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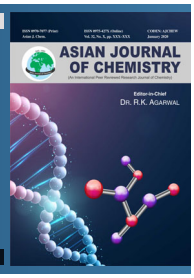

in silico Design, ADME Prediction, Molecular Docking, Synthesis of Novel Triazoles, Indazoles & Aminopyridines and *in vitro* Evaluation of Antitubercular Activity

S. Triveni[1], C. Naresh Babu[2], E. Bhargav[2], M. Vijaya Jyothi[1,*]

[1]Department of Pharmaceutical Chemistry, Raghavendra Institute of Pharmaceutical Education and Research, Ananthapuramu-515001, India
[2]Molecular Modelling and Drug Discovery Division, RERDS-CPR, Raghavendra Institute of Pharmaceutical Education and Research, Ananthapuramu-515001, India

*Corresponding author: Fax: +91 8554 255646; E-mail: drmvjyothiriper@gmail.com

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To design and synthesize novel triazoles, indazoles and aminopyridines from various (thiophene-2-yl)prop-2-en-1-one derivatives as antitubercular leads by *in silico* and *in vitro* methods. *in silco* Drug design, ADME prediction and molecular docking studies were performed to assess drug likeliness and antitubercular potential of all 30 novel triazoles, indazoles and aminopyridines. *in silico* Drug design studies revealed that the synthetic routes applied were appropriate according to the calculations of Swiss-ADME that measure synthetic accessibility. Most of the synthesized compounds found to have considerable binding score with enoyl ACP reductase enzyme of *Mycobacterium tuberculosis*. All the synthesized compounds were evaluated for antitubercular potential against Drug Resistant *Mycobacterium tuberculosis* H37Rv strain by Luciferase reporter assay method. Most of the synthesized compounds exhibited remarkable antitubercular potential against resistant strain.

Keywords: Triazoles, Indazoles and Aminopyridines, Enoyl ACP reductase, Luciferase reporter assay.

INTRODUCTION

Indazoles, triazoles and aminopyridine derivatives are the important pharmacophores in modern drug discovery [1,2]. Several therapeutic activities like antimicrobial, antifungal anticancer, analgesic, antitubercular, *etc*. were reported for these molecules [3]. Among various methods available for the synthesis of chalcones (α,β-unsaturated carbonyl compounds), Claisen-Schmidt condensation reaction is the most versatile, economic method to synthesize chalcones with appreciable yields. It involves condensation of aromatic/hetero aromatic aldehydes with aromatic or heteroaromatic ketone in presence of aqueous base yield a chalcone [4].

In present study, an attempt is made to synthesize aminopyridines by condensation of chalcones with a nucleophile containing acidic moiety, where ammonium acetate being an acidic nucleophile in presence of ethanol imparts condensation to obtain substituted pyridines in the form of nicotine nitriles. In continuation of our work to develop novel heterocyclic compounds, the present research is aimed to synthesize the above moieties from chalcones [4,5] *via* Claisen-Schmidt condensation reaction [6,7] using 2-acetyl thiophene and several aromatic aldehydes.

in silico ADME tool, helps to find a drug/a molecule which reach its specific target of enzyme or receptor in sufficient concentration to show biological activity. *in silico* Drug design approach has been made using Glide docking approach prior to synthesize the molecules. For molecular docking crystal structure of *Mycobacterium tuberculosis* enoyl ACP reductase [8-10] (InhA) inhibited by triclosan (2B35) had been selected from protein data bank since the enzymes play an important role in synthesis of mycolic acid, an essential component of mycobacterial cell wall. The results obtained has been supported the present research for evaluation of antitubercular activity by Luciferase reporter assay method.

EXPERIMENTAL

Chemsketch software was used to draw the structures of designed molecules. Molecular properties like log P, solubility, Total polar surface area, number of hydrogen bond acceptors

and donors, Lipinski violations, drug likeliness were calculated using SWISS ADME online drug design software. Scrodinger's Glide version was used for molecular docking. Melting points were determined on a capillary melting point apparatus. ^{1}H NMR spectra were recorded in the indicated solvent on Bruker AMX 400 MHz spectrophotometer using TMS as an internal standard. An elemental analysis was performed on carlo Ebra 1108 element analyzer and were within the ± 0.5% of the theoretical values. Mass spectra were run on Hewlett Packard 5988 spectrophotometer. All the chemicals used in the study were purchased from Sigma-Aldrich.

General procedure for synthesis of unsaturated carbonyl compounds (C_{1-10}): Aromatic aldehydes (0.005 M) were dissolved in a minimum amount of menthol. To this 10% sodium hydroxide (not to exceed 0.001 M) was added dropwise then stirred with a glass rod to get clear solution. This mixture was tested with litmus for alkalinity. To this alkaline solution, 2-acetyl thiophene (0.005 M) was added slowly. This reaction mixture was stirred about 4-6 h at room temperature. The obtained solid was dried and recrystallized with methanol. The completion of the reaction was monitored by TLC by using the solvent system ethyl acetate:*n*-hexane (7:3) (**Scheme-I**).

3-(4-Nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (C_1): m.f.: $C_{13}H_9NO_3S$, Yield: 85%, m.p. 140-142 ºC; R_f value 0.818; IR (KBr, ν_{max}, cm^{-1}): 1600.97 (arom. C=C *str.*), 1731.56 (C=O *str.*), 1341.73 (C-N *str.* nitro group), 1106.21 (C-S *str.*), 835.93 (C-H arom.); ^{1}H NMR (500 MHz, CH_3OD) δ 7.165-7.891 (7H, d and t aromatic and thiophene rings), δ 4.912 (1H, d, CH), δ 5.395 (1H, d, CH); Mass: *m/z* 259.3016.

3-(Pyridine-2yl)-1-(thiophene-2-yl)prop-2-en-1-one (C_2): m.f.: $C_{12}H_9O_1N_1S$, Yield: 83%, m.p. 90 ºC; R_f value 0.72; IR (KBr, ν_{max}, cm^{-1}): 1606.08 (arom. C=C *str.*), 1729.25 (C=O *str.*), 1519.66 (C-N *str.* nitro group), 661.23 (C-S *str.*), 1655.50 (C-H arom.); Mass: *m/z* 215.274.

3-(1*H*-Pyrrol-2yl)-1-(thiophene-2-yl)prop-2-en-1-one (C_3): m.f.: $C_{11}H_9O_1N_1S$, Yield: 71%, m.p. 140 ºC; R_f value 0.83; IR (KBr, ν_{max}, cm^{-1}): 1746.64 (C-H arom.); 1729.25 (C=O *str.*), 1513.72 (C-N *str.* nitro group), 980.10 (arom. C=C *str.*), 689.21 (C-S *str.*); Mass: *m/z* 203.84.

3-(4-Methoxyphenyl)-1-(thiophene-2-yl)prop-2-en-1-one (C_4): m.f.: $C_{14}H_{12}O_2S$, Yield: 76%, m.p. 110 ºC; R_f value 0.68; IR (KBr, ν_{max}, cm^{-1}): 1746.64 (C-H arom.); 1729.25 (C=O *str.*), 1513.72 (C-N *str.* nitro group), 980.10 (arom. C=C *str.*), 689.21 (C-S *str.*); Mass: *m/z* 244.33.

3-(4-Hydroxy-3-methoxyphenyl)-1-(thiophene-2-yl)-prop-2-en-1-one (C_5): m.f.: $C_{14}H_{12}O_3S$, Yield: 68%, m.p. 125 ºC; R_f value 0.853; IR (KBr, ν_{max}, cm^{-1}): 2857.59 (C-O *str.* methoxy group), 1657.76 (C=O *str.*), 1061.52 (C-S *str.*), 1414.26 (C=C arom.), 938.61 (arom. C=C *str.*); Mass: *m/z* 260.3047.

3-(Anthraene-10-yl)-1-(thiophene-2-yl)prop-2-en-1-one (C_6): m.f.: $C_{21}H_{14}OS$, Yield: 76%, m.p. 212-214 ºC; R_f value 0.76; IR (KBr, ν_{max}, cm^{-1}): 2857.59 (C-O *str.* methoxy group), 1657.76 (C=O *str.*), 1612 (arom. C=C *str.*), 1414.26 (C=C arom.), 1061.52 (C-S *str.*); Mass: *m/z* 314.304.

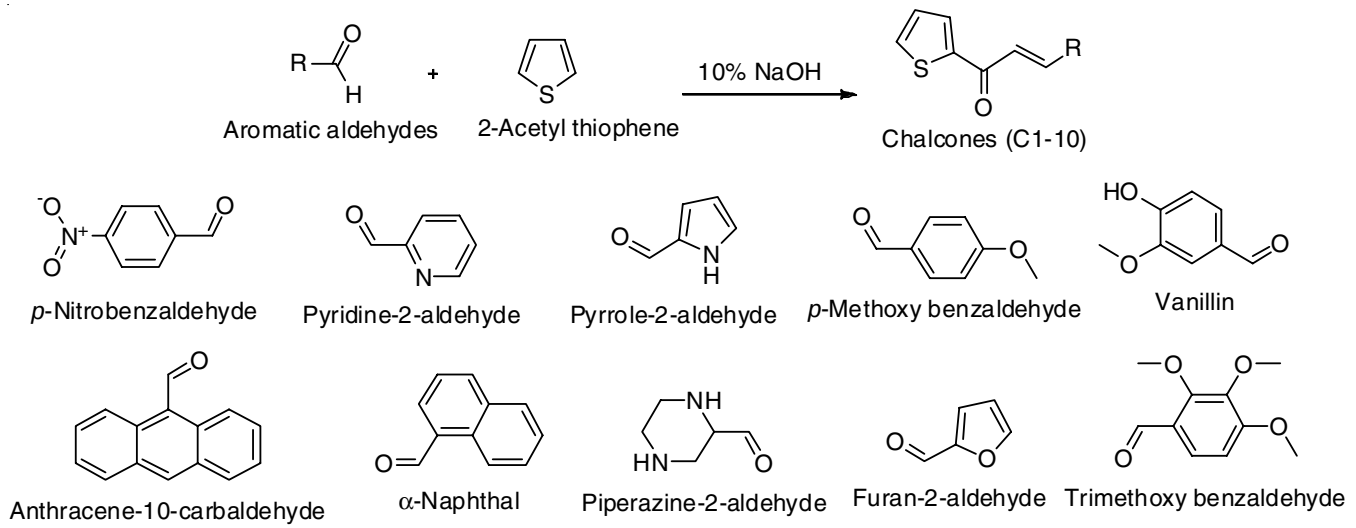
3-(1-Napthyl)-1-(thiophene-2-yl)prop-2-en-1-one (C_7): m.f.: $C_{17}H_{12}OS$, Yield: 78%, m.p. 182-184 ºC; R_f value 0.81; IR (KBr, ν_{max}, cm^{-1}): 1673 (C=O *str.*), 1617 (arom. C=C *str.*), 853 (C-S *str.*); Mass: *m/z* 264.30.

3-(2-Piperazinyl)-1-(thiophene-2-yl)prop-2-en-1-one (C_8): m.f.: $C_{11}H_{14}N_2OS$, Yield: 64%, m.p. 164-166 ºC; R_f value 0.6; IR (KBr, ν_{max}, cm^{-1}): 1679 (C=O *str.*), 1621 (arom. C=C *str.*), 862 (C-N-H piperazine), 852 (C-S *str.*); Mass: *m/z* 222.304.

3-(2-Furanyl)-1-(thiophene-2-yl)prop-2-en-1-one (C_9): m.f.: $C_{11}H_8O_2S$, Yield: 69%, m.p. 176-178 ºC; R_f value 0.81; IR (KBr, ν_{max}, cm^{-1}): 1673 (C=O *str.*), 1617 (arom. C=C *str.*), 1024 (C-O *str.* in furan), 853 (C-S *str.*); Mass: *m/z* 204.247.

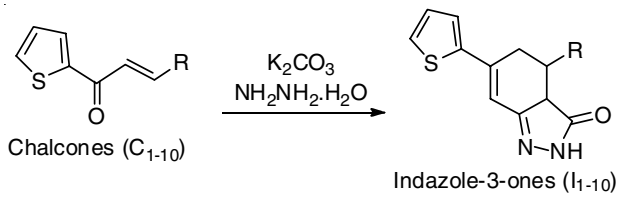
3-(3,4,5-Tri methoxy phenyl-1-yl)-1-(thiophene-2-yl)-prop-2-en-1-one (C_{10}): m.f.: $C_{16}H_{16}O_4S$, Yield: 66%, m.p. 252-254 ºC; R_f value 0.71; IR (KBr, ν_{max}, cm^{-1}): 1684 (C=O *str.*), 1622 (arom. C=C *str.*), 1142 (C-O *str.* in methoxy, 849 (C-S *str.*); Mass: *m/z* 304.37.

General procedure for synthesis of indazole-3-ones (I_{1-10}): To a 0.0025 M of chalcones (C_{1-10}), a mixture of 0.0025 M of ethyl acetoacetate, 1 or 2 drops of acetone, 0.3265 g of K_2CO_3 and 0.0025 M of hydrazine hydrate was added then stirred to get a clear solution. Acetone (1-2 drops) was added to ensure the solubility. Then this mixture was stirred about 2-3 h. The



Scheme-I: Synthetic route of chalcones (C_{1-10})

obtained solid was dried and recrystallized with methanol. The completion of the reaction was monitored by TLC using the solvent system toluene:methanol (6:4) [11] (**Scheme-II**).



Scheme-II: Synthetic route of indazole-3-ones (I_{1-10})

4-(4-Nitrophenyl)-6-(thiophene-2-yl)-4,5-dihydro-2*H*-indazol-3*H*-one (I_1): m.f.: $C_{17}H_{13}N_3O_3S$, Yield: 75%, m.p. 257 ºC; R_f value 0.82; IR (KBr, ν_{max}, cm^{-1}): 3412.21 (N-H indazole), 3010 (arom. C-H *str.*), 1673.48 (C=O *str.*), 1421 (C=C arom. *str.*), 1358 (C=N indazole), 1072 (N-N indazole), 1058.52 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz) 7.0 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.0 (1H, d, t, thiophene ring), 8.11 (1H, d, aromatic ring), 7.39 (2H, d, aromatic ring); Mass: *m/z* 339.3.

4-(Pyridin-2-yl)-6-(thiophene-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_2): m.f.: $C_{15}H_{13}N_3OS$, Yield: 86%, m.p. 386 ºC; R_f value 0.748; IR (KBr, ν_{max}, cm^{-1}): 3296.14 (N-H indazole), 2924.08 (arom. C-H *str.*), 1358 (C=N indazole), 1069.71 (N-N indazole), 838.51 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz) (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 7.29 (1H, d, pyridine ring), 8.62 (1H, d, pyridine ring), 7.23 (1H, t, pyridine ring), 7.67 (1H, t, pyridine ring); Mass: *m/z* 281.0582.

4-(1*H*-Pyrrol-2-yl)-6-(thiophene-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_3): m.f.: $C_{16}H_{13}N_3OS$, Yield: 82%, m.p. 469 ºC; R_f value 0.782; IR (KBr, ν_{max}, cm^{-1}): 3312.04 (N-H indazole), 3097.78 (arom. C-H *str.*), 1689.18 (C=O *str.*), 1421.65 (C=C arom. *str.*), 1361.02 (C=N indazole), 1068.76 (N-N indazole), 857.65 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz) 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 6.36 (1H, t, pyrrole ring), 5.89 (1H, d, pyrrole ring), 5.72 (1H, d, pyrrole ring); Mass: *m/z* 814.7.

4-(4-Methoxyphenyl)-6-(thiophene-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_4): m.f.: $C_{18}H_{16}N_2O_2S$, Yield: 79%, m.p. 234 ºC; R_f value 0.722; IR (KBr, ν_{max}, cm^{-1}): 3452.42 (N-H indazole), 1663.57 (C=O *str.*), 1510.27 (arom. C=C *str.*), 1465.81 (C=C arom.), 1357.32 (C=N indazole), 1071.32 (N-N indazole), 849.98 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz) 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 6.69 (2H, d, aromatic ring), 7.02 (1H, d, aromatic ring); Mass: *m/z* 324.09.

4-(4-Hydroxy-3-methoxyphenyl)-6-(thiophene-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_5): m.f.: $C_{18}H_{16}N_2O_3S$, Yield: 79%, m.p. 295 ºC; R_f value 0.853; IR (KBr, ν_{max}, cm^{-1}): 3478.42 (N-H indazole), 3228.17 (O-H *str.*), 1674.23 (C=O *str.*), 1617.32 (arom. C=C *str.*), 1423.36 (C=C arom.), 1348.67 (C=N indazole), 1077.38 (N-N indazole); 853.21 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz) 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 5.0 (1H, S, aromatic ring, OH), 6.52 (1H, d, aromatic ring), 6.54 (1H, d, aromatic ring), 6.47 (1H, S, aromatic ring); Mass: *m/z* 340.4.

4-(Anthracene-10-yl)-6-(thiophen-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_6): m.f.: $C_{25}H_{18}N_2OS$, Yield: 81%, m.p. 257 ºC; R_f value 0.835; IR (KBr, ν_{max}, cm^{-1}): 3442.05 (N-H indazole); 1679.78 (C=O *str.*), 1620.37 (arom. C=C stretch), 1409.34 (C=C arom.) 1356.42 (C=N indazole) 1075.67 (N-N indazole), 851.67 (C-S *str.*); Mass: *m/z* 394.1, ^{1}H NMR (DMSO, 300 MHz) 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 7.30 (2H, t, anthracene ring), 7.31 (2H, t, anthracene ring), 7.51 (1H, s, anthracene ring), 7.65 (2H, d, anthracene ring), 7.72 (2H, d, anthracene ring).

4-(Naphthalene-1-yl)-6-(thiophen-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_7): m.f.: $C_{21}H_{16}N_2OS$, Yield: 76%, m.p. 232 ºC; R_f value 0.721; IR (KBr, ν_{max}, cm^{-1}): 3512.23 (N-H indazole); 3081 (arom. C-H *str.*), 1678.84 (C=O *str.*), 1517.23 (C=C arom.), 1457.67 (arom. C=C *str.*), 1354.48 (C=N indazole), 1067 (N-N indazole), 854.31 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 7.19 (1H, t, naphthalene ring), 7.10 (1H, d, naphthalene ring), 7.29 (1H, t, naphthalene ring), 7.31 (1H, t, naphthalene ring), 7.77 (1H, d, naphthalene ring), 7.64 (1H, d, naphthalene ring), 7.51 (1H, d, naphthalene ring); Mass: *m/z* 344.43.

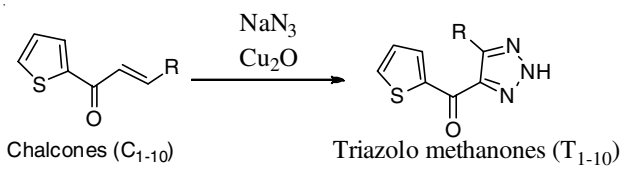
4-(Piperazine-2-yl)-6-(thiophen-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_8): m.f.: $C_{15}H_{18}N_4OS$, Yield: 82%, m.p. 219 ºC; R_f value 0.797; IR (KBr, ν_{max}, cm^{-1}): 3490.35 (N-H indazole); 1684.45 (C=O *str.*), 1601 (C=C arom.), 1518 (arom. C=C *str.*), 1351.23 (C=N indazole), 1071.87 (N-N indazole), 859.71 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 2.0 (2H, s, piperazine ring, NH), 2.76, 2.51 (2H, t, piperazine ring), 2.69, 2.66 (2H, Q, piperazine ring), 2.72, 2.62 (2H, Q, piperazine ring); Mass: *m/z* 302.39.

4-(Furan-2-yl)-6-(thiophen-2-yl)-4,5-dihydro-2*H*-indazol-3-one (I_9): m.f.: $C_{15}H_{12}N_2O_2S$, Yield: 74%, m.p. 234 ºC; R_f value 0.813; IR (KBr, ν_{max}, cm^{-1}): 3457.87 (N-H indazole); 1668.72 (C=O *str.*), 1464.37 (arom. C=C *str.*), 1350.13 (C=N indazole), 1076.78 (N-N indazole), 1023 (C-O *str.* furan group), 849.93 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 5.88

(1H, d, furan ring), 6.18 (1H, t, furan ring), 7.21 (1H, d, furan ring); Mass: *m/z* 284.33.

4-(Thiophene-2-yl)-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-2*H*-indazol-3-one (I_{10}): m.f.: $C_{20}H_{20}N_2O_4S$, Yield: 78%, m.p. 238 ºC; R_f value 0.753; IR (KBr, ν_{max}, cm^{-1}): 3507.89 (N-H indazole); 2849.78 (C-O *str.* methoxy group), 1663.45 (C=O *str.*), 1489.89 (C=C arom.), 1487.23 (arom. C=C *str.*), 1351.78 (C=N indazole), 1075.45 (N-N indazole),849.89 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, s, indazole ring), 5.3 (1H, s, indazole ring), 3.0 (1H, t, indazole ring), 2.8 (1H, d, indazole ring), 2.38, 2.13 (2H, d, indazole ring), 7.0 (1H, d, t, thiophene ring), 7.2 (1H, d, thiophene ring), 6.09 (2H, S, aromatic ring); Mass: *m/z* 384.45.

General procedure for synthesis of triazolo methanones (T_{1-10}): To 0.0025 M of chalcone (C_{1-10}), mixture of 0.0025 M of sodium azide and 0.0025 M of cupric oxide as a catalyst and 1-2 drops of methanol to ensure the solubility of reactants were added then stirred well. The obtained mixture was refluxed for 6-8 h. The obtained solid was dried and recrystallized from methanol. The completion of the reaction was monitored by TLC using the solvent system ethyl acetate:*n*-hexane (7:3) **(Scheme-III)**.



Scheme-III: Synthetic route of triazolo methanones (T_{1-10})

(5-(4-Nitrophenyl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_1): m.f.: $C_{13}H_8N_4O_3S$, Yield: 79%, m.p. 252 ºC; R_f value 0.768; IR (KBr, ν_{max}, cm^{-1}): 3459.87 (N-H triazole); 1668.89 (C=O *str.*), 1554 (N-O in nitro group), 1415.34 (arom. C=C *str.*), 1353.26 (C=N triazole), 1076.09 (N-N triazole), 861.56 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 7.74 (2H, d, aromatic ring), 8.25 (2H, d, aromatic ring), 5.0 (1H, s, triazole); Mass: *m/z* 300.2034.

(5-(Pyridine-2-yl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_2): m.f.: $C_{12}H_8N_4OS$, Yield: 74%, m.p. 285 ºC; R_f value 0.812; IR (KBr, ν_{max}, cm^{-1}): 3527.29 (N-H triazole); 1653.05 (C=O *str.*), 1497.11 (C=C arom.), 1392.12 (C=N triazole), 1094.97 (N-N triazole), 864.97 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 7.34 (1H, t, pyridine ring), 7.60 (1H, d, pyridine ring), 7.81 (1H, t, pyridine ring), 8.65 (1H, d, pyridine ring); Mass: *m/z* 256.2135.

(5-(1*H*-Pyrrol-2-yl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_3): m.f.: $C_{11}H_8N_4OS$, Yield: 81%, m.p. 231 ºC; R_f value 0.792; IR (KBr, ν_{max}, cm^{-1}): 3326.33 (N-H indazole, 3089.24 (arom. C-H *str.*), 1566.06 (arom. C=C *str.*), 1361.58 (C=N indazole), 1079.56 (N-N indazole), 862.29 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 6.1 (2H, d, t, pyrrole ring), 5.0 (1H, s, pyrrole ring, NH), 6.6 (1H, d, pyrrole ring); Mass: *m/z* 244.2035.

(5-(4-Methoxyphenyl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_4): m.f.: $C_{14}H_{11}N_3O_2S$, Yield: 86%, m.p. 247 ºC; R_f value 0.862; IR (KBr, ν_{max}, cm^{-1}): 3510.87 (N-H triazole), 2785.67 (C-O *str.* methoxy group), 1685.23 (C=O *str.*), 1567.42 (arom. C=C *str.*), 1357.68 (C=N triazole), 1072.76 (N-N triazole), 1013.23 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 5.0 (1H, s, pyrrole ring, NH), 7.37 (2H, d, aromatic ring), 6.83 (2H, d, aromatic ring); Mass: *m/z* 285.2176.

(5-(4-Hydroxy-3-methoxyphenyl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_5): m.f.: $C_{14}H_{11}N_3O_3S$, Yield: 76%, m.p. 234 ºC; R_f value 0.761; IR (KBr, ν_{max}, cm^{-1}): 3389.34 (N-H triazole), 3319.70 (O-H), 2849.76 (C-O *str.* in methoxy), 1663.91 (C=O *str.*), 1348.87 (C=N triazole), 1052.34 (C-S *str.*), 1068.21 (N-N triazole), 852.23 (arom. C=C *str.*); Mass: *m/z* 301.32, ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 5.0 (1H, s, pyrrole ring, NH), 6.82 (1H, s, aromatic ring), 6.87 (1H, d, aromatic ring), 6.68 (1H, d, aromatic ring), 5.0 (1H, s, aromatic ring).

(5-(Anthracen-10-yl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2yl)methanone (T_6): m.f.: $C_{21}H_{13}N_3OS$, Yield: 81%, m.p. 259 ºC; R_f value 0.864; IR (KBr, ν_{max}, cm^{-1}): 3498.41 (N-H triazole); 3096.64 (arom. C-H), 1678.34 (C=O *str.*), 1567.56 (arom. C=C *str.*), 1478.64 (C=C arom.), 1351.43 (C=N triazole), 1078.35, (N-N *str.* triazole), 957.23 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 5.0 (1H, s, pyrrole ring, NH), 7.32 (4H, t, anthracene ring), 7.67 (4H, d, anthracene ring), 7.63 (1H, s, anthracene ring); Mass: *m/z* 355.41.

(5-(Naphthalen-1-yl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_7): m.f.: $C_{17}H_{11}N_3OS$, Yield: 72%, m.p. 231-234 ºC; R_f value 0.771; IR (KBr, ν_{max}, cm^{-1}): 3519.63 (N-H indazole); 3083.87 (aromatic C-H *str.*), 1665.68 (C=O *str.*), 1587.31 (arom. C=C *str.*), 1354.35 (C=N triazole), 1037.31 (C-S *str.*), 1069.87 (N-N triazole); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 5.0 (1H, s, pyrrole ring, NH), 7.32 (2H, t, naphthalene ring), 7.67 (2H, d, naphthalene ring), 7.63 (1H, d, naphthalene ring), 7.38 (1H, t, naphthalene ring), 7.54 (1H, d, naphthalene ring); Mass: *m/z* 305.06.

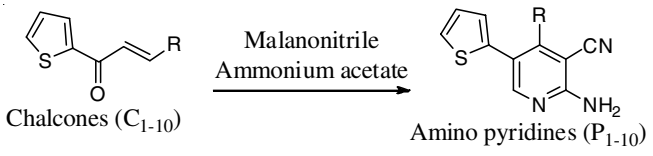
(5-(Piperazine-2-yl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_8): m.f.: $C_{11}H_{13}N_3OS$, Yield: 84%, m.p. 243-246 ºC; R_f value 0.852; IR (KBr, ν_{max}, cm^{-1}): 3348.23 (N-H triazole); 3091.54 (C-H arom.), 1682.46 (C=O *str.*), 1497.78 (arom. C=C *str.*), 1353.67 (C=N triazole), 1071.42 (N-N triazole), 1059.87 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 4.14 (1H, t, piperazine ring), 2.0 (2H, s, piperazine ring, NH), 3.09, 2.84 (2H, t, piperazine ring), 2.72, 2.62 (2H, Q, piperazine ring), 2.69, 2.66 (2H, Q, piperazine ring); Mass: *m/z* 263.32.

(5-(Furan-2-yl)-2*H*-1,2,3-triazol-4-yl)(thiophene-2-yl)methanone (T_9): m.f.: $C_{11}H_7N_3O_2S$, Yield: 75%, m.p. 221-224 ºC; R_f value 0.763; IR (KBr, ν_{max}, cm^{-1}): 3346.89 (N-H triazole), 3087.32 (C=C arom.), 1663.21 (C=O *str.*), 1402.23 (arom. C=C *str.*), 1353.67 (C=N triazole), 1068.93 (N-N triazole), 1021.22 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t,

thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 5.0 (1H, s, pyrrole ring, NH), 6.3 (1H, d, t, furan ring), 7.4 (1H, d, furan ring); Mass: *m/z* 245.26.

Thiophen-2-yl-(5-(3,4,5-trimethoxyphenyl)-2*H*-1,2,3-triazol-4-yl)methanone (T_{10}): m.f.: $C_{16}H_{15}N_3O_4S$, Yield: 79%, m.p. 266-269 °C; R_f value 0.824; IR (KBr, ν_{max}, cm^{-1}): 3423.75 (N-H triazole), 3098.67 (C-H arom.), 2798.59 (C-O *str.* methoxy group), 1675.87 (C=O *str.*), 1498.76 (arom. C=C *str.*), 1348.90 (C=N triazole), 1069.23 (N-N triazole), 897.87 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.06 (1H, t, thiophene), 7.61 (1H, d, thiophene), 7.65 (1H, d, thiophene), 5.0 (1H, s, pyrrole ring, NH), 6.44 (1H, s, aromatic ring); Mass: *m/z* 345.08.

General procedure for synthesis of aminopyridine derivatives (P_{1-10}): To 0.0025 M of chalcone **(C_{1-10})**, mixture of 0.0025 M of malanonitrile and 0.0025 M of ammonium acetate were taken in a beaker, stirred well with a magnetic stirrer about 6-8 h. The obtained solid was dried and recrystallized with methanol. The completion of the reaction was monitored by TLC using the solvent system ethyl acetate:*n*-hexane (6:4) [12] (**Scheme-IV**).



Chalcones (C_{1-10}) Amino pyridines (P_{1-10})

Scheme-IV: Synthetic route of aminopyridine derivatives (**P_{1-10}**)

2-Amino-4-(4-nitrophenyl)-6-(thiophene-2-yl)nicotinonitrile (P_1): m.f.: $C_{16}H_{10}N_4O_2S$, Yield: 78%, m.p. 255-259 ºC; R_f value 0.821; IR (KBr, ν_{max}, cm^{-1}): 3487.76 (N-H *str.*), 3164.37 (C-H arom.), 2247 (-C≡N), 1587.64 (arom. C=C *str.*), 864.43 (C-S *str.*), 1518.469 (N-O *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 7.74 (2H, d, aromatic ring), 8.25 (2H, d, aromatic ring); Mass: *m/z* 322.05.

2-Amino-4-(pyridine-2-yl)-6-(thiophene-2-yl)nicotinonitrile (P_2): m.f.: $C_{15}H_{10}N_4S$, Yield: 84%, m.p. 271-274 ºC; R_f value 0.872; IR (KBr, ν_{max}, cm^{-1}): 3339.28 (NH group), 3209.47 (arom. C-H *str.*), 2210.53 (-C≡N), 1412.81 (arom. C=C *str.*), 854.31 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 7.98 (1H, s, pyridine ring), 7.6 (1H, d, pyridine ring), 8.65 (1H, d, pyridine ring), 7.81 (1H, t, pyridine ring), 7.34 (1H, t, pyridine ring); Mass: *m/z* 278.25.

2-Amino-4-(1*H*-pyrrol-2-yl)-6-(thiophene-2-yl)nicotinonitrile (P_3): m.f.: $C_{15}H_{10}N_4S$, Yield: 84%, m.p. 271-274 ºC; R_f value 0.872; IR (KBr, ν_{max}, cm^{-1}): 3384.76 (N-H *str.*), 3098.57 (C-H arom.), 2247.00 (-C≡N), 1523.66 (arom. C=C *str.*), 1365.09 (C=N *str.*), 856.23 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 5.0 (1H, S, pyrrole ring, NH), 6.1 (1H, d, t, pyrrole ring), 6.6 (1H, d, pyrrole ring); Mass: *m/z* 278.06.

2-Amino-4-(4-methoxyphenyl)-6-(thiophene-2-yl)-nicotinonitrile (P_4): m.f.: $C_{17}H_{13}N_3OS$, Yield: 84%, m.p. 251-253 ºC; R_f value 0.798; IR (KBr, ν_{max}, cm^{-1}): 3166.59 (C-H arom.), 2834.24 (C-O *str.* methoxy group), 2211.61 (-C≡N), 1435.63 (arom. C=C *str.*), 1361.13 (C=N in pyrimidine), 857.10 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 7.37 (2H, d, aromatic ring), 6.83 (2H, d, aromatic ring); Mass: *m/z* 307.25.

2-Amino-4-(4-hydroxy-3-methoxyphenyl)-6-(thiophene-2-yl)nicotinonitrile (P_5): m.f.: $C_{17}H_{13}N_3O_2S$, Yield: 89%, m.p. 286-288 ºC; R_f value 0.832; IR (KBr, ν_{max}, cm^{-1}): 3382.87 (NH *str.*), 3087.21 (C-H arom.), 2837 (C-O-C in methoxy), 2243.37 (-C≡N), 1564.21 (arom. C=C *str.*), 857.12 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 6.82 (1H, s, aromatic ring), 6.68 (1H, d, aromatic ring), 6.87 (1H, d, aromatic ring), 5.0 (1H, s, aromatic ring, OH); Mass: *m/z* 323.07.

2-Amino-4-(anthracen-10-yl)-6-(thiophene-2-yl)nicotinonitrile (P_6): m.f.: $C_{24}H_{15}N_3S$, Yield: 76%, m.p. 234-237 ºC; R_f value 0.765; IR (KBr, ν_{max}, cm^{-1}): 1485.43 (arom. C=C *str.*), 845.87 (C-S *str.*), 3097.23 (C-H arom.), 2210.45 (-C≡N), 3387.89 (N-H *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 7.32 (4H, t, anthracene ring), 7.67 (4H, d, anthracene ring), 7.63 (1H, s, anthracene ring); Mass: *m/z* 377.1.

2-Amino-4-(naphthalen-1-yl)-6-(thiophene-2-yl)-nicotinonitrile (P_7): m.f.: $C_{20}H_{13}N_3S$, Yield: 82%, m.p. 257-259 ºC; R_f value 0.812; IR (KBr, ν_{max}, cm^{-1}): 3456.87 (NH *str.*), 3102.26 (C-H arom.), 2255.65 (-C≡N), 1437.63 (arom. C=C *str.*), 843.67 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 7.32 (2H, t, naphthalene ring), 7.67 (2H, d, naphthalene ring), 7.54 (1H, d, naphthalene ring), 7.38 (1H, t, naphthalene ring), 7.63 (1H, d, naphthalene ring); Mass: *m/z* 327.08.

2-Amino-4-(piperazin-2-yl)-6-(thiophene-2-yl)nicotinonitrile (P_8): m.f.: $C_{14}H_{15}N_5S$, Yield: 87%, m.p. 272-275 ºC; R_f value 0.865; IR (KBr, ν_{max}, cm^{-1}): 3346.38 (NH *str.*), 3094.72 (C-H arom.), 2175.36 (-C≡N), 1487.33 (arom. C=C *str.*), 863.56 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.28 (1H, d, pyridine ring), 2.0 (2H, s, piperazine ring, NH), 3.09, 2.84 (2H, t, piperazine ring), 2.72, 2.62 (2H, Q, piperazine ring), 2.69, 2.66 (2H, Q, piperazine ring); Mass: *m/z* 285.1.

2-Amino-4-(furan-2-yl)-6-(thiophene-2-yl)nicotinonitrile (P_9): m.f.: $C_{14}H_9N_3OS$, Yield: 87%, m.p. 265-267 ºC; R_f value 0.795; IR (KBr, ν_{max}, cm^{-1}): 3286.82 (NH *str.*), 3103.72 (C-H arom.), 2255.13 (-C≡N), 1407.83 (arom. C=C *str.*), 1023.17 (C-O *str.* in furan), 835.75 (C-S *str.*); ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 6.3 (1H, d, t, furan ring), 7.4 (1H, d, furan ring); Mass: *m/z* 269.05.

2-Amino-6-(thiophene-2-yl)-4-(3,4,5-trimethoxyphenyl)nicotinonitrile (P_{10}): m.f.: $C_{19}H_{17}N_3O_3S$, Yield: 83%,

m.p. 224-226 ºC; R_f value 0.834; IR (KBr, ν_{max}, cm^{-1}): 3379.73 (NH *str.*), 3087.76 (C-H arom.), 2846.61 (C-O-C *str.* in trimethoxy), 2245.33 (-C≡N), 1434.47 (arom. C=C *str.*), 857.75 (C-S *str.*); Mass: *m/z* 367.1, ^{1}H NMR (DMSO, 300 MHz): 7.0 (1H, t, thiophene ring), 7.0 (1H, d, thiophene ring), 7.2 (1H, d, thiophene ring), 4.0 (2H, s, pyridine ring), 7.47 (1H, s, pyridine ring), 6.44 (2H, d, aromatic ring).

***in silico* ADME studies:** *in silico* online data base Swiss ADME tool was used to get ADME properties like log P, molar refractivity, TPSA, HBA, HBD, RB, GI absorption, BBB permeability, log K_p, solubility, synthetic accessibility, *etc*. by providing synthesized molecular structures SMILES notation.

Molecular docking

Ligand preparation: The synthesized chemical compounds structures were imported into maestro Schrodinger software by their SMILES notation in 2D Sketcher. All ligands were subjected to Ligprep, the required parameters ionization (Neutralize), chirality, computation *etc*., were selected and energy minimized ligands saved in working directory file.

Macromolecule (protein) preparation: In protein preparation wizard, the protein is included into workspace by giving the code 2B35 (it uses protein data bank (PDB) to import the protein). This protein is initially pre-processed, in review and modify chain A is kept along with co-crystal TCL (Triclosan) and rest of the chains B, C, D, E and F (unique chains as like chain A) were deleted. Further in refine it was optimized and minimized. The Ramachandran plot is a plot of the torsional angles (ϕ) and (ψ) of the residues (amino acids) contained in a peptide represented in Fig. 1.

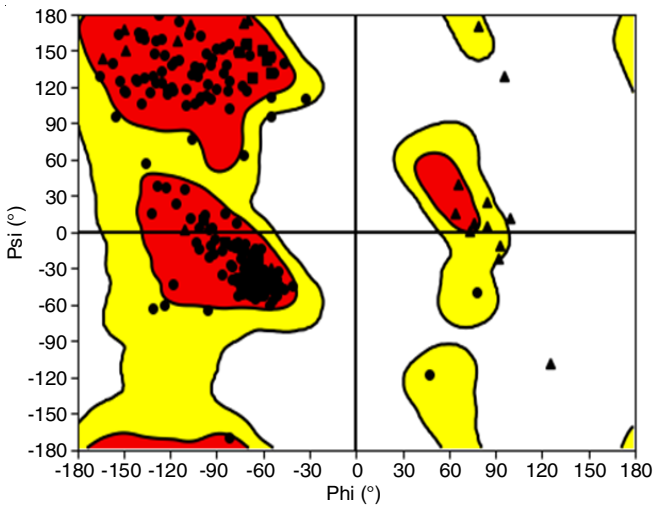


Fig. 1. Ramachandran plot of ψ and φ of 2B35 amino acids

Receptor grid generation: In receptor grid generation, a grid is generated at active site by selecting atom of ligand on workspace, it shows grid box with X, Y and Z coordinates 60.07, -7.07 and 34.74, respectively.

Ligand docking: Ligand docking (virtual screening) was performed by XP descriptor taking glide grid and ligand outmaegz zip files from the working directory. The results of virtual screening were tabulated as per minimum binding energy to maximum as shown in Fig. 2.

Luciferase reporter phage (LRP) assay: The basic principle in Luciferase reporter phage (LRP) assay involves measurement of bioluminescence produced by viable mycobacterial strains when infected with bacteriophages (reporter phases) expressing luciferase genes. Luciferase enzyme produces light only in presence of a substrate called Luciferin & co-factors *viz*. ATP & $FMNH_2$ of metabolically active viable cells [13].

Drug sensitive mycobacterial strains when treated with antituberculosis drugs do not produce light even after a specific incubation time. But drug resistant mycobacterial strains may produce some amount of light similarly to control (untreated *Mycobacterium* stains) if those are viable even after the treatment with drugs.

Luciferase reporter phage (LRP) assay: Antitubercular potential of synthesized indazoles, triazoles and amino pyridines was studied by luciferase reporter phage (LRP) assay method described by Sivakumar *et al.* [14] with some modifications. About 350 µL of G7H9 broth supplemented with 10% albumin dextrose complex and 0.5% glycerol was taken in cryo vials and added with 50 µL of above mentioned synthesized compounds in order to get the final concentration of 100 µg/mL. *M. tuberculosis* H37Rv cell suspension (100 µL) was added to all the vials. DMSO (1%) was also used in the assay as a solvent control. All the vials were incubated at 37 ºC for 72 h. After incubation, 50 µL of high titre mycobacteriophage phAETRC202 and 40 µL of 0.1 M $CaCl_2$ solution was added into the test and control vials. All the vials were incubated at 37 ºC for 4 h. After incubation, 100 µL cell suspension from each vial was transferred to Luminometer cuvette. About 100 µL of D-luciferin was added and relative light unit (RLU) was measured by luminometer.

$$\text{RLU reduction (\%)} = \frac{\text{Control RLU} - \text{Test RLU}}{\text{Control RLU}} \times 100$$

Synthesized compounds showing RLU reduction by 50% or more when compared to control were considered as having antitubercular potential against drug resistant *M. tuberculosis* H37Rv strain.

RESULTS AND DISCUSSION

The synthesized compounds (**C_1-C_{10}**) in step 1 are sterically α,β-unsaturated ketones commonly known as chalcones and characterized as 1,3-diaryl-2-propen-1-ones. All the synthesized molecules exist in the (*E*)-configuration to render the molecule thermodynamically stable. These compounds possess two electrophilic reactive moieties attached to C=C-C=O system. Because of delocalization of electrons in this system, it facilitates the synthesis of various heterocyclic compounds through 1,2-addition at carbonyl group or 1,4-conjugate addition.

Indazoles (**I_1-I_{10}**) as derivatives of chalcones were prepared by Michael addition reaction in which ethyl aceto acetate being a carbanion would be added to α,β-unsaturated ketones to form less stable C-C bonds. In the presence of a base catalyst (K_2CO_3), addition hydrazine hydrate would bring conjugate addition and subsequent cyclization to produce substituted aminopyridines.

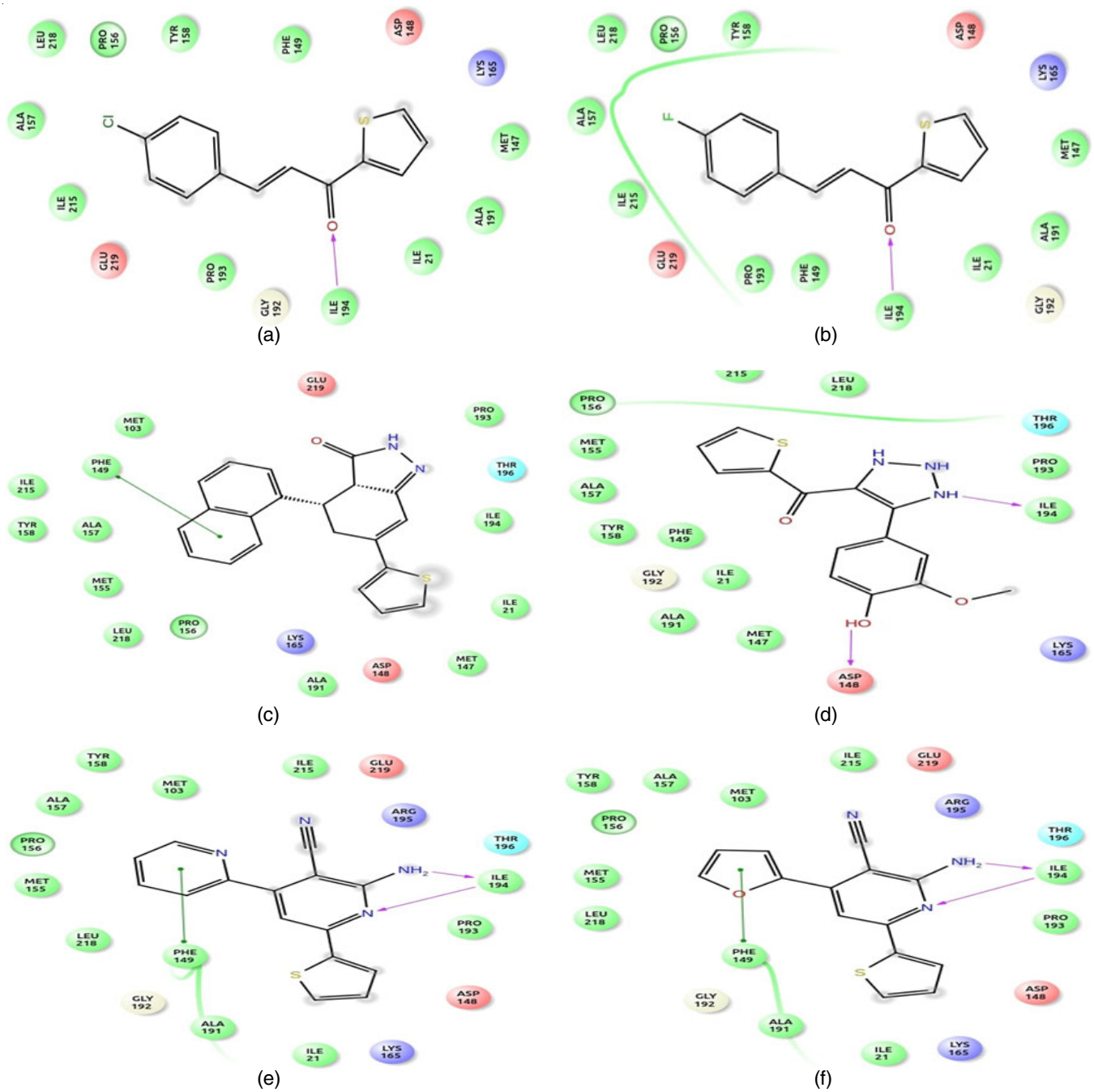


Fig. 2. (A) 2D interaction diagrams of compounds **C7** and **C10** with chain A of 2B35 protein (B) 2D interaction diagrams of compounds **I7** and **T10** with chain A of 2B35 protein (C) 2D interaction diagrams of compounds **P2** and **P9** with chain A of 2B35 protein

In the third step, triazoles (**T_1-T_{10}**) were synthesized by 1,3-dipolar cycloaddition of sodium azide in presence of cupric oxide to C=C of chalcones to yield 1,2,3-triazoles. Finally, aminopyridines (**P_1-P_{10}**) were synthesized by the condensation of chalcones with a nucleophile containing acidic moiety. In this, ammonium acetate being an acidic nucleophile in presence of ethanol imparts condensation to obtain substituted pyridines.

Biological studies

Swiss ADME studies of all the synthesized compounds *viz.*, chalcones, indazoles, triazoles and aminopyridines (**C_1-C_{10}, I_1-I_{10}, T_1-T_{10}** and **P_1-P_{10}**) had revealed that all these have acceptable range of synthetic accessibility. However, indazoles and aminopyrimidines have profound synthetic acceptability when compared with other derivatives (Table-1).

Molecular docking studies of these compounds indicated that aminopyrimidines have high binding score with the binding sites of enoyl ACP reductase enzyme. Triazoles with pyridine substituent & amino pyridines with pyrrole substituent did not exhibit binding score because of in appropriate bonds with binding site of the protein (Table-2).

Observations of Luciferase reporter assay of all the compounds indicated that among the chalcones **C_{10}** with trimethoxy substitutent and **C_7** with naphthyl substitutent have shown

TABLE-1
MOLECULAR ADME PROPERTIES OF COMPOUNDS BY SWISS ADME

Compd.	log P	Molar refractivity	TPSA	HBA	HBD	RB	GI absorption & BBB permeant	log K_p (cm/s)	Solubility		Synthetic accessibility
									Logs	Soluble class	
C_1	2.72	70.62	54.54	2	0	4	High & Yes	-5.18	-3.89	Soluble	2.67
C_2	2.56	72.64	74.77	3	1	4	High & Yes	-5.53	-3.73	Soluble	2.76
C_3	2.91	69.14	45.31	1	0	3	High & Yes	-4.74	-4.42	Moderately soluble	2.72
C_4	2.25	56.39	58.45	2	0	3	High & Yes	-5.44	-3.3	Soluble	2.96
C_5	2.72	70.62	54.54	2	0	4	High & Yes	-5.18	-3.89	Soluble	2.67
C_6	2.56	72.64	74.77	3	1	4	High & Yes	-5.53	-3.73	Soluble	2.76
C_7	2.91	69.14	45.31	1	0	3	High & Yes	-4.74	-4.42	Moderately soluble	2.72
C_8	2.25	56.39	58.45	2	0	3	High & Yes	-5.44	-3.3	Soluble	2.96
C_9	2.89	77.11	63.77	3	0	5	High & Yes	-5.38	-3.94	Soluble	2.86
C_{10}	2.77	64.08	45.31	2	0	3	High & Yes	-5.02	-3.98	Soluble	2.70
I_1	1.87	101.45	115.52	4	1	3	High & No	-6.52	-3.72	Soluble	4.15
I_2	2.29	90.43	82.59	3	1	2	High & No	-6.87	-3.02	Soluble	4.10
I_3	2.3	86.98	85.49	2	2	2	High & No	-6.89	-2.84	Soluble	4.13
I_4	2.65	99.12	78.93	3	1	3	High & No	-6.33	-3.73	Soluble	4.18
I_5	2.49	101.15	99.16	4	2	3	High & No	-6.68	-3.6	Soluble	4.22
I_6	3.07	127.64	69.7	2	1	2	High & No	-4.96	-5.96	Moderately soluble	4.58
I_7	2.74	110.14	69.7	2	1	2	High & Yes	-5.55	-4.82	Moderately soluble	4.36
I_8	2.25	98.69	93.76	4	3	2	High & No	-7.96	-1.92	Very soluble	4.46
I_9	2.18	84.9	82.84	3	1	2	High & No	-6.71	-3.02	Soluble	4.23
I_{10}	2.96	112.11	97.39	5	1	5	High & No	-6.74	-3.88	Soluble	4.49
P_1	1.91	90.93	136.76	4	1	3	Low & No	-5.7	-4.46	Moderately soluble	2.91
P_2	1.96	79.9	103.83	3	1	2	High & No	-6.05	-3.79	Soluble	2.91
P_3	2.24	76.46	106.73	2	2	2	High & No	-6.08	-3.62	Soluble	2.89
P_4	2.59	88.6	100.17	3	1	3	High & No	-5.51	-4.48	Moderately soluble	2.85
P_5	2.53	90.62	120.4	4	2	3	High & No	-5.87	-4.33	Moderately soluble	2.95
P_6	3.03	117.12	90.94	2	1	2	Low & No	-4.14	-6.67	Poorly soluble	3.23
P_7	2.67	99.61	90.94	2	1	2	High & No	-4.73	-5.55	Moderately soluble	3.02
P_8	2.13	87.38	115	4	3	2	High & No	-7.4	-2.45	Soluble	3.37
P_9	2.22	74.37	104.08	3	1	2	High & No	-5.89	-3.8	Soluble	3.05
P_{10}	2.94	101.58	118.63	5	1	5	High & No	-5.92	-4.6	Moderately soluble	3.22
T_1	1.45	78.39	132.7	5	1	4	High & No	-6.11	-3.8	Soluble	2.8
T_2	1.51	67.37	99.77	4	1	3	High & No	-6.45	-3.14	Soluble	2.87
T_3	1.44	63.92	102.67	3	2	3	High & No	-6.48	-2.97	Soluble	2.90
T_4	2.13	76.06	96.11	4	1	4	High & No	-5.92	-3.82	Soluble	2.83
T_5	1.79	78.09	116.34	5	2	4	High & No	-6.26	-3.67	Soluble	2.93
T_6	2.31	104.58	86.88	3	1	3	High & No	-4.55	-6.01	Poorly soluble	3.20
T_7	2.18	87.08	86.88	3	1	3	High & No	-5.13	-4.9	Moderately soluble	2.99
T_8	1.21	74.84	110.94	5	3	3	High & No	-7.81	-1.77	Very soluble	3.34
T_9	1.66	61.84	100.02	4	1	3	High & No	-6.29	-3.15	Soluble	2.96
T_{10}	2.35	89.05	114.57	6	1	6	High & No	-6.32	-3.93	Soluble	3.19

TABLE-2
GLIDE DOCKING AND ANTITUBERCULAR SCREENING OF COMPOUNDS

Compd.	Docking score against 2B35 *Mycobacterium tuberculosis* enoyl reductase (InhA)	Luciferase reporter assay method	
		RLU values	Inhibition (%)
C_1	-6.963	229	81.82
C_2	-6.02	680	46.03
C_3	-6.96	120	90.47
C_4	-6.168	253	79.92
C_5	-6.236	580	53.96
C_6	-6.041	172	86.34
C_7	-7.997	59	95.31
C_8	-6.254	360	71.42
C_9	-5.423	750	40.47
C_{10}	-7.863	40	96.82
I_1	-6.346	418	66.82
I_2	-6.148	248	80.31
I_3	-6.072	320	74.60
I_4	-6.508	78	93.80
I_5	-6.885	61	95.15
I_6	-5.768	842	33.11
I_7	-7.245	58	95.39
I_8	-6.149	742	41.11
I_9	-5.274	937	25.63
I_{10}	-6.416	375	70.23
P_1	-6.82	115	91.26
P_2	-8.479	41	96.74
P_3	No interactions	1260	00 (No activity)
P_4	-7.195	176	89.88
P_5	-7.527	238	81.11
P_6	-7.19	249	80.23
P_7	-7.726	371	70.55

P_9	-8.519	38	96.98
P_{10}	-7.26	789	37.38
T_1	-6.595	342	72.85
T_2	No interactions	1258	0.15 (No activity)
T_3	-5.991	987	21.66
T_4	-6.687	47	96.26
T_5	-7.376	39	97.38
T_6	-6.633	317	74.84
T_7	-6.274	422	66.50
T_8	-6.584	233	81.50
T_9	-6.627	846	33.01
T_{10}	-6.165	412	67.30
DMSO (Control)	–	1260	No activity

highest % inhibition against drug resistant *M. tuberculosis* H37Rv and the compounds **C_9** with furan & **C_2** with pyridine moiety have minimum % inhibition.

Among the synthesized indazoles, **I_7** with naphthyl and **I_5** with 4-hydroxy3-methoxy phenyl substituents demonstrated maximum % inhibition. Indazole **I_9** with furanoyl and **I_6** with anthracene have least % inhibition. Triazole with pyridine **T_2** substituent did not show any inhibition against H37Rv. Triazoles with *p*-methoxy (**T_4**) and 4-hydroxy-3-methoxyphenyl (**T_5**) substitutents have shown the highest % inhibition whereas triazoles with pyrrolyl **T_3** and trimethoxy **T_{10}** have lowest % inhibition.

Among amino pyrimidines **P_3** with pyrrole has not shown any % inhibition against H37Rv. **P_9** with furan & **P_2** with pyridine have exhibited maximum % inhibition. **P_{10}** with trimethoxy and **P_8** with piperazine have shown least % inhibition.

Conclusion

In this work, novel chalcones, triazoles, indazoles and aminopyridines from (thiophene-2-yl)prop-2-en-1-one derivatives have been synthesized and characterized successfully. All the synthesized compounds were evaluated for the antitubercular activity using docking studies. Except compounds **T_2** and **P_3**, all the remaining compounds have considerable % inhibition against H37Rv and exhibited notable antitubercular activity against drug resistant tuberculosis. Molecules with high binding score will be considered for further structural refinement and toxicity prediction.

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CONFLICT OF INTEREST

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

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