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Synthesis and *in silico* studies of some new Schiff bases as antimicrobial and antitubercular agents

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ABSTRACT Ten pyridine carbohydrazide Schiff bases **(3a-3e)** and **(5a-5e)** were synthesized by refluxing pyridine carbohydrazides **1** and **4** with different ketones in the presence of ethanol and a few drops of glacial acetic acid. The synthesized compounds were biologically screened for antitubercular and antibacterial activity studies. The fit of these compounds within the active sites of the dihydrofolate reductase (DHFR) and enoyl ACP reductase was evaluated using molecular modeling techniques. The findings of the anticipated ADMET investigation showed that the compounds with the given names have drug-like characteristics. The newly synthesized molecules were subsequently tested for *in vitro* enoyl ACP reductase and DHFR enzyme inhibition, and molecules disclosed good inhibition values against enoyl ACP reductase and DHFR enzymes. The compounds **3b** and **5b** showed good antitubercular activity and antibacterial activity with 0.8 µg/mL along with promising InhA and DHFR enzyme inhibition evaluation.

KEYWORDS Carbohydrazide, Docking, Enzyme, Pyridine, Schiff base.

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INTRODUCTION

Tuberculosis (TB) is a chronic communicable infection and a leading cause of death, especially in developing countries. It is caused by the bacterial strain bacillus *Mycobacterium tuberculosis (Mtb)*, which primarily infects the lungs (pulmonary), along with other parts of the body (extrapulmonary).[1] According to the World Health Organization (WHO), TB stands among the top 10 causes of death globally and the most common cause of death from a single infectious agent.[2] Several therapeutics have been approved by the US Food and Drug Administration to improve the treatment of TB.[3] A number of attempts have been made to find novel antituberculosis drugs. Unfortunately, the process of antituberculosis drug discovery is very slow. Isoniazid (INH) is one of the two most effective first-line antitubercular drugs and is still used at the present time as a scaffold for developing new compounds to fight TB. Schiff bases possess diverse biological and pharmacological properties such as antimicrobial, anti-inflammatory, analgesic, antifungal, antitubercular, antiviral, anticancer, antiplatelet, antimalarial, anticonvulsant, cardioprotective, antihelmintic, antiprotozoal, antitrypanosomal, antischistosomiasis, etc.[4] Recently, pyrrole derivatives have emerged as chemotherapeutic agents potentially useful for inhibiting the activities of Mtb.[5] Here, we report the synthesis, *in silico* studies, and antimicrobial activity of a few Schiff bases.

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Anal. of $C_{15}H_{13}N_3O$: Calcd: C, 71.70; H, 5.21; N, 16.72; O, 6.37 Found: C, 71.69; H, 5.20; N, 16.71; O, 6.36.

N'-(2-Isopropyl-5-methylcyclohexylidene) nicotinohydrazide (5d)

Compound **5d** was obtained as a yellow solid. Mp: 168–170°C. Yield: 56 %. FTIR (KBr- cm^{-1}): 3437, 3169, 3011, 2948, 2881, 1936, 1644, 1553, 1480.

^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 10.45 (s, 1H, NH-amide), 9.00 (s, 1H, C_2-H-pyridine), 8.76–8.20 (m, 3H, C_3, C_4, C_5-H-pyridine), 2.17–1.92 (m, 3H, C_8-H, C_{12} (CH_2) -2H-cyclohexane), 1.63–1.06 (m, 4H, $2CH_2$, C_9, C_{10}-H-cyclohexane), 1.6 (s, 1H, C_{14}-H-cyclohexane), 1.5 (s, 1H, C_{11}-H-cyclohexane), 0.95–0.88 (m, 3(CH_3), 9H, C_{13}, C_{15}, C_{16}-H-cyclohexane).

Mass (m/z): 274.2 [M+1], 272.1 [M-2]; Calcd. 273.3

Anal. of $C_{16}H_{23}N_3O$: Calcd: C, 70.30; H, 8.48; N, 15.37; O, 5.85. Found: C, 70.29; H, 8.47; N, 15.36; O, 5.85.

N'-(2-Methyl-5-(prop-1-en-2-yl) cyclohex-2-en-1-ylidene)nicotinohydrazide (5e)

Compound **5e** was obtained as a yellow solid. Mp: 170–172°C. Yield: 62%. FTIR (KBr- cm^{-1}): 3428, 3205, 3033, 2963, 2918, 1654, 1591, 1539, 1420, 1353, 1291.

^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 10.87 (s, 1H, NH-amide), 9.00 (s, 1H C_2-H-pyridine), 8.76–8.20 (m, 3H, C_4, C_5, C_6-H-pyridine), 5.56–4.92 (m, 6H, C_9-H, C_{14}-2H, C_{15}-CH_3-3H-cyclohexene), 2.2 (s, 1H, C_{11}-H-cyclohexene) 2.23–1.98 (m, 3H, C_{13}-H, C_{12}-2H-cyclohexene), 2.06–1.81 (s, 2H, C_{10}-CH_2-H-cyclohexene), 1.79 (s, H, C_{15}-H-pyridine).

Mass (m/z): 270.2 [M+1], 268.2 [M-2]; Calcd. 269.3.

Anal. of $C_{16}H_{19}N_3O$: Calcd: C, 71.35; H, 7.11; N, 15.60; O, 5.94. Found: C, 71.34; H, 7.10; N, 15.59; O, 5.94.

Molecular docking using Surflex-Dock

Surflex-Dock was used for molecular docking to clarify the binding mechanism of compounds in the active sites of the dihydrofolate reductase and ENR enzymes using the patented Sybyl-X 2.0 search engine.

ADMET studies

ProTox-II was used to predict toxicities, and molecular ADME properties were calculated using *in silico* Swiss ADME online program.

Antitubercular activity

All the newly synthesized compounds were evaluated against Mtb strain H_{37}Rv by means of Microplate Alamar Blue assay results are reported in **Table 1** with MIC values.[7]

Antibacterial activity

Antibacterial inhibition study for all molecules was determined in comparison with ciprofloxacin as a reference drug against *S. aureus* (Gram +ve) and *E. coli* (Gram −ve) by broth microdilution method.[8] Antibacterial activity data are briefed in **Table 1** with their MIC values.

CONCLUSION

The synthesized compounds demonstrated strong antitubercular and antibacterial properties, as well as efficaciousness against InhA and DHFR enzyme inhibition assessments. Following an ADMET study, all of the molecules had minimal toxicity values and favorable pharmacokinetic parameters. Compounds *N'*-(9*H*-fluoren-9-ylidene)isonicotinohydrazide (**3b**) and *N'*-(9H-fluoren-9-ylidene)nicotinohydrazide (**5b**) have demonstrated highly potent antibacterial and antitubercular properties. The enzyme inhibition activity was also found to be effective for these compounds. The optimization of compounds **3b** and **5b** may thus provide a viable lead molecule for further scientific investigation, which may lead to the synthesis of novel compounds with notable antitubercular action in the future, depending on the results of the investigation.

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