

Synthesis of novel fluorine containing imidazolyl aurones and benzofurans

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Imidazolyl aldehyde **1** on reaction with substituted 2-hydroxyacetophenone **2** gives chalcone **3**, which on treatment with mercuric acetate in dry pyridine gives compound **4** and when treated with dry acetone in K_2CO_3 with 4-bromophenacylbromide gives compound **5**. The structures of all the synthesized compounds have been confirmed by spectroscopic techniques.

Keywords: Imidazoles, aurones, chromones

Unique properties associated with fluorine are highest electronegativity, smallest size, high thermal stability and lipophilicity due to which the substitution of hydrogen by fluorine has become a common strategy in development of drugs^{1,2}. Organofluorine compounds can increase the herbicidal³, fungicidal⁴ and insecticidal⁵ activities of certain compounds.

Imidazole is a planar 5-membered ring containing 3C-2N at 1,3-position. It exists in two equivalent tautomeric forms. Imidazole scaffold is one of the most valuable pharmacophores for medicinal research⁶. The essential amino acid histidine, biotin and alkaloids are well known natural products that have imidazole moiety⁷. There are many clinical drugs being used in different therapeutic areas based on the imidazole structure such as antihypertensive (losartan), anticancer (decarbazepine), antihistaminic (cimetidine) and antiparasitic (metronidazole). Due to its importance it has become an attractive target for synthetic and medicinal chemists. There are many synthetic methodologies that have been developed to assemble imidazole ring with diverse functional groups. Various biological activities associated with imidazole are antitubulin⁸, mGAT3 selective GABA uptake inhibitors⁹, antitubercular¹⁰, antitumour¹¹, hemeoxygenase-1 and hemeoxygenase-2 (Ref 12) inhibitors.

Chalcones are a family of aromatic ketones bridged by an enone¹³ linkage and these are Michael acceptors and constitute important group of natural products belonging to the flavonoid family. Derivatives of chalcones have been reported to possess various biological activities including antiinflammatory¹⁴, anticancer¹⁵, α -glucosidase inhibitor¹⁶ *in vitro*,

antimalarial¹⁷, Nrf2 activators¹⁸, antimicrobial¹⁹, antifungal²⁰, antihyperglycemic²¹, antibacterial²² and antioxidant²³.

Aurones are structural isomers of flavones that contain an exocyclic carbon-carbon double bond bridging the benzofuranone and phenyl rings^{24,25}. Aurones are the natural yellow pigments of plants and have a limited occurrence. The important biological activities of aurones have been highlighted with recent studies that revealed their anticancer²⁶, anti-inflammatory²⁷, antimicrobial²⁷, antiparasitic²⁸, antiviral²⁹, inhibitory activities against acetylcholinesterase³⁰ and MAO-B³¹.

Benzofuran derivatives are an important class of organic compounds, which are known to be present in many natural products³² and possess physiological activity. They have found applications in agrochemicals^{33,34}, pharmaceuticals³⁵ and cosmetics³⁶. Benzofurans are building blocks of optical brighteners³⁷. Baker's yeast contains benzofuran derivatives showing antioxidant properties³⁸.

Experimental Section

The synthesis of 1-((4-(2,2,2-trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde **1** was performed by using the literature method³⁹. Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. Mass spectra were recorded on Waters Acquity TQD mass spectrometer. 1H NMR spectra were recorded on Bruker Avance II 400 MHz NMR spectrometer in $DMSO-d_6$ as a solvent and TMS as an internal standard. Peak values are

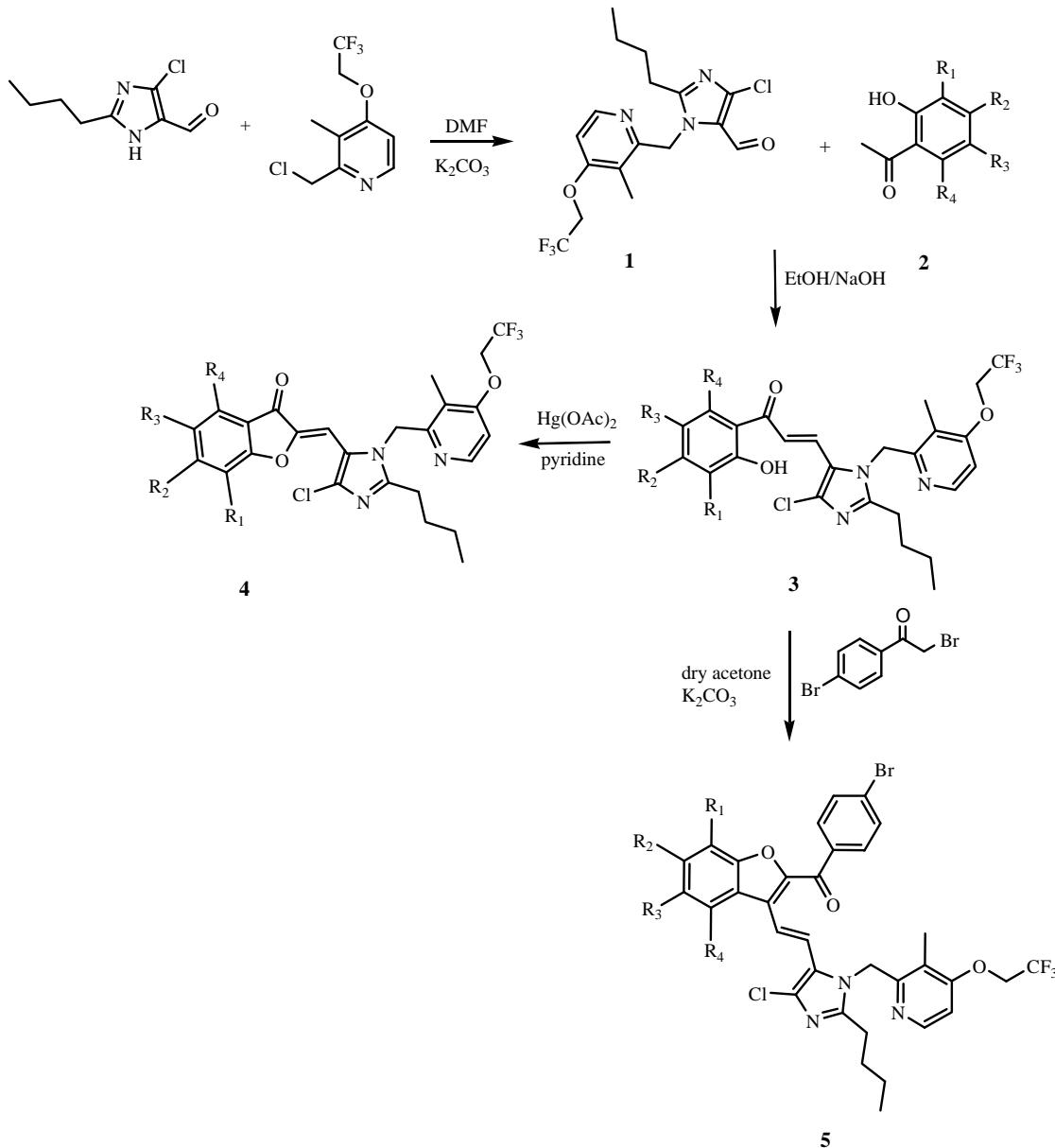
shown in δ (ppm). IR spectra were recorded on Shimadzu IR Affinity-1S spectrophotometer.

(E)-3-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one, 3a-e

Equimolar quantity of compound **1** (2.5 mmol) and substituted 2-hydroxyacetophenone **2** (2.5 mmol) were dissolved in 25 mL ethanol. 10 mL of 40% NaOH was added to the above solution. The reaction mixture was stirred at RT for 24 h. After completion of reaction, the contents were poured over crushed ice and neutralized with dil. acetic acid. The yellow

solid thus obtained was filtered and purified by recrystallization from alcohol to afford compound **3** (Scheme I).

(E)-3-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(5-bromo-2-hydroxyphenyl)prop-2-en-1-one, 3a: m.p.138°C. Yield 72%. IR: 3301 (O-H), 1644 (C=O), 1573 (-C=N), 1527 (C=C, aliphatic), 1510 (C=C, aromatic) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.82 (t, 3H, CH₃), 1.29 (m, 2H, CH₂), 1.61 (m, 2H, CH₂), 2.31 (s, 3H, CH₃), 2.63 (t, 2H, CH₂), 4.76 (q, 2H, CH₂), 5.46 (s, 2H, CH₂), 6.89-8.19 (m, 7H, Ar-H and =CH) 12.30



Scheme 1

(s, OH); MS: *m/z* 586. Anal. Calcd: C, 51.17; H, 4.12; N, 7.16. Found: C, 51.21; H, 4.16; N, 7.19%.

(E)-3-(1-(4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(2-hydroxy-3,5-dimethylphenyl)prop-2-en-1-one, 3b: m.p.170°C. Yield 68%. IR: 3301 (O-H), 1647 (C=O), 1576 (-C=N), 1524 (C=C, aliphatic), 1511 (C=C, aromatic) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.80 (t, 3H, CH₃), 1.30 (m, 2H, CH₂), 1.62 (m, 2H, CH₂), 2.23 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.64 (t, 2H, CH₂), 4.74 (q, 2H, CH₂), 5.44 (s, 2H, CH₂), 6.74-8.20 (m, 6H, Ar-H and =CH), 12.31 (s, OH); MS: *m/z* 536. Anal. Calcd: C, 60.50; H, 5.45; N, 7.84. Found: C, 60.53; H, 5.49; N, 7.88%.

(E)-3-(1-(4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(3-chloro-6-hydroxy-2,4-dimethylphenyl)prop-2-en-1-one, 3c: m.p.130°C. Yield 76%. IR: 3302 (O-H), 1647 (C=O), 1577 (-C=N), 1527 (C=C, aliphatic), 1514 (C=C, aromatic) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.82 (t, 3H, CH₃), 1.31 (m, 2H, CH₂), 1.61 (m, 2H, CH₂), 2.33 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 2.64 (t, 2H, CH₂), 4.75 (q, 2H, CH₂), 5.46 (s, 2H, CH₂), 6.76-8.16 (m, 5H, Ar-H and =CH) 12.32 (s, OH); MS: *m/z* 570. Anal. Calcd: C, 56.85; H, 4.95; N, 7.37. Found: C, 56.89; H, 4.97; N, 7.40%.

(E)-3-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(5-fluoro-2-hydroxyphenyl)prop-2-en-1-one, 3d: m.p.160°C. Yield 80%. IR: 3300 (O-H), 1645 (C=O), 1575 (-C=N), 1525 (C=C, aliphatic), 1512 (C=C, aromatic), 1163 (Ar-F) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.83 (t, 3H, CH₃), 1.30 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 2.33 (s, 3H, CH₃), 2.64(t, 2H, CH₂), 4.77 (q, 2H, CH₂), 5.49 (s, 2H, CH₂), 6.92-8.21 (m, 7H, Ar-H and =CH), 12.33 (s, OH); MS: *m/z* 524. Anal. Calcd: C, 57.09; H, 4.60; N, 7.99. Found: C, 57.12; H, 4.64; N, 8.01%.

(E)-3-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-(4-ethyl-2-hydroxyphenyl)prop-2-en-1-one, 3e: m.p.140°C. Yield 66%. IR: 3300 (O-H), 1643 (C=O), 1573 (-C=N), 1524 (C=C, aliphatic), 1511 (C=C, aromatic) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.80 (t, 3H, CH₃), 1.29 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 1.63 (t, 3H, CH₃), 2.19 (q, 2H, CH₂), 2.30 (s, 3H, CH₃), 2.64 (t, 2H, CH₂), 4.74 (q, 2H, CH₂), 5.45 (s, 2H, CH₂),

6.72-8.10 (m, 7H, Ar-H and =CH), 12.31 (s, OH); MS: *m/z* 536. Anal. Calcd: C, 60.50; H, 5.45; N, 7.84. Found: C, 60.54; H, 5.49; N, 7.89%.

(Z)-2-(1-(4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene)benzofuran-3(2*H*)-one, 4a-e

Compound 3 (1 mmol) was dissolved in 10 mL dry pyridine and mercuric acetate (1 mmol) was added to it. The reaction mixture was refluxed for 4-5 h. After completion of reaction (as indicated by TLC), the reaction mixture was cooled to RT and poured over crushed ice and acidified with conc. HCl. The solid product thus obtained was filtered and purified by recrystallization from acetic acid to afford compounds 4 (Scheme I).

(Z)-2-(1-(4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene)-5-bromobenzofuran-3(2*H*)-one, 4a: m.p.128°C. Yield 64%. IR: 2971 (C-H, aromatic), 1702 (C=O), 1603 (C=N), 1580(-C=C-), 1255 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.84 (t, 3H, CH₃), 1.30 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 2.26 (s, 3H, CH₃), 2.59 (t, 2H, CH₂), 4.81 (q, 2H, CH₂), 5.52 (s, 2H, CH₂), 6.62 (s, 1H, =CH), 7.01-8.19 (m, 5H, Ar-H); MS: *m/z* 582. Anal. Calcd: C, 51.34; H, 3.79; N, 7.19. Found: C, 51.39; H, 3.82; N, 7.23%.

(Z)-2-(1-(4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene)-5,7-dimethylbenzofuran-3(2*H*)-one, 4b: m.p.132°C. Yield 68%. IR: 2968 (C-H, aromatic), 1698 (C=O), 1602 (C=N), 1580(-C=C-), 1256 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.82 (t, 3H, CH₃), 1.29 (m, 2H, CH₂), 1.61 (m, 2H, CH₂), 2.22 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.64 (t, 2H, CH₂), 4.80 (q, 2H, CH₂), 5.50 (s, 2H, CH₂), 6.60 (s, 1H, =CH), 6.91-8.16 (m, 4H, Ar-H); MS: *m/z* 534. Anal. Calcd: C, 60.73; H, 5.10; N, 7.87. Found: C, 60.77; H, 5.15; N, 7.91%.

(Z)-2-((1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene)-5-chloro-4,6-dimethylbenzofuran-3(2*H*)-one, 4c: m.p.120°C. Yield 67%. IR: 2971 (C-H, aromatic), 1702 (C=O), 1602 (C=N), 1579 (-C=C-), 1256 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.84 (t, 3H, CH₃), 1.32 (m, 2H, CH₂), 1.62 (m, "2H, CH₂), 2.23 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 2.64 (t, 2H, CH₂), 4.82 (q, 2H, CH₂), 5.51 (s, 2H, CH₂), 6.62 (s, 1H, =CH), 6.89-8.11 (m, 3H, Ar-H);

MS: *m/z* 568. Anal. Calcd: C, 57.05; H, 4.61; N, 7.39. Found: C, 57.10; H, 4.64; N, 7.41%.

(Z)-2-((1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene)-5-fluorobenzofuran-3(2*H*)-one, 4d: m.p.140°C. Yield 76%. IR: 2970 (C-H, aromatic), 1703 (C=O), 1604 (C=N), 1581(-C=C-), 1257 (C-O-C), 1166 (Ar-F) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.85 (t, 3H, CH₃), 1.31 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 2.27 (s, 3H, CH₃), 2.59 (t, 2H, CH₂), 4.82 (q, 2H, CH₂), 5.53 (s, 2H, CH₂), 6.62 (s, 1H, =CH), 7.02-8.21 (m, 5H, Ar-H); MS: *m/z* 523. Anal. Calcd: C, 57.31; H, 4.23; N, 8.02. Found: C, 57.35; H, 4.29; N, 8.06%.

(Z)-2-((1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene)-6-ethylbenzofuran-3(2*H*)-one, 4e: m.p.110°C. Yield 60%. IR: 2969 (C-H, aromatic), 1702 (C=O), 1603 (C=N), 1580 (-C=C-), 1255 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.82 (t, 3H, CH₃), 1.28 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 1.64 (t, 3H, CH₃), 2.21 (q, 2H, CH₂), 2.31 (s, 3H, CH₃), 2.66 (t, 2H, CH₂), 4.80 (q, 2H, CH₂), 5.50 (s, 2H, CH₂), 6.60 (s, 1H, =CH), 6.87-8.12 (m, 5H, Ar-H); MS: *m/z* 532. Anal. Calcd: C, 60.73; H, 5.10; N, 7.87. Found: C, 60.77; H, 5.15; N, 7.90%.

(3-((0-2-(1-(4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)vinyl)benzofuran-2-yl)(4-bromophenyl)methanone, 5a-e

A solution of **3** (1 mmol) and K₂CO₃ (3 mmol) in dry acetone (25 mL) was refluxed for 30 min. After cooling to RT, a solution of 4-bromophenacyl bromide (1 mmol) in acetone was added dropwise and refluxed for 5-8 h. After completion of reaction (as indicated by TLC), the reaction mixture was poured into ice cold water and extracted with DCM. The combined organic extract was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product. The crude product was purified by recrystallization from ethanol to give compound **5** (Scheme I).

(3-((E)-2-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)vinyl)-5-bromobenzofuran-2-yl)(4-bromophenyl)methanone, 5a: m.p.160°C. Yield 68%. IR: 2969 (C-H, aromatic), 1644 (C=O), 1581 (C=N), 1560 (-C=C-, aliphatic), 1510 (C=C, aromatic), 1256 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.81 (t, 3H, CH₃), 1.33 (m, 2H, CH₂), 1.63 (m, 2H, CH₂), 2.31 (s, 3H, CH₃), 2.65

(t, 2H, CH₂), 4.77 (q, 2H, CH₂), 5.51 (s, 2H, CH₂), 7.02-8.20 (m, 11H, Ar-H and =CH); MS: *m/z* 764. Anal. Calcd: C, 51.75; H, 3.55; N, 5.49. Found: C, 51.79; H, 3.59; N, 5.52%.

(3-((E)-2-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)vinyl)-5,7-dimethylbenzofuran-2-yl)(4-bromophenyl)methanone, 5b: m.p.150°C. Yield 77%. IR: 2968 (C-H, aromatic), 1644 (C=O), 1582 (C=N), 1559 (-C=C-, aliphatic), 1509 (C=C, aromatic), 1256 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.81 (t, 3H, CH₃), 1.28 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 2.64 (t, 2H, CH₂), 4.76 (q, 2H, CH₂), 5.50 (s, 2H, CH₂), 6.98-8.18 (m, 10H, Ar-H and =CH); MS: *m/z* 714. Anal. Calcd: C, 58.79; H, 4.51; N, 5.88. Found: C, 58.82; H, 4.55; N, 5.92%.

(3-((E)-2-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)vinyl)-5-chloro-4,6-dimethylbenzofuran-2-yl)(4-bromophenyl)methanone, 5c: m.p.170°C. Yield 76%. IR: 2970 (C-H, aromatic), 1646 (C=O), 1584 (C=N), 1562 (-C=C-, aliphatic), 1512 (C=C, aromatic), 1258 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.83 (t, 3H, CH₃), 1.31 (m, 2H, CH₂), 1.61 (m, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 2.66 (t, 2H, CH₂), 4.79 (q, 2H, CH₂), 5.52 (s, 2H, CH₂), 7.01-8.21 (m, 9H, Ar-H and =CH); MS: *m/z* 746. Anal. Calcd: C, 56.09; H, 4.17; N, 5.61. Found: C, 56.13; H, 4.20; N, 5.64%.

(3-((E)-2-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)vinyl)-5-fluorobenzofuran-2-yl)(4-bromophenyl)methanone, 5d: m.p.200°C. Yield 82%. IR: 2970 (C-H, aromatic), 1645 (C=O), 1583 (C=N), 1560 (-C=C-, aliphatic), 1511 (C=C, aromatic), 1257 (C-O-C) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 0.80 (t, 3H, CH₃), 1.34 (m, 2H, CH₂), 1.62 (m, 2H, CH₂), 2.32 (s, 3H, CH₃), 2.66 (t, 2H, CH₂), 4.78 (q, 2H, CH₂), 5.52 (s, 2H, CH₂), 7.02-8.20 (m, 11H, Ar-H and =CH); MS: *m/z* 703. Anal. Calcd: C, 56.23; H, 3.86; N, 5.96. Found: C, 56.26; H, 3.89; N, 5.98%.

(3-((E)-2-(1-((4-(2,2,2-Trifluoroethoxy)-3-methylpyridin-2-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)vinyl)-6-ethylbenzofuran-2-yl)(4-bromophenyl)methanone, 5e: m.p.156°C. Yield 74%. IR: 2969 (C-H, aromatic), 1643 (C=O), 1583 (C=N), 1559 (-C=C-, aliphatic), 1510 (C=C, aromatic), 1255

(C-O-C) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 0.81 (t, 3H, CH_3), 1.27 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.62 (t, 3H, CH_3), 2.20 (q, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.64 (t, 2H, CH_2), 4.77 (q, 2H, CH_2), 5.49 (s, 2H, CH_2), 7.01-8.21 (m, 11H, Ar-H and =CH); MS: m/z 714. Anal. Calcd: C, 58.79; H, 4.51; N, 5.88. Found: C, 58.82; H, 4.54; N, 5.92%.

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