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Synthesis, antimycobacterial activity and docking studies of L-proline derived hydrazones

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ABSTRACT

*In this paper, we describe the synthesis of new L-proline based hydrazones (**3a-j**) from easily accessible (S)-2-carbomethoxypyrrolidine hydrochloride. All the synthesized hydrazones were characterized by ^{1}H NMR, mass and elemental analysis data. All the titled compounds were evaluated for anti-mycobacterial activity against Mycobacterium smegmatis mc^{2}155 (ATCC 35797). The compounds **3b, 3d, 3f and 3g** showed moderate activity. Compound **3h** showed maximum activity against Mycobacterium smegmatis mc^{2}155. Docking studies using Auto dock program version 4.2 revealed that compound **3h** exhibited very good binding energy with minimum inhibition constant value.*

Key words: *L*-proline, hydrazones, anti-mycobacterial activity, *Mycobacterium smegmatis*, Rifampicin

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INTRODUCTION

Globally, tuberculosis (TB) remains the leading infectious disease, killing an estimated two million people per year [1]. Emergence of multi-drug resistant (MDR), extensively-drug resistant (XDR) TB, immune deficiency virus (HIV) co-infection and other bacterial infections has further complicated the treatment and management of this disease [2-3]. In absence of an effective vaccine, treatment is the main tool for controlling the dissemination of TB. Moreover, the characteristics of the tubercle bacillus such as slow growth, an impermeable envelop, ability to enter a latent stage and its intracellular location impedes the number of available drugs for treatment [4].

Only a few drugs have been approved by the Food and Drug Administration (FDA) to cure TB, reflecting the inherent difficulties in discovery of new anti-tuber agents. Also, the presently available anti-TB drugs, both FDA approved and non-approved, and other promising drug candidates are still under investigation as potential antimycobacterial drugs [5]. The increase in *Mycobacterium tuberculosis* strains resistant to front-line antimycobacterial drugs such as Rifampin and INH pose serious concerns [6-8], which clearly indicates the need for more effective drugs for the efficient management of TB. These factors have stimulated extensive research efforts to combat the spread of TB, worldwide.

Hydrazone derivatives constitute a considerable pharmacophore group [9]. Many researchers have synthesized these compounds as target structures and evaluated their biological activities. Recently, various hydrazones have been synthesized because of the development of isoniazid-resistant *M. tuberculosis* strains [10]. Few novel acylhydrazones are assessed for their antiviral activities and in *vivo cytotoxicities* [11].

L-proline is a unique amino acid and its utility has been evaluated extensively over the decades in the field of medicinal chemistry. Modification of the intrinsic proline structure results in new proline-based surrogates which in

turn lead to the discovery of novel therapeutics. This ideology encouraged us to synthesize new *L*-proline based hydrazones and evaluate their antimycobacterial activity against *Mycobacterium smegmatis* (ATCC 35797).

MATERIALS AND METHODS

Chemistry

Thin-layer chromatography (TLC) was performed on Merck AL silica gel 60 F_{254} plates and visualized under UV light. The column chromatography was performed using Merck silica gel (60-120 mesh). The ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 at 400 MHz on a VARIAN spectrometer. All the chemical shift values are reported in δ units using TMS as internal standard. The Mass spectra were recorded using PE-SCIEX-API-3000 system. Elemental analysis was done on Vario elemental analyzer.

General procedure for synthesis of 1a-c:

To a solution of (S)-2-carbomethoxypyrrolidine hydrochloride (1 mmol) in DMF (25 ml) was added potassium carbonate (3 mmol) and corresponding benzyl chloride (1.2 mmol). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to obtain crude product which was further purified by column chromatography using 60-120 mesh silica gel to afford compounds **1a-c**.

(*S*)-Methyl 1-(4-fluorobenzyl)pyrrolidine-2-carboxylate (1a): ^{1}H NMR ($CDCl_3$): δ 7.30-7.26 (m, 2H), 7.00-6.96 (m, 2H), 3.86-3.83 (d, J = 12.8Hz, 1H), 3.65 (s, 3H), 3.54-3.51 (d, J = 12.8 Hz, 1H), 3.22-3.21 (m, 1H), 3.05-3.01 (m, 1H), 2.40-2.33 (m, 1H), 2.14-2.10 (m, 1H), 1.97-1.88 (m, 3H); Mass (m/z): 238.1(M^+); Anal calc for $C_{13}H_{16}FNO_2$ Calcd.: %C 65.81; H, 6.80; N, 5.90. Found: %C 65.76, H 6.75, N 5.96.

(*S*)-Methyl 1-(4-nitrobenzyl)pyrrolidine-2-carboxylate (1b): ^{1}H NMR (DMSO-d_6): δ 8.20- 8.19 (d, J = 8.8Hz, 2H), 8.15-8.13 (d, J = 8.8Hz, 2H), 4.05-4.03 (d, J = 10 Hz,1H), 3.65-3.63 (d, J = 10Hz, 1H), 3.58 (s, 3H), 2.89-2.83 (m, 1H), 2.45-2.40 (m, 1H), 2.14-2.03 (m, 1H), 1.93-1.74 (m,4H); Mass (m/z): 265.1 (M^+); Anal calc for $C_{13}H_{16}N_2O_4$ Calcd.: % C, 59.08; H, 6.10; N, 10.60. Found: %C 59.02, H 6.05, N 10.63.

(*S*)-Methyl 1-(4-methoxybenzyl)pyrrolidine-2-carboxylate (1c): ^{1}H NMR ($CDCl_3$): δ 7.26-7.22 (m, 2H), 6.85-6.82 (m, 2H), 3.82-3.81 (d, J = 5.2 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.54-3.53 (d, J = 5.2Hz, 1H), 3.23-3.19 (m, 1H), 2.40-2.34 (m, 1H), 2.13-2.04 (m, 1H)**,** 2.09-1.95 (m, 2H), 1.93-1.78 (m, 2H); Mass (m/z): 250.2 (M^+); Anal calc for $C_{14}H_{19}NO_3$ Calcd.: % C, 67.45; H, 7.68; N, 5.62. Found: %C 67.50, H 7.73, N 5.60.

General procedure for synthesis of 2a-c: A mixture of **1a-c** (1 mmol) in methanol (5 ml), hydrazine hydrate (5 mmol) was heated at 80^{0}C for 5h. After completion of the reaction, methanol was removed and the resulting crude product was washed hexane to afford **2a-c**.

(*S*)-1-(4-fluorobenzyl)pyrrolidine-2-carbohydrazide (2a): ^{1}H NMR (DMSO-d_6): δ 7.39-7.38 (m, 2H), 7.37-7.36 (m, 2H), 4.32-4.21 (bs, 2H), 3.77-3.73 (d, J = 13.2 Hz, 1H), 3.39-3.36 (d, J = 13.2 Hz, 1H), 3.07-3.03 (m, 1H), 2.84-2.81 (m, 1H), 2.21-2.19 (m, 1H), 2.01-1.96 (m, 1H), 1.72-1.68 (m, 4H); Mass (m/z): 238.2 (M^+); Anal calc for $C_{12}H_{16}FN_3O$ Calcd.: % C, 60.74; H, 6.80; N, 17.71. Found: %C 60.71, H 6.75, N 17.75.

(*S*)-1-(4-nitrobenzyl)pyrrolidine-2-carbohydrazide (2b): ^{1}H NMR (DMSO-d_6)**:** δ 8.21-8.16 (m, 2H), 7.66-7.57 (m, 2H), 4.21-4.03 (bs, 2H), 3.91-3.88 (d, J = 14Hz, 1H), 3.58-3.54 (d, J = 14Hz, 1H), 3.13-3.10 (m, 1H), 2.88-2.86 (m, 1H), 2.33-2.32 (m, 1H), 2.21-2.00 (m, 1H), 1.78-1.71 (m, 4H); Mass (m/z): 238.2 (M^+); Anal calc for $C_{12}H_{16}N_4O_3$ Calcd.: % C, 54.54; H, 6.10; N, 21.20. Found: %C 54.59, H 6.14, N 21.17.

(*S*)-1-(4-methoxybenzyl)pyrrolidine-2-carbohydrazide (2c): ^{1}H NMR ($CDCl_3$): δ 7.26-7.22 (m, 2H), 6.85-6.82 (m, 2H), 3.65 (s, 3H), 3.54-3.51 (d, J = 8.8Hz, 1H), 3.23-3.21 (d, J = 8.8Hz, 1H), 3.19-3.03 (m, 1H), 2.38-2.36 (m, 1H), 2.15-2.12 (m, 2H), 2.09-1.91 (m, 2H), 1.89-1.78 (m, 4H); Mass (m/z): 250.3 (M^+); Anal calc for $C_{13}H_{19}N_3O_2$ Calcd.: % C, 62.63; H, 7.68; N, 16.85. Found: %C 62.60, H 7.70, N 16.81.

General procedure for synthesis of 3a-j:

A mixture of **2a-c** (1mmol), appropriate aromatic aldehyde (1.1 mmol), ethanol (3 ml/mmol) and few drops of glacial acetic acid were refluxed for 6 h. After completion of the reaction, the solvent was distilled off to obtain crude products. All these crude products were recrystallized from ethyl acetate / petroleum ether (95:5).

(*S,E*)-*N'*-(biphenyl-4-ylmethylene)-1-(4-fluorobenzyl)pyrrolidine-2-carbohydrazide (3a): ^{1}H NMR (DMSO-d_6): δ 11.07 (s, 1H), 8.38 (s, 1H), 7.74-7.71 (m, 5H), 7.50-7.37 (m, 6H), 7.15-7.11 (m, 2H), 3.81-3.77 (d, J = 13.2Hz, 1H), 3.56-3.53 (d, J = 13.2Hz, 1H), 3.21-3.18 (m, 1H), 2.49-2.33 (m, 1H), 2.13-2.01 (m, 1H), 1.83-1.77 (m, 4H)); Mass (m/z): 402.1 (M^+); Anal calc for $C_{25}H_{24}FN_3O$ Calcd.: %C, 74.79; H, 6.03; N, 10.47. Found: %C 74.75, H 5.99, N 10.50.

(*S,E*)-1-(4-fluorobenzyl)-*N'*-(4-fluorobenzylidene)pyrrolidine-2-carbohydrazide (3b): ^{1}H NMR (DMSO-d_6): δ 11.03 (s, 1H), 8.34 (s, 1H), 7.73-7.72 (m, 2H), 7.71-7.70 (m, 2H), 7.42-7.40 (m, 2H), 7.30-7.26 (m, 2H), 3.73-3.76 (d, J = 13.2Hz, 1H), 3.55-3.52 (d, J = 13.2Hz, 1H), 3.17-3.16 (m, 1H), 2.34-2.32 (m, 1H), 2.18-2.17 (m, 1H), 1.78-1.76 (m, 4H); Mass (m/z): 344 (M^+); Anal calc for $C_{19}H_{19}F_2N_3O$ Calcd.: %C 66.46; H, 5.58; N, 12.24. Found: %C 66.50, H 5.55, N 12.20.

(*S,E*)-1-(4-fluorobenzyl)-*N'*-(4-methoxybenzylidene)pyrrolidine-2-carbohydrazide (3c): ^{1}H NMR (DMSO-d_6): δ 11.04 (s, 1H), 8.31 (s, 1H), 7.41-7.41 (m, 2H), 7.36-7.21 (m, 4H), 6.98 (m, 2H), 3.78 (s, 3H), 3.78 (d, J = 12.8Hz, 1H), 3.77-3.76 (d, J = 12.8Hz, 1H), 3.20-3.19 (m, 1H), 2.35-2.33 (m, 1H), 2.14-2.10 (m, 1H), 1.94-1.74 (m, 4H); Mass (m/z): 356.1 (M^+); Anal calc for $C_{20}H_{22}FN_3O_2$ Calcd.: %C 67.59; H, 6.24; N, 11.82. Found: %C 67.63, H 6.21, N 11.80.

(*S,E*)-methyl 4-((2-(1-(4-fluorobenzyl)pyrrolidine-2-carbonyl)hydrazono)methyl)benzoate (3d): ^{1}H NMR (DMSO-d_6): δ 11.2(s, 1H), 8.40 (s, 1H), 8.19-8.00 (m, 2H), 7.99-7.80 (m, 2H), 7.43-7.41 (m, 2H), 7.14-7.07 (m, 2H), 3.87 (s, 3H), 3.79-3.76 (d, J = 13.2 Hz, 1H), 3.46-3.43 (d, J = 13.2 Hz, 1H), 3.21-3.18 (m, 1H), 2.39-2.35 (m, 1H), 2.22-2.10 (m, 1H), 1.97-1.77 (m, 4H); Mass (m/z): 384.2 (M^+); Anal calc for $C_{21}H_{22}FN_3O_3$ Calcd.: %C 65.78; H, 5.78; N, 10.96. Found: %C 65.80, H 5.75, N 11.00.

(*S,E*)-*N'*-(biphenyl-4-ylmethylene)-1-(4-nitrobenzyl)pyrrolidine-2-carbohydrazide (3e): ^{1}H NMR (DMSO-d_6): δ 11.14 (s, 1H), 8.36 (s, 1H), 8.20-8.18 (m, 2H), 7.96-7.60 (m, 8H), 7.50-7.47 (m, 2H), 7.41-7.39 (m, 1H), 3.98-3.94 (d, J = 14Hz, 1H), 3.73-3.69 (d, J = 14Hz, 1H), 3.29-3.27 (m, 1H), 2.44-2.39 (m, 1H), 2.17-2.12 (m, 1H), 1.84-1.82 (m, 4H); Mass (m/z): 429.2.2 (M^+); Anal calc for $C_{25}H_{24}N_4O_3$ Calcd.: %C, 70.08; H, 5.65; N, 13.08. Found: %C 70.10, H 5.62, N 13.10.

(*S,E*)-*N'*-(3-methoxybenzylidene)-1-(4-nitrobenzyl)pyrrolidine-2-carbohydrazide (3f): ^{1}H NMR (DMSO-d_6)**:** δ 10.98 (s, 1H), 8.25 (s, 1H), 8.19-8.17 (m, 1H), 7.69-7.59 (m, 5H), 7.01-6.99 (m, 2H), 3.96-3.93 (d, J = 14Hz, 1H), 3.80 (s, 3H), 3.71-3.67 (d, J = 14 Hz, 1H) 3.24-2.29 (m, 1H), 2.37-2.35 (m, 1H) 2.17-2.13 (m, 1H), 1.92-1.81 (m, 4H); Mass (m/z): 382.2 (M^+); Anal calc for $C_{20}H_{22}N_4O_4$ Calcd.: %C, 62.82; H, 5.80; N, 14.65; Found: %C 62.79, H 5.83, N 14.60.

(*S,E*)-*N'*-(3-fluoro-4-methoxybenzylidene)-1-(4-methoxybenzyl)pyrrolidine-2-carbohydrazide (3g): ^{1}H NMR ($CDCl_3$): δ 10.23 (bs, 1H), 7.96 (s, 1H), 7.55-7.53 (m, 1H), 7.26-7.20 (m, 4H), 6.88-6.86 (m, 2H), 3.94 (s, 3H), 3.81-3.79 (d, J = 8.4Hz, 1H), 3.75 (s, 3H), 3.64-3.60 (d, J = 8.4Hz, 1H), 3.18-3.17 (m, 1H), 3.12-3.11 (m, 1H), 2.50-2.48 (m, 1H), 2.30-2.21 (m, 1H), 2.04-2.00 (m, 1H), 1.82-1.76 (m, 2H); Mass (m/z): 386.4 (M^+); Anal calc for $C_{21}H_{24}FN_3O_3$ Calcd.: %C, 65.44; H, 6.28; N, 10.90. Found: %C 65.47, H 6.30, N 10.93.

(*S,E*)-*N'*-(biphenyl-4-ylmethylene)-1-(4-methoxybenzyl)pyrrolidine-2-carbohydrazide (3h): ^{1}H NMR ($CDCl_3$): δ 10.26 (s, 1H), 8.06 (s, 1H), 7.82-7.80 (m, 2H), 7.64-7.61 (m, 4H), 7.47-7.36 (m, 3H), 7.24-7.22 (m, 2H), 6.89-6.87 (m, 2H), 3.84-3.89 (d, J = 12.8Hz, 1H), 3.75 (s, 1H), 3.63-3.59 (d, J = 12.8Hz, 1H), 3.42-3.38 (m, 1H), 3.14-3.11 (m, 1H), 2.51-2.45 (m, 1H), 2.34-2.28 (m, 1H), 2.08-2.03 (m, 1H), 1.84-1.75 (m, 2H); Mass (m/z): 414.2 (M^+); Anal calc for $C_{26}H_{27}N_3O_2$ Calcd.: %C, 75.52; H, 6.58; N, 10.16. Found: %C 75.50, H 6.60, N 10.12.

(*S,E*)-*N'*-(3,4-dihydroxybenzylidene)-1-(4-methoxybenzyl)pyrrolidine-2-carbohydrazide (3i): ^{1}H NMR (DMSO-d_6): δ 11.28 (s, 1H), 11.11 (s, 1H), 9.14 (s, 1H), 8.50 (s, 1H), 7.92-7.27 (m, 2H), 6.89-6.82 (m, 5H), 3.74-3.71(d, J = 12.8Hz, 1H), 3.68 (s, 3H), 3.51-3.47 (d, J = 12.8Hz, 1H), 3.31-3.32 (m, 1H), 2.32-2.22 (m, 1H), 2.18-2.05 (m, 1H), 1.80-1.74 (m, 4H); Mass (m/z): 370.2 (M^+); Anal calc for $C_{20}H_{23}N_3O_4$ Calcd.: %C, 65.03; H, 6.28; N, 11.37. Found: %C 65.10, H 6.25, N 11.40.

Antimycobacterial activity

IC_{50} values for compounds **3a-3j** were determined against *M. smegmatis mc^{2}155* cells which were grown to saturation in broth medium at 37^{0}C. Antimycobacterial activity of the compounds was assayed by the broth dilution method. Rifampicin was used as the reference compound.

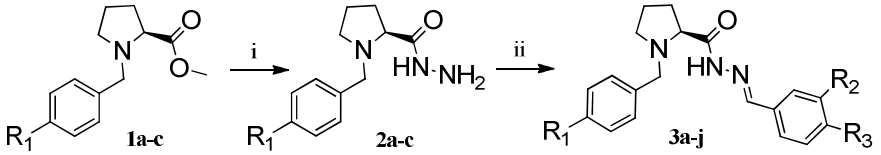
Docking Studies

High-throughput docking-based virtual screening was performed by using Auto Dock program version 4.2 [12]. The rotational bonds of the ligands were treated as flexible while those of the protein were kept rigid. Grid boxes were fixed around the *Smegmatis* Methionyl-TrnaSynthetasesite using erlotinib as the grid box center.

RESULTS AND DISCUSSION

Our research commenced with the synthesis of N-substituted esters **1a-c** from easily accessible (*S*)-2-carbomethoxypyrrolidine hydrochloride. Then compounds **1a-c** was treated with hydrazine hydrate to obtain corresponding pyrrolidine-2-carbohydrazides **2a-c.** Finally, these carbohydrazides **2a-c** were reacted with various aldehydes using catalytic amount of acetic acid in ethanol to afford novel hydrazones **3a-j** (**Scheme 1**) [13]. The structures of **3a-j** were established by ^{1}H NMR, mass and elemental analysis data.

Scheme 1. Synthesis of hydrazones 3a-i



a, R_1= F
b, R_1= NO_2
c, R_1= OCH_3

(a) R_1 = F, R_2 = H, R_3 = Ph (b) R_1= F, R_2 = H, R_3 = F
(c) R_1= F, R_2= H, R_3= OCH_3 (d) R_1= F, R_2= H, R_3= $COOCH_3$
(e) R_1= NO_2, R_2= H, R_3= Ph (f) R_1= NO_2 , R_2= OCH_3, R_3= H
(g) R_1= OCH_3, R_2= F , R_3= OCH_3 (h) R_1= OCH_3, R_2= H, R_3= Ph
(i) R_1= OCH_3, R_2= R_3= OH (j) R_1= R_2= F, R_3= $COOCH_3$

Reagents and conditions: (i) NH_2-NH_2, MeOH, 80 ^oC, 5 h (ii) aldehyde, EtOH, AcOH (cat), 80 ^oC, 6 h

The synthesized compounds **3a-j** were evaluated for their antimycobacterial activity in vitro against *M. smegmatis* (ATCC 35797) by broth dilution method and their IC_{50} values were determined [14] by employing Rifampicin as reference. Of all the tested compounds, **3h** was found to be more potent (**Table 1**). High activity of compound **3h** may be attributed to the presence of electron donating group on the benzyl moiety and electronically neutral phenyl group on the aldehyde motif. The compounds **3b**, **3d**, **3f** and **3g** showed mild activity while **3a**, **3c**, **3e**, **3i** and **3j** did not exhibit any activity. These results indicate that hydrazones synthesized from pyrrolidine-2-carboxylic acid have shown moderate activity against *M. smegmatis.*

On the other hand, molecular docking studies were performed with the crystallographic structure of smegmatis methionyl-trna synthetase to predict the binding confirmations of the experimentally proved biologically active ligands (**3b**, **3d**, **3f**, **3g**, **3h**) to that of targeted protein.

Table 1. Antimycobacterial of 3a-i against *M. smegmatis*

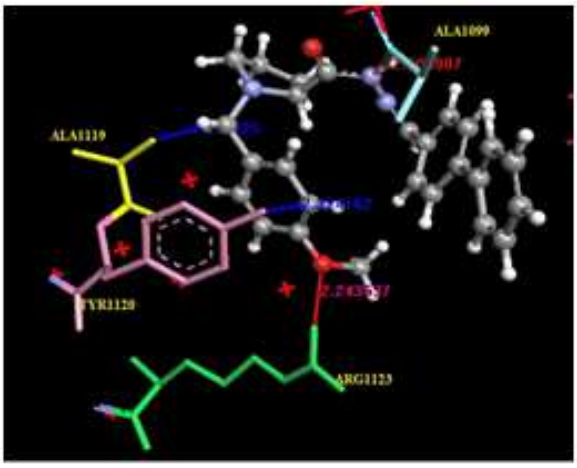
S.No.	Compound	IC_{50} (µg/mL)
1	**3a**	-[a]
2	**3b**	1218
3	**3c**	-
4	**3d**	1209
5	**3e**	-
6	**3f**	1100
7	**3g**	1070
8	**3h**	527
9	**3i**	-
10	**3j**	-
11	Rifampicin	2.0

[a] *No inhibition detected*

The binding model of compound **3h** with smegmatis methionyl-*trna* synthetase was depicted in **Figure 1**. The docking study of 3h (-7.12Kcal/mol, inhibition constant ki 6.03uM) with protein target reveals that both H-bonds as well as electrostatic interactions are formed with active site residues. In the binding model, **3h** is nicely bound to the smegmatis methionyl-*trna* synthetase with its oxygen atom of methoxy group projecting towards the active site residue of ARG1123 and the oxygen atom forms strong hydrogen bond (2.24A^o) interaction with ARG1123. Meanwhile, the hydrazide group of **3h** forms hydrogen bond with ALA1099, whereas TYR1120 (2.32A^o) and ALA1119 (2.4A^o) are involved in other non-bonded interactions like polar, electrostatic and hydrophobic

interactions. The experimental bioassay and docking studies suggested that the compound **3h** was potential inhibitor for smegmatis methionyl-*trna* synthetase.

Figure 1. Docked conformation of 3h[a]



[a]3h (Grey colored ball and stick model), red dotted lines represent H-bond interactions and blue dotted lines represent hydrophobic interactions

CONCLUSION

In conclusion, a series of novel *L*-Proline based hydrazones **3a-j** were synthesized and characterized for screening of potential antimycobacterial smegmatis agents. The structure **3h** is considered as preferred compound with low Average IC_{50} value 527 uM. Docking results also revealed that the compound **3h** exhibited very good binding energy with minimum inhibition constant value. Further structural tuning of these new hydrazones would provide valid lead compounds against *M. smegmatis*.

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