

Supplementary Information

Structure-guided optimisation of fenofibrate-derived oxidative phosphorylation inhibitors modify tumour hypoxia

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Materials and Methods

Cell culture

All cell lines were from the American Type Culture Collection (ATCC). STR profiling (DNA Diagnostics Centre, UK) and mycoplasma testing (Lonza) are conducted routinely for these cell lines. Cells were cultured at 37C with 5% CO₂ in Dulbecco's modified Eagle's medium (DMEM, Sigma) supplemented with 10% foetal bovine serum (FBS, Lonza) and 1% Penicillin-Streptomycin (PenStrep, Sigma).

OCR Seahorse Assays

The oxygen consumption rate (OCR) was measured using an automated Seahorse XF96 Analyzer (Agilent). For fenofibrate (**1**) (Sigma) dose response curves, cell culture media of cells seeded in 96-well XF Cell Culture plates (Agilent) was replaced with pre-warmed Seahorse Assay Medium (Agilent) with 5mM glucose (Sigma), 5mM sodium pyruvate (Sigma) and 4mM L-glutamine (Sigma) to a final pH of 7.4; the mixture and placed in a non-CO₂ incubator for 40-60 minutes prior to assay. Following three baseline measurements, port injections of fenofibrate (**1**) were conducted at varying concentrations and measurements are recorded for up to 2.5 hours. For screening derivative compounds, HCT116 or FaDu cells are treated for 24 hours with respective compounds prior to replacing medium with pre-warmed Seahorse Assay Medium formulated as aforementioned and placed in a non-CO₂ incubator for 40-60 minutes before taking an average of three OCR measurements. Immediately after all assays, the cell plates are fixed with 4% aqueous paraformaldehyde (PFA_{aq}), a nuclear stain was conducted with 1 µg/mL Hoechst 33258 (Sigma) and cells were counted by fluorescent images taken with Celigo Imaging Cytometer (Nexcelom Bioscience).

For complex I and II dependant respiration assays, HCT116 cells were seeded in 96-well XF Cell Culture plates (Agilent) overnight. Cell culture media was replaced with 3X MAS buffer, supplemented with 4mM adenosine 5-diphosphate (Sigma, #01905), and 1nM XF PMP (Agilent, #102504-100) either 10mM pyruvic acid (Sigma, #107360), 1mM malic acid (Sigma, #240176) for complex I dependant respiration or 10mM succinate acid (Sigma, #S9512) and 2µM rotenone (Sigma, #R8875) for complex II dependant respiration as previously described.⁽¹⁾ Following three baseline measurements, port injections of test compounds or known inhibitors were conducted. Fenofibrate (**1**), fenofibric acid (**2**) (Sigma) and derivative compounds are injected at 30µM. The known inhibitors used for the assay were 2µM rotenone for complex I, 800µM 2-thenoyltrifluoroacetone (TTFA) (Cayman chemical company,

#15517) for complex II, 2 μ M antimycin A (Sigma, #A8674) for complex III and 2 μ M oligomycin (Sigma, # 75351) for complex V.

Clonogenic assays

Cells were plated as single cells in 6-well plates, where seeding densities were optimised for each cell line; increasing cell numbers were used for higher ionising radiation (IR) doses to account for cell death. Following treatment with fenofibrate (**1**), cells were irradiated in a Cs-137 irradiator (GSR D1 from Gamma Service; dose rate 1.2 Gy/min) and colonies were grown for 8 to 14 days, stained with crystal violet, and counted using the Gelcount automated colony counter (Oxford Optronics). The plating efficiency (PE = average colony number/cells plated) and the surviving fraction ($SF = PE_{IR\ Dose}/PE_{0\ Gy}$) at a given IR dose was calculated. Survival data were fitted according to a linear quadratic equation.

Spheroid Assays

FaDu spheroids were grown using the liquid overlay technique, and HCT116 and H1299 spheroids were grown in Ultra Low Attachment U-bottom plates (Grenier Bio-One, #650970). Cells were seeded high-glucose (4g/L) DMEM (10% FBS 1% PenStrep) and grown until they reached an average diameter of 550-650 μ m, which was confirmed and recorded with a GelCount Colony Counter (Oxford Optronix). After treatments, spheroids are incubated in 200 μ M EF5 (Merk Millipore, #152721-37-4) for 6 hours and fixed in 4% PFA_{aq} overnight at 4°C prior to cryoprotecting spheroids in 30 % sucrose for a minimum of 2.5 hours at 4°C. Spheroids were embedded in O.C.T. Compound (VWR, TissueTek) and stored in -80°C freezer until sectioning and staining.

Immunohistochemistry

All sectioning was conducted using a cryostat (Leica Biosystems) at -22°C. Spheroid sections were taken at 5 μ m and stored in -20°C until processed. Sections were hydrated in 1 x PBS, 0.3% Tween 20 (Sigma) (1 x PBST), blocked with TNB blocking reagent (PerkinElmer, #FP1020) for 60 minutes, washed with 1 x PBST and incubated with 70 μ L of 66 μ g/mL anti-EF5 488 antibody (Merck Millipore, #EF5010 or #EF5012) overnight at 4°C. Samples were washed 3 times with 1 x PBST, incubated in 1 μ g/mL Hoechst 33258 for 5 minutes and mounted on slides with ProLong Diamond Antifade (Life Technologies). Slides were imaged using fluorescence microscopy (Nikon 90i, Nikon) and analysed with Imaris Microscopy

Image Analysis Software (Oxford Instruments). For spheroid analyses, the Imaris cell detection function was applied to outline spheroids, where spheroid areas were classified as cells and hypoxic cores classified as nuclei. Samples that were folded, broken, and deformed were excluded from analysis. For all images, the same look up table (LUT) settings were applied to all fluorescent channels for each experiment.

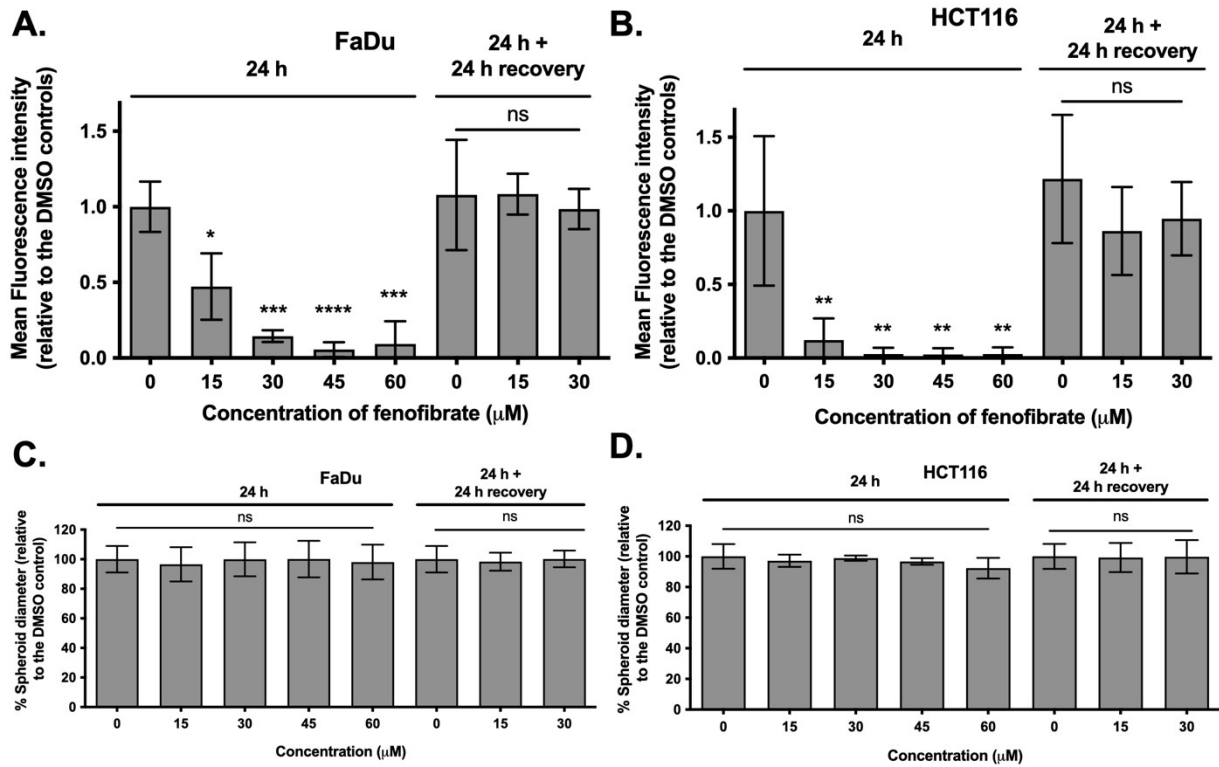
The following formula was used where S represents individual spheroids.

Mean EF5 fluorescence intensity relative to control:

$$\frac{\text{Average}_{\text{Treatment}} \left(\frac{(\text{Area of EF5} \times \text{EF5 intensity per S})}{(\text{Total area per S})} \right)}{\text{Average}_{\text{Control}} \left(\frac{(\text{Area of EF5} \times \text{EF5 intensity per S})}{(\text{Total area per S})} \right)} \times 100\%$$

Statistical Analysis

Statistical analysis was performed with Prism 10 software (GraphPad Software Inc.). All values are presented as mean \pm s.d. Two-way ANOVAs with Bonferroni post-hoc correction were used on clonogenic survival curve analysis. For all other experiments, one-way ANOVAs were performed to assess statistical significance with Bonferroni post-hoc correction. P values < 0.05 were considered significant. All *in vitro* experiments were repeated between 2-4 times as indicated. The linear quadratic model, $S = \exp(\alpha D - \beta D^2)$, was used to fit clonogenic survival graphs, with S denoting survival and D the IR dose in Gy. GraphPad Prism (RRID:SCR_000306) was used for all statistical calculations and curve fitting.

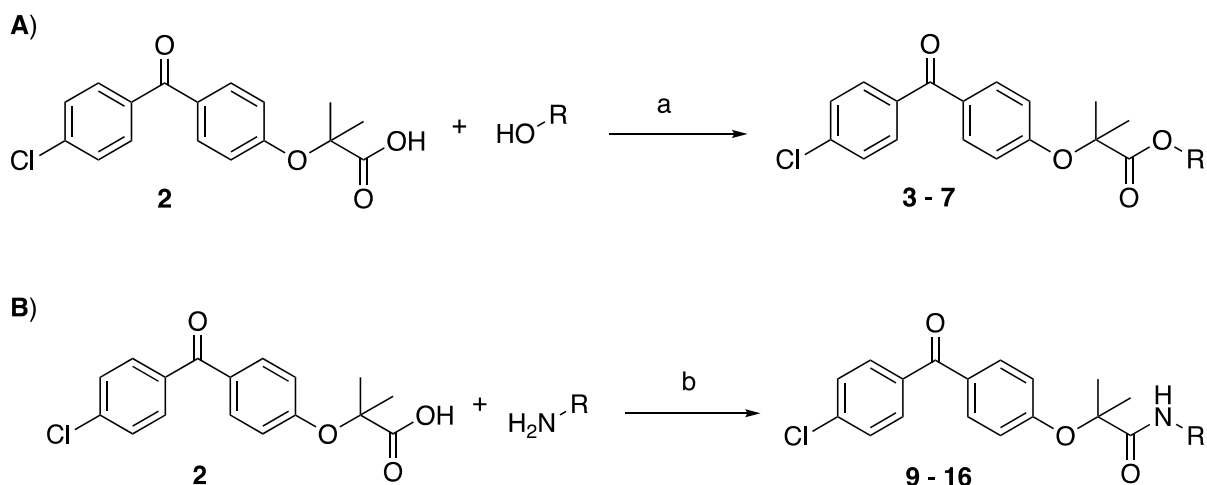


Supporting Figure S1. Fenofibrate (1) alleviates spheroid hypoxia without affecting spheroid size

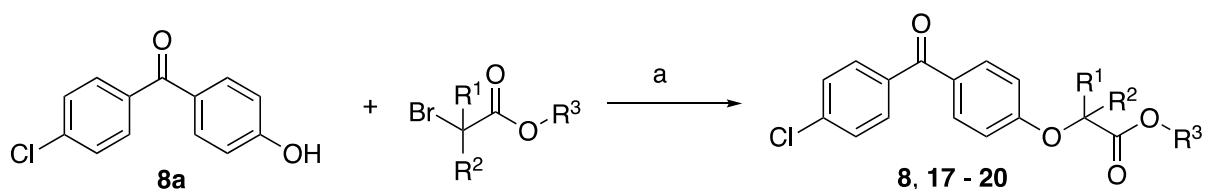
- (A) Mean EF5 fluorescence intensity relative to DMSO controls of FaDu spheroids treated with DMSO or fenofibrate (1) either for 24 hours, or for 24 hours followed by recovery for 24 hours in drug-free medium, as indicated.
- (B) Same as (A) with HCT116 spheroids.
- (C) Percent spheroid diameter relative to DMSO control in FaDu spheroids from (A).
- (D) Percent spheroid diameter relative to DMSO control in FaDu spheroids from (B).

Data corresponds to an average \pm SD from three independent experiments. One-way ANOVA with Bonferroni was performed for all the experiments (n.s. not significant, **** $P < 0.0001$, *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$).

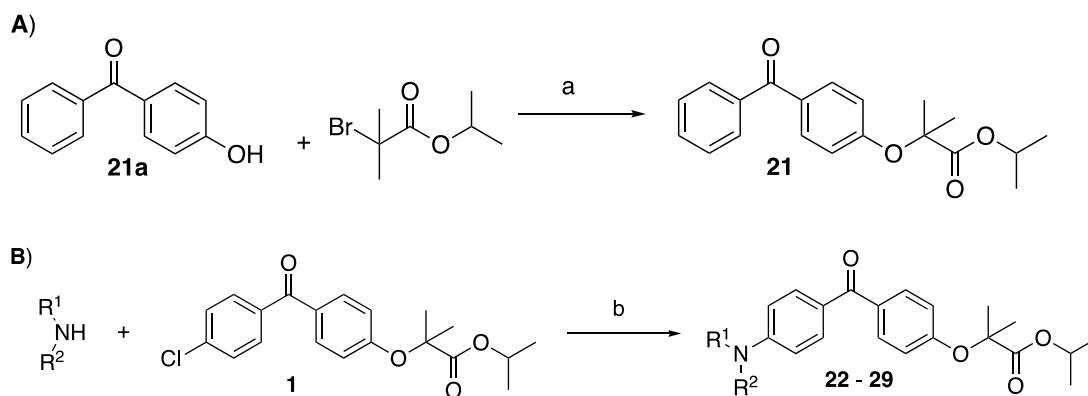
Synthetic Routes



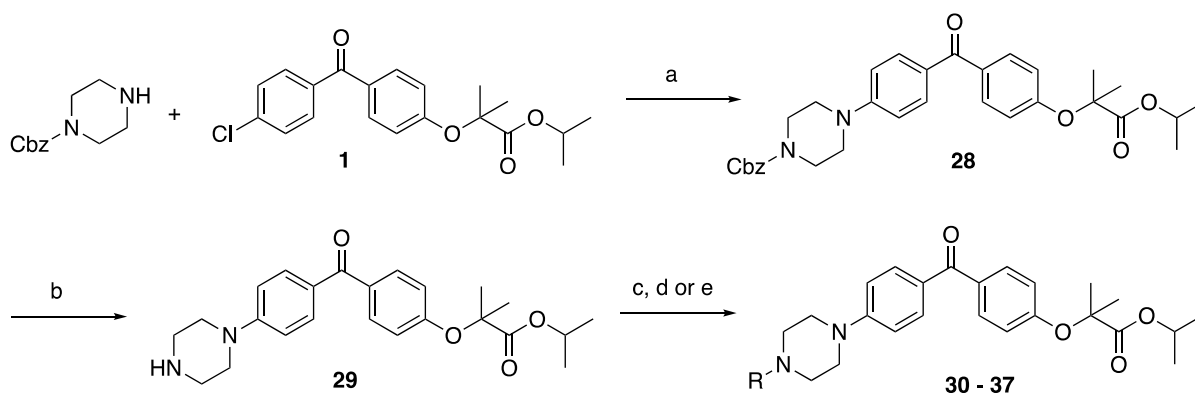
Supporting Figure S2. Synthesis of derivatives 3-7 and 9-16. SAR series investigating the isopropyl group (Region 1 of fenofibrate (1))^{a,b}. A) Compounds 3-7, were prepared in one step from fenofibric acid (2) using the coupling reagent COMU and the corresponding alcohol (yields: 22% - 63%). B) The amides (9 - 16) were synthesised using the coupling reagent HATU and the corresponding amine (yields: 33% - 89%). ^a Reagents and conditions: (a) COMU, DIPEA, DMF, rt, 22 - 63%; (b) HATU, DIPEA, DMF, rt, 33 - 89%. ^b Chemical structures of R groups are shown in Table 1.



Supporting Figure S3. Synthesis of derivatives 8, 17-20. SAR series investigating the role of the dimethyl group (Region 2 of fenofibrate (1))^{a,b}. Compounds 8, 17-20 were synthesised in one step *via* an S_N2 reaction using the commercially sourced (4-chlorophenyl)(4-hydroxyphenyl)methanone (8a) with the corresponding α -halo carbonyl (yields: 16% - 94%). ^a Reagents and conditions: (a) Cs₂CO₃, DMAc, 80°C, 16 - 94%. ^b Chemical structures of R groups are shown in Table 2.

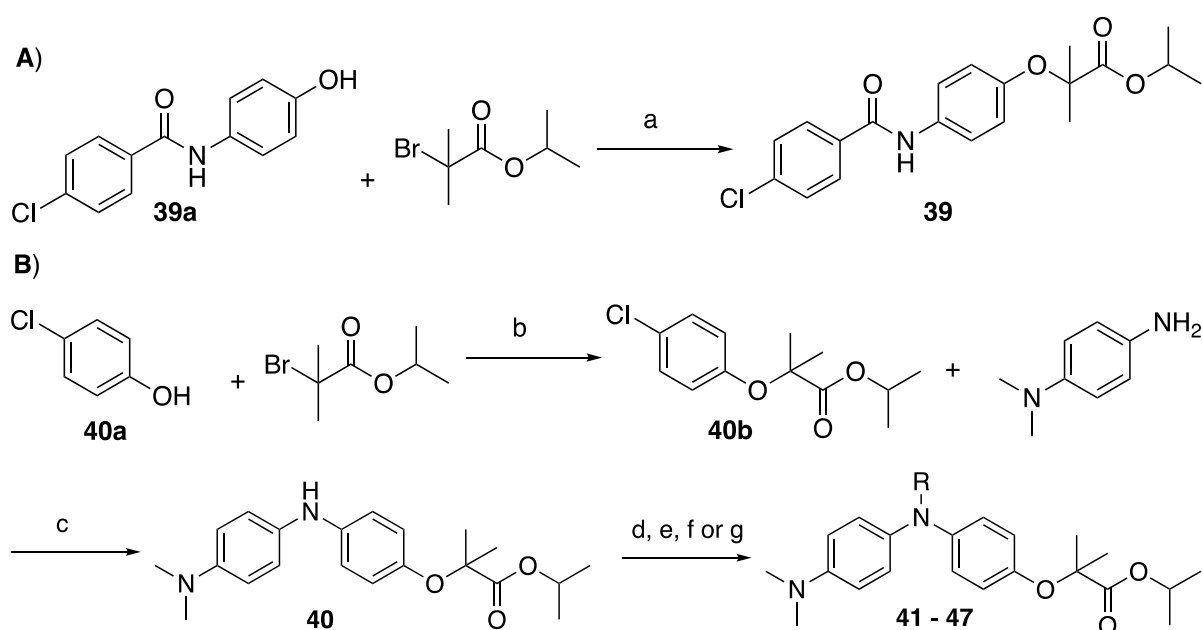


Supporting Figure S4. Synthesis of derivatives 21-28. Initial SAR series investigating the chloro group (Region 3 of fenofibrate (1))^{a,b}. **A)** **21** was synthesized in one step *via* an S_N2 reaction using commercially sourced (4-chlorophenyl) (4-hydroxyphenyl) methanone (**21a**) and isopropyl 2-bromo-2-methylpropanoate (yield 16%). **B)** Compounds **22-28** were prepared in one step *via* a palladium catalysed amination with **1**. The corresponding amine and specific ligand depending on whether a 1° or 2° amine was used, i.e. Brettphos for primary amines and RuPhos for secondary amines (yields: 17% - 86%). ^a Reagents and conditions: (a) Cs_2CO_3 , DMAc, 80°C, 25%; (b) Pd Ligand (BrettPhos for 1° amines and RuPhos for 2° amines), Cs_2CO_3 , ^tBuOH, 80°C, 17 - 86%. ^b Chemical structures of R groups are shown in Table 3.



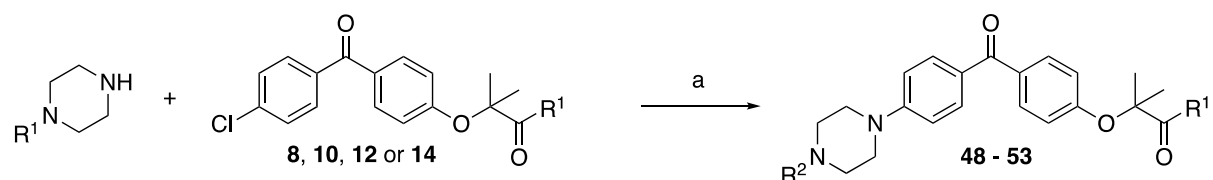
Supporting Figure S5. Synthesis of derivatives 29-37. SAR series investigating the role of the group off the N-1 piperazine of compound 28 (Region 3 of fenofibrate (1))^{a,b}. Compounds **29 – 37** were prepared in three steps. **28** was prepared *via* a palladium catalysed amination with the commercially available **1** and benzyl piperazine-1-carboxylate. **28** underwent a palladium catalysed hydrogenation to the corresponding secondary amine **29**. The final step varied dependent on which functional group was used. The tertiary amines, **30** and **31**, were prepared *via* a reductive amination using sodium borohydride and the corresponding

aldehyde (yield 45% and 37% respectively). The amide derivatives, **32-35**, were prepared using the coupling reagent HATU and the corresponding carboxylic acid (yields: 56% - 63%). The urea derivatives, **36** and **37**, were prepared using the corresponding isocyanate (66% and 72% respectively).^a Reagents and conditions: (a) RuPhos Pd G3, Cs₂CO₃, ^tBuOH, 80°C, 34%; (b) H₂, Pd/C, MeOH, rt, 86%; (c) HATU, DIPEA, DMF, rt, 56 - 68%; (d) aldehyde, NaBH(OAc)₃, CH₂Cl₂, rt, 16hr, 46%; (e) isocyanate, DIPEA, DMAc, rt, 16hr, 36 - 71%. ^b Chemical structures of R groups are shown in Table 4.

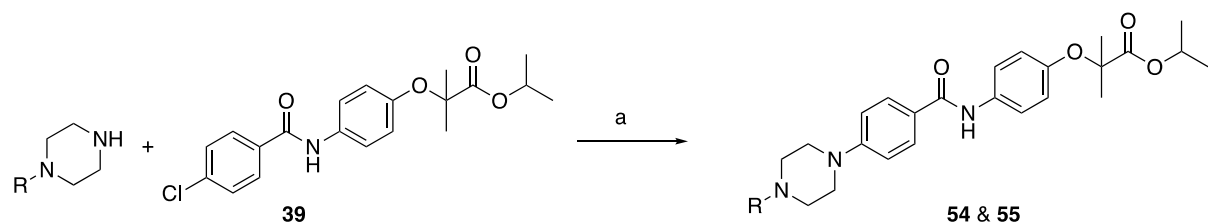


Supporting Figure S6. Synthesis of Compounds 39–47. SAR series investigating the role of the ketone (Region 4 of fenofibrate (1))^{a,b}. **A)** The amide derivative **39** was prepared via S_N2 reaction with the commercially available **39a** and isopropyl 2-bromo-2-methylpropanoate (yield 56%). **B)** **40** was prepared in 2 steps from commercially sourced 4-chlorophenol (**40a**). Etherification of **40a** with the isopropyl 2-bromo-2-methylpropanoate to give **40b** (yield 76%). A palladium catalysed amination with *N,N*-dimethylbenzene-1,4-diamine gave **40** (yield 65%). The final step for **41–47** varied depending on the functional group. The tertiary amine derivatives, **41–44**, were synthesised via a reductive amination of **40** with the corresponding aldehyde (yields: 42% – 71%). **44** was prepared via a palladium catalysed amination with ethyl 6-chloronicotinate and **40** (27%). The amide derivative **45** was prepared with using acetyl chloride (76%). The urea derivatives, **46** and **47**, were prepared using the corresponding isocyanate with **40** (yield 15% and 19% respectively). **38** was from Santa Cruz Biotechnology. ^a Reagents and conditions: (a) Cs₂CO₃, DMAc, 80°C, 56%; (b) Cs₂CO₃, DMAc, 80°C, 76%;

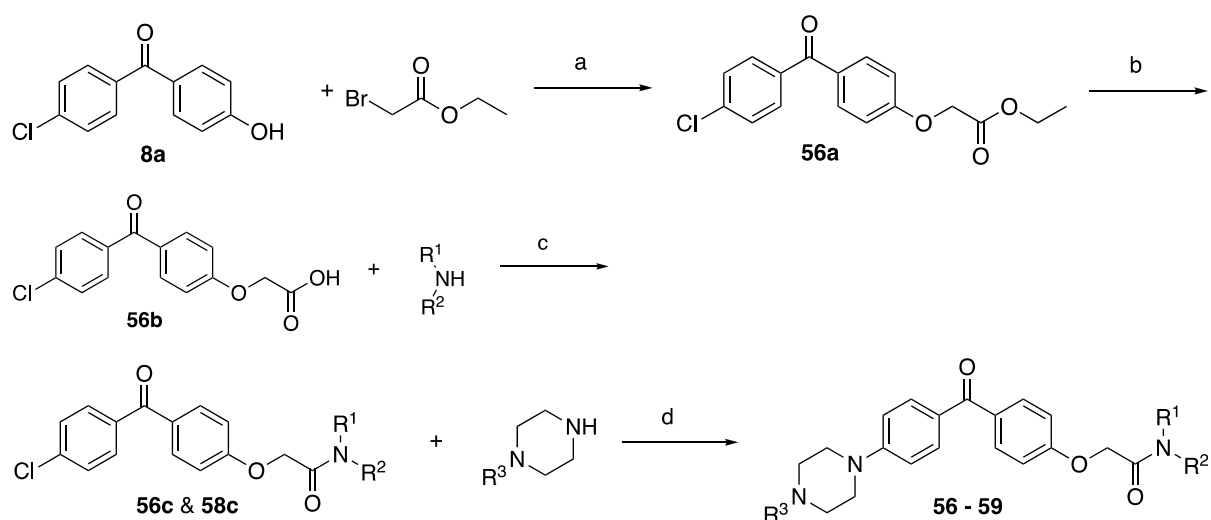
(c) BrettPhos Pd G3, Cs₂CO₃, ^tBuOH, 65%; (d) aldehyde, NaBH(OAc)₃, CH₂Cl₂, rt, 16hr, 42 - 71%; (e) RuPhos Pd G3, Cs₂CO₃, ^tBuOH, 80°C, 27%; (f) AcCl, DIPEA (76%); (g) Isocyanate, DIPEA, DMAc, rt, 16hr, 15 and 19%. ^b Chemical structures of R groups are shown in Table 5.



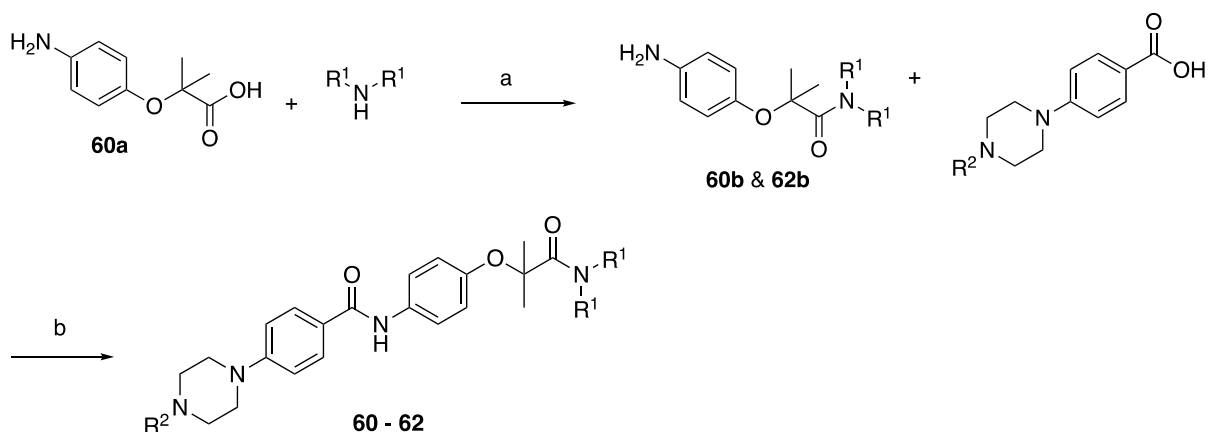
Supporting Figure S7. Synthesis of derivatives 48–53. SAR series investigating the combination of regions 1 and 3 of fenofibrate (1)^{a,b}. The corresponding ketone (8) or amide (10, 12 or 14) derivatives were used. Compounds 48–53 were synthesised *via* a palladium catalysed amination using RuPhos Pd G3 and the corresponding substituted piperazine derivative to give the target compounds (yields ranging from 34% - 58%). ^a Reagents and conditions: (a) RuPhos Pd G3, Cs₂CO₃, ^tBuOH, 80°C, 34% - 58%. ^b Chemical structures of R groups are shown in Table 6.



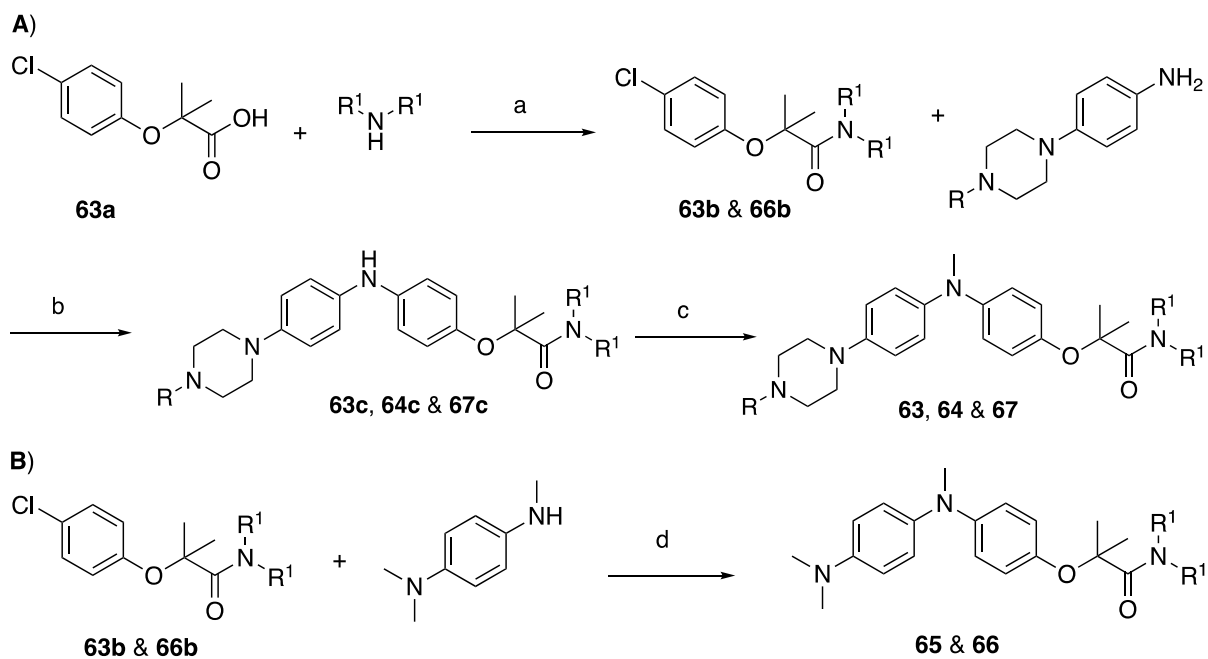
Supporting Figure S8. Synthesis of derivatives 54 and 55. SAR series investigating the combination of regions 3 and 4 of fenofibrate (1)^{a,b}. Compounds 54 and 55 were prepared in one step from t amide 39 *via* the palladium catalysed amination using RuPhos Pd G3 and the corresponding substituted piperazine (yield 31% and 15% respectively). ^a Reagents and conditions: (a) RuPhos Pd G3, Cs₂CO₃, ^tBuOH, 80°C, 15 and 31%. ^b Chemical structures of R groups are shown in Table 6.



Supporting Figure S9. Synthesis of 56–59. SAR series investigating the combination of regions 1, 2 and 3 of fenofibrate (1)^{a,b}. Compounds **56–59** were prepared in three steps from commercially-sourced (4-chlorophenyl) (4-hydroxyphenyl)methanone (**8a**). S_N2 addition with ethyl 2-bromoacetate gave **56a**. Base catalysed ester hydrolysis with lithium hydroxide gave the carboxylic acid **56b**. Amide coupling using HATU and the corresponding amine to give the amides **56c** and **58c** (yield 54% and 63% respectively). Introduction of the corresponding substituted piperazine using a palladium catalysed amination gave target compounds **56–59** (yields: 24% – 35%). ^a Reagents and conditions: (a) Cs₂CO₃, DMAc, 80°C, 75%; (b) LiOH, THF: H₂O (10:1), rt, 89%; (c) HATU, DIPEA, DMAc, rt, 54% and 63%; (d) RuPhosPdG3, Cs₂CO₃, ^tBuOH, 80°C, 24% - 35%. ^b Chemical structures of R groups are shown in Table 6.



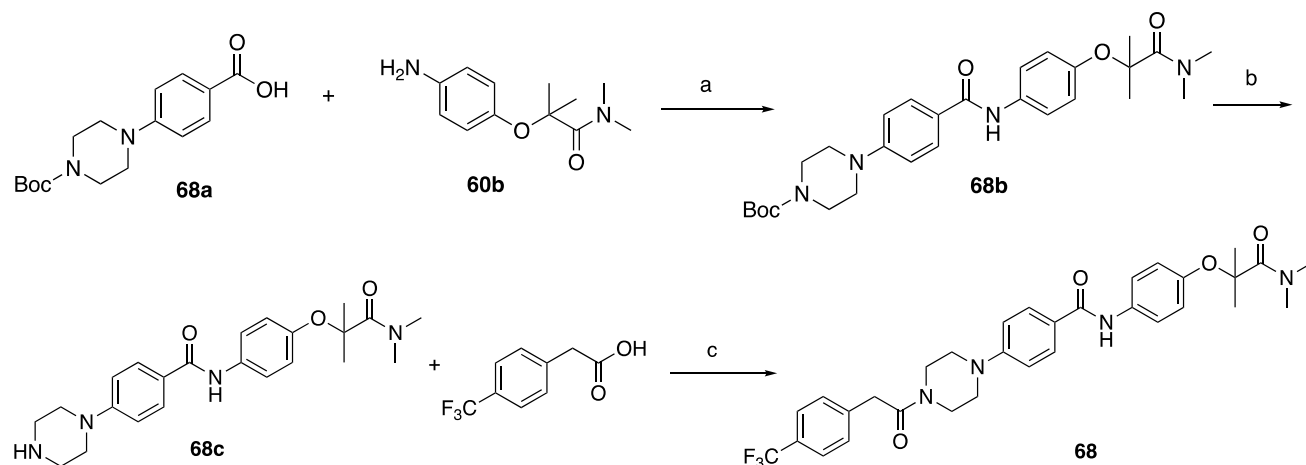
Supporting Figure S10. Synthesis of derivatives 60-62. SAR series investigating combination of regions 1, 3 and 4 of fenofibrate (1): amide analogues. ^{a,b} Compounds **60-62** were prepared in two steps from the commercially sourced 2-(4-aminophenoxy)-2-methylpropanoic acid (**60a**). Amide coupling of **60a** using the coupling agent HATU and the corresponding amines gave **60b** and **62b** (yield 55% and 67% respectively). An additional amide coupling of the corresponding 4-(piperazin-1-yl) benzoic acid gave the targeted compounds **60-62** (yields: 34% - 41%). ^a Reagents and conditions: (a) HATU, DIPEA, DMAc, rt, 55 and 67%; (b) HATU, DIPEA, DMAc, rt, 34 - 41%. ^b Chemical structures of R groups are shown in Table 6.



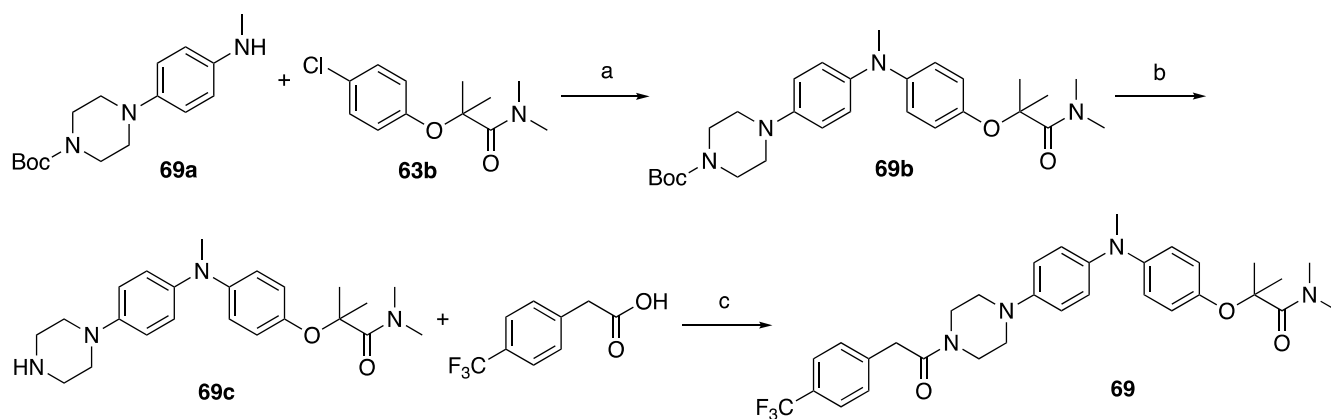
Supporting Figure S11. Synthesis of derivatives 63-67. SAR series investigating the combination of region 1, 3 and 4 of fenofibrate (1): tertiary amine analogues. ^{a,b} **A)**

Compounds **63**, **64** and **67** were prepared in three steps from the commercially sourced Clofibric acid **63a**. An amide coupling of **63a** was carried out using HATU and the corresponding amines to give the amides **63b** and **66b**. Followed by a palladium amination with either **63b** or **66b** and the corresponding 4-(piperazin-1-yl) aniline gave the secondary amines intermediates **63c**, **64c** and **67c** (yields: 49% - 64%). Conversion to the tertiary amine was *via* a reductive amination using formaldehyde and sodium triacetoxyborohydride to give **63**, **64** and **67** (yields: 34% – 62%). **B)** Compounds **65** and **66** were prepared via an additional step using commercially available *N*¹, *N*¹, *N*⁴-trimethylbenzene-1,4-diamine, which was coupled with either **63b** or **66b** *via* palladium catalysed amination to give target compounds (yields 37 % and 56% respectively).

^a Reagents and conditions: (a) HATU, DIPEA, DMAc, rt, 84% and 68%; (b) BrettPhosPdG3, Cs₂CO₃, ^tBuOH, 80°C, 49% - 64%; (c) formaldehyde, NaBH(OAc)₃, CH₂Cl₂, 50°C, 16hr, 34% - 62%; (d) RuPhosPdG3, Cs₂CO₃, ^tBuOH, 80°C, 37% and 56%. ^b Chemical structures of R groups are shown in Table 6.



Supporting Figure S12. Synthesis of 68^a. Compound **68** were prepared in three steps from the commercially sourced 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid **68a**. Amide coupling with **60b** using HATU gave **68b**. Acid catalysed Boc deprotection gave **68c**. Amide coupling with 2-(4-(trifluoromethyl)phenyl)acetic acid using HATU gave the target compound **68** (yield 35%). ^a Reagents and conditions: (a) HATU, DIPEA, DMAc, rt, 45%; (b) trifluoroacetic acid, CH₂Cl₂, 3hr, rt, 94%; (c) HATU, DIPEA, DMF, rt, 35%.



Supporting Figure S13. Synthesis of derivative 69^a. Compound **69** were prepared in three steps from the commercially sourced *tert*-butyl 4-(4-(methylamino)phenyl)piperazine-1-carboxylate **69a** (yield 64%). Palladium coupling amination with **63b** gave **69b** (yield 86%). Acid catalysed Boc deprotection gave **69c**. Amide coupling with 2-(4-(trifluoromethyl)phenyl)acetic acid using HATU gave the target compound **69** (yield 32%).^a Reagents and conditions: (a) RuPhos Pd G3, Cs₂CO₃, ^tBuOH, 80°C, 64%; (b) trifluoroacetic acid, CH₂Cl₂, 3hr, rt, 86%; (c) HATU, DIPEA, DMF, rt, 32%.

General Synthesis Information

All reagents were purchased from commercial sources (Sigma-Aldrich, Inc.; Fluorochem Ltd; Tokyo Chemical Industries) and were used as received. Anhydrous solvents (Sigma-Aldrich, Inc.) were kept under an atmosphere of nitrogen. Purifications were performed using a Biotage Isolera One purification machine or a Biotage Selekt purification machine (wavelengths monitored: 254 and 280 nm) equipped with pre-packed Biotage® Sfar Duo flash chromatography cartridges. The cartridge type and size as well as solvent gradients (in column volumes, CV) used, are specified in the individual experimental procedures. HPLC grade solvents (Sigma-Aldrich Inc.) were used for purifications, reaction workups, and extractions.

Thin layer chromatography (TLC) was carried out using Merck silica gel 60 F254 TLC plates and visualized using UV light. Melting points (m.p.) were determined using a Stuart SMP-40 automated melting point apparatus. Infrared (IR) spectroscopy was performed using a Bruker Tensor-27 Fourier transform infrared (FT-IR) spectrometer. High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) mass spectrometry (MS) in the positive or negative ionization mode employing a Thermo Scientific Exactive mass spectrometer (ThermoFisher Scientific); data are presented as a mass-to-charge ratio (m/z).

Nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker AVANCE AVIIIHD 600 machine equipped with a 5 mm BB-F/1H Prodigy N₂ cryoprobe. Chemical shifts for ¹H NMR are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual protium in the NMR solvent (CDCl₃: δ = 7.26 ppm; DMSO-*d*₆: δ = 2.50 ppm). For ¹³C NMR, chemical shifts are reported in the scale relative to the NMR solvent (CDCl₃: δ = 77.2 ppm; DMSO-*d*₆: δ = 39.5 ppm). For ¹⁹F NMR, chemical shifts are reported relative to CFCl₃. NMR data are reported as follows: chemical shift, multiplicity (s: singlet, d:

doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (J , Hz; accurate to 0.5 Hz), and integration. All compounds are >95% pure by NMR.

General Synthetic Procedures

General Procedure A – Amide Coupling

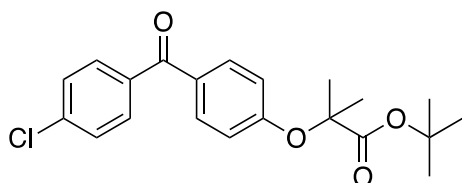
The carboxylic acid (1 equiv.) and *N,N*-diisopropylethylamine (DIPEA) (2.5 equiv.) were dissolved in *N,N*-dimethylacetamide (DMAc) (0.1 M), followed by the addition of propylphosphonic anhydride solution (T3P, 2 equiv., unless another amide coupling agent is stated). The resultant reaction mixture was stirred at room temperature for 30 mins, when the amine (1.2 equiv) was added. The resultant mixture was stirred overnight at room temperature. Water (200 mL) was then added, and the mixture was extracted with ethyl acetate (EtOAc) (3 x 30 mL). The organic fractions were combined, washed with brine, and dried with anhydrous sodium sulfate (Na_2SO_4). The crude compound was then purified using flash column chromatography using over 20 column volumes to give the desired compound .

General Procedure B – Pd-catalysed Amination

The aryl halide (1 equiv), amine (1.2 equiv), caesium carbonate (Cs_2CO_3 , 2 equiv), Pd-ligand conjugate (0.1 equiv) were added to a dried microwave vial. The resultant mixture was flushed with N_2 which was removed under vacuum; the procedure was repeated 3 times. The reaction mixture was dissolved in an anhydrous solvent (0.1 M) and heated 16 h at 80°C in a sandbath. The reaction mixture was allowed to cool to room temperature. Water (200 mL) was then added and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined then washed with brine and dried with anhydrous Na_2SO_4 . The crude mixture was then purified using flash column chromatography to give the desired compound.

Synthetic Procedures and Compound Characterisations

Tert-Butyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate – (4)

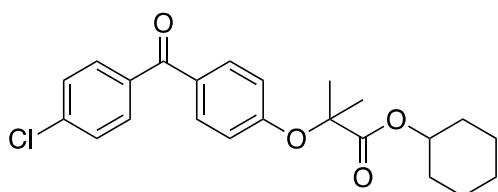


Fenofibric acid (**2**) (100 mg, 0.314 mmol), di-*tert*-butyl dicarbonate (101 mg, 0.47 mmol) and 4-dimethylaminopyridine (DMAP) (57 mg, 0.47 mmol)

were dissolved in anhydrous *tert*-butanol (3 mL) under N₂. The resultant mixture was stirred at room temperature overnight. Water (30 mL) was then added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 % - 50%, in cyclohexane) over 15 column volumes to give **4** (84 mg, 0.22 mmol, 48%).

¹H NMR (400 MHz, DMSO) δ 7.78 – 7.68 (m, 4H), 7.64 – 7.59 (m, 2H), 6.94 – 6.87 (m, 2H), 1.58 (s, 6H), 1.38 (s, 9H). ¹³C NMR (101 MHz, DMSO) δ 193.22, 171.66, 159.39, 137.00, 136.31, 131.83, 131.14, 129.36, 128.59, 117.01, 81.71, 79.42, 27.31 (3C, C(CH₃)₃), 25.06 (2C, C(CH₃)₂). IR (film): $\tilde{\nu}$ = 1723, 1700 cm⁻¹. HRMS (ESI-TOF) calc'd for C₂₁H₂₄O₄³⁵Cl [M+H]⁺: 375.1358, found: 375.1364.

Cyclohexyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate – (5)

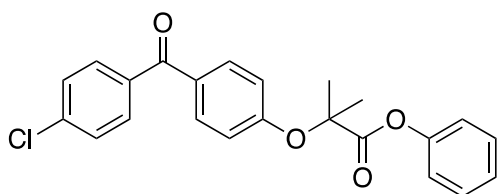


General Procedure A using fenofibric acid (**2**) (100 mg, 0.314 mmol), (1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-

carbenium hexafluorophosphate (COMU) (399 mg, 0.943 mmol), *N,N*-diisopropylethylamine (DIPEA) (116 mg, 0.943 mmol) and cyclohexanol (94 mg, 0.943 mmol) gave **5** (79 mg, 0.197 mmol, 63 %) as a colourless oil.

m.p. 85-92°C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 7.74 – 7.53 (m, 6H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.48 (tq, *J* = 7.0, 3.5 Hz, 1H), 2.05 – 1.41 (m, 16H). **¹³C NMR** (101 MHz, DMSO-*d*₆) δ 193.21, 171.95, 159.28, 157.67, 137.04, 136.25, 131.85, 131.15, 129.49, 128.59, 117.05, 79.13, 73.07, 39.52, 30.60 (2C, (CH₂)₂), 25.10 (2C, C(CH₃)₂), 24.59, 22.81 (2C, (CH₂)₂). **IR** (film): $\tilde{\nu}$ = 1733, 1656, 1597 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₅H₂₆O₄³⁵Cl [M+H]⁺: 401.1514, found : 401.1510.

Phenyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate – (6)

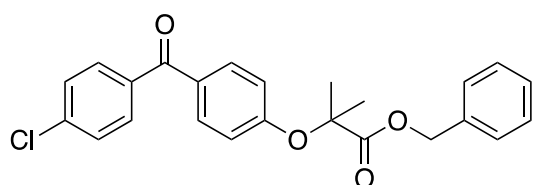


General Procedure A using fenofibric acid (**2**) (100 mg, 0.314 mmol), COMU (399 mg, 0.943 mmol), DIPEA (116 mg, 0.943 mmol) and phenol (90 mg,

0.943 mmol) gave **6** (48 mg, 0.121 mmol, 39 %) as a colourless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 – 7.55 (m, 6H), 7.50 – 7.23 (m, 3H), 7.15 – 7.03 (m, 4H), 1.79 (s, 6H). **¹³C NMR** (101 MHz, DMSO-*d*₆) δ 193.25, 171.70, 158.99, 150.07, 137.08, 136.22, 131.19, 129.67, 128.59, 126.34, 121.40, 117.28, 79.09, 25.09 (2C, C(CH₃)₂). **IR** (film): $\tilde{\nu}$ = 1728, 1651, 1595 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₃H₂₀O₄³⁵Cl [M+H]⁺: 395.1044, found: 395.1042.

Benzyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate – (7)

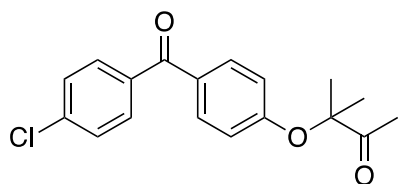


General Procedure A using fenofibric acid (**2**) (100 mg, 0.314 mmol), COMU (399 mg, 0.943 mmol), DIPEA (116 mg, 0.943 mmol) and benzyl

alcohol (101 mg, 0.943 mmol) gave **7** (39 mg, 0.0955 mmol, 31%) as a colourless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.48 (m, 4H), 7.48 – 7.13 (m, 8H), 6.87 – 6.65 (m, 2H), 5.16 (s, 2H), 1.64 (s, 6H). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 194.38, 173.70, 159.81, 138.62, 136.66, 135.40, 132.27, 131.48, 130.58, 129.47, 129.20, 129.08, 128.84, 128.83, 128.79, 128.76, 117.54, 79.72, 67.63, 25.73 (2C, C(CH₃)₂). **IR** (film): $\tilde{\nu}$ = 1730, 1655, 1593 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₄H₂₁O₄³⁵Cl²³Na [M+H]⁺: 431.1015, found: 431.1015.

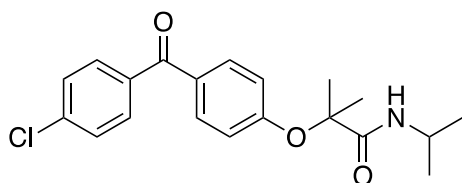
3-(4-(4-Chlorobenzoyl)phenoxy)-3-methylbutan-2-one – (8)



A solution of 4-chlorophenone (426 mg, 1.84 mmol), caesium carbonate (Cs₂CO₃) (994 mg, 3.06 mmol) and *N,N*-dimethylacetamide (DMAc) (10 mL) was prepared; 3-bromo-3-methyl-2-butanone (230 mg, 1.53 mmol) was then added. The resultant mixture was stirred at room temperature overnight. Water (30 mL) was then added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 50%, in cyclohexane) over 15 column volumes to give **8** (308 mg, 0.97 mmol, 53%).

¹H NMR (400 MHz, DMSO) δ 7.78 – 7.67 (m, 4H), 7.64 – 7.58 (m, 2H), 6.92 – 6.84 (m, 2H), 2.24 (s, 3H), 1.52 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 209.66, 193.21, 159.15, 137.11, 136.18, 132.07, 131.23, 129.74, 128.62, 117.38, 84.42, 24.50 (2C, C(CH₃)₂), 23.66. **IR** (film): $\tilde{\nu}$ = 1774, 1691 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₁₈H₁₈O₃³⁵Cl [M+H]⁺: 317.0939, found: 317.0941.

2-(4-(4-Chlorobenzoyl)phenoxy)-*N*-isopropyl-2-methylpropanamide – (9)

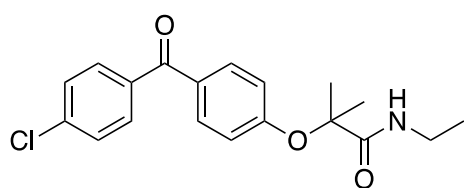


General Procedure A using fenofibric acid (**2**) (80 mg, 0.25 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide

hexafluorophosphate (HATU) (190 mg, 0.50 mmol), DIPEA (258 μ L, 1.50 mmol) and isopropylamine (32 μ L, 0.375 mmol) gave **9** (55 mg, 0.155 mmol, 62%) as a colourless oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 7.84 (d, J = 8.0 Hz, 1H), 7.75 – 7.67 (m, 4H), 7.64 – 7.58 (m, 2H), 6.99 – 6.92 (m, 2H), 3.93 (dhept, J = 8.0, 6.5 Hz, 1H), 1.51 (s, 6H), 1.00 (d, J = 6.5 Hz, 6H). $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 193.25, 171.49, 159.23, 137.00, 136.25, 131.55, 131.11, 129.65, 128.56, 118.23, 80.62, 24.97 (2C, C(CH₃)₂), 21.86 (2C, NH(CH₃)₂). **IR** (film): $\tilde{\nu}$ = 1751, 1696 cm^{-1} . **HRMS** (ESI-TOF) calc'd for C₂₀H₂₃O₃³⁵Cl [M+H]⁺: 360.1361, found: 360.1363.

2-(4-(4-Chlorobenzoyl)phenoxy)-*N*-ethyl-2-methylpropanamide – (10)

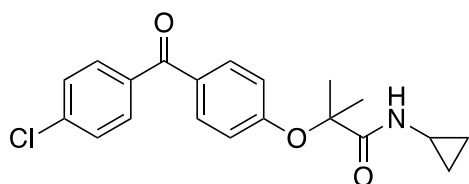


General Procedure A using fenofibric acid (**2**) (250 mg, 0.78 mmol), HATU) 745 mg, 1.96 mmol), DIPEA (386 μ L, 2.34 mmol) and Ethylamine (2M in THF (780 μ L,

1.56 mmol)) gave **10** (219 mg, 0.63 mmol, 81%) as a white solid.

m.p. 137-139°C. $^1\text{H NMR}$ (400 MHz, DMSO-*d*₆) δ 8.16 (t, J = 6.0 Hz, 1H), 7.76 – 7.56 (m, 6H), 7.01 – 6.90 (m, 2H), 3.12 (qd, J = 7.0, 6.0 Hz, 2H), 1.51 (s, 6H), 0.95 (t, J = 7.0 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, DMSO-*d*₆) δ 193.24, 172.28, 159.21, 137.06, 136.22, 131.63, 131.16, 129.69, 128.58, 118.24, 80.65, 33.65, 25.01 (2C, C(CH₃)₂), 14.49. **IR** (film): $\tilde{\nu}$ = 1679, 1649 cm^{-1} . **HRMS** (ESI-TOF) calc'd for C₁₉H₂₁O₃N³⁵Cl [M+H]⁺: 346.1207, found : 346.1207.

2-(4-(4-Chlorobenzoyl)phenoxy)-N-cyclopropyl-2-methylpropanamide – (11)

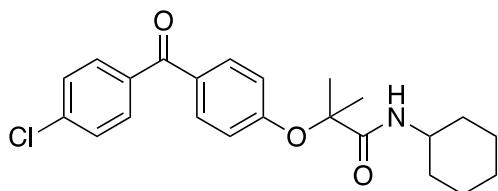


General Procedure A using fenofibric acid (**2**) (80 mg, 0.25 mmol), HATU (190 mg, 0.50 mmol), DIPEA (258 μ L, 1.50 mmol) and cyclopropylamine (26 μ L, 0.375

mmol) gave **11** (38 mg, 0.107 mmol, 43%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 8.13 (d, $J = 4.0$ Hz, 1H), 7.75 – 7.68 (m, 4H), 7.64 – 7.58 (m, 2H), 6.97 – 6.89 (m, 2H), 2.64 (ddt, $J = 11.0, 7.0, 4.0$ Hz, 1H), 1.50 (s, 6H), 0.62 – 0.54 (m, 2H), 0.44 – 0.35 (m, 2H). **¹³C NMR** (101 MHz, DMSO) δ 193.25, 173.90, 159.22, 137.01, 136.24, 131.61, 131.13, 129.66, 128.57, 118.08, 80.53, 24.91(2C, C(CH₃)₂), 22.62, 5.42 (2C, (CH₂)₂). **HRMS** (ESI-TOF) calc'd for C₂₀H₂₁O₃N³⁵Cl [M+H]⁺: 358.1204, found: 358.1206.

2-(4-(4-Chlorobenzoyl)phenoxy)-N-cyclohexyl-2-methylpropanamide – (12)

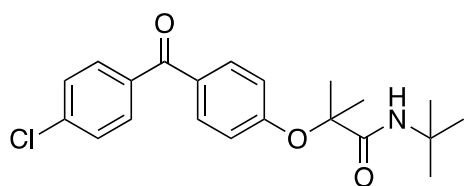


General Procedure A using fenofibric acid (**2**) (250 mg, 0.78 mmol), T3P (623 mg, 1.96 mmol), DIPEA (386 μ L, 2.34 mmol) and cyclohexylamine (178 μ L,

1.56 mmol) gave **12** (278 mg, 0.69 mmol, 89%) as a white solid.

m.p. 137-139°C. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 7.85 (d, $J = 8.0$ Hz, 1H), 7.74 – 7.52 (m, 6H), 7.00 – 6.90 (m, 2H), 3.65 – 3.53 (m, 1H), 1.67 – 1.58 (m, 4H), 1.51 (s, 6H), 1.29 – 0.95 (m, 6H). **¹³C NMR** (101 MHz, DMSO-*d*₆) δ 193.29, 171.49, 159.26, 137.05, 136.27, 131.63, 131.19, 129.59, 128.62, 118.15, 80.62, 47.96, 31.96 (2C, (CH₂)₂), 25.06 (2C, C(CH₃)₂), 24.87 (2C, (CH₂)₂). **IR** (film): $\tilde{\nu} = 3643, 1720, 1650, 1596$ cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₃H₂₇O₃N³⁵Cl [M+H]⁺: 400.1674, found : 400.1674

***N*-(*tert*-Butyl)-2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanamide – (13)**

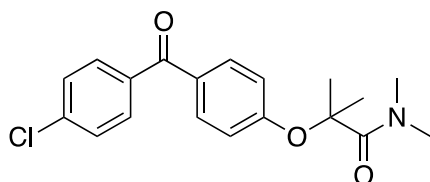


General Procedure A using fenofibric acid (**2**) (80 mg, 0.25 mmol), HATU (190 mg, 0.50 mmol), DIPEA (258 μ L, 1.50 mmol) and *tert*-butylamine (39 μ L, 0.375

mmol) gave **13** (31 mg, 0.0825 mmol, 33%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.75 – 7.67 (m, 4H), 7.63 – 7.57 (m, 2H), 7.19 (s, 1H), 7.02 – 6.95 (m, 2H), 1.51 (s, 6H), 1.24 (s, 9H). **¹³C NMR** (101 MHz, DMSO) δ 193.25, 171.97, 159.12, 137.01, 136.24, 131.57, 131.12, 129.75, 128.56, 118.27, 81.09, 50.43, 28.16 (3C, C(CH₃)₃), 24.86 (2C, C(CH₃)₂). **IR** (film): $\tilde{\nu}$ = 1756, 1694 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₁H₂₅O₃³⁵Cl [M+H]⁺: 374.1517, found: 374.1519.

2-(4-(4-Chlorobenzoyl)phenoxy)-*N,N*,2-trimethylpropanamide – (14)

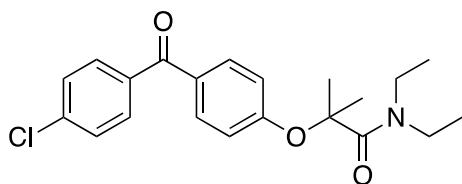


General Procedure A using fenofibric acid (**2**) (80 mg, 0.25 mmol), HATU (190 mg, 0.50 mmol), DIPEA (258 μ L, 1.50 mmol) and dimethylamine (25 μ L, 0.375 mmol)

gave **14** (58 mg, 0.16 mmol, 64%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.77 – 7.68 (m, 4H), 7.64 – 7.57 (m, 2H), 6.95 – 6.87 (m, 2H), 3.04 (s, 3H), 2.84 (s, 3H), 1.61 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 193.14, 171.00, 159.14, 137.01, 136.19, 132.09, 131.15, 129.61, 128.56, 116.30, 81.11, 36.77 (2C, N(CH₃)₂), 25.45 (2C, C(CH₃)₂). **IR** (film): $\tilde{\nu}$ = 1698, 1688 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₁₉H₂₁O₃N³⁵Cl [M+H]⁺: 346.1204, found: 346.1204.

2-(4-(4-Chlorobenzoyl)phenoxy)-*N,N*-diethyl-2-methylpropanamide – (15)

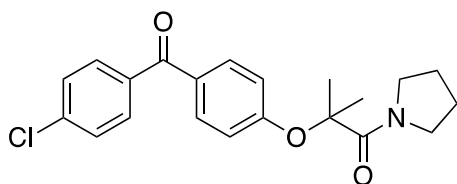


General Procedure A using fenofibric acid (**2**) (80 mg, 0.25 mmol), HATU (190 mg, 0.50 mmol), DIPEA (258 μ L, 1.50 mmol) and diethylamine (39 μ L, 0.375 mmol)

gave **15** (61 mg, 0.162 mmol, 65%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.75 – 7.65 (m, 4H), 7.63 – 7.56 (m, 2H), 6.97 – 6.91 (m, 2H), 3.56 (q, $J = 7.0$ Hz, 2H), 3.27 (q, $J = 7.0$ Hz, 2H), 1.60 (s, 6H), 0.98 (t, $J = 7.0$ Hz, 3H), 0.85 (t, $J = 7.0$ Hz, 3H). **¹³C NMR** (101 MHz, DMSO) δ 193.14, 170.17, 159.33, 137.02, 136.19, 131.91, 131.12, 129.55, 128.56, 116.65, 81.27, 40.82 (2C, CH₂), 25.86 (2C, C(CH₃)₂), 13.53, 12.02. **IR** (film): $\tilde{\nu} = 1698, 1688$ cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₁H₂₅O₃N³⁵Cl [M+H]⁺: 374.1517, found: 374.1517.

2-(4-(4-Chlorobenzoyl)phenoxy)-2-methyl-1-(pyrrolidin-1-yl)propan-1-one – (16)

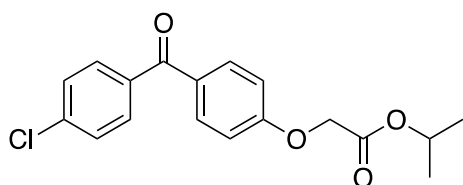


General Procedure A using fenofibric acid (**2**) (80 mg, 0.25 mmol), HATU (190 mg, 0.50 mmol), DIPEA (258 μ L, 1.50 mmol) and pyrrolidine (31 μ L, 0.375 mmol)

gave **16** (52 mg, 0.14 mmol, 56%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.76 – 7.68 (m, 4H), 7.64 – 7.57 (m, 2H), 6.95 – 6.90 (m, 2H), 3.46 – 3.35 (m, 4H), 1.75 – 1.60 (m, 4H), 1.58 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 193.16, 169.97, 159.22, 137.00, 136.21, 132.09, 131.15, 129.60, 128.57, 116.44, 80.86, 47.30, 46.34, 26.39, 24.80 (2C, (CH₃)₂), 22.45. **HRMS** (ESI-TOF) calc'd for C₂₁H₂₃O₃N³⁵Cl [M+H]⁺: 372.1361, found: 372.1363.

Isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)acetate – (17)

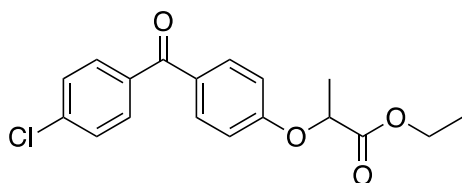


General Procedure A using **56b** (50 mg, 0.172 mmol), COMU (221 mg, 0.517 mmol), DIPEA (88 μ L, 0.517 mmol) and isopropanol (395 μ L, 5.17 mmol) gave **17**

(26 mg, 0.078 mmol, 46%) as a colourless oil.

$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 7.80 – 7.56 (m, 6H), 7.12 – 7.05 (m, 2H), 5.01 (hept, J = 6.0 Hz, 1H), 4.88 (s, 2H), 1.22 (d, J = 6.0 Hz, 6H). **$^{13}\text{C NMR}$** (101 MHz, DMSO- d_6) δ 193.25, 167.75, 161.42, 137.03, 136.30, 132.07, 131.17, 129.64, 128.60, 114.52, 64.85, 62.62, 20.13 (2C, CH(CH $_3$) $_2$). **IR** (film): $\tilde{\nu}$ = 1729, 1654, 1597 cm^{-1} . **HRMS** (ESI-TOF) calc'd for C $_{18}$ H $_{18}$ O $_4$ ^{35}Cl [M+H] $^+$: 333.0888, found : 333.0889.

Ethyl 2-(4-(4-chlorobenzoyl)phenoxy)propanoate – (18)



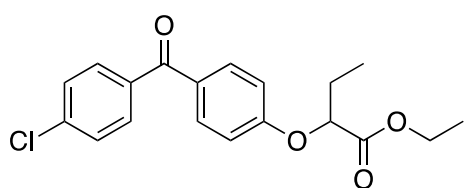
A mixture of (4-chlorophenyl)(4-hydroxyphenyl)methanone (300 mg, 1.29 mmol), Ethyl 2-bromopropanoate (280 mg, 1.55 mmol), Cs $_2$ CO $_3$ (504

mg, 1.55 mmol) and *N,N*-dimethylacetamide (10 mL) was prepared. The resultant mixture was heated at 80°C overnight. Water (30 mL) was then added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na $_2$ SO $_4$) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 25%, in cyclohexane) over 10 column volumes to give **18** (402 mg, 1.21 mmol, 94 %) as a white solid.

m.p. 123-126°C. **$^1\text{H NMR}$** (400 MHz, DMSO- d_6) δ 7.79 – 7.56 (m, 6H), 7.08 – 6.99 (m, 2H), 5.13 (q, J = 6.5 Hz, 1H), 4.18 – 4.13 (q, J = 7.0 Hz, 2H), 1.55 (d, J = 6.5 Hz, 3H), 1.17 (t, J =

7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 193.21, 170.92, 161.04, 137.04, 136.27, 132.14, 131.17, 129.58, 128.60, 128.60, 114.75, 71.74, 61.01, 39.52, 18.10, 13.98. **IR** (film): $\tilde{\nu}$ = 1733, 1653, 1593 cm^{-1} . **HRMS** (ESI-TOF) calc'd for $\text{C}_{18}\text{H}_{18}\text{O}_4^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$: 333.0885, found: 333.0885.

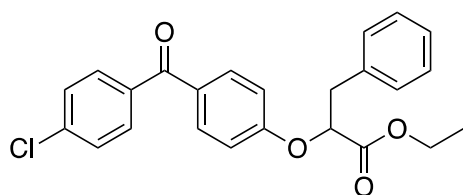
Ethyl 2-(4-(4-chlorobenzoyl)phenoxy)butanoate – (19)



A mixture of (4-chlorophenyl)(4-hydroxy-phenyl) methanone (300 mg, 1.29 mmol), Ethyl 2-bromobutanoate (302 mg, 1.55 mmol), Cs_2CO_3 (504 mg, 1.55 mmol) and *N,N*-dimethylacetamide (10 mL) was prepared. The resultant mixture was heated at 80°C overnight. Water (30 mL) was then, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na_2SO_4) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 % - 25%, in cyclohexane) over 10 column volumes to give **19** (375 mg, 1.08 mmol, 84%) as a white solid.

m.p. 114-116°C. ^1H NMR (400 MHz, DMSO- d_6) δ 7.80 – 7.55 (m, 6H, Ar), 7.07 – 6.99 (m, 2H, Ar), 4.96 (t, J = 7.0, 5.0 Hz, 1H), 4.16 (qt, J = 7.0, 3.5 Hz, 2H), 1.95 (dq, J = 14.5, 7.0 Hz, 2H), 1.18 (t, J = 7.0 Hz, 3H), 1.00 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 193.19, 170.27, 161.35, 137.06, 136.27, 132.15, 131.18, 129.60, 128.58, 114.76, 76.42, 60.93, 39.52, 25.41, 14.03, 9.22. **IR** (film): $\tilde{\nu}$ = 1731, 1656, 1597 cm^{-1} . **HRMS** (ESI-TOF) calc'd for $\text{C}_{19}\text{H}_{20}\text{O}_4^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$: 347.1044, found: 347.1043.

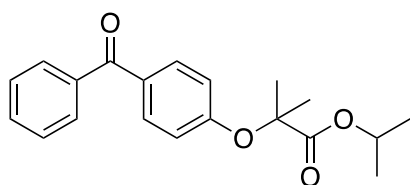
Ethyl 2-(4-(4-chlorobenzoyl)phenoxy)-3-phenylpropanoate – (20)



A mixture of (4-chlorophenyl)(4-hydroxyphenyl)methanone (300 mg, 1.29 mmol), ethyl 2-bromo-3-phenylpropanoate (396 mg, 1.55 mmol), Cs_2CO_3 (504 mg, 1.55 mmol) and *N,N*-dimethylacetamide (10 mL) was prepared. The resultant mixture was heated at 80°C overnight. Water (30 mL) was then added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na_2SO_4) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 25%, in cyclohexane) over 15 column volumes gave **20** (82 mg, 0.20 mmol, 16%) with the colourless oil.

$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 7.74 – 7.55 (m, 6H), 7.37 – 7.18 (m, 5H), 7.07 – 6.98 (m, 2H), 5.27 (t, $J = 7.0, 5.5$ Hz, 1H), 4.10 (d, $J = 7.0$ Hz, 2H), 3.24 (dd, $J = 7.0, 2.0$ Hz, 2H), 1.11 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO}-d_6$) δ 193.24, 169.78, 161.09, 137.08, 136.03, 132.15, 131.21, 128.62, 128.29, 126.81, 114.83, 76.27, 61.05, 39.52, 37.96, 13.94. **IR** (film): $\tilde{\nu} = 1727, 1652, 1595$ cm^{-1} . **HRMS** (ESI-TOF) calc'd for $\text{C}_{24}\text{H}_{22}\text{O}_4^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$: 409.1201, found: 409.1202.

Isopropyl 2-(4-benzoylphenoxy)-2-methylpropanoate – (21)

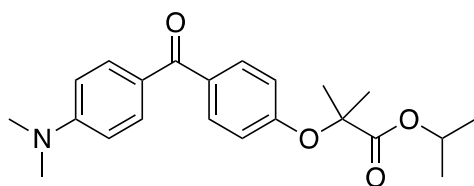


A mixture of (4-hydroxyphenyl)(phenyl)methanone (300 mg, 1.51 mmol), isopropyl 2-bromo-2-methylpropanoate (380 mg, 1.81 mmol), Cs_2CO_3 (588 mg, 1.81 mmol) and *N,N*-dimethylacetamide (10 mL) was prepared. The resultant mixture was heated at 80°C overnight. Water (30 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL).

The organic fractions were combined, washed with brine, dried (Na_2SO_4) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 25%, in cyclohexane) over 15 column volumes gave **21** (123 mg, 0.377 mmol, 25 %) as a white solid.

m.p. 85-88°C. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 7.76 – 7.50 (m, 7H), 6.93 – 6.86 (m, 2H), 4.95 (hept, $J = 6.0$ Hz, 1H), 1.60 (s, 6H), 1.14 (d, $J = 6.0$ Hz, 6H). $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$) δ 194.32, 172.12, 159.07, 137.59, 132.13, 131.82, 129.83, 129.25, 128.44, 117.04, 79.02, 68.90, 25.02 (2C, $\text{C}(\text{CH}_3)_2$), 21.20 (2C, $\text{CH}(\text{CH}_3)_2$). **IR** (film): $\tilde{\nu} = 1728, 1672, 1593$ cm^{-1} . **HRMS** (ESI-TOF) calc'd for $\text{C}_{20}\text{H}_{23}\text{O}_4$ $[\text{M}+\text{H}]^+$: 327.1590, found: 327.1588.

Isopropyl 2-(4-(4-(dimethylamino)benzoyl)phenoxy)-2-methylpropanoate – (22)

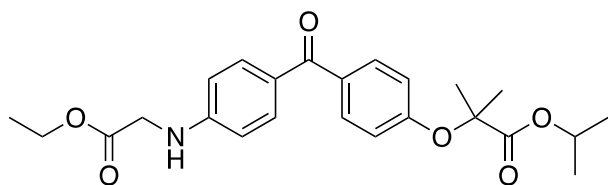


General Procedure B using fenofibrate (**1**) (200 mg, 0.555 mmol), RuPhos Pd G3 (23 mg, 0.0277 mmol), Cs_2CO_3 (541 mg, 1.66 mmol) and dimethylamine (2M

in THF (333 μL , 0.666 mmol)) gave **22** (34 mg, 0.092 mmol, 17%) as a white solid.

m.p. 91-93°C. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 7.79 – 7.47 (m, 4H), 7.02 – 6.39 (m, 4H), 4.98 (hept, $J = 6.0$ Hz, 1H), 3.03 (s, 6H), 1.59 (s, 6H), 1.16 (d, $J = 6.0$ Hz, 6H). $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$) δ 192.39, 172.30, 157.92, 153.02, 131.89, 130.98, 123.99, 116.98, 110.70, 78.90, 68.83, 39.52 (2C, $\text{N}(\text{CH}_3)_2$), 25.07 (2C, $\text{C}(\text{CH}_3)_2$), 21.24 (2C, $\text{CH}(\text{CH}_3)_2$). **IR** (film): $\tilde{\nu} = 1732, 1594$ cm^{-1} . **HRMS** (ESI-TOF) calc'd for $\text{C}_{22}\text{H}_{28}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^+$: 370.2013, found: 370.2006.

Isopropyl 2-(4-(4-((2-ethoxy-2-oxoethyl)amino)benzoyl)phenoxy)-2-methylpropanoate – (23)

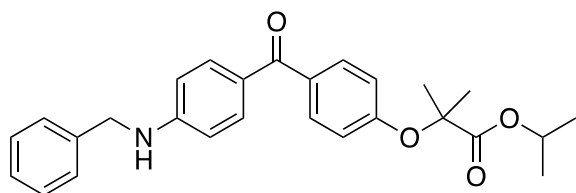


General Procedure B using fenofibrate (**1**) (200 mg, 0.555 mmol), BrettPhos Pd G3 (25 mg, 0.0277 mmol), Cs₂CO₃ (541 mg,

1.66 mmol) and glycine ethyl ester (92 mg, 0.666 mmol) gave **23** (212 mg, 0.49 mmol, 89%) as a clear oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.62 (m, 4H), 6.86 – 6.81 (m, 2H), 6.61 – 6.55 (m, 2H), 5.07 (hept, *J* = 6.0 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.94 (s, 2H), 1.63 (s, 6H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 193.96, 173.06, 170.11, 158.40, 150.23, 132.39, 131.61, 131.20, 127.08, 118.94, 116.93, 111.36, 78.99, 77.16, 68.99, 61.38, 44.80, 25.11 (2C, C(CH₃)₂), 21.26 (2C, CH(CH₃)₂), 13.93. **IR** (film): $\tilde{\nu}$ = 3352, 1731, 1599 cm⁻¹. **HRMS** (ESI-TOF) calc'd for C₂₄H₃₀O₆N [M+H⁺: 428.2068, found: 428.2066.

Isopropyl 2-(4-(4-(benzylamino)benzoyl)phenoxy)-2-methylpropanoate – (24)



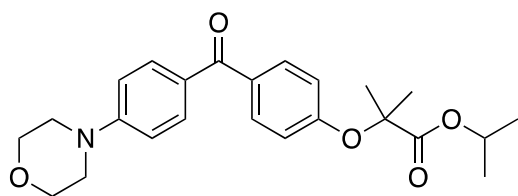
General Procedure B using fenofibrate (**1**) (200 mg, 0.55 mmol), BrettPhos Pd G3 (25 mg, 0.0277 mmol), Cs₂CO₃ (541 mg, 1.66 mmol) and benzylamine (71 mg, 0.66 mmol),

tert butanol (0.1 M) gave **24** (194 mg, 0.45 mmol, 82%) as a clear oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.47 (m, 4H), 7.29 – 7.17 (m, 5H), 6.78 – 6.74 (m, 2H), 6.54 – 6.50 (m, 2H), 5.00 (hept, *J* = 6.0 Hz, 1H), 4.74 (t, *J* = 5.5 Hz, 1H), 4.31 (d, *J* =

5.5 Hz, 2H), 1.56 (s, 6H), 1.12 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (101 MHz, Chloroform- d) δ 193.89, 173.09, 158.28, 151.42, 138.11, 132.44, 131.80, 131.14, 128.49, 127.05, 116.93, 111.24, 78.97, 68.98, 47.27, 25.11 (2C, $\text{C}(\text{CH}_3)_2$), 21.27 (2C, $\text{CH}(\text{CH}_3)_2$). IR (film): $\tilde{\nu} = 3339$, 1729, 1598 cm^{-1} . HRMS (ESI-TOF) calc'd for $\text{C}_{27}\text{H}_{30}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^+$: 432.2169, found: 432.2159.

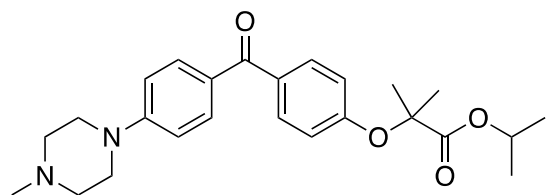
Isopropyl 2-methyl-2-(4-(4-morpholinobenzoyl)phenoxy)propanoate – (25)



General Procedure B using fenofibrate (**1**) (100 mg, 0.277 mmol), RuPhosPd G3 (23 mg, 0.0277 mmol), Cs_2CO_3 (225 mg, 0.69 mmol), morpholine (35 μL , 0.415 mmol) and tert-butanol (0.1 M) to give **25** (40 mg, 0.096 mmol, 35%) as a yellow oil.

^1H NMR (400 MHz, DMSO) δ 7.67 – 7.56 (m, 4H), 7.06 – 7.00 (m, 2H), 6.91 – 6.82 (m, 2H), 4.98 (hept, $J = 6.0$ Hz, 1H), 3.74 (dd, $J = 5.0$ Hz, 4H), 3.30 (dd, $J = 5.0, 5.0$ Hz, 4H), 1.60 (s, 6H), 1.15 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 192.65, 172.28, 158.24, 153.71, 131.65, 131.19, 126.71, 117.02, 113.03, 78.95, 68.86, 65.88 (2C, $\text{O}(\text{CH}_2)_2$), 46.86 (2C, $\text{N}(\text{CH}_2)_2$), 25.06 (2C, $\text{C}(\text{CH}_3)_2$), 21.23 (2C, $\text{CH}(\text{CH}_3)_2$). HRMS (ESI-TOF) calc'd for $\text{C}_{27}\text{H}_{30}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^+$: 412.2118, found: 412.2120.

Isopropyl 2-methyl-2-(4-(4-(4-methylpiperazin-1-yl)benzoyl)phenoxy)propanoate – (26)

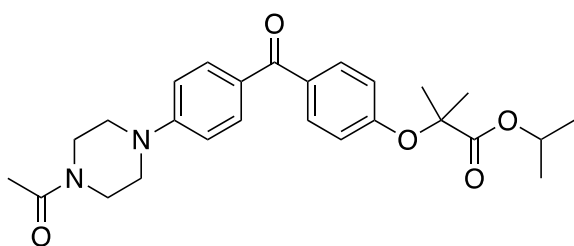


General Procedure B using fenofibrate (**1**) (100 mg, 0.277 mmol), RuPhosPd G3 (23 mg, 0.0277 mmol), Cs_2CO_3 (225 mg, 0.69 mmol), 1-

methylpiperazine (46 μ L, 0.415 mmol) and tert-butanol (0.1 M) to give **26** (54 mg, 0.127 mmol, 46%) as a yellow oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 7.67 – 7.58 (m, 4H), 7.02 – 6.98 (m, 2H), 6.89 – 6.83 (m, 2H), 4.98 (hept, J = 6.0 Hz, 1H), 3.33 (t, J = 5.0 Hz, 4H), 2.43 (d, J = 5.0 Hz, 4H), 2.21 (s, 3H), 1.59 (s, 6H), 1.14 (d, J = 6.0 Hz, 6H). **$^{13}\text{C NMR}$** (101 MHz, DMSO) δ 192.57, 172.28, 158.17, 153.53, 131.71, 131.31, 131.14, 126.18, 117.01, 113.11, 78.93, 68.85, 54.30 (2C, $\text{NCH}_3(\text{CH}_2)_2$), 46.51 (2C, $\text{N}(\text{CH}_2)_2$), 45.71, 25.06 (2C, $\text{C}(\text{CH}_3)_2$), 21.24 (2C, $\text{CH}(\text{CH}_3)_2$). **HRMS** (ESI-TOF) calc'd for $\text{C}_{25}\text{H}_{33}\text{O}_4\text{N}_2$ $[\text{M}+\text{H}]^+$: 425.2435, found: 425.2436.

Isopropyl 2-(4-(4-(4-acetylpiperazin-1-yl)benzoyl)phenoxy)-2-methylpropanoate – (**27**)

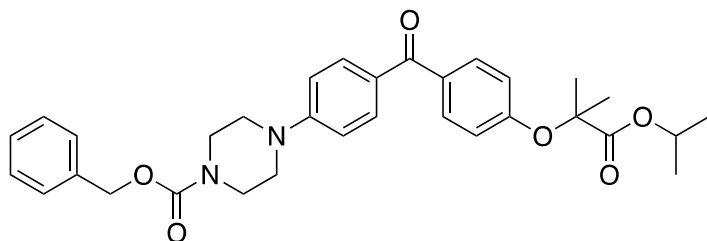


General Procedure A using **29** (50 mg, 0.121 mmol), DIPEA (63 μ L, 0.365 mmol), HATU (63 mg, 0.166 mmol), acetic acid (9.5 μ L, 0.166 mmol) in *N,N*-dimethylacetamide (3

mL) gave **27** (37 mg, 0.0823 mmol, 68%) as a yellow oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 7.67 – 7.61 (m, 4H), 7.07 – 7.01 (m, 2H), 6.91 – 6.84 (m, 2H), 4.98 (h, J = 6.0 Hz, 1H), 3.67 – 3.57 (m, 4H), 3.44 – 3.33 (m, 4H), 2.06 (s, 3H), 1.60 (s, 6H), 1.16 (d, J = 6.0 Hz, 6H). **$^{13}\text{C NMR}$** (101 MHz, DMSO) δ 193.06, 172.75, 168.91, 158.67, 153.66, 132.20, 131.63, 126.89, 117.48, 113.71, 79.41, 69.32, 47.15 (2C, $\text{CON}(\text{CH}_2)_2$), 45.50 (2C, $\text{N}(\text{CH}_2)_2$), 25.53 (2C, $\text{C}(\text{CH}_3)_2$), 21.70 (3C, $\text{CH}(\text{CH}_3)_2$ & COCH_3). **HRMS** (ESI-TOF) calc'd for $\text{C}_{26}\text{H}_{33}\text{O}_5\text{N}_2$ $[\text{M}+\text{H}]^+$: 453.2384, found: 453.2386.

Benzyl 4-(4-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)piperazine-1-carboxylate – (28)

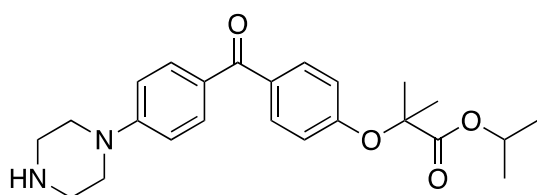


General Procedure B using fenofibrate (**1**) (200 mg, 0.555 mmol), RuPhos Pd G3 (23 mg, 0.0277 mmol), Cs₂CO₃ (541 mg,

1.66 mmol) and Benzyl piperazine-1-carboxylate (145 mg, 0.666 mmol) gave **28** (102 mg, 0.187 mmol, 34%) as a yellow oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 – 7.58 (m, 4H), 7.43 – 7.28 (m, 5H), 7.07 – 6.96 (m, 2H), 6.92 – 6.80 (m, 2H), 5.11 (s, 2H), 4.97 (hept, J = 6.0 Hz, 1H), 3.62 – 3.51 (m, 4H), 3.40 – 3.37 (m, 4H), 1.59 (s, 6H), 1.15 (d, J = 6.0 Hz, 6H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 192.58, 172.27, 158.23, 154.45, 153.20, 136.81, 131.73, 131.19, 128.46, 127.91, 127.65, 116.99, 113.38, 78.93, 68.86, 66.38, 46.43 (2C, CON(CH₂)₂), 42.95 (2C, N(CH₂)₂), 25.07 (2C, CH(CH₃)₂), 21.24 (2C, CH(CH₃)₂). IR (film): $\tilde{\nu}$ = 2981, 1703, 1644, 1599 cm⁻¹. HRMS (ESI-TOF) calc'd for C₃₂H₃₇O₆N₂ [M-H]⁺: 545.2646, found: 545.2643.

Isopropyl 2-methyl-2-(4-(4-(piperazin-1-yl)benzoyl)phenoxy)propanoate – (29)

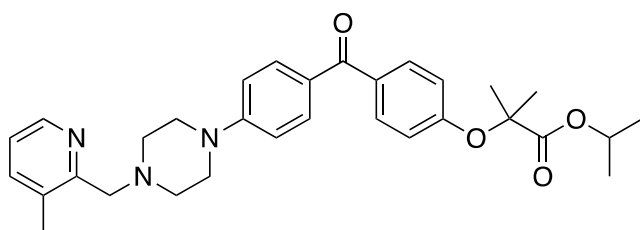


28 (1 g, 1.83 mmol) was dissolved in MeOH (50 mL); 10% Pd/C (193 mg) was then added. The mixture was degassed three times (vacuum/H₂)

and was stirred at room temperature overnight. The reaction mixture was filtered through a celite pad and the pad was washed with MeOH (30 mL). The filtrate was concentrated to give **29** (645 mg, 1.57 mmol, 86 %) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.67 – 7.58 (m, 4H), 7.08 – 6.98 (m, 2H), 6.91 – 6.84 (m, 2H), 4.98 (h, J = 6.0 Hz, 1H), 3.74 (dd, J = 5.9, 3.8 Hz, 4H), 3.29 (dd, J = 6.0, 3.7 Hz, 4H), 1.59 (s, 6H), 1.15 (d, J = 6.3 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 192.63, 172.26, 158.22, 153.69, 131.62, 131.16, 126.71, 117.02, 113.01, 78.94, 68.84, 65.87 (2C, N(CH₃)₂), 46.85 (2C, NH(CH₃)₂), 25.05 (2C, C(CH₃)₂), 21.22 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₄H₃₁O₄N₂ [M+H]⁺: 411.2278, found: 411.2286.

Isopropyl 2-methyl-2-(4-(4-(4-((3-methylpyridin-2-yl)methyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (30)



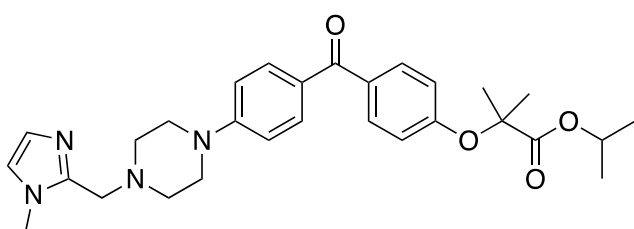
A solution of **29** (70 mg, 0.17 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; 3-methylpyridine-2-carbaldehyde (19 μ L, 0.170 mmol) was

then added. The resultant mixture was stirred at room temperature for 10 minutes before the addition of sodium triacetoxyborohydride (104 mg, 0.495 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0% - 20%, in CH₂Cl₂) over 20 column volumes to give **30** (49 mg, 0.0952 mmol, 56%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 8.31 (ddd, J = 4.8, 1.8, 0.7 Hz, 1H), 7.65 – 7.52 (m, 5H), 7.21 (dd, J = 7.6, 4.8 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.89 – 6.83 (m, 2H), 4.98 (p, J = 6.3 Hz, 1H), 3.64 (s, 2H), 3.29 (d, J = 5.5 Hz, 4H), 2.56 – 2.51 (m, 4H), 2.40 (s, 3H), 1.59 (s, 6H), 1.15 (d, J = 6.3 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 192.47, 172.17, 158.10, 155.91, 153.43,

145.64, 137.77, 132.90, 131.58, 131.36, 130.97, 126.17, 122.46, 117.10, 113.01, 78.94, 68.74, 62.42, 52.49 (2C, CH₂N(CH₃)₂), 46.67 (2C, N(CH₃)₂), 25.00 (2C, C(CH₃)₂), 21.14 (2C, CH(CH₃)₂), 17.88. **HRMS** (ESI-TOF) calc'd for C₃₁H₃₈O₄N₃ [M+H]⁺: 516.2857, found: 516.2859.

Isopropyl-2-methyl-2-(4-(4-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (31)



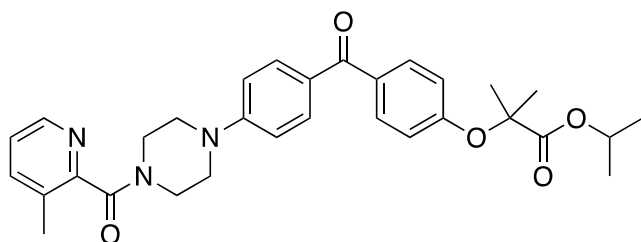
A solution of **29** (70 mg, 0.17 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; 1-methyl-1H-imidazole-2-carbaldehyde (19 mg, 0.170 mmol) was

then added. The resultant mixture was stirred at room temperature for 10 minutes before the addition of sodium triacetoxyborohydride (104 mg, 0.495 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0% - 20%, in CH₂Cl₂) over 20 column volumes to give **31** (38 mg, 0.0765 mmol, 45%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.66 – 7.54 (m, 4H), 7.09 (d, *J* = 1.2 Hz, 1H), 7.02 – 6.95 (m, 2H), 6.89 – 6.84 (m, 2H), 6.77 (d, *J* = 1.2 Hz, 1H), 4.98 (p, *J* = 6.2 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 2H), 3.34 – 3.27 (m, 4H), 2.56 – 2.43 (m, 4H), 1.59 (s, 6H), 1.15 (d, *J* = 6.2 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 192.56, 172.26, 158.17, 153.48, 144.04, 131.69, 131.31, 131.12, 126.22, 122.03, 117.03, 113.12, 78.94, 68.84, 53.66, 52.20 (2C, CH₂N(CH₃)₂), 46.63 (2C,

$N(CH_3)_2$, 32.52, 25.06 (2C, $C(CH_3)_2$), 21.22 (2C, $CH(CH_3)_2$). **HRMS** (ESI-TOF) calc'd for $C_{29}H_{37}O_4N_4$ $[M+H]^+$: 505.2809, found: 505.2810.

Isopropyl 2-methyl-2-(4-(4-(4-(3-methylpicolinoyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (32)

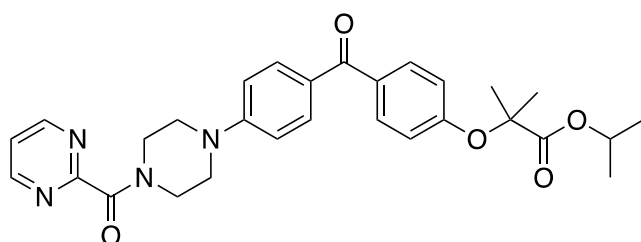


General Procedure A using **29** (50 mg, 0.121 mmol), DIPEA (63 μ L, 0.365 mmol), HATU (63 mg, 0.166 mmol), 3-methylpicolinic acid (22 mg, 0.166

mmol) in *N,N*-dimethylacetamide (0.1 M) gave **32** (24 mg, 0.0447 mmol, 37%) as a yellow oil.

1H NMR (400 MHz, DMSO) δ 8.42 (ddd, $J = 4.8, 1.6, 0.7$ Hz, 1H), 7.76 (ddd, $J = 7.9, 1.7, 0.8$ Hz, 1H), 7.66 – 7.58 (m, 4H), 7.38 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.09 – 7.00 (m, 2H), 6.94 – 6.81 (m, 2H), 4.98 (p, $J = 6.2$ Hz, 1H), 3.86 – 3.75 (m, 2H), 3.52 – 3.46 (m, 2H), 3.26 (dd, $J = 6.8, 3.6$ Hz, 2H), 2.26 (s, 3H), 1.59 (s, 6H), 1.15 (d, $J = 6.2$ Hz, 6H). **^{13}C NMR** (151 MHz, DMSO) δ 192.60, 172.24, 166.57, 158.23, 153.47, 153.13, 146.33, 138.50, 131.67, 131.15, 130.12, 126.72, 123.94, 117.04, 113.52, 78.95, 68.83, 47.09, 46.61, 45.34, 40.47, 25.05 (2C, $C(CH_3)_2$), 21.22 (2C, $CH(CH_3)_2$), 17.13. **HRMS** (ESI-TOF) calc'd for $C_{31}H_{36}O_5N_3$ $[M+H]^+$: 530.2649, found: 530.2650.

Isopropyl 2-methyl-2-(4-(4-(4-(pyrimidine-2-carbonyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (33)



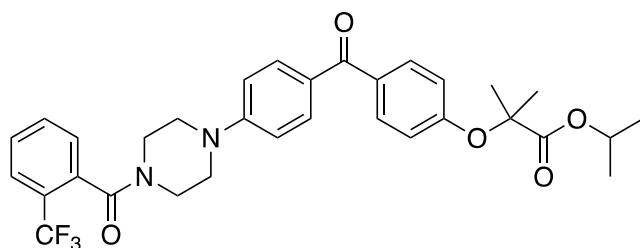
General Procedure A using **29** (50 mg, 0.121 mmol), DIPEA (63 μ L, 0.365 mmol), HATU (63 mg, 0.166 mmol), pyrimidine-2-carboxylic acid (21 mg,

0.166 mmol) in N,N-dimethylacetamide (0.1 M) gave **33** (35 mg, 0.0677 mmol, 56%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 8.93 (d, *J* = 5.0 Hz, 2H), 7.69 – 7.56 (m, 5H), 7.06 – 6.99 (m, 2H), 6.90 – 6.82 (m, 2H), 4.97 (hept, *J* = 6.0 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.54 – 3.47 (m, 2H), 1.59 (s, 7H), 1.15 (d, *J* = 6.0 Hz, 6H). ¹³C NMR (101 MHz, DMSO) δ 193.09, 172.74, 165.05, 162.02, 158.71, 158.25, 153.56, 132.18, 131.66, 131.63, 127.21, 122.31, 117.48, 114.00, 79.41, 69.32, 47.43, 46.91, 45.93, 41.16, 25.52 (2C, C(CH₃)₂), 21.70 (2C, CH(CH₃)₂).

HRMS (ESI-TOF) calc'd for C₂₉H₃₃O₅N₄ [M+H]⁺: 517.2445, found: 517.2448.

Isopropyl-2-methyl-2-(4-(4-(4-(2-(trifluoromethyl)benzoyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (34)

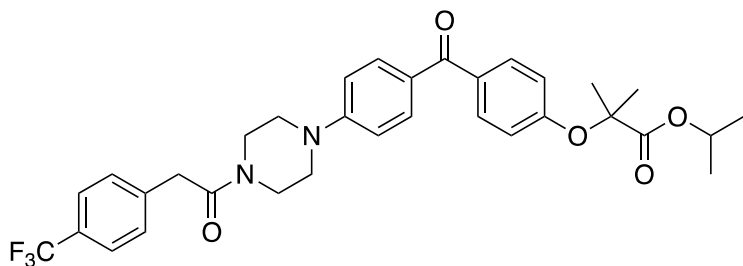


General Procedure A using **29** (50 mg, 0.121 mmol), DIPEA (63 μL, 0.365 mmol), HATU (63 mg, 0.166 mmol), 2-(Trifluoromethyl)benzoic acid (31 mg,

0.166 mmol) in N,N-dimethylacetamide (0.1 M) gave **34** (44 mg, 0.076 mmol, 63%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.86 – 7.82 (m, 1H), 7.80 – 7.74 (m, 1H), 7.69 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.67 – 7.60 (m, 4H), 7.57 – 7.52 (m, 1H), 7.17 – 6.91 (m, 2H), 6.93 – 6.77 (m, 2H), 4.98 (p, *J* = 6.3 Hz, 1H), 3.99 – 3.67 (m, 2H), 3.60 – 3.41 (m, 2H), 1.60 (s, 6H), 1.16 (d, *J* = 6.2 Hz, 6H). ¹³C NMR (101 MHz, DMSO) δ 192.48, 172.08, 166.10, 158.14, 152.94, 132.77, 131.49, 131.22, 130.94, 129.46, 127.47, 126.77, 126.45 (q, ²J_{CF} = 31.8 Hz), 117.13, 113.43, 78.94, 68.68, 46.43, 46.32, 45.86, 40.70, 24.96 (2C, CH(CH₃)₂), 21.08 (2C, CH(CH₃)₂). ¹⁹F NMR (376 MHz, DMSO) δ -58.51. HRMS (ESI-TOF) calc'd for C₃₂H₃₄O₅N₂F₃ [M+H]⁺: 583.2414, found: 583.2442.

Isopropyl 2-methyl-2-(4-(4-(4-(2-(4-(trifluoromethyl)phenyl)acetyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (35)



General Procedure A using **29**

(50 mg, 0.121 mmol), DIPEA (63

μ L, 0.365 mmol), HATU (63 mg,

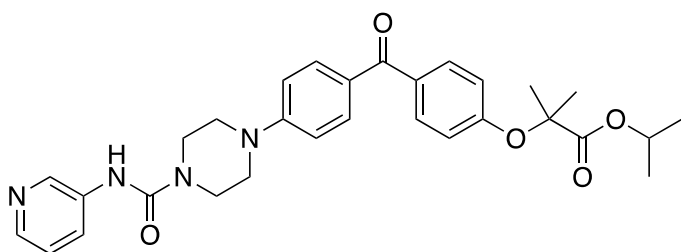
0.166 mmol), 4-

(Trifluoromethyl)phenyl acetic

acid (34 mg, 0.166 mmol) in *N,N*-dimethylacetamide (0.1 M) gave **35** (42 mg, 0.0714 mmol, 59%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.74 – 7.59 (m, 6H), 7.48 (d, J = 8.0 Hz, 2H), 7.07 – 7.00 (m, 2H), 6.91 – 6.85 (m, 2H), 4.99 (h, J = 6.0 Hz, 1H), 3.92 (s, 2H), 3.67 (dt, J = 20.3, 5.2 Hz, 4H), 1.60 (s, 6H), 1.15 (d, J = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 192.57, 172.24, 168.45, 158.20, 153.09, 131.68, 131.24, 131.12, 130.16, 126.49, 124.96, 117.04, 113.22, 78.94, 68.82, 46.63, 46.31, 44.67, 40.82, 25.04 (2C, C(CH₃)₂), 21.20 (2C, CH(CH₃)₂). **¹⁹F NMR** (376 MHz, DMSO) δ -60.80. **HRMS** (ESI-TOF) calc'd for C₃₃H₃₆O₅N₂F₃ [M+H]⁺: 597.2571, found: 597.2573.

Isopropyl 2-methyl-2-(4-(4-(4-(pyridin-3-ylcarbamoyl)piperazin-1-yl)benzoyl)phenoxy)propanoate – (36)



General Procedure A using **29** (50 mg,

0.121 mmol), DIPEA (63 μ L, 0.365

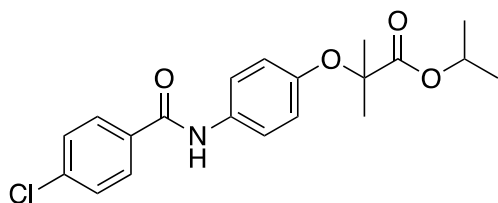
mmol), pyridine-3-isocyanate (29 mg,

0.242 mmol) in *N,N*-

dimethylacetamide (0.1 M) gave **36** (46 mg, 0.086 mmol, 71%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 8.82 (s, 1H), 8.66 (d, *J* = 2.6 Hz, 1H), 8.16 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.90 (ddd, *J* = 8.4, 2.6, 1.5 Hz, 1H), 7.64 (dd, *J* = 8.2, 1.3 Hz, 3H), 7.28 (ddd, *J* = 8.3, 4.6, 0.7 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.92 – 6.82 (m, 2H), 4.98 (h, *J* = 6.0 Hz, 1H), 3.64 (dd, *J* = 6.8, 3.8 Hz, 4H), 3.47 – 3.41 (m, 4H), 1.60 (s, 6H), 1.15 (d, *J* = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 192.62, 172.28, 154.79, 153.30, 141.39, 137.14, 131.72, 131.17, 126.50, 123.24, 117.04, 113.28, 78.96, 68.86, 46.45 (2C, CON(CH₃)₂), 43.25 (2C, N(CH₃)₂), 25.08 (2C, C(CH₃)₂), 21.25 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₃₀H₃₅O₅N₄ [M+H]⁺: 531.2602, found: 531.2612.

Isopropyl 2-(4-(4-chlorobenzamido)phenoxy)-2-methylpropanoate – (39)

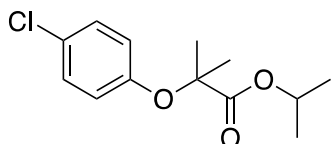


A mixture of 4-Chloro-*N*-(4-hydroxyphenyl)benzamide (300 mg, 1.21 mmol) and Cs₂CO₃ (786 mg, 1.42 mmol) in *N,N*-dimethylacetamide (10 mL) was prepared; isopropyl 2-bromo-2-methylpropanoate (303 mg, 1.45 mmol) was then added. The reaction mixture was heated at 120°C for 16 hr. The reaction mixture was allowed to cool to room temperature. Water (30 mL) was then added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 100%, in cyclohexane) over 10 column volumes gave **39** (254 mg, 0.677 mmol, 56%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.01 – 7.90 (m, 2H), 7.69 – 7.54 (m, 4H), 6.84 – 6.79 (m, 2H), 4.98 (h, *J* = 6.0 Hz, 1H), 1.50 (s, 6H), 1.18 (d, *J* = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 172.70, 164.10, 151.21, 136.29, 133.67, 133.38, 129.55, 128.45, 121.54,

119.15, 78.87, 68.53, 25.01 (2C, C(CH₃)₂), 21.32 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₀H₂₃NO₄³⁵Cl [M+H]⁺: 376.1310, found: 376.1318.

Isopropyl 2-(4-chlorophenoxy)-2-methylpropanoate – (40b)



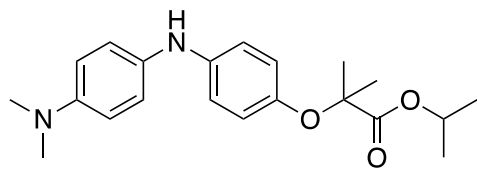
A mixture of 4-chlorophenol (2 g, 0.0156 mol), isopropyl 2-bromo-2-methylpropanoate (3.7 mL, 0.023 mol) and Cs₂CO₃ (10 g, 0.0312 mol) in *N,N*-dimethylacetamide (50 mL) was prepared.

The resultant mixture was heated at 80°C overnight. Water (200 mL) was then added, and the mixture was extracted with EtOAc (3 x 50 mL). The organic fractions were combined, washed with brine, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 25%, in cyclohexane) over 10 column volumes to give **40b** (3.03 g, 0.0118 mol, 76 %) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.15 (m, 2H), 6.80 – 6.74 (m, 2H), 5.07 (hept, *J* = 6.0 Hz, 1H), 1.56 (s, 6H), 1.20 (d, *J* = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ 173.47, 154.14, 129.01, 127.00, 120.32, 116.68, 78.83, 69.11, 25.26 (2C, CH(CH₃)₂), 21.54 (2C, CH(CH₃)₂).

HRMS (ESI-TOF) calc'd for C₁₃H₁₇O₃³⁵Cl [M+H]⁺: 257.0939, found: 257.0940

Isopropyl 2-(4-((4-(dimethylamino)phenyl)amino)phenoxy)-2-methylpropanoate – (40)



General Procedure B using **40b** (100 mg, 0.39 mmol),

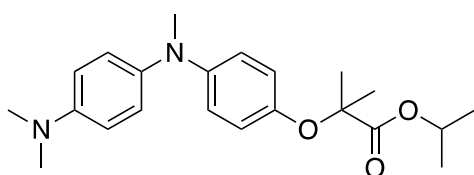
BrettPhos Pd G3 (35 mg, 0.039 mmol), Cs₂CO₃ (253 mg, 0.78 mmol), 4-(dimethylamino)aniline (53 mg,

0.39 mmol) and tert-butanol (1.5 mL) gave **40** (90 mg, 0.253 mmol, 65%) as a blue oil.

¹H NMR (400 MHz, DMSO) δ 7.46 (s, 1H), 6.95 – 6.89 (m, 2H), 6.79 – 6.73 (m, 2H), 6.72 – 6.66 (m, 4H), 4.94 (h, *J* = 6.0 Hz, 1H), 2.81 (s, 6H), 1.42 (s, 6H), 1.19 (d, *J* = 6.0 Hz, 6H). **¹³C**

NMR (101 MHz, DMSO) δ 172.86, 146.78, 145.72, 141.25, 133.66, 120.38, 115.20, 114.02, 79.07, 68.28, 40.96 (2C, N(CH₃)₂), 24.99 (2C, C(CH₃)₂), 21.37 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₁H₂₉N₂O₃ [M+H]⁺: 357.2173, found: 357.2173.

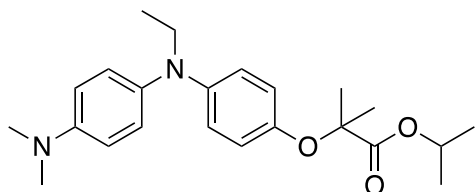
Isopropyl 2-(4-((4-(dimethylamino)phenyl)(methylamino)phenoxy)-2-methylpropanoate – (41)



A solution of **40** (50 mg, 0.14 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; paraformaldehyde (6.3 mg, 0.21 mmol) was then added. The resultant mixture was heated to 50°C for 10 minutes before the addition of sodium triacetoxymethylborohydride (88 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated NaHCO₃ solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was then extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0% - 20%, in CH₂Cl₂) over 20 column volumes to give **41** (39 mg, 0.106 mmol, 76%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 6.96 – 6.91 (m, 2H), 6.74 – 6.66 (m, 4H), 6.64 – 6.59 (m, 2H), 4.94 (p, *J* = 6.2 Hz, 1H), 3.10 (s, 3H), 2.85 (s, 6H), 1.42 (s, 6H), 1.18 (d, *J* = 6.2 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 172.81, 147.34, 146.92, 145.48, 138.67, 125.13, 120.85, 116.02, 113.63, 79.02, 68.27, 40.54 (3C, N(CH₃)₂ & NCH₃), 24.98 (2C, C(CH₃)₂), 21.34 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₂H₃₁N₂O₃ [M+H]⁺: 371.2324, found: 371.2324.

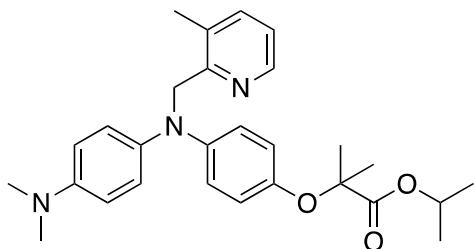
**Isopropyl 2-(4-((4-(dimethylamino)phenyl)(ethylamino)phenoxy)-2-methylpropanoate –
(42)**



A solution of **40** (50 mg, 0.14 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; acetaldehyde (9.98 mg, 0.21 mmol) was then added. The resultant mixture was stirred at room temperature for 5 minutes before the addition of sodium triacetoxyborohydride (88 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated NaHCO₃ solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0%- 20%, in CH₂Cl₂) over 20 column volumes to give **42** (31 mg, 0.0798 mmol, 57%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.09 – 6.41 (m, 8H), 4.94 (h, *J* = 6.0 Hz, 1H), 3.55 (s, 2H), 2.86 (s, 6H), 1.41 (s, 6H), 1.18 (d, *J* = 6.0 Hz, 6H), 1.06 (t, *J* = 7.0 Hz, 3H). **¹³C NMR** (101 MHz, DMSO) δ 172.77, 146.47, 144.42, 136.47, 130.33, 126.39, 121.00, 115.74, 115.71, 113.64, 79.01, 68.21, 24.96 (2C, C(CH₃)₂), 21.30 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for for C₂₃H₃₃N₂O₃ [M+H]⁺: 385.2480, found: 385.2482.

Isopropyl 2-(4-((4-(dimethylamino)phenyl)((3-methylpyridin-2-yl)methyl)amino)phenoxy)-2-methylpropanoate – (43)

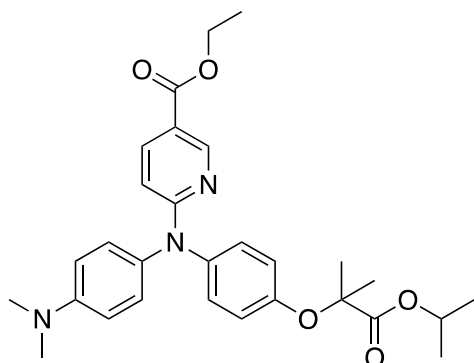


A solution of **40** (50 mg, 0.14 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; 3-pyridine-methyl aldehyde (25 mg, 0.21 mmol) was then added.

The resultant mixture was stirred at room temperature for 5 minutes before the addition of sodium triacetoxyborohydride (88 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0%- 20%, in CH₂Cl₂) over 20 column volumes to give **43** (27 mg, 0.0588 mmol, 42%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 8.31 – 8.22 (m, 1H), 7.52 – 7.47 (m, 1H), 7.17 – 7.10 (m, 1H), 7.04 – 6.99 (m, 2H), 6.73 – 6.50 (m, 6H), 4.92 (d, *J* = 6.0 Hz, 1H), 4.86 (s, 2H), 2.83 (s, 6H), 2.27 (s, 3H), 1.41 (s, 6H), 1.17 (d, *J* = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 173.27, 156.63, 147.80, 147.21, 146.48, 145.73, 138.13, 137.76, 132.06, 126.87, 122.51, 121.05, 116.74, 113.77, 79.43, 68.71, 56.39, 40.93 (2C, N(CH₃)₂), 25.46 (2C, C(CH₃)₂), 21.80 (2C, CH(CH₃)₂), 18.32. **HRMS** (ESI-TOF) calc'd for C₂₈H₃₆N₃O₃ [M+H]⁺: 462.2751, found: 462.2748.

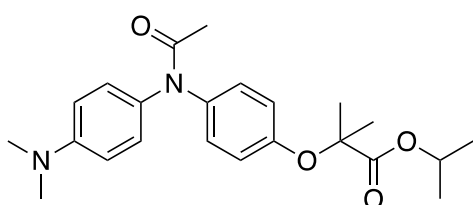
Ethyl 6-((4-(dimethylamino)phenyl)(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)amino)nicotinate – (44)



General Procedure B using **40** (50 mg, 0.14 mmol), RuPhos Pd G3 (11.5 mg, 0.014 mmol), Cs₂CO₃ (113 mg, 0.35 mmol), 6-chloro-ethylnicotinate (39 mg, 0.21 mmol) and tert-butanol (3 mL) gave **44** (19 mg, 0.0378 mmol, 27%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 8.55 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.89 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.11 – 7.06 (m, 2H), 6.81 – 6.72 (m, 4H), 6.40 (dd, *J* = 9.0, 0.8 Hz, 1H), 4.95 (p, *J* = 6.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.90 (s, 6H), 1.52 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 6H). ¹³C NMR (101 MHz, DMSO) δ 172.97, 165.34, 161.56, 153.20, 150.46, 149.37, 139.23, 138.25, 133.44, 128.93, 128.46, 119.66, 113.70, 108.92, 79.29, 69.06, 60.57, 41.41 (2C, N(CH₃)₂), 25.55 (2C, C(CH₃)₂), 21.73 (2C, CH(CH₃)₂), 14.71. HRMS (ESI-TOF) calc'd for C₂₉H₃₆N₃O₅ [M+H]⁺: 506.2649, found: 506.2644.

Isopropyl 2-(4-(*N*-(4-(dimethylamino)phenyl)acetamido)phenoxy)-2-methylpropanoate – (45)

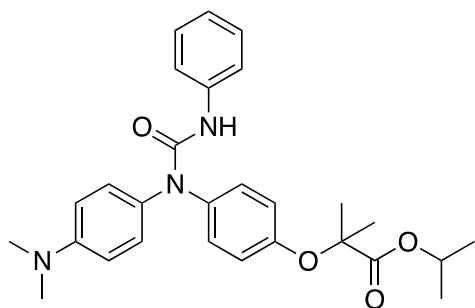


A solution of **40** (50 mg, 0.14 mmol), DIPEA (36 μL, 0.21 mmol) and anhydrous CH₂Cl₂ (2 mL) under anhydrous conditions was prepared; acetyl chloride (15 μL, 0.21 mmol) was then added. The reaction mixture was stirred at room temperature for 16 h. A mixture saturated NaHCO₃ solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the

aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0% - 100%, in CH₂Cl₂) over 20 column volumes to give **45** (15 mg, 0.0378 mmol, 27%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.38 – 6.98 (m, 4H), 6.85 – 6.60 (m, 4H), 4.94 (d, *J* = 6.0 Hz, 1H), 2.88 (s, 6H), 1.86 (s, 3H), 1.50 (s, 6H), 1.14 (d, *J* = 6.0 Hz, 6H). ¹³C NMR (101 MHz, DMSO) δ 219.00, 172.52, 152.62, 149.42, 137.64, 132.20, 128.83, 127.26, 118.54, 112.67, 78.75, 68.59, 25.03 (2C, C(CH₃)₂), 23.22, 21.26 (2C, CH(CH₃)₂). HRMS (ESI-TOF) calc'd for C₂₃H₃₁N₂O₄ [M+H]⁺: 399.2273, found: 399.2275.

Isopropyl 2-(4-(1-(4-(dimethylamino)phenyl)-3-phenylureido)phenoxy)-2-methylpropanoate – (46)

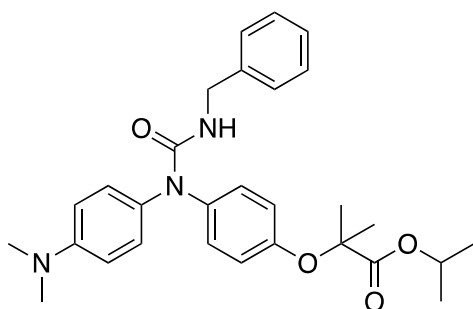


A solution of **40** (50 mg, 0.14 mmol), DIPEA (48 μL, 0.28 mmol) and *N,N*-dimethylacetamide (2 mL) under anhydrous conditions was prepared; phenyl isocyanate (28 mg, 0.21 mmol) was then added. The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0%- 100%, in CH₂Cl₂) over 20 column volumes to give **46** (10 mg, 0.021 mmol, 15%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.82 (s, 1H), 7.42 – 7.37 (m, 2H), 7.23 – 7.18 (m, 2H), 7.13 – 7.06 (m, 4H), 6.98 – 6.90 (m, 1H), 6.79 – 6.69 (m, 4H), 4.96 (h, *J* = 6.0 Hz, 1H), 2.90 (s, 6H),

1.50 (s, 6H), 1.17 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 172.56, 154.28, 152.35, 148.92, 139.74, 138.04, 131.31, 128.65, 128.25, 127.47, 122.15, 119.80, 118.91, 112.91, 78.80, 68.55, 25.05 (2C, $\text{C}(\text{CH}_3)_2$), 21.28 (2C, $\text{CH}(\text{CH}_3)_2$). HRMS (ESI-TOF) calc'd for $\text{C}_{28}\text{H}_{34}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 476.2544, found: 476.2542.

Isopropyl 2-(4-(3-benzyl-1-(4-(dimethylamino)phenyl)ureido)phenoxy)-2-methylpropanoate – (47)

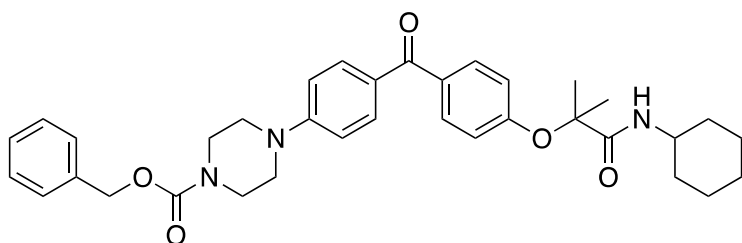


A solution of **40** (50 mg, 0.14 mmol), DIPEA (48 μL , 0.28 mmol) and *N,N*-dimethylacetamide (2 mL) under anhydrous conditions was prepared; benzyl isocyanate (31.5 mg, 0.23 mmol) was then added. The reaction mixture was stirred at room temperature for 16 h. A

mixture saturated sodium bicarbonate solution and CH_2Cl_2 (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The organic fractions were combined, dried (Na_2SO_4) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0% - 100%, in CH_2Cl_2) over 20 column volumes to give **47** (13 mg, 0.0266 mmol, 19%) as a yellow oil.

^1H NMR (400 MHz, DMSO) δ 7.35 – 7.16 (m, 5H), 7.12 – 7.06 (m, 4H), 6.74 – 6.68 (m, 4H), 6.23 (t, $J = 6.0$ Hz, 1H), 4.94 (h, $J = 6.0$ Hz, 1H), 4.22 (d, $J = 6.0$ Hz, 2H), 2.89 (s, 6H), 1.48 (s, 6H), 1.17 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 172.59, 156.36, 151.92, 148.98, 140.91, 138.35, 131.20, 129.07, 128.08, 127.16, 126.84, 126.35, 118.84, 112.98, 78.76, 68.53, 43.60, 25.02 (2C, $\text{C}(\text{CH}_3)_2$), 21.28 (2C, $\text{CH}(\text{CH}_3)_2$). HRMS (ESI-TOF) calc'd for $\text{C}_{29}\text{H}_{36}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 490.2695, found: 490.2696.

Benzyl 4-(4-((1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)piperazine-1-carboxylate – (48)

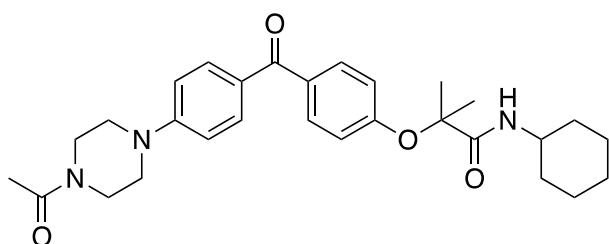


General Procedure B using **12** (70 mg, 0.175 mmol), RuPhosPdG3 (14.5 mg, 0.0175 mmol), Cs₂CO₃ (113 mg, 0.35 mmol), 1-cbz-

piperazine (46 mg, 0.21 mmol) in ^tBuOH (0.1 M) gave **48** (59 mg, 0.101 mmol, 58%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.81 (d, *J* = 8.3 Hz, 1H), 7.66 – 7.55 (m, 4H), 7.41 – 7.37 (m, 4H), 7.04 – 6.98 (m, 2H), 6.96 – 6.90 (m, 2H), 5.12 (s, 2H), 3.58 (dt, *J* = 18.3, 6.9 Hz, 6H), 3.41 – 3.35 (m, 5H), 1.70 – 1.55 (m, 4H), 1.50 (s, 6H), 1.24 – 1.15 (m, 4H), 1.08 – 0.99 (m, 1H). ¹³C NMR (101 MHz, DMSO) δ 192.64, 171.70, 158.16, 154.45, 153.20, 136.81, 131.71, 131.37, 130.92, 128.44, 127.89, 127.63, 126.56, 118.15, 113.36, 80.47, 66.36, 47.92, 46.42 (2C, CON(CH₂)₂), 42.98 (2C, N(CH₂)₂), 31.95 (2C, cyclohexane), 25.08 (2C, C(CH₃)₂), 24.84 (3C, cyclohexane). HRMS (ESI-TOF) calc'd for C₃₅H₄₂O₅N₃ [M+H]⁺: 584.3119, found: 584.3121.

2-(4-(4-(4-Acetylpiperazin-1-yl)benzoyl)phenoxy)-*N*-cyclohexyl-2-methylpropanamide – (49)

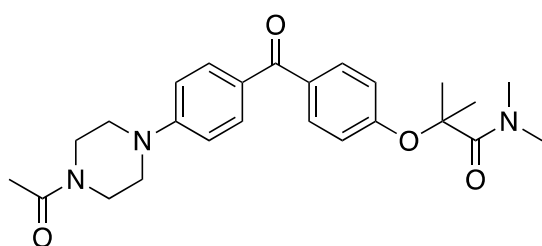


General Procedure B using **12** (70 mg, 0.175 mmol), RuPhosPdG3 (14.5 mg, 0.0175 mmol), Cs₂CO₃ (113 mg, 0.35 mmol), 1-acetylpiperazine (26 mg, 0.21 mmol) in

^tBuOH (0.1 M) gave **49** (29 mg, 0.0595 mmol, 34%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.67 – 7.59 (m, 4H), 7.06 – 6.98 (m, 2H), 6.97 – 6.91 (m, 2H), 3.65 – 3.55 (m, 4H), 3.44 – 3.38 (m, 4H), 2.05 (s, 3H), 1.64 (dd, $J = 11.1, 4.7$ Hz, 4H), 1.50 (s, 6H), 1.30 – 0.96 (m, 7H). **¹³C NMR** (101 MHz, DMSO) δ 192.60, 171.70, 168.39, 158.11, 153.15, 131.68, 131.42, 130.86, 129.22, 128.41, 126.46, 118.18, 113.19, 80.48, 47.91, 46.67, 46.37, 45.01, 40.35, 31.92 (2C, cyclohexane), 25.05 (2C, C(CH₃)₂), 24.81 (3C, cyclohexane), 21.15. **HRMS** (ESI-TOF) calc'd for C₂₉H₃₈O₄N₃ [M+H]⁺: 492.2857, found: 492.2857.

2-(4-(4-(4-Acetylpiperazin-1-yl)benzoyl)phenoxy)-*N,N*,2-trimethylpropanamide – (50)

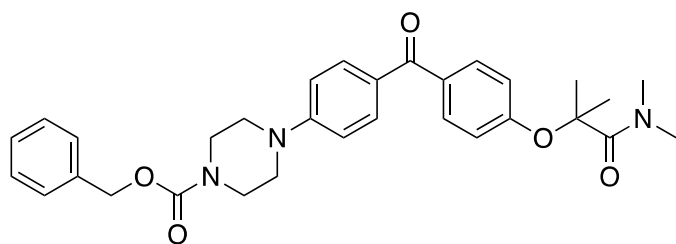


General Procedure B using **14** (100 mg, 0.289 mmol), RuPhosPdG3 (24 mg, 0.0289 mmol), Cs₂CO₃ (187 mg, 0.378 mmol), 1-acetylpiperazine (44 mg, 0.346 mmol) in tBuOH

(0.1 M) gave **50** (47 mg, 0.106 mmol, 37%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.69 – 7.60 (m, 4H), 7.05 – 6.97 (m, 2H), 6.92 – 6.83 (m, 2H), 3.62 – 3.53 (m, 4H), 3.40 (dd, $J = 6.6, 3.9$ Hz, 4H), 3.06 (s, 3H), 2.84 (s, 3H), 2.04 (s, 3H), 1.60 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 192.47, 171.19, 168.39, 158.12, 153.16, 131.72, 131.39, 131.29, 126.39, 116.11, 113.20, 80.91, 46.66, 46.37, 45.01, 40.35, 36.78 (2C, N(CH₃)₂), 25.49 (2C, C(CH₃)₂), 21.16. **HRMS** (ESI-TOF) calc'd for C₂₅H₃₂O₄N₃ [M+H]⁺: 438.2387, found: 438.2390.

Benzyl 4-(4-(4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)piperazine-1-carboxylate – (51)



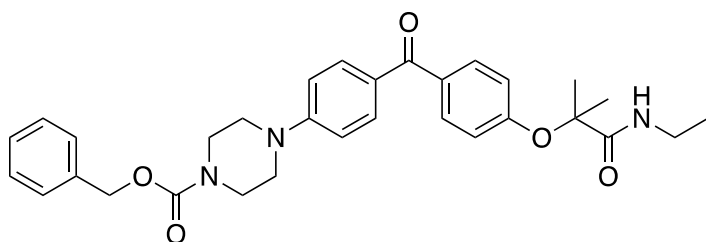
General Procedure B using **14** (100 mg, 0.289 mmol), RuPhosPdG3 (24 mg, 0.0289 mmol), Cs₂CO₃ (187 mg, 0.378 mmol), 1-cbz-piperazine (76

mg, 0.346 mmol) in ^tBuOH (0.1 M) gave **51** (66 mg, 0.124 mmol, 43%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.69 – 7.58 (m, 4H), 7.42 – 7.29 (m, 5H), 7.05 – 6.99 (m, 2H), 6.92 – 6.84 (m, 2H), 5.12 (s, 2H), 3.60 – 3.52 (m, 4H), 3.42 – 3.35 (m, 4H), 3.06 (s, 3H), 2.84 (s, 3H), 1.60 (s, 6H). ¹³C NMR (101 MHz, DMSO) δ 192.50, 171.19, 158.13, 154.45, 153.18, 136.80, 131.72, 131.41, 131.27, 128.42, 127.87, 127.60, 126.49, 116.12, 113.34, 80.92, 66.34, 46.40 (2C, CON(CH₂)₂), 42.92 (2C, N(CH₂)₂), 36.80 (2C, N(CH₃)₂), 25.50 (2C, C(CH₃)₂).

HRMS (ESI-TOF) calc'd for C₃₁H₃₆O₅N₃ [M+H]⁺: 530.2649, found: 530.2652.

Benzyl 4-(4-(4-((1-(ethylamino)-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)piperazine-1-carboxylate – (52)



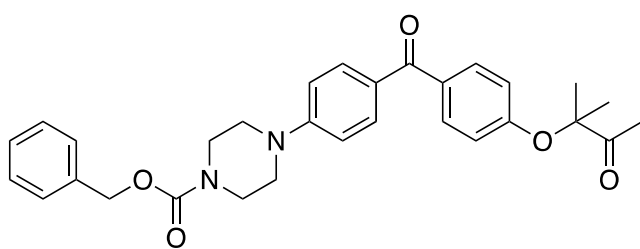
General Procedure B using **10** (70 mg, 0.2 mmol), RuPhosPdG3 (16.9 mg, 0.02 mmol), Cs₂CO₃ (130 mg, 0.40 mmol), 1-cbz-piperazine (52

mg, 0.24 mmol) in ^tBuOH (0.1 M) gave **52** (41 mg, 0.078 mmol, 39%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 8.14 (t, *J* = 6.0 Hz, 1H), 7.63 (dd, *J* = 8.8, 1.6 Hz, 4H), 7.44 – 7.28 (m, 5H), 7.05 – 6.98 (m, 2H), 6.97 – 6.91 (m, 2H), 5.12 (s, 2H), 3.60 – 3.52 (m, 4H), 3.40 – 3.37 (m, 4H), 3.17 – 3.08 (m, 2H), 1.50 (s, 6H), 0.97 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 192.65, 172.51, 158.12, 154.46, 153.21, 136.81, 131.74, 131.47, 130.95,

128.45, 127.91, 127.64, 126.53, 118.26, 113.37, 80.51, 66.37, 46.41 (2C, CON(CH₂)₂), 42.94 (2C, N(CH₂)₂), 33.63, 25.05 (2C, C(CH₃)₂), 14.51. **HRMS** (ESI-TOF) calc'd for C₃₁H₃₆O₅N₃ [M+H]⁺: 530.2649, found: 530.2650.

Benzyl 4-(4-(4-((2-methyl-3-oxobutan-2-yl)oxy)benzoyl)phenyl)piperazine-1-carboxylate – (53)

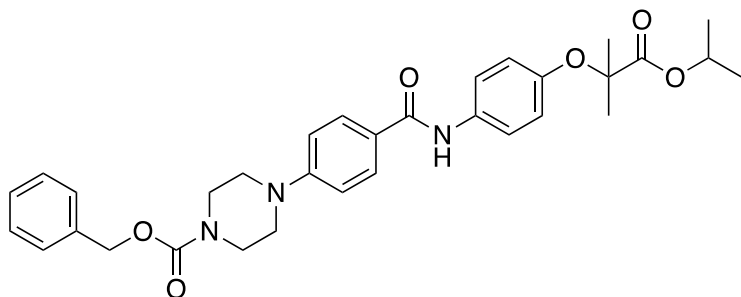


General Procedure B using **8** (100 mg, 0.316 mmol), RuPhosPdG3 (26 mg, 0.0316 mmol), Cs₂CO₃ (205 mg, 0.632 mmol), 1-cbz-piperazine (73 μL, 0.55

mmol) in tert-butanol (0.1 M) gave **53** (84 mg, 0.167 mmol, 53%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.68 – 7.61 (m, 4H), 7.42 – 7.28 (m, 5H), 7.04 – 6.96 (m, 2H), 6.88 – 6.82 (m, 2H), 5.12 (s, 2H), 3.59 – 3.52 (m, 4H), 3.42 – 3.35 (m, 4H), 2.24 (s, 3H), 1.50 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 209.93, 192.53, 158.08, 154.46, 153.23, 136.81, 131.77, 131.48, 131.36, 128.87, 128.45, 127.90, 127.63, 126.47, 117.30, 113.36, 84.22, 66.37, 46.40 (2C, CON(CH₂)₂), 43.00 (2C, N(CH₂)₂), 26.34, 24.46 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₃₀H₃₃O₅N₂ [M+H]⁺: 501.2384, found: 501.2386.

Benzyl 4-(4-((4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)carbamoyl)phenyl)piperazine-1-carboxylate – (54)

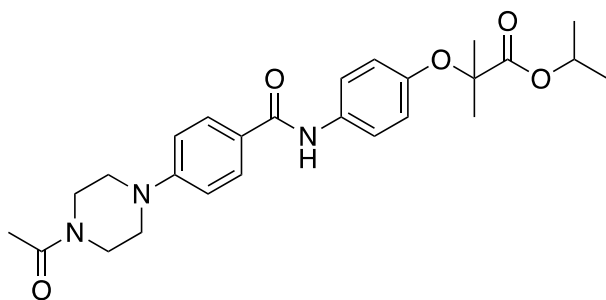


General Procedure B using **39** (100 mg, 0.266 mmol), RuPhos Pd G3 (22 mg, 0.0226 mmol), Cs₂CO₃ (172 mg, 0.53 mmol), 1-Z-piperazine (56 μL, 0.292

mmol) and tert-butanol (3 mL) gave **54** (46 mg, 0.0824 mmol, 31%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 9.89 (s, 1H), 7.90 – 7.81 (m, 2H), 7.68 – 7.58 (m, 2H), 7.42 – 7.28 (m, 5H), 7.07 – 6.96 (m, 2H), 6.84 – 6.74 (m, 2H), 5.12 (s, 2H), 4.96 (hept, J = 6.0 Hz, 1H), 3.55 (s, 4H), 3.33 – 3.28 (m, 4H), 1.49 (s, 6H), 1.18 (d, J = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 172.75, 164.68, 154.46, 152.71, 150.74, 136.85, 134.02, 129.00, 128.47, 127.92, 127.64, 124.17, 121.36, 119.21, 113.92, 78.87, 68.50, 66.36, 46.98 (2C, CON(CH₂)₂), 43.07 (2C, N(CH₂)₂), 25.02 (2C, C(CH₃)₂), 21.33 (2C, CH(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₃₂H₃₇N₃O₆ [M+H]⁺: 559.2682, found: 559.2690.

Isopropyl 2-(4-(4-(4-acetylpiperazin-1-yl)benzamido)phenoxy)-2-methylpropanoate – (55)

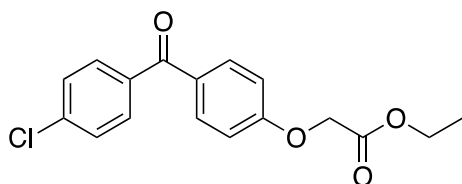


General Procedure B using **39** (40 mg, 0.106 mmol), RuPhos Pd G3 (22 mg, 0.0106 mmol), Cs₂CO₃ (86 mg, 0.265 mmol), 1-acetyl-piperazine (16.2 mg, 0.127 mmol) and tert-butanol (1.5 mL) gave **55** (7

mg, 0.0159 mmol, 15%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 9.87 (s, 1H), 7.90 – 7.84 (m, 2H), 7.67 – 7.58 (m, 2H), 7.05 – 6.99 (m, 2H), 6.84 – 6.74 (m, 2H), 4.97 (hept, J = 6.0 Hz, 1H), 3.64 – 3.55 (m, 4H), 3.29 – 3.23 (m, 4H), 2.05 (s, 3H), 1.49 (s, 6H), 1.19 (d, J = 6.0 Hz, 6H). **¹³C NMR** (101 MHz, DMSO) δ 172.69, 168.34, 164.66, 152.65, 150.71, 134.02, 128.96, 124.03, 121.31, 119.24, 113.73, 78.87, 68.45, 47.27 (2C, CON(CH₂)₂), 45.12 (2C, N(CH₂)₂), 24.99 (2C, C(CH₃)₂), 21.29 (2C, CH(CH₃)₂), 21.17. **HRMS** (ESI-TOF) calc'd for C₂₆H₃₄N₃O₅ [M+H]⁺: 468.2493, found: 468.2494.

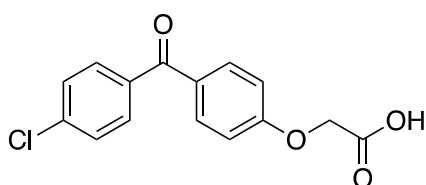
Ethyl 2-(4-(4-chlorobenzoyl)phenoxy)acetate – (56a)



A mixture of (4-chlorophenyl)(4-hydroxyphenyl)methanone (1.1 g, 0.004 mol) and Cs_2CO_3 (3.0 g, 0.0094 mol) in *N,N*-dimethylacetamide (7 mL) was prepared before the addition of ethyl bromoacetate (534 μL , 0.0048 mol). The resultant mixture was heated at 100°C overnight. Water (30 mL) was then added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic fractions were combined, washed with brine, dried (Na_2SO_4) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (EtOAc 0 %- 25%, in cyclohexane) over 10 column volumes gave **56a** (960 mg, 0.0030 mol, 75%) with the colourless oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 7.79 – 7.67 (m, 4H), 7.65 – 7.56 (m, 2H), 7.13 – 7.05 (m, 2H), 4.92 (s, 2H), 4.18 (q, $J = 7.0$ Hz, 2H), 1.22 (t, $J = 7.0$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 193.22, 168.22, 161.38, 137.04, 136.27, 132.04, 131.14, 129.68, 128.57, 114.51, 64.72, 60.78, 13.99. **HRMS** (ESI-TOF) calc'd for $\text{C}_{17}\text{H}_{16}\text{O}_4^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$: 319.0732, found: 319.0742.

2-(4-(4-Chlorobenzoyl)phenoxy)acetic acid – (56b)

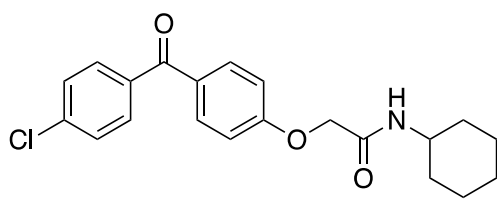


56a (920 mg, 2.89 mmol) was dissolved in a mixture of THF (50 mL) and H_2O (5 mL) before the addition of lithium hydroxide monohydrate (355 mg, 8.67 mmol). The resultant mixture was stirred for 16 hrs. H_2O (50 mL) was added to the reaction mixture before the THF was removed in *vacuo*. The aqueous mixture was extracted with EtOAc (50 mL) before being acidified to pH 3. The aqueous solution was then extracted with EtOAc (3 x 50 mL). The organic fractions were combined, dried (Na_2SO_4) and the solvent was removed in

vacuo. The crude mixture was then purified using flash column chromatography using (0 – 100% EtOAc, in cyclohexane (0.1% formic acid)) over 20 column volumes gave **56b** (746 mg, 2.57 mmol, 89%) with the colourless oil.

¹H NMR (400 MHz, DMSO) δ 13.05 (s, 1H), 7.78 – 7.59 (m, 6H), 7.18 – 7.02 (m, 2H), 4.82 (s, 2H). **¹³C NMR** (101 MHz, DMSO) δ 193.27, 169.68, 161.59, 137.02, 136.34, 132.07, 131.17, 129.51, 128.59, 114.48, 64.59. **HRMS** (ESI-TOF) calc'd for C₁₅H₁₀O₄³⁵Cl [M+H]⁺: 289.0273, found: 289.0270.

2-(4-(4-Chlorobenzoyl)phenoxy)-*N*-cyclohexyl acetamide – (56c)

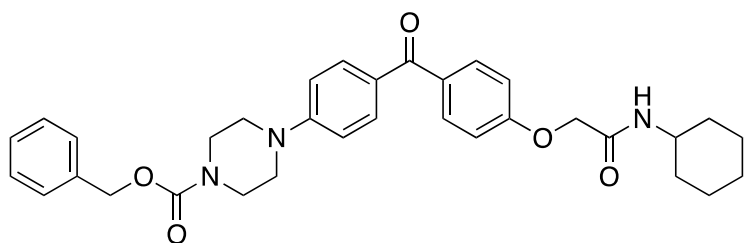


General Procedure A using **56b** (400 mg, 1.37 mmol), HATU (1.04 g, 2.75 mmol), DIPEA (706 μ L, 4.11 mmol) and cyclohexylamine (235 μ L, 2.05

mmol) gave **56c** (275 mg, 0.74 mmol, 54%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.97 (d, J = 8.0 Hz, 1H), 7.79 – 7.64 (m, 4H), 7.64 – 7.54 (m, 2H), 7.13 – 7.02 (m, 2H), 4.58 (s, 2H), 3.63 (qd, J = 10.0, 4.0 Hz, 1H), 1.78 – 1.50 (m, 5H), 1.32 – 1.02 (m, 6H). **¹³C NMR** (101 MHz, DMSO) δ 193.29, 165.89, 161.70, 137.03, 136.35, 132.04, 131.15, 129.51, 128.59, 114.66, 66.95, 47.52, 32.24 (2C, (CH₂)₂), 25.15, 24.63 (2C, (CH₂)₂). **HRMS** (ESI-TOF) calc'd for C₂₁H₂₃NO₃³⁵Cl [M+H]⁺: 372.1361, found: 372.1363.

Benzyl 4-(4-(4-(2-(cyclohexylamino)-2-oxoethoxy)benzoyl)phenyl)piperazine-1-carboxylate – (56)

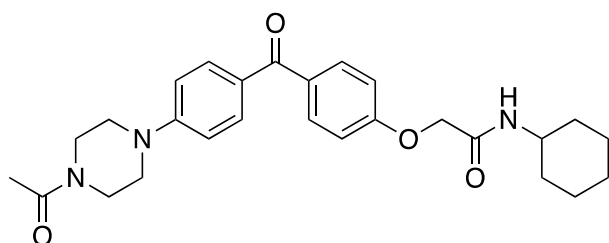


General Procedure B using **56c** (100 mg, 0.269 mmol), RuPhos Pd G3 (23 mg, 0.0269 mmol), Cs₂CO₃ (171 mg, 0.52 mmol), 1-

Z-piperazine (62 μL, 0.322 mmol) and tert-butanol (3 mL) gave **57** (48 mg, 0.0860 mmol, 32%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.61 (m, 4H), 7.39 – 7.30 (m, 5H), 7.10 – 6.97 (m, 4H), 5.12 (s, 2H), 4.56 (s, 2H), 3.58 – 3.52 (m, 4H), 3.42 – 3.36 (m, 4H), 1.80 – 1.50 (m, 5H), 1.31 – 1.06 (m, 6H). ¹³C NMR (101 MHz, DMSO) δ 192.64, 166.02, 160.70, 154.45, 153.16, 136.80, 131.68, 131.36, 131.10, 128.42, 127.87, 127.59, 126.66, 114.33, 113.35, 66.95, 66.34, 47.48, 46.42 (2C, CON(CH₂)₂), 42.95 (2C, N(CH₂)₂), 32.23 (2C, (CH₂)₂), 25.13, 24.61 (2C, (CH₂)₂). HRMS (ESI-TOF) calc'd for C₃₃H₃₈N₃O₃ [M+H]⁺: 556.2806, found: 556.2809.

2-(4-(4-(4-Acetylpiperazin-1-yl)benzoyl)phenoxy)-N-cyclohexylacetamide – (57)

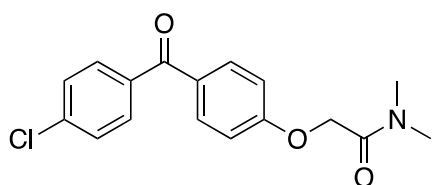


General Procedure B using **56c** (100 mg, 0.269 mmol), RuPhos Pd G3 (23 mg, 0.0269 mmol), Cs₂CO₃ (171 mg, 0.55 mmol), 1-acetyl-piperazine (41 mg, 0.322

mmol) and tert-butanol (3 mL) gave **56** (44 mg, 0.0945 mmol, 35%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.69 – 7.61 (m, 4H), 7.09 – 6.99 (m, 4H), 4.56 (s, 2H), 3.61 – 3.54 (m, 4H), 3.43 – 3.38 (m, 4H), 2.05 (s, 3H), 1.75 – 1.50 (m, 7H), 1.31 – 1.19 (m, 4H). **¹³C NMR** (101 MHz, DMSO) δ 192.62, 168.41, 166.02, 160.69, 153.13, 131.68, 131.35, 131.12, 126.56, 114.33, 113.21, 66.95, 47.49, 46.68, 46.39, 45.02, 40.36, 32.23 (2C, (CH₂)₂), 25.14, 24.62 (2C, (CH₂)₂), 21.16. **HRMS** (ESI-TOF) calc'd for C₂₇H₃₄N₃O₄ [M+H]⁺: 464.2544, found: 464.2546.

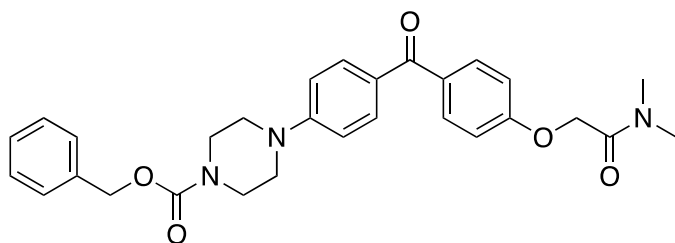
2-(4-(4-Chlorobenzoyl)phenoxy)-*N,N*-dimethylacetamide – (58c)



General Procedure A using **56b** (400 mg, 1.37 mmol), HATU (1.04 g, 2.75 mmol), DIPEA (706 μ L, 4.11 mmol) and dimethylamine HCl (167 mg, 2.05 mmol) in *N,N*-dimethylacetamide (5 mL) gave **58c** (274 mg, 0.863 mmol, 63%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.71 (m, 4H), 7.65 – 7.55 (m, 2H), 7.09 – 7.00 (m, 2H), 4.96 (s, 2H), 3.00 (s, 3H), 2.85 (s, 3H). **¹³C NMR** (101 MHz, DMSO) δ 193.27, 166.58, 162.12, 150.90, 137.01, 136.40, 131.94, 131.17, 128.73, 128.58, 120.60, 114.62, 65.67, 35.48 (2C, N(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₁₇H₁₇NO₃³⁵Cl [M+H]⁺: 318.0891, found: 318.0892.

Benzyl 4-(4-(4-(2-(dimethylamino)-2-oxoethoxy)benzoyl)phenyl)piperazine-1-carboxylate – (58)



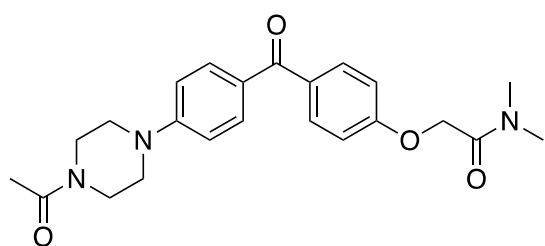
General Procedure B using **58c** (100 mg, 0.315 mmol), RuPhos Pd G3 (26 mg, 0.0315 mmol), Cs₂CO₃ (204 mg, 0.63 mmol), 1-Cbz-piperazine (73 μ L, 0.378 mmol) and tert-butanol (3 mL) gave **58** (44 mg, 0.0882 mmol, 28%) as a yellow oil.

0.378 mmol) and tert-butanol (3 mL) gave **58** (44 mg, 0.0882 mmol, 28%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.66 – 7.62 (m, 4H), 7.40 – 7.30 (m, 5H), 7.04 – 6.99 (m, 4H), 5.12 (s, 2H), 4.93 (s, 2H), 3.59 – 3.51 (m, 4H), 3.41 – 3.37 (m, 4H), 3.00 (s, 3H), 2.86 (s, 3H).

¹³C NMR (101 MHz, DMSO) δ 192.64, 166.69, 161.10, 154.45, 153.15, 136.80, 131.68, 131.26, 130.80, 128.42, 127.87, 127.59, 126.72, 114.26, 113.35, 66.34, 65.65, 46.42 (2C, CON(CH₂)₂), 42.97 (2C, N(CH₂)₂), 34.95 (2C, N(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₉H₃₂N₃O₅ [M+H]⁺: 502.2336, found: 502.2340.

2-(4-(4-(4-Acetylpiperazin-1-yl)benzoyl)phenoxy)-N,N-dimethylacetamide – (59)



General Procedure B using **58c** (100 mg, 0.315 mmol), RuPhos Pd G3 (26 mg, 0.0315 mmol), Cs₂CO₃ (204 mg, 0.63 mmol), 1-acetyl-piperazine (48 mg, 0.378 mmol) and tert-butanol

(3 mL) gave **59** (31 mg, 0.0756 mmol, 24%) as a yellow oil.

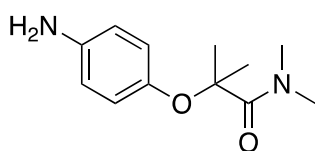
¹H NMR (400 MHz, DMSO) δ 7.66 – 7.61 (m, 4H), 7.04 – 6.99 (m, 4H), 4.93 (s, 2H), 3.64 – 3.53 (m, 4H), 3.47 – 3.38 (m, 4H), 3.01 (s, 3H), 2.86 (s, 3H), 2.05 (s, 3H). **¹³C NMR** (101

MHz, DMSO) δ 192.64, 168.43, 166.70, 161.09, 153.14, 131.70, 131.26, 130.83, 126.61,

114.27, 113.22, 65.65, 46.69 (2C, CON(CH₂)₂), 45.02 (2C, N(CH₂)₂), 35.49, 34.96, 21.18.

HRMS (ESI-TOF) calc'd for C₂₃H₂₈N₃O₄ [M+H]⁺: 410.2074, found: 410.2077.

2-(4-Aminophenoxy)-*N,N*,2-trimethylpropanamide – (60b)

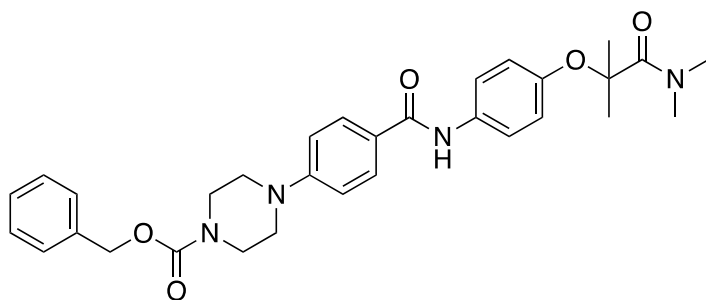


General Procedure A using 2-(4-Aminophenoxy)-2-methylpropanoic acid (3.165 g, 16.23 mmol), HATU (7.40 g, 19.45 mmol), DIPEA (8.37 mL, 48.6 mmol) and dimethylamine HCl

(2.62 g, 32.46 mmol) gave **60b** (1981 mg, 8.92 mmol, 55%) as a brown oil.

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 3.10 (s, 3H), 2.88 (s, 3H), 1.56 (s, 6H). **¹³C NMR** (101 MHz, CDCl₃) δ 173.23, 155.51, 124.39, 118.16, 81.22, 37.67, 37.49, 25.71 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₁₂H₁₉N₂O₂ [M+H]⁺: 223.1441, found: 223.1443.

Benzyl 4-(4-((4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)carbamoyl)-phenyl)piperazine-1-carboxylate – (60)

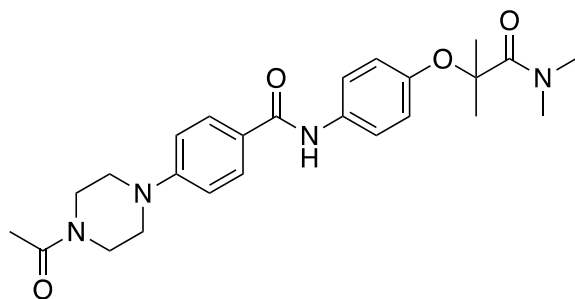


General Procedure A using 4-(4-((Benzyloxy)carbonyl)piperazin-1-yl)benzoic acid (100 mg, 0.29 mmol), HATU (134 mg, 0.35 mmol), DIPEA (150 μL, 0.87

mmol), **60b** (128 mg, 0.58 mmol) in *N,N*-dimethylformamide (50 mL) gave **60** (65 mg, 0.1189 mmol, 41%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 9.85 (s, 1H), 7.89 – 7.82 (m, 2H), 7.65 – 7.58 (m, 2H), 7.41 – 7.29 (m, 5H), 7.05 – 6.98 (m, 2H), 6.77 – 6.71 (m, 2H), 5.12 (s, 2H), 3.62 – 3.51 (m, 4H), 3.14 (s, 3H), 2.86 (s, 3H), 1.51 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 171.82, 164.65, 154.44, 152.67, 150.82, 136.81, 133.55, 128.95, 128.42, 127.86, 127.58, 124.17, 121.73, 117.28, 113.88, 80.41, 68.50, 66.31, 46.96 (2C, CON(CH₂)₂), 43.07 (2C, N(CH₂)₂), 36.90 (2C, N(CH₃)₂), 25.55 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₃₁H₃₇N₄O₅ [M+H]⁺: 545.2753, found: 545.2755.

4-(4-Acetylpiperazin-1-yl)-*N*-(4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)benzamide – (61)

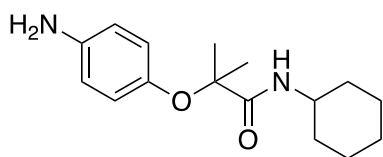


General Procedure A using 4-(4-Acetylpiperazin-1-yl)benzoic acid (100 mg, 0.40 mmol), HATU (183 mg, 0.48 mmol), DIPEA (206.4 μ L, 1.2 mmol), **60b** (178 mg, 0.80 mmol) in *N,N*-dimethylformamide (50

mL) gave **61** (61 mg, 0.136 mmol, 34%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 9.86 (s, 1H), 7.90 – 7.81 (m, 2H), 7.67 – 7.57 (m, 2H), 7.05 – 6.98 (m, 2H), 6.79 – 6.71 (m, 2H), 3.61 – 3.52 (m, 4H), 3.30 – 3.24 (m, 4H), 3.14 (s, 3H), 2.86 (s, 3H), 2.05 (s, 3H), 1.52 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 171.81, 168.32, 164.66, 152.64, 150.81, 133.56, 128.94, 124.05, 121.71, 117.28, 113.74, 80.41, 47.27, 46.92, 45.11, 40.39, 36.90 (2C, N(CH₃)₂), 25.54 (2C, C(CH₃)₂), 21.16. **HRMS** (ESI-TOF) calc'd for C₂₅H₃₃N₄O₄ [M+H]⁺: 453.2491, found: 453.2493.

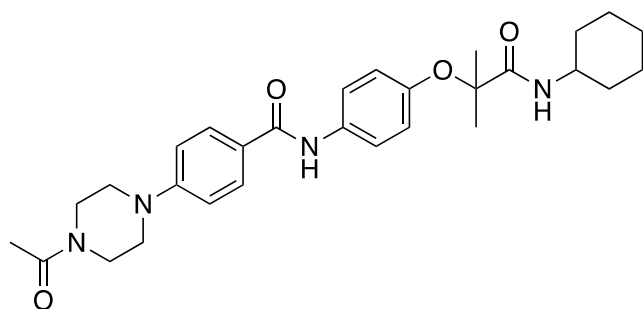
2-(4-Aminophenoxy)-*N*-cyclohexyl-2-methylpropanamide – (62b)



General Procedure A using 2-(4-Aminophenoxy)-2-methylpropanoic acid (500 mg, 2.56 mmol), HATU (1169 mg, 3.07 mmol), DIPEA (661 μ L, 3.84 mmol), cyclohexylamine (1.2 mL, 12.8 mmol) in *N,N*-dimethylformamide (20 mL) gave **62b** (473 mg, 1.71 mmol, 67%) as a colourless oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 10.20 (s, 2H), 7.79 (d, $J = 8.3$ Hz, 1H), 7.33 – 7.25 (m, 2H), 7.00 – 6.90 (m, 2H), 3.58 (td, $J = 9.5, 4.9$ Hz, 1H), 1.70 – 1.60 (m, 4H), 1.55 (dt, $J = 15.4, 4.5$ Hz, 1H), 1.42 (s, 6H), 1.29 – 1.14 (m, 4H), 1.08 – 0.97 (m, 1H). $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 171.89, 154.24, 125.75, 123.88, 120.30, 80.38, 47.86, 31.98 (2C, $(\text{CH}_2)_2$), 25.10 (2C, $\text{C}(\text{CH}_3)_2$), 24.93, 24.84. **HRMS** (ESI-TOF) calc'd for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 277.1911, found: 277.1912.

4-(4-Acetylpiperazin-1-yl)-*N*-(4-((1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-benzamide – (62)



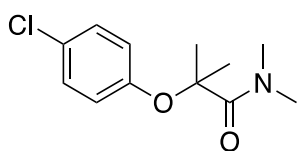
General Procedure A using 4-(4-Acetylpiperazin-1-yl)benzoic acid (250 mg, 1.01 mmol), HATU (766 mg, 2.01 mmol), DIPEA (434 μ L, 2.52 mmol), **62b** (418 mg, 1.51 mmol) in *N,N*-dimethylformamide (10 mL) gave **62** (184 mg, 0.363 mmol, 36%) as a colourless oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 9.86 (s, 1H), 7.90 – 7.83 (m, 2H), 7.69 – 7.59 (m, 2H), 7.08 – 6.98 (m, 2H), 6.90 – 6.78 (m, 2H), 3.63 – 3.56 (m, 5H), 3.29 – 3.25 (m, 2H), 2.05 (s, 3H), 1.75 – 1.50 (m, 7H), 1.39 (s, 6H), 1.30 – 1.20 (m, 4H). $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 172.48,

168.34, 164.67, 152.66, 150.34, 134.20, 128.96, 124.03, 121.17, 120.31, 113.74, 80.22, 47.79, 47.26, 46.92, 45.13, 40.40, 32.03 (2C, (CH₂)₂), 25.12 (2C, N(CH₂)₂), 24.99, 24.84, 21.72.

HRMS (ESI-TOF) calc'd for C₂₉H₃₉N₄O₄ [M+H]⁺: 507.2960, found: 507.2983.

2-(4-Chlorophenoxy)-*N,N*,2-trimethylpropanamide – (63b)

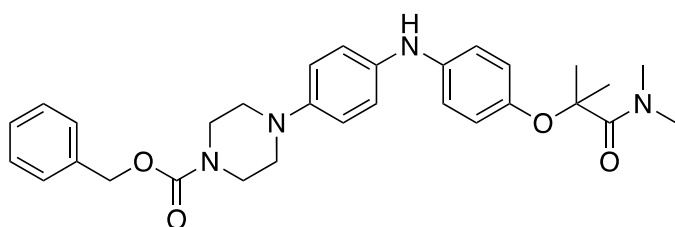


General Procedure A using **63a** (500 mg, 2.33 mmol), HATU (1.70 g, 4.67 mmol), DIPEA (1.2 mL, 0.87 mmol), dimethylamine (128 mg, 0.58 mmol) in *N,N*-dimethylformamide (50 mL) gave **63b** (470

mg, 1.95 mmol, 84%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.34 – 7.28 (m, 2H), 6.81 – 6.75 (m, 2H), 3.07 (s, 3H), 2.83 (s, 3H), 1.52 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 171.30, 153.94, 129.35, 129.01, 125.23, 120.18, 118.60, 80.71, 36.78 (2C, N(CH₃)₂), 25.37 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₁₂H₁₇NO₂³⁵Cl [M+H]⁺: 242.0942, found: 242.0942.

Benzyl 4-(4-((4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)amino)phenyl)piperazine-1-carboxylate – (63c)

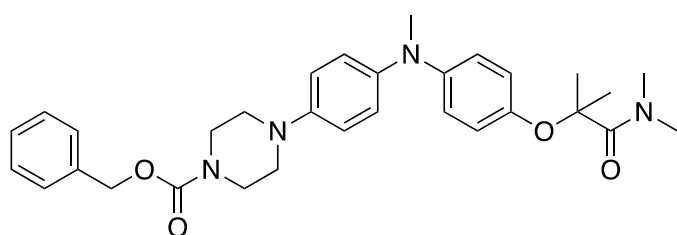


General Procedure B using Benzyl 4-(4-aminophenyl)piperazine-1-

carboxylate (250 mg, 0.80 mmol), BrettPhos Pd G3 (72 mg, 0.080 mmol), Cs₂CO₃ (520 mg, 1.6 mmol), **63b** (290 mg, 1.20 mmol) and tert-butanol (10 mL) gave **63c** (239 mg, 0.464 mmol, 58%) as a blue oil.

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.30 (m, 5H), 6.98 – 6.90 (m, 2H), 6.88 – 6.83 (m, 4H), 6.73 – 6.68 (m, 2H), 5.34 (s, 1H), 5.16 (s, 2H), 3.70 – 3.63 (m, 4H), 3.24 (s, 3H), 3.09 – 3.01 (m, 4H), 2.97 (s, 3H), 1.59 (s, 6H). ¹³C NMR (151 MHz, DMSO) δ 172.01, 154.24, 149.50, 144.36, 128.51, 128.03, 127.78, 121.78, 120.19, 118.71, 115.41, 80.54, 66.79, 53.47 (2C, CON(CH₂)₂), 41.26 (2C, N(CH₂)₂), 36.98 (2C, N(CH₃)₂), 25.63 (2C, C(CH₃)₂). HRMS (ESI-TOF) calc'd for C₃₀H₃₆N₄O₄ [M+H]⁺: 516.2737, found: 516.2738.

Benzyl 4-(4-((4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)(methyl)amino)phenyl)piperazine-1-carboxylate – (63)

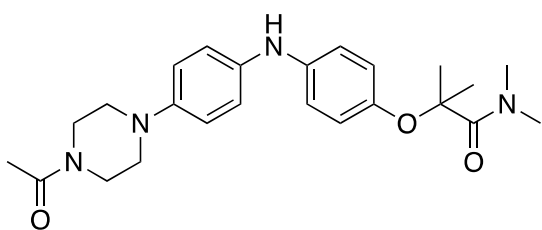


A solution of **63c** (70 mg, 0.135 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; paraformaldehyde (6 mg, 0.20 mmol)

was then added. The resultant mixture was heated to 50°C for 10 minutes before the addition of sodium triacetoxyborohydride (88 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0% - 20%, in CH₂Cl₂) over 20 column volumes to give **63** (44 mg, 0.0837 mmol, 62%) as a purple oil.

¹H NMR (400 MHz, DMSO) δ 7.38 (d, J = 4.0 Hz, 5H), 6.90 (s, 4H), 6.77 – 6.73 (m, 2H), 6.68 – 6.63 (m, 2H), 5.10 (s, 2H), 3.53 (d, J = 7.0 Hz, 4H), 3.18 (s, 3H), 3.12 (s, 3H), 3.04 (t, J = 5.2 Hz, 4H), 2.85 (s, 3H), 1.46 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 172.03, 154.41, 148.33, 146.30, 144.27, 141.92, 136.86, 128.44, 127.87, 127.59, 122.62, 119.00, 118.73, 117.47, 80.49, 66.28, 49.13 (2C, CON(CH₂)₂), 43.47 (2C, N(CH₂)₂), 40.41, 36.93 (2C, N(CH₃)₂), 25.60 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₃₁H₃₉N₄O₄ [M+H]⁺: 531.2971, found: 531.2973.

2-(4-((4-(4-Acetylpiperazin-1-yl)phenyl)amino)phenoxy)-*N,N*,2-trimethylpropanamide – (64c)

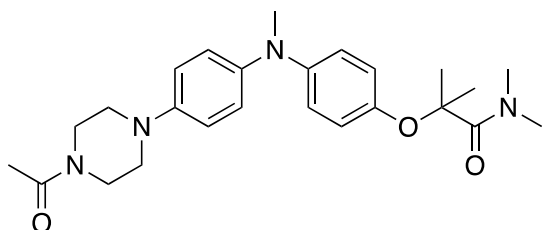


General Procedure B using 1-(4-(4-Aminophenyl)piperazin-1-yl)ethan-1-one (250 mg, 1.14 mmol), BrettPhos Pd G3 (103 mg, 0.114 mmol), Cs₂CO₃ (741 mg, 2.28 mmol), **64c** (412

mg, 1.71 mmol) and tert-butanol (10 mL) gave **1150** (309 mg, 0.729 mmol, 64%) as a purple oil.

¹H NMR (400 MHz, DMSO) δ 7.78 – 7.45 (m, 1H), 7.14 – 6.88 (m, 4H), 6.84 – 6.36 (m, 2H), 4.04 – 3.78 (m, 4H), 3.57 – 3.29 (m, 4H), 3.17 (s, 3H), 2.86 (s, 3H), 2.08 (s, 2H), 1.49 (s, 6H). **¹³C NMR** (151 MHz, DMSO) δ 172.03, 168.71, 149.80, 145.37, 136.33, 133.36, 122.23, 120.60, 119.26, 118.70, 115.79, 115.08, 80.59, 54.30 (2C, CON(CH₂)₂), 43.23 (2C, N(CH₂)₂), 37.07 (2C, N(CH₃)₂), 25.66 (2C, C(CH₃)₂), 21.12. **HRMS** (ESI-TOF) calc'd for C₂₄H₃₃N₄O₃ [M+H]⁺: 425.2553, found: 425.2554.

2-(4-((4-(4-Acetylpiperazin-1-yl)phenyl)(methyl)amino)phenoxy)-*N,N*,2-trimethylpropanamide – (64)

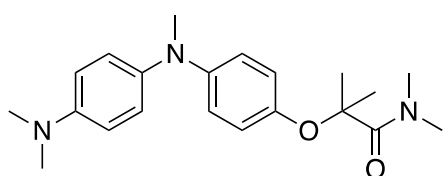


A solution of **64c** (70 mg, 0.165 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.1 mL) was prepared; paraformaldehyde (6.3 mg, 0.21 mmol) was then added. The resultant mixture was heated to 50°C

for 10 minutes before the addition of sodium triacetoxyborohydride (104 mg, 0.495 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0% - 20%, in CH₂Cl₂) over 20 column volumes to give **64** (31 mg, 0.070 mmol, 43%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 6.91 (s, 4H), 6.78 – 6.72 (m, 2H), 6.69 – 6.62 (m, 2H), 3.56 (q, *J* = 5.0 Hz, 4H), 3.18 (s, 3H), 3.13 (s, 3H), 3.07 (t, *J* = 5.0 Hz, 2H), 3.00 (t, *J* = 5.0 Hz, 2H), 2.85 (s, 3H), 2.03 (s, 3H), 1.46 (s, 6H). ¹³C NMR (101 MHz, DMSO) δ 172.01, 168.20, 148.29, 146.27, 144.28, 141.81, 122.65, 118.93, 118.73, 117.31, 80.48, 49.44 (2C, CON(CH₂)₂), 45.56 (2C, N(CH₂)₂), 40.75, 37.00 (2C, N(CH₃)₂), 25.58 (2C, C(CH₃)₂), 21.16. HRMS (ESI-TOF) calc'd for C₂₅H₃₅N₄O₄ [M+H]⁺: 439.2709, found: 439.2709.

2-(4-((4-(Dimethylamino)phenyl)(methyl)amino)phenoxy)-*N,N*,2-trimethylpropanamide – (65)

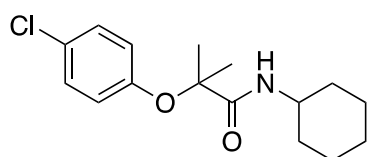


General Procedure B using *N*¹,*N*¹,*N*⁴-Trimethylbenzene-1,4-diamine (50 mg, 0.33 mmol), RuPhos Pd G3 (25 mg, 0.033 mmol), Cs₂CO₃ (214 mg,

0.66 mmol), **1140** (119 mg, 0.495 mmol) and tert-butanol (3 mL) gave **65** (43.37 mg, 0.122 mmol, 37%) as a yellow oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.96 – 6.90 (m, 2H), 6.75 – 6.70 (m, 2H), 6.62 (s, 4H), 3.20 (s, 3H), 3.11 (s, 3H), 2.86 (s, 9H), 1.45 (s, 6H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 172.10, 147.27, 147.16, 145.03, 138.74, 124.93, 118.81, 116.55, 113.63, 80.44, 40.54 (3C, $\text{N}(\text{CH}_3)_2$ & NCH_3), 37.02 (2C, $\text{N}(\text{CH}_3)_2$), 25.58 (2C, $\text{C}(\text{CH}_3)_2$). **HRMS** (ESI-TOF) calc'd for $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 356.2327, found: 356.2329.

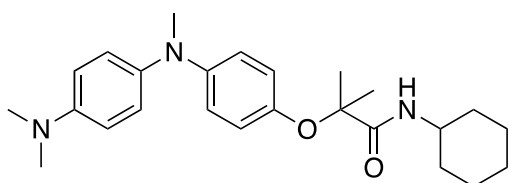
2-(4-Chlorophenoxy)-*N*-cyclohexyl-2-methylpropanamide – (**66b**)



General Procedure A using **63a** (500 mg, 2.33 mmol), HATU (1700 mg, 4.67 mmol), DIPEA (1.2 mL, 6.99 mmol), cyclohexylamine (319 μL , 2.796 mmol) in *N,N*-dimethylacetamide (10 mL) gave **66b** (467 mg, 1.58 mmol, 68%) as a colourless oil.

$^1\text{H NMR}$ (400 MHz, DMSO) δ 7.77 (d, $J = 8.5$ Hz, 1H), 7.35 – 7.26 (m, 2H), 6.92 – 6.83 (m, 2H), 3.58 (td, $J = 14.0, 8.0$ Hz, 1H), 1.71 – 1.49 (m, 5H), 1.41 (s, 6H), 1.31 – 0.97 (m, 5H). $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 171.91, 153.73, 128.88, 125.78, 121.22, 80.41, 47.84, 31.96 (2C, $(\text{CH}_2)_2$), 24.88 (2C, $\text{C}(\text{CH}_3)_2$), 24.83 (2C, $(\text{CH}_2)_2$). **HRMS** (ESI-TOF) calc'd for $\text{C}_{16}\text{H}_{23}\text{NO}_2^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$: 296.1412, found: 296.1417.

N-Cyclohexyl-2-(4-((4-(dimethylamino)phenyl)(methyl)amino)phenoxy)-2-methylpropanamide – (**66**)

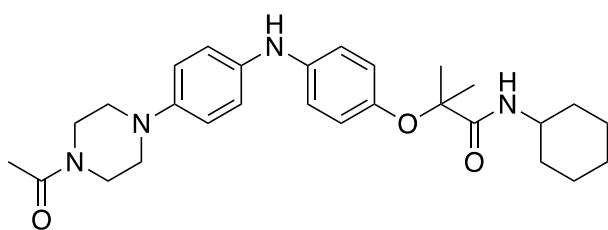


General Procedure B using N^1,N^1,N^4 -Trimethylbenzene-1,4-diamine (50 mg, 0.33 mmol), RuPhos Pd G3 (25 mg, 0.033 mmol),

Cs₂CO₃ (214 mg, 0.66 mmol), **66b** (146 mg, 0.495 mmol) and tert-butanol (3 mL) gave **66** (76 mg, 0.184 mmol, 56%) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.63 (d, *J* = 8.0 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.78 – 6.69 (m, 4H), 6.64 – 6.59 (m, 2H), 3.64 – 3.53 (m, 1H), 3.11 (s, 3H), 2.86 (s, 6H), 1.74 – 1.52 (m, 6H), 1.32 (s, 6H), 1.30 – 1.01 (m, 4H). ¹³C NMR (101 MHz, DMSO) δ 172.76, 147.33, 146.39, 145.60, 138.65, 125.12, 121.81, 115.85, 113.60, 80.26, 47.70, 40.50 (2C, N(CH₃)₂), 32.05 (2C, (CH₂)₂), 25.12 (2C, C(CH₃)₂), 24.99, 24.82. HRMS (ESI-TOF) calc'd for C₂₅H₃₆N₃O₂ [M+H]⁺: 410.2802, found: 410.2808.

2-(4-((4-(4-Acetylpiperazin-1-yl)phenyl)amino)phenoxy)-*N*-cyclohexyl-2-methylpropanamide – (67c)

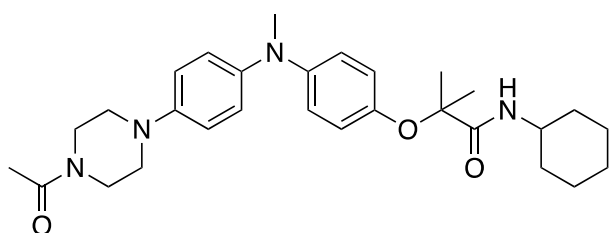


General Procedure B using 1-(4-(4-Aminophenyl)piperazin-1-yl)ethan-1-one (250 mg, 1.14 mmol), BrettPhos Pd G3 (103 mg, 0.114 mmol), Cs₂CO₃ (741 mg, 2.28

mmol), **66b** (504 mg, 1.71 mmol) and tert-butanol (10 mL) gave **67c** (266 mg, 0.558 mmol, 49%) as a purple oil.

¹H NMR (400 MHz, CDCl₃) δ 7.03 – 6.97 (m, 2H), 6.92 – 6.79 (m, 6H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.48 (s, 1H), 3.84 – 3.71 (m, 3H), 3.68 – 3.56 (m, 2H), 3.08 (dq, *J* = 13.7, 5.0 Hz, 4H), 2.13 (s, 3H), 1.97 – 1.57 (m, 6H), 1.44 (s, 6H), 1.40 – 1.12 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 173.84, 168.80, 147.46, 145.77, 140.16, 137.00, 122.71, 119.87, 118.28, 117.38, 81.38, 50.59, 50.23, 47.72, 46.19, 41.30, 32.81 (2C, (CH₂)₂), 25.34 (2C, C(CH₃)₂), 24.84, 24.65 (2C, (CH₂)₂), 21.14. HRMS (ESI-TOF) calc'd for C₂₈H₃₉N₄O₃ [M+H]⁺: 479.3022, found: 479.3024.

2-(4-((4-(4-Acetylpiperazin-1-yl)phenyl)(methyl)amino)phenoxy)-*N*-cyclohexyl-2-methylpropanamide – (67)

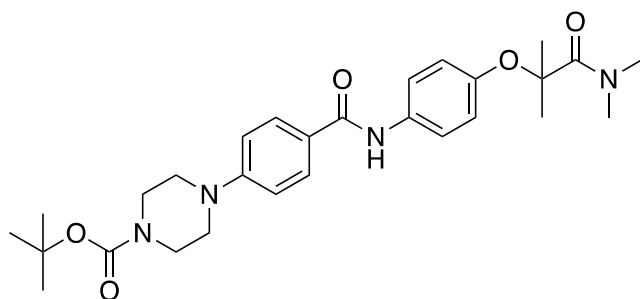


A solution of **67c** (70 mg, 0.165 mmol), CH₂Cl₂ (2 mL) and acetic acid (0.01 mL) was prepared; paraformaldehyde (6.3 mg, 0.21 mmol) was then added. The resultant

mixture was heated to 50°C for 10 minutes before the addition of sodium triacetoxyborohydride (104 mg, 0.495 mmol). The reaction mixture was stirred at room temperature for 16 h. A mixture saturated sodium bicarbonate solution and CH₂Cl₂ (20 mL (1:1)) was added. The organic and aqueous phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in *vacuo*. The crude mixture was then purified using flash column chromatography using (MeOH 0% - 20%, in CH₂Cl₂) over 20 column volumes to give **1155** (28 mg, 0.0561 mmol, 34%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.65 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 4H), 6.83 – 6.71 (m, 4H), 3.56 (q, *J* = 5.0 Hz, 4H), 3.13 (s, 3H), 3.07 (t, *J* = 5.0 Hz, 2H), 3.01 (t, *J* = 5.0 Hz, 2H), 2.03 (s, 3H), 1.71 – 1.51 (m, 6H), 1.34 (s, 6H), 1.30 – 1.01 (m, 5H). ¹³C NMR (101 MHz, DMSO) δ 172.66, 168.21, 147.59, 146.39, 144.85, 141.73, 122.92, 121.65, 118.17, 117.28, 80.27, 49.39, 49.02, 47.72, 45.56, 40.75, 32.04 (2C, (CH₂)₂), 25.12 (2C, C(CH₃)₂), 25.02, 24.82 (2C, (CH₂)₂), 21.16. HRMS (ESI-TOF) calc'd for C₂₉H₄₁N₄O₃ [M+H]⁺: 493.3179, found: 493.3180.

***tert*-Butyl 4-(4-((4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-carbamoyl)-phenyl)-piperazine-1-carboxylate – (68b)**

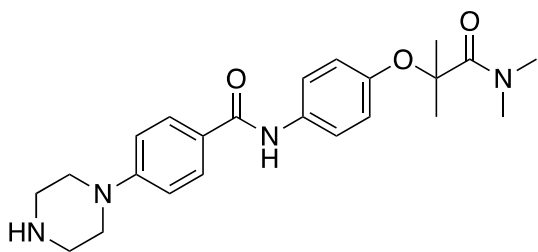


General Procedure A using 4-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)benzoic

acid (2.5 g, 8.17 mmol), HATU (6.2 g, 16.3 mmol), DIPEA (2.80 mL, 16.3 mmol), Feno-19 (2.17 g, 9.80 mmol) in *N,N*-dimethylformamide (100 mL) gave **68b** (1875 mg, 3.67 mmol, 45%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 8.75 (s, 1H), 7.96 – 7.80 (m, 2H), 7.67 – 7.56 (m, 2H), 7.11 – 6.99 (m, 2H), 6.78 – 6.70 (m, 2H), 3.55 – 3.40 (m, 4H), 3.30 – 3.21 (m, 4H), 3.14 (s, 3H), 2.86 (s, 3H), 1.52 (d, $J = 1.0$ Hz, 6H), 1.42 (s, 9H). **¹³C NMR** (151 MHz, DMSO) δ 171.86, 164.70, 153.88, 152.78, 151.99, 150.85, 133.58, 128.98, 124.14, 121.84, 121.77, 117.30, 114.30, 113.92, 80.44, 79.09, 47.06 (2C, CON(CH₂)₂), 42.55 (2C, N(CH₂)₂), 36.94 (2C, N(CH₃)₂), 28.08 (3C, C(CH₃)₃), 25.58 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₈H₃₉N₄O₅ [M+H]⁺: 511.2915, found: 511.2914.

***N*-(4-((1-(Dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-4-(piperazin-1-yl)benzamide – (68c)**



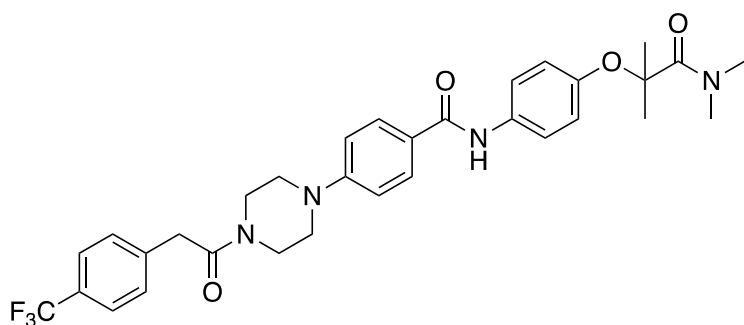
68b (1.85 g, 3.67 mmol) was dissolved in dichloromethane (CH₂Cl₂, 50 mL) and trifluoroacetic acid (25 mL). The resultant mixture was stirred at room temperature for 3 h. The

mixture was concentrated under vacuum and was purified using flash reverse phase chromatography (95% - 5% H₂O (0.05N HCl), 5% - 95% acetonitrile) to give **68c** (1.41 g, 3.44 mmol, 94%).

¹H NMR (400 MHz, DMSO) δ 9.91 (s, 1H), 9.04 – 8.92 (m, 1H), 7.91 – 7.87 (m, 2H), 7.64 – 7.58 (m, 2H), 7.12 – 7.02 (m, 2H), 6.78 – 6.70 (m, 2H), 3.55 – 3.47 (m, 4H), 3.27 – 3.19 (m, 4H), 3.14 (s, 3H), 2.86 (s, 3H), 1.52 (s, 6H). **¹³C NMR** (101 MHz, DMSO) δ 171.82, 164.54, 151.97, 150.90, 133.47, 129.03, 125.02, 121.81, 117.30, 114.26, 80.43, 53.48, 44.43, 42.44,

41.72, 36.92 (2C, N(CH₂)₂), 25.56 (2C, C(CH₃)₂). **HRMS** (ESI-TOF) calc'd for C₂₃H₃₁N₄O₃ [M+H]⁺: 411.2391, found: 411.2393.

***N*-4-((1-(Dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-4-(4-(2-(4-(trifluoromethyl)phenyl)acetyl)piperazin-1-yl)benzamide – (68)**



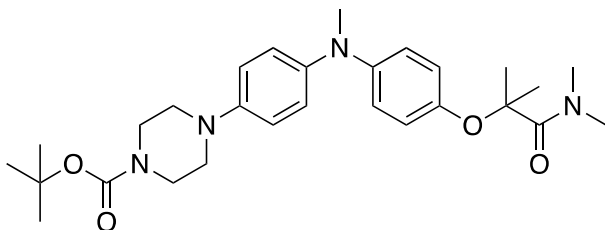
General Procedure A

using **68c** (856 mg, 2.08 mmol),
HATU (1586 mg, 4.17 mmol),
DIPEA (1795 μL, 10.43 mmol),
2-(4-

(trifluoromethyl)phenyl)acetic acid (851 mg, 4.17 mmol) gave **68** (434 mg, 0.728 mmol, 35%) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.72 – 7.60 (m, 4H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.77 – 6.69 (m, 2H), 3.91 (s, 2H), 3.66 (dt, *J* = 18.3, 5.5 Hz, 4H), 3.30 (dt, *J* = 7.2, 3.8 Hz, 4H), 3.14 (s, 3H), 2.86 (s, 3H), 1.51 (s, 6H).
¹³C NMR (101 MHz, DMSO) δ 171.82, 168.38, 164.66, 152.57, 150.82, 140.86, 133.57, 130.13, 128.96, 127.26 (q, ²*J*_{CF} = 31.8 Hz), 126.94, 125.73, 125.02, 124.98, 124.95, 124.91, 124.13, 123.03, 121.72, 120.24, 117.28, 113.74, 80.40, 79.15, 47.24, 46.86, 44.79, 40.88, 36.89 (2C, N(CH₃)₂), 25.54 (2C, C(CH₃)₂). **¹⁹F NMR** (376 MHz, DMSO) δ -60.78. **HRMS** (ESI-TOF) calc'd for C₃₂H₃₆N₄O₄F₃ [M+H]⁺: 597.2683, found: 597.2690.

***tert*-Butyl 4-(4-((4-((1-(dimethylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenyl)(methylamino)phenyl)piperazine-1-carboxylate – (69b)**

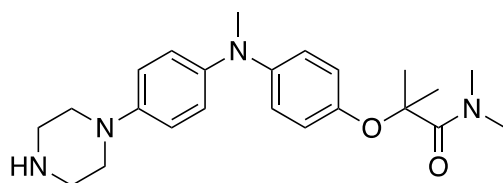


General Procedure B using **63b** (1000 mg, 4.14 mmol), RuPhosPdG3 (350 mg, 0.041 mmol), Cs₂CO₃ (4.05 g, 12.46 mmol) and *tert*-butyl

4-(4-(methylamino)phenyl)piperazine-1-carboxylate (1448 mg, 4.975 mmol) gave **69b** (1314 mg, 2.64 mmol, 64%) as a purple oil.

¹H NMR (400 MHz, DMSO) δ 7.54 (s, 2H), 7.04 (s, 2H), 6.85 – 6.72 (m, 4H), 3.85 – 3.39 (m, 6H), 3.28 – 3.09 (m, 8H), 2.86 (s, 3H), 1.52 (s, 6H), 1.47 (s, 3H), 1.43 (s, 6H). ¹³C NMR (151 MHz, DMSO) δ 171.82, 153.53, 151.70, 149.18, 143.74, 141.90, 125.28, 121.26, 120.54, 118.67, 118.11, 116.11, 80.56, 79.81, 53.44 (2C, CON(CH₂)₂), 46.84 (2C, N(CH₂)₂), 42.43, 36.99 (2C, N(CH₃)₂), 28.03 (3C, C(CH₃)₃), 25.62 (2C, C(CH₃)₂). HRMS (ESI-TOF) calc'd for C₂₈H₄₁N₄O₄ [M+H]⁺: 497.3128, found: 497.3135.

***N,N*,2-Trimethyl-2-(4-(methyl(4-(piperazin-1-yl)phenyl)amino)phenoxy)propanamide – (69c)**

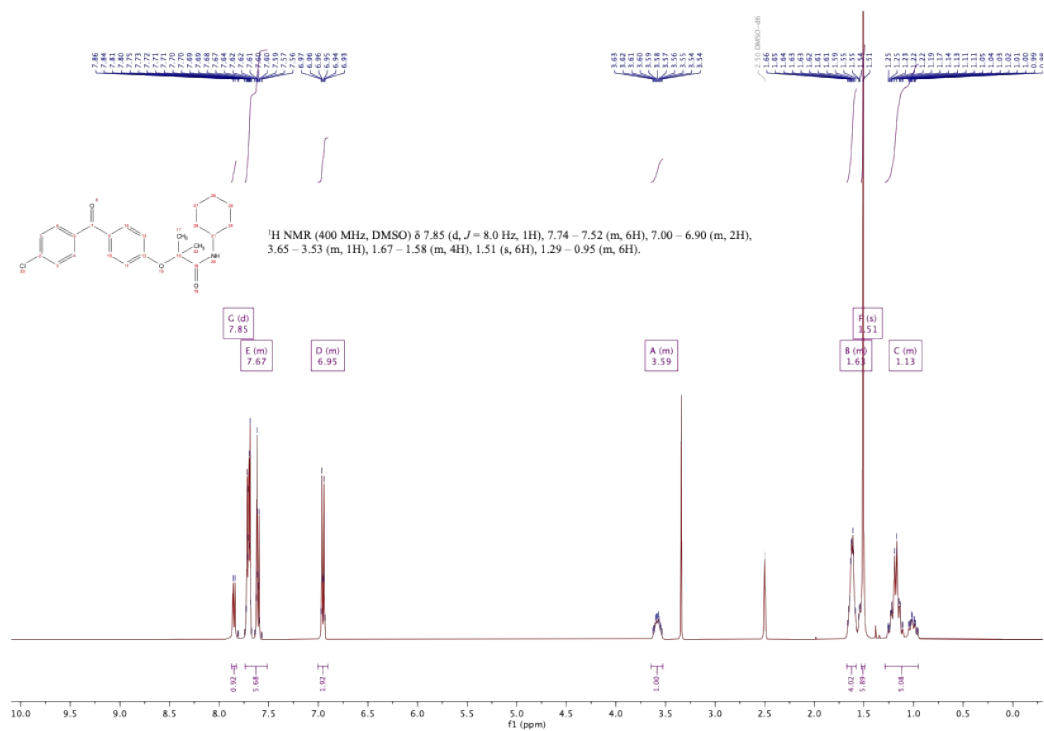


A solution of **69b** (1275 mg, 2.57 mmol) in CH₂Cl₂ (45 mL) was prepared; trifluoroacetic acid (30 mL) was then added. The resultant mixture was stirred for

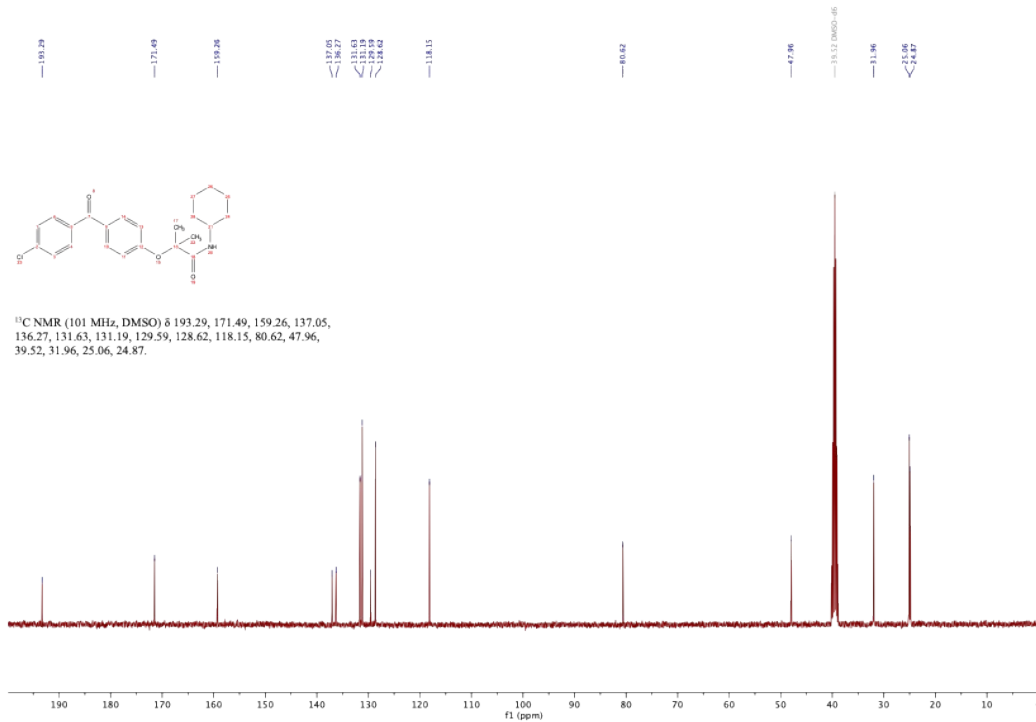
3 h. The solvent was removed under vacuum. The crude mixture was purified using flash reverse phase chromatography (5% - 95% ACN, in H₂O (0.005 N HCl)) to give **69c** (875 mg, 2.21 mmol, 86%).

NMR Spectra of Key Compounds

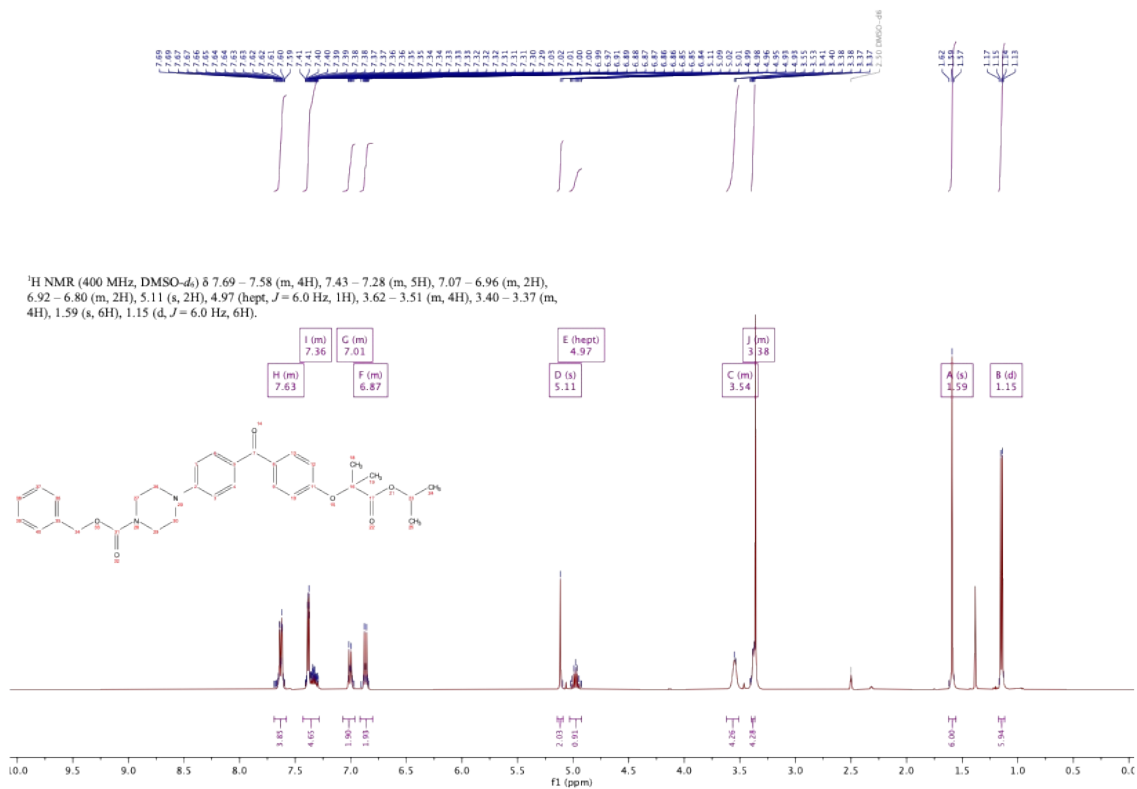
12 – ¹H



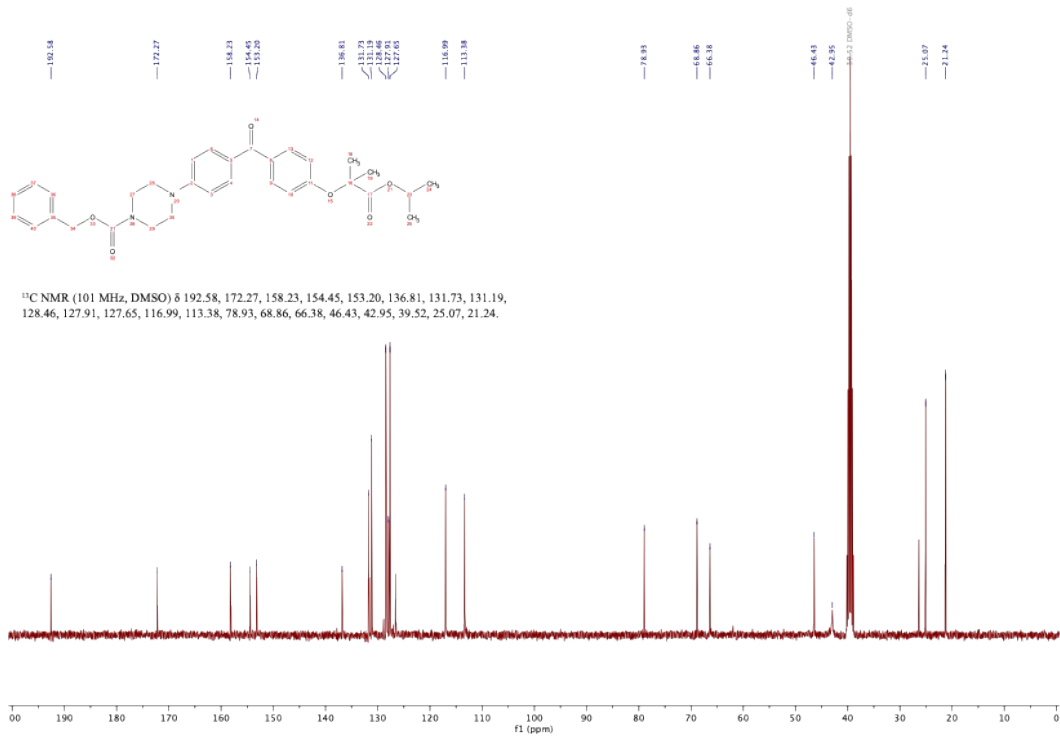
12 – ¹³C



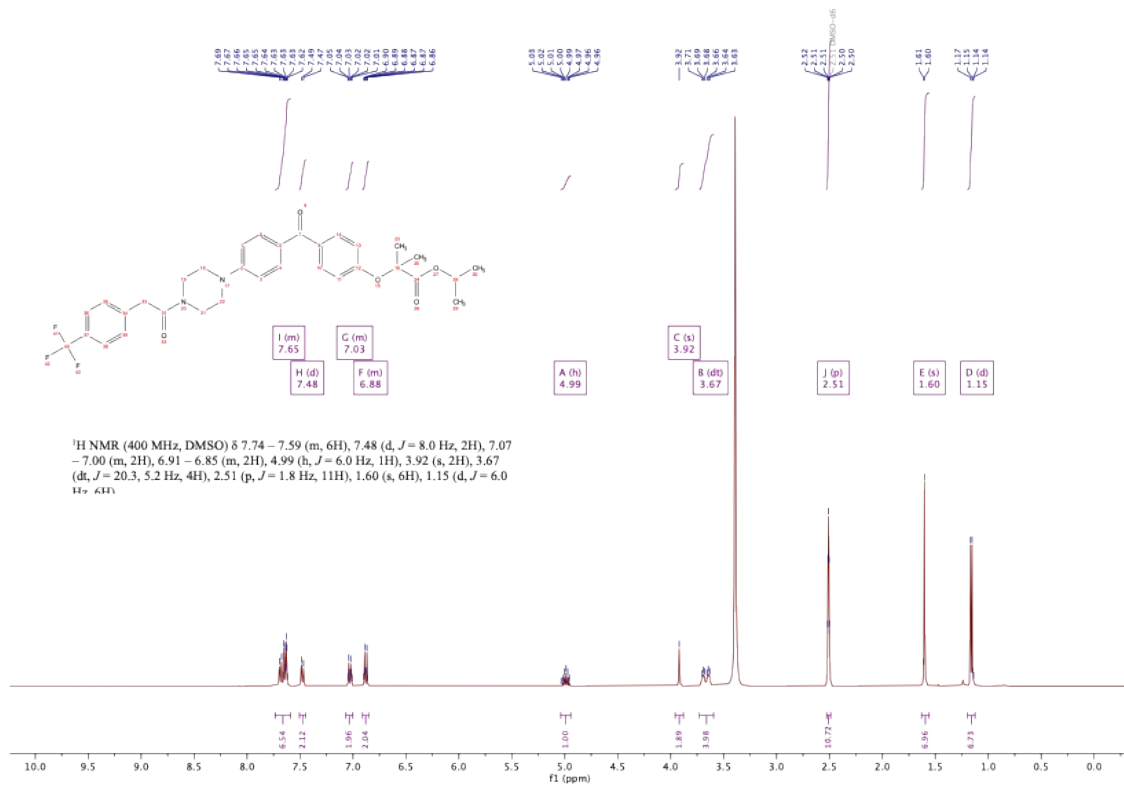
28 – ¹H



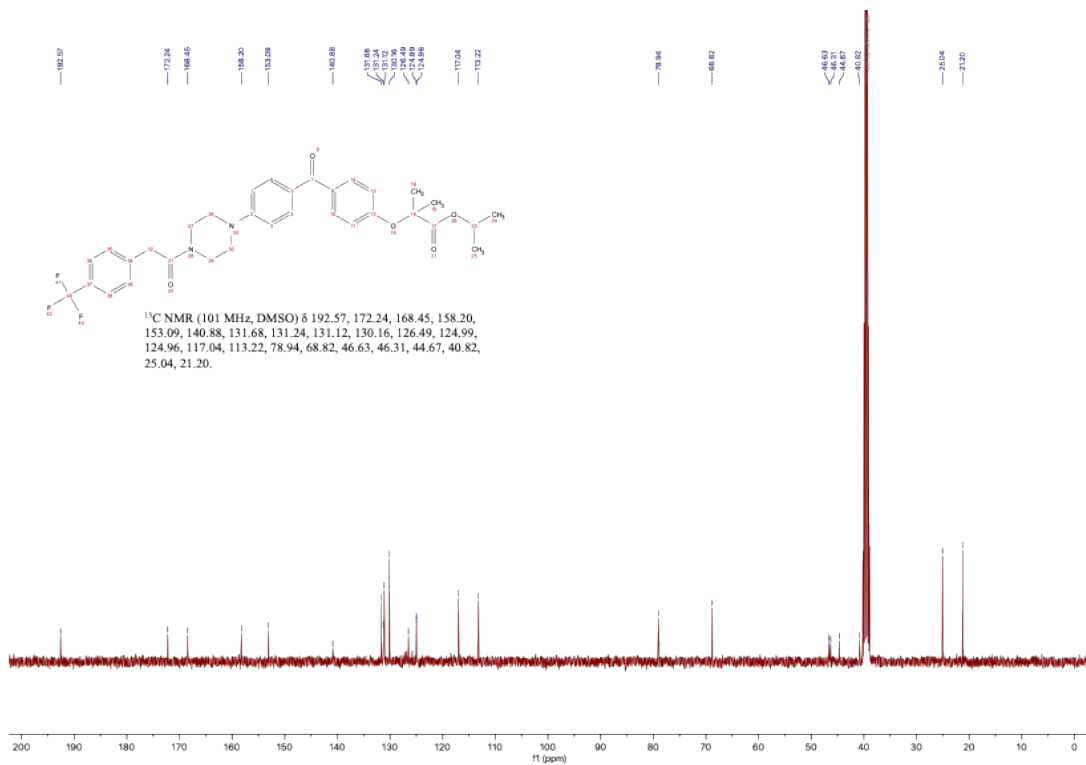
28 – ¹³C



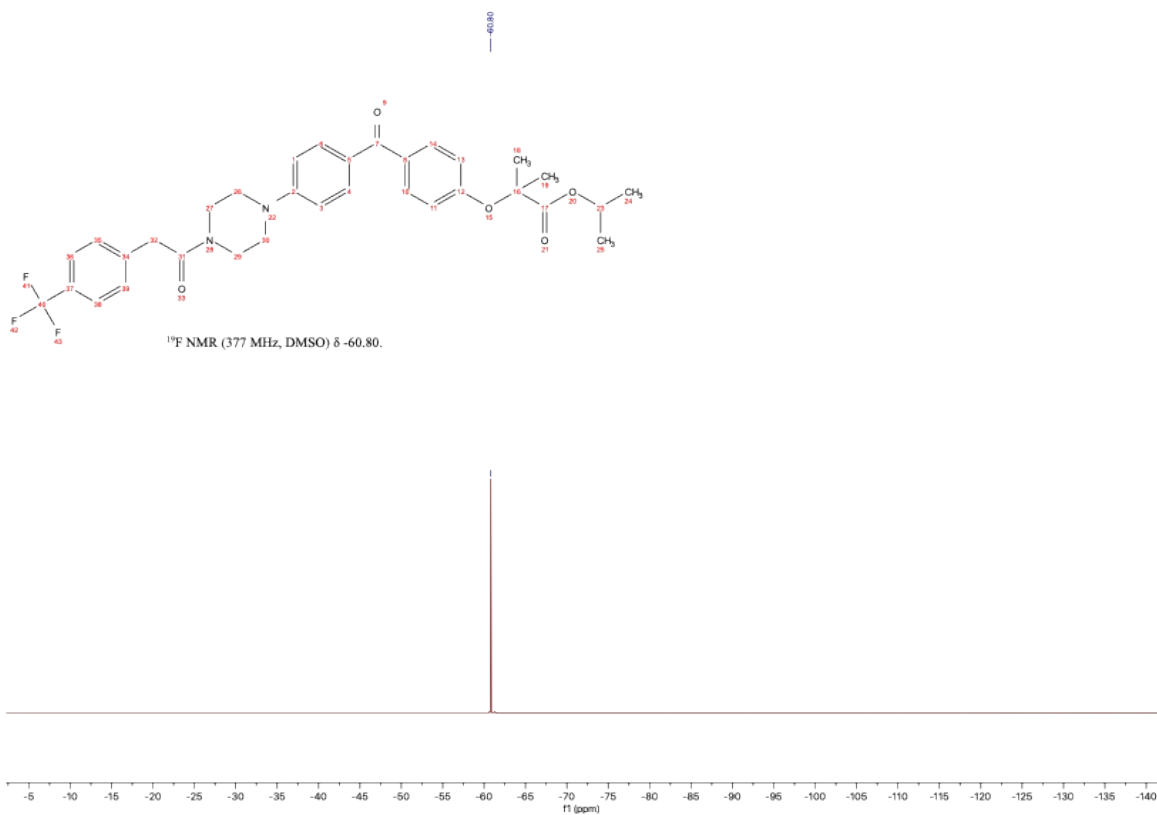
35 – ¹H



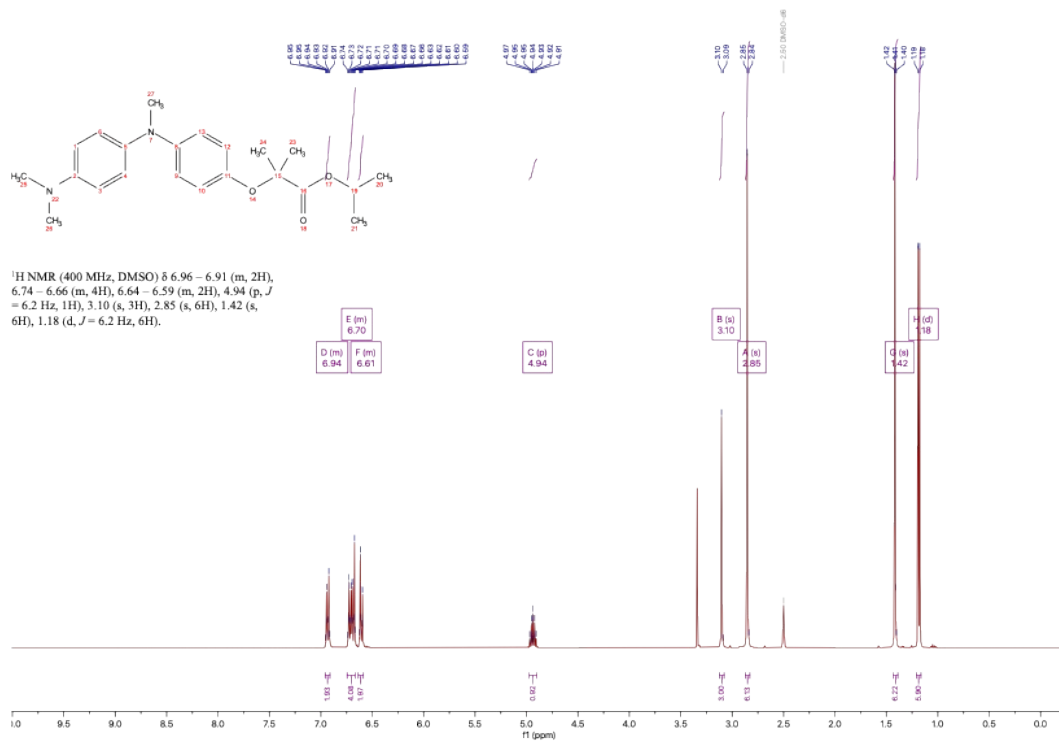
35 – ¹³C



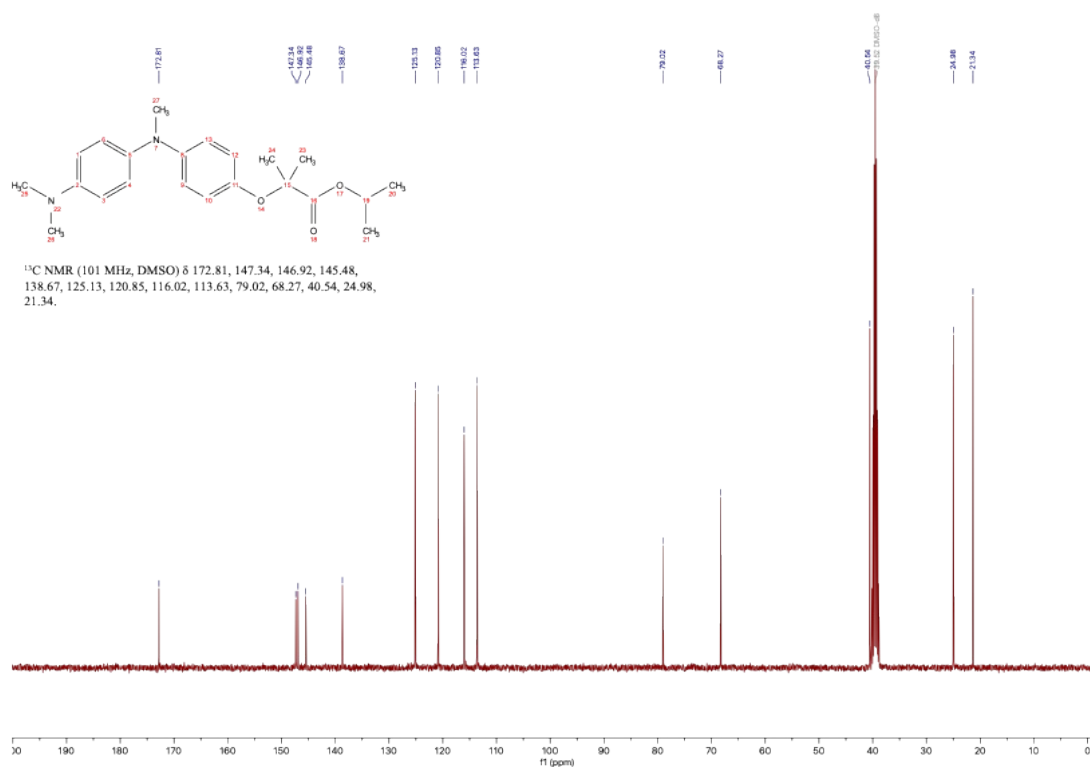
35 – ¹⁹F



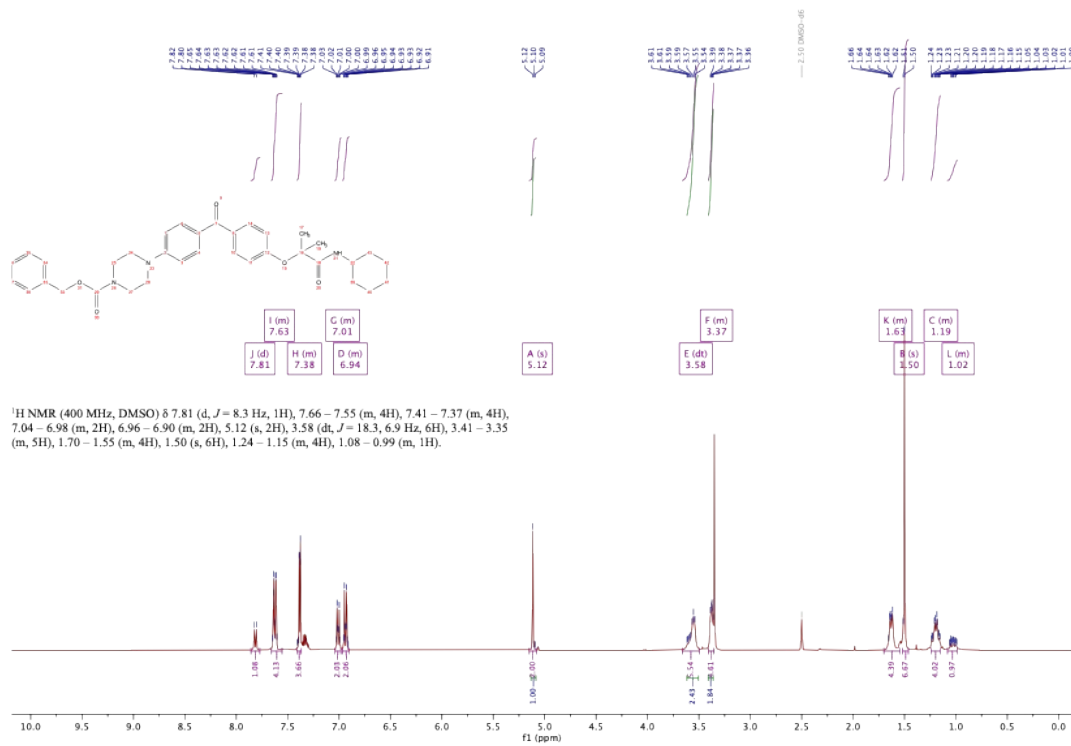
41 – ¹H



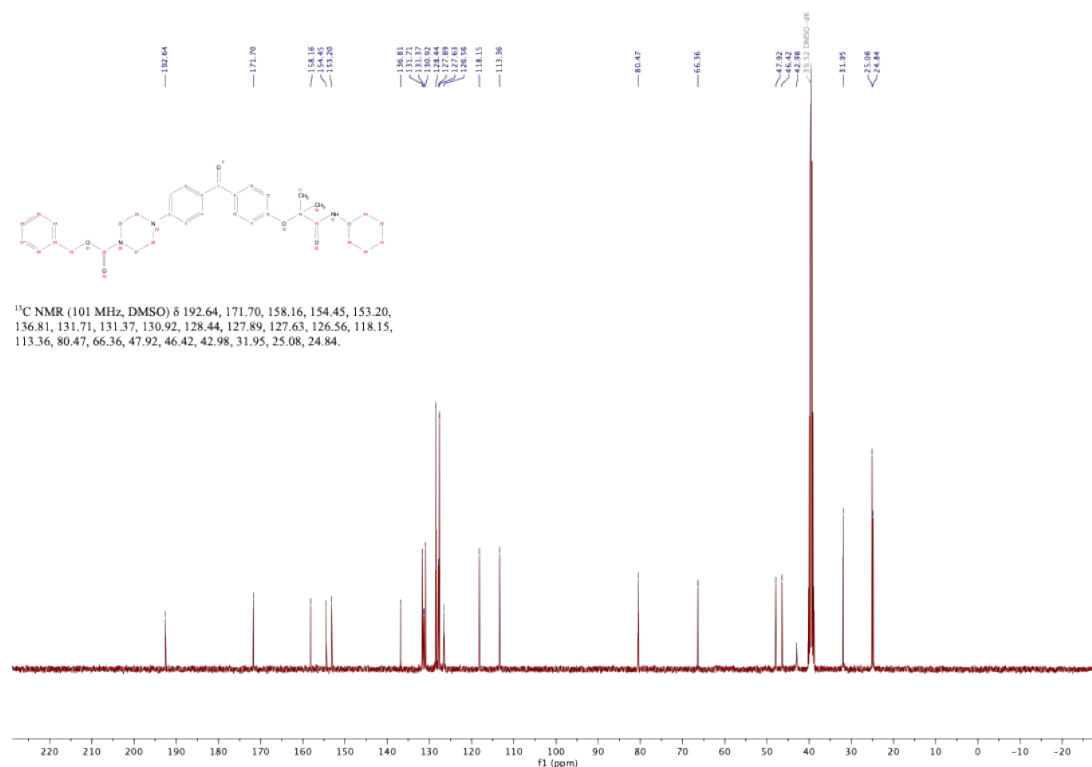
41 – ¹³C



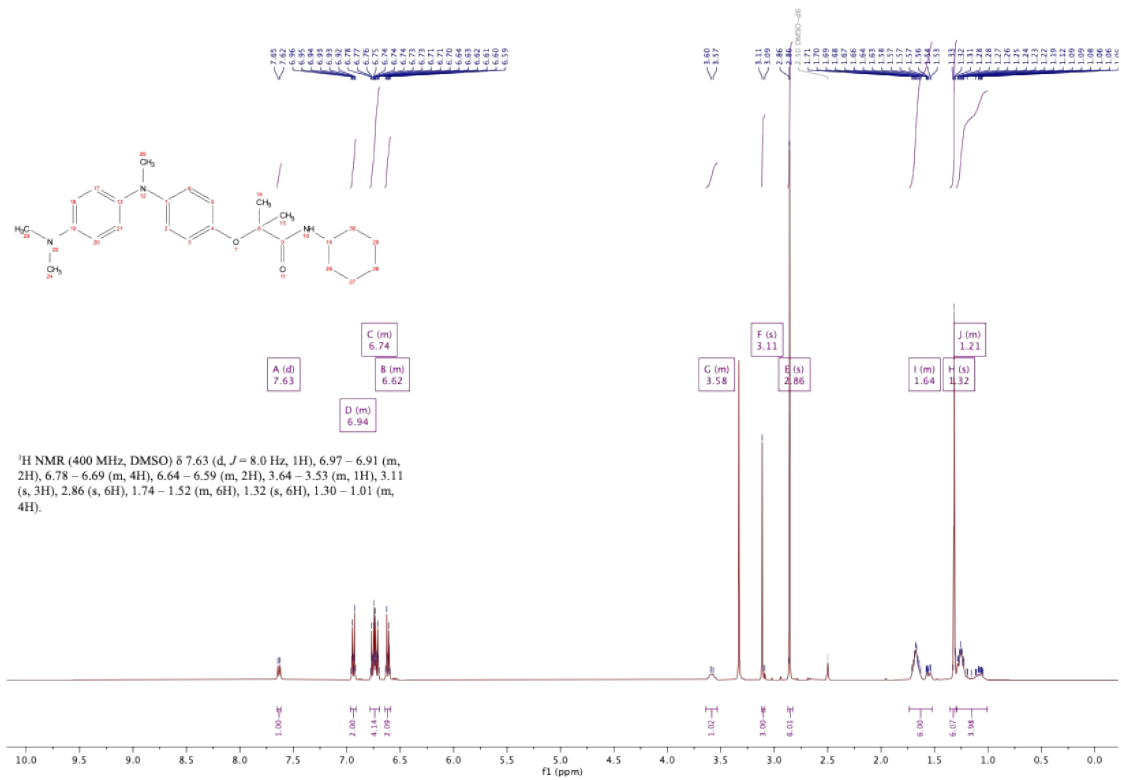
42 – ¹H



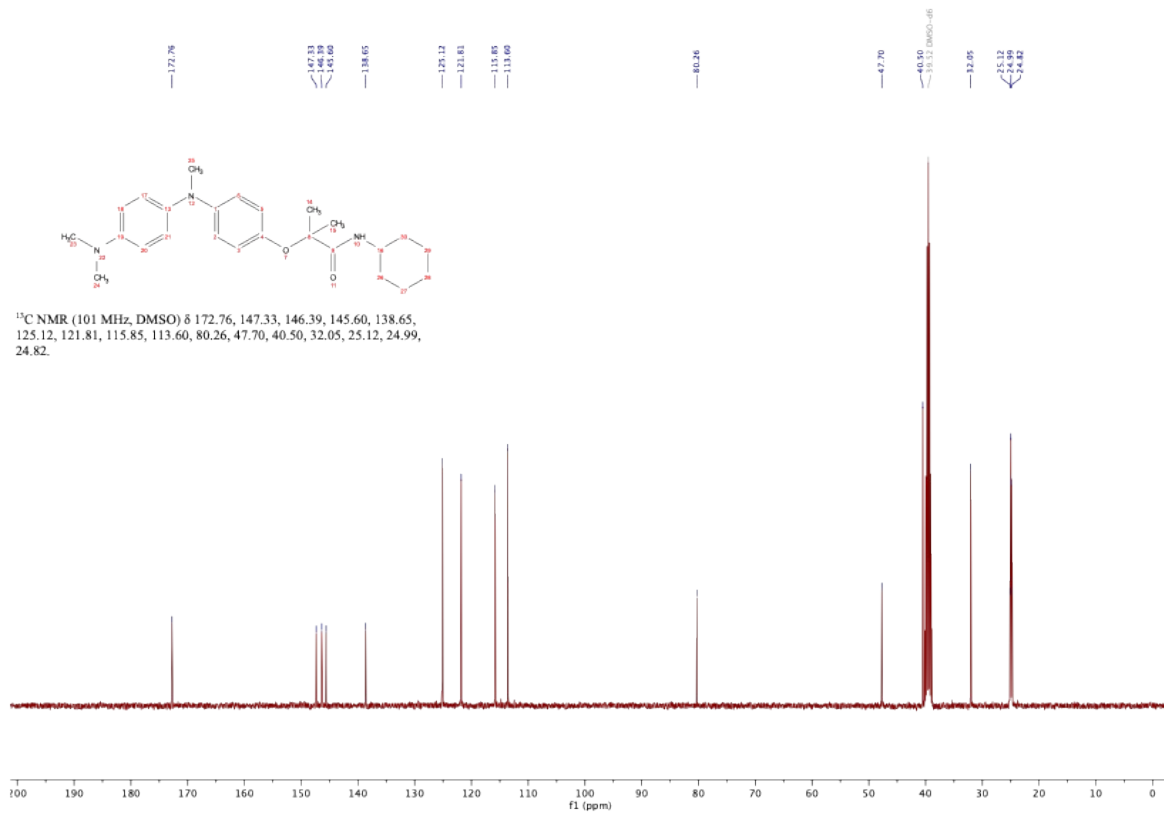
42 - ¹³C



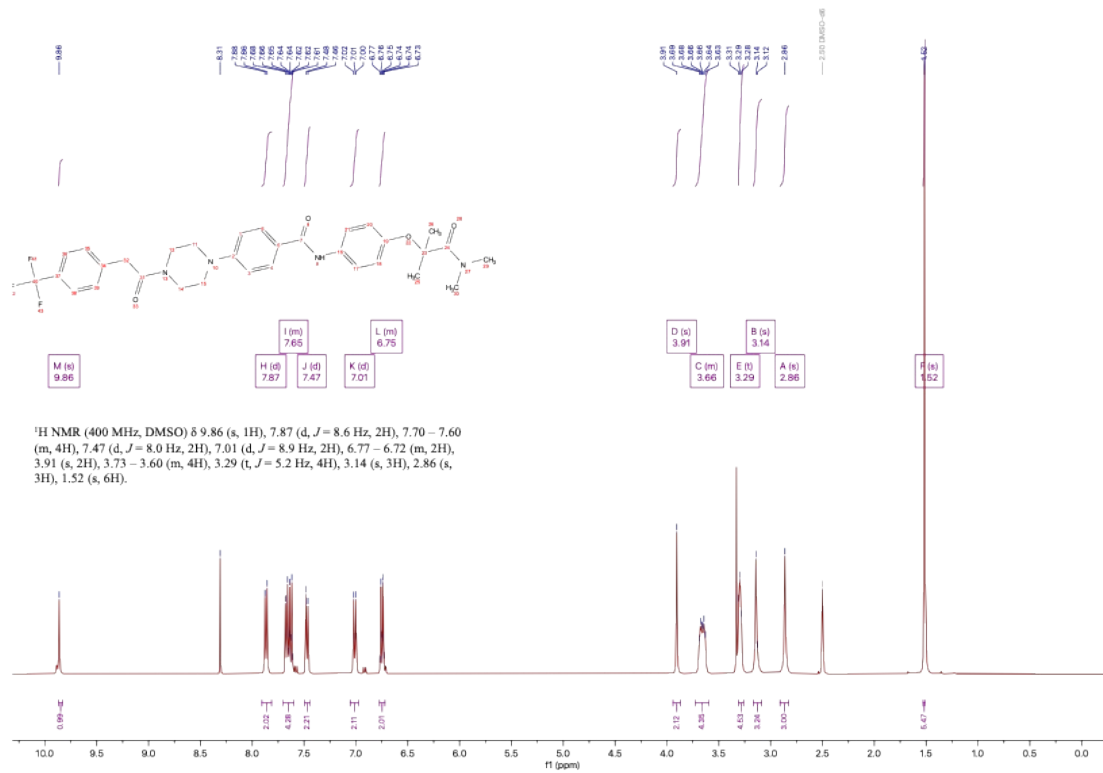
66 - ¹H



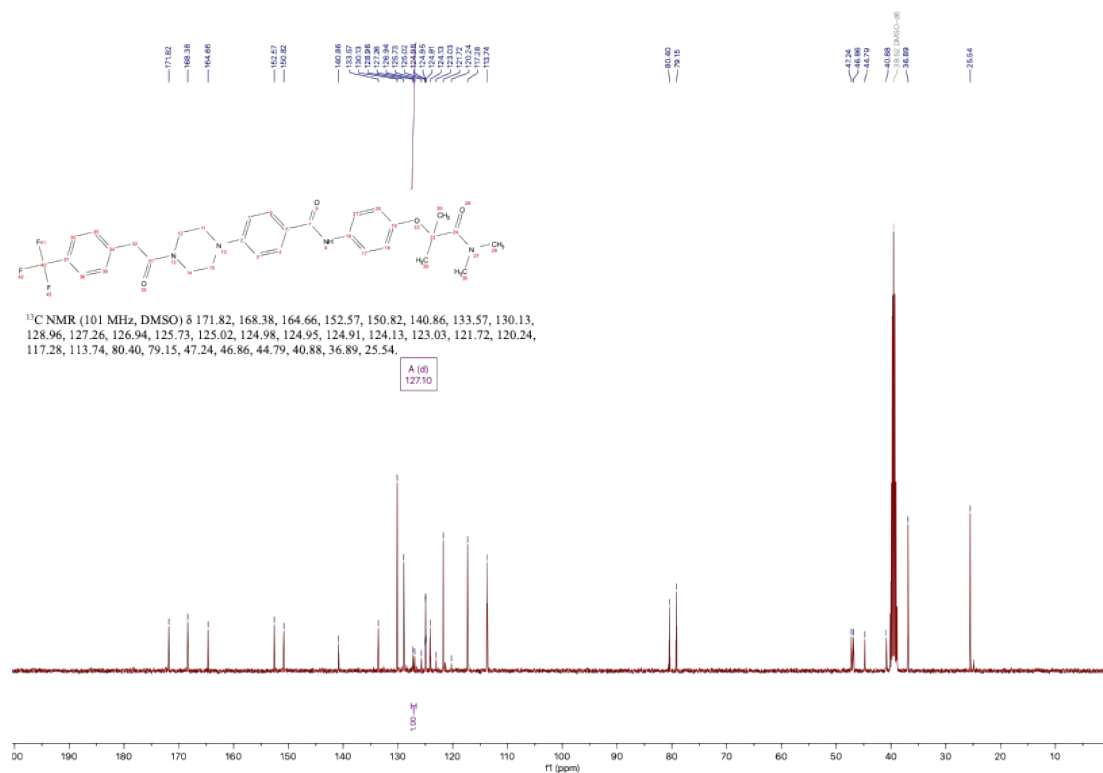
66 – ¹³C



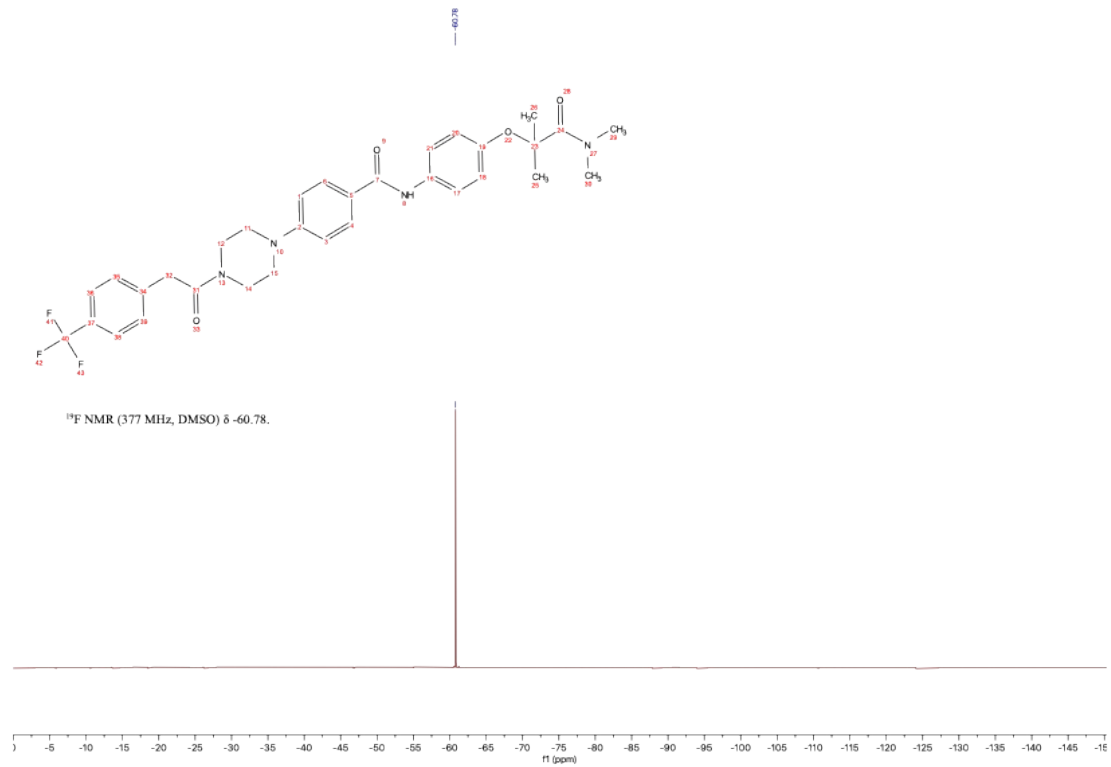
68 – ¹H



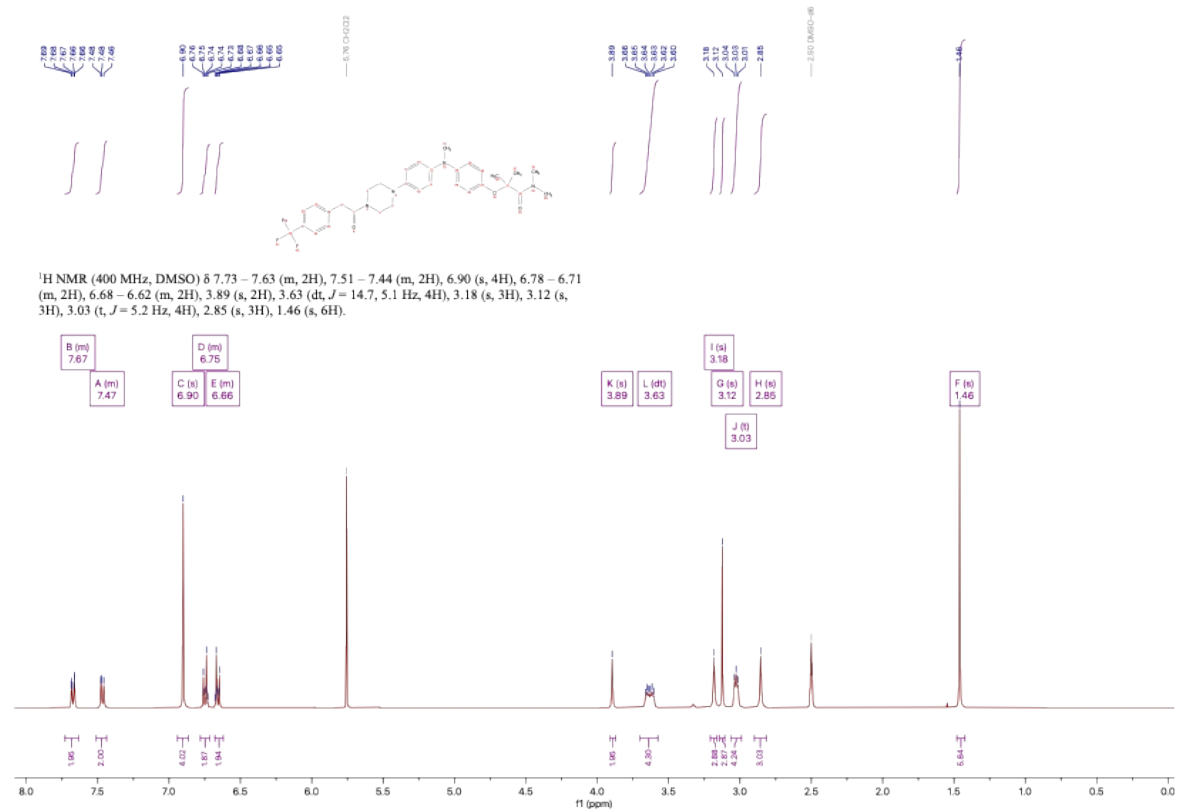
68 – ¹³C



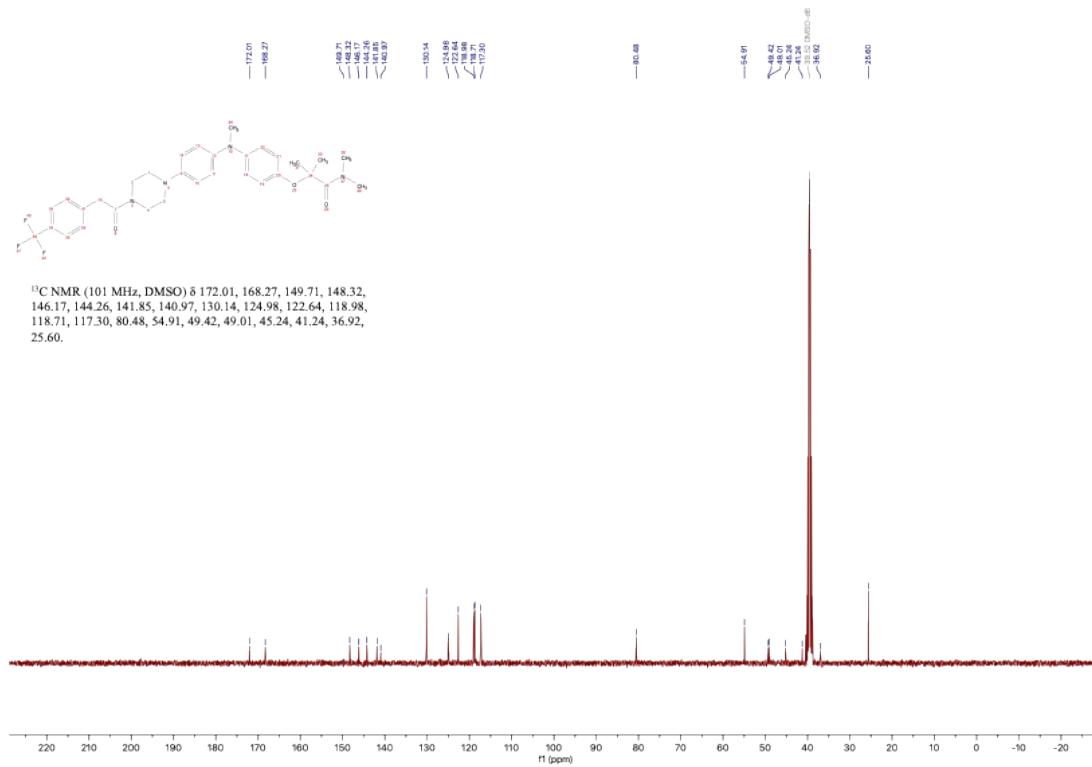
68 – ¹⁹F



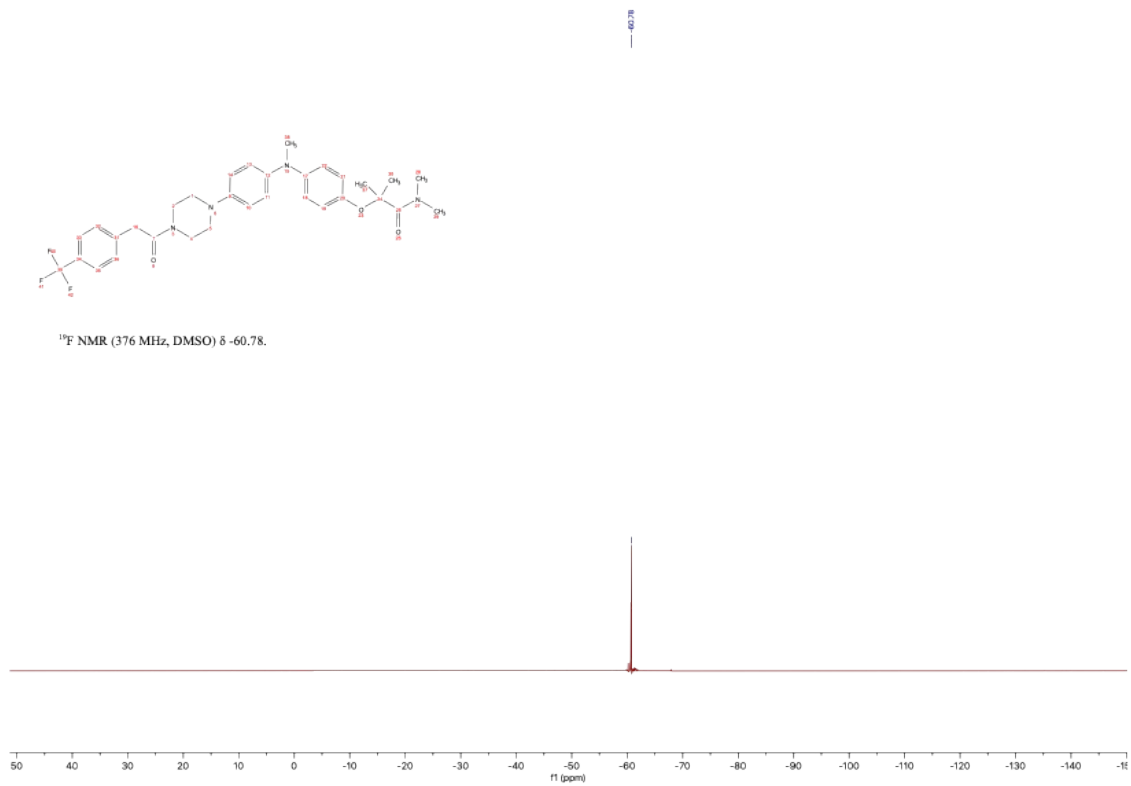
69 (IOX7) – ¹H



69 (IOX7) – ¹³C

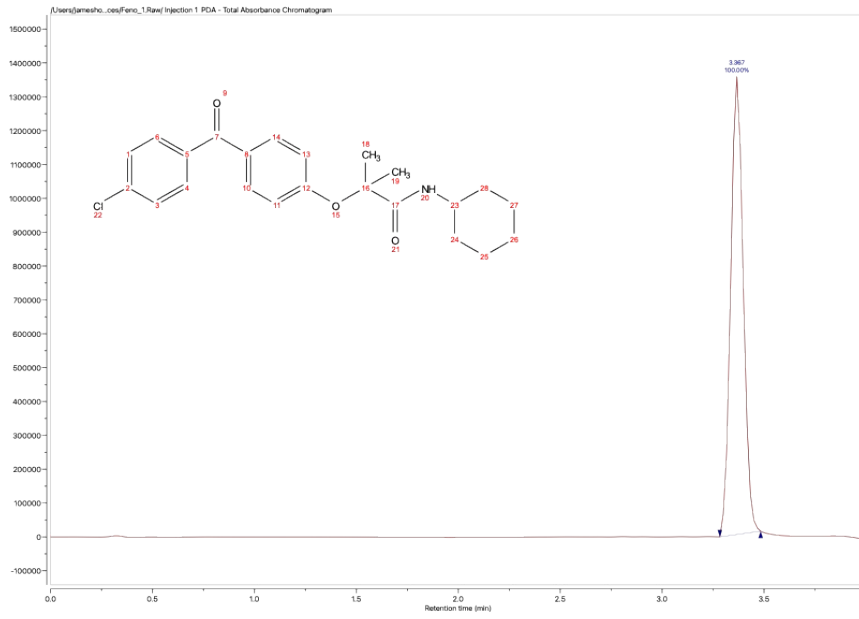


69 (IOX7) – ¹⁹F

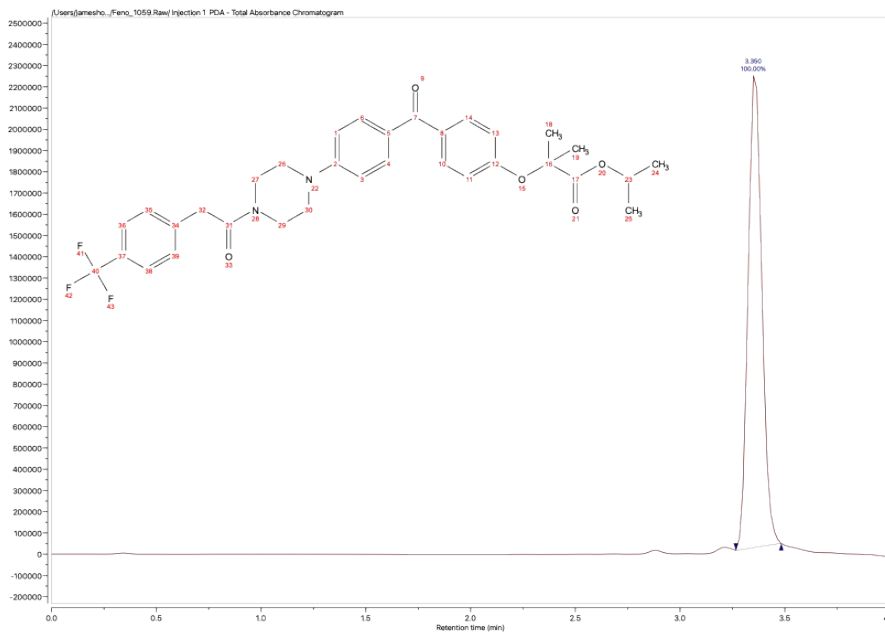


UPLC Traces of Key Compounds

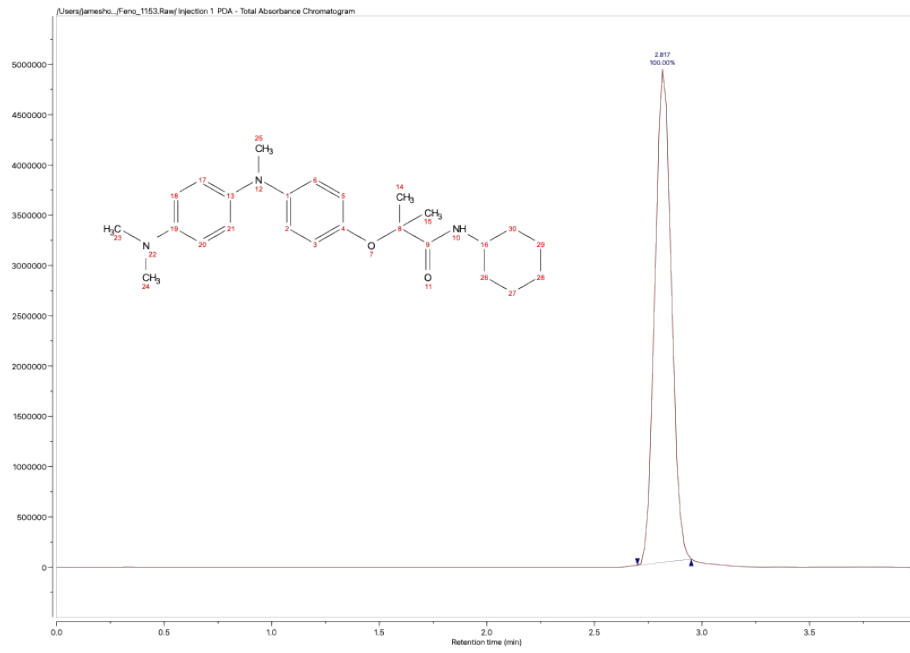
Samples were analysed using an ACQUITY H-Class PLUS UPLC instrument (Waters) equipped with a pre-equilibrated ACQUITY BEH C18 column (2.1 × 50 mm, 1.7 μM pore size, Waters) using a gradient of 1–99%v/v acetonitrile with 0.1%v/v formic acid in water with 0.1%v/v formic acid over 4.0 minutes at a flow rate of 0.5 mL min⁻¹. Instrument control and data processing were performed using MassLynx V4.1 software. The resultant file was then processed in MestreNova.



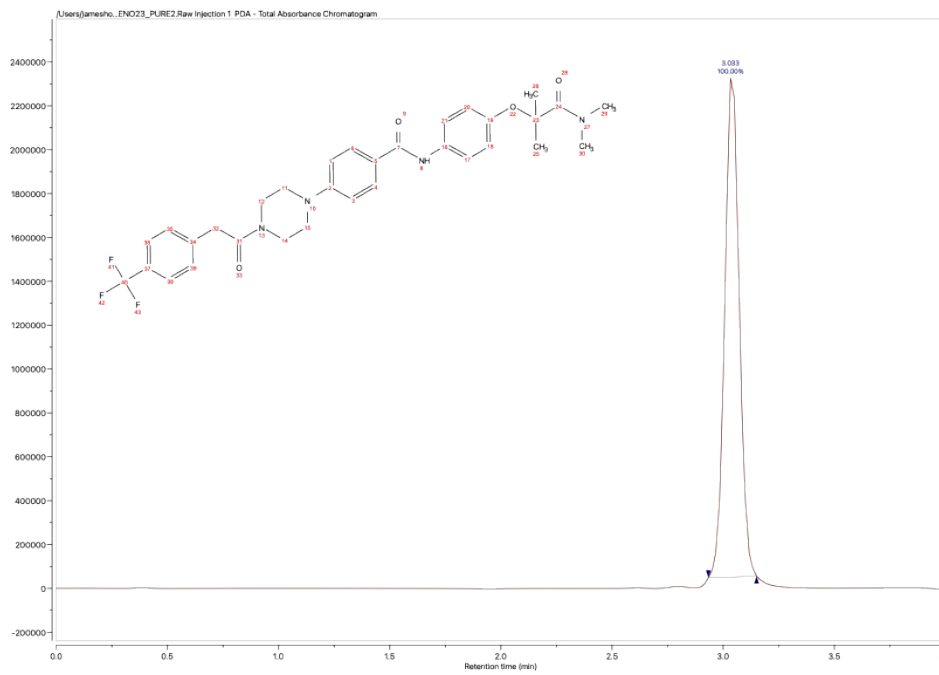
35



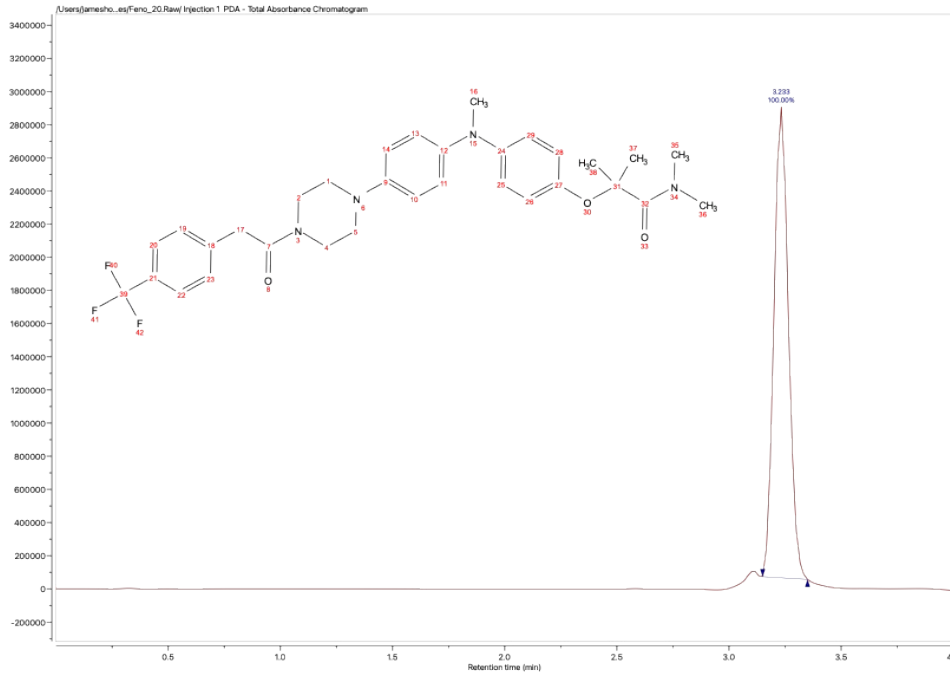
66



68



69 (IOX7)



References

1. Divakaruni AS, Rogers GW, Murphy AN. Measuring Mitochondrial Function in Permeabilized Cells Using the Seahorse XF Analyzer or a Clark-Type Oxygen Electrode. *Current Protocols in Toxicology*. 2014/05/01;60(1).