Supporting information:

Enabling the (3+2) cycloaddition reaction to engineer a newer anti-tubercular lead acting through the inhibition of Gyrase ATPase domain: Lead optimization and structure activity profiling

Variam Ullas Jeankumar[a], Rudraraju Reshma Srilakshmi[a], Renuka Janupally[a], Shalini Saxena[a], Jonnalagadda Padma Sridevi[a], Brahmam Medapi[a], Pushkar Kulkarni[b,c], Perumal Yogeeswari[a], Dharmarajan Sriram[a]*

[a]*Department of Pharmacy, Birla Institute of Technology & Science-Pilani, Hyderabad Campus, Shameerpet, R.R. District, Hyderabad-500078, Andhra Pradesh, India.*

[b]*Dr Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500046, India.*

[c.]*Zephase Therapeutics (an incubated company at the Dr Reddy's Institute of Life Sciences), University of Hyderabad Campus, Gachibowli, Hyderabad 500046, India.*

Corresponding Author*

D. Sriram

Chair Professor,

Department of Pharmacy,

Birla Institute of Technology & Science-Pilani, Hyderabad Campus,

Jawahar Nagar, R.R. Dist., Hyderabad- 500 078.

INDIA

Telephone: +91-40663030506

Fax: +91-4066303998

Email: dsriram@hyderabad.bits-pilani.ac.in.

Chemistry:

General:

All commercially available chemicals and solvents were used without further purification. TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on silica gel 40 F254 coated on aluminum plates, visualized by UV light and $KMnO_4$ treatment. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz, 75.12 MHz) NMR spectrometer, Bruker BioSpin Corp, Germany. Molecular weights of the synthesized compounds were checked by LCMS 6100B series Agilent Technology. Chemical shifts are reported in ppm (δ) with reference to the internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet. Elemental analyses were carried out on an automatic Flash EA 1112 Series, CHN Analyzer (Thermo).

General procedure for synthesis of Ethyl 4-hydroxy-2-(phenyl/pyridyl)-thiazole-5-carboxylate (6a-d): The synthesis followed the literature procedure [Kerdesky et al[R1]]. Diethyl-2-bromomalonate (1 equiv) was added drop wise to a well stirred solution of the corresponding phenyl/pyridyl thioamide (1 equiv) and pyridine (3 equiv) in toluene (60 mL) at 27^{o}C. The reaction mixture was then heated to reflux for 2-4 hours (monitored by TLC & LCMS for completion) and allowed to cool. The precipitate formed was filtered and re-crystallized form ethanol to afford the desired product in good yield as described below.

Ethyl 4-hydroxy-2-phenylthiazole-5-carboxylate (6a): The compound was synthesized according to the above general procedure using thiobenzamide (**5a**, 0.5 g, 3.64 mmol),

diethylbromomalonate (0.87 g, 3.64 mmol), and pyridine (0.86 g, 10.9 mmol) to afford **6a** (0.79 g, 86.81%) as pale yellow solid. ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.26 (t, J = 7.2 Hz, 3H), 4.23 (d, J = 7.2 Hz, 2H), 7.49- 7.95 (m, 5H). ^{13}C NMR (DMSO-d_6): δc. 167.3, 165.7, 161.3, 132.1, 131.6, 129.4, 126, 97.8, 60.3, 14.3. ESI-MS m/z 250.1 $(M+H)^+$. Anal Calcd for $C_{12}H_{11}NO_3S$; C, 57.82; H, 4.45; N, 5.62; Found: C, 57.79; H, 4.43; N, 5.61.

Ethyl 4-hydroxy-2-(pyridin-2-yl)thiazole-5-carboxylate (6b): The compound was synthesized according to the above general procedure using 2-pyridylthioamide (**5b,** 0.5 g, 3.61 mmol), diethylbromomalonate (0.86 g, 3.61 mmol), and pyridine (0.86 g, 10.9 mmol) to afford **6b** (0.73 g, 80.21%) as pale green solid; ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.28 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 7.41- 8.53 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.6, 161.8 155.9, 149, 148.1, 142.3, 137.6, 125.3, 123.2, 60.4, 14.2. ESI-MS m/z 251.1 $(M+H)^+$. Anal Calcd for $C_{11}H_{10}N_2O_3S$ C, 52.79; H, 4.03; N, 11.19; Found: C, 52.8; H, 4.02; N, 11.21.

Ethyl 4-hydroxy-2-(pyridin-3-yl)thiazole-5-carboxylate (6c): The compound was synthesized according to the above general procedure using 3-pyridylthioamide (**5c**, 0.5 g, 3.61 mmol), diethylbromomalonate (0.86 g, 3.61 mmol), and pyridine (0.86 g, 10.9 mmol) to afford **6c** (0.71 g, 78.02%) as pale green solid; ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.27 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 7.63- 8.93 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.5, 153.1, 148.7, 147.9, 147.6, 141.9, 133.8, 133.1, 123.7, 60.4, 14.3. ESI-MS m/z 251 $(M+H)^+$. Anal Calcd for $C_{11}H_{10}N_2O_3S$ C, 52.79; H, 4.03; N, 11.19; Found: C, 52.78; H, 4.0; N, 11.19.

Ethyl 4-hydroxy-2-(pyridin-4-yl)thiazole-5-carboxylate (6d): The compound was synthesized according to the above general procedure using 4-pyridylthioamide (**5d**, 0.5 g, 3.61 mmol), diethylbromomalonate (0.86 g, 3.61 mmol), and pyridine (0.86 g, 10.9 mmol) to afford **6d** (0.76

g, 83.52%) as pale green solid; ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ $\delta_{H.}$ 1.26 (t, J = 7 Hz, 3H), 4.24 (q, J = 7 Hz, 2H), 7.98- 8.69 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.7, 154, 150.1, 148, 143.6, 142.8, 121.4, 60.3, 14.3 ESI-MS m/z 251.1 $(M+H)^+$. Anal Calcd for $C_{11}H_{10}N_2O_3S$ C, 52.79; H, 4.03; N, 11.19; Found: C, 52.81; H, 4.01; N, 11.23.

General procedure for synthesis Ethyl 4-(prop-2-yn-1-yloxy)-2-(phenyl/pyridyl)thiazole-5-carboxylate (7a-d): To an ice cooled (0 ^{o}C) solution of Ethyl 4-hydroxy-2-(phenyl/pyridyl)-thiazole-5-carboxylate (**6a-d**, 1 equiv) in dry THF (50mL) were added the propargyl alcohol (3 equiv) and triphenylphosphine (3 equiv) one after another and maintained the same temperature for 15 min. To the above mixture, diethyl azodicarboxylate (3 equiv) was added drop wise and the reaction mixture was stirred at 27^{o}C for 12 hours (monitored by TLC & LCMS for completion). The reaction mixture was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane: ethyl acetate as eluent to give the desired product in good yield as described below.

Ethyl 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylate (7a): The compound was synthesized according to the above general procedure using Ethyl 4-hydroxy-2-phenylthiazole-5-carboxylate (**6a**, 0.5 g, 2 mmol), propargyl alcohol (0.34 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) and diethyl azodicarboxylate (1.05 g, 6 mmol) to afford **3a** (0.43 g, 74.65%) as white solid.^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.27 (t, J = 6.9 Hz, 3H), 3.6 (s, 1H), 4.24 (q, J = 6.9 Hz, 2H), 5.21 (s, 2H), 7.54- 8.01 (m, 5H). ^{13}C NMR (DMSO-d_6): δc.167, 163.5, 160, 131.9, 131.8, 129.4, 126.4, 101.2, 78.9, 78.2, 60.6, 58, 14.2. ESI-MS m/z 288.1 $(M+H)^+$. Anal Calcd for $C_{15}H_{13}NO_3S$; C, 62.70; H, 4.56; N, 4.87; Found: C, 62.68; H, 4.55; N, 4.85.

Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylate (7b): The compound was synthesized according to the above general procedure using ethyl 4-hydroxy-2-(pyridin-2-yl)thiazole-5-carboxylate (**6b**, 0.5 g, 2 mmol), propargyl alcohol (0.34 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) and diethyl azodicarboxylate (1.05 g, 6 mmol) to afford **7b** (0.41 g, 71.2%) as off white solid. ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.27 (t, J = 6.7 Hz, 3H), 3.62 (s, 1H), 4.23 (q, J = 6.7 Hz, 2H), 5.23 (s, 2H), 7.43- 8.54 (m, 4H). ^{13}C NMR (DMSO-d_6): δc. 166.8, 162.1, 157.2, 149.4, 147.8, 146.2, 137.3, 124.4, 123.8, 78.8, 77.9, 60.6, 58.3, 14.3. ESI-MS *m*/*z* 289.2 $(M+H)^+$. Anal Calcd for $C_{14}H_{12}N_2O_3S$; C, 58.32; H, 4.20; N, 9.72; Found: C, 58.29; H, 4.18; N, 9.73.

Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylate (7c): The compound was synthesized according to the above general procedure using ethyl 4-hydroxy-2-(pyridin-3-yl)thiazole-5-carboxylate (**6c**, 0.5 g, 2 mmol), propargyl alcohol (0.34 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) and diethyl azodicarboxylate (1.05 g, 6 mmol) to afford **7c** (0.36 g, 62.5%) as off white solid.^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.26 (t, J = 7 Hz, 3H), 3.61 (s, 1H), 4.24 (q, J = 7 Hz, 2H), 5.22 (s, 2H), 7.67- 8.98 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.4, 153.3, 149, 148.2, 147.8, 147.5, 133.9, 133.2, 123.8, 78.7, 77.8, 60.5, 57.8, 14.2. ESI-MS *m*/*z* 289 $(M+H)^+$. Anal Calcd for $C_{14}H_{12}N_2O_3S$; C, 58.32; H, 4.20; N, 9.72; Found: C, 58.33; H, 4.19; N, 9.75.

Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylate (7d): The compound was synthesized according to the above general procedure using ethyl 4-hydroxy-2-(pyridin-4-yl)thiazole-5-carboxylate (**6d**, 0.5 g, 2 mmol), propargyl alcohol (0.34 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) and diethyl azodicarboxylate (1.05 g, 6 mmol) to afford **7d** (0.39 g, 67.7%) as off white solid. ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 1.29 (t, J = 6.8 Hz, 3H), 3.6 (s, 1H),

4.23 (q, J = 6.8 Hz, 2H), 5.23 (s, 2H), 7.96- 8.71 (m, 4H). ^{13}C NMR (DMSO-d_6): δc. 166.7, 153.8, 149.8, 147.6, 143.6, 143.1, 121.2, 78.9, 78.1, 60.5, 57.9, 14.2. ESI-MS m/z 289.0 $(M+H)^+$. Anal Calcd for $C_{14}H_{12}N_2O_3S$; C, 58.32; H, 4.20; N, 9.72; Found: C, 58.34; H, 4.21 N, 9.7.

General procedure for synthesis of 4-(prop-2-yn-1-yloxy)-2-(phenyl/pyridyl) thiazole-5-carboxylic acid (8a-d): To a solution of the corresponding ethyl 4-hydroxy-2-(phenyl/pyridyl)-thiazole-5-carboxylate (**7a-d**, 1 equiv) in THF:Methanol:Water (1:1:1) system, was added lot wise lithium hydroxide (2 equiv). The reaction mixture was then heated at 60^{o}C for 4-5 hours (monitored by TLC & LCMS for completion) and allowed to cool. Solvent was evaporated under vacuum, and the reaction mixture was diluted with water and acidified to pH 2 with 1N HCl. The precipitate formed was filtered and re-crystallized form ethanol to afford the desired product in good yield as described below.

4-(Prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylic acid (8a): The compound was synthesized according to the above general procedure using ethyl 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylate (**7a**, 0.3 g, 1 mmol), and lithium hydroxide monohydrate (0.088 g, 2 mmol), to afford **8a** (0.24 g, 88.6%) as white solid. ^{1}H NMR (DMSO-d_6):). $\delta_{H.}$ 3.61 (s, 1H), 5.18 (s, 2H), 7.54 – 8.00 (m, 5H). ^{13}C NMR (DMSO-d_6): δc.166.4, 162.9, 161.6, 132, 131.7, 129.4, 126.1, 102.7, 79.1, 78.2, 57.9. ESI-MS m/z 258.1 $(M-H)^+$. Anal Calcd for $C_{13}H_9NO_3S$; C, 60.22; H, 3.50; N, 5.40; Found: C, 60.21; H, 3.49; N, 5.38.

4-(Prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid (8b): The compound was synthesized according to the above general procedure using ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylate (**7b**, 0.3 g, 1 mmol), and lithium hydroxide monohydrate (0.088 g, 2 mmol), to afford **8a** (0.22 g, 81.8%) as white solid. ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 3.62 (s,

1H), 5.22 (s, 2H), 7.39 – 8.57 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.3, 161, 156.3, 149.2, 148.4, 143, 137.4, 124.8, 123.3, 79.1, 78, 60. ESI-MS *m*/*z* 259 $(M-H)^+$. Anal Calcd for $C_{12}H_8N_2O_3S$; C, 55.38; H, 3.10; N, 10.76; Found: C, 55.35; H, 3.12; N, 10.74.

4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid (8c): The compound was synthesized according to the above general procedure using ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylate (**7c**, 0.3 g, 1 mmol), and lithium hydroxide monohydrate (0.088 g, 2 mmol), to afford **8c** (0.21 g, 77.49%) as white solid. ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 3.6 (s, 1H), 5.2 (s, 2H), 7.63 – 8.96 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.1, 153.1, 149.1, 147.7, 147.5, 142.5, 134.1, 133.6, 123.9, 78.9, 77.8, 57.7. ESI-MS *m*/*z* 259.1 $(M-H)^+$. Anal Calcd for $C_{12}H_8N_2O_3S$; C, 55.38; H, 3.10; N, 10.76; Found: C, 55.37; H, 3.11; N, 10.76.

4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (8d): The compound was synthesized according to the above general procedure using ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylate (**7d**, 0.3 g, 1 mmol), and lithium hydroxide monohydrate (0.088 g, 2 mmol), to afford **7d** (0.21 g, 77.49%) as white solid. ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 3.63 (s, 1H), 5.21 (s, 2H), 7.99 – 8.69 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.166.3, 153.6, 149.9, 147.7, 143.4, 142.8, 121.3, 79.1, 77.9, 57.8. ESI-MS *m*/*z* 259.2 $(M-H)^+$. Anal Calcd for $C_{12}H_8N_2O_3S$; C, 55.38; H, 3.10; N, 10.76; Found: C, 55.40; H, 3.09; N, 10.78.

General procedure for synthesis of 4-(prop-2-yn-1-yloxy)-2-(phenyl/pyridyl) thiazole-5-carboxamide (9a-d): The synthesis followed the literature procedure [Kerdesky et al[25]].To a solution of the corresponding 4-(prop-2-yn-1-yloxy)-2-(phenyl/pyridyl) thiazole-5-carboxylic acid (**8a-d**, 1 equiv) in DCM at 0^{o}C was added the oxalyl chloride (1.5 equiv) and catalytic amount of DMF. The reaction mixture was the stirred at 27^{o}C (for the formation of the

corresponding acid chloride) for about 2-3 hours and quenched into excess of ammonium hydroxide solution at 0^{o}C. The reaction mixture was then repeatedly extracted with ethyl acetate (2 * 20 mL), washed with brine (5 ml) dried over sodium sulphate. The combined organic phases were concentrated under reduced and re-crystallized form diethyether to afford the desired product in good yield as described below.

4-(Prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxamide (9a): The compound was synthesized according to the above general procedure using 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylic acid (**8a**, 0.25 g, 0.096 mmol) via 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carbonyl chloride to afford **9a** (0.19 g, 76.3 %) as off white solid. ^{1}H NMR (DMSO-d$_6$): $\delta_{H.}$ 3.65 (s, 1H), 5.2 (s, 2H), 6.98 – 7.97 (m, 5H). ^{13}C NMR (DMSO-d$_6$): δc.165.6, 161.2, 158.8, 132.2, 131.4, 129.3, 125.9, 109.5, 78.9, 78.5, 58.3. ESI-MS *m*/*z* 259.1 $(M+H)^{+}$. Anal Calcd for $C_{13}H_{10}N_2O_2S$; C, 60.45; H, 3.90; N, 10.85; Found: C, 60.43; H, 3.89; N, 10.83.

4-(Prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxamide (9b): The compound was synthesized according to the above general procedure using 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid (**8b**, 0.25 g, 0.096 mmol) via 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carbonyl chloride to afford **9b** (0.17 g, 68.3 %) as off white solid. . ^{1}H NMR (DMSO-d$_6$): $\delta_{H.}$ 3.67 (s, 1H), 5.22 (s, 2H), 7.36 – 8.58 (m, 4H). ^{13}C NMR (DMSO-d$_6$): δc.165.4, 160.8, 156.2, 149.2, 147.8, 142.9, 137.4, 124.6, 123.5, 78.9, 78.3, 58.1. ESI-MS *m*/*z* 259.2 $(M+H)^{+}$. Anal Calcd for $C_{12}H_9N_3O_2S$; C, 55.59; H, 3.50; N, 16.21; Found: C, 55.61; H, 3.51; N, 16.19.

4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxamide (9c): The compound was synthesized according to the above general procedure using 4-(prop-2-yn-1-yloxy)-2-(pyridin-3-

yl)thiazole-5-carboxylic acid (**8c**, 0.25 g, 0.096 mmol) via 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carbonyl chloride to afford **9c** (0.21 g, 84.3 %) as off white solid. . ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 3.64 (s, 1H), 5.21 (s, 2H), 7.65 – 8.99 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.165.3, 152.9, 149, 147.7, 147.4, 142.5, 134.2, 133.4, 123.9, 78.7, 78.1, 58. ESI-MS *m*/*z* 259.1 $(M+H)^+$. Anal Calcd for $C_{12}H_9N_3O_2S$; C, 55.59; H, 3.50; N, 16.21; Found: C, 55.58; H, 3.51; N, 16.2.

4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxamide (9d): The compound was synthesized according to the above general procedure using 4-(prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid (**8d,** 0.25 g, 0.096 mmol) via 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carbonyl chloride to afford **9d** (0.19 g, 76.3 %) as off white solid. . ^{1}H NMR (DMSO-d_6): $\delta_{H.}$ 3.66 (s, 1H), 5.21 (s, 2H), 8.01 – 8.70 (m, 4H). ^{13}C NMR (DMSO-d_6): δc.165.5, 153.4, 149.7, 147.8, 143.4, 143, 121.1, 79, 78.4, 58.2. ESI-MS *m*/*z* 259.1 $(M+H)^+$. Anal Calcd for $C_{12}H_9N_3O_2S$; C, 55.59; H, 3.50; N, 16.21; Found: C, 55.61; H, 3.52; N, 16.23.

General procedure utilised for developing the designed analogues (10-45): To a mixture of the corresponding acetylene (1 equiv) and corresponding azide (1.1equiv) in THF:H_2O (1:1) system was added $CuSO_4.5H_2O$ (0.05 equiv), sodium ascorbate (0.1equiv) at 27^{o}C. The reaction was then stirred at 27^{o}C for 12-15 hours (monitored by TLC & LCMS for completion). The residue was further diluted with water (2 mL) and dichloromethane (4 mL) and the layers separated. The aqueous layer was re-extracted with dichloromethane (2 x 4 mL) and the combined organic layer was washed with brine (3 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure and the residue re-crystallized form diethyether/ethanol to afford the desired product in good yield as described below.

Ethyl 4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-phenylthiazole-5-carboxylate (10) The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylate **(7a**, 0.1 g, 0.35 mmol) , 3-azido-2H-chromen-2-one (0.073 g, 0.39 mmol) $CuSO_4.5H_2O$ (0.0044 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **10** (0.14 g, 85.4 %) as buff coloured solid. M.p: 204 – 206^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.27 (t, *J* = 6.9 Hz, 3H), 4.24 (q, *J* = 6.9 Hz, 2H), 5.77 (s, 2H), 6.97 – 8.81 (m, 11H). ^{13}C NMR ($CDCl_3$): δc. 166.3, 163.3, 161.8, 153.3, 148.4, 144.2, 143.5, 141, 131.2, 129.3, 128.9, 128.7, 128.4, 127.8, 125.2, 123.4, 123.1, 121.9, 115.8, 63.4, 60.4, 14.2. ESI-MS *m*/*z* 475.1 $(M+H)^+$. Anal Calcd for $C_{24}H_{18}N_4O_5S$; C, 60.75; H, 3.82; N, 11.81; Found: C, 60.73; H, 3.81; N, 11.79.

ethyl 4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-phenylthiazole-5-carboxylate (11): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylate **(7a**, 0.1 g, 0.35 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.079 g, 0.39 mmol) $CuSO_4.5H_2O$ (0.0044 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **11** (0.13 g, 76.5 %) as buff coloured solid. M.p: 235 – 237^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.26 (t, *J* = 6.9 Hz, 3H), 4.23 (q, *J* = 6.9 Hz, 2H), 5.76 (s, 2H), 6.86 – 8.78 (m, 10H). ^{13}C NMR ($CDCl_3$): δc.166, 163.4, 161.5, 156.3, 154.2, 148.3, 144, 143.3, 141.1, 131, 130.3, 129.4, 128.6, 128.4, 123.1, 122.9, 114.6, 112.8, 102.6, 63.2, 60.1, 14.3. ESI-MS *m*/*z* 491.2 $(M+H)^+$. Anal Calcd for $C_{24}H_{18}N_4O_6S$; C, 58.77; H, 3.70; N, 11.42; Found: C, 58.75; H, 3.72; N, 11.4.

Ethyl 4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-phenylthiazole-5-carboxylate (12): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylate **(7a**, 0.1 g,

0.35 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.085, 0.39 mmol) $CuSO_4.5H_2O$ (0.0044 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **12** (0.11 g, 62.9 %) as buff coloured solid. M.p: 219 – 221°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.27 (t, *J* = 7 Hz, 3H), 4.23 (q, *J* = 7 Hz, 2H), 3.9 (s, 3H), 5.75 (s, 2H), 6.93 – 8.8 (m, 10H). ^{13}C NMR ($CDCl_3$): δc. 166.2, 163.4, 161.5, 159.6, 156.3, 148.6, 143.8, 143.3, 140.9, 131.1, 129.6, 129.1, 128.6, 128.4, 123.2, 122.9, 114.6, 110.9, 100.3, 63.5, 60.3, 56.3, 14.3. ESI-MS *m*/*z* 505.1 $(M+H)^+$. Anal Calcd for $C_{25}H_{20}N_4O_6S$; C, 59.52; H, 4.00; N, 11.11; Found: C, 59.50; H, 4.02; N, 11.09.

4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-phenylthiazole-5-carboxylic acid (13) The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylic acid **(8a**, 0.1 g, 0.39 mmol), 3-azido-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.0047 g, 0.019 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **13** (0.12 g, 69.8 %) as buff coloured solid. M.p: 184 – 186°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.74 (s, 2H), 6.98 – 8.78 (m, 11H). ^{13}C NMR ($CDCl_3$): δc.165.7, 163.1, 161.5, 152.9, 148.2, 143.8, 143.2, 141.2, 131, 129.2, 128.8, 128.6, 128.3, 127.9, 125.4, 123.6, 123.4, 122, 116, 63. ESI-MS *m*/*z* 447.1 $(M+H)^+$. Anal Calcd for $C_{22}H_{14}N_4O_5S$; C, 59.19; H, 3.16; N, 12.55; Found: C, 59.21; H, 3.13; N, 12.56.

4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-phenylthiazole-5-carboxylic acid (14): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylic acid **(8a**, 0.1 g, 0.39 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.087 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.0047 g, 0.019 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **14** (0.14 g, 77.8 %) as buff coloured solid. M.p: 224 – 226°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.73 (s, 2H), 6.84 – 8.77 (m, 10H). ^{13}C NMR ($CDCl_3$): δc.165.5, 163, 161.3, 156.3, 154.2, 148.3, 143.8, 143.2, 140.9, 130.9, 130.3,

129.2, 128.5, 128.3, 123.3, 123.1, 114.5, 112.3, 102.2, 62.9. ESI-MS *m/z* 463.2 $(M+H)^+$. Anal Calcd for $C_{22}H_{14}N_4O_6S$; C, 57.14; H, 3.05; N, 12.12; Found: C, 57.12; H, 3.06; N, 12.09.

4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-phenylthiazole-5-carboxylic acid (15): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-phenylthiazole-5-carboxylic acid **(8a**, 0.1 g, 0.39 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.093 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.0047 g, 0.019 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **15** (0.15 g, 82 %) as buff coloured solid. M.p: 179 – 181°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 3.82 (s, 3H), 5.73 (s, 2H), 6.95 – 8.79 (m, 10H). ^{13}C NMR ($CDCl_3$): δc.165.1, 163.1, 161.4, 159.4, 156.2, 148.4, 143.7, 143.1, 141, 130.8, 129.4, 129.1, 128.6, 128.3, 123.2, 122, 114.5, 111, 100.3, 63, 56.1. ESI-MS *m/z* 477.2 $(M+H)^+$. Anal Calcd for $C_{23}H_{16}N_4O_6S$; C, 57.98; H, 3.38; N, 11.76; Found: C, 58; H, 3.39; N, 11.74.

Ethyl 4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-2-yl)thiazole-5-carboxylate (19): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylate **(7b**, 0.1 g, 0.35 mmol), 3-azido-2H-chromen-2-one (0.073 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **19** (0.15 g, 91 %) as buff coloured solid. M.p: 195 – 197°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$1.27 (t, *J* = 6.9Hz, 3H), 4.24 (q, *J* = 6.9Hz, 2H), 5.75 (s, 2H), 7.01 – 8.72 (m, 10H). ^{13}C NMR ($CDCl_3$): δc.164.2, 163.1, 160.6, 154.6, 153.1, 149, 147.6, 142.8, 141.3, 137.3, 128.7, 128.4, 127.8, 125.1, 124.1, 123.7, 123.4, 123.3, 122.1, 115.9, 63.2, 60.5, 14.2. ESI-MS *m/z* 476.1 $(M+H)^+$. Anal Calcd for $C_{23}H_{17}N_5O_5S$; C, 58.10; H, 3.60; N, 14.73; Found: C, 58.09; H, 3.62; N, 14.71.,

Ethyl 4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-2-yl)thiazole-5-carboxylate (20): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylate **(7b)**, 0.1 g, 0.35 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.079 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **20** (0.16 g, 94%) as buff coloured solid. M.p: 260-263^oC. ^1H NMR ($CDCl_3$): δ_H.1.27 (t, J = 6.9Hz, 3H), 4.23 (q, J = 6.9Hz, 2H), 5.75 (s, 2H), 6.89 – 8.70 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 163.9, 163, 160.4, 156.1, 154.3, 154.6, 148.9, 147.6, 143, 141.2, 137.3, 130.2, 128.4, 123.9, 123.4, 123.1, 123, 112.6, 114.9, 102.4, 63.2, 60.6, 14.2. ESI-MS *m/z* 492.1 $(M+H)^+$. Anal Calcd for $C_{23}H_{17}N_5O_6S$; C, 56.21; H, 3.49; N, 14.25; Found: C, 56.2; H, 3.51; N, 14.23.

Ethyl-4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-, (pyridin-2-yl)thiazole-5-carboxylate (21): The compound was synthesized according to thea, bove general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-2-yl)th, iazole-5-carboxylate **(7b**, 0.1 g, 0.35 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.085 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **21** (0.16 g, 91.4 %) as buff coloured solid. M.p: 247 – 249^oC. ^1H NMR (DMSO-d_6): δ_H. 1.26 (t, 3H *J* = 6.9 Hz), 3.89 (s, 3H), 4.23 (q, 2H *J* = 6.9 Hz), 5.76 (s, 2H), 7.06 – 7.14 (m, 2H) 7.58 - 8.75 (m, 7H). ^{13}C NMR ($CDCl_3$): δc. 164.2, 163.4, 160.3, 159.9, 156.5, 156.1, 149.1, 148.2, 142.9, 141, 137.4, 129.6, 128.4, 124.2, 123.8, 123.2, 123.1 114.7, 111.5, 100.7, 63.2, 60.6, 56.2, 14.2. ESI-MS *m/z* 506.2 $(M+H)^+$. Anal Calcd for $C_{24}H_{19}N_5O_6S$; C, 57.02; H, 3.79; N, 13.85; Found: C, 56.99; H, 3.8; N, 13.83.

4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid (22): The compound was synthesized according to the above general procedure

using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid **(8b**, 0.1 g, 0.38 mmol), 3-azido-2H-chromen-2-one (0.079 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **22** (0.14 g, 81.4 %) as buff coloured solid. M.p: 169 – 171^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.74 (s, 2H), 6.96 – 8.81 (m, 10H). ^{13}C NMR ($CDCl_3$): δc. 163.9, 162.6, 160.4, 154.4, 152.9, 148.9, 147.6, 142.9, 141.1, 137, 128.5, 128.3, 127.9, 125.2, 124, 123.4, 123.1, 121.9, 116, 63. ESI-MS *m*/*z* 446 $(M-H)^+$. Anal Calcd for $C_{21}H_{13}N_5O_5S$; C, 56.37; H, 2.93; N, 15.65; Found: C, 56.35; H, 2.91; N, 15.62.

4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-, (pyridin-2-yl)thiazole-5-carboxylic acid (23): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid **(8b**, 0.1 g, 0.38 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.085 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **23** (0.16 g, 90 %) as buff coloured solid. M.p: 224 – 226 ^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.73 (s, 2H), 6.84 – 6.91 (m, 2H), 7.59 – 8.74 (m, 7H). ^{13}C NMR ($CDCl_3$): δc. 163.6, 162.5, 156.3, 154.6, 150, 142.6, 138, 136.4, 131, 126.3, 126.1, 119.7, 119.3, 114.3, 110.3, 102.2, 63. ESI-MS *m*/*z* 462 $(M-H)^+$. Anal Calcd for $C_{21}H_{13}N_5O_6S$; C, 54.43; H, 2.83; N, 15.11; Found: C, 54.41; H, 2.84; N, 15.09.

4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid (24): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-2-yl)thiazole-5-carboxylic acid **(8b**, 0.1 g, 0.38 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.091 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **24** (0.15 g, 82 %) as buff coloured solid. M.p: 209 – 211^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.73 (s, 2H), 3.89 (s, 3H), 6.98 – 8.79 (m, 9H) ^{13}C NMR ($CDCl_3$): δc.163.8, 162.7, 160.5, 160, 154.6, 154.1, 148.7, 147.5, 143,

140.9, 137.1, 129.6, 128.5, 124, 123.8, 123.5, 123.2, 115.2, 110.8, 100.3, 62.9, 56.3. ESI-MS *m*/*z* 476.1 $(M-H)^+$. Anal Calcd for $C_{22}H_{15}N_5O_6S$; C, 55.34; H, 3.17; N, 14.67; Found: C, 55.32; H, 3.18; N, 14.65.

Ethyl 4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxylate (28): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylate **(7c**, 0.1 g, 0.35 mmol), 3-azido-2H-chromen-2-one (0.073 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **28** (0.13 g, 78.8 %) as buff coloured solid. M.p: 184 – 186^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.28 (t, 3H, *J* = 7Hz), 4.26 (q, 2H, *J* = 7 Hz), 5.78 (s, 2H), 7.03 – 8.87 (m, 10H). ^{13}C NMR ($CDCl_3$): δc. 165.9, 160.3, 153.2, 152.8, 148.6, 147.8, 147.6, 143.2, 141.1, 133.9, 133.1, 128.4, 128.1, 127.7, 125.5, 124.1, 123.4, 123.2, 122.1, 115.9, 63.3, 60.5, 14.3. ESI-MS *m*/*z* 476.1 $(M+H)^+$. Anal Calcd for $C_{23}H_{17}N_5O_5S$; C, 58.10; H, 3.60; N, 14.73; Found: C, 58.12; H, 3.61; N, 14.74.

Ethyl 4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxylate (29): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylate **(7c**, 0.1 g, 0.35 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.079 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **29** (0.14 g, 82.4%) as buff coloured solid. M.p: 241 – 243^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.26 (t, 3H, *J* = 6.9 Hz), 4.25 (q, 2H, *J* = 6.9 Hz), 5.76 (s, 2H), 6.94 – 8.80 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.6, 160.1, 156.3, 154.9, 153.1, 148.6, 147.8, 147.5, 142.8, 141.1, 133.8, 133, 129.8, 128.3, 123.8, 123.2, 122.9, 114.6, 112.3, 102.1, 63.1, 60.4, 14.2. ESI-MS *m*/*z* 492.2 $(M+H)^+$. Anal Calcd for $C_{23}H_{17}N_5O_6S$; C, 56.21; H, 3.49; N, 14.25; Found: C, 56.23; H, 3.51; N, 14.24.

Ethyl 4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxylate (30): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylate **(7c**, 0.1 g, 0.35 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.085 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **30** (0.15 g, 85.7) as buff coloured solid. M.p: 209 – 211^oC. ^1H NMR ($CDCl_3$): $\delta_{H.}$ 1.27 (t, 3H, J = 7 Hz), 3.91 (s, 3H), 4.27 (q, 2H, J = 7 Hz), 5.78 (s, 2H), 7.04 – 8.86 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.8, 160.2, 159.9, 154.8, 153, 148.5, 147.7, 147.5, 143, 141.2, 133.9, 133.1, 129.8, 128.4, 123.8, 123.4, 123.1, 114.8, 110.9, 100.6, 63.3, 60.4, 56.3, 14.2. ESI-MS *m*/*z* 506 $(M+H)^+$. Anal Calcd for $C_{24}H_{19}N_5O_6S$; C, 57.02; H, 3.79; N, 13.85; Found: C, 57.03; H, 3.78; N, 13.86.

4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid (31): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid **(8c**, 0.1 g, 0.38 mmol), 3-azido-2H-chromen-2-one (0.079 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **31** (0.15 g, 87.2 %) as buff coloured solid. M.p: 179 – 181^oC. ^1H NMR ($CDCl_3$): $\delta_{H.}$ 5.76 (s, 2H), 7.01 – 8.84 (m, 10H). ^{13}C NMR ($CDCl_3$): δc. 165.3, 160.2, 153.1, 152.6, 148.7, 147.7, 147.4, 142.9, 141.2, 133.8, 133.2, 128.7, 128.3, 127.6, 125.2, 123.8, 123.2, 122.9, 121.8, 115.8, 62.9. ESI-MS *m*/*z* 446 $(M-H)^+$. Anal Calcd for $C_{21}H_{13}N_5O_5S$; C, 56.37; H, 2.93; N, 15.65; Found: C, 56.39; H, 2.94; N, 15.66.

4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid (32): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid **(8c**, 0.1 g, 0.38 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.085 g, 0.42 mmol), $CuSO_4.5H_2O$

(0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **32** (0.13 g, 73 %) as buff coloured solid. M.p: 191 – 193^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.76 (s, 2H), 6.89 – 8.78 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165, 160, 156.2, 154.3, 152.4, 148.7, 147.8, 147.3, 142.7, 141.1, 133.8, 133.3, 130, 128.6, 123.9, 123.3, 123.1, 114.3, 112.4, 102.3, 62.8. ESI-MS *m*/*z* 462 $(M-H)^{+}$. Anal Calcd for $C_{21}H_{13}N_5O_6S$; C, 54.43; H, 2.83; N, 15.11; Found: C, 54.42; H, 2.81; N, 15.13.

4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid (33):): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxylic acid **(8c**, 0.1 g, 0.38 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.091 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **33** (0.14 g, 76.5 %) as buff coloured solid. M.p: 178 – 180^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 3.89 (s, 3H), 5.77 (s, 2H), 6.98 – 8.81 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.4, 160.2, 160, 154.5, 152.7, 148.8, 147.8, 147.4, 142.9, 141.2, 133.9, 133.3, 129.8, 128.4, 123.9, 123.3, 123.2, 114.6, 111.1, 100.4, 63, 56.3. ESI-MS *m*/*z* 476.1 $(M-H)^{+}$. Anal Calcd for $C_{22}H_{15}N_5O_6S$; C, 55.34; H, 3.17; N, 14.67; Found: C, 55.35; H, 3.18; N, 14.66.

4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxamide (34): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxamide **(9c**, 0.1 g, 0.39 mmol), 3-azido-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.02 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **34** (0.15 g, 87.2 %) as buff coloured solid. M.p: 179 – 181^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.77 (s, 2H), 7.03 – 8.86 (m, 10H). ^{13}C NMR ($CDCl_3$): δc. 165.7, 160.3, 153.2, 152.6, 148.7, 147.8, 147.6, 142.6, 141, 134, 133.2, 128.6, 128.2, 127.8, 125.3, 124,

123.2, 123, 121.9, 115.8, 63.2. ESI-MS *m/z* 447.1 $(M+H)^+$. Anal Calcd for $C_{21}H_{14}N_6O_4S$; C, 56.50; H, 3.16; N, 18.82; Found: C, 56.51; H, 3.14; N, 18.8.

4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxamide (35): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxamide **(9c**, 0.1 g, 0.39 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.02 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **35** (0.11 g, 61.8 %) as buff coloured solid. M.p: 221 – 223°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.75 (s, 2H), 6.87 – 8.81 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.4, 160.2, 156.2, 154.8, 153, 148.7 147.7, 147.4, 142.5, 141.1, 133.8, 133.1, 130, 128.7, 123.9, 123.3, 123, 114.6, 112.5, 102.3, 63. ESI-MS *m/z* 463.2 $(M+H)^+$. Anal Calcd for $C_{21}H_{14}N_6O_5S$; C, 54.54; H, 3.05; N, 18.17; Found: C, 54.52; H, 3.07; N, 18.16.

4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-3-yl)thiazole-5-carboxamide (36): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-3-yl)thiazole-5-carboxamide **(9c**, 0.1 g, 0.39 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.02 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **36** (0.15 g, 81.5 %) as buff coloured solid. M.p: 224 – 226°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 3. 91 (s, 3H), 5.78 (s, 2H), 7.01 – 8.87 (m, 9H).^{13}C NMR ($CDCl_3$): δc.165.8, 160.3, 159.7, 154.6, 153.2, 148.8, 147.8, 147.4, 142.7, 141.2, 133.9, 133.2, 129.6, 128.4, 123.9, 123.2, 122.9, 114.5, 111.2, 100.3, 63.1, 56.2. ESI-MS *m/z* 477.1 $(M+H)^+$. Anal Calcd for $C_{22}H_{16}N_6O_5S$; C, 55.46; H, 3.38; N, 17.64; Found: C, 55.44; H, 3.39; N, 17.63.

Ethyl 4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxylate (37): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylate **(7d**, 0.1 g, 0.35 mmol), 3-azido-2H-chromen-2-one (0.073 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **37** (0.15 g, 90.9 %) as buff coloured solid. M.p: 165 – 167^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.28 (t, J = 6.9Hz, 3H), 4.24 (q, J = 6.9Hz, 2H), 5.76 (s, 2H), 6.98 – 8.74 (m, 10H).^{13}C NMR ($CDCl_3$): δc. 165.7, 160.2, 153, 152.6, 149.4, 147.6, 143.2, 142.8, 141.3, 128.7, 128.3, 127.8, 125.5, 123, 122.8, 122, 121.1, 115.8, 63.4, 60.5, 14.2. ESI-MS *m*/*z* 476.2 $(M+H)^+$. Anal Calcd for $C_{23}H_{17}N_5O_5S$; C, 58.10; H, 3.60; N, 14.73; Found: C, 58.11; H, 3.62; N, 14.71.

Ethyl 4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxylate (38): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylate **(7d**, 0.1 g, 0.35 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.079 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **38** (0.13 g, 76.5%) as buff coloured solid. M.p: 249 – 251^{o}C . ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.27 (t, J = 6.9Hz, 3H), 4.23 (q, J = 6.9Hz, 2H), 5.76 (s, 2H), 6.89 – 8.71 (m, 9H).^{13}C NMR ($CDCl_3$): δc. 165.3, 159.8, 156.3, 154.7, 152.7, 149.3, 147.6, 143.2, 142.6, 141.1, 129.9, 128.4, 123.1, 122.9, 121.1, 114.8, 112.3, 101.9, 63.2, 60.3, 14.1. ESI-MS *m*/*z* 492.1 $(M+H)^+$. Anal Calcd for $C_{23}H_{17}N_5O_6S$; C, 56.21; H, 3.49; N, 14.25; Found: C, 56.2; H, 3.48; N, 14.24.

Ethyl 4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxylate (39): The compound was synthesized according to the above general procedure using Ethyl 4-(prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylate **(7d**,

0.1 g, 0.35 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.085 g, 0.39 mmol), $CuSO_4.5H_2O$ (0.004 g, 0.018 mmol), sodium ascorbate (0.007 g, 0.035 mmol) to afford **39** (0.13 g, 74.3%) as buff coloured solid. M.p: 184 – 186°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 1.28 (t, J = 6.9Hz, 3H), 3.83 (s, 3H), 4.25 (q, J = 6.9Hz, 2H), 5.78 (s, 2H), 7.03 – 8.79 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.8, 160, 159.8, 154.8, 152.8, 149.4, 147.7, 143.2, 142.8, 141.2, 129.6, 128.4, 123, 122.8, 121, 114.5, 111.2, 100.3, 63.3, 60.2, 56.1, 14.2. ESI-MS *m/z* 506.1 $(M+H)^+$. Anal Calcd for $C_{24}H_{19}N_5O_6S$; C, 57.02; H, 3.79; N, 13.85; Found: C, 57.04; H, 3.78; N, 13.83.

4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (40): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid **(8d**, 0.1 g, 0.38 mmol), 3-azido-2H-chromen-2-one (0.079 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **40** (0.16 g, 93 %) as buff coloured solid. M.p: 173 – 175 °C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.73 (s, 2H), 6.89 – 7.73 (m, 10H). ^{13}C NMR ($CDCl_3$): δc. 165.4, 160.1, 152.8, 152.2, 149.3, 147.6, 143.5, 142.8, 141, 128.5, 128.1, 127.6, 125.3, 123, 122.8, 121.9, 121.2, 115.9, 63.3. ESI-MS *m/z* 446.2 $(M-H)^+$. Anal Calcd for $C_{21}H_{13}N_5O_5S$; C, 56.37; H, 2.93; N, 15.65; Found: C, 56.39; H, 2.94; N, 15.66.

4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (41): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid **(8d**, 0.1 g, 0.38 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.085 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **41** (0.15 g, 84.3 %) as buff coloured solid. M.p: 189 – 191°C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.73 (s, 2H), 6.83 – 7.75 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.1, 159.8, 156.2, 154.8, 152.5, 149.3, 147.4, 143.4, 142.7, 140.9,

130, 128.5, 123, 122.8, 121.2, 114.6, 112.3, 102.2, 63.1. ESI-MS *m/z* 462 $(M-H)^+$. Anal Calcd for $C_{21}H_{13}N_5O_6S$; C, 54.43; H, 2.83; N, 15.11; Found: C, 54.42; H, 2.81; N, 15.13.

4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (42): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxylic acid **(8d**, 0.1 g, 0.38 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.091 g, 0.42 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.019 mmol), sodium ascorbate (0.0075 g, 0.038 mmol) to afford **42** (0.14 g, 76.5 %) as buff coloured solid. M.p: 188 – 190^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 3.85 (s,3H), 5.74 (s, 2H), 6.94 – 7.79 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165.5, 160, 159.8, 154.6, 152.7, 149.5, 147.6, 143.6, 142.9, 140.9, 129.6, 128.5, 123.2, 122.9, 121.3, 114.3, 111, 100.3, 63.3, 56.2. ESI-MS *m/z* 476 $(M-H)^+$. Anal Calcd for $C_{22}H_{15}N_5O_6S$; C, 55.34; H, 3.17; N, 14.67; Found: C, 55.32; H, 3.18; N, 14.65.

4-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxamide (43): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxamide **(9d**, 0.1 g, 0.39 mmol), 3-azido-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.02 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **39** (0.12 g, 69.76 %) as buff coloured solid. M.p: 162 – 164^{o}C. ^{1}H NMR ($CDCl_3$): $\delta_{H.}$ 5.76 (s, 2H), 6.96 – 7.79 (m, 10H). ^{13}C NMR ($CDCl_3$): δc.165.5, 160.2, 152.9, 152.4, 149.5, 147.7, 143.5, 143, 141.1, 128.5, 128.1, 127.7, 125.2, 123, 122.8, 121.9, 121.1, 116, 63.5. ESI-MS *m/z* 447.2 $(M+H)^+$. Anal Calcd for $C_{21}H_{14}N_6O_4S$; C, 56.50; H, 3.16; N, 18.82; Found: C, 56.48; H, 3.14; N, 18.84.

4-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxamide (44): The compound was synthesized according to the above general

procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxamide **(9d**, 0.1 g, 0.39 mmol), 3-azido-6-hydroxy-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.02 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **44** (0.12 g, 67.4 %) as buff coloured solid. M.p: 239 – 241^oC. ^1H NMR ($CDCl_3$): $\delta_{H.}$ 5.74 (s, 2H), 6.85 – 7.76 (m, 9H). ^{13}C NMR ($CDCl_3$): δc. 165, 159.8, 156, 154.6, 152.3, 149.4, 147.6, 143.4, 142.7, 141.1, 130.2, 128.4, 123.1, 122.9, 121.3, 114.6, 112, 102.1, 63.3. ESI-MS *m*/*z* 463.2 $(M+H)^+$. Anal Calcd for $C_{21}H_{14}N_6O_5S$; C, 54.54; H, 3.05; N, 18.17; Found: C, 54.53; H, 3.07; N, 18.19.

4-((1-(7-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-5-yl)methoxy)-2-(pyridin-4-yl)thiazole-5-carboxamide (45): The compound was synthesized according to the above general procedure using 4-(Prop-2-yn-1-yloxy)-2-(pyridin-4-yl)thiazole-5-carboxamide **(9d**, 0.1 g, 0.39 mmol), 3-azido-6-methoxy-2H-chromen-2-one (0.08 g, 0.43 mmol), $CuSO_4.5H_2O$ (0.005 g, 0.02 mmol), sodium ascorbate (0.008 g, 0.04 mmol) to afford **45** (0.15 g, 81.5 %) as buff coloured solid. M.p: 209 – 211^oC. ^1H NMR ($CDCl_3$): $\delta_{H.}$ 3.83 (s,3H), 5.75 (s, 2H), 6.98 – 7.81 (m, 9H).^{13}C NMR ($CDCl_3$): δc. 165.4, 160 159.9, 154.6, 152.6, 149.6, 147.6, 143.3, 142.6, 141.2, 129.6, 128.5, 123.2, 123, 121.1, 114.4, 110.9, 100.4, 63.4, 56.3. ESI-MS *m*/*z* 477.1 $(M+H)^+$. Anal Calcd for $C_{22}H_{16}N_6O_5S$; C, 55.46; H, 3.38; N, 17.64; Found: C, 55.43; H, 3.39; N, 17.63.

Biological evaluation:

As the activity of GyrB protein from *Mycobacterium tuberculosis* was found to be very low when compared to that of *Mycobacterium smegmatis* GyrB protein; the ATPase assay was performed utilizing the *Mycobacterium smegmatis* GyrB protein. The use of *Mycobacterium smegmatis* GyrB protein as a surrogate for GyrB protein from *Mycobacterium tuberculosis* has been well demonstrated in literature.[R2-R4] ClustalW was used to know the sequence similarity

between the *Mycobacterium tuberculosis* DNA GyrB and the *Mycobacterium smegmatis* GyrB (as shown below) and was found to be 87.4%.

Figure S1: ClustalW used to know the sequence similarity between the *Mycobacterium tuberculosis* DNA GyrB and the *Mycobacterium smegmatis* GyrB.

Cloning and purification:

Cloning of *Mycobacterium smegmatis* gyrB was done by amplifying the gene from MS155 genomic DNA using the specific forward and reverse primers 5' CACCCATATGGTGGCTGCCCAGAAGAACAA 3' (NdeI), and 5' AGCTAAGCTTTTAAACATCCAGGAAGCGAA 3' (Hind III) respectively. The final PCR

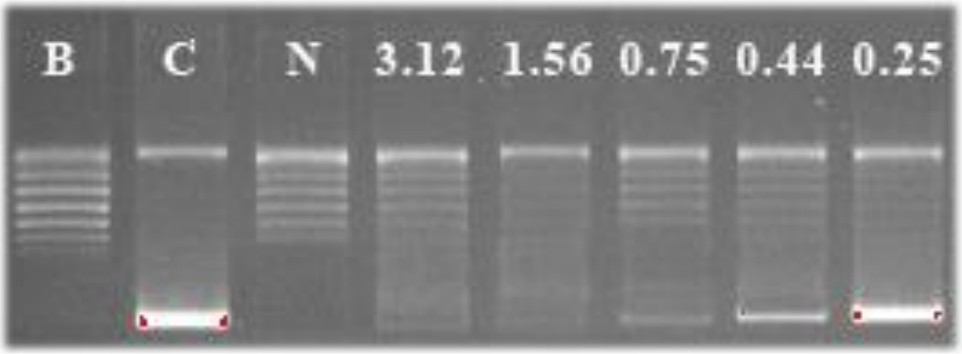
amplicons were cloned in expression vector pQE2 (Qiagen) with a 6-His-tagged cloned vector was then transformed into *BL21 (DE3) pLysS* cells. The transformed cells were later grown at 37°C in LB broth containing 50 µg/ml ampicillin to an optical density (OD) of 0.6 (A595). Further bacterial cells were induced with Isopropyl-β-D-thiogalactopyranoside at a final concentration of 0.2mM while the cells were in exponential growth phase and the cell growth was further continued for another 12 h at 18^{o}C. The bacterial cells were then centrifuged at 10,000 g at 4°C for 15 min. The cell pellet were resuspended in PBSG buffer (PBS containing 5% glycerol) further lysed using sonicator (20sec pulse and 45sec halt) and centrifuged the crude lysate at 8000 rpm at 4°C for 10 min, subsequently centrifugation was repeated for the supernatant of previous step at 10000 rpm at 4°C for 35min for a clear supernatant. The cell extract was later applied to Ni-NTA column (Bio-Rad), the column was with washed with wash buffer (5% glycerol in PBS and 500mM NaCl) and the protein was eluted using different concentration of imidazole ranging from 10mM to 200mM in the elution buffer (5% Glycerol, 140mM NaCl in 25 mM Tris-Cl (pH 8.0)). Fractions containing the desired GyrB subunit was identified by sodium dodecyl sulphate-polyacrylamide gel electro-phoresis (SDS-PAGE), later pooled the 100mM and 200mM fractions and dialyzed against the dialyses buffer (15% Glycerol, 140mM NaCl in 25 mM Tris-HCl (pH 7.4)) frozen in liquid nitrogen and stored at -80°C.

***Mycobacterium tuberculosis* DNA Super coiling assay:**

Mycobacterium tuberculosis DNA supercoiling assay was performed using the supercoiling assay kit (**Inspiralis Limited,** Norwich). Supercoiling assay was done with gyrase enzyme which constituted two gyraseA subunits and two gyraseB subunits, the reaction was performed in 30 µL volume for 30 min duration at 37^{o}C in assay buffer containing 50mM HEPES. KOH (pH

7.9), 6mM magnesium acetate, 100mM potassium glutamate, 4mM DTT, 1mM ATP, 2mM spermidine and 0.05 mg/ml of albumin. According to the kit protocol 1U of DNA gyrase was incubated with 0.5 µg of relaxed pBR322 in 1X assay buffer. Further inhibitors too were incubated at different concentrations to determine the IC_{50} along with the standard drug novobiocin. Ultimately, the reaction was quenched by the addition of 30µl of chloroform:isoamylalcohol (24:1) and STEB buffer (40% sucrose, 100mM Tris–HCl (pH 8.0), 100mM EDTA and 0.5mg/ml bromophenol blue) in equal volume, after a brief vortex and centrifugation, the samples were loaded onto 1% agarose gel in TAE buffer. Further, the products were analysed by electrophoresis and stained with ethidium bromide. Using Image lab software (Bio-Rad) the picture was captured and the intensity of bands were measured and analysed against control to know the enzyme inhibition by relative band intensity.

Figure S2: Inhibitory profile of *Mycobacterium tuberculosis* DNA Gyrase supercoiling activity by compound **27**.

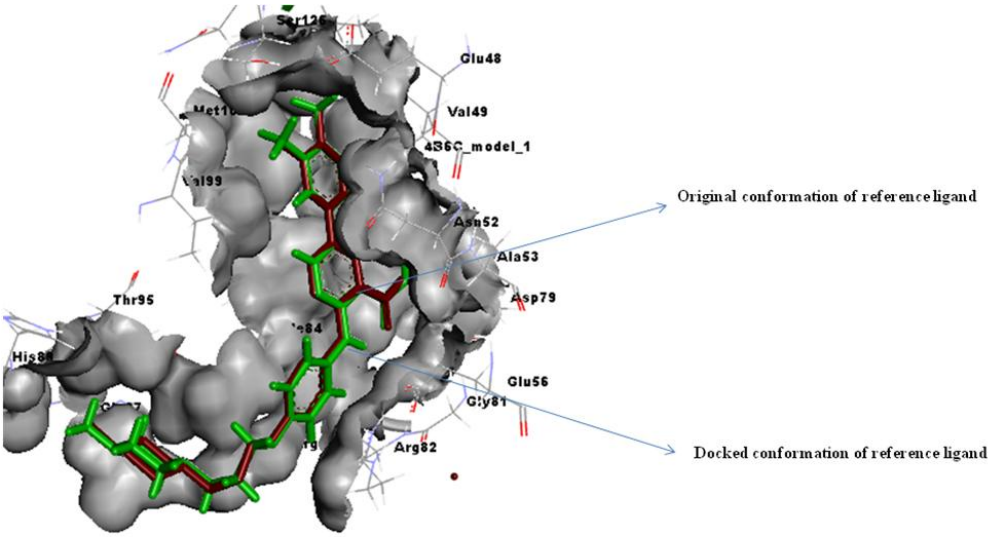


A representative gel obtained from the analysis of the inhibition of DNA Gyrase supercoiling activity is shown above. (B) represents relaxed closed circular DNA; (C) represents the supercoiled DNA in the presence of Gyrase enzyme; (N) novobiocin shown as positive standard.

Computational Details:

All computations were carried out on an Intel Core 2 Duo 63 E7400 2.80 GHz capacity processor with memory of 2 GB RAM 64 running with the RHEL 5.2 operating system. The crystal structure of *Mycobacterium smegmatis* co-crystallized with (3,4-dimethylphenyl)-3-[[4-[3-(4-methylpiperazin-yl)propoxy]phenyl]amino]pyrazine-2-carboxamide [PDB: 4B6C][R5] was retrieved from the Protein Data Bank (www.rcsb.org). The protein was initially processed using the Protein Preparation Wizard of Schrödinger Suite 2012.[R6] The optimization of the hydrogen-bonding network and the ligands to be docked were sketched in Maestro panel of Schrödinger [R6] and optimized with OPLS force field. Hydrogen atoms, bond orders and formal charges were added using the Maestro software package. [R6] Water molecules were removed from the atomic coordinates and the resulting structure was energy minimized. The reference ligand was further re-docked with the active site residues of the *Mycobacterium smegmatis* protein to validate the active site cavity. The ligand exhibited a Glide score of -6.93 kcal/mol and was found in the vicinity of amino acids Asn52, Ile84, Val99, Val98, Asp97, Pro85, Arg141, Arg82, Glu56, Ala53, Asp79, Ile171, Val99, Val123, Ser126, Val128, and Glu4. Re-docking results showed that the compound exhibited similar interactions as that of the original crystal structure and exhibited a RMSD of 0.86 A^0.

Figure S3: Docked and original conformation of the reference ligand [(3,4-dimethylphenyl)-3-[[4-[3-(4-methylpiperazin-yl)propoxy]phenyl]amino]pyrazine-2-carboxamide [PDB: 4B6C][S2]] used for active site validation.



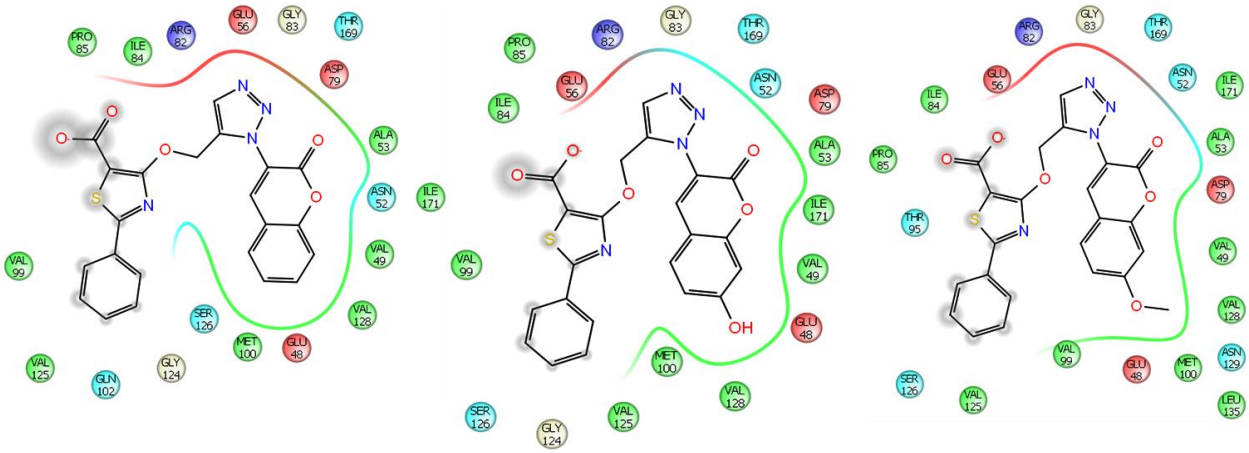
RMSD between original and docked conformation of the reference ligand is 0.87A

The reference ligand 6-(3,4-dimethylphenyl)-3-[[4-[3-(4-methylpiperazin-yl)propoxy]phenyl]amino]pyrazine-2-carboxamide exhibited two important hydrogen bonding interactions in the active site pocket, one between amino group of the carboxamide moiety and the oxygen atom of Asp79 and the other was seen between the nitrogen atom of piperazine and hydrogen atom of guanidine moiety of Arg82. The molecule was stabilized by hydrophobic interaction in the hydrophobic pocket; considered as important for bringing the specificity observed at the enzyme level. [R5]

Later compounds **10**-**45** were docked onto the active pocket of the GyrB ATPase domain of *Mycobacterium smegmatis*. Glide XP (extra precision) module of Schrödinger (Glide, version 5.8, Schrödinger, LLC, New York, NY, 81 2012) was utilized for docking.

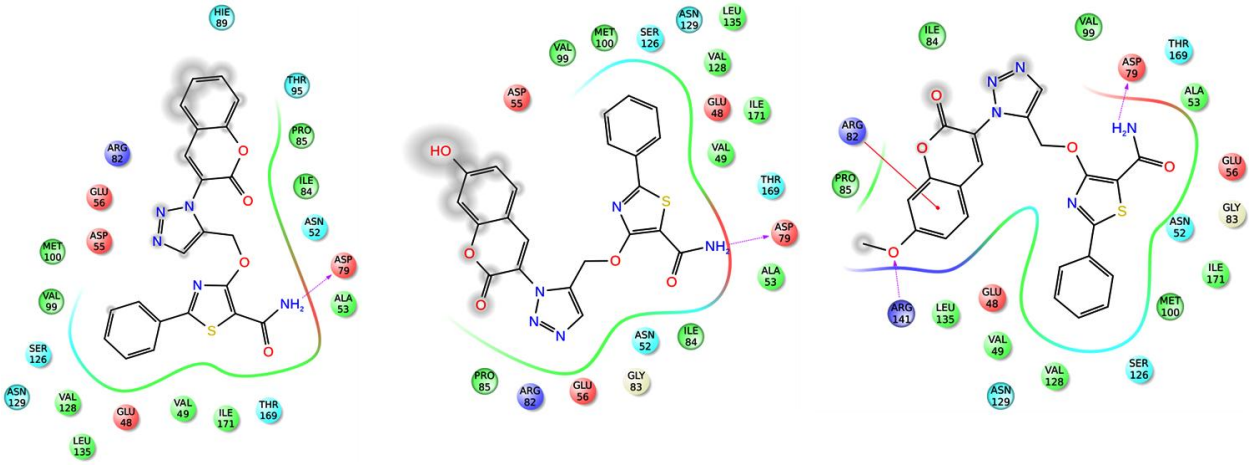
Figure S4-S9: 2D finger print profile diagram of representative molecule

Figure S4: Binding mode of the active compounds **13, 14** and **15** the interacting pattern in the active site of the *Mycobacterium smegmatis* protein.



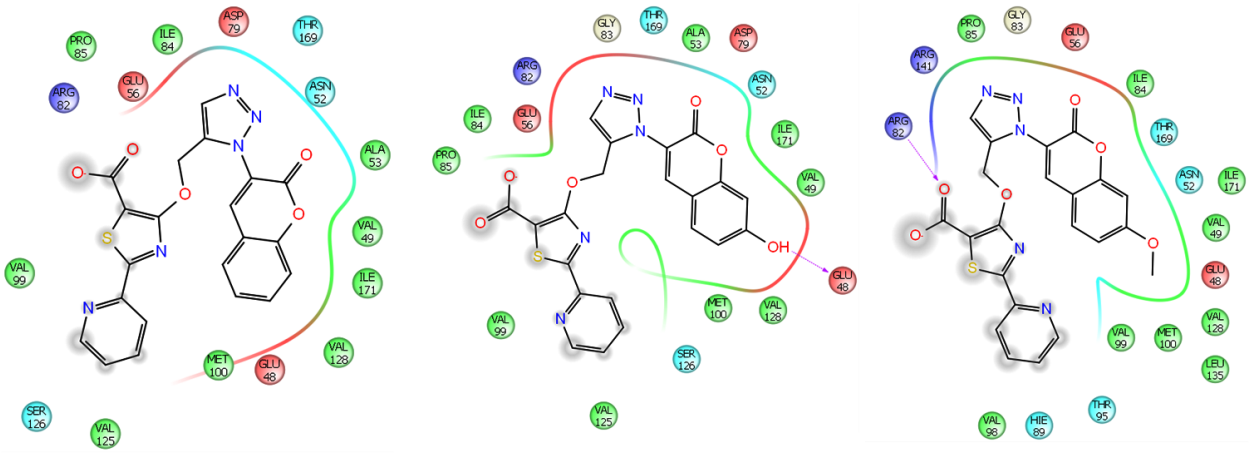
Compound 13 Compound 14 Compound 15

Figure S5: Binding mode of the active compounds **16, 17** and **18** the interacting pattern in the active site of the *Mycobacterium smegmatis* protein.



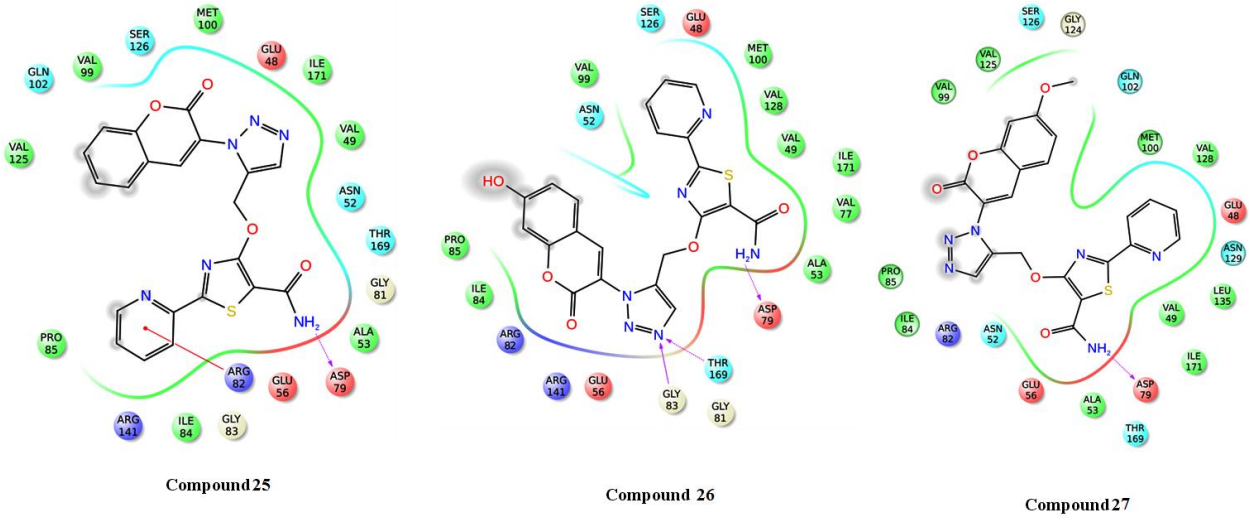
Compound 16 Compound 17 Compound 18

Figure S6: Binding mode of the active compounds **22, 23** and **24** the interacting pattern in the active site of the *Mycobacterium smegmatis* protein.



Compound 22 Compound 23 Compound 24

Figure S7: Binding mode of the active compounds **25, 26** and **27** the interacting pattern in the active site of the *Mycobacterium smegmatis* protein.



Compound 25 Compound 26 Compound 27

Figure S8: Binding mode of the active compounds **31, 32** and **33** the interacting pattern in the active site of the *Mycobacterium smegmatis* protein.

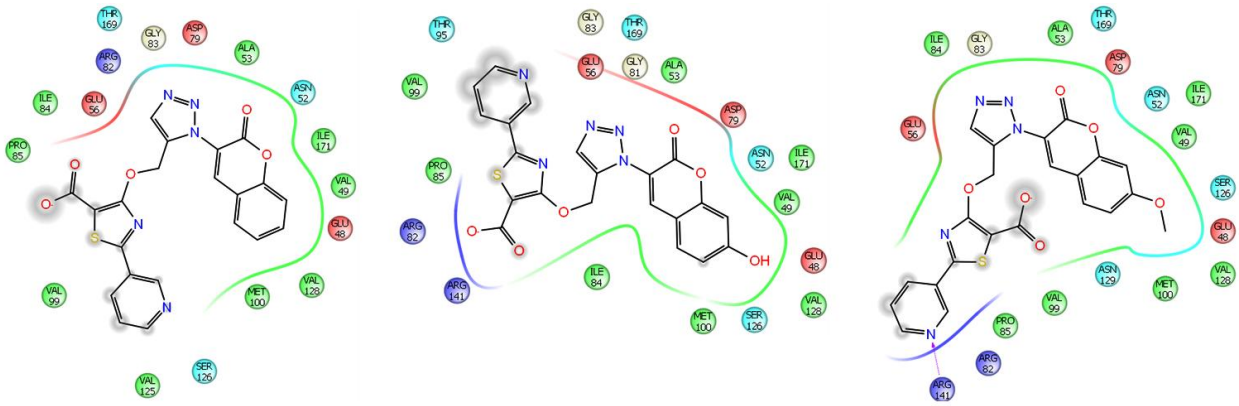
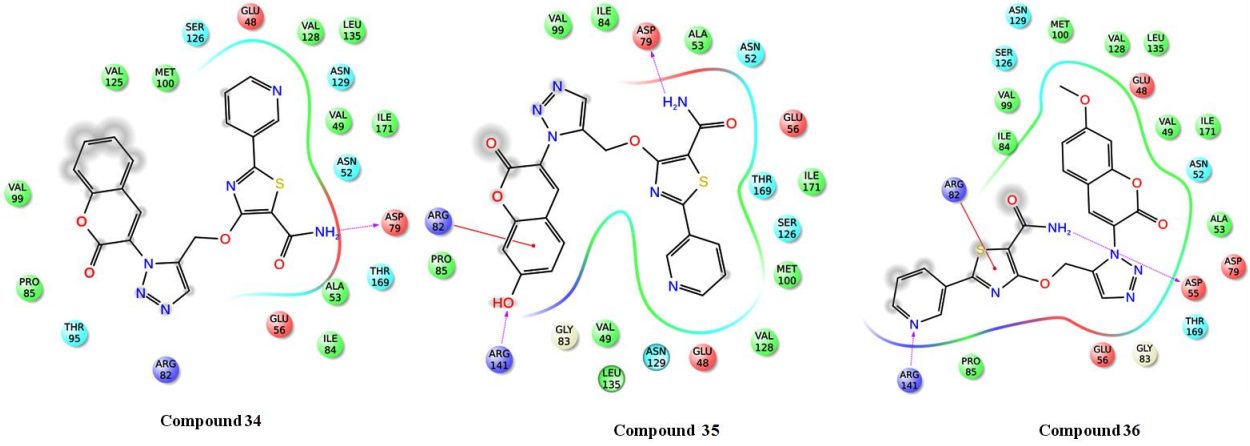


Figure S9: Binding mode of the active compounds **34, 35** and **36** the interacting pattern in the active site of the *Mycobacterium smegmatis* protein.



In-vitro cytotoxicity screening:

The cytotoxic activity in-vitro was measured against mouse macrophages RAW 264.7 cells using the MTT assay. The macrophage cells were cultured in a flat bottomed 96-well plate till a density of 5×10^5 cells as reached and different concentrations of test compounds were respectively added to each well. While the incubation was permitted at 37 °C, with 5% CO_2 and 95% O_2 atmosphere for 48 h before the cytotoxicity assessments. Just before 4 h of the end of the incubation, 10 μL of MTT reagent (10 mg mL−1) was added per well. Four hours later, the 96-well plate was centrifuged at 1200 rcf for about 3 min and the supernatants were removed, subsequently to each well 200 μL of DMSO was added. The absorbance was measured at a wavelength of 490 nm on Victor-3-microplate reader against the blank. Three replicate wells were done for each concentration of drug to minimise the error rate. The cytotoxicity of each compound was expressed as % inhibition.

Biophysical characterization using differential scanning fluorimetry experiments:

DSF technique is used to know the binding affinities of the most potent ligand by measuring the fluorescence of the native protein and protein-ligand complex in presence of a fluorescent dye SYPRO orange whose fluorescence increases when exposed to non-polar residues of the protein and reaches the maximum when the protein denatures. The ability of the compounds to stabilize the catalytic domain of the gyraseB protein was assessed utilizing the DSF technique by which the thermal stability of the catalytic domain of gyrase B native protein and of the protein-ligand complex was measured. In brief, native protein (7.5µl of protein (1.5mg/ml) + 3.5ul of buffer (50mMTris pH 7.4, 1mM EDTA, 5mM DTT)) was subjected to stepwise heating in a PCR instrument (Bio-Rad) from 25^oC to 100^oC with an increment of 0.6^0C/min in presence of the

fluorescent dye SYPRO orange (2.5µl, (1:100) (Sigma)). As the temperature increases the protein unfolds and thus the stability of the protein decreases and becomes zero at equilibrium, dye exhibits the maximum fluorescence at this point as it is exposed to hydrophobic portion of the protein as a result of protein denaturing. Thereby subsequently the concentration of folded and unfolded protein is equal, this temperature is considered as the melting temperature (T_M). A positive shift or shift towards right of melting temperature T_M of protein-ligand complex compared to the native protein T_M signifies a better stabilization of the protein-ligand complex, which in turn is a reflection of the inhibitor binding.

hERG channel inhibition screening:

The more potent compounds were further examined for hERG channel inhibition by assessing arrhythmogenic potential on Zebrafish ether-a-go-go-related gene (zERG) which is orthologus to the human ether-a-go-go-related gene (hERG). Zebrafish were acquired commercially and were maintained as previously described. All experiments were performed following the guidelines published by the National Institutes of Health for care and use of zebrafish. In brief, male and female fish were maintained separately in the re-circulatory system with 14 hr light and 10hr dark cycle, with 27˚C as optimum temperature. Breeding was carried out using 2 female: 3 male in a separate breeding cage. Embryos were collected into petridishes and allowed to grow in the incubator in E3 medium at 27˚C temperature. On the 3rd day embryos were removed and washed. Stock solution of the drug was prepared in 100% DMSO and the working concentrations were prepared accordingly by serial dilutions. 6 embryos were transferred into each well of 24 well plate along with 250µl of 0.1% DMSO. Each well was then added with 250µl of working concentration of the drug. Embryos were allowed to incubate at the optimum temperature for 4 hrs. After 4 hrs of incubation, embryos were treated with tricaine and

immediately used for reading the heart rate. 30 heart beats were counted for atrium and ventricle per embryo and the corresponding time was noted, from which no. of heart beats per minute was calculated by the formula: 1800/X = beats /minute (where X = time in seconds).Terfenadine (20µM) was used as a positive control. All the statistical analysis was done using GraphPad Prism® software using Two way & One way ANOVA followed by Bonferroni's & Dunnet's post test.

Preliminary QikProp analysis of the ADMET properties of the active hits

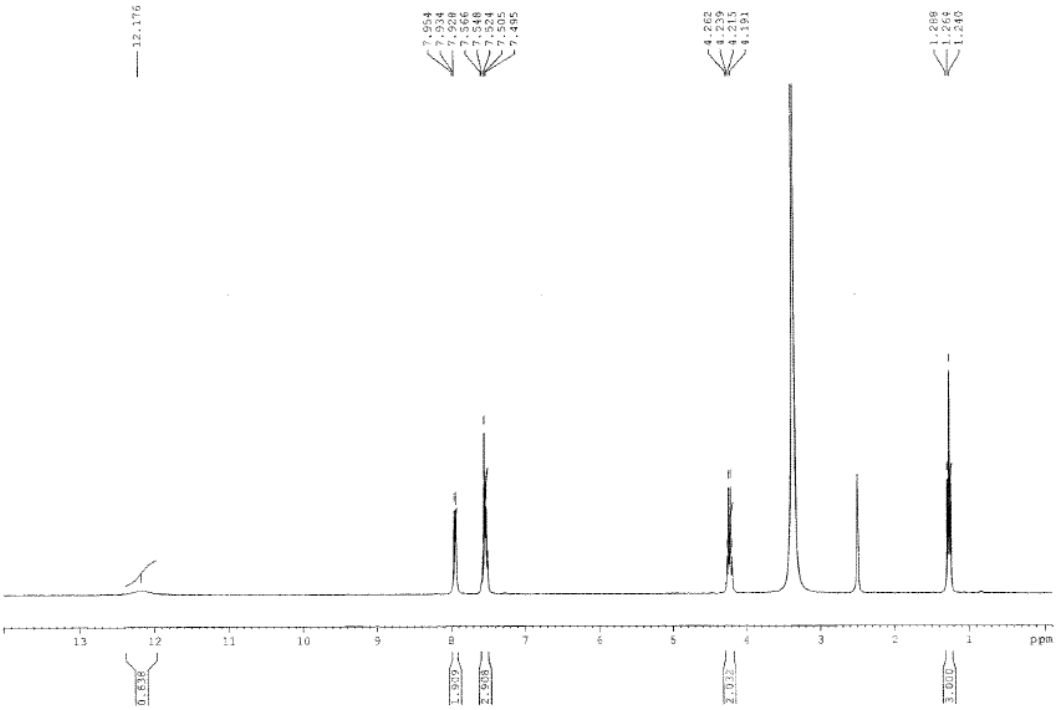
Table S1: A QikProp analysis of the ADMET properties of the active hits.

Properties[a]	**Compounds**					**Range**[b]
	16	**17**	**18**	**25**	**27**	
QPPCaco	212.95	67.91	221.86	143.58	150.00	<25 poor, >500 great
QPlogBB	-1.27	-1.84	-1.37	-1.45	-1.55	-3.0 to 1.2
QPPMDCK	128.99	37.48	134.75	84.43	88.48	<25 poor, >500 great
QPlogKp	-2.88	-3.90	-2.93	-3.92	-3.34	-8.0 to -1.0
QPlogKhsa	0.12	0.012	0.12	-0.072	-0.079	-1.5 to 1.5
Percentage of human oral absorption	84.12	71.39	85.19	77.69	75.65	>80% high <25% poor
Rule of five violations	0	0	0	0	1	Concern above 1

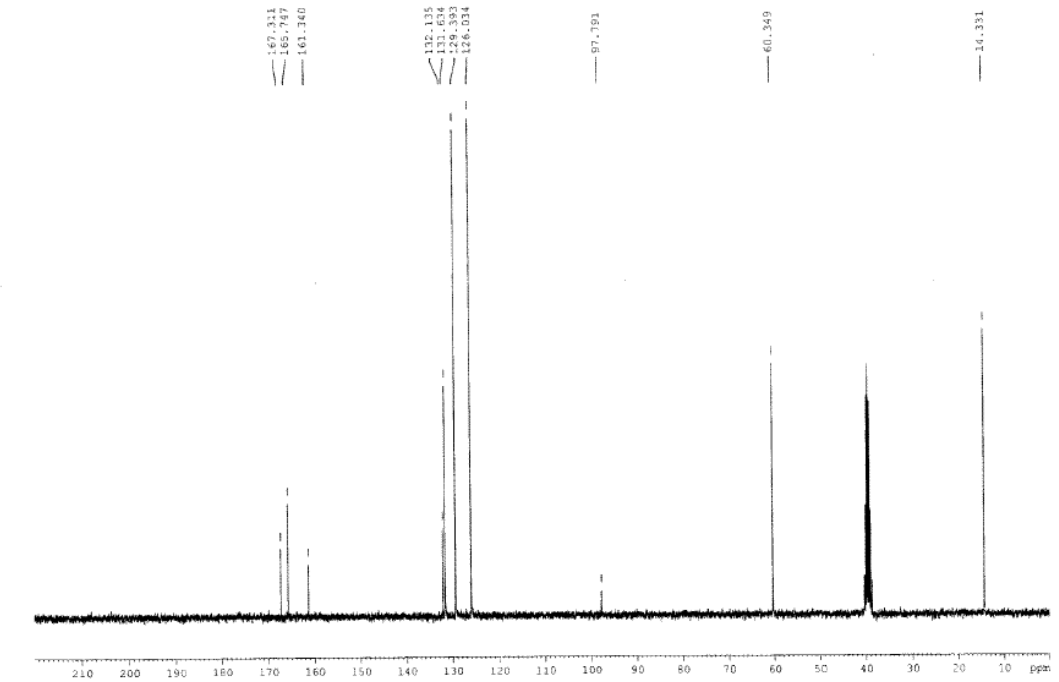
[a] Parameter range indicating value desired for drug like compound: **QPPCaco** – Predicted apparent Caco-2 cell (model for gut-blood barrier) permeability in nm/s. **QPlogBB** – Predicted brain/blood partition coefficient. **QPPMDCK** – Predicted apparent MDCK cell (model for blood-brain barrier) permeability in nm/s. **QPlogK_p** – Predicted skin permeability. **QPlogKhsa** – Prediction of binding to human serum albumin. **Rule of 5 violations** – an orally active drug has no more than one violation of the rule of 5 criteria**.** [b] Range indicates the values desired for drug-like compound.

Representative ^{1}H NMR and ^{13}C NMR spectra.

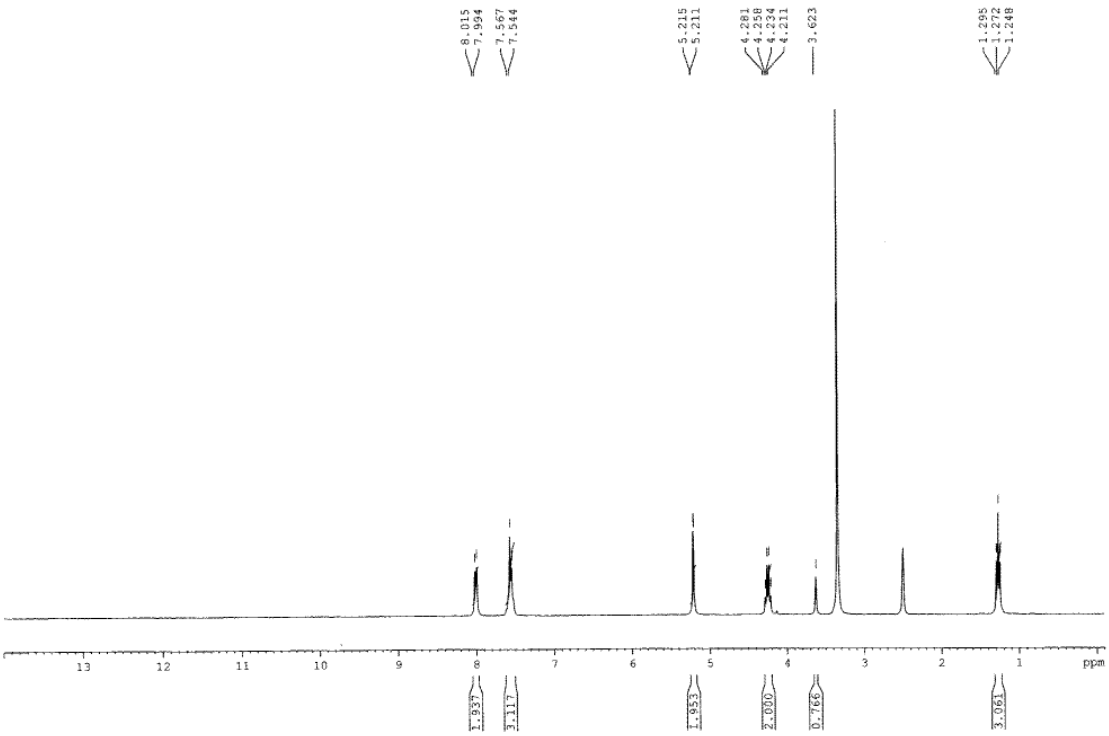
^{1}H NMR spectra of compound 6a



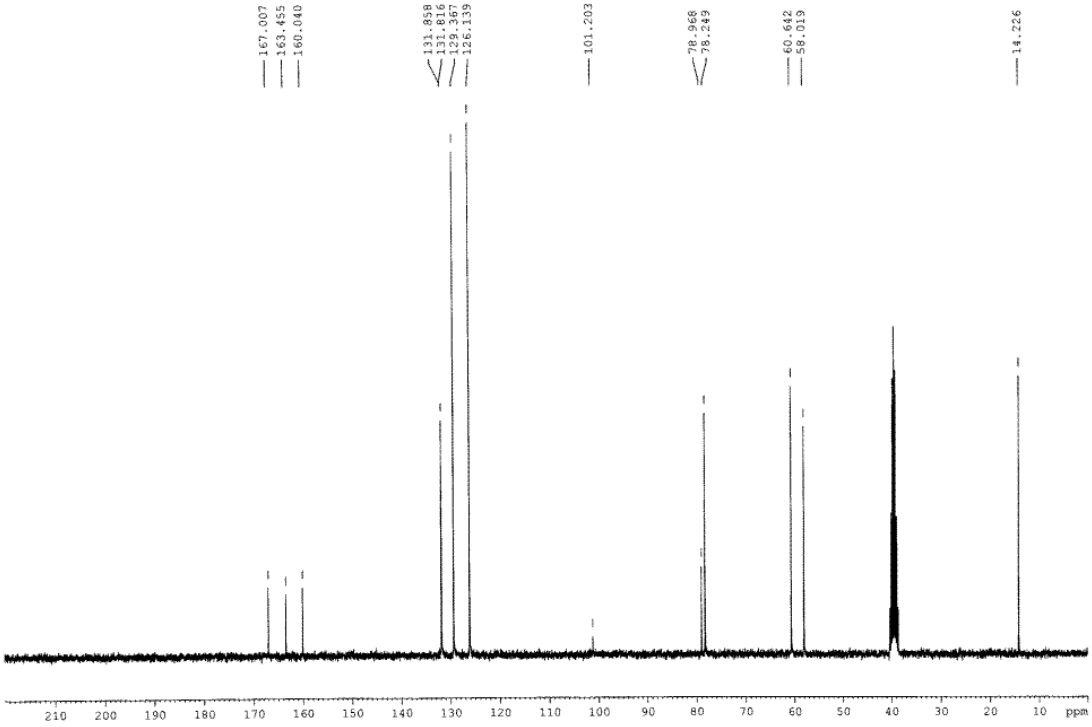
^{13}C NMR spectra of compound 6a



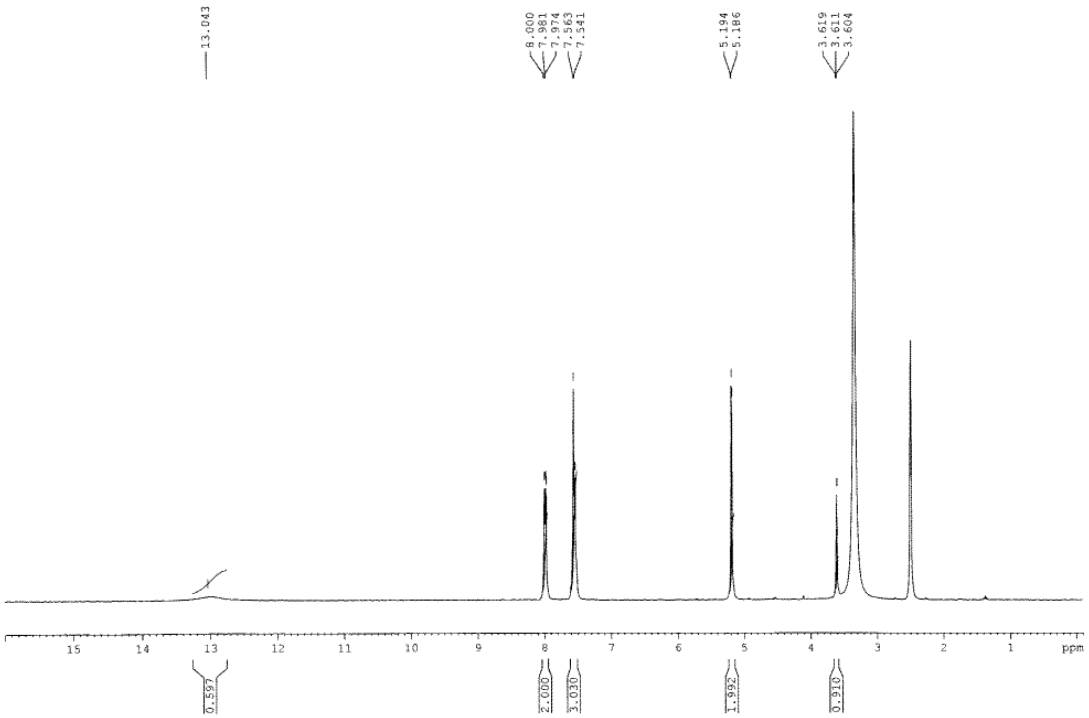
^{1}H NMR spectra of compound 7a



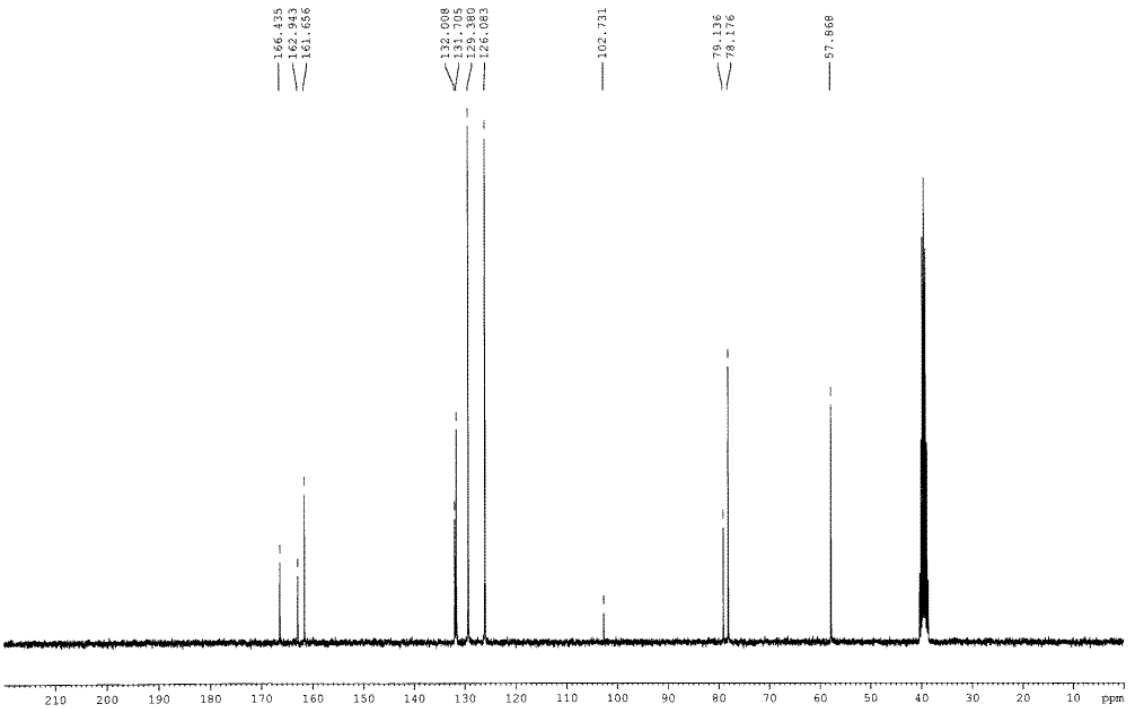
^{13}C NMR spectra of compound 7a



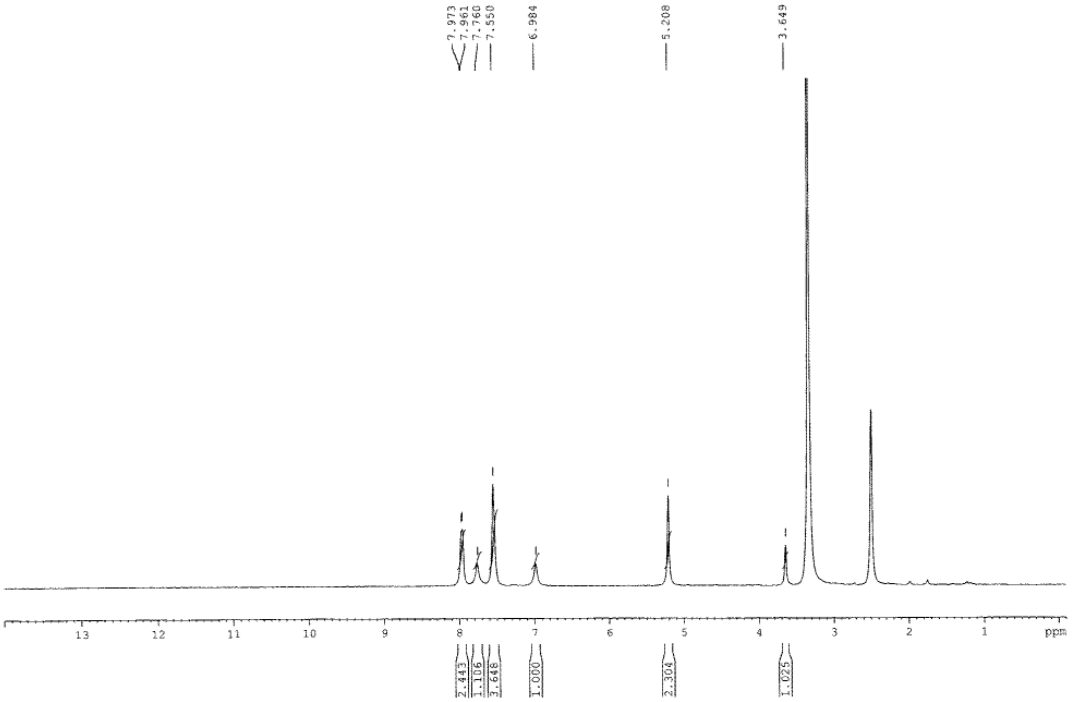
^{1}H NMR spectra of compound 8a



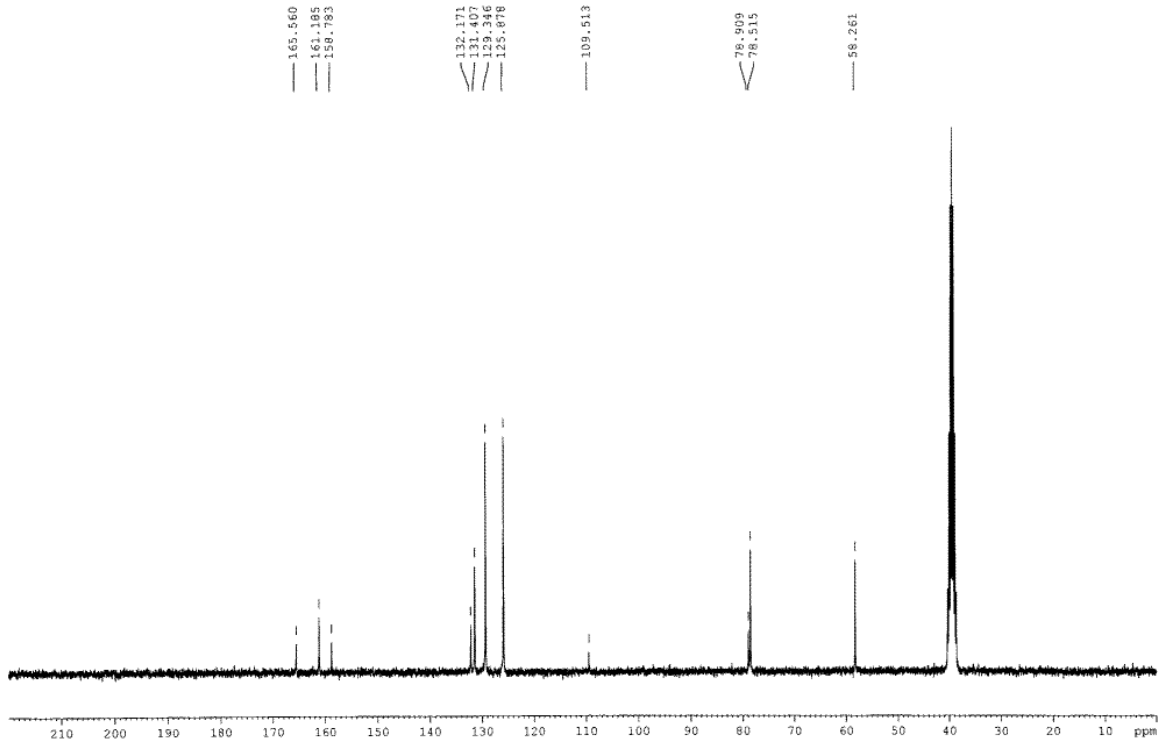
^{13}C NMR spectra of compound 8a



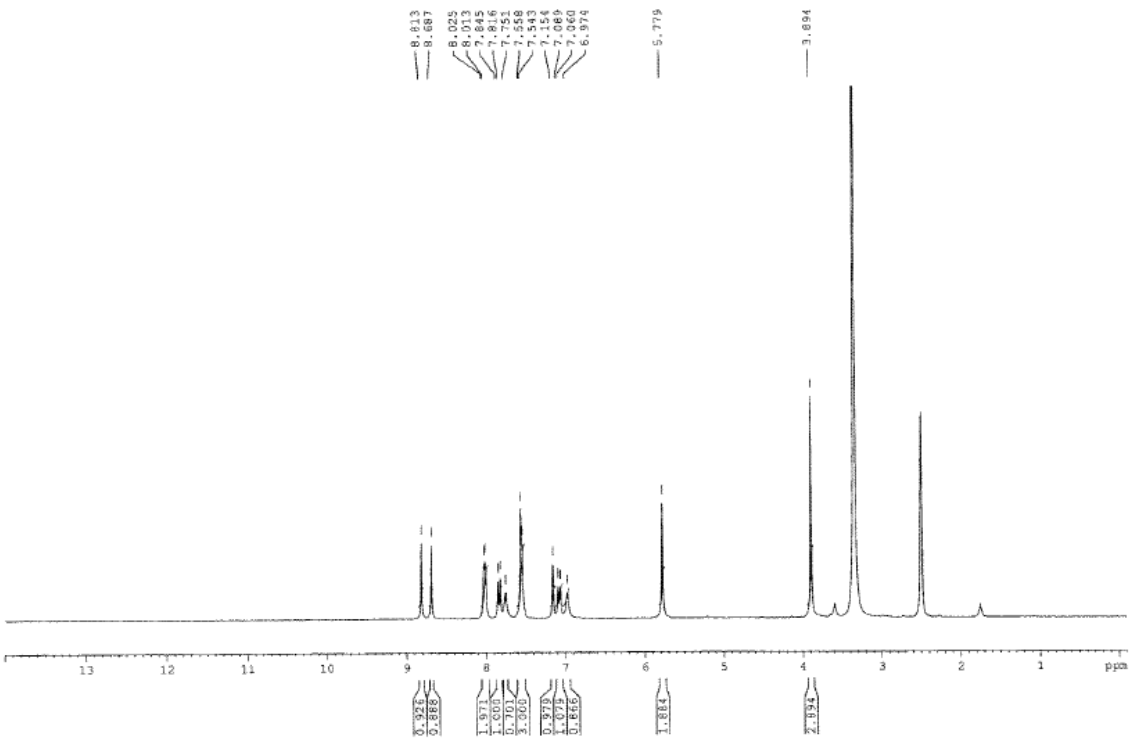
^{1}H NMR spectra of compound 9a



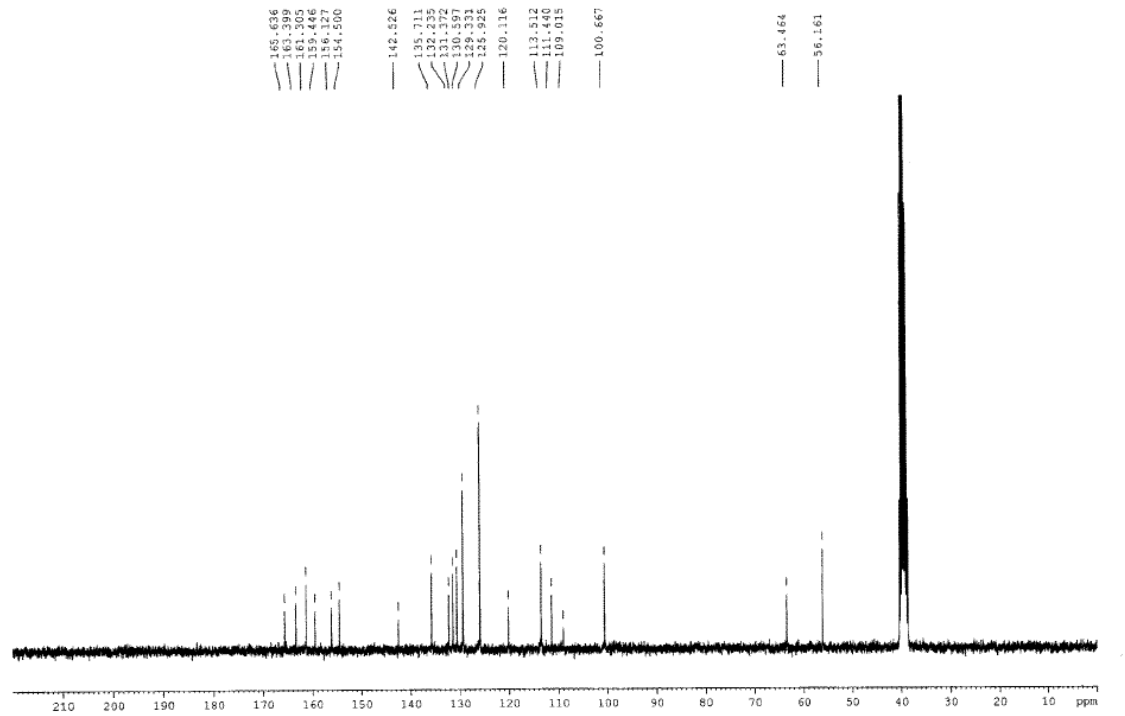
^{13}C NMR spectra of compound 9a



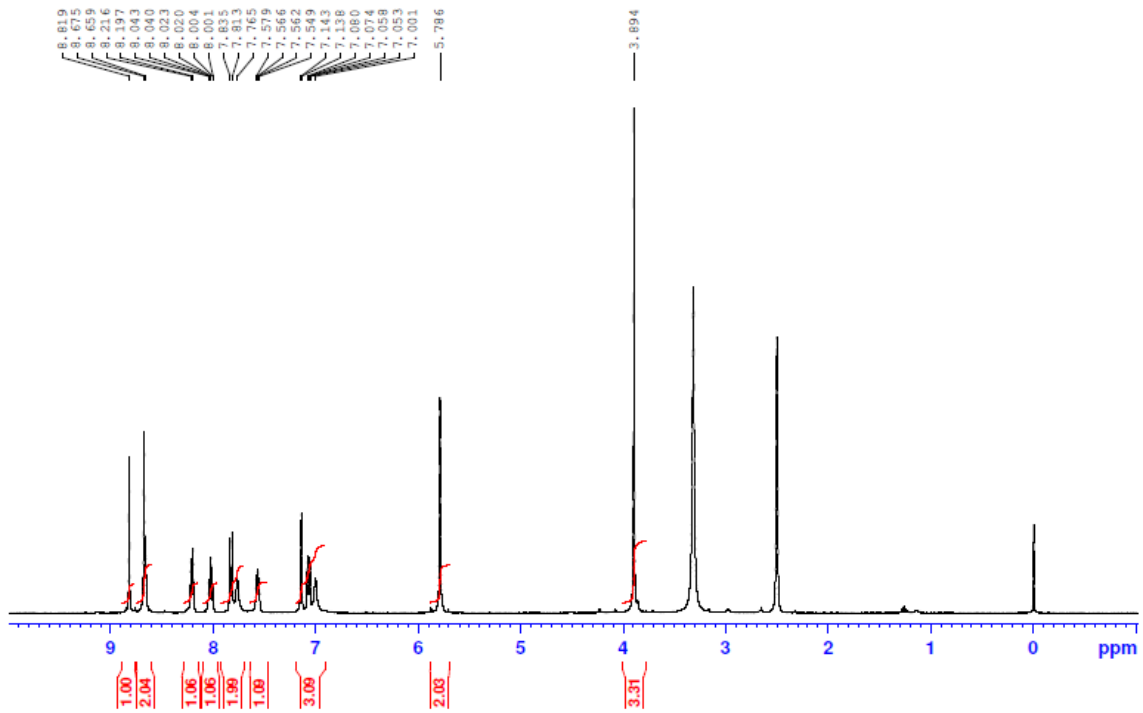
^{1}H NMR spectra of compound 18



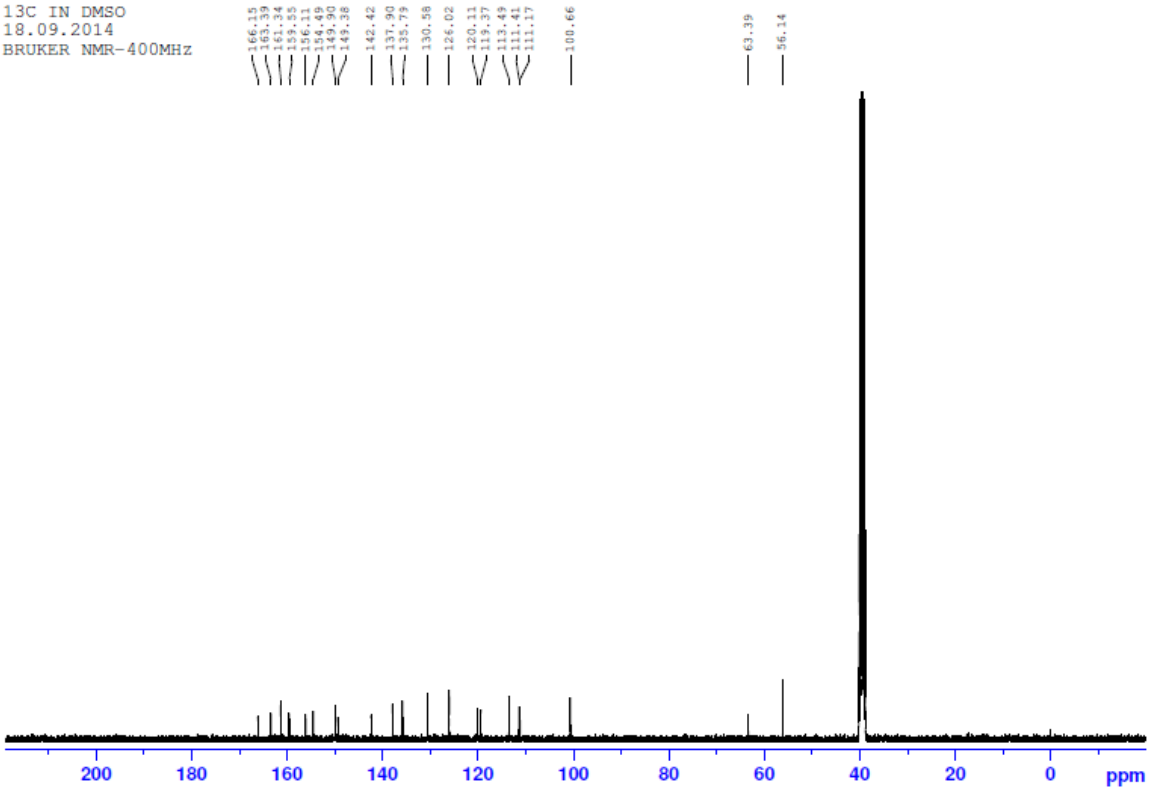
^{13}C NMR spectra of compound 18



[1]H NMR spectra of compound 27



[13]C NMR spectra of compound 27



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R6. Schrödinger Suite 2012 Protein Preparation Wizard; Epik version 2.2, Schrödinger, LLC, New York, NY, 2012; Impact version 5.7, Schrödinger, LLC, New York, NY, 2012; Prime version 2.3, Schrödinger, LLC, New York, NY, 2012.