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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Fluorophenols bearing nitrogenated heterocycle moieties, a class of novel Keap1-Nrf2 protein-protein interaction inhibitors: synthesis, antioxidant stress screening and molecular docking

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Abstract

In the present study, we introduced the nitrogenated heterocycles and fluorine atoms into the 2,5′-dibromo-4,5,2′-trihydroxyl diphenylmethanone (**LM49**), a bromophenol analog previously reported for its strong antioxidant ability involving in the Keap1–Nrf2 pathway. Twenty-seven fluorophenols **6a–6g**, **8a–8k**, **10a–10g**, and **12a–12b** were prepared, evaluated for their antioxidant activity in EA.hy926 cells, and investigated their interacted approach and probable mode of action with key protein Keap1 by molecular docking. Fluorophenols **6f**, **8d**, **8f**, **8h**, and **8i** with EC_{50} values ranging from 0.82 to 6.71 μM were found to be more active compared with the standard control quercetin ($EC_{50} = 18$ μM). Among them, compound **8h** with an EC_{50} value of 0.82 μM showed the identical activity to lead compound **LM49** ($EC_{50} = 0.7$ μM). Moreover, the preferable water solubility and forming salt possibility of **8h** contribute to its druggability. Further molecular docking of the optimal compound **8h** with key protein Keap1 indicated that **8h** stably bonded to the receptor protein by the formation of hydrogen bonds, the conjugated six-membered ring was close to the key residue Arg-415 attached to the Nrf2 on Keap1-Kelch, affecting its properties, and the change leaded to the dissociation of Nrf2 from the junction with Keap1-Kelch into the nucleus exerting its antioxidant protective effect. This study introduced a class of fluorophenols containing nitrogenated heterocycles for the development of novel Keap1-Nrf2 protein–protein interaction (PPI) inhibitors. Keap1-Kelch is suggested the most potential target protein for such class of halophenols.

Keywords Fluorophenol · Synthesis · Nitrogenated heterocycle · Molecular docking · Antioxidant activity

Introduction

Many natural-derived halophenols possess unique skeletons and admirable pharmacological properties like carbonic anhydrase inhibitory, antioxidant, AChE inhibitory, anti-inflammatory, anti-cancer, aldose reductase inhibitory and other actions (Gribble 2000; Balaydın et al. 2012; Öztaşkın et al. 2015; Luana et al. 2010; Lee et al. 2013; Wang et al. 2005). Previously, we prepared a series of halophenols bearing benzophenone, benzylbenzene, and phenylfuran 2-yl ketone skeletons by modifying and optimizing the structure of natural halophenol (Zhao et al. 2010; Zheng et al. 2011). Many obtained bromophenols and chlorophenols have earlier been reported by our group with strong protective effects against oxidative stress injury in human umbilical vein endothelial cells, one of which, 2,5′-dibromo-4,5,2′-trihydroxyl diphenylmethanone (**LM49**) (Fig. 1) exhibited the optimal cytoprotective ability with an EC_{50} value of 0.4 μM (Zhao et al. 2010). However, primary pharmacokinetic evaluation on **LM49** presented the lower bioavailability in rats (unpublished).

Nitrogenated heterocycle, an important structural unit in many drug molecules, contributes to the antitumor, anti-diabetic, inhibitory nephritis, and antimicrobial activities; moreover, existence of nitrogenated heterocycles can

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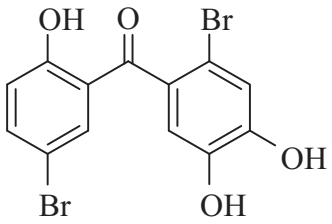


Fig. 1 The structure of lead compound **LM49**

improve the bioavailability (Shukla et al. 2017; Hu et al. 2009; Ali et al. 2018). In addition, the presence of fluorine atom also favors for the extension of biological half-life and increase of bioabsorption by impeding oxidative metabolism (Hoffmann and Rychlewsk 2002; Emilia et al. 2017; Schabe et al. 2002); therefore, the fluorinated drugs usually were applied in the treatment of central nervous system diseases and other cardiovascular diseases (Kirk 2006). Inspired by these facts, our initial efforts in this study focus on the design and synthesis of novel fluorophenols by replacing bromine atoms with fluorine atoms and introducing piperidine, piperazine, imidazole, and morpholine rings into the structure of the lead compound **LM49**, and try to find the optimal candidate compound with potent druggability.

Keap1–Nrf2 pathway is recognized as a key endogenous antioxidant system. Under basal conditions, the antioxidant transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is bound to the Kelch-like ECH-associated protein 1 (Keap1) and targets for proteasomal degradation in the cytoplasm. In response to cellular injury or chemical treatment, Nrf2 dissociates from Keap1, activates the transcription of protective genes, and defends against injury (Abed et al. 2015; Ishi et al. 2000). In that **LM49** displayed the strong cytoprotective activity against oxidative stress injury. How to influence the keap1–Nrf2 pathway exerting the protective action about **LM49**? As evidenced by our subsequent molecular mechanism study, which revealed that **LM49** protected vascular endothelial cells by activating Nrf2 transcription to up-regulate heme oxygenase-1 (HO-1) protein expression, reduce the ROS and TNF-α level. More importantly, a series of obtained bromophenols and chlorophenols with strong cytoprotective activity, all also can increase the expression of HO-1 protein in parallel with their protective ability (Feng et al. 2017). These findings confirmed the significance of keap1–Nrf2–HO-1 pathway involving in the protective action of halophenols. Now therefore, our another purpose in present paper is to explore fluorophenols' interacted approach and action mechanism with key protein Keap1 by molecular docking and to provide scientific bases for further theoretical research and the optimal design of halophenols.

Materials and methods

Chemistry

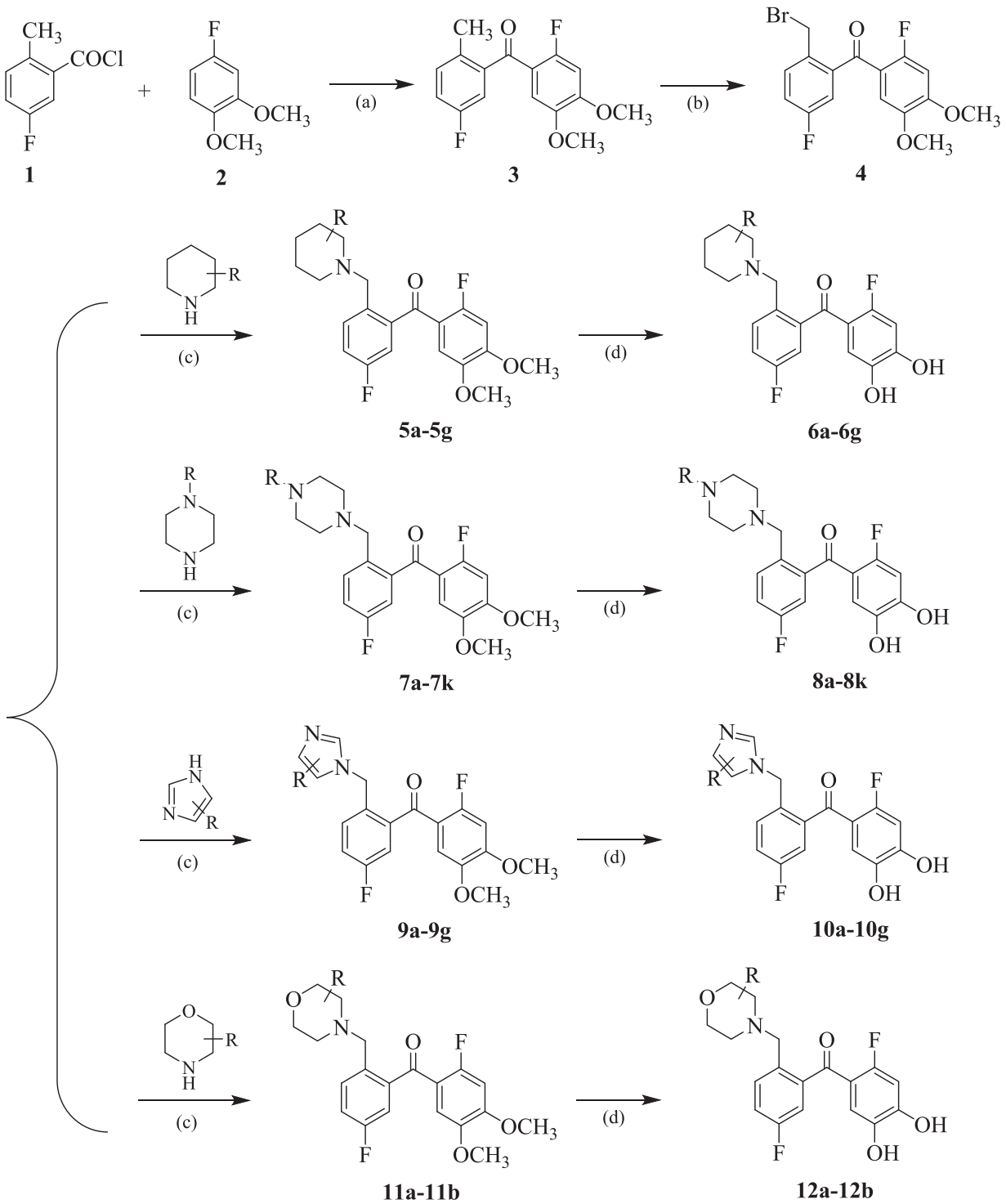
Main reagents including 5-fluoro-2-methylbenzoyl chloride and 4-fluoro-1,2-dimethoxybenzene, substituted piperdine, piperazine, imidazole, and morpholine were purchased from J & K Chemical Technology®. Other chemical reagents and solvents were commercially available unless otherwise indicated. Dichloromethane was distilled from calcium hydride.

Melting points were taken on a micromelting point apparatus, which were uncorrected. The ^{1}H, ^{13}C-NMR, and ^{19}F NMR spectra were obtained in a Bruker-AV 400 or 600 spectrometer in $CDCl_3$, DMSO-d_6, or MeOD with TMS as reference. Chemical shifts (δ values) and coupling constants (J values) were given in ppm and Hz, respectively. ESI mass spectra were recorded on a Waters ZQ-2000 spectrometer, and HRMS were recorded on a Bruker Daltonics Apex IV 70e FTICR-MS (Varian 7.0T). All synthesized compounds were confirmed by ESI-MS, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra. The representative target compounds **6f**, **8h**, and **8i** were further characterized with ^{19}F NMR spectrum.

The synthetic pathway leading to target fluorophenols (**6a–6g**, **8a–8k**, **10a–10g**, and **12a–12b**) is depicted in Scheme 1.

General procedures for the synthesis of (2-(bromomethyl)-5-fluorophenyl)(2-fluoro-4,5-dimethoxyphenyl)methanone (4)

Starting reagent 4-fluoro-1,2-dimethoxybenzene **2** (1.0 g, 6.41 mmol, 1.0 equiv) was added dropwise to anhydrous aluminum chloride (1.0 g, 7.58 mmol, 1.2 equiv, dissolved in 10 mL anhydrous dichloromethane) and stirred on ice bath. Substrate 5-fluoro-2-methylbenzoyl chloride **1** (0.78 mL, 5.76 mmol, 0.9 equiv) was added dropwise to the solution. The mixture was stirred at room temperature for 3 h and then quenched by addition of water, and extracted with anhydrous dichloromethane (30 mL × 3). The organic phases were combined and dried with anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography over silica gel with the system (9% ethyl acetate/petroleum ether) to afford the intermediate (5-fluoro-2-methylphenyl)(2-fluoro-4,5-dimethoxyphenyl)methanone **3** (1.5 g, 88.4%) as a white solid. m.p. = 98–100 °C. R_f = 0.27 (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 6.7 Hz, 1H, Ar-6-H), 7.20–7.24 (m, 1H, Ar-4-H), 7.01–7.09 (m, 2H, Ar-3, 3′-H), 6.58 (d, J = 11.6 Hz, 1H, Ar-6′-H), 3.94 (s, 3H, Ar-5′-OCH_3), 3.92 (s, 3H, Ar-4′-OCH_3), 2.33 (s, 3H, Ar-2-CH_3). ^{13}C{1H} NMR (100 MHz,



Scheme 1 Synthetic route of target compounds. Reagents and conditions: **a**) $AlCl_3$, anhydrous CH_2Cl_2, r.t., 4 h; **b** benzoperoxide, *N*-bromosuccinimide, CH_2Cl_2, sunlight, r.t.; **c** nitrogenated heterocycles, CH_2Cl_2, anhydrous K_2CO_3, reflux, 12 h; **d** BBr_3, CH_2Cl_2, −20 °C to r.t., 4 h

$CDCl_3$) δ 192.9, 160.6 (d, $J = 244$ Hz), 157.3 (d, $J = 251$ Hz), 154.6 (d, $J = 10.1$ Hz), 145.7, 141.8 (d, $J = 5.8$ Hz), 132.4 (d, $J = 7.2$ Hz), 131.7 (d, $J = 2.7$ Hz), 119.8 (d, $J = 20.8$ Hz), 117.2 (d, $J = 20.8$ Hz), 114.7 (dd, $J = 2.1$, 22.5 Hz), 111.6 (d, $J = 2.4$ Hz), 100.0 (d, $J = 28.7$ Hz), 56.5, 56.4, 19.1. MS (ESI+): *m/z* $[M + H]^+$ 293.0, 294.3. HRMS (ESI+): *m/z* calculated for $C_{16}H_{14}F_2O_3$ $[M + H]^+ =$ 293.0989, found 293.0993.

Intermediate (5-fluoro-2-methylphenyl)(2-fluoro-4,5-dimethoxyphenyl)methanone **3** (2.0 g, 6.8 mmol, 1.0

equiv), *N*-bromosuccinimide (NBS) (1.8 g, 10.1 mmol, 1.5 equiv) and benzoperoxide (BPO) (0.2 g, 0.83 mmol, 0.12 equiv) were added to anhydrous dichloromethane (10 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 5 h. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography over silica gel with the system (6% ethyl acetate/petroleum ether) to gain intermediate (2-(bromomethyl)-5-fluorophenyl)(2-fluoro-4,5-dimethoxyphenyl) methanone **4** (0.71 g, 63%) as a white solid. m.p. = 107–109 °C. $R_f = 0.20$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.50 (m, 1H, Ar-4-H), 7.31 (d, $J = 6.6$ Hz, 1H, Ar-6-H), 7.15 (td, $J = 8.3$, 2.6 Hz, 1H, Ar-3-H), 7.08 (d, $J = 8.6$ Hz, 1H, Ar-3′-H), 6.60 (d, $J = 11.6$ Hz, 1H, Ar-6′-H), 4.66 (s, 2H, Ar-2-CH_2-), 3.92 (s, 3H, Ar-5′-OCH_3), 3.95 (s, 3H, Ar-4′-OCH_3). ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 191.7, 161.9 (d, J = 248.5 Hz), 157.5 (d, $J = 251.6$ Hz), 155.1, 145.7, 142.0 (d, $J = 6.8$ Hz), 133.0 (d, $J = 0.8$ Hz), 132.4 (d, $J = 3.2$ Hz), 117.8 (d, $J = 21.3$ Hz), 116.6, 115.8 (dd, $J = 0.3$, 23.1 Hz), 111.8 (d, $J = 0.2$ Hz), 100.1 (d, $J = 28.5$ Hz), 56.6, 56.4, 29.5. MS (ESI+): *m/z* $[M + H]^+$ 373.0. HRMS (ESI+): *m/z* calculated for $C_{16}H_{13}BrF_2O_3$ $[M + H]^+ = 373.0016$, found 373.0020.

General procedure for synthesis of the intermediates 5a–5g, 7a–7k, 9a–9g, 11a–11b

(Bromomethyl)-5-fluorophenyl)(2-fluoro-4,5-dimethoxyphenyl)methanone **4** (0.25 g, 0.68 mmol, 1.0 equiv) and 4-hydroxyl piperidine (150 µL, 1.35 mmol, 2.0 equiv) were dissolved in anhydrous dichloromethane (10 mL) and dry K_2CO_3 (100 mg, 0.72 mmol, 1.1 equiv) was added, and then the mixture was stirred at room temperature for 12 h. The solvent was removed by rotary evaporation and the residue was purified by flash column chromatography over silica gel with the system (14% ethyl acetate/petroleum ether, adding 1.4% ammonia water) to obtain compound (5-fluoro-2-((4-hydroxypiperidin-1-yl)methyl)phenyl) 2-fluoro-4,5-dimethoxyphenyl) methanone **5a** (0.2 g, 77%) as a yellow solid.

The intermediates **5b–5g**, **7a–7k**, **9a–9g**, **11a–11b** were prepared in a similar manner.

General procedure for synthesis of the target compound 6a–6g, 8a–8k, 10a–10g, 12a–12b

BBr_3 (288 µL, 3.0 mmol, dissolved in 5 mL dichloromethane) was added to a −20 °C cooled solution of (5-fluoro-2-((4-hydroxypiperidin-1-yl)methyl)phenyl)2-fluoro-4,5-dimethoxyphenyl) methanone **5a** (117 mg, 0.3 mmol, 1.0 equiv) in dichloromethane (10 mL). The resulting mixture was allowed to warm to room temperature and was stirred for 4 h. And then, the reaction was quenched by addition of cooled water. The organic phase was separated, dried with anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was purified by flash column chromatography over silica gel with the system (11% methanol/dichloromethane) to gain (5-fluoro-2-((4-hydroxypiperidin-1-yl)methyl)phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone **6a** (0.2 g, 85.5%) as a yellow solid.

The target compounds **6b–6g**, **8a–8k, 10a–10g**, **12a–12b** were obtained in a similar manner.

Confirmation of the structures of intermediates

(5-Fluoro-2-((4-hydroxypiperidin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (5a) Yellow solid. final yield 43%. m.p. = 151–152 °C. $R_f = 0.40$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.31–7.35 (m, 1H, Ar-4-H), 7.19–7.25 (m, 2H, Ar-3, 6-H), 7.11 (dd, $J = 9.0$, 2.7 Hz, 1H, Ar-3′-H), 6.93 (d, J = 12.5 Hz, 1H, Ar-6′-H), 4.44 (s, 1H, piperidine-4″-OH), 3.85 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.31 (s, 2H, Ar-2-CH_2-), 3.24–3.29 (m, 1H, piperidine-4″-CH-), 2.27–2.30 (m, 2H, piperidine-2″, 6″-H), 1.84 (t, $J = 9.7$ Hz, 2H, piperidine-3″, 5″-H), 1.42 (m, 2H, piperidine-2″, 6″-H), 0.97–1.05 (m, 2H, piperidine-3″, 5″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.6, 161.7 (d, $J = 245.1$ Hz), 157.3 (d, $J = 250.5$ Hz), 154.1 (d, $J = 10.2$ Hz), 145.4, 143.1, 133.8, 130.5 (d, $J = 6.9$ Hz), 117.1 (d, $J = 10.9$ Hz), 115.8 (d, $J = 20.8$ Hz), 114.4 (d, $J = 23.1$ Hz), 111.5, 99.8 (d, J = 28.9 Hz), 67.9, 59.6, 58.5, 56.5, 50.4, 34.0. MS (ESI+): *m/z* $[M + H]^+$ 391.6, 393.2, 394.4. HRMS (ESI+): *m/z* calculated for $C_{21}H_{23}F_2NO_4$ $[M + H]^+ = 392.1595$, found 392.1597.

Fluoro -2-((4-(2-hydroxyethyl) piperidin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (5b) Yellow solid. final yield 40%. m.p. = 116-118 °C. $R_f = 0.41$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.31–7.35 (m, 1H, Ar-4-H), 7.19–7.26 (m, 2H, Ar-3-H, Ar-6-H), 7.12 (dd, $J = 9.0$, 2.7, 1H, Ar-3′-H), 6.93 (d, $J = 12.5$, 1H, Ar-6′-H), 4.26 (s, 1H, piperidine-4″-OH), 3.84 (s, 3H, Ar-5′-OCH_3), 3.77 (s, 3H, Ar-4′-OCH_3), 3.28-3.33 (m, 2H, Ar-2-CH_2-, piperidine-4″-C-CH_2-), 2.35 (d, J = 11.1 Hz, 2H, piperidine-2″, 6″-H), 1.76 (t, $J = 10.6$ Hz, 2H, piperidine-3″, 5″-H), 1.35 (d, $J = 11.9$ Hz, 2H, piperidine-2″, 6″-H), 1.12–1.16 (m, 3H, piperidine-3″, 4″, 5″-H), 0.62–0.70 (m, 2H, piperidine-4″-CH_2-). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.5, 161.6 (d, $J = 245$ Hz), 157.3 (d, $J = 250.3$ Hz), 154.0, 145.3, 143.1 (d, $J = 6.0$ Hz), 134.0, 130.4 (d, $J = 7.6$ Hz), 117.4, 115.7 (d, $J = 20.7$ Hz), 114.3 (d, $J = 24.7$ Hz), 111.5, 99.8 (d, $J = 28.9$ Hz), 60.5, 60.0,

58.5, 56.4, 53.1, 39.3, 31.8, 18.4. MS (ESI+): *m/z* $[M + H]^+$ 419.6, 421.2. HRMS (ESI+): *m/z* calculated for $C_{23}H_{27}F_2NO_4$ $[M + H]^+ = 420.1908$, found 420.1912.

Fluoro-2-((2,6-dimethylpiperidin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (5c) Yellow solid. final yield 43%. m.p. = 112–113 °C. $R_f = 0.37$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.86 (m, 1H, Ar-4-H), 7.30 (d, $J = 6.7$ Hz, 1H, Ar-6-H), 7.10 (td, $J = 8.5$, 2.7 Hz, 1H, Ar-3-H), 6.96–6.99 (m, 1H, Ar-6′-H), 6.57 (d, $J = 11.6$ Hz, 1H, Ar-3′-H), 3.94 (s, 3H, Ar-4′-OCH_3), 3.91 (s, 3H, Ar-5′-OCH_3), 3.73 (s, 2H, Ar-2-CH_2-), 2.47 (s, 2H, piperdine-4″-H), 1.42–1.49 (m, 2H, piperidine-2″, 6″-H), 1.24–1.30 (m, 4H, piperidine-3″, 5″-H), 0.91 (d, $J = 6.4$ Hz, 6H, piperidine-2″, 6″-CH_3). ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 192.5, 160.8 (d, $J =$ 243.9 Hz), 157.3 (d, $J = 250.9$ Hz), 154.5 (d, $J = 10.4$ Hz), 145.6, 140.0 (d, $J = 5.0$ Hz), 132.4 (d, $J = 7.1$ Hz), 131.0 (d, $J = 6.8$ Hz), 117.3, 116.7 (d, $J = 20.8$ Hz), 114.3 (d, $J =$ 1.9 Hz), 111.7 (d, $J = 2.3$ Hz), 100.0 (d, $J = 28.7$ Hz), 57.1, 56.5, 56.4, 52.6, 33.4, 21.8, 20.4. MS (ESI+): *m/z* $[M + H]^+$ 404.2, 405.1. HRMS (ESI+): *m/z* calculated for $C_{23}H_{27}F_2NO_3$ $[M + H]^+ = 404.1959$, found 404.1954.

Fluoro-2-((2-methylpiperidin-1-yl)methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (5d) Yellow solid. final yield 42%. m.p. = 93–94 °C. $R_f = 0.31$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.33–7.40 (m, 1H, Ar-4-H), 7.27 (d, $J = 7.1$ Hz, 1H, Ar-6-H), 7.21 (td, $J = 8.6$, 2.7 Hz, 1H, Ar-3-H), 7.09 (dd, $J = 9.0$, 2.7 Hz, 1H, Ar-3′-H), 6.93 (d, $J = 12.6$ Hz, 1H, Ar-3′-H), 3.77–3.96 (m, 7 H, Ar-2-CH_2-, Ar-4′, 5′-OCH_3), 3.12 (d, $J = 13.5$ Hz, 1H, Ar-2-CH_2-), 2.33–2.39 (m, 1H, piperidine-6″-H), 2.14–2.18 (m, 1H, piperidine-6″-H), 1.77-1.82 (m, 1H, piperidine-2″-H), 0.99-1.35 (m, 6 H, piperidine-3″, 4″, 5″-H), 0.76 (d, $J =$ 6.4 Hz, 3H, piperidine-2″-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.5, 161.4 (d, $J = 244.5$ Hz), 157.5 (d, $J =$ 251.2 Hz), 153.5, 145.4, 143.0 (d, $J = 5.4$ Hz), 130.6 (d, J = 6.4 Hz), 123.8 (d, $J = 8.4$ Hz), 122.1 (d, $J = 23.9$ Hz), 115.7 (d, $J = 20.7$ Hz), 114.1 (d, $J = 22.6$ Hz), 111.7 (d, J = 2.4 Hz), 99.9 (d, $J = 29.0$ Hz), 69.5, 58.5, 56.4, 56.2, 50.2, 33.3, 25.4, 22.3, 18.4. MS (ESI+): *m/z* $[M + H]^+$ 390.3, 391.3. HRMS (ESI+): *m/z* calculated for $C_{22}H_{25}F_2NO_3$ $[M + H]^+ = 390.1803$, found 390.1799.

Fluoro-2-((4-methylpiperidin-1-yl)methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (5e) Yellow solid. final yield 42%. m.p. = 86–88 °C. $R_f = 0.35$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.25 (d, $J =$ 7.1 Hz, 1H, Ar-6-H), 7.33 (m, 1H, Ar-4-H), 7.22 (m, 1H, Ar-3-H, Ar-6-H), 7.12 (dd, $J = 9.0$, 2.7 Hz, 1H, Ar-3'-H), 6.93 (d, $J = 12.5$ Hz, 1H, Ar-6′-H), 3.84 (s, 3H, Ar-4′-OCH_3), 3.77 (s, 3H, Ar-5′-OCH_3), 3.31 (s, 2H, Ar-2-CH_2-), 2.34 (d, $J = 11.3$ Hz, 2H, piperidine-2″, 6″-H), 1.77 (td, $J =$ 11.4, 9.8 Hz, 2H, piperidine-3″, 5″-H), 1.30 (d, $J = 11.2$ Hz, 2H, piperidine-2″, 6″-H), 1.13 (m, 1H, piperidine-4″-H), 0.70 (d, $J = 6.5$ Hz, 3 H, piperidine-4″-CH_3), 0.64 (td, $J =$ 11.4, 9.8 Hz, 2H, piperidine-3″, 5″-H). ^{13}C{1 H} NMR (100 MHz, $CDCl_3$) δ 191.4, 161.6 (d, $J = 244.6$ Hz), 157.2 (d, $J = 250.5$ Hz), 153.9 (d, $J = 10.1$ Hz), 145.4, 143.2 (d, J = 5.6 Hz), 134.2, 130.3 (d, $J = 7.5$ Hz), 117.4 (d, $J =$ 11.1 Hz), 115.7 (d, $J = 20.8$ Hz), 114.3 (d, $J = 22.9$ Hz), 111.6 (d, $J = 2.3$ Hz), 99.8 (d, $J = 28.9$ Hz), 60.1, 56.5, 56.4, 53.2, 33.8, 30.4, 21.9. MS (ESI+): *m/z* $[M + H]^+$ 390.1, 391.4. HRMS (ESI+): *m/z* calculated for $C_{22}H_{25}F_2NO_3$ $[M + H]^+ = 390.1803$, found 390.1807.

2((4-Benzylpiperidin-1-yl) methyl) -5-fluorophenyl) (2-fluoro-4,5-dimethoxybenzoyl) methanone (5f) Yellow solid. final yield 58%. m.p. = 84-85 °C. $R_f = 0.37$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.30–7.34 (m, 1H, Ar-4-H), 7.20–7.28 (m, 4H, Ar-6-H, Ar-3-H, Ar-3‴-H, Ar-5‴-H), 7.10–7.15 (m, 2H, Ar-3′-H, Ar-6′-H), 7.02–7.05 (m, 2H, Ar-2‴-H, Ar-6‴-H), 6.95 (d, $J =$ 12.6 Hz, 1H, Ar-4‴-H), 3.87 (s, 3H, Ar-5′-OCH_3), 3.80 (s, 3H, Ar-4′-OCH_3), 3.30 (s, 1H, Ar-2-CH_2-), 2.34 (d, $J =$ 11.4 Hz, 2H, piperidine-2″, 6″-H), 2.27 (d, $J = 6.8$ Hz, 2H, piperidine-4″-C-CH_2-), 1.73 (t, $J = 10.8$ Hz, 2H, piperazine-3″, 5″-H), 1.25–1.33 (m, 3H, piperidine-2″, 6″-H, piperidine-4″-CH-), 0.71 (q, $J = 11.4$ Hz, 2H, piperazine-3″, 5″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.4, 161.6 (d, J = 244.9 Hz), 157.2 (d, $J = 250.4$ Hz), 154.0 (d, $J = 9.9$ Hz), 145.4, 143.1 (d, $J = 5.7$ Hz), 140.7, 134.0, 130.4 (d, $J =$ 7.2 Hz), 129.0, 128.1, 125.7, 117.3 (d, $J = 11.0$ Hz), 115.8 (d, $J = 20.8$ Hz), 114.4 (d, $J = 23.0$ Hz), 111.6, 99.8 (d, $J =$ 28.9 Hz), 60.0, 56.5, 56.4, 53.1, 43.2, 37.6, 31.6. MS (ESI+): *m/z* $[M + H]^+$ 464.0, 465.5, 468.4. HRMS (ESI+): *m/z* calculated for $C_{28}H_{29}F_2NO_3$ $[M + H]^+ = 466.2116$, found 466.2120.

Ethyl 1-(4-fluoro-2-(2-fluoro-4,5-dimethoxybenzoyl) benzyl) piperidine-4-carboxylate (5g) Yellow solid. final yield 42%. m.p. = 194–96 °C. $R_f = 0.12$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, $J = 6.8$ Hz, 1H, Ar-6-H), 7.20–7.23 (m, 1H, Ar-4-H), 6.99–7.05 (m, 2H, Ar-3, 3′-H), 6.54 (d, $J = 11.8$ Hz, 1H, Ar-6′-H), 4.06 (q, $J = 7.1$ Hz, 2H, piperidine-4″-CH_2-), 3.93 (d, 3H, Ar-5′-OCH_3), 3.92 (d, 3H, Ar-4′-OCH_3), 3.40 (s, 2H, Ar-2-CH_2-), 2.52 (d, $J = 11.5$ Hz, 2H, piperdine-2″, 6″-H), 2.06–2.15 (m, 1H, piperidine-4″-H), 1.87(t, $J = 12$ Hz, 2H, piperdine-3″, 5″-H), 1.63 (d, $J = 10.8$ Hz, 2H, piperdine-2″, 6″-H), 1.30–1.40 (m, 2H, piperdine-3″, 5″-H), 1.19 (t, $J = 7.1$ Hz, 3H, piperidine-4″-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.5, 175.0, 161.7 (d, $J = 245.1$ Hz), 157.3 (d, $J =$ 250.1 Hz), 154.2, 145.5, 143.2 (d, $J = 5.2$ Hz), 133.5, 130.5 (d, $J = 7.6$ Hz), 117.2 (d, $J = 11.2$ Hz), 115.8 (d, $J =$

20.8 Hz), 114.4 (d, $J = 24.3$ Hz), 111.4 (d, $J = 1.9$ Hz), 99.8 (d, $J = 28.9$ Hz), 60.2, 59.9, 56.5, 56.4, 52.3, 40.9, 27.7, 14.2. MS (ESI+): *m/z* $[M + H]^+$ 447.5, 449.5, 450.4 ($[M + H]^+$). HRMS (ESI+): *m/z* calculated for $C_{24}H_{27}F_2NO_5$ $[M + H]^+ = 448.1857$, found 448.1852.

1-(4-(4-Fluoro-2-(2-fluoro-4,5-dimethoxybenzoyl) benzyl) piperazin-1-yl) ethanone (7a) Yellow solid. final yield 54%. m.p. = 151–152 °C. m.p. $R_f = 0.29$ (20% acetone/petroleum ether). 149–151 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.37–7.40 (m, 1H, Ar-4-H), 7.23–7.28 (m, 2H, Ar-3, 6-H), 7.14 (dd, $J = 8.9$, 2.5 Hz, 1H, Ar-3′-H), 6.94 (d, $J =$ 12.6 Hz, 1H, Ar-6′-H), 3.84 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.41 (s, 2H, Ar-2-CH_2-), 3.07 (s, 4H, piperazine-3″, 5″-H), 2.11 (t, $J = 4.4$ Hz, 2H, piperazine-2″, 6″-H), 2.05 (t, $J = 4.4$ Hz, 2H, piperazine-2″, 6″-H), 1.89 (s, 3H, piperazine-4″-$COCH_3$). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.6, 168.8, 161.8 (d, $J = 245.8$ Hz), 157.4 (d, $J = 250.4$ Hz), 154.5 (d, $J = 10.2$ Hz), 145.6, 143.2 (d, $J =$ 5.6 Hz), 132.8, 130.8 (d, $J = 7.5$ Hz), 117.0, 115.9 (d, $J =$ 20.9 Hz), 114.3 (dd, $J = 2.0$, 23.1 Hz), 111.3 (d, $J = 1.9$ Hz), 99.9 (d, $J = 28.8$ Hz), 59.4, 56.5, 52.3, 45.7, 41.0, 21.2. MS (ESI+): *m/z* $[M + H]^+$ 418.8, 420.3, 421.4. HRMS (ESI+): *m/z* calculated for $C_{22}H_{24}F_2N_2O_4$ $[M + H]^+ = 419.1704$, found 419.1707.

(5-Fluoro-2-((4-methylpiperazin-1-yl)methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7b) Yellow solid. final yield 58%. m.p. = 83–84 °C. $R_f = 0.42$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.34–7.37 (m, 1H, Ar-4-H), 7.20–7.27 (m, 2H, Ar-3, 6-H), 7.13 (dd, $J = 9.0$, 2.4 Hz, 1H, Ar-3′-H), 6.94 (d, $J =$ 12.5 Hz, 1H, Ar-6′-H), 3.85 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.35 (s, 2H, Ar-2-CH_2-), 2.09 (s, 8H, piperazine-2″-H, piperazine-3″, 5″, 6″-H), 1.96 (s, 3H, piperazine-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.6, 161.8 (d, $J = 245.7$ Hz), 157.3 (d, $J = 250.4$ Hz), 154.3 (d, $J = 10.0$ Hz), 145.5, 143.1 (d, $J = 5.7$ Hz), 132.9 (d, $J = 2.0$ Hz), 130.7 (d, $J = 7.5$ Hz), 117.1 (d, $J =$ 11.0 Hz), 116.0 (d, $J = 20.8$ Hz), 114.5 (d, $J = 22.8$ Hz), 111.5 (d, $J = 2.0$ Hz), 99.9 (d, $J = 28.8$ Hz), 59.2, 56.5, 56.5, 53.7, 51.0, 44.6. MS (ESI+): *m/z* $[M + H]^+$ 390.9, 392.5, 393.5. HRMS (ESI+): *m/z* calculated for $C_{21}H_{24}F_2N_2O_3$ $[M + H]^+ = 391.1755$, found 391.1759.

Fluoro-2-((4-(2-hydroxyethyl) piperazin-1-yl)methyl) phenyl) (2-fluoro-4,5- dimethoxyphenyl) methanone (7c) Yellow solid. final yield 58%. m.p. = 121–123 °C. $R_f =$ 0.36 (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.33–7.37 ((m, 1 H, Ar-4-H), 7.20–7.26 (m, 2H, Ar-3, 6-H), 7.13 (dd, $J = 9.0$, 2.4 Hz, 1 H, Ar-3′-H), 6.93 (d, $J = 12.5$ Hz, 1H, Ar-6′-H), 4.35 (s, 1H, piperazine-4″-OH), 3.84 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.36 (m, 6H, Ar-2-CH_2-, piperazine-3″, 5″-H), 2.20 (*t*, $J =$ 8 Hz, 2H, piperazine-4″-C-CH_2), 2.10 (s, 6H, piperazine-2″, 6″-H, piperazine-4″-CH_2). ^{13}C{1 H} NMR (100 MHz, $CDCl_3$) δ 191.5, 161.7 (d, $J = 245.3$ Hz), 157.3 (d, $J =$ 250.6 Hz), 154.1 (d, $J = 10.0$ Hz), 145.4, 143.1 (d, $J =$ 5.7 Hz), 133.2, 130.6 (d, $J = 7.6$ Hz), 117.2 (d, $J = 10.8$ Hz), 115.9 (d, $J = 20.8$ Hz), 114.4 (d, $J =$ 23.0 Hz), 111.5, 99.8 (d, $J = 28.9$ Hz), 59.5, 59.3, 57.6, 56.5, 56.4, 52.4, 52.3. MS (ESI+): *m/z* $[M + H]^+$ 420.7, 422.4, 423.4. HRMS (ESI+): *m/z* calculated for $C_{22}H_{26}F_2N_2O_4$ $[M + H]^+ = 421.1861$, found 421.1857.

Fluoro-2-((4-(2-methoxyphenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7d) Yellow solid. final yield 62%. m.p. = 114–116 °C. $R_f =$ 0.18 (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.39 (m, 1H, Ar-4-H), 7.24 (m, 2H, Ar-3, 6-H), 7.16 (dd, $J = 8.9$, 2.5 Hz, 1H, Ar-3′-H), 6.95 (d, $J =$ 12.5 Hz, 1H, Ar-6′-H), 6.88 (m, 2H, Ar-5‴, 6‴-H), 6.80 (td, $J = 11.5$, 4.7 Hz, 1H, Ar-4‴-H), 6.66 (d, $J = 7.4$ Hz, 1H, Ar-3‴-H), 3.82 (s, 3H, Ar-5′-OCH_3), 3.76 (s, 3H, Ar-4′-OCH_3), 3.70 (s, 3H, Ar-2‴-OCH_3), 3.42 (s, 2H, Ar-2-CH_2-), 2.59 (s, 4H, piperazine-3″, 5″-H), 2.23 (s, 4H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.6, 161.7 (d, $J = 245.2$ Hz), 157.3 (d, $J = 250.1$ Hz), 154.1, 152.2, 145.5 (d, $J = 1.6$ Hz), 143.3 (d, $J = 5.0$ Hz), 141.3, 133.4 (d, $J = 4.1$ Hz), 130.7 (d, $J = 7.1$ Hz), 122.8, 120.9, 118.0, 117.3, 115.8 (d, $J = 20.9$ Hz), 114.4 (d, $J =$ 22.8 Hz), 111.5 (d, $J = 2.2$ Hz), 111.1, 99.8 (d, $J =$ 28.9 Hz), 59.7, 56.5, 56.4, 55.3, 52.7, 50.2. MS (ESI+): *m/z* $[M + H]^+$ 483.0, 484.3. HRMS (ESI+): *m/z* calculated for $C_{27}H_{28}F_2N_2O_4$ $[M + H]^+ = 483.2017$, found 483.2021.

Fluoro-2-((4-(4-fluorophenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7e) Yellow solid. final yield 64%. m.p. = 168–170 °C. $R_f = 0.07$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.40–7.42 (m, 1H, Ar-4-H), 7.23–7.27 (m, 2H, Ar-3, 6-H), 7.16 (d, $J = 8.1$ Hz, 1H, Ar-3′-H), 6.98 (t, $J =$ 8.3 Hz, 2H, Ar-3‴, 5‴-H), 6.92 (d, $J = 12.2$ Hz, 1H, Ar-6′-H), 6.81 (s, 2H, Ar-2‴, 6‴-H), 3.80 (s, 3H, Ar-5′-OCH_3), 3.75 (s, 3H, Ar-4′-OCH_3), 3.42 (s, 2H, Ar-2-CH_2-), 2.73 (s, 4H, piperazine-3″, 5″-H), 2.25 (s, 4H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.7, 161.8 (d, $J =$ 245.6 Hz), 157.3 (d, $J = 250.4$ Hz), 157.1 (d, $J = 237.2$ Hz), 154.2 (d, $J = 10.2$ Hz), 147.9, 145.5, 143.2 (d, $J = 6.5$ Hz), 133.1, 130.8 (d, $J = 7.4$ Hz), 117.4 (d, $J = 7.5$ Hz), 117.2 (d, $J = 10.7$ Hz), 116.0 (d, $J = 21.0$ Hz), 115.4 (d, $J =$ 19.9 Hz), 114.5 (d, $J = 21.2$ Hz), 111.5, 99.8 (d, $J =$ 28.8 Hz), 59.6, 56.5, 56.4, 52.5, 49.7. MS (ESI+): *m/z* [M

$+ H]^+$ 471.4, 472.3, 473.4. HRMS (ESI+): *m/z* calculated for $C_{26}H_{25}F_3N_2O_3$ $[M + H]^+ = 471.1817$, found 471.1820.

Fluoro-2-((4-(2-fluorophenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7f) Yellow solid. final yield 64%. m.p. = 131–132 °C. $R_f = 0.13$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.39–7.42 (m, 1 H, Ar-4-H), 7.23–7.28 (m, 2H, Ar-3, 6-H), 7.17 (dd, $J = 9.0$, 2.7 Hz, 1H, Ar-3′-H), 7.02–7.09 (m, 2H, Ar-5‴, 6‴-H), 6.91–6.97 (m, 2H, Ar-6′-H, Ar-3‴-H), 6.83 (t, $J = 7.9$ Hz, 1H, Ar-4‴-H), 3.82 (s, 3H, Ar-5′-OCH_3), 3.77 (s, 3H, Ar-4′-OCH_3), 3.44 (s, 2H, Ar-2-CH_2-), 2.65 (s, 4H, piperazine-3″, 5″-H), 2.29 (s, 4H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.7, 161.8 (d, $J = 245.3$ Hz), 157.4 (d, $J = 250.4$ Hz), 155.7 (d, $J = 244.2$ Hz), 154.2 (d, $J = 9.8$ Hz), 145.5, 143.2 (d, $J = 6.2$ Hz), 140.1 (d, $J = 8.0$ Hz), 133.2, 130.8 (d, $J = 7.1$ Hz), 124.4 (d, $J = 3.0$ Hz), 122.3 (d, $J = 7.7$ Hz), 118.8 (d, $J = 2.3$ Hz), 117.2 (d, $J = 11.0$ Hz), 116.1(d, $J = 14.3$ Hz), 115.9 (d, $J = 14.3$ Hz), 114.5 (d, $J = 24.9$ Hz), 111.5, 99.8 (d, $J = 28.8$ Hz), 69.4, 59.7, 56.5, 52.5, 50.1. MS (ESI+): *m/z* $[M + H]^+$ 470.7, 472.5, 473.5. HRMS (ESI+): *m/z* calculated for $C_{26}H_{25}F_3N_2O_3$ $[M + H]^+ = 471.1817$, found 471.1812.

Fluoro-2-((4-(4-methoxyphenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7g) Yellow solid. final yield 62%. m.p. = 152–153 °C. $R_f = 0.20$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.39–7.41 (m, 1H, Ar-4-H), 7.23–7.28 (m, 2H, Ar-3, 6-H), 7.15 (dd, $J = 8.9$, 2.6 Hz, 1H, Ar-3′-H), 6.93 (d, $J = 12.5$ Hz, 1H, Ar-6′-H), 6.75 (s, 4H, Ar-2‴, 3‴, 5‴, 6‴-H), 3.81 (s, 3 H, Ar-5′-OCH_3), 3.75 (s, 3H, Ar-4′-OCH_3), 3.65 (s, 3H, Ar-4‴-OCH_3), 3.42 (s, 2H, Ar-2-CH_2-), 2.66 (s, 4H, piperazine-3″, 5″-H), 2.25 (d, $J = 4.2$ Hz, 4H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.6, 161.8 (d, $J = 245.3$ Hz), 157.3 (d, $J = 250.3$ Hz), 154.2 (d, $J = 10.5$ Hz), 153.7, 145.7,145.5, 143.3 (d, $J = 7.0$ Hz), 133.2, 130.7 (d, $J = 7.2$ Hz), 118.1, 117.2 (d, $J = 11.2$ Hz), 115.9 (d, $J = 20.8$ Hz), 114.6 (d, $J = 1.4$ Hz), 114.4, 111.5 (d, $J = 2.0$ Hz), 99.8 (d, $J = 28.8$ Hz), 59.6, 56.5, 56.4, 55.6, 52.6, 50.2. MS (ESI+): *m/z* $[M + H]^+$ 482.9, 483.5, 484.3. HRMS (ESI+): *m/z* calculated for $C_{27}H_{28}F_2N_2O_4$ $[M + H]^+ = 483.2017$, found 483.2013.

(2-((4-Benzhydrylpiperazin-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7h) Yellow solid. final yield 60%. m.p. = 196–198 °C. $R_f = 0.24$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.21–7.35 (m, 14H, Ar-H), 6.93 (d, $J = 12.5$ Hz, 1H, Ar-6′-H), 4.02 (s, 1H, piperazine-4″-CH-), 3.87 (s, 3H, Ar-5′-OCH_3), 3.36 (s, 2H, Ar-2-CH_2-), 3.77 (s, 3H, Ar-4′-OCH_3), 2.14 (s, 4H, piperazine-2″, 6″-H), 2.14 (s, 4H, piperazine-3″, 5″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.4, 161.7 (d, $J = 245.1$ Hz), 157.3 (d, $J = 250.5$ Hz), 154.0 (d, $J = 10.1$ Hz), 145.4, 142.7, 130.5 (d, $J = 5.6$ Hz), 128.4, 127.8, 126.8, 123.8 (d, $J = 8.4$ Hz), 122.1 (d, $J = 23.9$ Hz), 115.8 (d, $J = 20.7$ Hz), 114.4 (d, $J = 23.2$ Hz), 112.2 (d, $J = 23.6$ Hz), 111.5, 99.8 (d, $J = 28.8$ Hz), 76.2, 69.5, 59.6, 56.4, 52.7, 51.4. MS (ESI+): *m/z* $[M + H]^+$ 542.7, 544.7, 545.5. HRMS (ESI+): *m/z* calculated for $C_{33}H_{32}F_2N_2O_3$ $[M + H]^+ = 543.2381$, found 543.2376.

Fluoro-2-((4-(pyrimidin-2-yl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7i) Yellow solid. final yield 56%. m.p. = 115–116 °C. $R_f = 0.37$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 8.29 (d, $J = 4.7$ Hz, 2H, pyrimidine-3‴, 5‴-H), 7.8–7.41 (m, 1H, Ar-4-H), 7.23–7.29 (m, 2H, Ar-3, 6-H), 7.16 (dd, $J = 8.9$, 2.7 Hz, 1H, Ar-6′-H), 6.95 (d, $J = 12.6$ Hz, 1H, Ar-3′-H), 6.58 (t, $J = 4.7$ Hz, 1H, pyrimidine-4‴-H), 3.83 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.43 (s, 2H, Ar-2-CH_2-), 3.39 (s, 4H, piperazine-3″, 5″-H), 2.18 (t, $J = 4.8$ Hz, 4H, piperazine-2″,6″-H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.7, 160.1 (d, $J = 275.9$ Hz), 159.1 (d, $J = 286.3$ Hz), 156.2, 154.3 (d, $J = 10.6$ Hz), 145.6, 143.3 (d, $J = 6.7$ Hz), 133.2 (d, $J = 3.7$ Hz), 130.7, 117.1 (d, $J = 10.5$ Hz), 115.9 (d, $J = 20.0$ Hz), 114.3 (d, $J = 23.6$ Hz), 111.6 (d, $J = 3.0$ Hz), 111.3 (d, $J = 2.0$ Hz), 109.7, 99.9 (d, $J = 28.9$ Hz), 59.7, 56.5, 56.4, 52.4, 43.2. MS (ESI+): *m/z* $[M + H]^+$ 455.1, 456.3. HRMS (ESI+): *m/z* calculated for $C_{24}H_{24}F_2N_4O_3$ $[M + H]^+ = 455.1816$, found 455.1812.

Fluoro-2-((4-ethylpiperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7j) Yellow solid. final yield 56%. m.p. = 96–98 °C. $R_f = 0.39$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.33–7.39 (m, 1H, Ar-4-H), 7.24–7.26 (m, 2H, Ar-3, 6-H), 7.13 (dd, $J = 9.0$, 2.7 Hz, 1H Ar-6′-H), 6.93 (d, $J = 12.5$ Hz, 1H, Ar-3′-H), 3.84 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.34 (s, 2H, Ar-2-CH_2-), 2.10 (m, 10H, piperazine-4″-CH_2-, piperazine-2″, 3″, 5″, 6″-H), 0.85 (t, $J = 7.2$ Hz, 3H, piperazine-4″-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.5, 161.7 (d, $J = 245.2$ Hz), 157.3 (d, $J = 250.6$ Hz), 154.1 (d, $J = 9.9$ Hz), 145.4, 143.2 (d, $J = 6.8$ Hz), 133.4, 130.5 (d, $J = 7.6$ Hz), 117.3 (d, $J = 10.8$ Hz), 115.8 (d, $J = 20.8$ Hz), 114.3 (d, $J = 22.9$ Hz), 111.5 (d, $J = 2.1$ Hz), 99.8 (d, $J = 28.9$ Hz), 59.6, 56,5, 56.4, 52.3, 52.2, 52.1, 11.8. MS (ESI+): *m/z* $[M + H]^+$ 405.1, 406.3. HRMS (ESI+): *m/z* calculated for $C_{22}H_{26}F_2N_2O_3$ $[M + H]^+ = 405.1911$, found 405.1914.

Fluoro-2-((4-isopropylpiperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (7k) Yellow solid. final yield 64%. m.p. = 143–144 °C. $R_f = 0.13$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ

7.32–7.35 (m, 1H, Ar-4-H), 7.28 (d, $J = 7.0$ Hz, 1H, Ar-6-H), 7.21 (td, $J = 8.6$, 2.7 Hz, 1H, Ar-3-H), 7.13 (dd, $J = 9.0$, 2.6 Hz, 1H, Ar-3′-H), 6.93 (d, $J = 12.6$ Hz, 1H, Ar-6′-H), 3.83 (s, 3H, Ar-4′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 3.33 (s, 2H, Ar-2-CH_2-), 2.41–2.47 (m, 1H, piperazine-4″-CH-), 2.10 (s, 4H, piperazine-2″, 6″-H), 2.01 (s, 4H, piperazine-3″, 5″-H), 0.76 (d, $J = 6.5$ Hz, 6H, piperazine-4″-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.4, 161.7 (d, $J =$ 245.1 Hz), 157.4 (d, $J = 250.7$ Hz), 154.1 (d, $J = 9.9$ Hz), 145.4, 143.3 (d, $J = 5.4$ Hz), 133.5, 130.4 (d, $J = 7.6$ Hz), 117.3 (d, $J = 10.9$ Hz), 115.7 (d, $J = 20.8$ Hz), 114.2 (d, J = 23.0 Hz), 111.5, 99.8 (d, $J = 28.9$ Hz), 59.6, 56.5, 56.4, 54.2, 52.7, 48.0, 18.4. MS (ESI+): m/z $[M + H]^+$ 418.7, 420.0, 421.4. HRMS (ESI+): m/z calculated for $C_{23}H_{28}F_2N_2O_3$ $[M + H]^+ = 419.2068$, found 419.2072.

(5-Fluoro-2-((2-phenyl-1H-imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (9a) Yellow solid. final yield 46%. m.p. = 74–75 °C. $R_f = 0.06$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.49 (m, 2H, Ar-2″, 6″-H), 7.34–7.36 (m, 3H, Ar-3″, 4″, 5″-H), 7.20 (d, $J = 6.6$ Hz, 1H, imidazole-5″-H), 7.11–7.17 (m, 3H, Ar-3, 4, 6-H), 6.94–6.99 (m, 2H, Ar-3′, 6′-H), 6.58 (d, $J = 11.6$ Hz, 1H, imidazole-4″-H), 5.39 (s, 2H, Ar-2-CH_2-), 3.95 (s, 3H, Ar-5′-OCH_3), 3.90 (s, 3H, Ar-4′-OCH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.7, 161.6 (d, $J = 247.4$ Hz), 157.2 (d, $J = 249.6$ Hz), 155.1 (d, J = 10.2 Hz), 151.8, 149.5, 148.2, 145.9, 140.2 (d, $J =$ 4.7 Hz), 132.0 (d, $J = 2.9$ Hz), 130.3, 129.5 (d, $J = 7.8$ Hz), 128.9 (d, $J = 20.2$ Hz), 128.6, 121.6, 118.4 (d, $J = 21.2$ Hz), 116.6, 116.2 (dd, $J = 3.3$, 22.7 Hz), 111.5 (d, $J = 2.3$ Hz), 100.0 (d, $J = 28.6$ Hz), 56.5, 56.4, 47.8. MS (ESI+): m/z $[M + H]^+$ 434.9, 436.2, 43.2. HRMS (ESI+): m/z calculated for $C_{25}H_{20}F_2N_2O_3$ $[M + H]^+ = 435.1442$, found 435.1438.

(5-Fluoro-2-((2-isopropyl-1H-imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (9b) Yellow solid. final yield 40%. m.p. = 102–103 °C. $R_f = 0.07$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.39 (td, $J = 8.5$, 2.8 Hz, 1H, Ar-3-H), 7.30 (d, $J = 8.9$ Hz, 1H, Ar-6-H), 7.15 (d, $J = 6.9$ Hz, 1H, Ar-3′-H), 7.00 (d, J = 12.5 Hz, 1H, Ar-6′-H), 6.93-6.97 (m, 1H, Ar-4-H), 6.92 (d, $J = 1.2$ Hz, 1H,imidazole-5″-H), 6.74 (d, $J = 1.1$ Hz, 1H, imidazole-4″-H), 5.22 (s, 2H, Ar-2-CH_2-), 3.87 (s, 3 H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 2.83 (q, $J = 13.6$, 6.8 Hz, 1H, imidazole-2″-CH-), 1.04 (d, $J = 6.8$ Hz, 6H, imidazole-2″-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 192.0, 161.6 (d, $J = 247.6$ Hz), 157.2 (d, $J = 250.4$ Hz), 155.1 (d, $J = 10.4$ Hz), 153.6 (d, $J = 26.6$ Hz), 145.9, 140.4, 131.8 (d, $J = 2.4$ Hz), 129.5 (d, $J = 7.6$ Hz), 127.2, 119.7, 118.3 (d, $J = 21.2$ Hz), 116.1 (dd, $J = 3.4$, 23.0 Hz), 111.5, 100.0 (d, $J = 28.5$ Hz), 56.6, 56.5, 46.3, 28.3, 25.9, 21.8. MS (ESI+): m/z $[M + H]^+$ 400.6, 402.2, 403.4. HRMS (ESI+): m/z calculated for $C_{22}H_{22}F_2N_2O_3$ $[M + H]^+ =$ 401.1598, found 401.1594.

(5-Fluoro-2-((2-ethyl-1H-imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (9c) Yellow solid. final yield 42%. m.p. = 121–123 °C. $R_f = 0.07$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.38 (td, $J = 8.5$, 2.8 Hz, 1H, Ar-3-H), 7.30 (d, $J = 8.9$ Hz, 1H, Ar-6-H), 7.15 (d, $J = 6.9$ Hz, 1 H, Ar-3′-H), 6.94–7.01 (m, 3H, Ar-6′, 4-H, imidazole-5″-H), 6.73 (d, $J = 1.1$ Hz, 1H, imidazole-4″-H), 5.20 (s, 2H, Ar-2-CH_2-), 3.87 (s, 3H, Ar-5′-OCH_3), 3.78 (s, 3H, Ar-4′-OCH_3), 2.43 (q, $J =$ 7.5 Hz, 2H, imidazole-2″-CH_2), 1.05 (t, $J = 7.5$ Hz, 3H, imidazole-2″-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 192.0, 161.6 (d, $J = 247.4$ Hz), 157.2 (d, $J = 250$ Hz), 155.1 (d, $J = 10.1$ Hz), 149.7, 145.9, 140.4 (d, $J = 5.8$ Hz), 131.6 (d, $J = 3.0$ Hz), 129.6 (d, $J = 7.8$ Hz), 127.3, 121.2, 120.0, 118.3 (d, $J = 21.1$ Hz), 116.1 (dd, $J = 3.3$, 23.0 Hz), 111.5 (d, $J = 2.0$ Hz), 100.0 (d, $J = 28.5$ Hz), 56.6, 56.5, 46.5, 20.0, 11.9. MS (ESI+): m/z $[M + H]^+$ 387.2, 388.2, 389.4 ($[M + H]^+$). HRMS (ESI+): m/z calculated for $C_{21}H_{20}F_2N_2O_3$ $[M + H]^+ = 387.1442$, found 387.1445.

(2-((1H-Imidazol-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (9d) Yellow solid. final yield 42%. m.p. = 174–175 °C. $R_f = 0.27$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 7.49 (s, 1H, imidazole-2″-H), 7.21 (d, $J = 6.6$ Hz, 1H, Ar-3′-H), 7.12–7.17 (m, 3H, Ar-3, 4, 6-H), 7.01–7.02 (m,1H, imidazole-5″-H), 6.88–6.90 (m,1H, imidazole-4″-H), 6.56 (d, $J = 11.7$, 1H, Ar-6′-H), 5.28 (s, 2H, Ar-2-CH_2-), 3.94 (s, 3H, Ar-5′-OCH_3), 3.91 (s, 3H, Ar-4′-OCH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 191.8, 161.9 (d, $J = 248.3$ Hz), 157.3 (d, $J = 250.3$ Hz), 155.2 (d, $J =$ 10.3 Hz), 145.9, 141.1 (d, $J = 6.2$ Hz), 137.6, 135.2, 131.0 (d, $J = 7.9$ Hz), 129.3, 121.9, 119.6, 118.3 (d, $J = 21.2$ Hz), 116.2 (dd, $J = 3.3$, 25.4 Hz), 111.5 (d, $J = 1.8$ Hz), 100.0 (d, $J =$ 28.5 Hz), 56.6, 56.4, 47.6. MS (ESI+): m/z $[M + H]^+$ 358.9, 360.2. HRMS (ESI+): m/z calculated for $C_{19}H_{16}F_2N_2O_3$ $[M + H]^+ = 359.1129$, found 359.1134.

(2-((5,6-Dimethyl-1H-benzo[d]imidazol-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5- dimethoxyphenyl) methanone (9e) Yellow solid. final yield 42%. m.p. = 132–133 °C. R_f = 0.07 (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H, imidazole-2″-H), 7.51 (s, 1H, Ar-4‴-H), 7.02–7.15 (m, 4H, Ar-3, 4, 6, 3′-H), 6.95 (s, 1H, Ar-7‴-H), 6.55 (d, $J = 11.7$ Hz, 1H, Ar-6′-H), 3.93 (s, 3H, Ar-5′-OCH_3), 5.46 (s, 2H, Ar-2-CH_2-), 3.84 (s, 3H, Ar-4′-OCH_3), 2.34 (s, 3H, Ar-6‴-CH_3), 2.30 (s, 3H, Ar-5‴-CH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 190.4, 165.5 (d, $J = 256.8$ Hz), 157.9 (d, $J = 251.0$ Hz), 155.4 (d, $J = 10.2$ Hz), 152.3, 148.3, 146.4 (d, $J = 7.6$ Hz), 146.0, 143.1, 142.3, 141.3, 134.6, 133.2 (d, $J = 9.5$ Hz), 130.8, 117.7, 117.2 (d, $J =$

21.7 Hz), 116.3 (d, $J = 11.2$ Hz), 115.0 (dd, $J = 2.0$, 25.8 Hz), 110.9, 99.9 (d, $J = 28.7$ Hz), 56.6, 56.4, 47.7, 17.9, 17.6. MS (ESI +): *m/z* $[M + H]^+$ 436.6, 438.4, 439.3. HRMS (ESI +): *m/z* calculated for $C_{25}H_{22}F_2N_2O_3$ $[M + H]^+ = 437.1598$, found 437.1600.

(2-((1H-Benzo[d]imidazol-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (9f) Yellow solid. final yield 40%. m.p. = 142–143 °C. $R_f = 0.08$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, DMSO) δ 8.12 (s, 1H, (s, 1H, imidazole-2″-H), 7.56–7.60 (m, 1H, Ar-4-H), 7.36 (t, $J = 8.2$ Hz, 1H, Ar-3-H), 7.25–7.38 (m, 3H, Ar-6, 4‴, 7‴-H), 7.15 (m, 2H, Ar-5‴, 6‴-H), 7.00 (d, $J =$ 6.7 Hz, 1 H, Ar-3′-H), 6.92 (d, $J = 12.4$ Hz, 1H, Ar-6′-H), 5.55 (s, 2H, Ar-2-CH_2-), 3.85 (s, 3 H, Ar-5′-OCH_3), 3.69 (s, 3 H, Ar-4′-OCH_3). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 192.0, 161.8 (d, $J = 248.1$ Hz), 157.3 (d, $J = 250.9$ Hz), 155.1 (d, $J = 10.7$ Hz), 145.7, 143.6, 140.5, 137.6, 133.8, 130.5 (d, $J = 7.8$ Hz), 123.2, 122.9, 122.4, 120.2, 118.1 (d, $J = 21.3$ Hz), 116.2 (dd, $J = 3.1$, 26.5 Hz), 115.6, 111.3 (d, $J = 2.1$ Hz), 110.0, 100.0 (d, $J = 28.6$ Hz), 56.6, 56.4, 45.9. MS (ESI+): *m/z* $[M + H]^+$ 408.8, 410.2, 411.3. HRMS (ESI+): *m/z* calculated for $C_{23}H_{18}F_2N_2O_3$ $[M + H]^+ =$ 409.1285, found 409.1290.

(5-Fluoro-2-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (9g) White solid. final yield 46%. m.p. = 191–193 °C. $R_f = 0.07$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, $J = 7.6$, 1H, Ar-6-H), 7.14–7.24 (m, 5H, Ar-2‴, 3‴, 4‴, 5‴, 3′-H), 7.02 (dt, $J = 12$, 4 Hz, 1H, Ar-3-H), 6.71 (m, 1H, Ar-4-H), 6.59 (d, $J = 11.7$ Hz, 1H, Ar-6′-H), 5.48 (s, 2H, Ar-2-CH_2-), 3.96 (s, 3H, Ar-5′-OCH_3), 3.89 (s, 3H, Ar-4′-OCH_3), 2.51 (s, 3H, imidazole-2″-CH_3). ^{13}C {1 H} NMR (100 MHz, $CDCl_3$) δ 192.1, 161.5 (d, $J =$ 247.4 Hz), 157.3 (d, $J = 250.3$ Hz), 155.1 (d, $J = 10.3$ Hz), 152.1, 145.9, 142.7, 140.5, 135.3, 130.9 (d, $J = 3.1$ Hz), 128.8 (d, $J = 7.8$ Hz), 122.2 (d, $J = 24.0$ Hz), 119.1, 118.2 (d, $J = 21.1$ Hz), 116.1 (dd, $J = 3.2$, 23.1 Hz), 111.4 (d, $J =$ 2.0 Hz), 109.4, 100.0 (d, $J = 28.5$ Hz), 56.6, 56.4, 44.6, 13.8. MS (ESI+): *m/z* $[M + H]^+$ 422.6, 424.3, 425.3. HRMS (ESI+): *m/z* calculated for $C_{24}H_{20}F_2N_2O_3$ $[M + H]^+$ = 423.1442, found 423.1446.

(5-Fluoro-2-(morpholinomethyl) phenyl(2-fluoro-4,5-dimethoxyphenyl) methanone (11a) White solid. final yield 67%. m.p. = 141–142 °C. $R_f = 0.09$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 6.8 Hz, 1 H, Ar-6-H), 7.21–7.24 (m, 1H, Ar-4-H), 7.02–7.04 (m, 2H, Ar-3, 3′-H), 6.54 (d, $J = 11.8$ Hz, 1 H, Ar-6′-H), 3.95 (d, 3 H, Ar-5′-OCH_3), 3.91 (s, 3 H, Ar-4′-OCH_3), 3.46 (s, 2H, Ar-2-CH_2-), 3.36 (s, 4 H, morpholine-3″, 5″-H), 2.24 (t, $J = 4.5$ Hz, 4 H, morpholine-2″, 6″-H). ^{13}C{1 H} NMR (100 MHz, $CDCl_3$) δ 191.6, 161.8 (d, $J = 245.6$ Hz), 157.4 (d, $J = 250.5$ Hz), 154.3 (d, $J = 10.0$ Hz), 145.6, 143.3 (d, $J = 5.6$ Hz), 132.9, 130.7 (d, $J = 7.6$ Hz), 117.1, 115.9 (d, $J = 20.8$ Hz), 114.3 (d, $J = 2.3$, 23.2 Hz), 111.4 (d, $J = 2.3$ Hz), 99.8 (d, $J = 28.9$ Hz), 66.6, 60.0, 56.5, 56.4, 52.9. MS (ESI+): *m/z* $[M + H]^+$ 378.1, 379.0, 380.2. HRMS (ESI+): *m/z* calculated for $C_{19}H_{19}F_2NO_4$ $[M + H]^+ = 378.1517$, found 378.1516.

2-((2,6-Dimethylmorpholino) methyl)-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dimethoxyphenyl) methanone (11b) White solid. final yield 51%. m.p. = 108–109 °C. $R_f = 0.26$ (20% acetone/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, $J = 6.8$ Hz, 1 H, Ar-6-H), 7.21–7.25 (m, 1H, Ar-4-H), 7.00–7.07 (m, 2H, Ar-3, 3′-H), 6.53 (d, $J =$ 11.8 Hz, 1H, Ar-6′-H), 3.95 (s, 3 H, Ar-5′-OCH_3), 3.91 (s, 3H, Ar-4′-OCH_3), 3.42 (s, 2H, Ar-2-CH_2-), 3.16–3.24 (m, 2H, morpholine-3″, 5″-H), 2.83 (d, $J = 10.4$, 2H, morpholine-2″, 6″-H), 2.37 (d, $J = 10.5$ Hz, 2H, morpholine-2″, 6″-H), 1.01 (d, $J = 6.3$ Hz, 6 H, morpholine-3″, 5″-CH_3). ^{13}C {1 H} NMR (100 MHz, $CDCl_3$) δ 191.5, 161.7 (d, $J =$ 245.3 Hz), 157.3 (d, $J = 250.2$ Hz), 154.2 (d, $J = 10.0$ Hz), 145.5, 143.2 (d, $J = 6.0$ Hz), 133.1, 130.7 (d, $J = 7.6$ Hz), 117.0 (d, $J = 11.2$ Hz), 115.8 (d, $J = 20.9$ Hz), 114.4, 111.3 (d, $J = 1.6$ Hz), 99.7 (d, $J = 29.0$ Hz), 71.7, 71.2, 59.5, 58.6, 57.9, 56.5, 56.4, 19.1, 18.9. MS (ESI+): *m/z* $[M + H]^+$ 406.2, 407.1, 408.2. HRMS (ESI+): *m/z* calculated for $C_{19}H_{19}F_2NO_4$ $[M + H]^+ = 406.1830$, found 406.1831.

Confirmation of the structures of target compounds

(5-Fluoro-2-((4-hydroxypiperidin-1-yl)methyl)phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (6a) Yellow solid. final yield 36%. m.p. = 126–128 °C. $R_f = 0.58$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, DMSO) δ 8.97 (s, 1H, Ar-5′-OH), 7.42 (m, 2H, Ar-3, 4-H), 7.07 (d, J = 7.0 Hz, 1H, Ar-6-H), 6.59–6.66 (m, 1 H, Ar-3′, 6′-H), 3.91 (s, 2H, Ar-2-CH_2-), 3.65 (s, 1H, Ar-4′-OH), 3.01–3.03 (m, 1H, piperidine-4″-CH-), 1.88–1.94 (m, 2H, piperidine-2″, 6″-H), 1.72–1.74 (m, 4H, piperidine-2″, 6″, 3″, 5″-H), 1.60–1.65 (m, 2H, piperidine-3″, 5″-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 194.1, 162.5 (d, $J = 247.7$ Hz), 156.8 (d, $J = 249.6$ Hz), 153.7, 143.0, 142.1, 133.6, 128.6, 118.0, 117.4 (d, $J = 22.4$ Hz), 115.8, 115.3, 102.9 (d, $J = 26.3$ Hz), 65.3, 58.3, 49.4, 29.3. MS (ESI+): *m/z* $[M + H]^+$ 364.1, 365.2. HRMS (ESI+): *m/z* calculated for $C_{19}H_{19}F_2NO_4$ $[M + H]^+ = 364.1282$, found 364.1286.

(5-Fluoro-2-((4-(2-hydroxyethyl)piperidin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (6b) Yellow solid. final yield 36%. m.p. = 89–90 °C. $R_f = 0.95$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ

7.67 (s, 1H, Ar-4-H), 7.40 (s, 1H, Ar-3-H), 7.34 (d, J = 7.8 Hz, 1H, Ar-6-H), 7.15 (s, 1H, Ar-3′-H), 6.58 (d, J = 12.5, 1H, Ar-6′-H), 4.16 (s, 2H, Ar-2-CH_2-), 3.50 (t, J = 6.0 Hz, 2H, piperidine-4″-C-CH_2-), 3.39 (s, 2H, piperidine-2″, 6″-H), 2.92 (s, 2H, piperidine-3″, 5″-H), 1.83–1.92 (m, 5H, piperidine-2″, 3″, 4″, 5″, 6″-H), 1.43 (s, 2H, piperidine-4″-CH_2-). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.9, 162.8 (d, J = 248.9 Hz), 156.6 (d, J = 246.9 Hz), 153.5 (d, J = 9.8 Hz), 142.7 (d, J = 6.3 Hz), 142.2, 134.8 (d, J = 6.0 Hz), 126.4 (d, J = 8.9 Hz), 118.2 (d, J = 21.9 Hz), 117.5 (d, J = 21.6 Hz), 116.0, 115.6 (d, J = 11.1 Hz), 102.9 (d, J = 26.3 Hz), 58.1, 54.8, 52.2, 38.0, 32.0, 29.7. MS (ESI+): m/z $[M + H]^+$ 391.2, 392.3. HRMS (ESI+): m/z calculated for $C_{21}H_{23}F_2NO_4$ $[M + H]^+$ = 392.1595, found 392.1599.

(5-Fluoro-2-((2,6-dimethylpiperidin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (6c) Yellow solid. final yield 43%. m.p. = 96–98 °C. R_f = 0.84 (11% methanol/dichloromethane). ^{1}H NMR (400 MHz, DMSO) δ 7.01–7.76 (m, 5H, Ar-H), 4.35–4.57 (m, piperidine-3″, 4″, 5″-H), 3.54 (s, 2H, Ar-2-CH_2-), 2.15 (d, 1H, J = 13.4 Hz, piperidine-6″-H), 1.86-1.98 (m, 3H, piperidine-3″, 4″, 5″-H), 1.84 (d, 1H, J = 13.4 Hz piperidine-2″-H), 1.28 (d, 3H, J = 6.2 Hz piperidine-6″-CH_3), 1.15 (d, 3H, J = 6.2 Hz piperidine-2″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 193.0, 162.3 (d, J = 248.9 Hz), 156.7 (d, J = 247.2 Hz), 153.7 (d, J = 16.8 Hz), 142.3, 141.9, 133.7 (d, J = 7.4 Hz), 132.2 (d, J = 7.4 Hz), 118.2 (d, J = 21.5 Hz), 117.3 (d, J = 23.1 Hz), 115.9, 113.8 (d, J = 22.5 Hz), 102.9 (d, J = 26.3 Hz), 61.0, 54.7, 29.3, 28.1, 17.8. MS (ESI+): m/z $[M + H]^+$ 376.2, 377.3. HRMS (ESI+): m/z calculated for $C_{21}H_{23}F_2NO_3$ $[M + H]^+$ = 376.1646, found 376.1650.

(5-Fluoro-2-((2-methylpiperidin-1-yl)methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (6d) Yellow solid. final yield 36%. m.p. = 116–118 °C. R_f = 0.79 (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.73–7.75 (m, 1 H, Ar-4-H), 7.46 (td, J = 8.2, 2.4 Hz, 1H, Ar-3-H), 7.41 (d, J = 8.6 Hz, 1H, Ar-6-H), 7.16 (d, J = 6.9 Hz, 1H, Ar-3′-H), 6.59 (d, J = 16.5 Hz, 1 H, Ar-6′-H), 4.64(s, 1 H, Ar-2-CH_2-), 4.26 (s, 1H, piperidine-6″-H), 3.60 (s, 1H, Ar-2-CH_2-), 3.06 (s, 1H, piperidine-6″-H), 1.96-2.04 (m, 2H, piperidine-4″-H), 1.83 (s, 4H, piperidine-3″, 5″-H), 1.63 (d, J = 5.7 Hz, 1H, piperidine-2″-H), 1.53 (d, J = 6.3 Hz, 3 H, piperidine-2″-CH_3). ^{13}C{1 H} NMR (150 MHz, MeOD) δ 193.2, 162.8 (d, J = 249.5 Hz), 156.7 (d, J = 247.2 Hz), 153.5 (d, J = 12.0 Hz), 142.7 (d, J = 6.5 Hz), 142.3, 135.6 (d, J = 8.1 Hz), 125.5, 118.7 (d, J = 21.8 Hz), 118.0 (d, J = 24.2 Hz), 116.1, 115.6 (d, J = 11.7 Hz), 102.9 (d, J = 26.7 Hz), 56.9, 53.6, 46.6, 30.0, 21.8, 19.8, 17.0. MS (ESI+): m/z $[M + H]^+$ 361.9, 363.3, 364.4. HRMS (ESI+): m/z calculated for $C_{20}H_{21}F_2NO_3$ $[M + H]^+$ = 362.1489, found 362.1493.

(5-Fluoro-2-((4-methylpiperidin-1-yl)methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (6e) Yellow solid. final yield 36%. m.p. = 91–93 °C. R_f = 0.79 (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, DMSO) δ 8.94–9.53 (br, 2H, OH), 7.87–7.90 (m, 1H, Ar-4-H), 7.57 (td, J = 8.3, 2.3 Hz, 1 H, Ar-3-H), 7.40 (d, J = 8.4 Hz, 1H, Ar-6-H), 7.05 (dd, J = 34.5, 7.2 Hz, 1H, Ar-3′-H), 6.65 (d, J = 12.0 Hz, 1H, Ar-6′-H), 4.31 (d, J = 4.6 Hz, 1H, Ar-2-CH_2-), 3.34 (d, J = 11.3 Hz, 2H, piperidine-2″, 6″-H), 2.99 (q, J = 10.8 Hz, 2H, piperidine-3″, 5″-H), 1.76 (d, J = 13.9 Hz, 2H, piperidine-2″, 6″-H), 1.60 (s, 1H, piperidine-4″-CH), 1.41 (q, J = 11.8 Hz, 2 H, piperidine-3″, 5″-H), 0.89 (d, J = 6.4 Hz, 3H, piperidine-4″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 193.0, 162.9 (d, J = 249.8 Hz), 156.5 (d, J = 247.2 Hz), 153.2 (d, J = 11.7 Hz), 142.6 (d, J = 6.6 Hz), 142.2, 135.5 (d, J = 8.3 Hz), 125.1, 118.7 (d, J = 21.9 Hz), 118.0 (d, J = 27.3 Hz), 116.1, 115.7 (d, J = 12.2 Hz), 102.9 (d, J = 26.7 Hz), 58.5, 52.8, 31.2, 28.4, 20.0. MS (ESI+): m/z $[M + H]^+$ 361.7, 362.3, 363.1, 364.3. HRMS (ESI+): m/z calculated for $C_{20}H_{21}F_2NO_3$ $[M + H]^+$ = 362.1489, found 362.1485.

2((4-Benzylpiperidin-1-yl)methyl)-5-fluorophenyl)(2-fluoro-4,5-dihydroxybenzoyl) methanone (6f) Yellow solid. final yield 58%. m.p. = 126–128 °C. R_f = 0.93 (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.39 (t, J = 6.3 Hz, 1H, Ar-3-H), 7.65 (s, 1H, Ar-4-H), 7.35 (d, J = 8.4 Hz, 1H, Ar-6-H), 7.29 (t, J = 7.5 Hz, 2 H, Ar-3‴, 5‴-H), 7.16–7.21 (m, 4H, Ar-2‴, 4‴, 6‴, 3'-H), 6.60 (d, J = 11.8 Hz, 1H, Ar-6′-H), 4.12 (s, 1H, Ar-2-CH_2-), 3.35 (s, 2H, piperidine-2″, 6″-H), 2.83 (s, 2H, piperazine-3″, 5″-H), 2.57 (d, J = 6.4 Hz, 2H, piperidine-4″-C-CH_2-), 1.77–1.87 (m, 3H, piperidine-2″, 6″, 4″-CH), 1.43 (s, 2H, piperazine-3″, 5″-H). ^{19}F NMR (565 MHz, MeOD) δ −117.19(s), −112.87(s). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.9, 162.6 (d, J = 248.6 Hz), 156.6 (d, J = 247.1 Hz), 153.3 (d, J = 11.7 Hz), 142.8 (d, J = 6.3 Hz), 142.2, 139.4, 134.4 (d, J = 6.8 Hz), 128.8, 128.0, 127.1 (d, J = 3.8 Hz), 125.9, 117.9 (d, J = 21.6 Hz), 117.2 (d, J = 23.0 Hz), 116.0, 115.7 (d, J = 11.6 Hz), 102.9 (d, J = 26.4 Hz), 52.4, 46.6, 41.6, 35.6, 29.1. MS (ESI+): m/z $[M + H]^+$ 437.7, 439.3, 440.0. HRMS (ESI +): m/z calculated for $C_{26}H_{25}F_2NO_3$ $[M + H]^+$ = 438.1881, found 438.1829.

Ethyl 1-(4-fluoro-2-(2-fluoro-4,5-dihydroxybenzoyl) benzyl) piperidine-4-carboxylate (6g) Yellow solid. final yield 34%. m.p. = 81–83 °C. R_f = 0.88 (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.52 (s, 1H, Ar-4-H), 7.27 (t, J = 7.2 Hz, 1H, Ar-3-H), 7.13–7.18 (m, 2H, Ar-6, 3′-H), 6.51 (d, J = 11.5 Hz, 1H, Ar-6′-H), 4.06 (q, J = 7.1 Hz, 2H, piperidine-4″-CH_2-), 3.82 (s, 2H, Ar-2-CH_2-), 2.60–2.71 (m, 2H, piperidine-2″, 6″-H), 2.23–2.28 (m, 2H, piperidine-3″, 5″-H), 2.07–2.17 (m, 1H, piperidine-4″-CH-),

1.66–1.74 (m, 2H, piperidine-2″, 6″-H), 1.41–1.51 (m, 2H, piperidine-3″, 5″-H), 1.32 (t, $J = 7.1$ Hz, 3H, piperidine-4″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 191.6, 178.9, 162.4 (d, $J = 247.5$ Hz), 156.8 (d, $J = 248.0$ Hz), 153.5 (d, $J = 12.2$ Hz), 149.1, 142.2, 132.3 (d, $J = 8.1$ Hz), 128.3, 121.8, 119.2, 117.6 (d, $J = 21.2$ Hz), 115.5, 102.9, 56.1, 29.4, 26.7, 18.4, 15.9, 9.7. MS (ESI+): *m/z* $[M + H]^+$ 420.1, 421.3. HRMS (ESI+): *m/z* calculated for $C_{22}H_{23}F_2NO_5$ $[M + H]^+ = 420.1544$, found 420.1549.

1-(4-(4-Fluoro-2-(2-fluoro-4,5-dihydroxybenzoyl) benzyl) piperazin-1-yl) ethanone (8a) Yellow solid. final yield 48%. m.p. = 188–190 °C. $R_f = 0.97$ (11% methanol/dichloromethane). ^{1}H NMR (400 MHz, DMSO) δ 10.37 (s, 1H, OH), 9.40 (s, 1H, OH), 7.36–7.40 (m, 1H, Ar-4-H), 7.23 (t, $J = 7.2$ Hz, 1H, Ar-3-H), 7.12 (d, $J = 8.2$ Hz, 1H, Ar-6-H), 7.08 (d, $J = 7.3$ Hz, 1H, Ar-3′-H), 6.56 (d, $J = 12.1$ Hz, 1 H, Ar-6′-H), 3.37 (s, 2H, Ar-2-CH_2-), 3.07 (s, 4H, piperazine-3″, 5″-H), 2.08 (s, 2H, piperazine-2″, 6″-H), 2.04 (s, 2H, piperazine-2″, 6″-H), 1.91 (s, 3H, piperazine-4″-$COCH_3$). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.7, 170.1, 161.9 (d, $J = 243.9$ Hz), 156.7 (d, $J = 248.4$ Hz), 152.4 (d, $J = 12.8$ Hz), 143.3 (d, $J = 6.8$ Hz), 141.8, 132.2 (d, $J = 3.9$ Hz), 131.2, 116.2 (d, $J = 11.4$ Hz), 115.7, 115.6, 114.4 (d, $J = 16.4$ Hz), 102.9 (d, $J = 26.4$ Hz), 58.9, 52.0, 51.6, 45.4, 40.6, 19.6. MS (ESI+): *m/z* $[M + H]^+$ 391.2, 392.2. HRMS (ESI+): *m/z* calculated for $C_{20}H_{20}F_2N_2O_4$ $[M + H]^+ = 391.1391$, found 391.1386.

(5-Fluoro-2-((4-methylpiperazin-1-yl)methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8b) Yellow solid. final yield 48%. m.p. = 252–254 °C. $R_f = 0.44$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.36–7.38 ((m, 1 H, Ar-4-H), 7.13–7.17 (m, 2H, Ar-3, 6-H), 7.06 (dd, $J = 8.7$, 2.2 Hz, 1 H, Ar-3′-H), 6.57 (d, $J = 12.1$ Hz, 1 H, Ar-6′-H), 3.56 (s, 2H, Ar-2-CH_2-), 3.35 (s, 4H, piperazine-2″, 6″-H), 2.71 (s, 3H, piperazine-CH_3), 2.50 (s, 4H, piperazine-3″, 5″-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.7, 162.0 (d, $J = 245.4$ Hz), 156.8 (d, $J = 248.4$ Hz), 153.1 (d, $J = 13.2$ Hz), 143.3, 142.0, 131.7, 131.3 (d, $J = 7.4$ Hz), 115.9, 115.7, 115.4, 114.3 (d, $J = 23.3$ Hz), 103.1 (d, $J = 26.3$ Hz), 58.1, 53.3, 48.9, 48.5, 46.6, 42.4. MS (ESI+): *m/z* $[M + H]^+$ 362.7, 363.5, 364.2. HRMS (ESI+): *m/z* calculated for $C_{19}H_{20}F_2N_2O_3$ $[M + H]^+ = 363.1442$, found 363.1446.

(5-Fluoro-2-((4-(2-hydroxyethyl) piperazin-1-yl)methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8c) Yellow solid. final yield 42%. m.p. = 141–143 °C. $R_f = 0.31$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.86–7.92 (s, 1H, Ar-4-H), 7.38–7.52 (m, 2H, Ar-3, 6-H), 7.17 (d, $J = 6.8$ Hz, 1H, Ar-3′-H), 6.63 (d, $J = 11.8$ Hz, 1H, Ar-6′-H), 4.55(s, 2H, Ar-2-CH_2-), 3.96 (m, 2H, piperazine-4″-CH_2-), 3.84 (m, 4H, piperazine-2″, 6″-H), 3.50 (s, 2H, piperazine-4″-C-CH_2-), 3.37 (m, 4H, piperazine-3″, 5″-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.8, 163.1(d, $J = 249.6$ Hz), 156.4 (d, $J = 247.5$ Hz), 153.1 (d, $J = 12.3$ Hz), 142.5, 142.1, 135.5 (d, $J = 4.8$ Hz), 118.8 (d, $J = 21.8$ Hz), 118.2, 116.2, 115.7, 115.6, 102.9 (d, $J = 26.6$ Hz), 58.2, 58.1, 56.1, 55.0, 52.0, 51.8, 51.6. MS (ESI+): *m/z* $[M + H]^+$ 393.1, 394.3. HRMS (ESI+): *m/z* calculated for $C_{20}H_{22}F_2N_2O_4$ $[M + H]^+ = 393.1548$, found 393.1551.

(5-Fluoro-2-((4-(2-hydroxyphenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8d) Yellow solid. final yield 54%. m.p. = 107–109 °C. $R_f = 0.89$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, DMSO) δ 10.27 (s, 1H, OH), 9.35 (s, 1H, OH), 8.80 (s, 1H, OH), 7.39 (s, 1H, Ar-4-H), 7.23 (s, 1H, Ar-6-H), 7.11 (m, 1H, Ar-3, 3′-H), 6.78 (m, 4H, Ar-3‴, 4‴, 5‴, 6‴-H), 6.55(m,1H, Ar-6′-H), 3.41 (s, 2H, Ar-2-CH_2-), 2.61 (S, 4H, piperazine-3″, 5″-H), 2.27 (s, 4H, piperazine-2″, 6″-H). ^{13}C{1 H} NMR (150 MHz, MeOD) δ 192.7, 161.8 (d, $J = 244.1$ Hz), 254.4 (d, $J = 254.4$ Hz), 152.4, 150.6, 143.4, 141.7, 140.9, 139.4, 130.8, 124.3, 123.2, 120.7, 119.4(d, $J = 22.1$ Hz), 118.0, 115.8, 114.5, 111.3, 102.9 (d, $J = 26.9$ Hz), 59.2, 59.1, 54.5. MS (ESI+): *m/z* $[M + H]^+$ 441.1. HRMS (ESI+): *m/z* calculated for $C_{24}H_{22}F_2N_2O_4$ $[M + H]^+ = 441.1626$, found 441.1604.

(5-Fluoro-2-((4-(4-fluorophenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8e) Yellow solid. final yield 64%. m.p. = 232–234 °C. $R_f = 0.33$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, DMSO) δ 7.79–7.81 (m, 1H, Ar-4-H), 7.55 (t, $J = 7.0$ Hz, 1H, Ar-3-H), 7.36 (d, $J = 8.4$ Hz, 1H, Ar-6-H), 7.00–7.11 (m, 4H, Ar-2‴, 3‴, 5‴, 6‴-H), 6.59 (d, $J = 6.7$ Hz, 1H, Ar-3′-H), 6.31 (d, $J = 11.9$ Hz, 1H, Ar-6′-H), 4.42 (s, 2H, Ar-2-CH_2-), 3.72 (d, $J = 11.3$ Hz, 2H, piperazine-3″, 5″-H), 3.47 (d, $J = 11.2$ Hz, 2H, piperazine-2″, 6″-H), 3.28 (s, 2H, piperazine-3″, 5″-H), 3.06 (d, $J = 12.2$ Hz, 2 H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 193.0, 163.0 (d, $J = 249.9$ Hz), 158.1 (d, $J = 237.6$ Hz), 154.5 (d, $J = 354.7$ Hz), 146.4, 142.5 (d, $J = 6.9$ Hz), 142.2, 135.5 (d, $J = 8.3$ Hz), 124.9, 118.9, 118.8 (d, $J = 7.7$ Hz), 118.3 (d, $J = 23.7$ Hz), 116.2, 115.7 (d, $J = 11.4$ Hz), 115.4, 115.2, 102.9 (d, $J = 26.7$ Hz), 58.2, 51.7. MS (ESI+): *m/z* $[M + H]^+$ 443.2, 444.2. HRMS (ESI+): *m/z* calculated for $C_{24}H_{21}F_3N_2O_3$ $[M + H]^+ = 443.1583$, found 443.1587.

(5-Fluoro-2-((4-(2-fluorophenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8f) Yellow solid. final yield 51%. m.p. 184–185 °C. $R_f = 0.97$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz,

DMSO) δ 9.56 (s, 1H, OH), 9.37 (s, 1H, OH), 7.88 (s, 1H, Ar-4-H), 7.61 (s, 1H, Ar-3-H), 7.46 (d, $J = 5.9$ Hz, 1H, Ar-6-H), 7.05–7.20 (m, 5H, Ar-3′, 3‴, 4‴, 5‴, 6‴-H), 6.66 (d, $J = 11.5$ Hz, 1H, Ar-6′-H), 4.46 (s, 2H, Ar-2-CH_2-), 3.49 (s, 4H, piperazine-3″, 5″-H), 3.38 (m, 4H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (150 MHz, MeOD δ 193.0, 162.8 (d, $J = 248.4$ Hz), 156.6 (d, $J = 247.1$ Hz), 155.8 (d, $J = 243.2$ Hz), 153.1 (d, $J = 12.2$ Hz), 142.7 (d, $J = 6.6$ Hz), 142.1, 138.4, 134.8 (d, $J = 10.8$ Hz), 129.5, 124.6, 123.7 (d, $J = 6.6$ Hz), 119.4, 118.3, 117.6, 116.1, 115.9, 115.8 (d, $J = 8.3$ Hz), 102.9 (d, $J = 26.4$ Hz), 58.5, 51.9. MS (ESI+): *m/z* $[M + H]^+$ 443.5, 444.3. HRMS (ESI+): *m/z* calculated for $C_{24}H_{21}F_3N_2O_3$ $[M + H]^+ = 443.1504$, found 443.1508.

(5-Fluoro-2-((4-(4-hydroxyphenyl) piperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8g) Yellow solid. final yield 52%. m.p. = 146–148 °C. R_f = 0.61 (11% methanol/dichloromethane). ^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H, OH), 9.48 (s, 1H, OH), 8.99 (s, 1H, OH), 7.93–7.95 (m, 1H, Ar-4-H), 7.60 (t, J = 8.2 Hz, 1H, Ar-3-H), 7.44 (d, $J = 8.9$ Hz, 1H, Ar-6-H), 7.09 (d, $J = 7.3$ Hz, 1H, Ar-3′-H), 6.83 (d, $J = 8.3$ Hz, 2H, Ar-3‴, 5‴-H), 6.66–6.69 (m, 3H, Ar-2‴, 6‴, 6′-H), 4.44 (s, 2H, Ar-2-CH_2-), 3.55 (d, $J = 13.1$ Hz, 2H, piperazine-3″, -5″-H), 3.40–3.44 (m, 4H, piperazine-3″, 5″, 2″, 6″-H), 3.00 (t, $J = 11.9$ Hz, 2H, piperazine-2″, 6″-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.9, 173.8, 172.1, 162.9 (d, $J = 254.1$ Hz), 156.5 (d, $J = 247.5$ Hz), 153.2 (d, $J = 12.5$ Hz), 142.7, 142.2, 135.6 (d, $J = 6.8$ Hz), 131.0, 128.5, 119.5, 118.1, 116.1, 115.8 (d, $J = 11.6$ Hz), 115.6, 103.0 (d, $J = 26.1$ Hz), 58.1, 56.1, 51.9. MS (ESI+): *m/z* $[M + H]^+$ 441.1, 442.3. HRMS (ESI+): *m/z* calculated for $C_{24}H_{22}F_2N_2O_4$ $[M + H]^+ = 441.1626$, found 441.1627.

(2-((4-Benzhydrylpiperazin-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8h) Yellow solid. final yield 42%. m.p. = 215–217 °C. $R_f = 0.38$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.38–7.81 (m, 13H, Ar-H), 7.16 (d, $J = 6.9$ Hz, 1H, Ar-3′-H), 6.62 (d, $J = 11.7$ Hz, 1H, Ar-6′-H), 5.42 (s, 1H, piperazine-4″-CH-), 4.50 (s, 2H, Ar-2-CH_2-), 3.76 (m, 4H, piperazine-2″, 6″-H), 3.41 (m, 4H, piperazine-3″,5″-H). ^{19}F NMR (565 MHz, MeOD) δ −125.00(s), −117.33(s). ^{13}C {1 H} NMR (150 MHz, MeOD) δ 192.9, 174.4, 163.1 (d, $J = 250.1$ Hz), 156.5 (d, $J = 247.5$ Hz), 153.2 (d, $J = 12.2$ Hz), 142.4 (d, $J = 6.6$ Hz), 142.2, 135.5 (d, $J = 8.6$ Hz), 129.4, 129.2, 128.3, 124.8, 118.9 (d, $J = 21.3$ Hz), 118.3 (d, $J = 22.5$ Hz), 116.2, 115.6 (d, $J = 11.6$ Hz), 102.9 (d, $J = 26.6$ Hz), 75.4, 68.9, 60.5. MS (ESI+): *m/z* $[M + H]^+$ 515.3, 516.3, 517.4. HRMS (ESI+): *m/z* calculated for $C_{31}H_{28}F_2N_2O_3$ $[M + H]^+ = 515.2146$, found 515.2147.

(5-Fluoro-2-((4-(pyrimidin-2-yl) piperazin-1-yl) methyl) phenyl) (2- fluoro -4,5-dihydroxyphenyl) methanone (8i) Yellow solid. final yield 51%. m.p. = 75–77 °C. $R_f = 0.08$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, DMSO) δ 9.49 (s, 1H, Ar-OH), 8.45 (d, $J = 4.7$ Hz, 2H, pyrimidine-4‴, 6‴-H), 7.88 (s, 1H, Ar-4-H), 7.59–7.63 (m, 1H, Ar-3-H), 7.45 (d, $J = 8.3$ Hz, 1H, Ar-6-H), 7.07 (d, $J = 7.2$ Hz, 1H, Ar-3′-H), 6.77 (t, $J = 4.7$ Hz, 1H, pyrimidine-4‴-H), 6.66 (d, $J = 12.0$ Hz, 1H, Ar-6′-H), 4.69 (d, $J = 14.0$ Hz, 2H, piperazine-3″, 5″-H), 4.40 (s, 2H, Ar-2-CH_2-), 3.47 (d, $J = 10.5$ Hz, 2H, piperazine-2″, 6″-H), 3.38(t, $J = 12.8$ Hz, 2H, piperazine-3″, 5″-H), 3.17 (m, 2H, piperazine-2″, 6″-H). ^{19}F NMR (565 MHz, MeOD) δ −117.04(s), −111.13(s). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.9, 163.1 (d, $J = 250.1$ Hz), 157.3, 156.1 (d, $J = 123.0$ Hz), 153.2 (d, $J = 12.5$ Hz), 142.5 (d, $J = 6.0$ Hz), 142.2, 135.7 (d, $J = 8.3$ Hz), 124.7, 124.5, 121.8 (d, $J = 24.6$ Hz), 118.9 (d, $J = 21.8$ Hz), 118.3 (d, $J = 26.9$ Hz), 116.2, 115.7 (d, $J = 12.0$ Hz), 111.1, 102.9 (d, $J = 26.4$ Hz), 69.9, 58.5, 50.7. MS (ESI+): *m/z* $[M + H]^+$ 427.4, 427.7. HRMS (ESI+): *m/z* calculated for $C_{22}H_{20}F_2N_4O_3$ $[M + H]^+ = 427.1582$, found 427.1535.

(5-Fluoro-2-((4-ethylpiperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8j) Yellow solid. final yield 49%. m.p. = 175–177 °C. $R_f = 0.63$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.84–7.88 (m, 1H, Ar-4-H), 7.49 (td, $J = 8.1$, 2.1 Hz, 1H, Ar-3-H), 7.45 (d, $J = 8.3$ Hz, 1H, Ar-6-H), 7.17 (d, $J = 7.0$ Hz, 1H, Ar-3′-H), 6.64 (d, $J = 11.8$ Hz, 1H, Ar-6′-H), 4.51 (s, 2H, Ar-2-CH_2-), 3.39–3.73((m, 10H, piperazine-4″-CH_2-, piperazine-2″, 3″, 5″, 6″-H), 1.44(t, $J = 7.2$ Hz, 3H, piperazine-4″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.9, 163.1 (d, $J = 249.8$ Hz), 156.5 (d, $J = 247.1$ Hz), 153.2 (d, $J = 12.0$ Hz), 142.6 (d, $J = 7.1$ Hz), 142.2, 135.4, 124.9, 118.8 (d, $J = 21.9$ Hz), 118.1 (d, $J = 23.3$ Hz), 116.2, 115.6 (d, $J = 11.7$ Hz), 103.0 (d, $J = 26.9$ Hz), 52.3, 52.0, 48.2, 40.6, 8.2. MS (ESI+): *m/z* $[M + H]^+$ 337.2, 338.2. HRMS (ESI+): *m/z* calculated for $C_{20}H_{22}F_2N_2O_3$ $[M + H]^+ = 377.1677$, found 377.1682.

(5-Fluoro-2-((4-isopropylpiperazin-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (8k) Yellow solid. final yield 58%. m.p. = 247–249 °C. $R_f = 0.83$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, DMSO) δ 10.46 (s, 1H, OH), 7.41 (s, 1H, Ar-4-H), 9.24 (s, 1H, OH), 7.17 (d, $J = 7.4$ Hz, 1H, Ar-6-H), 7.26 (s, 1H, Ar-3-H), 7.09 (d, $J = 6.5$ Hz, 1H, Ar-3′-H), 6.61 (d, $J = 11.8$ Hz, 1 H, Ar-6′-H), 3.48 (s, 2 H, Ar-2-CH_2-), 3.34 (s, 4H, piperazine-2″, 6″-H), 3.19–3.21 (m, 1H, piperazine-4″-CH-), 2.34 (s, 4H, piperazine-3″-H, piperazine-5″-H), 1.09 (d, $J = 5.2$ Hz, 6H, piperazine-4″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ

192.5, 162.0 (d, $J = 245.3$ Hz), 156.7 (d, $J = 248.3$ Hz), 152.7 (d, $J = 12.2$ Hz), 143.3 (d, $J = 6.3$ Hz), 142.0, 131.9, 131.0 (d, $J = 7.8$ Hz), 116.1 (d, $J = 10.2$ Hz), 115.6, 115.5, 114.0 (d, $J = 23.1$ Hz), 103.2 (d, $J = 26.4$ Hz), 58.1, 58.0, 48.8, 47.3, 15.3. MS (ESI+): *m/z* $[M + H]^+$ 391.2, 392.3. HRMS (ESI+): *m/z* calculated for $C_{21}H_{24}F_2N_2O_3$ $[M + H]^+ = 391.1755$, found 391.1760.

(5-Fluoro-2-((2-phenyl-1H-imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10a) Yellow solid. final yield 39%. m.p. = 156–158 °C. $R_f = 0.90$ (11% methanol/dichloromethane). ^{1}H NMR (400 MHz, DMSO) δ 7.44 (s, 2 H, Ar-2″, 6″-H), 7.35 (s, 3H, Ar-3″, 4″, 5″-H), 7.24 (s, 1H, imidazole-5″-H), 7.19 (t, $J = 8.7$ Hz, 1H, Ar-3-H), 7.11 (d, $J = 7.4$ Hz, 1H, Ar-6-H), 7.04 (s, 1H, imidazole-4″-H), 6.68–6.76 (m, 1H, Ar-4-H, Ar-3′-H), 5.91 (d, $J = 14.7$ Hz, 1H, Ar-6′-H), 5.21 (s, 2H, Ar-2-CH_2-). ^{13}C{1H} NMR (150 MHz, MeOD) δ 191.5, 162.4 (d, $J = 247.5$ Hz), 156.8 (d, $J = 248.9$ Hz), 153.2 (d, $J = 12.2$ Hz), 142.3 (d, $J = 8.1$ Hz), 130.2 (d, $J = 7.2$ Hz), 128.6 (d, $J = 4.2$ Hz), 126.8, 124.9, 117.0 (d, $J = 21.2$ Hz), 115.6, 115.2 (d, $J = 23.0$ Hz), 102.8 (d, $J = 26.7$ Hz), 48.2. MS (ESI+): *m/z* $[M + H]^+$ 407.1, 408.2, 409.3. HRMS (ESI+): *m/z* calculated for $C_{23}H_{16}F_2N_2O_3$ $[M + H]^+ = 407.1129$, found 407.1133.

(5-Fluoro-2-((2-isopropyl-1H-imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10b) Yellow solid. final yield 36%. m.p. = 156–158 °C. $R_f = 0.87$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.25 (t, $J = 7.0$ Hz, 1H, Ar-3-H), 7.12–7.17 (m, 2H, Ar-4, 64-H), 7.10 (d, $J = 5.5$ Hz, 1H, Ar-3′-H), 6.90 (d, $J = 15.6$ Hz, 2H, imidazole-4″, 5″-H), 6.48 (d, $J = 11.7$ Hz, 1H, Ar-6′-H), 5.29 (s, 2H, Ar-2-CH_2-),3.01 (q, $J = 13.6$, 6.8 Hz, 1H, imidazole-2″-CH-), 1.18 (d, $J = 6.8$ Hz, 6H, imidazole-2″-CH_3). ^{13}C{1 H} NMR (150 MHz, MeOD) δ 191.6, 178.0, 161.9 (d, $J = 246.2$ Hz), 156.7, 153.0, 142.7, 142.2, 130.6 (d, $J = 7.2$ Hz), 130.3, 124.2, 120.2, 116.9 (d, $J = 21.0$ Hz), 115.1, 115.0, 114.8, 103.0 (d, $J = 24.3$ Hz), 46.2, 25.4, 21.7, 20.2. MS (ESI+): *m/z* $[M + H]^+$ 373.3, 374.2, 375.3. HRMS (ESI+): *m/z* calculated for $C_{20}H_{18}F_2N_2O_3$ $[M + H]^+ = 373.1364$, found 373.1366.

(5-Fluoro-2-((2-ethyl-1H-imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10c) Yellow solid. final yield 42%. m.p. = 186–188 °C. $R_f = 0.87$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.43–7.47 (m, 1H, Ar-4-H), 7.36 (td, $J = 8.3$, 2.6 Hz, 1H, Ar-3-H), 7.25 (d, $J = 7.5$ Hz, 1H, Ar-6-H), 7.24 (s, 1H, imidazole-5″-H), 7.17 (s, 1H, imidazole-4″-H), 7.10 (d, $J = 7.0$ Hz, 1H, Ar-3′-H), 6.54 (d, $J = 11.9$ Hz, 1H, Ar-6′-H), 5.43 (s, 2H, Ar-2-CH_2-), 2.89 (q, $J = 7.6$ Hz, 2H, imidazole-2″-CH_2-), 1.30 (t, $J = 7.6$ Hz, 3H, imidazole-2″-CH_3). ^{13}C {1H} NMR (150 MHz, MeOD) δ 191.6, 162.4 (d, $J = 247.5$ Hz), 156.8 (d, $J = 248.0$ Hz), 153.5 (d, $J = 12.2$ Hz), 149.1, 142.2, 132.3 (d, $J = 8.1$ Hz), 128.3, 121.8, 119.2, 117.6 (d, $J = 21.2$ Hz), 115.9 (d, $J = 13.4$ Hz), 115.5, 115.2 (d, $J = 10.8$ Hz), 102.9 (d, $J = 26.7$ Hz), 56.1, 18.4, 9.7. MS (ESI+): *m/z* $[M + H]^+$ 359.1, 360.2, 361.2. HRMS (ESI+): *m/z* calculated for $C_{19}H_{16}F_2N_2O_3$ $[M + H]^+ = 359.1129$, found 359.1134.

(2-((1H-Imidazol-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10d) Yellow solid. final yield 34%. m.p. = 82–84 °C. $R_f = 0.28$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.62 (s, 1H, imidazole-2″-H), 7.22–7.27 (m, 1H, Ar-6-H), 7.26 (td, $J = 8.4$, 2.4 Hz, 1H, Ar-3′-H), 7.14 (d, $J = 8.9$ Hz, 1H, Ar-3-H), 7.08 (d, $J = 7.1$ Hz, 1H, Ar-3′-H), 7.03 (s,1H, imidazole-5″-H), 6.89 (s,1H, imidazole-4″-H), 6.50 (d, $J = 11.7$, 1H, Ar-6′-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 191.8, 162.4 (d, $J = 248.3$ Hz), 156.8 (d, $J = 247.5$ Hz), 153.4 (d, $J = 11.7$ Hz), 142.2, 135.9, 134.0, 133.1 (d, $J = 8.0$ Hz), 128.4, 121.7, 121.0, 119.3, 117.8 (d, $J = 21.5$ Hz), 116.0 (d, $J = 23.0$ Hz), 102.9 (d, $J = 26.7$ Hz), 49.1. MS (ESI+): *m/z* $[M + H]^+$ 331.2, 332.3. HRMS (ESI+): *m/z* calculated for $C_{17}H_{12}F_2N_2O_3$ $[M + H]^+ = 331.0816$, found 331.0814.

(2-((5,6-Dimethyl-1H-benzo[d]imidazol-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10e) Yellow solid. final yield 31%. m.p. = 180–182 °C. $R_f = 0.70$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 9.12 (s, 1H, imidazole-2″-H), 7.66-7.71 (m, 1H, Ar-4-H), 7.47 (s, 1H, Ar-4‴-H), 7.42 (s, 1H, Ar-7‴-H), 7.36 (td, $J = 8.4$, 2.7 Hz, 1H, Ar-3-H), 7.22 (d, $J = 8.5$ Hz, 1H, Ar-6-H), 6.92 (d, $J = 7.1$ Hz, 1H, Ar-3′-H), 6.38 (d, $J = 12.0$ Hz, 1H, Ar-6′-H), 5.73 (s, 2H, Ar-2-CH_2-), 2.41 (s, 3H, Ar-6‴-CH_3), 2.39 (s, 3H, Ar-5‴-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 191.6, 162.5 (d, $J = 248.4$ Hz), 156.8 (d, $J = 248.9$ Hz), 153.5 (d, $J = 12.2$ Hz), 142.7 (d, $J = 6.6$ Hz), 142.1, 140.0, 137.1 (d, $J = 60.2$ Hz), 132.7 (d, $J = 8.3$ Hz), 129.4 (d, $J = 54.0$ Hz), 127.2, 117.5 (d, $J = 276.5$ Hz), 115.7 (d, $J = 23.6$ Hz), 115.4, 115.0 (d, $J = 11.1$ Hz), 113.6, 112.6, 102.6 (d, $J = 26.7$ Hz), 48.5, 19.2, 19.0. MS (ESI+): *m/z* $[M + H]^+$ 409.2, 410.2, 411.4. HRMS (ESI+): *m/z* calculated for $C_{23}H_{18}F_2N_2O_3$ $[M + H]^+ = 409.1285$, found 409.1289.

(2-((1H-Benzo[d]imidazol-1-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10f) Yellow solid. final yield 32%. m.p. = 171–173 °C. $R_f = 0.76$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ8.07 (s, 1H, imidazole-2″-H), 7.53-7.60 (m, 1H, Ar-4-H), 7.35–7.40 (m, 1H, Ar-3-H), 7.30–7.34 (m, 1H, Ar-6-H), 7.21–7.25 (m, 3 H, Ar-3′, 4‴, 7‴-H), 7.13 (d, $J = 7.3$ Hz, 1H, Ar-5‴-H), 6.97 (d, $J = 6.8$ Hz, 1H, Ar-6‴-H), 6.41 (d,

$J = 11.9$ Hz, 1 H, Ar-6′-H), 5.57 (s, 2H, Ar-2-CH_2-). ^{13}C {1H} NMR (150 MHz, MeOD) δ 192.1, 161.9 (d, $J =$ 246.8 Hz), 156.9 (d, $J = 249.0$ Hz), 153.2 (d, $J = 11.6$ Hz), 143.8, 142.2 (d, $J = 7.5$ Hz), 141.9, 133.3, 131.2 (d, $J =$ 8.1 Hz), 130.0, 123.2, 122.5, 118.3, 117.0 (d, $J = 21.2$ Hz), 115.6, 115.2 (d, $J = 24.0$ Hz), 110.6, 102.8 (d, $J = 26.7$ Hz), 45.7. MS (ESI+): m/z $[M + H]^+$ 381.0, 382.2. HRMS (ESI+): m/z calculated for $C_{21}H_{14}F_2N_2O_3$ $[M + H]^+ =$ 381.0972, found 381.0976.

(5-Fluoro-2-((2-methyl-1H-benzo[d]imidazol-1-yl) methyl) phenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (10g) Yellow solid. final yield 34%. m.p. = 151–153 °C. $R_f =$ 0.35 (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.44–7.58 (m, 5H, Ar-2‴, 3‴, 4‴, 5‴, 4-H), 7.32 (td, $J = 8.4$, 2.4 Hz,1H, Ar-3-H), 7.17 (d, J = 8.1 Hz, 1H, Ar-6-H), 6.84 (d, $J = 7.1$ Hz, 1H, Ar-3′-H), 6.33 (d, $J = 12.1$ Hz, 1H, Ar-6′-H), 5.75 (s, 2H, Ar-2-CH_2-), 2.81 (s, 3H, imidazole-2″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 191.1, 162.2 (d, $J = 248.1$ Hz), 156.8 (d, $J = 249.2$ Hz), 153.6 (d, $J = 12.0$ Hz), 151.8, 142.2 (d, $J = 6.3$ Hz), 142.0, 131.9, 131.6 (d, $J = 8.0$ Hz), 129.8, 127.3, 126.3, 125.8, 117.2 (d, $J = 21.5$ Hz), 115.1, 114.3 (d, $J = 10.1$ Hz), 113.1 (d, $J = 21.2$ Hz), 102.6 (d, J = 27.0 Hz), 46.5, 10.9. MS (ESI+): m/z $[M + H]^+$ 395.3, 396.2, 397.3. HRMS (ESI+): m/z calculated for $C_{22}H_{16}F_2N_2O_3$ $[M + H]^+ = 395.1129$, found 395.1126.

(5-Fluoro-2-(morpholinomethyl) phenyl(2-fluoro-4,5-dihydroxyphenyl)methanone (12a) Yellow solid. final yield 61%. m.p. = 97–99 °C. $R_f = 0.70$ (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.31–7.35 (m, 1H, Ar-4-H), 7.16 (d, $J = 7.1$ Hz, 1H Ar-6-H), 7.12 (td, $J = 8.2$, 1.8 Hz, 1H, Ar-3-H), 7.02 (d, $J = 8.6$ Hz, 1H, Ar-3′-H), 6.54 (d, $J = 12.0$ Hz, 1H, Ar-6′-H), 3.44 (s, 2H, Ar-2-CH_2-),3.37 (s, 4H, morpholine-3″, 5″-H), 2.21 (s, 4H, morpholine-2″, 6″-H). ^{13}C{1H} NMR (150 MHz, MeOD) δ 196.7, 165.8 (d, J = 244.5 Hz), 160.7 (d, $J = 248.4$ Hz), 156.2 (d, $J = 12.0$ Hz), 147.3 (d, $J = 5.7$ Hz), 145.7, 136.7, 134.8 (d, $J = 7.5$ Hz), 120.2 (d, $J = 10.2$ Hz), 119.6, 119.3 (d, $J = 21.2$ Hz), 118.0 (d, $J = 23.1$ Hz), 106.8 (d, $J = 26.6$ Hz), 70.0, 63.5, 56.4. MS (ESI+): m/z $[M + H]^+$ 349.6, 351.2. HRMS (ESI+): m/z calculated for $C_{18}H_{17}F_2NO_4$ $[M + H]^+ = 350.1126$, found 350.1121.

2-((2,6-Dimethylmorpholino) methyl)-yl) methyl)-5-fluorophenyl) (2-fluoro-4,5-dihydroxyphenyl) methanone (12b) Yellow solid. final yield 43%. m.p. = 100–102 °C. $R_f =$ 0.82 (11% methanol/dichloromethane). ^{1}H NMR (600 MHz, MeOD) δ 7.29–7.33 (m, 1H, Ar-4-H), 7.09–7.15 (m, 1H, Ar-3, 6-H), 7.02 (dd, $J = 8.6$, 2.2 Hz, 1H, Ar-3′-H), 6.53 (d, J = 12.0 Hz, 1H, Ar-6′-H), 3.42 (s, 2H, Ar-2-CH_2-), 3.19–7.24 (m, 2H, morpholine-2″, 6″-CH), 2.35 (d, $J =$ 10.9 Hz, 2H, morpholine-3″, 5″-H), 1.63 (t, $J = 10.7$ Hz, 2H, morpholine-3″, 5″-H), 0.98 (d, $J = 6.3$ Hz, 6H, morpholine-3″, 5″-CH_3). ^{13}C{1H} NMR (150 MHz, MeOD) δ 192.7, 161.8 (d, $J = 244.2$ Hz), 156.7 (d, $J = 247.8$ Hz), 152.2 (d, $J = 13.4$ Hz), 143.3, 141.8, 132.8, 130.9 (d, $J =$ 7.7 Hz), 116.2 (d, $J = 10.4$ Hz), 115.6, 115.4 (d, $J =$ 21.2 Hz), 114.1 (d, $J = 23.3$ Hz), 102.8 (d, $J = 26.9$ Hz), 71.2, 59.1, 58.2, 17.7. MS (ESI+): m/z $[M + H]^+$ 377.7, 378.7. HRMS (ESI+): m/z calculated for $C_{20}H_{21}F_2NO_4$ $[M + H]^+ = 378.1439$, found 378.1443.

Bioactive screening assay

Before the tested compounds were used in biological experiments, they were purified by slica gel column chromatography, and their purity were higher than 99.0%, as assessed by RP-HPLC on a column of Diamonsil C18 (250 mm × 4.6 mm, 5 μm) with a mobile phase of acetonitrile/water (80/20), flow rate of 1.0 mL min^{-1}, column temperature of 25 °C, injection volume of 20 μL, and detection wavelength of 254 nm (Agilent 1200, Palo Alto, CA, USA).

EA.hy926 cells were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Compounds were dissolved in DMSO, stored at −20 °C, and diluted to the desired concentrations with culture medium RPMI-1640 immediately prior to the experiment. The final concentration of DMSO in the culture medium was less than 0.1%. Cells were seeded in 96-well culture plates at the confluence of 1×10^4 cells/well, kept in a 37 °C, 5% CO_2 incubator for 24 h. Cells were pretreated with designated concentrations of compounds for 4 h, and then exposed to 200 μM H_2O_2 (BHKT Clinical Reagent, Beijing, China) for another 6 h in fresh medium. No H_2O_2-treated cells were used as controls and were incubated under the same conditions. Cell viability was determined by CCK-8 (Boster Biological Engineering Co., USA) assay. The absorbance was detected at 450 nm.

Determination of solubility in water

The excess amount **LM49** and **8 h** bulk drugs were added to 6 mL deionized water in test tubes sealed with stoppers, respectively. The test tubes were vortexed for 5 min and then sonicated for 30 min. They were kept in a constant-temperature shaking bath maintained at 37 °C for 48 h and then centrifuged for 15 min with 5000 rev min^{-1}. A portion of the solution was taken and filtered through a membrane filter (0.45 μm). The filtrate was suitably diluted with deionized water, and the absorbance was detected at 261 and 280 nm by a UV spectrophotometer (UV T6, Beijing Persee General Instrument Co. Ltd. China), respectively. The solubilities of **LM49** and **8h** were analyzed according to their standard curve, respectively.

Molecular docking

The three-dimensional structures of compounds were drawn and all molecular modeling calculations were performed in Sybyl 2.0 software (Tripos Associates, St. Louis, MO, USA). The X-ray cocrystal structure of Keap1 Kelch domain with the 16mer Nrf2 peptide (PDB code: 2FLU) comes from the RCSB Protein Data Bank. All molecule charges were calculated by the Gasteiger-Huckel method. The energy minimization and conformational search were performed using the Tripos force field by the Powell method. The protein was prepared for docking simulation by deleting all water molecules, adding hydrogen atoms, selecting minimized biopolymer hydrogens, minimizing sidechains, minimizing biopolymer hydrogens without C-Alpha in the Stage Minimization module, and assigning AMBER charge and AMBER7 FF99 force field. Surflex docking module was used. A small molecule ligand was docked in the active site of the binding pocket.

Results and discussion

Chemistry

Friedel-Crafts acylation

Friedel-Crafts acylation of 5-fluoro-2-methylbenzoyl chloride (**1**) with 4-fluoro-1,2-dimethoxybenzene (**2**) were carried out in condition of anhydrous $AlCl_3$ as the catalyst and anhydrous CH_2Cl_2 as the solvent, aluminum trichloride needed to be added in batches and dichloromethane was requested to treat with calcium hydride under refluxing, the intermediate **3** was gained with a 90–95% yield. In compound **2**, the electron cloud was the most abundant in the C-5 position and the steric hindrance was also relatively small. Therefore, the C-5 position was the most active reaction site. The equivalent ratio of substrates **1** and **2** was 1:1, a single product point is generated and no by-product was found by monitoring reaction process with thin-layer chromatography (TLC) in petroleum ether-ethyl acetate developing solvent.

Radical substitution reaction

The key intermediate **4** was prepared from compound **3** by radical substitution reaction involving BPO and NBS with the good yield of 60–70%. The molecular oxygen was the free radical inhibitor, in the presence of which the reaction rate of radical substitution will be reduced. But the sunlight is benefit to the radical substitution. Therefore, this reaction needed to be exposed to sunlight condition and also protected under nitrogen. When the molar ratio of compound **3** and NBS was 1.1:1, the reaction time was 6 h and the yield attained to 74.3%.

Nucleophilic substitution reaction

Nitrogenated heterocycle as a nucleophilic reagent attacked the benzyl carbon of key intermediate **4**, and then substituted the bromine atom to give the corresponding compounds **5a–5g**, **7a–7k**, **9a–9g**, and **11a–11b** by nucleophilic substitution. Potassium carbonate and excess heterocyclic reactants were served as the acid-binding agent. The reacted speed of piperazine was fastest, followed by morpholine and piperidine in accordance with their nucleophilic ability.

Demethylation reaction

Compound **5a–5g**, **7a–7k**, **9a–9g**, and **11a–11b** were then demethylated in the presence of BBr_3 at −20 °C to afford the target compounds **6a–6g**, **8a–8k**, **10a–10g**, **12a–12b**.

Biological evaluation

All the synthesized compounds were subjected to in vitro antioxidant stress screening by CCK-8 assay against H_2O_2-induced injury in EA.hy926 cells. The primary protective activity was screened at a concentration of 10 μM. If the protection rates of compounds were more than 40%, their protective effects will further be screened at the concentrations of 0.31, 0.63, 1.25, 2.5, 5, 10, 20, 40 , and 80 μM, and their EC_{50} values will be calculated. Quercetin was used as the positive control drug.

As can be seen in Table 1, to the class of piperidine fluorophenols, compound **6f** with 4-benzyl group in the piperidine ring, showed the strong cytroprotective activity with an EC_{50} value of 1.73 ± 0.35 μM compared with the corresponding intermediate **5f**. Other target compounds

Table 1 Structures of piperidine compounds **5a–5g**, **6a–6g** and their protective effects against H_2O_2 induced injury in EA.hy926 cells

R	Compd.	EC_{50}[a] (μM)	Compd.	EC_{50}[a] (μM)
4-OH	**5a**	>30	**6a**	>30
4-CH_2-CH_2-OH	**5b**	>30	**6b**	>30
2-CH_3, 6-CH_3	**5c**	>30	**6c**	>30
2-CH_3	**5d**	>30	**6d**	>30
4-CH_3	**5e**	>30	**6e**	>30
4-CH_2-Ph	**5f**	>30	**6f**	1.73 ± 0.35
4-$COOCH_2CH_3$	**5g**	>30	**6g**	>30
	Quercetin[b]	18.00 ± 3.60	**LM49**[c]	0.70 ± 0.14

[a]EC_{50} values were an average of three separate determinations

[b]Used as a positive control

[c]Used as a lead compound

Table 2 Structures of piperazine compounds **7a–7k**, **8a–8k** and their protective effects against H_2O_2 induced injury in EA.hy926 cells

Compd.	R	EC_{50} [a] (μM)	Compd.	R	EC_{50} [a] (μM)
7a	-$COCH_3$	> 30	**8a**	-$COCH_3$	> 30
7b	-CH_3	> 30	**8b**	-CH_3	> 30
7c	-CH_2-CH_2-OH	> 30	**8c**	-CH_2-CH_2-OH	> 30
7d	-(2-OCH_3)Ph	> 30	**8d**	-(2-OH)Ph	3.41 ± 1.05
7e	-(4-F)Ph	> 30	**8e**	-(4-F)Ph	> 30
7f	-(2-F)Ph	> 30	**8f**	-(2-F)Ph	6.71 ± 2.12
7g	-(4-OCH_3)Ph	> 30	**8g**	-(4-OH)Ph	> 30
7h	-$CH(Ph)_2$	> 30	**8h**	-$CH(Ph)_2$	0.82 ± 0.23
7i		> 30	**8i**		4.22 ± 1.21
7j	-CH_2-CH_3	> 30	**8j**	-CH_2-CH_3	> 30
7k	$CH(CH_3)_2$	> 30	**8k**	$CH(CH_3)_2$	> 30
Quercetin [b]		18.00 ± 3.60	**LM49** [c]		0.70 ± 0.14

[a]EC_{50} values were an average of three separate determinations

[b]Used as a positive control

[c]Used as a lead compound

6a–6e, **6g** with aliphatic substituents in the piperidine ring and their corresponding intermediates showed no protective activity. These results indicated that the introduction of aromatic group in the piperidine ring was essential for the increase of protective activity.

In Table 2, it should be noted that four piperazine target compounds **8d**, **8f**, **8h**, and **8i** showed strong activity, among of them, compound **8h** with a −$CH(Ph)_2$ group at the 4-position of piperazine exhibited optimal activity with an EC_{50} value of 0.82 ± 0.23 μM, compound **8d**, **8f**, and **8i** presented the moderate activity with the EC_{50} values 3.41 ± 1.05 μM, 6.71 ± 2.12 μM, and 4.22 ± 1.21 μM, respectively. However, their parallel intermediates **7d**, **7f**, **7h**, and **7i** exhibited the negative activity. In addition, compound **8f** with a −(2-F)Ph group at the 4-position of piperazine showed the better activity, but compound **8e** with a −(4-F)Ph group at the same position showed no activity. Similarly, compound **8d** with a −(2-OH)Ph group at the 4-position of piperazine displayed strong activity. However, the activity of compound **8g** with a −(4-OH)Ph group was found to be disappeared.

The protective activity of target compounds **10a–10g**, **12a–12b** and their parallel intermediates **9a–9g**, **11a–11b** were summarized in Tables 3 and 4. All imidazole, morpholine target fluorophenols, and their corresponding intermediates showed no protective activity.

In all obtained compounds, five target fluorophenols **6f**, **8d**, **8f,** **8h**, and **8i** presented the moderate to strong

Table 3 Structures of imidazole compounds **9a–9g**, **10a–10g** and their protective effects against H_2O_2 induced injury in EA.hy926 cells

R	Compd.	EC_{50}[a] (μM)	Compd.	EC_{50}[a] (μM)
2-Ph	**9a**	>30	**10a**	>30
2-$CH(CH_3)_2$	**9b**	>30	**10b**	>30
2-CH_2-CH_3	**9c**	>30	**10c**	>30
2-H	**9d**	>30	**10d**	>30
-[4,5(4,5-di-methyl)]Ph	**9e**	>30	**10e**	>30
-[4,5]Ph	**9f**	>30	**10f**	>30
-2-CH_3-[4,5]Ph	**9g**	>30	**10g**	>30
	Quercetin[b]	18.00 ± 3.60	**LM49**[c]	0.70 ± 0.14

[a]EC_{50} values were an average of three separate determinations

[b]Used as a positive control

[c]Used as a lead compound

Table 4 Structures of morpholine compounds **11a–11b**, **12a–12b** and their protective effects against H_2O_2 induced injury in EA.hy926 cells

R	Compd.	EC_{50}[a] (μM)	Compd.	EC_{50}[a] (μM)
	11a	>30	**12a**	>30
3-CH_3, -5-CH_3	**11b**	>30	**12b**	>30
	Quercetin[b]	18.00 ± 3.60	**LM49**[c]	0.70 ± 0.14

[a]EC_{50} values were an average of three separate determinations

[b]Used as a positive control

[c]Used as a lead compound

Table 5 Solubility of the tested compounds in water ($n = 3$)

Compd.	Solubility (μg mL^{-1})	RSD (%)
LM49	10.00 ± 0.16	1.16
8 h	53.28 ± 0.67	1.26

antioxidant activity with the EC_{50} values of 0.82 to 6.71 μM compared with the standard control quercetin (EC_{50} = 18 μM). Among them, compound **8h** showed the identical activity to lead compound **LM49**. In view of the existence of nitrogenated heterocycles and fluorine atom contribute to the increase of bioavailability, fluorophenol **8h** (EC_{50} = 0.82 μM) may possess preferable druggability.

Judging from structure–activity relationship, the hydroxyl groups were the essential groups to the increase of activity, which was consistent with what summarized in our previous study. Moreover, the sterically hindered phenyl or pyrimidinyl at the 4-position of piperidine and piperazine favored for the antioxidant property.

Solubility of compounds in water

Drug solubility is a key factor affecting the drug absorption. Thus, we selected the most active compound **8h** to compare its water solubility with lead compound **LM49**. As listed in Table 5, the water solubility of **8h** attained to 53.28 μg mL^{-1}, which showed a fivefold increase compared with the **LM49** (10.00 μg mL^{-1}). It turned out that introducing the nitrogenated heterocycles and flurine atoms into the structure of **LM49** can significantly improve the water solubility.

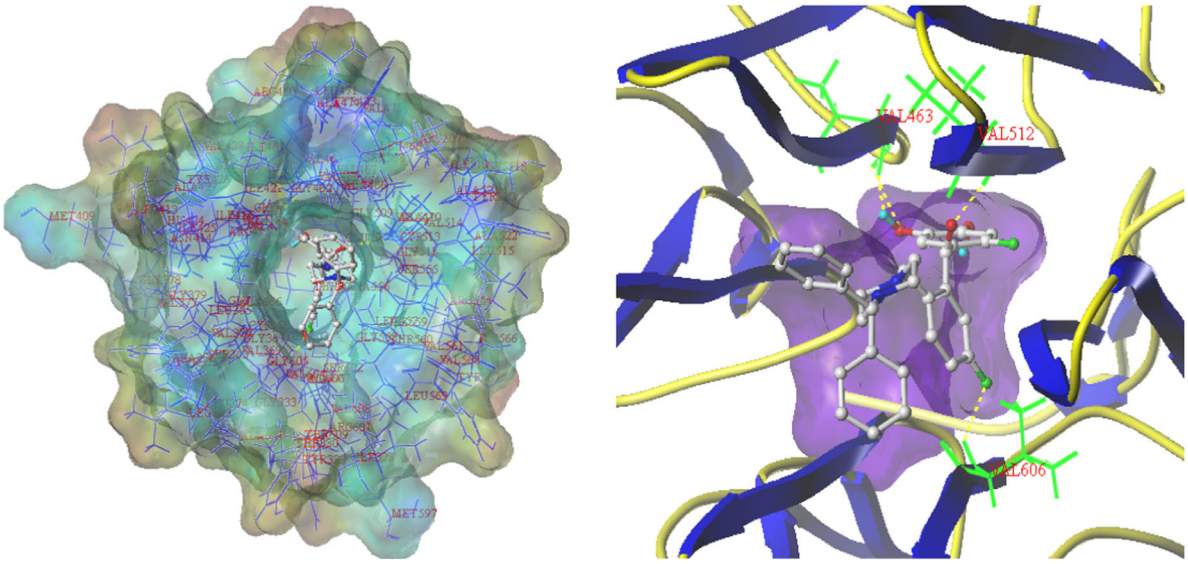
To weak alkalinity and weak acidity drugs, forming salt is an important mean to improve the solubility and bioavailability. The optimal compound **8h** belongs to an amphoteric compound containing both tertiary amine and phenolic hydroxyl groups, such structural features are benefit to its druggability in future.

Molecular docking

Nrf2 is a key factor in cell oxidative stress response, which is regulated by Keap1 and interacts with antioxidant response element (ARE) to induce a series of protective proteins, including glutathione *S*-transferase (GST), NAD (P)H: quinone oxidoreductase 1 (NQO1), and HO-1 to alleviate the oxidative stress damage. The proposed mechanism for activation of Nrf2 involves covalent modification of sulfhydryl groups in critical cysteine residues of Keap1 and subsequent prevention of the E3 ligase activity of the Cul3–Keap1 complex, but such electrophilic compounds lack selectivity and may be associated with target toxicity (Abed et al. 2015; Ishi et al. 2000; Feng et al. 2017). In addition, some activators of Nrf2 including many natural products (e.g., sulforaphane, curcumin, and epigallocatechin gallate from natural sources such as fruits, vegetables, and tea products) and synthetic compounds (e.g., oltipraz, anethole dithiolethione, and bardoxolone methyl), have been reported as direct inhibitors of the protein–protein interaction (PPI) between Keap1 and Nrf2 at the ETGE motif of Nrf2. In this case, an inhibitor would occupy the site on Keap1's Kelch domain where the ETGE motif of Nrf2 is bound, which is distal from the binding site of known electrophilic activators (Atul et al. 2015; Hu et al. 2013; Thomas et al. 2016).

In the present paper, all synthesized small molecules cannot be expected to modify sulfhydryl groups of cysteine residues in Keap1 protein because of the absence of reactive functional groups. Moreover, directly inhibitor targeting PPI has been an emerging strategy to selectively and effectively activate Nrf2. In order to develop new direct PPI inhibitors and clarify the binding interaction of the most active analogs, molecular docking study was performed in Sybyl 2.0 software (Tripos Associates, St. Louis, MO, USA). The most active compound **8h** was selected for docking study. We docked **8h** to the Nrf2 peptide binding site in Keap1 Kelch domain starting from the cocrystal structure of Keap1 Kelch domain with the 16mer Nrf2 peptide (PDB code: 2FLU); Fig. 2a showed a representative binding pose of **8h** in the site of Keap1 Kelch domain, Fig. 2b depicted the overlay of **8h** to Keap1 and major interactions between Keap1 and the ligand. Based on this model, the hydroxyl group, carbonyl group, and fluorine atom of **8h** form three hydrogen bonds with Val 463, Val 512, and Val606, respectively. The existence of hydrogen bonds is conducive to the stability of small molecules bound to protein.

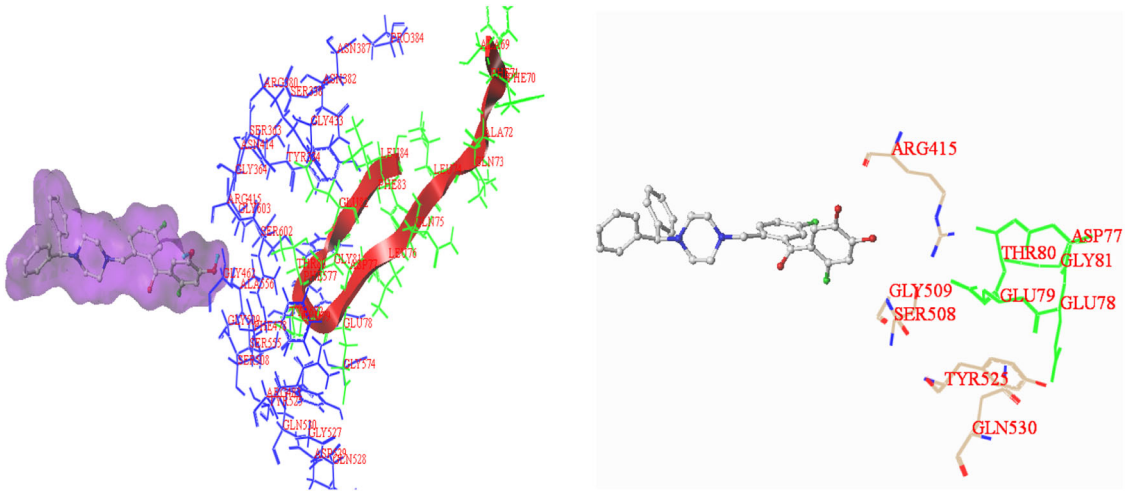
Nrf2 binds to the bottom surface of Keap1 Kelch (shown in Fig. 3a), and the connection site is the active site. When small molecules reach and affect the binding of the active sites, the affinity will be weakened, and then Nrf2 gets off from the active sites into the nucleus to complete the mission of protein expression. Nrf2 being rich in basic residues, possesses a tight four-residue β hairpin conformation comprised of the residues Asp-77, Glu-78, Glu-79, Thr-80, Gly-81 (Thomas et al. 2016). The side chain of Glu-79 is wedged between Arg-415 and Ser-508. Arg-415 has a unique feature which adopts an unusual left-handed helical conformation (58°, 49°), and potentially interacts with Glu-79, which is one of critical functional residues in the Keap1 protein that is essential for its interaction with Nrf2. Compound **8h** occupies a region closed to Arg-415, which may lead to a change in rotamer of Arg-415 (shown in Fig. 3b). The electrostatic interaction of phenol may also interact with amino residues around it, and the presence of acidic groups around the active pocket also favor the detachment of Nrf2.



(A) Top view of **8h** docked to Kelch

(B) Overlay of the **8h** to the Keap1 Kelch

Fig. 2 Docking of **8h** to the Nrf2 binding site of Keap1 Kelch domain. **a** Top view with **8h** (shown in stick model) was colored by element type, bound to Keap1 Kelch domain was shown in interacting Keap1 residues in surface. **b** Overlay of the **8h** to the Keap1 Kelch with purple surface and the yellow dotted lines indicated the hydrogen bonds formed by **8h** and the amino residues, and the amino residues were presented with green color



(A) The Nrf2 binding site of Keap1

(B) Detail of the Nrf2 bound to Keap1

Fig. 3 The direct action mechanism of **8h** on the interaction of Nrf2 and Keap1. **a** The Nrf2-binding site of Keap1 Kelch domain. **8h** was colored by element type with the purple surface. The blue described the residues of Kelch domain and the distance from which to Nrf2 is **5**A, and green represented all the residues of Nrf2. The red ribbon represented Nrf2. **b** Details of the Nrf2 ETGE motif with residues. Asp-77, Glu-78, Glu-79, Thr-80, and Gly-81 were colored by green. Arg-415, Gly-509, Ser-508, Tyr-525, and Gln-530 belonged to Kelch domain were colored by element type

Conclusion

In this study, 27 novel nitrogenated fluorophenols **6a–6g**, **8a–8k**, **10a–10g**, and **12a–12b** were synthesized and evaluated for their antioxidant property in EA.hy926 cells. Of which, five target compounds **6f**, **8d**, **8f**, **8h**, and **8i** showed the excellent activity with EC_{50} values ranging from 0.82 to 6.71 μM. Moreover, the preferable water solubility and forming salt possibility of the most active **8h** contributes to its druggability in future. Docking study of **8h** with key protein Keap1 exhibited significant binding affinity in the active site of Keap1's Kelch domain. This study introduced a class of fluorophenols containing nitrogenated heterocycles for the development of novel Keap1-Nrf2 PPI

inhibitors. Combining with our former studies, it has been suggested that Keap1-Kelch is a most potential target protein for such class of halophenols.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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