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Design and Synthesis of (3′-Benzyloxy)-3-fluoro-5-(4-methylpiperazine-1-yl)-[1,1′-biphenyl] carbaldehyde and Indanone Derivatives and their Antibacterial Activity Close to Fab I Inhibitors

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Several bacterial targets are screened for the development of anti-infective medicines, but still finding new pharmacological targets and chemotherapeutics is still necessary in this field. Many anti-infective drugs and Fab I inhibitors with center cores like pyridines, pyridones, benzoxazole, benzothiazoles, quinolines, quinazolines and pyrazoles, *etc*. are in an advanced stage. In present work, we have designed an simple and efficient synthetic route of novel molecules based on the structure and binding modes of Fab I inhibitors with enzymes. The derivatives of (3′-benzyloxy-3-fluoro-5-(4-methylpiperazine-1-yl)-[1.1′-biphenyl]carbaldehyde (**7a-j**) and indanone (**14a-f**) were synthesized and characterized. Compared to earlier synthetic approaches, the derived synthetic routes are thought to be the shortest and most efficient. The reagent titanium isopropoxide was used for the nucleophilic aromatic substitution (SNAr) in the synthesis of carbaldehyde derivatives. The bacterial activity of synthesized novel molecules was evaluated against the Gram-positive bacteria (*S. aureus* and *B. subtilis)* and Gram-negative (*E. coli* and *P. aeruginosa*) bacteria. The synthesized compounds are found to be effective against S. *aureus* at 16 µg/mL and at 8 µg/mL concentration against *B. subtilis*. The molecular modeling study of these molecules has shown that the binding energies of some of the synthesized molecules are higher than the standard molecule triclosan. The binding interactions of the molecule with the protein with more hydrogen bonds prove that the synthesized molecules are well fit in the protein pocket.

Keywords: Carbaldehyde, Indanone, Piperazine, Biphenyl ether, Fab inhibitors.

INTRODUCTION

With the advent of the modern era of drug development in late 1930, the discoveries of several antibiotics have set the groundwork. The first antibiotic that proved useful in treating tuberculosis was streptomycin [1-4]. The mortality rate from tuberculosis significantly declined following the emergence of streptomycin and other tuberculosis treatments. However, as drug-resistant infections emerged later in the 20th century, it became imperative to find new medications and chemotherapeutics. In this field of drug discovery, the bacterial fatty acid production pathway is a proven and comparatively under utilized target [5-8]. The fatty acid biosynthesis (FAS) pathway produces the bacterial phospholipids membrane, which is essential for the survival of both Gram-positive and Gram-negative bacteria. The enzymes have potential as targets for antimicrobial therapy due to the low sequence homology and significant structural variations between bacterial FAS (FAS-II) and human FAS (FAS-I) systems [9-12]. With regard to this, the majority of inhibitor development work has focused on the NAD(P)H-dependent enoyl-ACP reductase (ENR), which catalyzes the FAS-II elongation cycle's final reaction and is sensitive to antibacterial drugs like isoniazid, triclosan and diaza-borines (Fig. 1).

Diazoborines, isoniazid, triclosan and MUT056399 are the Fab I inhibitors that inhibit the transfer of hydride ions from NADPH coenzyme to convert enoyl ACP to acyl ACP [13-15]. The conversion of enoyl-ACP to acyl-ACP is an elongation process, which has to inhibit. The Fab I inhibitors mainly concentrate on this reduction process in the biosynthetic pathway to stop the transfer of hydride ion (H^-) [16-19].

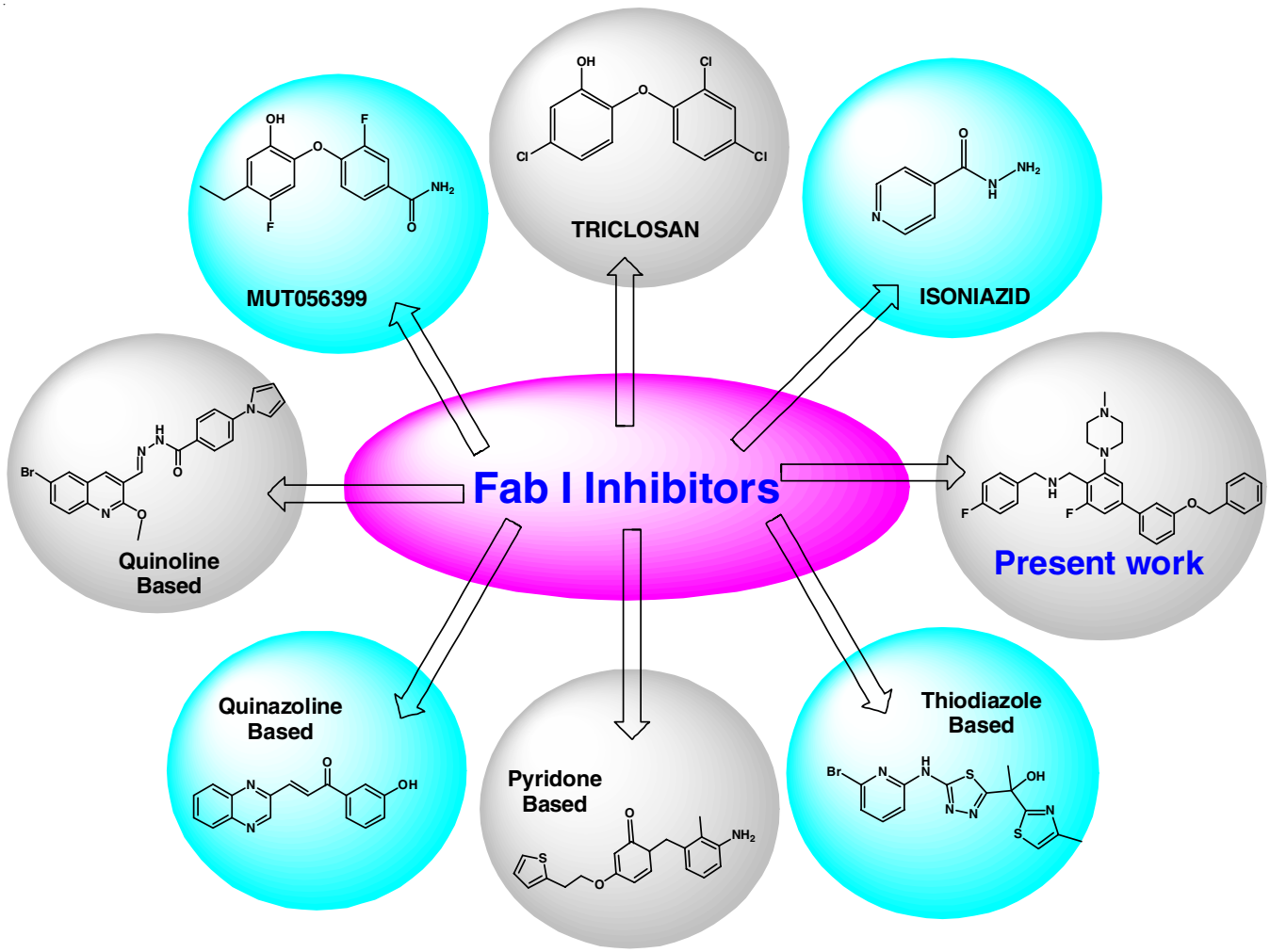


Fig. 1. Fab I inhibitors with different core moieties

In present work, the Fab I inhibitor triclosan as a reference was chosen and synthesize very effective novel molecules. Triclosan has a biphenyl ethereal linkage and it is an important skeleton in the structure [20-24]. Later, based on the structure of triclosan, MUT056399 was prepared with the same skeleton. The carbaldehyde molecules had the biphenyl ether skeleton like in trichlosan with *n*-methyl piperazine ring [25-27] whereas the indanone molecules has more π-stacking by introducing double bond *via* aldol condensation. Both carbaldehyde and indanone molecules are prepared in the shortest and feasible manner. Based on the binding mode of MUT056399, the biphenyl ethereal oxygen bound with phosphate of the NADPH coenzyme. The synthesized compounds in this study, which exhibit activity against *S. aureus* and *B. subtilis*, possess biphenyl ether skeletons linked to an additional phenyl ring.

EXPERIMENTAL

The reagents and solvents were precured from Spectrochem, BLD Pharma, Rankem, India and Sigma-Aldrich, USA. The alumina plates (Merck) coated with silica gel 60 F_{254}, thin layer chromatography was carried out using 5% methanol/DCM as eluent for the spot visualization process, which was carried out by exposure to UV light or iodine vapour. The purification of crude compounds was done on silica gel using combiflash. Using Fisher-Johns melting point equipment, the melting points were measured in open capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded by using JEOL 600 MHz and 100 MHz systems. FT-IR-8400S instrument for KBr pellets was used to record the FT-IR spectra and the HRMS spectra of the samples were recorded on the Waters system.

Synthesis of carbaldehyde analogous

Synthesis of 4-bromo-2-fluoro-6-(4-methylpiperazine-1-yl)benzaldehyde (3): A solution containing 4-bromo-2,6-difluoro benzaldehyde (22.624 mmol, 1 equiv.) and *n*-methyl piperazine (22.624 mmol, 1 equiv.) in THF (50 mL) were mixed followed by the addition of titanium isopropoxide (45.248 mmol, 2 equiv.) at 0 ºC. The reaction was refluxed for 2 h at room temperature and the progress of the reaction was observed by TLC. Afterward, NH_4OH solution was utilized to quench the reaction, the celite bed was used to filter the solid. After being dried over Na_2SO_4, the filtrate was washed with saturated brine solution and concentrated under low pressure. The crude 4-bromo-2-fluoro-6-(4-methylpiper-azine-1-yl)benzaldehyde (**3**) was refined on silica gel in the presence of 50% ethyl acetate/hexane as eluent to yield 6.20 g (90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18 (s, 1H), 6.95-6.94 (m, 1H), 6.92-

6.91 (m, 1H), 3.15-3.12 (m, 4H), 2.63-2.61 (m, 4H), 2.26 (s, 3H). LC-MS: *m/z* 303.1 [M + 2].

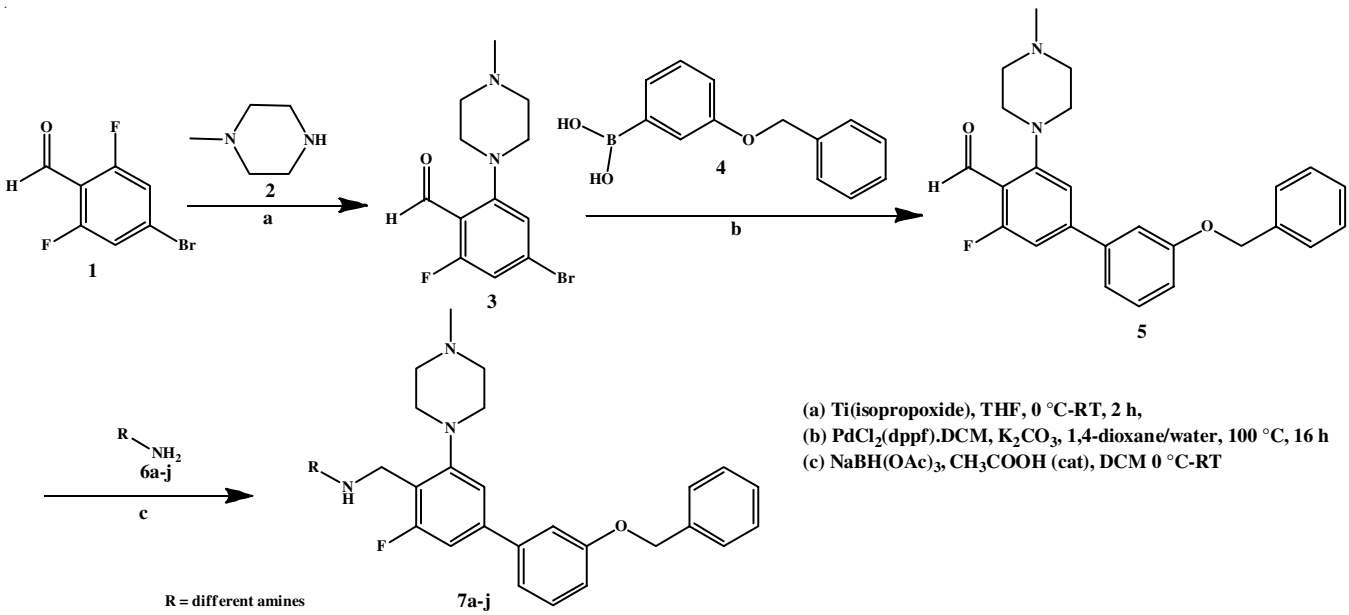
Synthesis of 3′-benzyloxy-3-fluoro-5-(4-methyl piperazine-1-yl)-[1,1′-biphenyl]carbaldehyde (5): 4-Flouro-2-(4-methylpiperazine-1-yl)benzaldehyde (3.333 mmol, 1 equiv.) dissolved in 1,4-dioxane/water (4:1) (40 mL:10 mL) and then added to 3-benzyloxy phenylboronic acid (3.333 mmol, 1.0 equiv.) and K_2CO_3 (6.666 mmol, 2 equiv.). After degassing for 5 min with N_2, added Pd_2Cl_2(dppf) and DCM (0.333 mmol, 0.1 equiv.). At 100 ºC, the reaction mixture was maintained up to 16 h and the TLC was used to monitor the progress of the reaction. The reaction mixture was diluted with ethyl acetate and washed with water followed by brine solution and finally concentrated under reduced pressure to obtain as a brown-coloured gummy liquid. Yield: 0.8 g, 59%. FT-IR (KBr, ν_{max}, cm^{-1}): 1734.14 (-C=O *str.*), 1684.75 (-C-N *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 10.28 (s, 1H), 7.47-7.45 (m, 2H), 7.42-7.36 (m, 4H), 7.18-7.16 (m, 2H) 7.05-7.03 (m, 1H), 6.97-6.93 (m, 2H), 5.13 (s, 2H), 3.20-3.11 (m, 4H), 2.84-2.67 (m, 4H), 2.04 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 186.97, 166.08, 163.49, 159.17, 155.53, 148.71, 148.60, 140.61, 136.61, 130.12, 128.68, 128.13, 127.51, 119.78, 115.32, 115.24, 114.94, 114.07, 112.90, 108.03, 107.80,70.16, 54.93, 53.27 and 45.97. HRMS-ESI of $C_{25}H_{25}FN_2O_2$: *m/z* 405.7404 $(M+H)^+$; [calcd. 404.19].

General procedure for the synthesis of 4-((3′-(benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)amino derivatives (7a-j): A solution of 3′-benzyloxy-3-fluoro-5-(4-methylpiperazine-1-yl)-[1,1′-biphenyl]-carbaldehyde (0.494 mmol, 1.0 equiv.) in DCM (20 mL) was added 2-methoxy benzylamine (0.067 g, 0.494 mmol, 1 equiv.) with catalytic amount of acetic acid at room temperature. For 16 h, the reaction mixture was agitated at room temperature then added sodium triacetoxy borohydride (2.474 mmol, 5 equiv.) at the same temperature. The reaction mixture was further stirred for 2 h and then the reaction mixture was diluted with excess DCM, washed with saturated brine solution, filtered and dried with Na_2SO_4. The crude product was purified in silica (100-200 mesh) employing 5% DCM/methanol as eluent to afford 4-((3′-(benzyloxy)-3-fluoro-5-(4-methyl piperazine-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-*N*-(2-methoxybenzyl)-methenamine as light brown coloured solid (**Scheme-I**).

4-((3′-(Benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-2-(3,4-diflourophenyl)morpholine) (7a): Yield: 120 mg (41%), light yellow solid; m.p.: > 305 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 2922.16 (-NH *str.*), 1697.75 -C-O *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 10.28 (s, 1H), 7.47-7.45 (m, 2H), 7.42-7.34 (m, 4H), 7.13-7.09 (m, 2H) 7.09-7.02 (m, 2H), 7.01-7.00 (m, 3H), 5.11 (s, 2H), 4.40-4.37 (m, 2H), 4.00-3.99 (m, 1H) 3.68-3.67 (m, 3H), 3.30-3.26 (m, 4H), 2.80 (d, *J* = 12 Hz, 1H).2.81-2.50 (m, 5H), 2.46 (s, 3H) 2.24-2.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.82, 160.37, 158.15, 153.70, 150.01, 149.89, 147.55, 141.48, 140.30, 136.51, 135.77, 127.62, 127.03, 126.50, 118.63, 116.05, 113.72, 113.06, 112.78, 108.49, 108.25, 69.90, 66, 15, 58.75, 54.45, 51.55, 51.45, 49.96, 44.65 HRMS-ESI of $C_{35}H_{36}F_3N_3O_2$: *m/z* 588.3823 $[M]^+$, [calculated 587.28].

4-((3′-(Benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-*N*-methyl cyclohexaneamine (7b): Yield: 115 mg (46.3%), light brown solid; m.p.: > 301 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3062.96 (-NH *str.*), 1454.33 (-CH_2 *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 7.47-7.35 (m, 6H), 7.16-7.15 (m, 3H), 7.13-6.99 (m, 2H), 5.12 (s, 2H), 3.81 (s, 2H), 3.19-3.10 (m, 4H), 2.73-2.72 (m, 4H), 2.43 (s, 3H) 2.32 (s, 3H), 1.87-1.83 (m, 2H), 1.85 (d, *J* = 12.4 Hz, 2H).1.67 (d, *J* = 8 Hz, 1H), 1.34-1.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.92, 162.95, 160.51, 158.14, 153.70, 153.64, 141.70, 141.59, 140.29, 135.80, 128.92, 127.62, 126.52, 118.67, 114.01, 113.12, 112.77, 108.97, 108.72, 69.09, 62.31, 54.10, 51.49, 51.28, 45.22, 44.37, 35.34, 27.11, 25.14, 23.73. HRMS-ESI of $C_{32}H_{40}FN_3O$: *m/z* 502.4042 $[M]^+$, [calculated 501.32].

**4-((3′-(Benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-*N*-(2-methoxybenzyl)methan-



Scheme-I: Synthetic route of 4-((3′-(benzyl-oxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)amino derivatives

amine (7c): Yield: 85 mg (32.8%), off white solid; m.p.: > 325 ºC ; FT-IR (KBr, ν_{max}, cm^{-1}): 3545.16 (-NH *str.*), 2843.07 (–$COCH_3$ *str.*); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.47-7.39 (m, 7H), 7.08-7.06 (m, 6H), 7.05-7.01 (m, 1H), 6.99-6.98 (m, 1H), 5.12 (s, 2H), 4.20 (s, 2H), 4.08 (s, 2H), 3.78 (s, 3H), 2.94-2.89 (m, 4H), 2.55-2.54 (m, 4H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.16, 160.71, 159.22, 157.57, 152.74, 143.95, 140.54, 136.71, 131.36, 130.29, 130.07, 128.63, 128.07, 127.50, 120.95, 119.59, 115.31, 114.39, 113.88, 110.80, 110.56, 70.16, 55.51, 54.26, 51.60, 47.64, 44.74, 41.09, 29.66; HRMS-ESI of $C_{33}H_{36}FN_3O_2$: *m/z* 526.3676 $[M]^+$, [calculated 525.28].

4-((3′-(Benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-4-(triflouromethyl)cyclohexane-1-amine (7d): Yield: 110 mg (44.8%), light yellow solid; m.p.: > 300 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3048.45 (-NH str.), 1664.94 (-C=N *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 8.57-8.51 (m, 2H), 7.46 (d, *J* = 8 Hz, 1H), 7.42-7.35 (m, 7H) 7.26-7.14 (m, 2H), 7.12-7.03 (m, 3H), 5.12 (s, 2H), 3.87 (s, 2H), 3.83 (s, 2H) 3.07-3.06 (m, 4H), 2.54-2.37 (m, 4H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.14, 152.51, 152.44, 148.86, 147.41, 141.16, 135.79, 135.18, 134.56, 128.93, 127.63, 127.04, 126.51, 122.47, 119.39, 119.23, 118.64, 113.34, 112.99, 112.83, 108.64, 108.40, 69.11, 54.18, 51.33, 49.89, 46.16, 44.68, 41.52, HRMS-ESI of $C_{31}H_{33}FN_4O$: *m/z* 497.3536 $[M]^+$, [calculated 496.26].

4-((3′-(Benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-4-(triflouromethyl)cyclohexane-1-amine (7e): Yield: 120 mg (43.7%), light brown solid; m.p.: > 310 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 2933.37 (-NH *str.*), 2853.57 (–CH_2 *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 7.47-7.35 (m, 6H), 7.15-7.14 (m, 2H), 7.12-6.99 (m, 3H) 5.12 (s, 2H), 3.83 (s, 2H), 3.12-3.08 (m, 4H), 2.88-2.87 (m, 1H), 2.62-2.61 (m, 4H) 2.38 (s, 3H), 1.86-1.84 (m, 2H), 1.71-1.68 (m, 2H).1.67-1.66 (m, 5H), 1.60-1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.96, 161.54 159.26, 153.87, 153.80, 141.99, 141.90, 141.69, 136.94, 128.76, 128.17, 127.65, 121.07, 120.92, 119.78, 114.61, 114.32, 114.03, 113.95, 109.55, 109.32, 70.22, 55.67, 55.45, 52.77, 51.53, 46.16, 41.57, 41.30, 41.24, 31.69, 29.82, 29.06, 23.86, 19.61. HRMS-ESI of $C_{32}H_{37}F_4N_3O$: *m/z* 556.3850 $[M]^+$, [calculated 555.29].

1-(3′-(Benzyloxy)-5-flouro-4-((2-(thiophen-3-yl)pyrrolidin-1-yl)methyl)-[1,1′-biphenyl]-3-yl))methyl)-4-methylpiperazine (7f): Yield: 110 mg (41.1%), light yellow solid; m.p.: > 315 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1143.79 (-C-N *str.*), 848.68 -C-S *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 10.28 (s, 1H), 7.47-7.39 (m, 6H), 7.34-7.29 (m, 4H), 7.26-7.08 (m, 5H), 6.91-6.90 (m, 1H), 6.82-6.80 (m, 1H), 5.12 (s, 2H), 4.11 (s, 2H), 4.00 (s, 2H) 3.79 (s, 3H), 3.07-3.06 (m, 4H), 2.69-2.44 (m, 6H).2.01-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 175.84, 164.00, 161.55, 159.08, 153.90, 153.82, 144.71, 141.84, 141.38, 136.79, 129.85, 128.59, 127.40, 125.44, 121.79, 119.61, 114.30, 113.96, 113.69, 109.70, 109.45, 70.05, 65.14, 54.69, 53.48, 51.94, 46.39, 45.10, 33.65, 22.46. HRMS-ESI of $C_{33}H_{36}FN_3OS$: *m/z* 542.3571 $[M]^+$, [calculated 541.26].

***N*-((3′-(Benzyloxy)-3-flouro-5-(4-methyl piperazin-1-yl)-[1,1′-biphenyl]-4-yl))methyl)-3-phenylpropan-1-amine cyclohexane-1-amine (7g):** Yield: 120 mg (46.5%), light yellow solid; m.p.: > 300 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3061.63 N-H *str.*), 2937.57 (-C-H *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 7.45-7.39 (m, 6H), 7.26-7.25 (m, 3H), 7.15-7.13 (m, 6H), 7.12 (d, *J* = 8 Hz, 1H), 5.13 (s, 2H), 4.14 (s, 2H), 3.09-3.08 (m, 4H), 2.84-2.77 (m, 6H) 2.64-2.63 (m, 2H), 2.48 (s, 3H), 1.97-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.06, 163.48, 161.02, 159.38, 153.17, 144.00, 143.90, 140.78, 136.86, 128.80, 128.65, 127.66, 119.77, 116.26, 116.12, 115.62, 114.55, 114.05, 111.07, 110.83, 70.29, 54.94, 52.86, 52.00, 46.89, 44.95, 41.07, 33.41, 33.13, 29.32. HRMS-ESI of $C_{34}H_{38}FN_3O$: *m/z* 524.3887 $[M]^+$, [calculated 523.30].

***N*-(3′-(Benzyloxy)-5-flouro-4-((4-phenylpiperidin-1-yl)methyl)-[1,1′-biphenyl]-3-yl)-4-methylpiperazine (7h):** Yield: 125 mg (46.2%), light brown solid; m.p.: > 310 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3962.56 Ar-CH_2 *str.*), 1684.75 (-C-N *str.*); ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm: 7.45-7.39 (m, 6H), 7.26-7.25 (m, 3H), 7.15-7.13 (m, 6H), 7.12 (d, *J* = 8 Hz, 1H), 5.13 (s, 2H), 4.14 (s, 2H), 3.09-3.08 (m, 4H), 2.84-2.77 (m, 6H) 2.64-2.63 (m, 2H), 2.48 (s, 3H), 1.97-1.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.06, 163.48, 161.02, 159.38, 153.17, 144.00, 143.90, 140.78, 136.86, 128.80, 128.65, 127.66, 119.77, 116.26, 116.12, 115.62, 114.55, 114.05, 111.07, 110.83, 70.29, 54.94, 52.86, 52.00, 46.89, 44.95, 41.07, 33.41, 33.13, 29.32. HRMS-ESI of $C_{36}H_{40}FN_3O$: *m/z* 550.4105 $[M]^+$, [calculated 549.32].

1-(3′-(Benzyloxy)-3-flouro-5-(4-methylpiperazine-1-yl-[1,1′-biphenyl]-4-yl)-*N*-(4-flouro benyl))methanamine (7i): Yield: 125 mg (49.4%), off white solid; m.p.: > 360 ºC ; FT-IR (KBr, ν_{max}, cm^{-1}): 3034.03 (-NH *str.*), 1668.43 (-C-O *str.*); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.47-745 (m, 2H), 7.40-7.30 (m, 4H), 7.26-7.13 (m, 2H), 7.13-7.03 (m, 7H), 5.12 (s, 2H), 3.92 (s, 2H), 3.13 (s, 2H), 3.12-3.01 (m, 4H), 2.70-2.62 (m, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 166.46, 162.63, 162.46, 160.20, 160.02, 151.84, 151.78, 139.98, 132.89, 129.49, 129.41, 129.00, 127.63, 127.05, 126.51, 118.62, 117.81, 117.64, 114.54, 114.33, 113.68, 113.17, 112.85, 109.29, 109.05, 69.12, 53.48, 53.19, 51.48, 51.03, 50.36, 43.50, 43.38, 40.62, 40.58. HRMS-ESI of $C_{32}H_{33}F_2N_3O$: *m/z* 514.3521 $[M]^+$, [calculated 513.26].

***N*-((3′-(Benzyloxy)-3-flouro-5-(4-methylpiperazine-1-yl-[1,1′-biphenyl]-4-yl)methyl)-2-methylpropan-1-amine (7j):** Yield: 110 mg (48.2%), light yellow solid; m.p.: > 300 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 2935.66 (-NH *str.*), 2558.94 -$(CH_3)_2CH$ *str.*); 7.47-7.45 (m, 2H), 7.42-7.39 (m, 4H), 7.37-7.19 (m, 2H) 7.19-7.12 (m, 1H), 5.15 (s, 2H), 4.21 (s, 2H), 3.18-3.17 (m, 4H), 2.98-2.91 (m, 4H), 2.57 (d, *J* = 32 Hz, 1H).2.52 (s, 3H), 2.06-2.01 (m, 1H) 0.97-086 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.20, 163.48, 161.02, 159.41, 153.07, 144.16, 140.75, 136.88, 128.81, 127.65, 119.78, 115.76, 114.63, 114.35, 114.08, 111.14, 110.90, 70.32, 55.51, 54.83, 52.22, 51.72, 47.57, 41.88, 40.94, 26.87, 20.58. HRMS-ESI of $C_{29}H_{36}FN_3O$: *m/z* 462.3958 $[M]^+$, [calculated 461.28].

Synthesis of indanone analogous

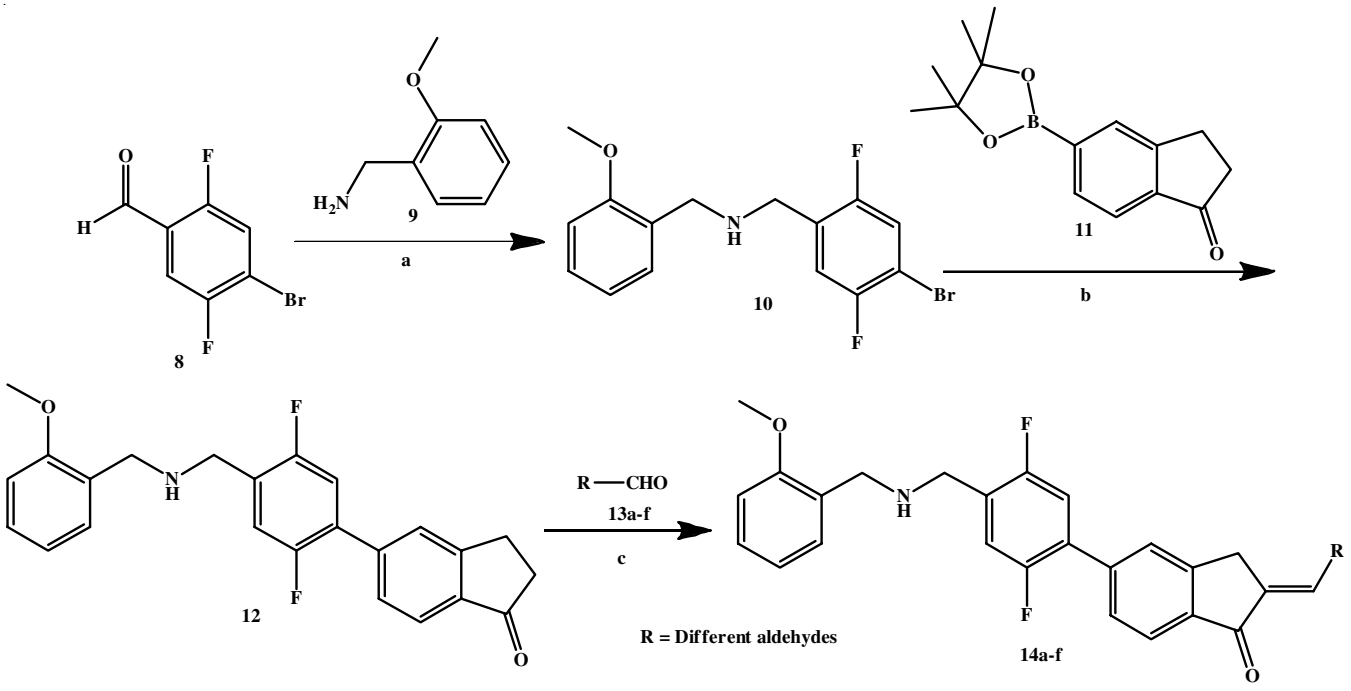
Synthesis of *N*-(4-bromo-2,5-diflourobenzyl)-1-(2-methoxyphenyl)methanamine (10): In a round bottom flask, a solution of 4-bromo-2,5-diflouro benzaldehyde (13.640 mmol,

1 equiv.) in DCM (50 mL) was mixed to 2-methoxy benzylamine (13.640 mmol, 1 equiv.) containing catalytic amount of acetic acid at room temperatur and then the reaction mixture was agitated for 16 h, follwed by the addition of sodium triacetoxy borohydride (68.203 mmol, 5 equiv.) at 0 ºC. The entire reaction mixture was stirred again at room temperature for 3 h. The mixture diluted with DCM, rinsed with water, saturated with brine solution, concentrated and finally dried on sodium sulfate. The product was purified on silica gel using 50-60% ethylacetate/hexane as eluent to afford *N*-(4-bromo-2,5-diflourobenzyl)-1-(2-methoxyphenyl)methenamine (**10**). Yield: 3.50 g, 75% yield. m.p.: 322-324 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3057.17 (-NH *str.*), 1697.43 (-C=O *str.*); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.65-7.63 (m, 1H), 7.61-7.53 (m, 1H), 7.34-7.33 (m, 1H) 7.32-7.31 (m, 1H), 6.96-6.94 (m, 2H), 3.76 (s, 3H), 3.70 (s, 2H), 3.65 (s, 2H).

Synthesis of 5-(2,5-diflouro-4-(((2-methoxybenzyl)-amino)methyl)phenyl)-2,3-dihydro-1*H*-indene-1-one (12): Compound **10** (2.932 mmol, 1 equiv.) dissolved in 1,4-dioxane/water (4:1) (40 mL:10 mL) was added to 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-1-one (2.932 mmol, 1.0 equiv.) and K_2CO_3 (5.864 mmol, 2 equiv.). After degassing for 5 min with N_2, added Pd_2Cl_2(dppf) and DCM (0.293 mmol, 0.1 equiv.). The mixture was heated at 100 ºC and maintained up to 16 h. The reaction mixture was diluted with ethyl acetate, rinsed with water, submerged in a brine solution, dried on Na_2SO_4 and then concentrated under low pressure to obtain a brown coloured, sticky liquid. Yield: 1 g, 86.9%, m.p.: 300-305 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3290.56 (-NH *str.*), 1695.43 (-C=O *str.*); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.82 (d, *J* = 8 Hz, 1H),7.53 (s, 1H),7.52 (d, *J* = 8 Hz, 1H), 7.28-7.25 (m, 3H), 7.15-7.11 (m, 1H), 6.94-6.87 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 206.43, 174.86, 158.08, 157.59, 156.71, 155.67, 155.31, 141.02, 136.39, 129.90, 128.45, 128.18, 127.02, 123.73, 120.40, 110.16.55.12, 48.74, 48.51, 45.69, 36.36, 25.76, 25.56. HRMS-ESI of $C_{24}H_{21}F_2NO_2$: *m/z* 394.1503 [calcd. 393.15].

General procedure for the synthesis of (*E*)-5-(2,5-difluoro-4-(((2-methoxybenzyl)amino)methyl)phenyl)benzylidene)-2,3-dihydro-1*H*-indene derivatives (14a-f): Compound **12** (0.2 g, 0.508 mmol) in methanol (10 mL) was added to a solution containing KOH (0.08 g,1.526 mmol) and substituted benzaldehyde (0.084 g, 0.508 mmol). The reaction mixture was stirred at room temperature for 16 h. TLC was used to monitor the progress of the reaction. Subsequently, the reaction mixture was evaporated, diluted with ethyl acetate, rinsed with water and concentrated under vacuum. The crude product was refined on silica gel with an eluent consisting of 2-3% methanol/DCM. to afford compound **14** as off white solid (**Scheme-II**).

(*E*)-5-(2,5-Diflouro-4-(((2-methoxybenzyl)amino)-methyl)phenyl)-2-(3,4-dimethoxy benzylidene)-2,3-dihydro-1*H*-indene-1-one (14a): Yield: 110 mg (40%), white solid; m.p.: > 350 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3057.17 (NH *str.*), 1697.43 (-C=O *str.*); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.89 (d, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.22 (d, *J* = 14.4 Hz, 1H), 7.20-7.12 (m, 4H), 6.90-6.88 (m, 2H), 6.87-6.80 (m, 3H), 4.08 (s, 2H) , 3.86 (s, 3H), 3.85 (s, 3H), 3.83-3.76 (m, 4H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:193.70, 176.62, 158.23, 157.65, 156.74, 150.67, 149.58, 149.06, 137.74, 134.42, 132.59, 130.34, 128.96, 128.47, 128.29, 126.51, 124.75, 124.46,



Scheme-II: Synthetic route of (*E*)-5-(2,5-diflouro-4-(((substituted)amino)-methyl)phenyl)-2-(3,4-dimethoxy benzylidene)-2,3-dihydro-1*H*-indene-1-one (**14a-f**)

120.55, 116.73, 116.48, 113.40, 111.25, 110.23, 55.96, 55.93, 55.18, 48.46, 45.19, 32.38, 21.48. HRMS-ESI of $C_{33}H_{29}F_2NO_4$: *m/z* 542.7404 $[M]^+$, [calculated 541.21].

(*E*)-5-2-(2-Chloro-4-flourobenzylidene)-5-(2,5-diflouro-4-(((2-methoxybenzyl)amino)methyl) phenyl)-2,3-dihydro-1*H*-indene-1-one (14b): Yield: 120 mg (44%), light yellow solid; m.p.: > 325 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3336.85 (NH *str.*), 1699.29 (-C=O *str.*); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.00-7.98 (m, 2H), 7.74-7.73 (m, 3H), 7.59 (d, *J* = 8 Hz, 1H), 7.28-7.24 (m, 3H), 7.15-7.13 (s, 2H), 6.94-6.88 (m, 2H), 4.02 (s, 2H), 3.87 (s, 3H), 3.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 193.03, 163.86, 161.33, 158.14, 157.62, 156.79, 155.74, 154.36, 149.62, 141.26, 137.22, 136.66, 131.01, 130.93, 129.90, 128.87, 128.66, 128.46, 126.50, 126.47, 124.68, 120.43, 117.89, 117.64, 110.22, 55.63, 55.17, 48.83, 45.79, 32.15, 31.86. HRMS-ESI of $C_{31}H_{23}ClF_3NO_2$: *m/z* 534.1456 $[M]^+$, [calculated 533.14].

(*E*)-5-(2,5-Diflouro-4-(((2-methoxybenzyl)amino)-methyl)-2-(3,4-dimethylbenzylidene)phenyl)-2,3-dihydro-1*H*-indene-1-one (14c): Yield: 110 mg (42%), white solid; m.p.: > 320 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3288.63 (NH *str.*), 1695.43 (-C=O *str.*); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.98-7.97 (m, 2H), 7.94 (s, 1H), 7.68-7.58 (m, 2H), 7.29-7.25 (m, 3H), 7.15-7.13 (m, 3H), 6.93-6.87 (m, 2H), 4.023 (s, 2H), 3.96 (s, 3H), 3.95-3.86 (m, 4H), 2.47 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 192.74, 174.28, 157.23, 156.67, 155.78, 154.80, 153.34, 149.10, 130.80, 130.74, 129.24, 127.82, 127.52, 123.53, 119.54, 109.25, 54.20, 47.59.44.41, 31.29, 20.35, 19.07. HRMS-ESI of $C_{33}H_{29}F_2NO_2$: *m/z* 510.1804 $[M]^+$, [calculated 509.22].

(*E*)-2-(3,5-Dichlorobenzylidene-5-(2,5-diflouro-4-(((2-methoxybenzyl)amino)methyl)phenyl)-2,3-dihydro-1*H*-indene-1-one (14d): Yield: 120 mg (43%), off-white solid; m.p.: > 315 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3338.78 NH (*str.*), 1699.29-(-C=O *str.*); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.00-7.98 (m, 2H), 7.73-7.71 (m, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.30-7.24 (m, 4H), 7.24-7.13 (m, 2H), 6.94-6.87 (m, 2H), 4.03 (s, 2H), 4.01 (s, 2H), 3.87 (s, 3H), 3.85 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 193.10, 163.88, 161.35, 158.15, 157.62, 156.80, 155.74, 154.37, 149.65, 131.03, 130.95, 129.92, 128.92, 128.68, 128.48, 126.53, 126.50, 124.47, 120.43, 117.91, 117.66, 116.58, 116.33, 114.51, 114.30, 110.21, 55.65, 55.18, 48.87, 45.82, 32.18, 31.88. HRMS-ESI of $C_{31}H_{23}Cl_2F_2NO_2$: *m/z* 550.1372 $[M]^+$, [calculated 549.11].

(*E*)-5-(2,5-Diflouro-4-(((2-methoxybenzyl)amino)-methyl)phenyl)-2-(4-hydroxy benzylidene)-2,3-dihydro-1*H*-indene-1-one (14e): Yield: 13 mg (82%), light yellow solid; m.p.: > 300 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3067.83 (-NH *str.*), 1717.64 (-C=O *str.*); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.93 (d, *J* = 8 Hz, 1H), 7.55-7.53 (m, 5H), 7.28-7.27 (m, 3H), 7.18-7.15 (m, 1H), 6.87-6.85 (m, 5H), 3.96 (s, 2H), 3.98 (s, 3H), 3.86-3.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 193.72, 158.93, 158.20, 157.66, 156.63, 155.78, 154.17, 149.56, 140.45, 137.69, 134.75, 132.79, 131.44, 130.56, 129.41, 128.33, 126.82, 126.19, 125.05, 124.48, 120.69, 116.36, 110.36, 61.71, 55.27, 48.90, 45.31, 32.33. HRMS-ESI of $C_{31}H_{25}F_2NO_3$: *m/z* 498.5463 $[M]^+$, [calculated 497.18].

(*E*)-5-(2,5-Diflouro-4-(((2-methoxybenzyl)amino)-methyl)phenyl)-2-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-methylene)-2,3-dihydro-1*H*-indene-1-one (14f): Yield: 110 mg (82%), light yellow solid; m.p.: > 300 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3076.46 (-NH *str.*), 1697.36 (-C=O *str.*); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.96 (d, *J* = 8 Hz, 1H), 7.70 (s, 1H), 7.60-7.56 (m, 2H), 7.40-7.10 (m, 6H), 6.96-6.88 (m, 3H), 4.57-4.56 (m, 4H), 4.06 (s, 2H), 3.90-3.89 (m, 4H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 193.72, 149.71, 137.68, 133.95, 132.94, 130.20, 128.91, 128.83, 128.43, 126.50, 126.47, 125.19, 124.41, 120.54, 119.27, 117.81, 117.56, 117.51, 116.66, 116.44, 110.24, 64.60, 64.31, 64.19, 55.19, 48.55, 45.39, 32.44. HRMS-ESI of $C_{33}H_{27}F_2NO_4$: *m/z* 540.3545 $[M]^+$, [calculated 539.19].

RESULTS AND DISCUSSION

The discovery of Fab I inhibitors was utilized for the purpose of improving drug discovery in the realm of anti-infective medicine. In the biosynthetic process, these Fab I inhibitors are NADH-dependent enoyl reductases from type II bacterial fatty acids. In our ongoing interest in the development of new derivatives, the present study aims to design and synthesize some novel biphenyl ether associated reductive aminated compounds in **Scheme-I** and also novel indanone derivatives through aldol condensation in **Scheme-II** based on the structure of previously developed standard Fab I inhibitors.

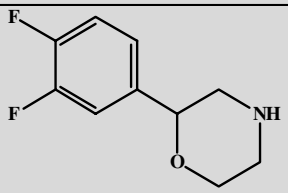
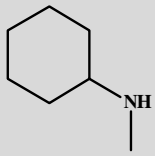
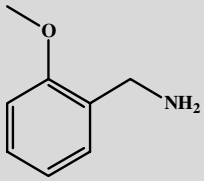
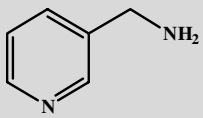
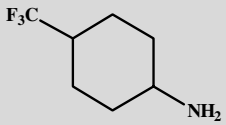
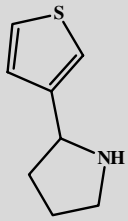
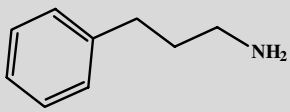
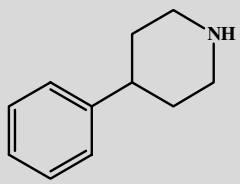
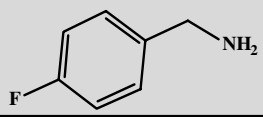
Titanium isopropoxide was utilized as a catalyst for the synthesis of acyclic and allylic epoxy alcohols, diastereoselective reduction of α-substituted β-keto esters, the asymmetric allylation of ketones and also for intramolecular formal [3+2] cycloaddition. Intermediate **3** was successfully synthesized by adding N-methyl piperazine *via* SNAr coupling in the presence of titanium isopropoxide using THF as solvent at room temperature and yielded 90% required product. The position of *N*-methyl piperazine on the phenyl ring adjacent to aldehyde was confirmed with fluorine NMR in intermediate **3** with 3-fluoropyridine phenyl-2-boronic acid. ^{13}C NMR spectra confirmed the position of the piperazine ring by analyzing the interactions of the piperazine $–CH_2$ groups with the aromatic proton on the phenyl ring at δ 112.04 ppm on one side and with the aldehyde proton at δ 154.81 ppm on the other side. These results have proven that the suggested method is efficient over the previous methods. The isolated bromo intermediate **3** was made to react with different boronated esters *via* the Suzuki reaction protocol and successfully obtained (3′-benzyloxy)-3-fluoro-5-(4-methyl-piperazine-1-yl)-[1,1′-biphenyl]carbaldehyde **5**. There after the derivatives **7a-j** were synthesized by reductive aminating the aldehyde **5** with different amines.

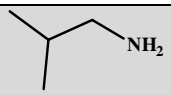
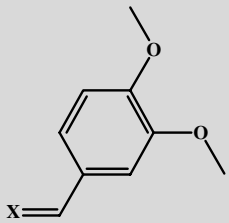
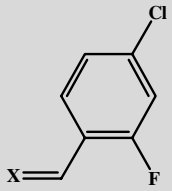
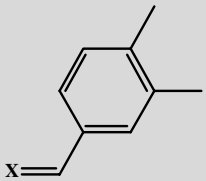
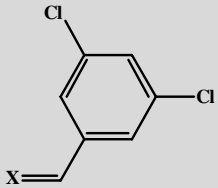
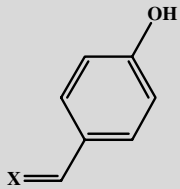
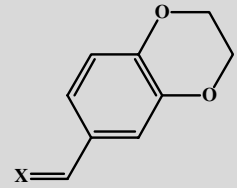
Based on docking results of MUT056399, the indanone derivatives were designed and synthesized, which is done by enhancing the binding to the NADPH coenzyme by adding more π-stacking and a double bond to indanone. Intermediate **10** was successfully synthesized *via* reductive amination of 4-bromo-2,5-diflouro benzaldehyde in the presence of sodium triacetoxy borohydride, then after intermediate **12** was synthesized by Suzuki protocol with indanone boranate ester. Conversion of intermediate **12** to **14a** is a crucial step and derivatized

some targets using different aldehydes through aldol condensation. The structure of the synthesized molecules was confirmed by different analytical techniques like ^{1}H NMR, ^{13}C NMR and FT-IR. HRMS technique was used to identify the desired mass number of required product.

***In vitro* antibacterial testing:** The antibacterial efficacy was assessed against the Gram-positive bacteria (S. *aureus*, B. *subtilis*) and Gram-negative-bacteria (*E. coli, P. aeruginosa*). Compounds **7a-j** and **14a-f** were evaluated in DMSO solvent at 8, 16, 32, 64, 128 and 256 µg/mL concentrations. Table-1 displays compound **7c** has better MIC at 16 µg/mL against *S. aureus* and 8 µg/mL against *B. subtilis* whereas compound **7i** was second best against *S. aureus* at 16 µg/mL and 16 µg/mL against *B. subtilis*. Among the synthesized indanone derivatives, compound **14e** has better MIC at 64 µg/mL against *S. aureus* and 32 µg/mL against *B. subtilis.*

TABLE-1
MIC RESULTS OF SYNTHESIZED COMPOUNDS AGAINST BACTERIA

Compounds	Different amines	MIC (µg/mL)			
		S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
7a		>128	>128	>128	>128
7b		64	>128	>128	>128
7c		16	8	>128	>128
7d		32	32	>128	>128
7e		32	16	>128	>128
7f		>128	>128	>128	>128
7g		>128	>128	>128	>128
7h		>128	>128	>128	>128
7i		16	16	>128	>128

7j		>128	>128	>128	>128
14a		64	64	>128	>128
14b		>128	128	>128	>128
14c		>128	>128	>128	>128
14d		64	64	>128	>128
14e		64	32	>128	>128
14f		64	64	>128	>128
	Triclosan	0.025	1.5	32	1
	MUT056399	0.06	64	32	64

Docking studies: The molecular docking for the synthesized compounds with the highest MIC values was corroborated theoretically using molecular docking studies. The protein used for the docking of molecules is 7ap6. The software used for the molecular docking is AutodockVina 1.5.7. The result shows that the synthesized novel molecules have higher binding energy than the standard trichlosan. The number of H-bonds formed with protein in compound **7c** is 10 with a binding energy of -8.43 kcal/mol, which is more in com-parison with the standard triclosan (-6.69 kcal/mol). The -OCH_3 group in compounds **14a-f** is responsible for additional hydrogen bond formation with the protein. Insertion of the aminoalkyl chain in LHS and the extended benzyloxy phenyl ether in RHS of the molecule helped a lot to better fit into the protein. The *n*-methyl piperazine in the upper end also played a vital role in binding with the protein. Although molecules **14a-f** have also shown significant binding with protein, but the lengthy chain went to solvent exposed region. Fig. 2 illustrates the interaction between compounds **7c** and **7i** with the target enzyme.

Conclusion

A novel series of carbaldehyde (**7a-j**) and indan-one (**14a-f**) derivatives designed, synthesized and biologically evaluated as Fab I Inhibitors. Compound **7c** exhibit better MIC at 16 µg/mL against *S. aureus* and 8 µg/mL against *B. subtilis* whereas compound **7i** was second best against *S. aureus* at 16 µg/mL and 16 µg/mL against *B. subtilis*. The synthesized molecules were well fit into the enzymatic pocket. The binding energy

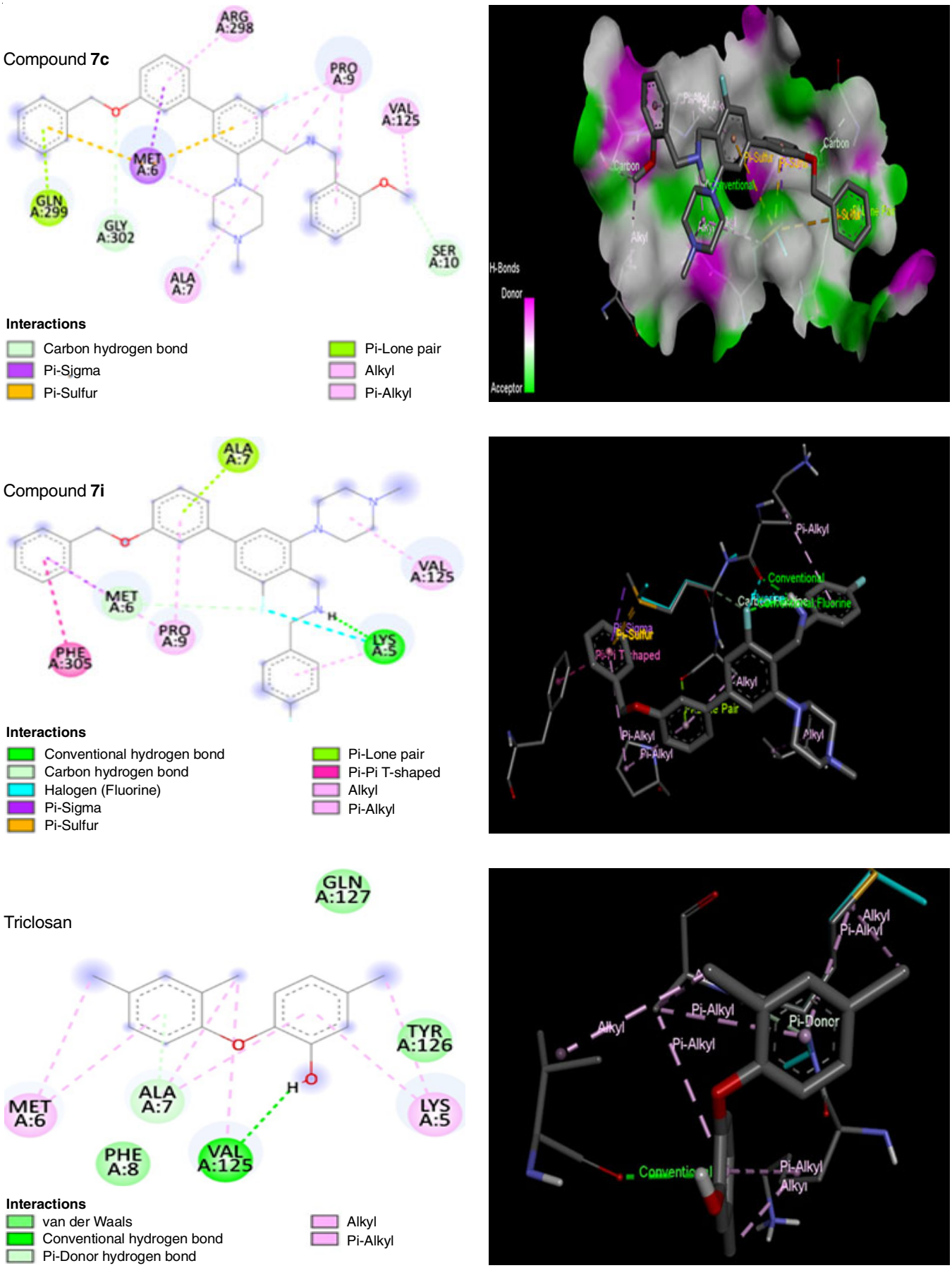


Fig. 2. 2D and 3D images of synthesized compounds **7c**, **7i** and triclosan with protein

of compounds **7c** & **7i** molecules was significant when compared to standard molecule triclosan.

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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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