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Design and synthesis of novel triazole-isofroxadin molecules: Docking studies against inflammatory and tuberculosis targets

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1,2,3-Triazole scaffolds are playing a vital role in various fields. These are not natural products but produced by synthetic chemists. Isafroxadin natural product and its 1,2,3-triazole derivatives have been synthesized using Click protocol. Thus, the newly generated scaffolds have been subjected to docking studies against inflammatory and tuberculosis activity.

Keywords: Isofroxadin, Triazoles, Click reaction, Inflammatory, Tuberculosis

Triazole compounds are important heterocyclic motifs with five member ring, having three nitrogen atoms in isomeric forms of 1,2,3 and 1,2,4 positions (Fig. 1). The triazole molecules have gained remarkable importance by their applications in pharmaceuticals, crop protection, polymers and in functional material sciences[1-5]. The 1,2,3-triazole systems are one of these and having very good dealings with biological targets, due to their non-covalent nature, leads to form hydrophobic interactions, hydrogen bonds, dipole-dipole bonds and van der Waals forces. Thus, these molecules processes a broad range of pharmaceutical properties like antiviral, antifungal, antibacterial, anticancer, *etc*.[6-10]

As part of our regular research program, in development of new synthetic protocols[11-15] and also synthesis of biologically active natural products[16-19], herein, we report, the synthesis of 1,2,3-triazole derivatives, for generation of hybrid mode new scaffolds, by the combination of a Coumarin units[20,21] using Click protocol[22]. Thus, synthesized new chemical entities were used for docking studies against inflammatory and tuberculosis targets.

Results and Discussion

Initially, isofraxadin (**4**) moiety was synthesized in three steps from commercially available, 2,4-dihydroxy benzaldehyde (**1**), which involved, a sequence of reactions such as bromination in ethanol, methoxylation with sodium methoxide and Wittig in *N*, *N*-dimethylaniline at reflux conditions[23,24]. In order to attain the terminal alkyne, the free hydroxyl group of isofraxidin (**4**) on reaction with propargyl bromide under basic conditions, in presence of PTC in DMF at RT afforded a key intermediate, 6,8-dimethoxy-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one **(5)** in very good yields. Further, the conversion of isofraxadin fragment, in to 1,2,3-triazole -isofroxadin hybrids involved step by step synthesis in very good yields.

The azide compounds **(6a-6l)** were prepared by applying modified Fischer conditions *via* diazotization of substituted anilines and amines with sodium nitrite at 0°C in acidic medium and on subsequent treatment with hydroxyl ammonium chloride in very good yields[25,26]. The aromatic systems containing electron withdrawing and electron donating groups worked well and the aliphatic (**6i**) and alicyclic (**6l**) systems also converted successfully to their respective azides in very yields. The coupling of 1,2,3-triazole isofroxadin hybrids **(7a-7l)** was carry out by treating the azides **(6a-6l)** with terminal alkyne **(5)** in presence of $CuSO_4.5H_2O$ and *l*-sodium ascorbate in ^tBuOH-H_2O (1:1) at RT and observed good yields as shown in the Scheme 1. This reaction pathway is well established in the literature and which proceeds by employing the copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC) protocol[27-29].

The synthesized, 1,2,3-triazole compounds (**7a-7l**, Fig. 2) were explore to anti-inflammatory activity through molecular docking studies. The method followed, x-ray crystal structures of COX-2 enzyme co-crystallized with Flurbiprofen and DprE1 enzyme

of Mycobacterium tuberculosis, RCS Protein Data with PDB ID-3PGH and 4FDO respectively[30-32]. The observation shows that among the compounds, **7d** and **7j** are shown nearby binding affinities –8.806 Kcal / mol and –8.642 Kcal/mol respectively with the standard Flurbiprofen –9.870 Kcal / mol and all are shown in the Table-S1.

The docking results shows that all the inhibitors snugly fit into the active site of DprE1 in positions very close to that of native ligand in the crystal

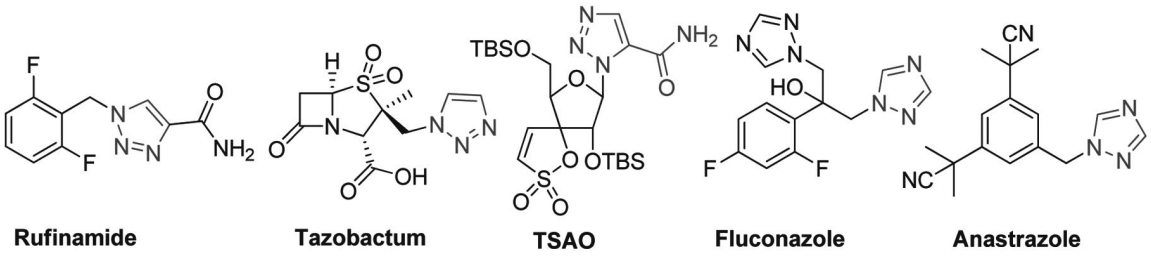
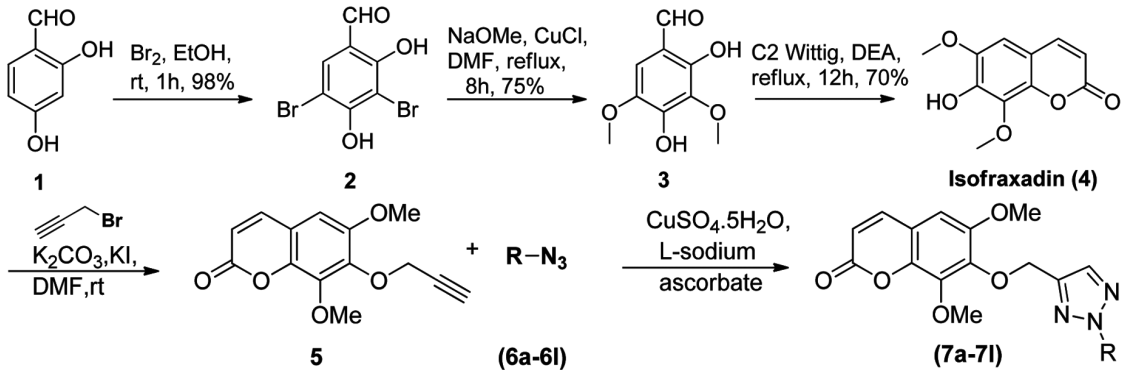


Fig. 1 — Triazole based drugs



Scheme 1 — Synthesis of 1,2,3-triazolemolecules (**13a-l**)

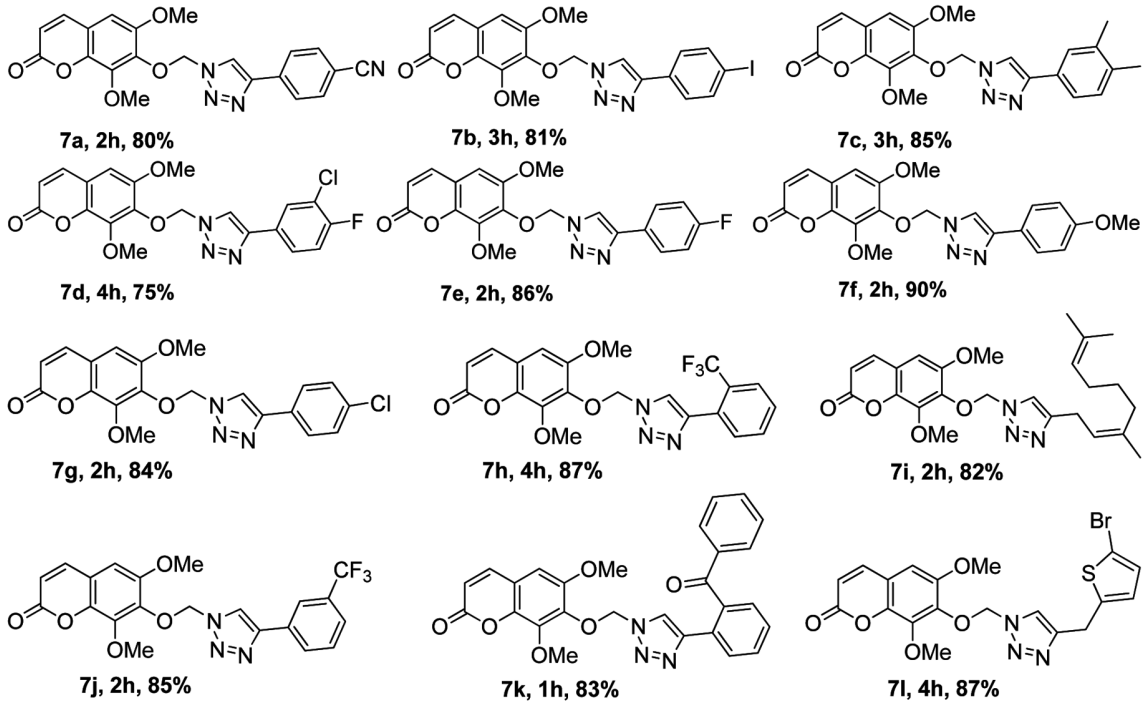


Fig. 2 — Synthesized 1,2,3-triazole chromen-2-one scaffolds

structure of its complex with DprE1. And all the compounds have shown good affinity (ranges -8.777 Kcal / mol to -6.415 Kcal / mol) toward DprE1 with a similar topology of binding. The enzyme inhibitor complex was stabilized by strong H-bonding interaction observed with the amino acid residues Lys418, Tyr115, Ser228, His132 and Tyr60 in the enzyme active site.

Experimental Section

All the air and moisture sensitive reactions were carried out under nitrogen atmosphere. Oven-dried glass apparatus were used to perform all the reaction. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such in reactions. Purification of compounds was carried out *via* column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz and 500 MHz spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-RT 240-c Spectrophotometer using KBr / Thin Film optics. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70eV. Optical rotation values were recorded on Horiba sepa300 polarimeter. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

6,8-Dimethoxy-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one, 5: To a stirred mixture of isofroxadin (1 g, 4.50 mmol), in DMF (15 mL) was added K_2CO_3 (0.25g, 18.01 mmol), propargyl bromide (1.64 mL, 18.01 mmol) and catalytic amount of KI at RT and continued stirring for 12 h at the same temperature. After the completion of reaction as indicated by the TLC, the reaction mixture was extracted with ethyl acetate (3×50 mL). The combined organic phases were dried over Na_2SO_4 and concentration under reduced pressure. The residue was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:1) mixture to give pure compound **5**, as light brown solid, 1.1 g yield (94%). m.p.168 - 170°C. IR (neat): 3420, 3239, 3045, 2925, 2865, 2119, 1726, 1516, 1456, 1312, 1287, 1151, 1085, 972, 867, 587 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 1H, *J* = 9.4 Hz), 6.68 (s, 1H), 6.36 (d, 1H, *J* = 9.4 Hz), 4.89 (d, 2H, *J* = 2.4 Hz), 4.08 (s, 3H), 3.90 (s, 3H), 2.49 (t, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 150.4, 143.4, 143.1, 142.8, 141.7, 115.6, 115.1, 114.9, 103.7, 78.6, 75.9, 62.0, 60.6, 56.4; *m/z* $[M+H]^+$: 261. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{14}H_{13}O_5$: 261.075. Found: 261.075.

General procedure for preparation of aryl azides 6a-l: To a stirred mixture of aromatic amine (0.6 mmol) and dil.HCl (15%, 60 mL), was added sat. $NaNO_2$ (0.8 mmol) solution drop-wise at 0°C and continued stirring for 15 mint, then added a sodium azide (0.6 mmol) solution drop-wise at 0°C and allowed to stir at same temperature for 30 mins. After the completion of reaction, as indicated by the TLC, the reaction mixture was extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over Na_2SO_4 and concentration under reduced pressure at low temperature to afford, the target compounds (**6a-6l)** in very good yields.

General procedure for the preparation of target molecules 7a-7l: To a stirred solution of 6,8-di methoxy-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one **(5)** (0.1g, 0.4 mmol**)** and 4-azido benzonitrile **(6a)** (83 mg, 0.6 mmol) in CH_2Cl_2 - water (1+1 mL) mixture were added $CuSO_4.5H_2O$ (0.1g, 0.4 mmol) and sodium ascorbate (8 mg, 0.044 mmol). The reaction was stirred for 2h at RT, until the completion of reaction, as indicated by TLC. Then, the reaction mixture was diluted with CH_2Cl_2 - water (10+10 mL) mixture. Then the organic layer was separated and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:3) mixture to afford pure compound **7a,** as a brown solid, 0.12 g, yield (80%).

Compound 7a: m.p.158-160°C. IR (neat): 3336, 3041, 2924, 2846, 2211, 1723, 1606, 1564, 1458, 1310, 1290, 1126, 1088, 960, 835, 711, 590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.44 (s, 1H), 8.02 (d, 2H, *J* = 8.8 Hz), 7.90 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 9.4 Hz), 6.77 (s, 1H), 6.37 (d, 1H, *J* = 9.4 Hz), 5.41 (s, 2H), 4.03 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 158.9, 152.8, 149.1, 144.1, 143.2, 143.0, 141.6, 138.7, 136.3, 132.9, 132.5, 132.4, 121.1, 119.6, 116.8, 114.1, 112.9, 103.3, 65.2, 60.7, 55.3; *m/z* $[M+H]^+$: 405. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{21}H_{17}N_4O_5$: 405.101. Found: 405.112.

Compound 7b: Brown solid. m.p.164-166°C. Yield 0.15 g (81%). IR (neat): 3282, 2924, 1714, 1609, 1563, 1294, 1085, 596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.33 (s, 1H), 7.87

(d, 2H, *J* = 8.7 Hz), 7.70 (d, 1H, *J* = 9.5 Hz), 7.56 (d, 2H, *J* = 8.7 Hz), 6.79 (s, 1H), 6.34 (d, 1H, *J* = 9.5 Hz), 5.38 (s, 2H), 4.02 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 158.7, 148.7, 142.7, 142.3, 141.1, 140.4, 139.6, 137.3, 135.1, 133.3, 120.6, 113.6, 103.2, 92.3, 64.8, 60.3, 54.9; *m/z* $[M+H]^+$: 506. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{20}H_{17}N_3O_5I$: 506.023. Found: 506.020.

Compound 7c: Brown solid. m.p.162-164°C. Yield 0.13 g (85%). IR (neat): 3378, 2944, 1710, 1611, 1562, 1458, 1294, 1086, 595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.34 (s, 1H), 7.77 (d, 2H, *J* = 9.5 Hz), 7.56 (s, 1H), 7.49 (d, 1H, *J* = 8.1 Hz), 7.27 (d, 1H, *J* = 8.1 Hz), 6.87 (s, 1H), 6.35 (d, *J* = 9.5 Hz, 1H), 5.35 (s, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 158.5, 148.6, 142.7, 142.1, 140. 9, 139.4, 136.6, 135.7, 133.2, 129.1, 119.7, 116.0, 113.4, 103.1, 64.7, 60.0, 54.7, 18.2, 17.8; *m/z* $[M+H]^+$: 408. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{22}H_{22}N_3O_5$: 408.156. Found: 408.155.

Compound 7d: Brown solid. m.p.172-174°C. Yield 0.1 g (65%). IR (neat): 3125, 3041, 2955, 2867, 1724, 1607, 1564, 1457, 1292, 1127, 1045, 839, 591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.71 (s, 1H), 8.05 - 8.02 (m, 1H), 7.82 - 7.75 (m, 2H), 7.40 (t, 1H, *J* = 8.7 Hz), 6.87 (s, 1H), 6.35 (d, 1H, *J* = 9.5 Hz), 5.39 (s, 2H), 3.99 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 162.6, 158.3, 157.3, 154.0, 136.02, 148.2, 144.1, 142.75, 140.1, 137.1, 132.0, 121.7, 120.9, 119.0, 116.5, 116.2, 113.1, 112.9, 103.7, 95.2, 64.9, 59.6, 54.6; *m/z* $[M+Na]^+$: 454. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{20}H_{16}N_3O_5ClF$: 432.074. Found: 432.075.

Compound 7e: Brown solid. m.p.160-162°C. Yield 0.13 g (86%). IR (neat): 3403, 2943, 1726, 1607, 1565, 1457, 1292, 1126, 1042, 593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.24 (s, 1H), 7.78 - 7.74 (m, 2H), 7.71 - 7.68 (d, 1H, *J* = 9.5 Hz), 7.26 (t, 2H, *J* = 8.3 Hz), 6.77 (s, 1H), 6.37 (d, 1H, *J* = 9.5 Hz), 5.40 (s, 2H), 4.03 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 163.5, 160.18, 159.8, 149.7, 144.3, 143.4, 143.2, 142.2, 140.8, 132.7, 122.1, 122.0, 121.3, 116.4, 116.0, 114.8, 114.5, 103.6, 66.1, 61.3, 55.8; *m/z* $[M+H]^+$: 398. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{20}H_{17}N_3O_5F$: 398.113. Found: 398.114.

Compound 7f: Brown solid. m.p.164-166°C. Yield 0.14 g (90%). IR (neat): 3404, 2939, 1723, 1610, 1563, 1457, 1253, 1044, 591 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.19 (s, 1H), 7.73 - 7.64 (m, 4H), 7.06 (d, 1H, *J* = 9.0 Hz), 6.79 (s, 1H), 6.37 (d, 1H, *J* = 9.0 Hz), 5.38 (s, 2H), 4.02 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 159.8, 159.3, 149.7, 143.9, 143.3, 142.2, 140.8, 139.6, 129.8, 121.6, 121.3, 114.7, 114.4, 114.3, 103.7, 66.1, 61.3, 55.8, 55.1; *m/z* $[M+H]^+$: 410. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{21}H_{20}N_3O_6$: 410.216. Found: 410.218.

Compound 7g: Brown solid. m.p.160-162°C. Yield 0.13 g (84%). IR (neat): 3424, 2925, 1717, 1607, 1563, 1456, 1292, 1045, 822, 591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.29 (s, 1H), 7.77 - 7.68 (m, 3H), 7.54 - 7.49 (m, 2H), 6.77 (s, 1H), 6.34 (d, 1H, *J* = 9.5 Hz), 5.40 (s, 2H), 4.02 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 159.8, 149.7, 143.6, 143.2, 142.1, 140.7, 134.0, 133.0, 130.4, 128.6, 126.9, 126.8, 126.0, 114.6, 114.3, 103.9, 65.7, 61.2, 55. 8; *m/z* $[M+H]^+$: 414. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{20}H_{17}N_3O_5Cl$: 414.084. Found: 414.085.

Compound 7h: Brown solid. m.p.148-150°C. Yield 0.13 g (77%). IR (neat): 3387, 2940, 1712, 1608, 1564, 1459, 1278, 1124, 1041, 591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.02 (s, 1H), 7.88 (d, 1H, *J* = 7.2 Hz), 7.80 - 7.69 (m, 3H), 7.57 (d, 1H, *J* = 9.4 Hz), 6.77 (s, 1H), 6.34 (d, 1H, *J* = 9.4 Hz), 5.44 (s, 2H), 4.02 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 159.2, 149.0, 143.0, 142.6, 132.4, 129.7, 127.9, 126.2, 125.3, 114.0, 103.2, 65.1, 60.5, 55.2; *m/z* $[M+H]^+$: 448. HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{21}H_{17}N_3O_5F_3$: 448.109. Found: 448.111.

Compound 7i: Brown solid. m.p.164-166°C. Yield 0.12 g (72%). IR (neat): 2929, 1727, 1564, 1456, 1288, 1044, 770, 587 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.60 (s, 1H), 6.67 (d, 1H, *J* = 7.4 Hz), 6.34 (t, 1H, *J* = 7.4 Hz), 5.47 - 5.40 (s, 1H), 5.32 (d, 2H, *J* = 10.3 Hz), 5.11 - 5.08 (m, 1H), 5.01 - 4.94 (m, 2H), 4.00 (s, 3H), 3.88 (s, 3H), 2.22 - 2.12 (m, 4H), 1.81 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 150.3, 144.1, 143. 4, 142.9, 141.5, 139.5, 132.7, 132.1, 123.2, 122.5, 117.8, 115.4, 115.0, 103.8, 67.0, 61.8, 56.4, 47.9, 39.4, 26.2, 25.7, 17.7, 16.5; $[M+H]^+$: 440; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{24}H_{30}N_3O_5$: 440.216. Found: 440.218.

Compound 7j: White solid. m.p.156-158°C. Yield 0.11 g (65%). IR (neat): 3422, 2926, 1461, 1235,

1123, 1041, 591 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.67 (s, 1H), 8.18 - 8.10 (m, 2H), 7.77 (t, 3H, *J* = 10.3 Hz), 6.88 (s, 1H), 6.34 (d, 1H, *J* = 9.5 Hz), 5.37 (s, 2H), 4.01 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 160.0, 149.9, 144.9, 144.8, 143.5, 143.4, 136.9, 130.4, 125.0, 123.4, 123.2, 123.1, 121.3, 117.1, 115.0, 114.7, 103.8, 66.2, 61.5, 56.0; $[M+H]^+$: 448; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{21}H_{17}F_3N_3O_5$: 448.109. Found: 448.111.

Compound 7k: Yellow solid: m.p.162-164°C. Yield 0.15 g (83%). IR (neat): 3425, 2935, 1722, 1600, 1563, 1454, 1287, 1041, 588 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 8.02 (s, 1H), 7.72 - 7.65 (m, 6H), 7.64 - 7.49 (m, 4H), 6.76 (d, 1H, *J* = 9.5 Hz), 6.33 (t, 1H, *J* = 8.5 Hz), 5.22 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 193.9, 159.9, 149.5, 144.5, 143.9, 143.4, 134.0, 133.0, 132.9, 131.1, 129.2, 128.9, 127.9, 124.2, 124.0, 114.7, 114.4 103.7, 74.7, 61.2, 55.8; $[M+H]^+$: 484; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{27}H_{22}N_3O_6$: 484.148. Found: 448.150.

Compound 7l: White solid. m.p.152-154°C. Yield 0.12 g (67%). IR (neat): 3417, 2925, 1725, 1606, 1563, 1455, 1036, 778, 738, 588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 7.67 (s, 1H), 7.59 (d, 1H, *J* = 9.5 Hz), 6.88 - 6.80 (m, 2H), 6.61 (s, 1H), 6.24 (t, 1H, *J* = 9.5 Hz), 5.56 (s, 2H), 5.22 (s, 2H), 3.87 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 158.8, 149.8, 148.2, 147.7, 145.8, 144.8, 144.0, 143.3, 129.6, 128.1, 125.3, 122.6, 114.9, 114.5, 110.0, 103.6, 66.2, 61.3, 55.9; $[M+2H]^+$: 480; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{19}H_{17}BrN_3O_5S$: 478.005. Found: 478.006.

Conclusion

In summary, the click synthesis of Isofroxadin triazole hybrids **(7a-7l)** with various azides under mild conditions in very good yields (75% - 90%). All the reactions are clean and easy to handle and all the synthesized compounds were confirmed by their spectral data. All the compounds are satisfied the rule of five, which enables them to be oral drug candidates. The molecular docking study showed that the newly synthesized oxindole derivatives have comparable binding patterns in both 3PGH and 4FDO. The triazole ring is accommodated in the hinge region interacting through hydrogen bonding with the backbone triazole ring and CO with the key amino acids Arg120, Glu524 and Tyr355 in anti-inflammatory, on another hand with Lys418 in anti-mycobacterial studies.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776

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