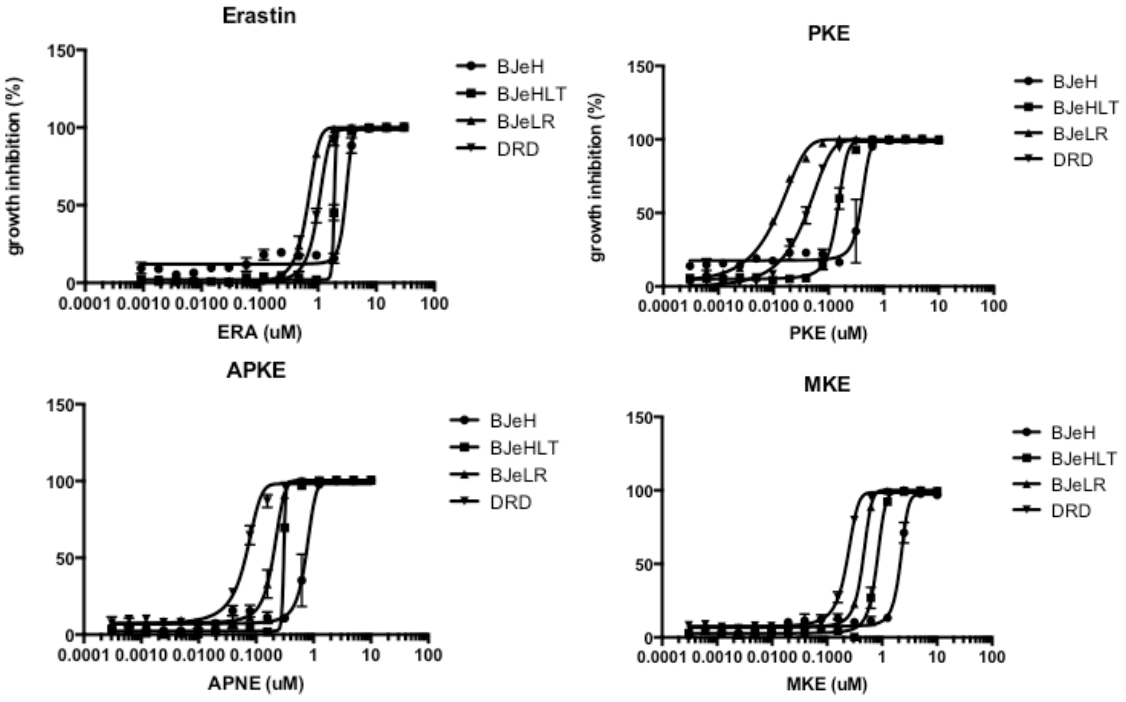
Incorporation of metabolically stable ketones into a small molecule probe to increase potency and water solubility - Supporting Information

Supplementary figures and protocols for the synthesis of carbonyl erastins and their full characterization

Contents

I. Supplementary figures

Potency of carbonyl erastin analogues in isogenic BJ cell lines (Figure S1)



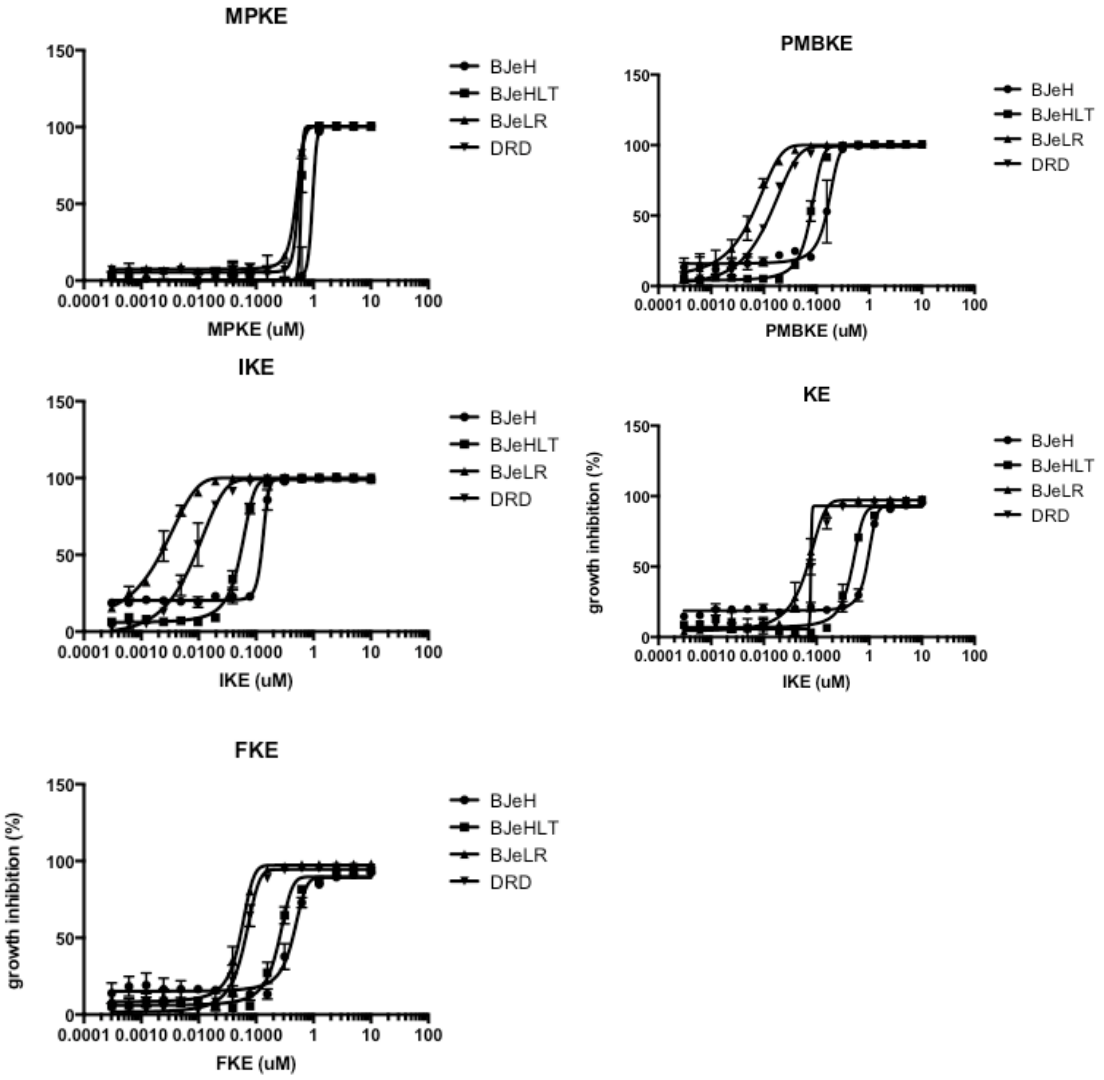
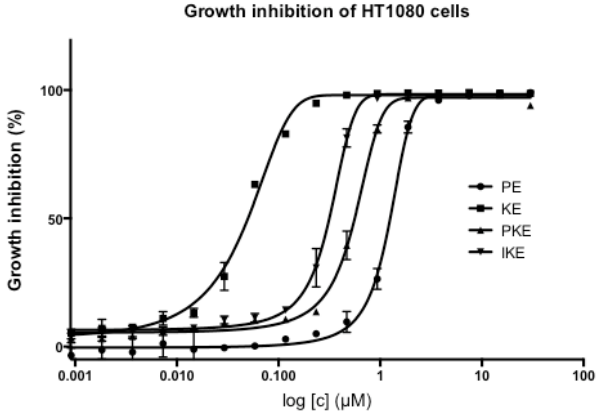


Figure S1. Compounds were tested in 4 isogenic cell lines: $HRAS^{G12V}$ overexpressing artifically transformed fibroblasts (BJeLR, BJeDRD) and non-transformed isogenic cells without mutant HRAS expression (BJeHLT, BJeH). Growth inhibition was measured after 48 h by alamar blue treatment.

Potency of carbonyl erastin analogues in HT1080 cell line (Figure S2)



Analog	IC_{50} HT1080 (nM)
PE	1196
KE	59
PKE	550
IKE	314

Figure S2. Growth inhibition of HT-1080 human fibrosarcoma cells after 48 h of treatment with KE, IKE, PKE or PE.

Metabolic stability of carbonyl erastin analogues in mice liver microsomes (Figure S3)

Remaining Rate (%)								
Time (min)	PE	KE	FKE	MKE	APKE	PMB-PKE	PKE	IKE
0.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
5.0		0.5	15.5	83.8	37.3	29.7	87.4	89.3
15.0	79.2	0.0	0.0	53.2	2.4	2.8	94.7	82.9
30.0	66.6	0.0	0.0	30.6	0.0	0.3	76.2	75.4
45.0	59.4	0.0	0.0	21.2	0.0	0.2	76.9	64.1
0	48.4	0.0	0.0					
T 1/2	55.3 min	3.8 min	4.7 min	23.4 min	4.2 min	3.4 min	> 90 min	78.5min

Figure S3. Metabolic stability of carbonyl erastin analogs in mouse liver microsomes

II. Methods

Imine formation. Detailed method for assessing the formation of imines between the carbonyl probes and *n*-butylamine are described in *supplementary methods*. Briefly, carbonyl probes (0.25 mmol) in MeOH (2 mL) were incubated with *n*-butylamine (10 equiv.) for 24 h at 37 °C. Subsequently $NaCNBH_3$ (1.2 equiv) was added and the mixture was stirred at room temperature for 2 hours. Upon completion the reaction mixture was concentrated under reduced pressure and purified to afford both the starting acetophenone as well as the final amine. The masses of both were obtained and compared to determine the final amine/ketone ratio.

Glutamate-release assay. Human astrocytoma cells (CCF-STTG1) were used as the source of the cystine-glutamate antiporter (xc-). Cells were grown in 96-well plates. At >95% confluence, medium was removed and cells washed with Earle's Balanced Salt Solution (EBSS) to remove the glutamate contained in the media. The cells were then incubated for 2 h at 37°C with either EBSS (Blanks) or EBSS containing cystine 80 µM (Totals) ± erastin (30 nM to 100 µM). Known inhibitors of the target, sulfasalazine (SAS) and (S)-4-carboxyphenylglycine (S-4CPG), were used as positive controls in the assay. Following the incubation period, the glutamate released into the medium was detected

fluorometrically. Tris buffer (100 mM, pH 7.4) containing glutamate oxidase (0.04 U/mL), horseradish peroxidase (0.125 U/mL) and Amplex UltraRed (50 μM) were added to the plate and the rate of change of fluorescence followed (ex 530, em 590). The data were normalized to the Totals and Blanks ((1-(Unknown-Blanks)/(Totals-Blanks))*100) and the half maximal inhibitory constant (IC50) of SAS, S-4CPG, erastin, erastin metabolites and erastin analogs were determined as a function of the normalized fluorescence intensity values. [Note: None of the compounds tested positive in the counter screen.]. Dose curves obtained for each of the analogs are supplied in Supplementary Methods.

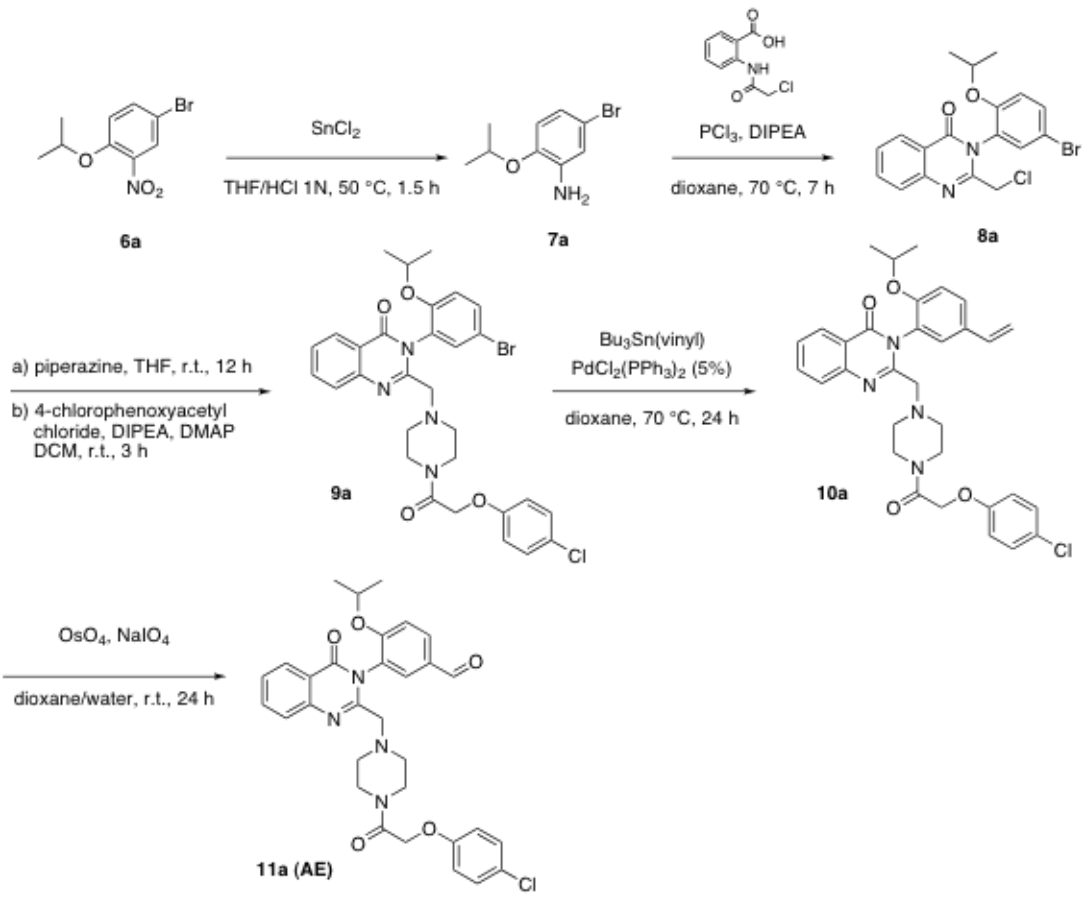
Generation of concentration-dependent curve of erastin analogs. An empty 384-well plate was filled with 30 μL growth media, except for columns 5, where 60 μL of compound solution (erastin analogs) was transferred. After the compound solution transfer, two-fold dilution series across columns 5 through 20 was made by transferring 30 μL of compound solution to the next column successively (16-point dilution series), with extensive mixing. Assay plates were prepared by seeding either BJ-derived cell lines or HT-1080 cells at 1,500 cells per well concentration in 36 μL growth medium. Cells in the assay plates were treated with compounds by transferring 4 μL volume from the compound plate. The final concentration of compound was typically 30 μM to 0.9 nM in this 16-point, 2-fold dilution series. Assay plates were returned to the culture incubator and maintained for 2 days before adding alamar blue. 10 μL of 50% alamar blue solution in cell growth media was transferred to the assay plates, which resulted in 10% final concentration alamar blue. Plates were incubated further for 16 h to allow reduction of alamar blue, which results in the generation of red fluorescence. The fluorescence intensity was determined using a Victor 3 plate reader (Perkin Elmer) with a 535 nm excitation filter and a 590 nm emission filter. Percent growth inhibition (% GI) was calculated from the following formula using the alamar blue fluorescence intensity values. % GI = 100 * (1 − (X − N) / (P − N)) X, cells treated with lethal compound; N, no cells - growth media only; P, no lethal compound - cells only. The concentration-dependent curves were generated using Prism software. Percent growth inhibition, measured using alamar blue is shown. Error bars indicate one standard deviation of triplicate data. Dose curves obtained for each of the analogues are supplied in Supporting Information (Figure S1 and S2).

Assessment of compound half-life in liver microsomes. Test compound (0.5 μM) was incubated at 37ºC for up to 45 minutes in 50 mM of potassium phosphate buffer (pH 7.4) containing microsomal protein (0.5 mg/mL) and an NADPH generating system (0.34 mg/mL β-nicotinamide adenine dinucleotide phosphate (NADP), 1.56 mg/mL

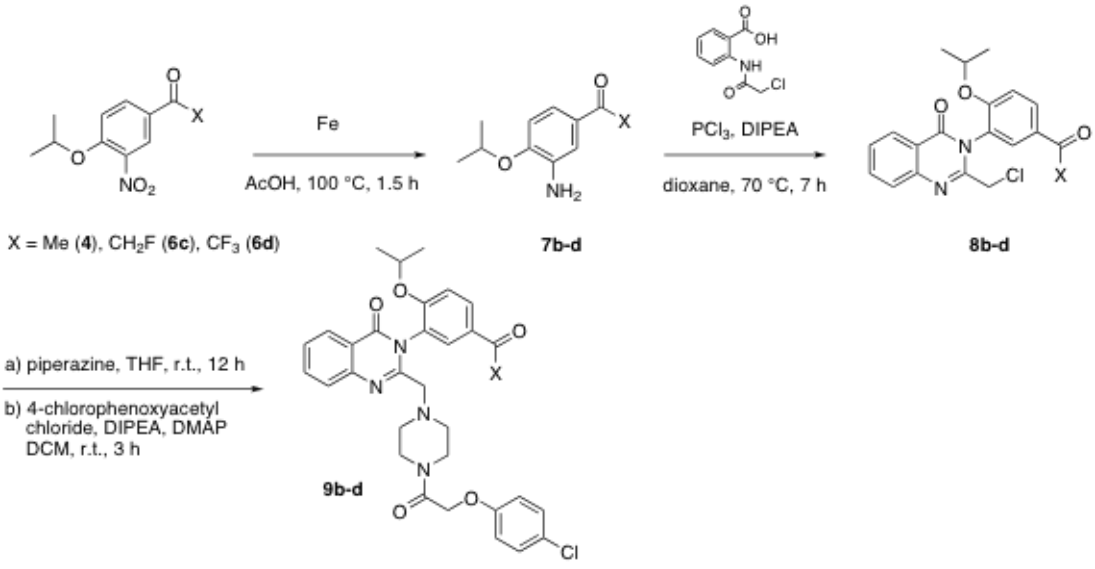
glucose-6-phosphate, 1.2 units/mL glucose-6-phosphate dehydrogenase). At 0, 5, 15, 30 and 45 min intervals, an aliquot was taken and quenched with acetonitrile containing an internal standard. No-cofactor controls at 45 min were prepared. Following completion of the experimentation, the samples were analyzed by LC-MS/MS. The LC-MS/MS method was developed for each compound individually. Instrument: Shimadzu HPLC, Applied Biosystem API4000 QTrap. Half-lives obtained for each of the analogs are supplied in Supporting Information (Figure S3).

III. General synthetic routes for carbonyl erastin analogues

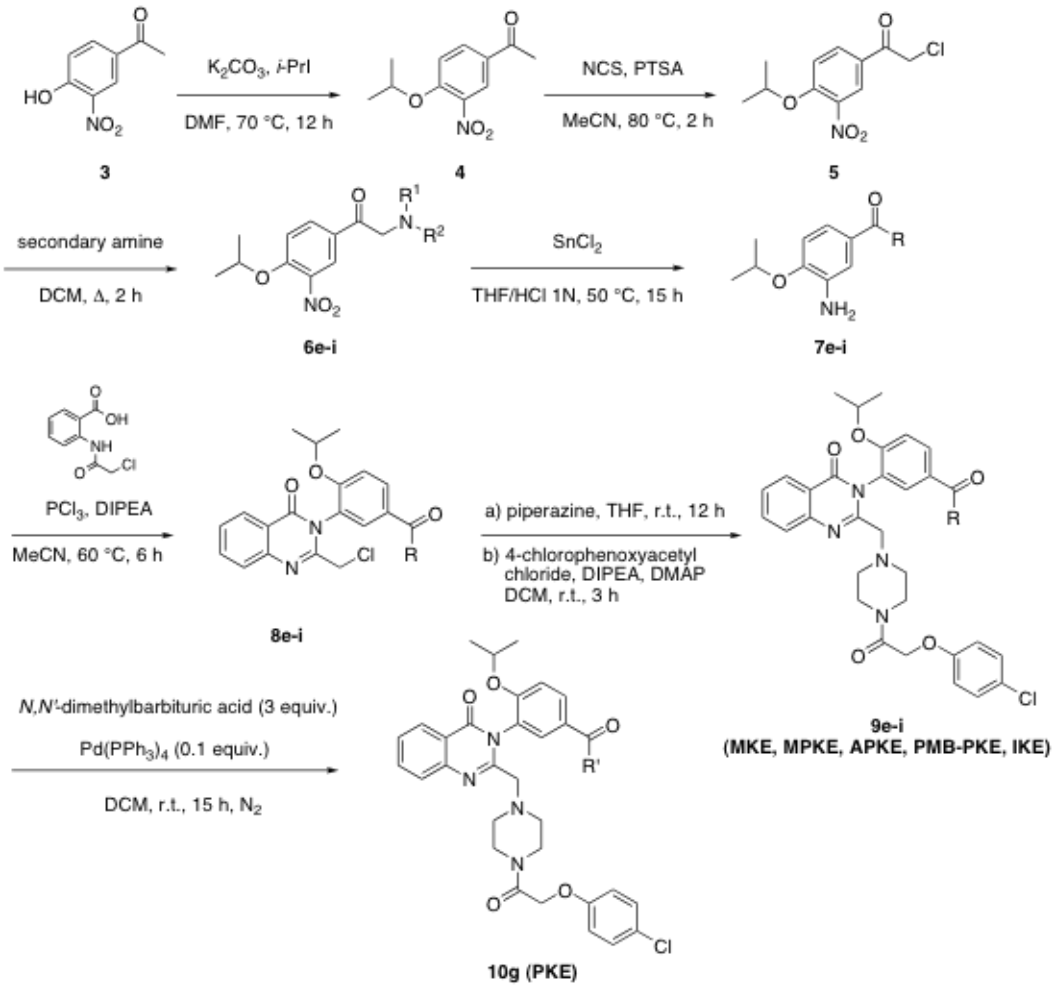
Synthetic route to AE



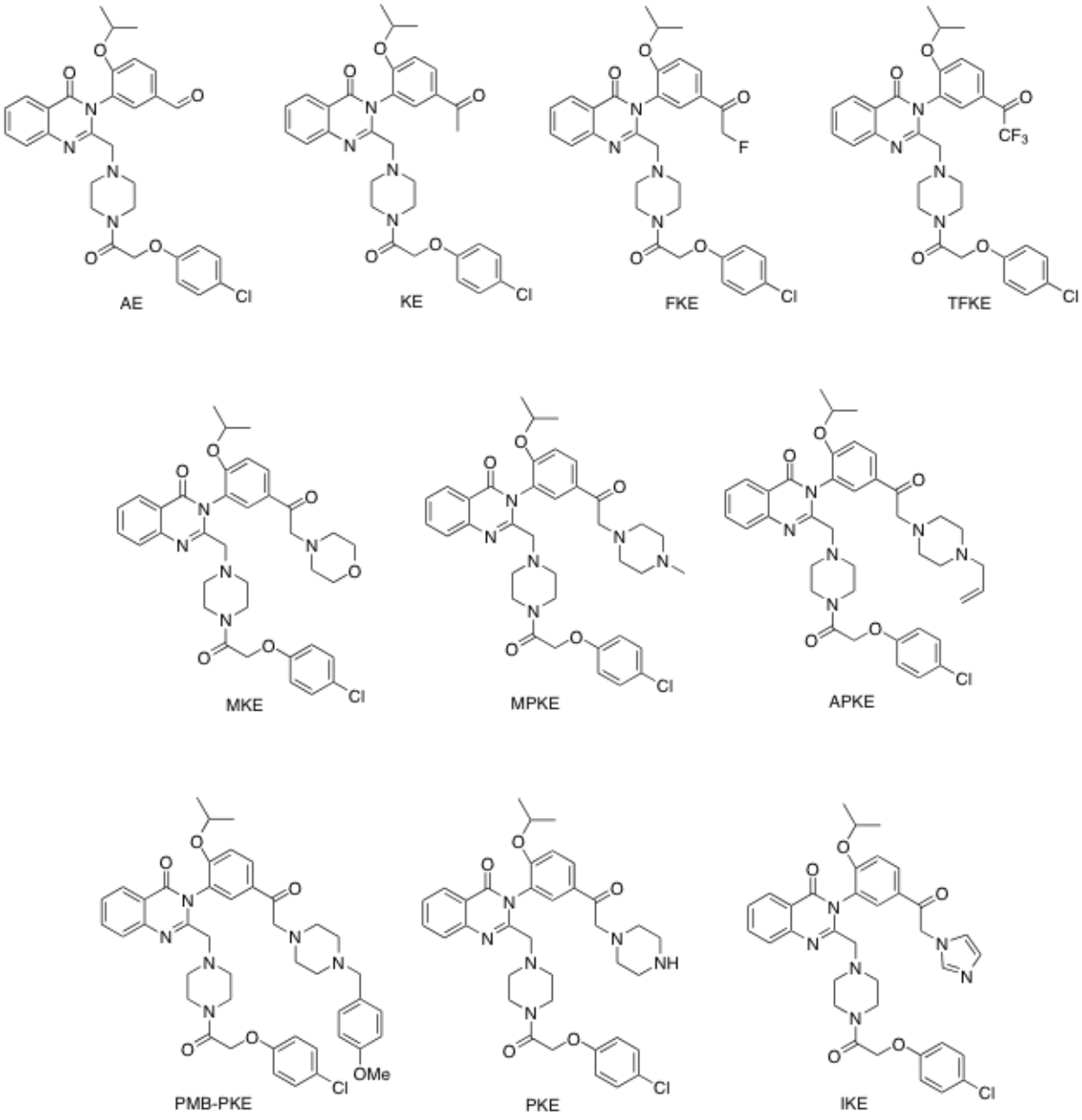
Synthetic route to KE, FKE and TFKE



Synthetic route to MKE, MPKE, APKE, PMB-PKE, PKE and IKE



IV. Structures of the carbonyl erastin analogues synthesized



V. Synthetic procedures

General information

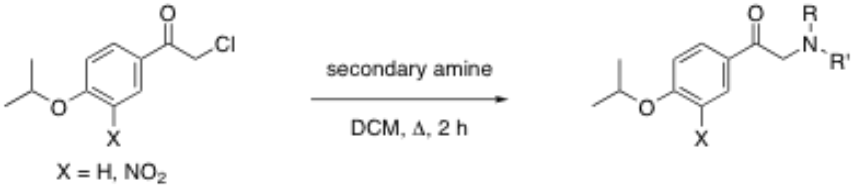
All reactions were carried out under a nitrogen atmosphere under anhydrous conditions unless indicated otherwise. Anhydrous methylene chloride (DCM), tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN) were purchased from Sigma-Aldrich. Reactions were magnetically stirred and monitored by thin layer chromatography carried out by Merck pre-coated 0.25 mm silica plates containing a 254 nm

fluorescence indicator. Flash chromatography was preformed on a Teledyne combiflash companion automatic flash chromatography system. Preparative thin layer chromatography was performed on 1 mm. Spectroscopy: NMR spectra were obtained on a Bruker DPX 400 MHz spectrometer. CI-MS spectra were taken on a Nermag R-10-10 instrument and high resolution MS were taken on a double focusing sector type mass spectrometer HX-110A (JEOL Ltd. Tokyo Japan).

Abbreviations. AcOH = acetic acid, DCM = dichloromethane, DIPEA = diisopropylethyl amine, DMAP = 4-dimethylaminopyridine, EtOAc = ethyl acetate, EtOH = ethanol, Et_2O = diethyl ether, MeCN = acetonitrile, MeOH = methanol, Na_2SO_4 = sodium sulfate, $NaHCO_3$ = sodium bicarbonate, NEt_3 = triethylamine, $Pd(PPh_3)_4$ = Tetrakis(triphenylphosphine)palladium$^{(0)}$, r.t. = room temperature, THF = terahydrofuran.

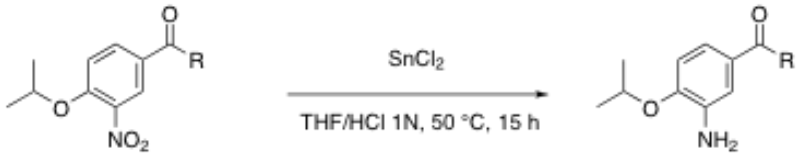
IV A. Synthetic procedures and characterization of carbonyl erastin analogues

General procedure 1: Synthesis of α-amino acetophenones



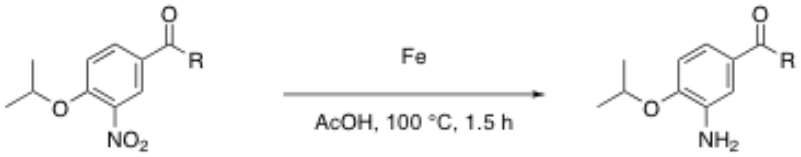
To a solution of 2-chloro-1-(4-isopropoxy)acetone (1equiv.) in DCM (0.5 M) was added the secondary amine (3 equiv.). The reaction mixture was stirred under reflux for 2 h, quenched with aqueous sodium bicarbonate, extracted two times with DCM. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Silica gel column chromatography (DCM/MeOH = 100/0 to 90/10) afforded the corresponding α-amino acetophenone.

General procedure 2a: Reduction of substituted nitrobenzenes to anilines using stannous chloride



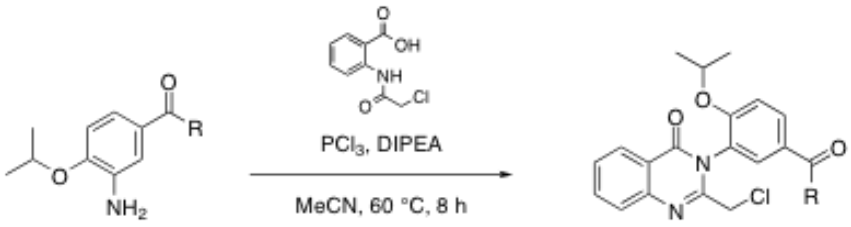
To a solution of substituted nitrobenzene (1 equiv.) in THF (0.25 M), HCl (1 N aqueous solution, 4 equiv.), and stannous chloride (3 equiv.) were added and the reaction mixture was heated to 50 °C for 15 h. Upon completion the mixture was quenched with saturated aqueous sodium bicarbonate, filtered and the crude product was extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Silica gel column chromatography (DCM/MeOH = 100/0 to 90/10) afforded the corresponding aniline.

General procedure 2b: Reduction of substituted nitrobenzenes to anilines using Fe(0)



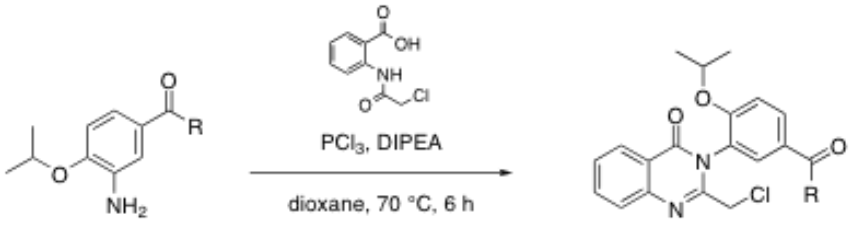
To a solution of substituted nitrobenzene (1 equiv.) in glacial acetic acid (0.10 M), iron powder (5 equiv.) was added in one batch and the reaction mixture was heated to 100 °C for 1.5 h. Upon completion the mixture was filtered through celite, and concentrated under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 100/0 to 40/60) afforded the corresponding aniline.

General procedure 3a: Phosphorus trichloride-triggered cyclocendensation in acetonitrile (for the most polar anilines)



DIPEA (1.2 equiv.) was added to a solution of 2-(2-chloroethanamido)benzoic acid (1 equiv.) at r.t. in acetonitrile (0.03 M) and stirred for 2 minutes before the dropwise addition of phosphorous trichloride (1.2 equiv.). After 10 minutes of stirring at r.t., the desired *O*-isopropoxyaniline (0.9 equiv.) was added dropwise as a 1.5 M solution in acetonitrile and the resulting mixture was heated to 60 °C and stirred for an additional 8 h. Upon completion the reaction was carefully quenched with saturated aqueous $NaHCO_3$, diluted with water, and extracted 3 times with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduce pressure. Silica gel column chromatography (DCM + 0.5% NEt_3/MeOH = 100/0 to 95/5) afforded the corresponding quinazolinones.

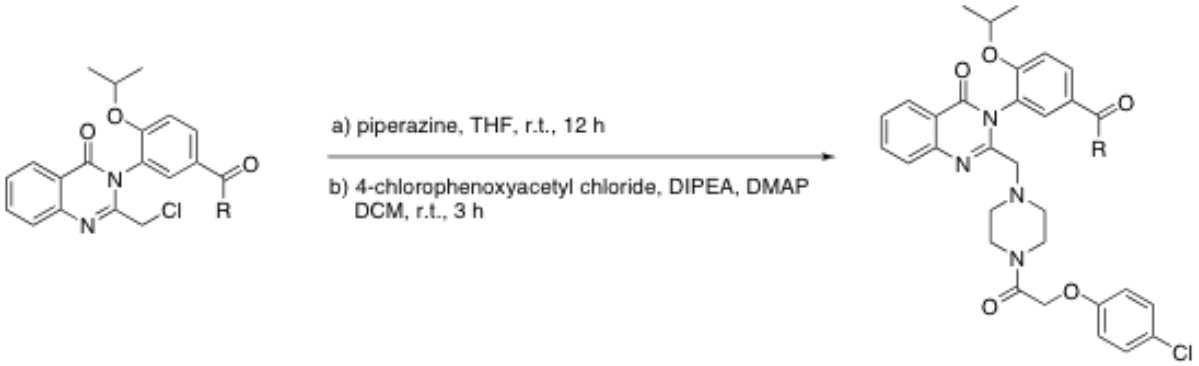
General procedure 3b: Phosphorus trichloride-triggered cyclocondensation in dioxane (for the less polar anilines)



DIPEA (1.2 equiv.) was added to a solution of 2-(2-chloroethanamido)benzoic acid (1 equiv.) at r.t. in dioxane (0.2 M) and stirred for 2 minutes before the dropwise addition of phosphorous trichloride (1.2 equiv.). After 10 minutes of stirring at r.t., the desired *O*-isopropoxyaniline (0.9 equiv.) was added dropwise as a 1.5 M solution in dioxane

and the resulting mixture was heated to 70 °C and stirred for an additional 6 h. Upon completion the reaction was carefully quenched with saturated aqueous $NaHCO_3$, diluted with water, and extracted 3 times with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduce pressure. Silica gel column chromatography (hexane/EtOAc = 100/0 to 50/50) afforded the corresponding quinazolinones.

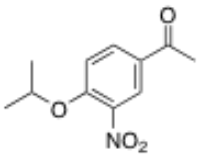
General procedure 4: functionalization of the quinazolinone ring with (4-chlorophenoxy)acyl piperazine moiety



Piperazine (3.0 equiv.) was added to a solution of the chloromethyl quinazolinone (1 equiv.) in THF (0.2 M) and the resulting mixture was stirred at r.t. for 12 h. The reaction mixture was then concentrated under reduce pressure. Silica gel column chromatography (DCM + 0.5% NEt_3/MeOH = 100/0 to 80/20) afforded the corresponding piperazine quinazolinones which was immediately used for the next step.

To a solution of the piperazine quinazolinine (1 equiv.) in DCM (0.1 M) was added EDIPA (1.2 equiv) at r.t.. The mixture was then cooled to 0 °C, before the sequential addition of 4-chlorophenoxyacetyl chloride (1.2 equiv.) and 4-DMAP (0.5 equiv.). The mixture was slowly warmed to r.t. and stirred for an additional 3 h. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted 3 times with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated under reduce pressure. Silica gel column chromatography (DCM + 0.5% NEt_3/MeOH = 100/0 to 95/5) afforded the corresponding acylated quinazolinones.

1-(4-isopropoxy-3-nitrophenyl)acetone (4)



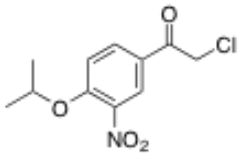
$C_{11}H_{13}NO_4$ MW = 223.23 g/mol

To a solution of 4-hydroxy-3-nitroacetophenone (4.15 g, 22.9 mmol, 1 equiv.) in DMF (50 mL) at r.t. was added potassium carbonate (3.80 g, 27.5 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 15 min and 2-iodopropane (4.60 mL, 45.8 mmol, 2.0 equiv.) was then added dropwise. The mixture was subsequently stirred at 70 °C for 12 h. Upon completion the reaction mixture was quenched with water and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 60/40) to afford 1-(4-isopropoxy-3-nitrophenyl)acetone

(4.43 g, 86% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.3 Hz, 1H), 8.07 (dd, *J* = 8.8 Hz, *J* = 2.3 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 4.77 (sept, *J* = 6.1 Hz, 1H), 2.55 (s, 3H), 1.38 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 154.8, 140.3, 133.6, 129.1, 126.1, 115.0, 73.2, 26.3, 21.8 (2C). MS (m/z): $[MH]^+$ calculated for $C_{11}H_{14}NO_4$, 224.08; found 224.17.

2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone (5)

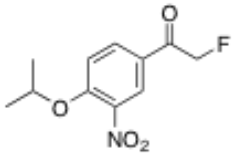


$C_{11}H_{12}ClNO_4$ MW = 257.67 g/mol

To a solution of **4** (3.50 g, 15.7 mmol, 1 equiv.) in acetonitrile (60 mL) at r.t. were added *p*-toluenesulfonic acid (4.47 g, 23.5 mmol, 1.5 equiv.) and *N*-chlorosuccinimide (2.10 g, 15.7 mmol, 1 equiv.). The mixture was refluxed for 3 h, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 70/30) to afford 2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone **5** (3.0 g, 74% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.9 Hz, *J* = 2.3 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 4.77 (sept, *J* = 6.1 Hz, 1H), 4.64 (s, 2H), 1.38 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4, 155.3, 140.3, 134.0, 126.3, 125.9, 115.2, 73.4, 45.4, 21.7 (2C). MS (m/z): $[MH]^+$ calculated for $C_{11}H_{13}ClNO_4$, 258.05; found 258.14.

2-fluoro-1-(4-isopropoxy-3-nitrophenyl)acetone (6c)



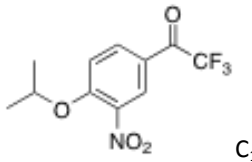
$C_{11}H_{12}FNO_4$ MW = 241.22 g/mol

To a solution of LiHMDS (1 M in THF, 3.76 mL, 3.76 mmol, 1.2 equiv.) in THF (25 mL) at r.t., was added a solution of **4** (700 mg, 3.14 mmol, 1 equiv.) in THF (1 mL) dropwise over 30 min. The reaction mixture was stirred at r.t. for 15 min, then concentrated under reduced pressure, dissolved in MeCN (20 mL) and filtrated. To a solution of selectfluor (1.45 g, 4.1 mmol, 1.3 equiv.) in acetonitrile (6 mL) at 0 °C was added the crude filtrate dropwise. The reaction mixture was stirred at r.t. for 30 min and concentrated under reduced pressure. The crude residue was dissolved in EtOAc (30 mL) and washed with water (2 x 30 mL). The organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 60/40) to afford 2-fluoro-1-(4-isopropoxy-3-nitrophenyl)acetone **6c** (600 mg, 79% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.0 Hz, 1H), 8.11 (dd, *J* = 8.9 Hz, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 5.43 (d, $J_{H\text{-}F}$ = 47 Hz, 2H), 4.80 (sept, *J* = 6.0 Hz, 1H), 1.44 (d, *J*= 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 155.6,

140.6, 133.7, 126.1, 125.7, 115.3, 84.8 (d, $^{1}J_{C\text{-}F}$ = 183 Hz), 73.5, 21.8 (2C). MS (m/z): [MH]+ calculated for $C_{11}H_{13}FNO_4$, 242.08; found 242.21.

trifluoro-1-(4-isopropoxy-3-nitrophenyl)acetone (6d)



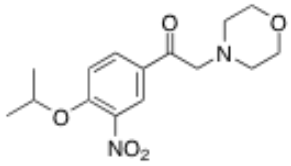
$C_{11}H_{10}F_3NO_4$ MW = 277.20 g/mol

To a solution of trifluoro-1-(4-hydroxy-3-nitrophenyl)ethanone (238 mg, 1.01 mmol) in DMF (10 mL) at r.t. was added potassium carbonate (1.2 equiv.). The mixture was stirred at r.t. for 15 min and 2-iodopropane (2.0 equiv.) was then added dropwise. The mixture was subsequently stirred at 70 °C for 12 h. Upon completion the reaction mixture was quenched with water and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 60/40) to afford **6d** (140 mg, 51% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.22−8.18 (m, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 4.87 (sept, *J* = 6.0 Hz, 1H), 1.45 (d, *J*= 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.89 (q, $^{2}J_{C\text{-}F}$ = 36Hz), 156.7, 137.9, 128.0, 121.6, 121.5, 116.6 (q, $^{1}J_{C\text{-}F}$ = 292 Hz), 115.1, 71.2, 21.7 (2C).

MS (m/z): $[MH]^+$ calculated for $C_{11}H_{11}F_3NO_4$, 278.0562; found 278.0600.

1-(4-isopropoxy-3-nitrophenyl)-2-morpholinoacetone (6e)

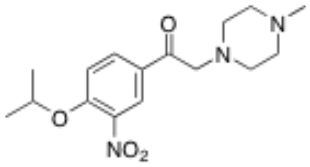


$C_{15}H_{20}N_2O_5$ MW = 308.33 g/mol

Following general procedure 1 with 2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone (230 mg, 0.89 mmol) and morpholine (232 mg, 2.67 mmol), 1-(4-isopropoxy-3-nitrophenyl)-2-morpholinoacetone **6e** (180 mg, 66% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.2 Hz, 1H), 8.20 (dd, *J* = 8.9 Hz, *J* = 2.2 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 4.79 (sept, *J* = 6.1 Hz, 1H), 3.76−3.74 (m, 4H), 3.71 (s, 2H), 2.59−2.56 (m, 4H), 1.43 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 154.9, 140.2, 133.8, 127.7, 126.3, 114.9, 73.2, 66.8 (2C), 65.1, 53.8 (2C), 21.8 (2C). MS (m/z): $[MH]^+$ calculated for $C_{15}H_{21}N_2O_5$, 309.14; found 309.23.

1-(4-isopropoxy-3-nitrophenyl)-2-(4-methylpiperazin-1-yl)acetone (6f)

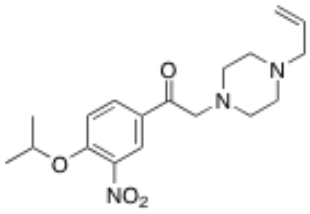


$C_{16}H_{23}N_3O_4$ MW = 321.37 g/mol

Following general procedure 1 with 2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone (330 mg, 1.28 mmol) and 1-*N*-methylpiperazine (426 µL, 3.84 mmol), 1-(4-isopropoxy-3-nitrophenyl)-2-(4-methylpiperazin-1-yl)acetone **6f** (250 mg, 61% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.2 Hz, 1H), 8.11 (dd, *J* = 8.9 Hz, *J* = 2.2 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 4.71 (sept, *J* = 6.1 Hz, 1H), 3.64 (s, 2H), 2.55−2.40 (m, 8H), 2.20 (s, 3H), 1.34 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 154.8, 140.1, 133.7, 127.7, 126.2, 114.8, 73.1, 64.7, 54.7 (2C), 53.2 (2C), 45.8, 21.7 (2C).

2-(4-allylpiperazin-1-yl)-1-(4-isopropoxy-3-nitrophenyl)acetone (6g)

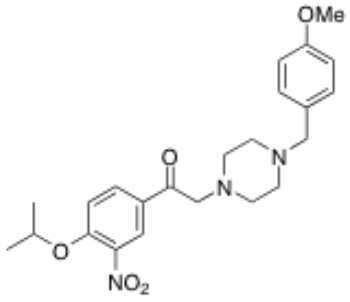


$C_{18}H_{25}N_3O_4$ MW = 347.41 g/mol

Following general procedure 1 with 2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone (600 mg, 2.33 mmol) and 1-*N*-allylpiperazine (977 µL, 6.99 mmol), 2-(4-allylpiperazin-1-yl)-1-(4-isopropoxy-3-nitrophenyl)acetone **6g** (595 mg, 74% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.2 Hz, 1H), 8.19 (dd, *J* = 8.9 Hz, *J* = 2.2 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.87−5.80 (m, 1H), 5.29−5.12 (m, 2H), 4.77 (sept, *J* = 6.1 Hz, 1H), 3.69 (s, 2H), 2.99 (d, *J* = 6.5 Hz, 1H), 2.60−2.45 (m, 8H), 1.43 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 154.9, 140.1, 135.0, 133.9, 128.0, 126.6, 118.2, 114.9, 73.2, 65.2, 61.8, 53.6 (2C), 53.0 (2C), 21.9 (2C). MS (m/z): $[MH]^+$ calculated for $C_{18}H_{26}N_3O_4$, 348.18; found 348.24.

2-(4-para-methoxybenzylpiperazin-1-yl)-1-(4-isopropoxy-3-nitrophenyl)acetone (6h)

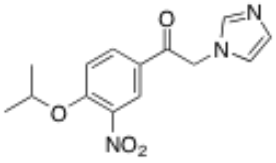


$C_{23}H_{29}N_3O_5$ MW = 427.49 g/mol

Following general procedure 1 with 2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone (1.00 g, 3.88 mmol) and 1-*N*-*para*-methoxybenzylpiperazine (1.00 g, 4.85 mmol), 2-(4-*para*-methoxybenzylpiperazin-1-yl)-1-(4-isopropoxy-3-nitrophenyl)acetone **6h** (1.60 g, 87% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.9 Hz, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.77 (sept, *J* = 6.1 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 2H), 3.49 (s, 2H), 2.65−2.45 (m, 8H), 1.41 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 159.0, 154.9, 140.3, 133.8, 130.7 (2C), 129.2, 127.9, 126.4, 114.9, 113.7 (2C), 73.2, 64.8, 62.1, 55.3, 53.2 (2C), 52.5 (2C), 21.8 (2C).

2-(1*H*-imidazol-1-yl)-1-(4-isopropoxy-3-nitrophenyl)acetone (6i)

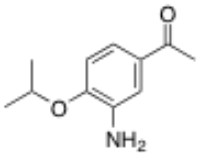


$C_{14}H_{15}N_3O_4$ MW = 289.29 g/mol

Following general procedure 1 with 2-chloro-1-(4-isopropoxy-3-nitrophenyl)acetone (460 mg, 1.78 mmol) and imidazole (363 mg, 5.34 mmol), 2-(1H-imidazol-1-yl)-1-(4-isopropoxy-3-nitrophenyl)acetone **6i** (350 mg, 68% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.0 Hz, 1H), 8.10 (dd, *J* = 8.9 Hz, *J* = 2.0 Hz, 1H), 7.48 (s, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 7.10 (s, 1H), 6.92 (s, 1H), 5.37 (s, 2H), 4.81 (sept, *J* = 6.0 Hz, 1H), 1.42 (d, *J*= 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 155.8, 140.6, 138.3, 133.6, 129.9, 126.0, 125.9, 120.4, 115.6, 73.7, 52.3, 21.8 (2C). MS (m/z): $[MH]^+$ calculated for $C_{14}H_{16}N_3O_4$, 290.10; found 290.19.

1-(3-amino-4-isopropoxyphenyl)acetone (7b)

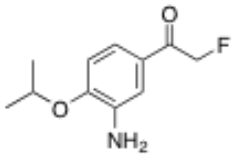


$C_{11}H_{15}NO_2$ MW = 193.24 g/mol

Following general procedure 2b with 1-(4-isopropoxy-3-nitrophenyl)acetone **4** (900 mg, 4.03 mmol), 1-(3-amino-4-isopropoxyphenyl)acetone **7b** (600 mg, 77% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.33 (m, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.63 (sept, *J* = 6.0 Hz, 1H), 3.85 (brs, 2H), 2.50 (s, 3H), 1.36 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 149.6, 137.0, 130.4, 120.4, 114.4, 111.4, 70.7, 26.3, 22.2 (2C). MS (m/z): $[M]^+$ calculated for $C_{11}H_{15}NO_2$, 193.1103; found 193.1098.

1-(3-amino-4-isopropoxyphenyl)-2-fluoroacetone (7c)

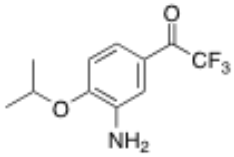


$C_{11}H_{14}FNO_2$ MW = 211.23 g/mol

Following general procedure 2b with **6c** (50 mg, 0.2 mmol), 1-(3-amino-4-isopropoxyphenyl)-2-fluoroacetone **7c** (43 mg, 100% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.17 (m, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.37 (d, $J_{H\text{-}F}$ = 47 Hz, 2H), 4.57 (sept, *J* = 6.0 Hz, 1H), 3.85 (brs, 2H), 1.31 (d, *J*= 6.1 Hz, 6H). MS (m/z): $[MH]^+$ calculated for $C_{11}H_{15}FNO_2$, 212.1009; found 212.1010.

1-(3-amino-4-isopropoxyphenyl)-2,2,2-trifluoroacetone (7d)

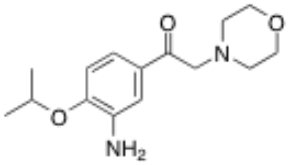


$C_{11}H_{12}F_3NO_2$ MW = 247.21 g/mol

Following general procedure 2b with **6d** (140 mg, 0.5 mmol), 1-(3-amino-4-isopropoxyphenyl)-2,2,2-trifluoroacetone **7d** (65 mg, 53% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.48 (m, 1H), 7.40 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.71 (sept, *J* = 6.0 Hz, 1H), 4.00 (brs, 2H), 1.41 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9 (q, $^2J_{C\text{-}F}$ = 36 Hz), 151.7, 137.6, 122.9, 122.7, 117.2 (q, $^1J_{C\text{-}F}$ = 292 Hz), 115.2, 111.3, 71.2, 22.1 (2C). MS (m/z): $[MH]^+$ calculated for $C_{11}H_{13}F_3NO_2$, 248.0820; found 248.0815.

1-(3-amino-4-isopropoxyphenyl)-2-morpholinoacetone (7e)

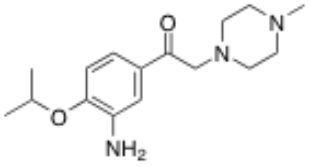


$C_{15}H_{22}N_2O_3$ MW = 278.34 g/mol

Following general procedure 2a with **6e** (500 mg, 1.62 mmol), 1-(3-amino-4-isopropoxyphenyl)-2-morpholinoacetone **7e** (236 mg, 52% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.56 (sept, *J* = 6.0 Hz, 1H), 3.90 (brs, 2H), 3.70−3.66 (m, 6H), 2.45−2.43 (m, 4H), 1.30 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 149.5, 137.0, 128.9, 119.5, 113.9, 111.1, 70.5, 66.7 (2C), 64.1, 53.8 (2C), 21.9 (2C). MS (m/z): $[MH]^+$ calculated for $C_{15}H_{23}N_2O_3$, 279.1709; found 279.1700.

1-(3-amino-4-isopropoxyphenyl)-2- (4-methylpiperazin-1-yl)acetone (7f)

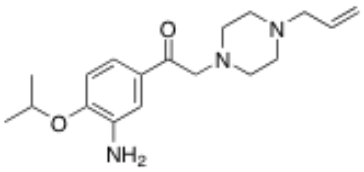


$C_{16}H_{25}N_3O_2$ MW = 291.39 g/mol

Following general procedure 2a with **6f** (150 mg, 0.47 mmol), 1-(3-amino-4-isopropoxyphenyl)-2- (4-methylpiperazin-1-yl)acetone **7f** (120 mg, 88% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 4.59 (sept, *J* = 6.1 Hz, 1H), 3.91 (brs, 2H), 3.70 (s, 2 H), 2.58−2.49 (m, 8H), 2.26 (s, 3H), 1.33 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 149.6, 137.0, 129.2, 119.8, 114.2, 111.3, 70.6, 64.1, 54.9 (2C), 53.5 (2C), 46.0, 22.1 (2C).

1-(3-amino-4-isopropoxyphenyl)-2- (4-allylpiperazin-1-yl)acetone (7g)

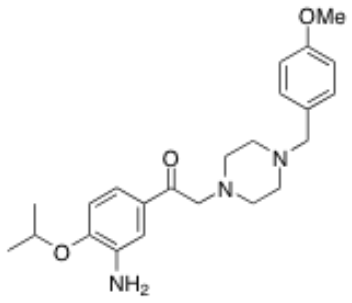


$C_{18}H_{27}N_3O_2$ MW = 317.43 g/mol

Following general procedure 2a with **6g** (350 mg, 1.00 mmol), 1-(3-amino-4-isopropoxyphenyl)-2- (4-allylpiperazin-1-yl)acetone **7g** (250 mg, 79% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz, 1H), 7.34 (d, *J* = 2.2 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.88−5.79 (m, 1H), 5.27−5.10 (m, 2H), 4.63 (sept, *J* = 6.0 Hz, 1H), 3.87 (bs, 2H), 3.71 (s, 2H), 2.98 (d, *J* = 6.2 Hz, 1H), 2.62−2.45 (m, 8H), 1.35 (d, *J*= 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 149.6, 137.0, 135.1, 129.3, 119.9, 118.1, 114.3, 111.3, 70.7, 64.2, 61.8, 53.7 (2C), 53.0 (2C), 22.2 (2C). MS (m/z): $[MH]^+$ calculated for $C_{18}H_{28}N_3O_2$, 318.2182; found 318.2193.

1-(3-amino-4-isopropoxyphenyl)-2-(4-(4-methoxybenzyl)piperazin-1-yl)acetone (7h)



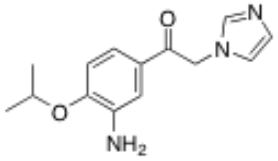
$C_{23}H_{31}N_3O_3$ MW = 397.51

Following general procedure 2a with **6h** (1.6 g, 3.7 mmol), 1-(3-amino-4-isopropoxyphenyl)-2-(4-(4-

methoxybenzyl)piperazin-1-yl)acetone **7h** (930 mg, 63% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.9 Hz, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 4.63 (sept, *J* = 6.0 Hz, 1H), 3.83 (brs, 2H), 3.78 (s, 3H), 3.72 (s, 2H), 3.45 (s, 2H), 2.65−2.45 (m, 8H), 1.36 (d, *J*= 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 158.8, 149.6, 137.0, 130.4 (2C), 130.1, 129.2, 119.8, 114.2, 113.6 (2C), 111.3, 70.7, 64.1, 62.4, 55.3, 53.6 (2C), 52.8 (2C), 22.1 (2C). MS (m/z): $[MH]^+$ calculated for $C_{23}H_{32}N_3O_3$, 398.2444; found 398.2436.

1-(3-amino-4-isopropoxyphenyl)-2-(1*H*-imidazol-1-yl) acetone (7i)

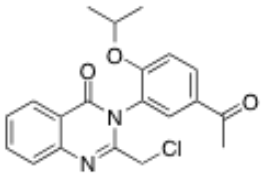


$C_{14}H_{17}N_3O_2$ MW = 259.30

Following general procedure 2a with **6i** (350 mg, 1.2 mmol), 1-(3-amino-4-isopropoxyphenyl)-2-(1H-imidazol-1-yl) acetone **7i** (210 mg, 67% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.36−7.33 (m, 2H), 7.13 (s, 1H), 6.94 (s, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.30 (s, 2H), 4.69 (sept, *J* = 6.0 Hz, 1H), 4.11 (brs, 2H), 1.40 (d, *J*= 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 150.5, 138.3, 137.7, 129.5, 120.4, 119.7, 113.7, 111.4, 71.1, 52.1, 22.2 (2C). MS (m/z): $[MH]^+$ calculated for $C_{14}H_{18}N_3O_2$, 260.1399; found 260.1395.

2-(chloromethyl)-3-(5-ethanoyl-2-isopropoxyphenyl)quinazolin-4(3*H*)-one (8b)



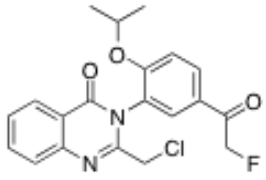
$C_{20}H_{19}ClN_2O_3$ MW = 370.83 g/mol

Following general procedure 3a with **7b** (610 mg, 3.15 mmol), 2-(chloromethyl)-3-(5-ethanoyl-2-isopropoxyphenyl)quinazolin-4(3H)-one **8b** (553 mg, 47% yield) was obtained as a white foaming solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.8 Hz, 1H), 8.12 (dd, J = 8.7 Hz, J = 1.8 Hz, 1H), 7.97 (s, 1H), 7.83−7.76 (m, 2H), 7.55−7.51 (m, 1H), 7.12 (d, J = 8.7 Hz, 1H), 4.67 (sept, J = 6.1 Hz, 1H), 4.36, 4.12 (ABq, JAB = 11.9 Hz, 2H), 2.56 (s, 3H), 1.26 (d, J= 6.0 Hz, 3H), 1.21 (d, J= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 161.5, 157.3, 151.9, 147.1, 134.9, 131.9, 131.7, 130.3, 127.9, 127.8, 127.3, 125.2, 121.3, 113.4, 72.0, 43.8, 26.4, 22.0, 21.8. Compound not

stable enough for MS.

2-(chloromethyl)-3-(5-(2-fluoroethanoyl)-2-isopropoxyphenyl)quinazolin-4(3H)-one (8c)

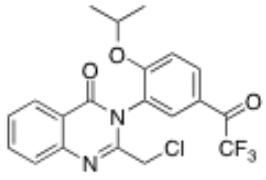


$C_{20}H_{18}ClFN_2O_3$ MW = 388.82 g/mol

Following general procedure 3a with **7c** (64 mg, 0.28 mmol), **8c** (65 mg, 60% yield) was obtained as a beige oily solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.8 Hz, 1H), 8.14−8.10 (m, 1H), 7.95 (s, 1H), 7.83−7.76 (m, 2H), 7.55−7.51 (m, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 5.46 (d, $J_{H\text{-}F}$ = 47 Hz, 2H), 4.67 (sept, *J* = 6.1 Hz, 1H), 4.36, 4.13 (ABq, J_{AB} = 11.9 Hz, 2H), 1.27 (d, *J*= 6.0 Hz, 3H), 1.22 (d, *J*= 6.0 Hz, 3H). Compound not stable enough for MS.

2-(chloromethyl)-3-(2-isopropoxy-5-(2,2,2-trifluoroethanoyl)phenyl)quinazolin-4(3H)-one (8d)

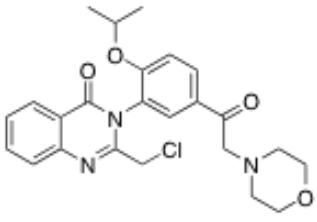


$C_{20}H_{16}ClF_3N_2O_3$ MW = 424.80 g/mol

Following general procedure 3a with **7d** (65 mg, 0.26 mmol), **8d** (55 mg, 49% yield) was obtained as a beige oily solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.25 (m, 2H), 8.11 (s, 1H), 7.83−7.76 (m, 2H), 7.57−7.51 (m, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 4.75 (sept, *J* = 6.1 Hz, 1H), 4.37, 4.11 (ABq, J_{AB} = 11.9 Hz, 2H), 1.27 (d, *J*= 6.0 Hz, 3H), 1.22 (d, *J*= 6.0 Hz, 3H). Compound not stable enough for MS.

2-(chloromethyl)-3-(2-isopropoxy-5-(2-morpholinoethanoyl)phenyl)quinazolin-4(3*H*)-one (8e)



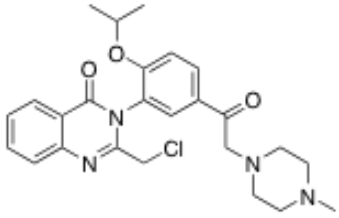
$C_{24}H_{26}ClN_3O_4$ MW = 455.94 g/mol

Following general procedure 3b with **7e** (155 mg, 0.55 mmol), 2-(chloromethyl)-3-(2-isopropoxy-5-(2-morpholinoethanoyl)phenyl)quinazolin-4(3H)-one **8e** (76 mg, 31% yield) was obtained as a white oily solid.

^{1}H NMR (400 MHz, CDCl3) δ 8.27 (d, J = 7.6 Hz, 1H), 8.19 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.80−7.75 (m, 2H), 7.54−7.52 (m, 1H), 7.10 (d, J = 8.8 Hz, 1H), 4.67 (sept, J = 6.1 Hz, 1H), 4.36, 4.13 (ABq, JAB = 11.9

Hz, 2H), 3.74−3.70 (m, 4H), 2.59−2.49 (m, 4H), 1.26 (d, J= 6.0 Hz, 3H), 1.20 (d, J= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 194.0, 161.5, 157.4, 151.8, 147.1, 134.8, 131.9, 131.7, 128.9, 127.9, 127.8 127.3, 125.0, 121.3, 113.4, 72.0, 66.9 (2C), 65.0, 53.9 (2C), 43.8, 21.9, 21.8. Compound not stable enough for MS.

2-(chloromethyl)-3-(2-isopropoxy-5-(2-(4-methylpiperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one (8f)

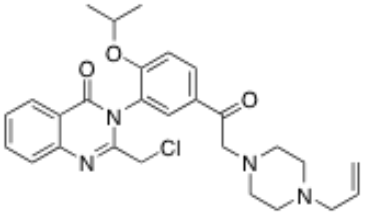


$C_{25}H_{29}ClN_4O_3$ MW = 468.98 g/mol

Following general procedure 3a with **7f** (380 mg, 1.30 mmol), 2-(chloromethyl)-3-(2-isopropoxy-5-(2-(4-methylpiperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3H)-one **8f** (275 mg, 45% yield) was obtained as a beige oily solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.4 Hz, 1H), 8.20 (dd, *J* = 8.8 Hz, *J* = 2.1 Hz, 1H), 8.06 (s, 1H), 7.81−7.77 (m, 2H), 7.27−7.23 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 4.67 (sept, *J* = 6.1 Hz, 1H), 4.36, 4.13 (ABq, J_{AB} = 11.9 Hz, 2H), 3.77, 3.65 (ABq, J_{AB} = 16.0 Hz, 2H), 2.65−2.45 (m, 8H), 2.26 (s, 3H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.20 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 161.5, 157.3, 151.9, 147.1, 134.8, 132.0, 131.7, 129.0, 127.8, 127.3, 124.9, 121.3, 113.3, 71.9, 64.8, 55.0 (2C), 53.6 (2C), 46.2, 46.1, 43.8, 21.9, 21.8. Compound not stable enough for MS.

3-(5-(2-(4-allylpiperazin-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-(chloromethyl)quinazolin-4(3*H*)-one (8g)

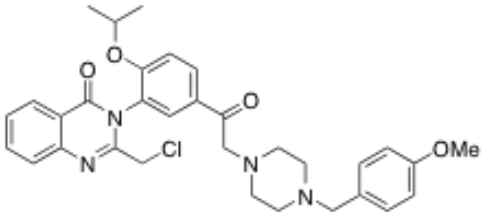


$C_{27}H_{31}ClN_4O_3$ MW = 495.01 g/mol

Following general procedure 3a with 7h (800 mg, 2.52 mmol), 3-(5-(2-(4-allylpiperazin-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-(chloromethyl)quinazolin-4(3*H*)-one **8h** (800 mg, 64% yield) was obtained as a beige oily solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.4 Hz, 1H), 8.20 (dd, *J* = 8.8 Hz, *J* = 2.1 Hz, 1H), 8.05 (s, 1H), 7.79−7.74 (m, 2H), 7.53−7.49 (m, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.87−5.78 (m, 1H), 5.26−5.10 (m, 2H), 4.64 (sept, *J* = 6.0 Hz, 1H), 4.35, 4.12 (ABq, J_{AB} = 11.9 Hz, 2H), 3.76, 3.65 (ABq, J_{AB} = 16.1 Hz, 2H), 2.98 (d, *J* = 6.6 Hz, 2H), 2.65−2.45 (m, 8H), 1.24 (d, *J*= 6.0 Hz, 3H), 1.18 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 161.5, 157.3, 151.9, 147.1, 134.8, 134.7, 132.0, 131.7, 129.0, 127.8 (2C), 127.3, 124.9, 121.3, 118.4, 113.3, 71.9, 64.8, 61.7, 53.4 (2C), 52.8 (2C), 43.8, 21.9, 21.8.

2-(chloromethyl)-3-(2-isopropoxy-5-(2-(4-(4-methoxybenzyl)piperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one (8h)

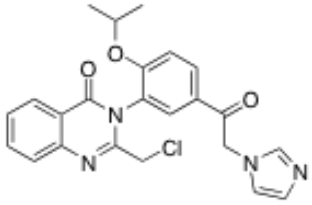


$C_{32}H_{35}ClN_4O_4$ MW = 575.10 g/mol

Following general procedure 3a with **7h** (230 mg, 0.52 mmol), 2-(chloromethyl)-3-(2-isopropoxy-5-(2-(4-(4-methoxybenzyl)piperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one **8h** (134 mg, 45% yield) was obtained as a white oily solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.4 Hz, 1H), 8.20 (dd, *J* = 8.8 Hz, *J* = 2.2 Hz, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 7.82−7.77 (m, 2H), 7.59−7.51 (m, 1H), 7.21 (d, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 1H), 6.84 (d, *J* = 7.4 Hz, 2H), 4.67 (sept, *J* = 6.1 Hz, 1H), 4.37, 4.13 (ABq, J_{AB} = 11.9 Hz, 2H), 3.75 (s, 3H), 3.74−3.64 (m, 2H), 3.44 (s, 2H), 2.62−2.45 (m, 8H), 1.28 (d, *J*= 6.0 Hz, 3H), 1.21 (d, *J*= 6.0 Hz, 3H).

3-(5-(2-(1*H*-imidazol-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-(chloromethyl)quinazolin-4(3*H*)-one (8i)

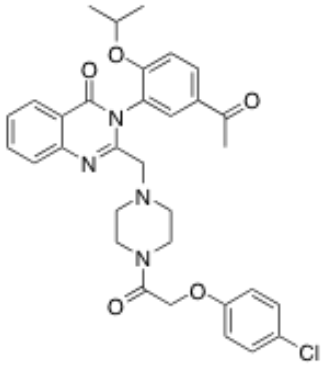


$C_{23}H_{21}ClN_4O_3$ MW = 436.89 g/mol

Following general procedure 3a with 1-(3-amino-4-isopropoxyphenyl)-2-(1H-imidazol-1-yl) acetone **7i** (190 mg, 0.73 mmol), 3-(5-(2-(1*H*-imidazol-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-(chloromethyl)quinazolin-4(3*H*)-one **8i** (170 mg, 53% yield) was obtained as a beige oily solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.4 Hz, 1H), 8.20 (dd, *J* = 8.8 Hz, *J* = 2.1 Hz, 1H), 8.00 (s, 1H), 7.78−7.71 (m, 2H), 7.52−7.50 (m, 1H), 7.45 (s, 1H), 7.13 (d, *J* = 8.9 Hz, 1H), 7.07 (s, 1H), 6.90 (s, 1H), 5.53 (s, 2H), 4.67 (sept, *J* = 6.1 Hz, 1H), 4.35, 4.08 (ABq, J_{AB} = 11.9 Hz, 2H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.19 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5, 161.4, 158.1, 151.4, 147.0, 138.2, 134.9, 131.8, 131.4, 129.5, 128.0, 127.8, 127.1, 127.0, 125.5, 121.0, 120.4, 113.8, 72.3, 52.2, 43.8, 21.8, 21.7. compound not stable enough for MS.

2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(5-ethanoyl-2-isopropoxyphenyl)quinazolin-4(3*H*)-one KE

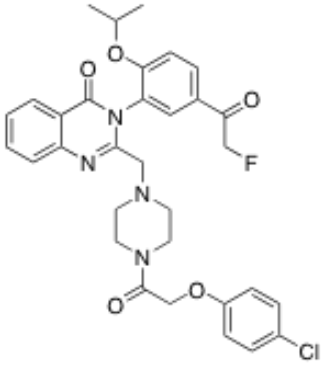


$C_{32}H_{33}ClN_4O_5$ MW = 589.08 g/mol

Following general procedure 4 with 2-(chloromethyl)-3-(5-ethanoyl-2-isopropoxyphenyl)quinazolin-4(3*H*)-one (365 mg, 0.88 mmol), **KE** (282 mg, 54% yield, 2 steps) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.4 Hz, 1H), 8.04 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 2.1 Hz, 1H), 7.79−7.72 (m, 2H), 7.52−7.48 (m, 1H), 7.21 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.65 (sept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.50−3.40 (m, 4H), 3.25, 3.18 (ABq, J_{AB} = 14.0 Hz, 2H), 2.56 (s, 3H), 2.44−2.40 (m, 2H), 2.21−2.12 (m, 2H), 1.24 (d, *J*= 6.0 Hz, 3H), 1.20 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 166.1, 161.9, 157.3, 156.6, 152.9, 147.1, 134.7, 131.6, 131.5, 130.1, 129.6 (2C), 127.6, 127.3, 127.2, 126.8, 126.5, 121.3, 116.1 (2C), 113.2, 72.0, 68.0, 61.3, 53.1, 52.7, 45.3, 42.1, 26.5, 22.3, 21.7. MS (m/z): $[MH]^+$ calculated for $C_{32}H_{33}ClN_4O_5$, 589.08; found 589.22.

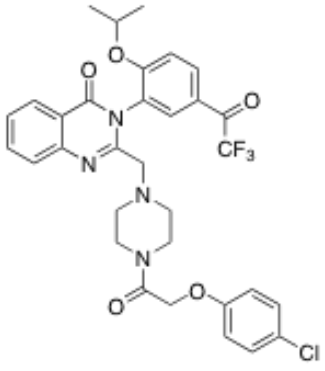
2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(5-(2-fluoroethanoyl)-2-isopropoxyphenyl)quinazolin-4(3H)-one FKE



$C_{32}H_{32}ClFN_4O_5$ MW = 607.07 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.4 Hz, 1H), 8.05−7.96 (m, 2H), 7.80−7.74 (m, 2H), 7.52−7.48 (m, 1H), 7.21 (d, *J* = 8.9 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.42 (d, J_{F-H} = 47 Hz, 2H), 4.67 (sept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.48−3.40 (m, 4H), 3.26, 3.18 (ABq, J_{AB} = 13.9 Hz, 2H), 2.44−2.40 (m, 2H), 2.21−2.12 (m, 2H), 1.24 (d, *J*= 6.0 Hz, 3H), 1.20 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6 (d, $^2J_{C-F}$= 16 Hz), 166.1, 161.8, 158.2 156.5, 152.7, 147.1, 134.8, 131.9, 131.6, 131.3, 129.7 (2C), 127.7, 127.4, 127.3, 126.9 (d, $^3J_{C-F}$= 15 Hz), 126.6, 121.2, 116.1 (2C), 113.4, 84.0 (d, $^1J_{C-F}$= 182 Hz), 72.3, 68.0, 61.4, 53.1, 52.7, 45.2, 42.0, 22.3, 21.7.

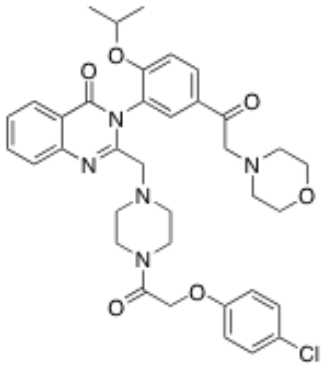
2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(2-isopropoxy-5-(2,2,2-trifluoroethanoyl)phenyl)quinazolin-4(3*H*)-one TFKE



$C_{32}H_{30}ClF_3N_4O_5$ MW = 643.05 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.9 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.09 (s, 1H), 7.81−7.73 (m, 2H), 7.52−7.48 (m, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 4.71 (sept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.48−3.16 (m, 6H), 2.44−2.40 (m, 2H), 2.21−2.12 (m, 2H), 1.28 (d, *J*= 6.1 Hz, 3H), 1.25 (d, *J*= 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6 (q, $^2J_{C\text{-}F}$= 16 Hz), 166.1, 161.7, 159.5, 156.5, 152.3, 147.0, 134.9, 133.7, 133.5, 129.7 (2C), 127.7, 127.5, 127.3, 127.2, 126.8, 122.4, 121.2, 116.0 (2C), 0117.1 (d, $^1J_{C\text{-}F}$= 182 Hz), 113.5, 72.7, 68.0, 61.5, 53.1, 52.7, 45.1, 41.9, 22.3, 21.7. MS (m/z): $[MH]^+$ calculated for $C_{32}H_{30}ClF_3N_4O_5$, 643.18; found 643.35.

2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(2-isopropoxy-5-(2-morpholinoethanoyl)phenyl)quinazolin-4(3*H*)-one MKE



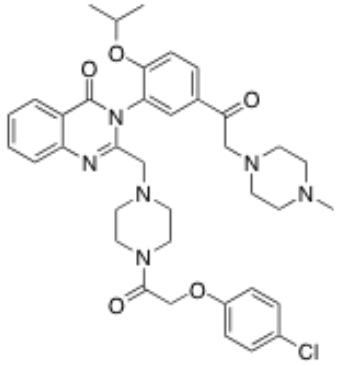
$C_{36}H_{40}ClN_5O_6$ MW = 674.19 g/mol

Following general procedure 4 with 2-(chloromethyl)-3-(2-isopropoxy-5-(2-morpholinoethanoyl)phenyl)quinazolin-4(3*H*)-one (75 mg, 0.16 mmol), MKE (63 mg, 62% yield, 2 steps) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 8.10 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.80−7.71 (m, 2H), 7.51−7.47 (m, 1H), 7.20 (d, J = 8.9 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 1H), 6.82 (d, J = 8.9 Hz, 2H), 4.65 (sept, J = 6.0 Hz, 1H), 4.58 (s, 2H), 3.75−3.73 (m, 4H), 3.50−3.40 (m, 4H), 3.25, 3.18 (ABq, J_{AB} = 14.0 Hz, 2H), 2.61−2.35 (m, 8H), 2.18−2.05 (m, 2H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.19 (d, *J* = 6.0 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$) δ

193.9, 166.0, 161.8, 157.4, 156.5, 152.8, 147.0, 134.6, 131.5, 131.2, 129.6 (2C), 128.7, 127.6, 127.3, 127.2, 126.7, 126.4, 121.2, 116.0 (2C), 113.0, 72.0, 67.9, 66.9 (2C), 64.9, 61.2, 54.0 (2C), 53.0, 52.7, 45.2, 42.0, 22.2, 21.7. MS (m/z): $[MH]^+$ calculated for $C_{36}H_{40}ClN_5O_6$, 674.19; found 674.27.

2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(2-isopropoxy-5-(2-(4-methylpiperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one MPKE

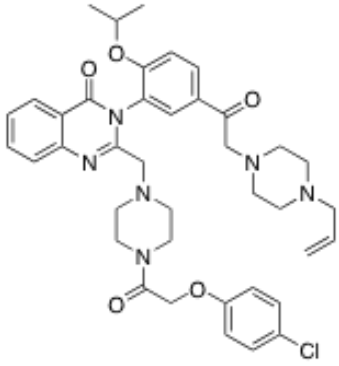


$C_{37}H_{43}ClN_6O_5$ MW = 687.23 g/mol

Following general procedure 4 with 2-(chloromethyl)-3-(2-isopropoxy-5-(2-(4-methylpiperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one (70 mg, 0.15 mmol), MPKE (13 mg, 20% yield, 2 steps) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.9 Hz, 1H), 8.13 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H), 7.79−7.72 (m, 2H), 7.53−7.48 (m, 1H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.65 (sept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.75−3.73 (m, 2H), 3.50−3.40 (m, 4H), 3.27, 3.19 (ABq, J_{AB} = 14.0 Hz, 2H), 2.61−2.35 (m, 10H), 2.30 (s, 3H), 2.18−2.05 (m, 2H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.21 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 166.0, 161.9, 157.5, 156.6, 152.9, 134.7, 131.6, 131.3, 129.7 (2C), 128.9, 127.6, 127.5, 127.3, 127.2, 121.3, 116.1 (2C), 113.1, 72.0, 68.0, 64.7, 61.3, 55.0 (2C), 53.7 (2C), 53.1, 52.7, 46.1, 45.3, 42.1, 22.3, 21.7.

3-(5-(2-(4-allylpiperazin-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)quinazolin-4(3H)-one APKE

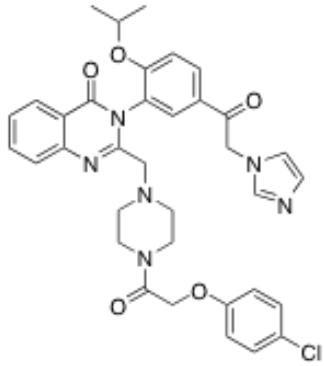


$C_{39}H_{45}ClN_6O_5$ MW = 713.26 g/mol

Following general procedure 4 with 3-(5-(2-(4-allylpiperazin-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-(chloromethyl)quinazolin-4(3*H*)-one (80 mg, 0.16 mmol), APKE (65 mg, 59% yield, 2 steps) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.9 Hz, 1H), 8.12 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.79−7.72 (m, 2H), 7.52−7.48 (m, 1H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.88−5.81 (m, 1H), 5.27−5.13 (m, 2H), 4.69 (sept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.74−3.73 (m, 2H), 3.46−3.39 (m, 4H), 3.26, 3.19 (ABq, J_{AB} = 14.0 Hz, 2H), 3.00 (d, *J* = 6.6 Hz, 2H), 2.61−2.35 (m, 10H), 2.18−2.05 (m, 2H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.21 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 165.8, 161.7, 157.3, 156.4, 152.8, 147.0, 134.8, 134.6, 131.5, 131.2, 129.5 (2C), 128.7, 127.5, 127.2, 127.1, 126.6, 126.4, 121.2, 118.2, 116.0 (2C), 113.0, 71.9, 67.8, 64.7, 61.7, 61.2, 53.6 (2C), 53.0, 52.8 (2C), 52.6, 45.1, 41.9, 22.3, 21.7. MS (m/z): $[MH]^+$ calculated for $C_{39}H_{45}ClN_6O_5$, 713.26; found 713.32.

3-(5-(2-(1*H*-imidazol-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)quinazolin-4(3*H*)-one IKE

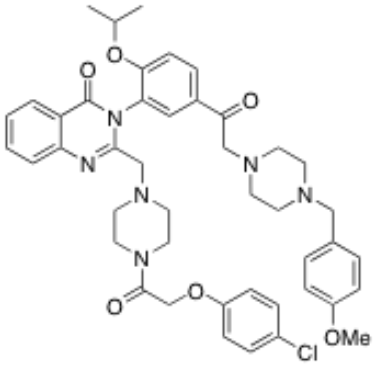


$C_{35}H_{35}ClN_6O_5$ MW = 655.14 g/mol

Following general procedure 4 with 3-(5-(2-(1H-imidazol-1-yl)ethanoyl)-2-isopropoxyphenyl)-2-(chloromethyl)quinazolin-4(3*H*)-one (120 mg, 0.27 mmol), IKE (110 mg, 61% yield, 2 steps) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.9 Hz, 1H), 8.01 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.77−7.70 (m, 2H), 7.50−7.45 (m, 2H), 7.19 (d, *J* = 9.0 Hz, 2H), 7.50−7.45 (m, 2H), 6.90 (s, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.40−5.25 (m, 2H), 4.66 (sept, *J* = 6.0 Hz, 1H), 4.57 (s, 2H), 3.43−3.35 (m, 4H), 3.24, 3.16 (ABq, J_{AB} = 14.0 Hz, 2H), 2.40−2.01 (m, 4H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.21 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 166.0, 161.8, 158.3, 156.5, 152.4, 147.0, 138.2, 134.7, 131.4, 130.9, 129.7, 129.5 (2C), 127.7, 127.3, 127.2, 127.0, 126.9, 126.7, 121.0, 120.3, 116.0 (2C), 113.4, 72.3, 67.8, 61.1, 52.7, 52.6, 52.2, 45.1, 41.9, 22.2, 21.6. MS (m/z): $[MH]^+$ calculated for $C_{35}H_{35}ClN_6O_5$, 655.14; found 655.24.

2-((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(2-isopropoxy-5-(2-(4-(4-methoxybenzyl)piperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one PMB-PKE

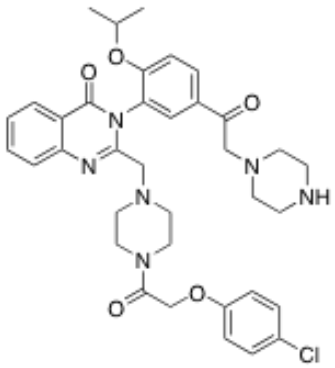


$C_{44}H_{49}ClN_6O_6$ MW = 793.34 g/mol

Following general procedure 4 with 2-(chloromethyl)-3-(2-isopropoxy-5-(2-(4-(4-methoxybenzyl)piperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3*H*)-one (104 mg, 0.18 mmol), PMB-PKE (61 mg, 43% yield, 2 steps) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.9 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.99 (s, 1H), 7.81−7.72 (m, 2H), 7.52−7.48 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 4H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 4H), 4.66 (sept, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 3.79 (s, 3H), 3.72 (s, 2H), 3.47−3.40 (m, 6H), 3.27, 3.19 (ABq, J_{AB} = 14.0 Hz, 2H), 2.61−2.35 (m, 10H), 2.19−2.13 (m, 2H), 1.24 (d, *J*= 6.0 Hz, 3H), 1.21 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 165.9, 161.8, 157.4, 156.5, 152.8, 147.1, 134.6, 131.5, 131.3, 130.5 (2C), 129.6 (4C), 128.8, 127.6, 127.3, 127.2, 126.7, 126.4, 121.2, 116.0 (4C), 113.7 (2C), 113.0, 71.9, 67.9, 64.7, 62.4, 61.2, 55.3, 53.6 (2C), 53.0, 52.8 (2C), 52.6, 45.2, 42.0, 22.2, 21.7. MS (m/z): $[MH]^+$ calculated for $C_{44}H_{49}ClN_6O_6$, 793.34; found 793.35.

((4-(2-(4-chlorophenoxy)ethanoyl)piperazin-1-yl)methyl)-3-(2-isopropoxy-5-(2-(piperazin-1-yl)ethanoyl)phenyl)quinazolin-4(3H)-one PKE

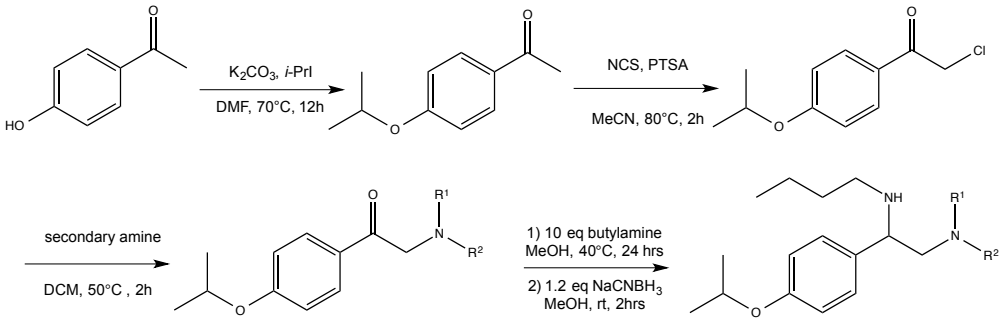


$C_{36}H_{41}ClN_6O_5$ MW = 673.20 g/mol

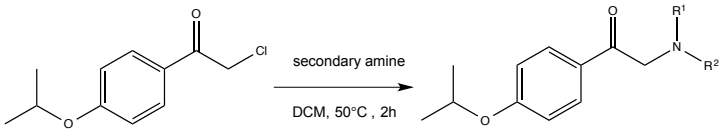
To a Schlenk reactor containing APKE (700 mg, 0.98 mmol, 1 equiv.) in DCM (20 mL) was added under nitrogen *N*,*N*-dimethylbarbituric acid (460 mg, 2.94 mmol, 3 equiv.) followed by $Pd(PPh_3)_4$ (115 mg, 0.1 mmol, 0.1 equiv.). The reaction mixture was stirred under nitrogen for 15 h at 40 °C. Upon completion, the reaction mixture was quenched with 2N aqueous HCl solution (10 mL), and the aqueous phase containing the desired product was extracted with DCM (2 x 10 mL). The aqueous phase was then basified with 6N aqueous NaOH, and the desired product was extracted into the organic phase (5 x 10 mL DCM/MeOH 5%). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduce pressure to yield PKE (571 mg, 87%) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.24−8.22 (m, 2H), 8.15 (d, *J* = 1.6 Hz, 1H), 7.91−7.89 (m, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.63−7.59 (m, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.85 (sept, *J* = 6.0 Hz, 1H), 4.75 (s, 2H), 3.91 (s, 2H), 3.46−3.27 (m, 6H), 2.93−2.91 (m, 4H), 2.64−2.61 (m, 4H), 2.36−2.17 (m, 4H), 1.27 (d, *J*= 6.0 Hz, 3H), 1.21 (d, *J*= 6.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 196.1, 168.4, 163.6, 158.9, 158.2, 155.0, 148.2, 136.2, 132.7, 132.5, 130.3, 129.8 (2C), 128.7, 128.2, 127.7, 127.4, 127.3, 122.0, 117.3 (2C), 114.5, 73.1, 67.7, 62.0, 54.6 (2C), 53.8, 53.5, 50.0, 45.9 (3C), 42.9, 22.5, 21.8. MS (m/z): $[MH]^+$ calculated for $C_{36}H_{41}ClN_6O_{5\ 6}$, 673.20; found 673.29.

IV B. Synthetic procedures and characterization for ketone formation and imine conversion

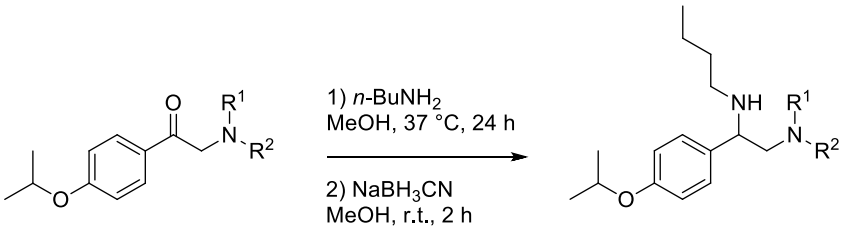


General procedure 5: Synthesis of acetophenones



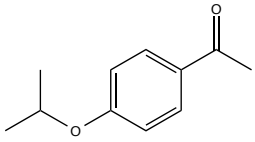
To a solution of 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (1 equiv.) in DCM (0.5 M) was added the secondary amine (3 equiv.). The reaction mixture was stirred under reflux for 2 h, quenched with water, extracted two times with DCM. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Silica gel column chromatography (DCM/MeOH = 100/0 to 90/10) afforded the corresponding acetophenone.

General procedure 6: Synthesis of amines through imine intermediates



To a solution of the acetophenone (150 mg, 1 equiv.) in MeOH (2 mL), was added the n-butylamine (10 equiv). The reaction mixture was stirred at 37°C for 24 hours, forming the imine intermediate. Subsequently $NaCNBH_3$ (1.2 equiv) was added and the mixture was stirred at room temperature for 2 hours. Upon completion the reaction mixture was concentrated under reduced pressure and purified by preparatory TLC (hexane : EtOAc = 5:2) to afford both the starting acetophenone as well as the final amine. The masses of both were obtained and compared to determine the final amine/ketone ratio.

(1b) 1-(4-isopropoxyphenyl)ethan-1-one

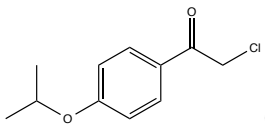


$C_{11}H_{14}O_2$ MW= 178.23

To a solution of 1-(4-hydroxyphenyl)ethan-1-one (5.00 g, 36.6 mmol, 1 equiv.) in DMF (50 mL) at r.t. was added potassium carbonate (5.80 g, 43.9 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 15 min and 2-iodopropane (7.31 mL, 73.3 mmol, 2.0 eq) was then added dropwise. The mixture was subsequently stirred at 70 °C for 12 h. Upon completion the reaction mixture was quenched with water and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 60/40) to afford 1-(4-isopropoxyphenyl)ethan-1-one (4.27 g, 65% yield) as a clear oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 – 7.66 (m, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.66 (p, *J* = 6.1 Hz, 1H), 2.56 (s, 3H), 1.38 (d, *J* = 6.1 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 196.67, 161.99, 130.59, 129.93, 115.05, 70.08, 26.27, 21.90. MS (m/z): [MH+] calculated for $C_{11}H_{14}O_2$, 178.23; found 178.55

2-chloro-1-(4-isopropoxyphenyl)ethan-1-one

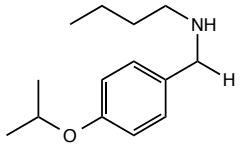


$C_{11}H_{13}ClO_2$ MW=212.67

To a solution of **1b** (4.27 g, 23.9 mmol, 1 equiv.) in acetonitrile (60 mL) at r.t. were added *p*-toluenesulfonic acid (6.84 g, 35.9 mmol, 1.5 equiv.) and *N*-chlorosuccinimide (3.52 g, 26.40 mmol, 1.1 equiv.). The mixture was refluxed for 3 h, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 70/30) to afford 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (2.88 g, 57% yield) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95-7.93 (d, *J* = 2.9 Hz, 2H), 6.96 – 6.94 (d, 2H), 4.71-4.65 (m, 3H), 1.40 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.73, 162.88, 131.11, 126.87, 115.51, 70.46, 45.75, 22.011 MS (m/z): [MH+] calculated for $C_{11}H_{13}ClO_2$, 212.67; found 212.53

***(*2a) *N*-(4-isopropoxybenzyl)butan-1-amine**

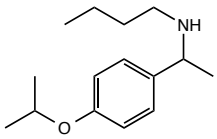


$C_{14}H_{23}NO$ MW=221.18

Following general procedure 6 with 4-isopropoxybenzaldehyde (50 mg, 0.30 mmol), *N*-(4-isopropoxybenzyl)butan-1-amine **1a** (53 mg, 79% yield) was obtained as a yellow oil. Remaining starting material, 4-isopropoxybenzaldehyde, was also obtained (4 mg, 8% yield), giving an amine/ketone ratio of 9.5:1.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.95 – 6.72 (m, 2H), 4.54 (p, *J* = 6.1 Hz, 1H), 3.74 (s, 2H), 2.72 – 2.52 (m, 2H), 1.70 – 1.36 (m, 5H), 1.35 (d, *J* = 6.0 Hz, 7H), 0.93 (t, *J* = 7.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.95, 132.11, 129.36, 115.85, 69.92, 53.35, 48.98, 46.99, 32.03, 22.07, 20.48, 13.99. MS (m/z): [MH+] calculated for $C_{14}H_{23}NO$, 222.18; found 222.19

(2b) *N*-(1-(4-isopropoxyphenyl)ethyl)butan-1-amine

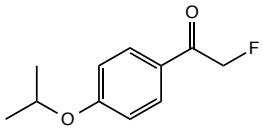


$C_{15}H_{25}NO$ MW=235.37

Following general procedure 6 with 1-(4-isopropoxyphenyl)ethan-1-one **1b** (100 mg, 0.56 mmol), *N*-(1-(4-isopropoxyphenyl)ethyl)butan-1-amine (69 mg, 52% yield) was obtained as a yellow oil. Remaining starting material, 1-(4-isopropoxyphenyl)ethan-1-one, was also obtained (18 mg, 18% yield), giving an amine/ketone ratio of 3:1.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.09 (m, 2H), 6.96 – 6.63 (m, 2H), 4.54 (p, *J* = 6.1 Hz, 1H), 3.72 (q, *J* = 6.6 Hz, 1H), 2.67 – 2.31 (m, 2H), 2.19 (s, 1H), 1.63 – 1.39 (m, 2H), 1.37 – 1.25 (m, 11H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.76, 137.82, 127.50, 115.67, 69.84, 57.71, 47.53, 32.43, 24.27, 22.14, 20.51, 14.00. MS (m/z): [MH+] calculated for $C_{15}H_{25}NO$ 235.19; found 235.47

(1c) 2-fluoro-1-(4-isopropoxyphenyl)ethan-1-one

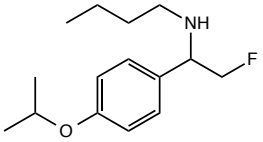


$C_{11}H_{13}FO_2$ MW=196.22

To a solution of LiHMDS (1 M in THF, 3.76 mL, 3.76 mmol, 1.2 equiv.) in THF (25 mL) at r.t., was added a solution of 1-(4-isopropoxyphenyl)ethan-1-one (1.0 g, 5.6 mmol, 1 equiv.) in THF (1 mL) dropwise over 30 min. The reaction mixture was stirred at r.t. for 15 min, then concentrated under reduced pressure, dissolved in MeCN (20 mL) and filtrated. To a solution of selectfluor (1.45 g, 4.1 mmol, 1.3 equiv.) in acetonitrile (6 mL) at 0 °C was added the crude filtrate dropwise. The reaction mixture was stirred at r.t. for 30 min and concentrated under reduced pressure. The crude residue was dissolved in EtOAc (30 mL) and washed with water (2 x 30 mL). The organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc = 100/0 to 60/40) to 2-fluoro-1-(4-isopropoxyphenyl)ethan-1-one **1c** (601 mg, 55% yield) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (dt, *J* = 8.0, 1.1 Hz, 2H), 7.10 – 6.82 (m, 2H), 4.72 (p, *J* = 6.1 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.92, 191.77, 162.82, 130.29, 130.26, 126.29, 115.44, 84.35, 82.55, 70.32, 21.87. MS (m/z): [MH+] calculated for $C_{11}H_{13}FO_2$ 196.09; found 196.45

(2c) (*E*)-*N*-butyl-2-fluoro-1-(4-isopropoxyphenyl)ethan-1-imine

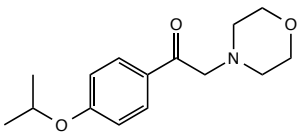


$C_{15}H_{22}FNO$ MW=253.36

Following general procedure 6 with 2-fluoro-1-(4-isopropoxyphenyl)ethan-1-one **1c** (90 mg, 0.46 mmol), (*E*)-*N*-butyl-2-fluoro-1-(4-isopropoxyphenyl)ethan-1-imine **2c** (47 mg, 40% yield) was obtained as a yellow oil. Remaining starting material, 2-fluoro-1-(4-isopropoxyphenyl)ethan-1-one, was also obtained (36 mg, 40% yield), giving an amine/ketone ratio of 1:1.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.60 , 4.51 (m, 1H), 4.49 , 4.25 (m, 2H), 3.97 (ddd, *J* = 12.7, 8.6, 4.1 Hz, 1H), 2.50 (t, *J* = 7.1 Hz, 2H), 1.52 , 1.43 (m, 2H), 1.40 (d, *J* = 6.1 Hz, 9H), 0.90 (t, *J* = 7.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.60, 130.33, 128.71, 115.41, 84.39, 70.29, 62.54, 62.35, 47.17, 32.36, 21.87, 20.40, 13.97. MS (m/z): [MH+] calculated for $C_{15}H_{22}FNO$ 251.35; found 253.36

(1d) 1-(4-isopropoxyphenyl)-2-morpholinoethan-1-one

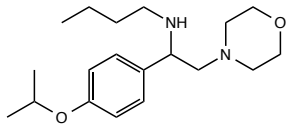


$C_{15}H_{21}NO_3$ MW=263.34

Following general procedure 5 with 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (550 mg, 2.6 mmol) and morpholine (680 µL, 678 mg, 7.8 mmol), 1-(4-isopropoxyphenyl)-2-morpholinoethan-1-one **1d** (482 mg, 71% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.64 (p, *J* = 6.1 Hz, 1H), 3.92-3.64 (m, 6H), 3.01-2.32 (m, 4H), 1.36 (d, *J* = 6.1 Hz, 7H), 1.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.67, 162.24, 130.52, 128.65, 115.12, 70.18, 66.89, 64.57, 60.45, 53.98, 50.73, 21.95, 21.09, 14.25. MS (m/z): [MH+] calculated for $C_{15}H_{21}NO_3$ 263.44; found 263.44

(2d) *N*-(1-(4-isopropoxyphenyl)-2-morpholinoethyl)butan-1-amine

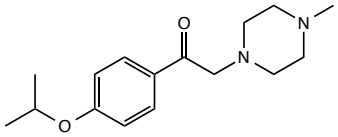


$C_{19}H_{32}N_2O_2$ MW=320.48

Following general procedure 6 with 1-(4-isopropoxyphenyl)-2-morpholinoethan-1-one (150 mg, 0.57 mmol), *N*-(1-(4-isopropoxyphenyl)-2-morpholinoethyl)butan-1-amine **2d** (62 mg, 34% yield) was obtained as a yellow oil. Remaining starting material, 1-(4-isopropoxyphenyl)-2-morpholinoethan-1-one, was also obtained (62.3 mg, 42% yield), giving an amine/ketone ratio of 1:1.2.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.55-4.45 (m, 1H), 3.87-3.56 (m, 6H), 3.37 (s, 1H), 2.75-2.05 (m, 9H), 1.33 (dd, *J* = 6.2, 0.8 Hz, 9H), 0.89 (td, *J* = 7.4, 0.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.57, 132.11, 128.66, 115.91, 69.94, 67.12, 65.18, 60.48, 59.10, 46.96, 31.35, 22.14, 20.38, 13.92. MS (m/z): [MH]+ calculated for $C_{19}H_{32}N_2O_2$ 320.48; found 320.40

(1e) 1-(4-isopropoxyphenyl)-2-(4-methylpiperazin-1-yl)ethan-1-one

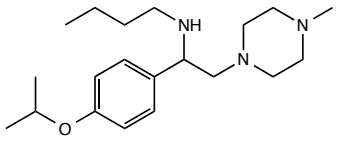


$C_{16}H_{24}N_2O_2$ MW=276.38

Following general procedure 5 with 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (550 mg, 2.6 mmol) and methylpiperazine (860 µL, 777 mg, 7.8 mmol), 1-(4-isopropoxyphenyl)-2-(4-methylpiperazin-1-yl)ethan-1-one **1e** (311 mg, 43% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.65 (p, *J* = 6.1 Hz, 1H), 3.75 (s, 2H), 2.80-2.43 (m, 8H), 2.30 (s, 4H), 1.37 (d, *J* = 6.1 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.95, 162.17, 130.59, 128.87, 115.11, 70.18, 64.47, 55.05, 53.70, 46.16, 22.02. MS (m/z): [MH]+ calculated for $C_{16}H_{24}N_2O_2$ 276.38; found 276.45

(2e) *N*-(1-(4-isopropoxyphenyl)-2-(4-methylpiperazin-1-yl)ethyl)butan-1-amine

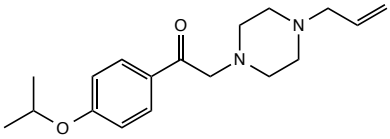


$C_{20}H_{35}N_3O$ MW=333.53

Following general procedure 6 with 1-(4-isopropoxyphenyl)-2-(4-methylpiperazin-1-yl)ethan-1-one **1e** (150 mg, 0.54 mmol), *N*-(1-(4-isopropoxyphenyl)-2-(4-methylpiperazin-1-yl)ethyl)butan-1-amine **2e** (11.5mg, 6% yield) was obtained as a yellow oil. Remaining starting material, 1-(4-isopropoxyphenyl)-2-(4-methylpiperazin-1-yl)ethan-1-one, was also obtained (24.2 mg, 16% yield), giving an amine/ketone ratio of 1:2.5.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.14 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.53 (p, *J* = 6.1 Hz, 1H), 3.70 (dd, *J* = 11.1, 3.4 Hz, 1H), 2.80 – 2.35 (m, 11H), 2.31 (s, 5H), 1.62 – 1.37 (m, 3H), 1.34 (d, *J* = 6.0 Hz, 8H), 0.90 (t, *J* = 7.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.15, 134.77, 128.44, 115.77, 69.95, 65.84, 59.36, 55.46, 47.55, 46.21, 32.32, 22.27, 20.59, 14.12. MS (m/z): [MH]+ calculated for $C_{20}H_{35}N_3O$ 333.53; found: 333.40

(1f) 2-(4-allylpiperazin-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one

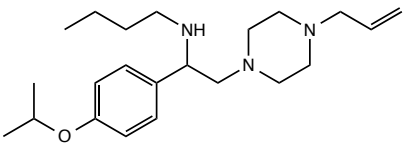


$C_{18}H_{26}N_2O_2$ MW=302.20

Following general procedure 5 with 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (550 mg, 2.6mmol) and allypiperazine (1.73 mL, 984 mg, 7.8 mmol),) 2-(4-allylpiperazin-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one **1f** (451 mg, 57% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.9 Hz, 2H), 6.98 – 6.63 (m, 2H), 5.90 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.29 – 5.07 (m, 2H), 4.66 (p, *J* = 6.1 Hz, 1H), 3.77 (s, 2H), 3.06 (dt, *J* = 6.7, 1.2 Hz, 2H), 2.63 (d, *J* = 30.0 Hz, 7H), 1.38 (d, *J* = 6.1 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.68, 162.29, 133.29, 130.50, 119.73, 115.15, 70.20, 63.89, 61.61, 61.41, 52.96, 52.64, 21.96. MS (m/z): [MH]+ calculated for $C_{18}H_{26}N_2O_2$ 302.20; found: 302.80

(2f) *N*-(2-(4-allylpiperazin-1-yl)-1-(4-isopropoxyphenyl)ethyl)butan-1-amine

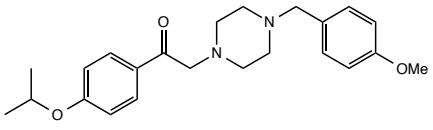


$C_{22}H_{37}N_3O$ MW=359.56

Following general procedure 6 with 2-(4-allylpiperazin-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one (150 mg, 0.49 mmol), *N*-(2-(4-allylpiperazin-1-yl)-1-(4-isopropoxyphenyl)ethyl)butan-1-amine (51 mg, 28% yield) was obtained as a yellow oil. Remaining starting material, 2-(4-allylpiperazin-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one, was also obtained (52mg, 35% yield), giving an amine/ketone ratio of 1:1.2.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 5.97 – 5.73 (m, 1H), 4.56 (p, *J* = 6.1 Hz, 1H), 4.30 – 3.90 (m, 1H), 3.43 – 3.26 (m, 2H), 3.24 – 3.01 (m, 2H), 1.66 (dt, *J* = 22.7, 7.3 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 7H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.18, 129.71, 123.65, 122.59, 116.59, 70.12, 60.64, 60.38, 59.89, 52.28, 51.65, 45.42, 28.31, 22.04, 22.02, 19.90, 13.59. MS (m/z): [MH]+ calculated for $C_{22}H_{37}N_3O$ 359.56; found: 360.83

(1g) 1-(4-isopropoxyphenyl)-2-(4-(4-methoxybenzyl)piperazin-1-yl)ethan-1-one

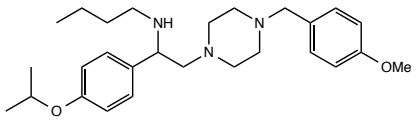


$C_{23}H_{30}N_2O_3$ MW= 382.50

Following general procedure 1 with 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (300 mg, 1.4mmol) and 1-(4-methoxybenzyl)piperazine (872 mg, 4.2 mmol), 1-(4-isopropoxyphenyl)-2-morpholinoethan-1-one **1g** (522 mg, 91% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (dd, *J* = 13.8, 8.7 Hz, 4H), 4.65 (p, *J* = 6.1 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 2H), 3.49 (s, 2H), 2.77 – 2.31 (m, 8H), 2.05 (s, 2H), 1.37 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.96, 162.15, 158.85, 130.54, 129.85, 128.81, 115.08, 113.67, 70.15, 64.36, 62.43, 60.46, 55.32, 53.56, 52.82, 21.99, 21.13, 14.28. MS (m/z): [MH]+ calculated for $C_{23}H_{30}N_2O_3$ 382.50; found: 382.66

(2g) *N*-(1-(4-isopropoxyphenyl)-2-(4-(4-methoxybenzyl)piperazin-1-yl)ethyl)butan-1-amine



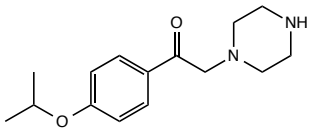
$C_{27}H_{41}N_3O_2$ MW=439.64

Following general procedure 2 with 1-(4-isopropoxyphenyl)-2-(4-(4-methoxybenzyl)piperazin-1-yl)ethan-1-one **1g** (100 mg, 0.26 mmol), *N*-(1-(4-isopropoxyphenyl)-2-(4-(4-methoxybenzyl)piperazin-1-yl)ethyl)butan-1-amine **2g** (9 mg, 8% yield) was obtained as a yellow oil. Remaining starting material, 1-(4-isopropoxyphenyl)-2-(4-(4-

methoxybenzyl)piperazin-1-yl)ethan-1-one, was also obtained (32mg, 32% yield), giving an amine/ketone ratio of 1:4.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.17 (m, 4H), 7.07 – 6.56 (m, 4H), 4.59 – 4.54 (m, 2H), 3.94 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.82 (s, 3H), 3.66 (s, 1H), 3.02 (t, *J* = 12.5 Hz, 2H), 2.91 – 2.46 (m, 8H), 1.65 (td, *J* = 17.8, 16.1, 8.2 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 9H), 1.28 (t, *J* = 7.1 Hz, 1H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.90, 131.07, 129.52, 116.49, 114.06, 70.14, 61.95, 59.80, 55.43, 52.57, 45.62, 29.12, 22.12, 20.06, 13.70. MS (m/z) [MH]+ calculated for $C_{27}H_{41}N_3O_2$ 439.64; found: 439.55

(1h) 1-(4-isopropoxyphenyl)-2-(piperazin-1-yl)ethan-1-one

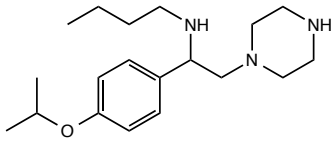


$C_{15}H_{22}N_2O_2$ MW=262.17

Following general procedure 5 with 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (550 mg, 2.6 mmol) and piperazine (668 mg, 7.8mmol), 1-(4-isopropoxyphenyl)-2-(piperazin-1-yl)ethan-1-one **1h** (404 mg, 59% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 7.76 (m, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.67 (ddt, *J* = 12.2, 8.5, 4.3 Hz, 1H), 3.95 – 3.69 (m, 2H), 3.29 – 2.79 (m, 4H), 2.59 (dd, *J* = 7.4, 3.0 Hz, 4H), 2.27 – 1.61 (m, 2H), 1.39 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.94, 162.34, 130.54, 128.54, 115.19, 70.22, 64.39, 53.69, 45.34, 22.15, 21.97. MS (m/z) [MH]+ calculated for $C_{15}H_{22}N_2O_2$ 262.17; found 262.63

(2h) *N*-(1-(4-isopropoxyphenyl)-2-(piperazin-1-yl)ethyl)butan-1-amine

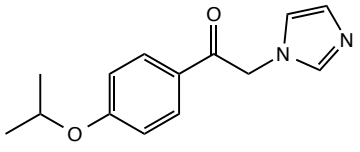


$C_{19}H_{33}N_3O$ MW=319.26

Following general procedure 2 with 1-(4-isopropoxyphenyl)-2-(piperazin-1-yl)ethan-1-one **1h** (150 mg, 0.57 mmol), *N*-(1-(4-isopropoxyphenyl)-2-(piperazin-1-yl)ethyl)butan-1-amine (6 mg, 3% yield) was obtained as a yellow oil. Remaining starting material, 1-(4-isopropoxyphenyl)-2-(piperazin-1-yl)ethan-1-one, was also obtained (37 mg, 25% yield), giving an amine/ketone ratio of 1:7.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 9.1 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.55 (p, *J* = 6.1 Hz, 1H), 3.84 – 3.60 (m, 1H), 2.90 – 2.65 (m, 3H), 2.65 – 2.31 (m, 5H), 1.53 (q, *J* = 7.3 Hz, 2H), 1.36 (d, *J* = 6.0 Hz, 6H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.66, 128.79, 116.00, 70.02, 59.36, 52.52, 46.97, 45.10, 31.37, 22.24, 20.51, 14.02. MS (m/z) [MH]+ calculated for $C_{19}H_{33}N_3O$ 319.26; found 319.64

(1i) 2-(1*H*-imidazol-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one

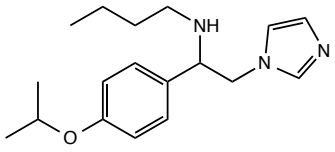


$C_{14}H_{16}N_2O_2$ MW=244.29

Following general procedure 5 with 2-chloro-1-(4-isopropoxyphenyl)ethan-1-one (500 mg, 2.4mmol) and imidazole (480 mg, 7.1 mmol), 2-(1*H*-imidazol-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one **1i** (160 mg, 27% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.74 (m, 2H), 7.54 (s, 1H), 7.16 (s, 1H), 7.04 – 6.73 (m, 3H), 4.70 (p, *J* = 6.0 Hz, 1H), 1.41 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.00, 163.14, 130.51, 126.84, 120.44, 115.71, 70.56, 52.22, 21.99. MS (m/z) [MH]+ calculated for $C_{14}H_{16}N_2O_2$ 244.29; found: 244.60

(2i) *N*-(2-(1*H*-imidazol-1-yl)-1-(4-isopropoxyphenyl)ethyl)butan-1-amine



$C_{18}H_{27}N_3O$ MW=301.43

Following general procedure 6 with 2-(1*H*-imidazol-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one (150 mg, 0.61 mmol) **1i**, *N*-(2-(1*H*-imidazol-1-yl)-1-(4-isopropoxyphenyl)ethyl)butan-1-amine **2i** (9 mg, 5% yield) was obtained as a yellow oil. Remaining starting material, 2-(1*H*-imidazol-1-yl)-1-(4-isopropoxyphenyl)ethan-1-one, was also obtained (11 mg, 7% yield), giving an amine/ketone ratio of 1:1.5.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (s, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.93 – 6.70 (m, 2H), 4.68 – 4.43 (m, 1H), 4.14 (td, *J* = 13.1, 6.5 Hz, 2H), 3.90 (s, 1H), 2.47 (ddt, *J* = 18.6, 11.8, 5.3 Hz, 2H), 1.57 – 1.30 (m, 10H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.86, 152.78, 145.44, 138.51, 131.92, 128.28, 116.17, 70.06, 47.41, 32.20, 22.20, 20.45, 14.05. MS (m/z) [MH]+ calculated for $C_{18}H_{27}N_3O$ 301.43; found: 301.62