base derivatives (**3a-e**) was estimated against *M. tuberculosis* H73Rv strain using MABA technique [40]. In brief, 96-well plates are rinsed with sterile deionized water. Each well was filled with 100 µL of 7H9GC broth. The Mannich base derivatives tested were 0.2 to 100 µg/mL. Inoculate *M. tuberculosis* H73Rv (100 µL) was inoculated. The well plates were covered with parafilm and incubated at 37 ºC for 7 days. Later, 50 µL of synthesized compounds (1:1) of MABA reagents and 10% Tween 80 was included in the plate and incubated overnight. The colour of the plate changes to pink pointing out the growth of *M. tuberculosis* H73Rv strain. The minimum inhibitory concentration (MIC) is defined as the least quantity of Mannich base which prohibits the formation of pink colour.

RESULTS AND DISCUSSION

A novel benzimidazole Mannich base derivatives were synthesized by performing the interaction between 1-(1*H*-benzo[*d*]imidazol-1-yl)ethanone and different aliphatic/aromatic amines.The FTIR spectrum of the Mannich bases exhibited a strong deep peak in the region of 3063, 3055, 3043, 3273, 3150,1587, 1537, 1508, 1534, 1525, 1680, 1678, 1658, 1685 and 1642 cm^{-1} could be attributed to aromatic proton, aromatic carbon and ketone groups present in it. The aromatic ring produced a stretching peak between 3273-3043 and 1587-1507 cm^{-1}. An intensive peak at 1685-1642 cm^{-1} is due to the existence of the ketone group in the synthesized analogues. The ^{1}H NMR spectroscopy of analogues gave the additional information for the conformation of the prepared benzimidazole Mannich base derivatives. The ^{1}H NMR spectra showed a triplet at δ 2.32-2.75 ppm related to CH_2-proton, a singlet at δ 2.32-2.92 ppm related to CH_3-proton; a triplet at δ 3.55-3.85 ppm indicating CH_2-proton, A multiplet at δ 8.01 ppm related to Ar-proton; a doublet at δ 6.62 ppm related to Ar-proton; a quartet at δ 2.81-3.02 related to CH_2-proton; a quartet at δ 6.76-6.84 related to Ar-proton. A singlet at δ 8.01-8.15 corresponds to CH proton. The weight of the compounds was estimated by the Shimadzu mass spectrometer. The molecular weights such as 217, 245, 231, 341 and 265 correspond to the **3a-e** compounds.

Docking studies: The therapeutic activity of the synthesized Mannich base derivatives (**3a-e**) has been assessed from iGEMDOCK score after the successful connection with *M. tuberculosis* cell wall enzyme InhA and regulatory protein EthR. The effective antitubercular drugs are absolutely docked to a hydrophilic and hydrophobic centre of the InhA and regulatory protein EthR target and exhibit excellent scores. The synthesized compounds **3d** and **3e** executed better than the standard drug (isoniazid) regarding binding nature and stability with the InhA and regulatory protein EthR. Each ligand molecule (**3a-e**) has shown an excellent affinity towards InhA/EthR target due to the development of the link between the ligand and some hydrophobic and hydrophobic residue present in the InhA/EthR. Among the synthesized compounds, **3d** and **3e** exhibited admirable scores due to the existence of electron-donating groups (Table-1). The overall decreasing order of InhA/EthR inhibition activity of synthesized analogues was found to be **3d > 3e > 3a > 3b > 3c**. The interaction of each Mannich base derivative with the InhA/EthR is shown Fig. 1.

TABLE-1
BINDING AFFINITY OF MANNICH BASE DERIVATIVES (**3a-e**) AGAINST *Mycobacterium tuberculosis* ENOYL ACYL CARRIER PROTEIN REDUCTASE InhA/REGULATORY PROTEIN EthR

Compound	InhA docking fitness	EthR docking fitness
3a	-76.5719	-92.0505
3b	-71.3316	-92.0651
3c	-71.3297	-79.3923
3d	-89.0493	-108.196
3e	-91.6251	-98.285
Isoniazide (std. drug)	-73.6466	-73.6054

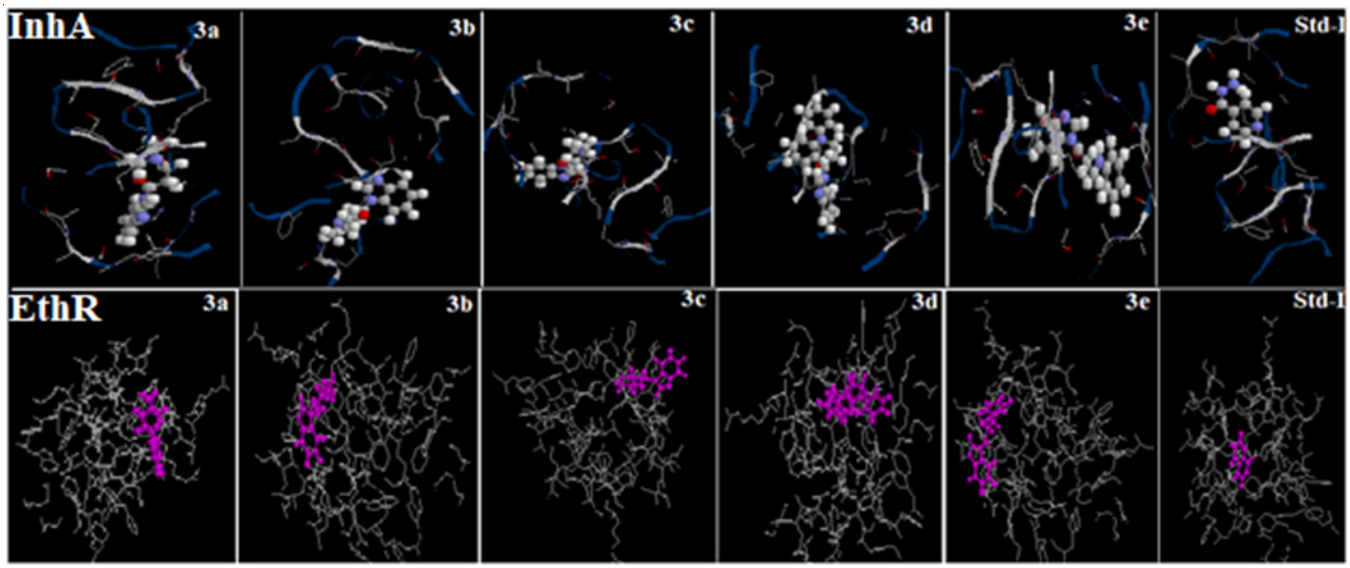


Fig. 1. Interaction of synthesized compounds and *Mycobacterium tuberculosis* InhA/EthR regulatory prtein

MABA: The MIC values of synthesized compounds (**3a-e**) were calculated using MABA method. The MIC investigation showed that all the Mannich base derivatives displayed strong inhibiting activity against Mt.b H37Rv with the ranges of 0.463 µM to 0.784 µM, respectively as mentioned in Table-2. The results demonstrated that all the synthesized Mannich base derivatives are highly effective against *M. tuberculosis*. The ability of Mannich base to inhibit H37Rv strain due to the strong bactericidal activity against *M. tuberculosis*. Therefore, these Mannich bases have the potency to develop anti-mycobacterial agents, although it requires for additional study to understand their function as an antitubercular agent.

TABLE-2
MINIMUM INHIBITORY CONCENTRATION VALUES OF MANNICH BASE DERIVATIVES (**3a-e**) AGAINST *Mycobacterium tuberculosis* H73Rv STRAIN

Compound	MIC (µM)
3a	0.584
3b	0.621
3c	0.673
3d	0.463
3e	0.522
Isoniazide (std. drug)	0.435

Conclusion

Benzimidazole Mannich base derivatives (**3a-e**) were synthesized by adopting the condensation reaction between 1-(1*H*-benzo[*d*]imidazol-1-yl)ethanone and aliphatic/aromatic amines. Furthermore, these analogues were screened for antitubercular activity using *in silco* and *in vivo* methods using iGEMDOCK and microplate alamar blue techniques. The results indicated that all the analogues demonstrated admirable activity against the InhA enzyme and regulatory protein EthR in M.tb H37Rv strain. Among the synthesized benzimidazole analogues, compounds **3d** and **3e** were found more efficiently attached to the target protein through electron donating groups and offered excellent antitubercular activity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. E. Kabir and M. Uzzaman, *Results Chem.*, **4**, 100606 (2022); https://doi.org/10.1016/j.rechem.2022.100606
2. O. Ebenezer, F. Oyetunde-Joshua, O.D. Omotoso and M. Shapi, *Results Chem.*, **5**, 100925 (2023); https://doi.org/10.1016/j.rechem.2023.100925
3. G. Satija, B. Sharma, A. Madan, A. Iqubal, M. Shaquiquzzaman, M. Akhter, S. Parvez, M.A. Khan and M.M. Alam, *J. Heterocycl. Chem.*, **59**, 22 (2022); https://doi.org/10.1002/jhet.4355
4. Y.T. Lee, Y.J. Tan and C.E. Oon, *Acta Pharm. Sin. B*, **13**, 478 (2023); https://doi.org/10.1016/j.apsb.2022.09.010
5. S. Tahlan, S. Kumar, S. Kakkar and B. Narasimhan, *BMC Chem.*, **13**, 66 (2019); https://doi.org/10.1186/s13065-019-0579-6
6. M. Tonelli, F. Novelli, B. Tasso, I. Vazzana, A. Sparatore, V. Boido, F. Sparatore, P. La Colla, G. Sanna, G. Giliberti, B. Busonera, P. Farci, C. Ibba and R. Loddo, *Bioorg. Med. Chem.*, **22**, 4893 (2014); https://doi.org/10.1016/j.bmc.2014.06.043
7. U. Kumar, R. Narang, S.K. Nayak, S.K. Singh and V. Gupta, *Res. J. Pharm. Tech.*, **10**, 2400 (2017); https://doi.org/10.5958/0974-360X.2017.00425.5
8. R.S. Kankate, P.S. Gide and D.P. Belsare, *Arab. J. Chem.*, **12**, 2224 (2019); https://doi.org/10.1016/j.arabjc.2015.02.002
9. P. Pattanayak, D. Panigrahi, S. Kumari, H.N. Yadav, C.R. Ashby, S. Kerber, M.J.S.A. Shahwan, A.K. Tiwari and G.P. Mishra, *J. Mol. Struct.*, **1295**, 136716 (2024); https://doi.org/10.1016/j.molstruc.2023.136716
10. J. Joseph, P. Perumal and P. Francis, *Res. J. Pharm. Tech.*, **9**, 1329 (2016); https://doi.org/10.5958/0974-360X.2016.00253.5
11. M.S. Vasava, M.N. Bhoi, S.K. Rathwa, D.J. Jethava, P.T. Acharya, D.B. Patel and H.D. Patel, *Mini Rev. Med. Chem.*, **20**, 532 (2020); https://doi.org/10.2174/1389557519666191122125453
12. T. Iwahi, H. Satoh, M. Nakao, T. Iwasaki, T. Yamazaki, K. Kubo, T. Tamura and A. Imada, *Antimicrob. Agents Chemother.*, **35**, 490 (1991); https://doi.org/10.1128/AAC.35.3.490

13. S.V. Bhandari, O.G. Nagras, P.V. Kuthe, A.P. Sarkate, K.S. Waghamare, D.N. Pansare, S.Y. Chaudhari, S.N. Mawale and M.C. Belwate, *J. Mol. Struct.*, **1276**, 134747 (2023); https://doi.org/10.1016/j.molstruc.2022.134747
14. C.K. Sachin, U. Ashutosh and M.K. Kale, *Res. J. Pharm. Tech.*, **11**, 5385 (2018); https://doi.org/10.5958/0974-360X.2018.00983.6
15. S. Bala, N. Sharma A. Kajal, S. Kamboj and V. Saini, *Int. J. Med. Chem.*, **2014**, 191072 (2014); https://doi.org/10.1155/2014/191072
16. S.S. Mansoor, K. Aswin, K. Logaiya and S.P.N. Sudhan, *J. Saudi Chem. Soc.*, **19**, 379 (2015); https://doi.org/10.1016/j.jscs.2012.04.008
17. I. Beltran-Hortelano, R.L. Atherton, M. Rubio-Hernández, J. Sanz-Serrano, V. Alcolea, J.M. Kelly, S. Pérez-Silanes and F. Olmo, *Eur. J. Med. Chem.*, **223**, 113646 (2021); https://doi.org/10.1016/j.ejmech.2021.113646
18. S. Farooq, A. Mazhar, A. Ghouri, N. Ihsan-Ul-Haq and N. Ullah, *Molecules*, **25**, 2710 (2020); https://doi.org/10.3390/molecules25112710
19. S. Farooq, I.-U. Haq and N. Ullah, *Arab. J. Chem.*, **14**, 103050 (2021); https://doi.org/10.1016/j.arabjc.2021.103050
20. G. Roman, *Eur. J. Med. Chem.*, **89**, 743 (2015); https://doi.org/10.1016/j.ejmech.2014.10.076
21. T. Manjuraj, G. Krishnamurthy, Y.D. Bodke, H.S.B. Naik and M. Shafeeulla, *Asian J. Res. Chem*, **10**, 470 (2017); https://doi.org/10.5958/0974-4150.2017.00076.1
22. S.A. Pishawikar and H.N. More, *Arab. J. Chem.*, **10**, S2714 (2017); https://doi.org/10.1016/j.arabjc.2013.10.016
23. R. Pavithra, K. Hemalatha and K. Girija, *Res. J. Pharm. Tech.*, **10**, 3346 (2017); https://doi.org/10.5958/0974-360X.2017.00595.9
24. P.H. Abrão, R.B. Pizi, T.B. de Souza, N.C. Silva, A.M. Fregnan, F.N. Silva, L.F. Coelho, L.C. Malaquias, A.L. Dias, D.F. Dias, M.P. Veloso and D.T. Carvalho, *Chem. Biol. Drug Des.*, **86**, 459 (2015); https://doi.org/10.1111/cbdd.12504
25. F. Alam, *Research J. Pharm. and Tech.*, **12**, 4225 (2019); https://doi.org/10.5958/0974-360X.2019.00726.1
26. K. Chaluvaraju and K. Bhat, *J. Young Pharm.*, **3**, 243 (2011); https://doi.org/10.4103/0975-1483.83775
27. M.K. Kumar Muthyala, R.N. Jamullamudi, G.P.V. Sangeeta and P.N. Kurre, *Curr. Computeraided Drug Des.*, **14**, 200 (2018); https://doi.org/10.2174/1573409914666180423093049
28. P.A. Datar and S.A. Limaye, *Antiinflamm. Antiallergy Agents Med. Chem.*, **14**, 35 (2015); https://doi.org/10.2174/1871523014666150312164625
29. S.N. Pandeya, D. Sriram, G. Nath and E. DeClercq, *Eur. J. Pharm. Sci.*, **9**, 25 (1999); https://doi.org/10.1016/S0928-0987(99)00038-X
30. J.E. Ruscoe, M.D. Tingle, P.M. O'Neill, S.A. Ward and B.K. Park, *Antimicrob. Agents Chemother.*, **42**, 2410 (1998); https://doi.org/10.1128/AAC.42.9.2410
31. M.K. Scott, G.E. Martin, D.L. DiStefano, C.L. Fedde, M.J. Kukla, D.L. Barrett, W.J. Baldy, R.J. Elgin Jr., J.M. Kesslick and J.R. Mathiasen, *J. Med. Chem.*, **35**, 552 (1992); https://doi.org/10.1021/jm00081a018
32. E.V. Tret'yakova, X. Ma, O.B. Kazakova, A.A. Shtro, G.D. Petukhova, A.M. Klabukov, D.S. Dyatlov, A.A. Smirnova, H. Xu and S. Xiao, *Phytochem. Lett.*, **51**, 91 (2022); https://doi.org/10.1016/j.phytol.2022.07.010
33. D. Tamilvendan, S. Rajeswari, S. Ilavenil, K. Chakkaravarthy and G. Venkatesa Prabhu, *Med. Chem. Res.*, **21**, 4129 (2012); https://doi.org/10.1007/s00044-011-9944-2
34. E.C. Wagner, W.H. Millett, W.W. Hartman and G.W. Sawdey, *Org. Synth.*, **19**, 12 (1939); https://doi.org/10.15227/orgsyn.019.0012
35. I.L. Finar, Organic Chemistry, Dorling Kindersley (India) Pvt. Ltd., edn. 6, pp 666 (2008).
36. V.K. Ahluwalia and R. Aggarwal, Comprehensive Practical Organic Chemistry, University Press India Private Ltd., edn 5, p. 120 (2008).
37. P.S. Mathapati, S.A. Durgad, K.C. Singh and S.D. Bhinge, *Indian Drugs*, **49**, 17 (2012); https://doi.org/10.53879/id.49.02.p0017
38. C. Gopi and M.D. Dhanaraju, *Beni Suef Univ. J. Basic Appl. Sci.*, **7**, 291 (2018); https://doi.org/10.1016/j.bjbas.2018.02.004
39. D. Bhowmik, R. Nandi, A. Prakash and D. Kumar, *Heliyon*, **7**, e06515 (2021); https://doi.org/10.1016/j.heliyon.2021.e06515
40. H.A. Sahile, M.S. Martinez-Martinez, M. Dillenberger, K. Becker and P. Imming, *ACS Omega*, **5**, 14451 (2020); https://doi.org/10.1021/acsomega.0c01065