Supporting Information

The Synthesis and Evaluation of Dihydroquinazolin-4-ones and Quinazolin-4-ones as Thyroid Stimulating Hormone Receptor Agonists

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General materials and methods: All commercially available reagents and solvents were purchased and used without further purification. All microwave reactions were carried out in a sealed microwave vial equipped with a magnetic stir bar and heated in a Biotage Initiator Microwave Synthesizer. ^{1}H spectra were recorded using an Inova 400 (100) MHz spectrometer (Varian). Samples were analyzed for purity on an Agilent 1200 series LC/MS equipped with a Zorbax™ Eclipse XDB-C18 reverse phase (5 micron, 4.6 x 150 mm) column having a flow rate of 1.1 mL/min. The mobile phase was a mixture of acetonitrile and H_2O each containing 0.05% trifluoroacetic acid. A gradient of 5% to 100% acetonitrile over 8 minutes was used during analytical analysis. High-resolution mass spectroscopy measurements were performed on an Agilent 6210 Electrospray TOF mass spectrometer.

General Procedure for the synthesis of 3:

Method 1:

To a solution of isatoic anhydride **4** (3.07 mmol, 1.0 equiv) in 15 mL acetonitrile (or N,N-dimethylacetamide) was added R^3NH_2 (3.22 mmol, 1.05 equiv). The mixture was put on a shaker and stirred for 24 h. Upon completion, the mixture was concentrated to dryness to afford **3** and taken on crude to the next reaction.

Method 2:

To a solution of **2** (0.841 g, 5.0 mmol, 1.0 equiv), R^3NH_2 (6.0 mmol, 1.2 equiv), and diisopropylethylamine (1.935 g, 15.0 mmol, 3.0 equiv) in 50 mL of dichloromethane was added 2-chloro-1,3-dimethylimidazolinium chloride (1.099 g, 6.5 mmol, 1.3 equiv) at room temperature. The mixture was stirred at room temperature for 6 h, poured into water, and extracted with dichloromethane. The organic solution was successively washed with aqueous saturated $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporator. The residue was purified by column chromatography to afford **3**.

General Procedure for the synthesis of 7:

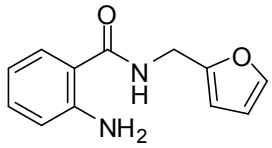
A solution of **5** (462 µmol, 1.0 equiv) and **6** (554 µmol, 1.2 equiv) in anhydrous acetonitrile (4.0 mL) was treated with K_2CO_3 (319 mg, 2.3 mmol, 5.0 equiv) and heated in the microwave for 20 min at 150 °C. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, filtered and concentrated under reduced pressure to afford **7**. This material was used crude.

General Procedure for the synthesis of 1 or 8:

A solution of **7** (400 µmol, 1.0 equiv) in EtOH (6 mL) was treated with **3** (440 µmol, 1.1 equiv) and ytterbium trifluoromethanesulfonate (200 µmol, 0.5 equiv) and heated to 80 °C for 2-6 h. The reaction mixture was concentrated under reduced pressure and purified *via* column chromatography on silica gel. The isolated product was triturated with Et_2O to afford the desired product.

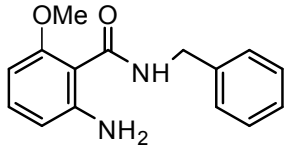
Synthesis of N-(4-(5-(3-(furan-2-ylmethyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1a).

2-amino-N-(furan-2-ylmethyl)benzamide



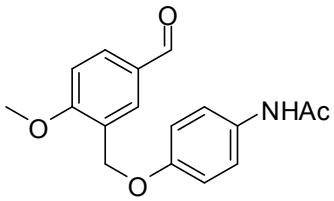
Method 1: To a solution of isatoic anhydride (500 mg, 3.07 mmol, 1.0 equiv) in 15 mL acetonitrile was added furfurylamine (313 mg, 3.22 mmol, 1.05 equiv). The reaction mixture was put on a shaker and stirred for 24 h. Upon completion, the mixture was concentrated to dryness and taken on crude to the next reaction.

2-Amino-N-benzyl-6-methoxybenzamide:



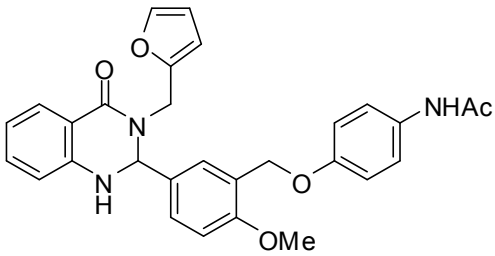
To a solution of 2-amino-6-methoxybenzoic acid (0.841 g, 5.0 mmol, 1.0 equiv), benzylamine (0.643 g, 6.0 mmol, 1.2 equiv), and diisopropylethylamine (1.935 g, 15.0 mmol, 3.0 equiv) in 50 mL of dichloromethane was added 2-chloro-1,3-dimethylimidazolinium chloride (1.099 g, 6.5 mmol, 1.3 equiv) at room temperature. The mixture was stirred at room temperature for 6 hours, poured into water, and extracted with dichloromethane. The organic solution was successively washed with aqueous saturated $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporator. The residue was purified by column chromatography (silica gel, 2% 2.0 M ammonia MeOH solution in CH_2Cl_2) to give 2-Amino-N-benzyl-6-methoxybenzamide (0.593 g, 46%) as a solid. HPLC: t_R = 4.72 min,UV_{254} = 99%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.62 (s, 1H), 4.63 (s, 1H), 6.07 (vb.s, 2H), 6.19 (d, *J*=8.2 Hz, 1H), 6.32 (d, *J*=8.2 Hz, 1H), 7.07 (t, *J*=8.2 Hz, 1H), 7.14 - 7.54 (m, 5H), 8.05 (br. s., 1H); HRMS (ESI): *m/z* calcd for $C_{15}H_{16}N_2O_2$ $[M+1]^+$ 257.1296, found 257.1294.

N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide



Following the general procedure for the synthesis of **7**, a solution of 3-(chloromethyl)-4-methoxybenzaldehyde (300 mg, 1.62 mmol, 1.0 equiv) and 4-acetamidophenol (271 mg, 1.79 mmol, 1.1 equiv) in 10 mL acetonitrile was treated with potassium carbonate (1.1 g, 8.12 mmol, 5.0 equiv). The mixture was heated to 150 °C in the microwave for 15 min. Upon completion, the mixture was filtered and concentrated to dryness to afford N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide (462 mg, 95% yield) as a solid, which was taken on crude to the next reaction.

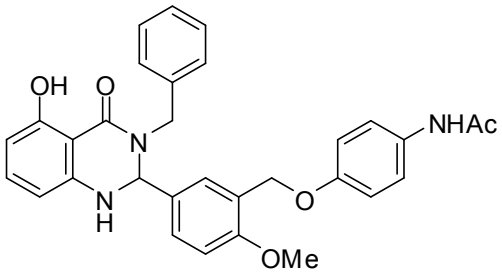
N-(4-(5-(3-(furan-2-ylmethyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1a).



Following the general procedure for the synthesis of **1**, a solution of N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide (120 mg, 400 µmol, 1.0 equiv) in EtOH (6 mL) was treated with 2-amino-N-(furan-2-ylmethyl)benzamide (95 mg, 440 µmol, 1.1 equiv) and ytterbium trifluoromethanesulfonate (50 mg, 80 µmol, 0.2 equiv) and heated to 80 °C for 6 h.

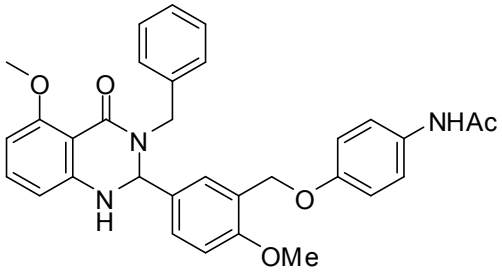
Upon completion, the reaction mixture was concentrated to dryness and purified by column chromatography over silica gel using 7-50% EtOAc/Hexanes gradient elution to afford **1a**. The isolated product was triturated with Et_2O to afford the desired product as a light tan solid (195 mg, 48% yield). HPLC: t_R = 5.36 min, UV_{254} = 95%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3 H), 3.79 (s, 3H), 3.82 (d, *J*=15.6 Hz, 1 H), 4.94 (s, 2 H), 5.16 (d, *J*=15.3 Hz, 1 H), 5.71 (s, 1 H), 6.26 (d, *J*=3.1 Hz, 1 H), 6.37 (d, *J*=2.0 Hz, 1 H), 6.61 (d, *J*=7.8 Hz, 1 H), 6.67 (t, *J*=7.4 Hz, 1 H), 6.87 (d, *J*=9.0 Hz, 2 H), 7.00 (d, *J*=8.6 Hz, 1 H), 7.12 - 7.51 (m, 6 H), 7.56 (s, 1 H), 7.67 (d, *J*=6.7 Hz, 1 H), 9.77 (s, 1 H); HRMS (ESI): m/z calcd for $C_{29}H_{27}N_3O_5$ $[M+H]^+$ 498.2029, found 498.2025.

N-(4-(5-(3-Benzyl-5-hydroxy-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1b).



1b was synthesized following the general procedures for the synthesis of **1** from 2-amino-N-benzyl-6-hydroxybenzamide (prepared according to the procedure described in Neumann et al, *PNAS*, 2009, 12471) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1b** as a solid (89 mg, 42% yield). HPLC: t_R = 6.27 min, UV_{254} = 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 3.78 (d, *J*=15.5 Hz, 1H), 3.80 (s, 3H), 4.96 (s, 2H), 5.15 (d, *J*=15.3 Hz, 1H), 5.73 (d, *J*=2.0 Hz, 1H), 6.05-6.08 (m, 2H), 6.86-6.90 (m, 2H), 7.01 - 7.11 (m, 2H), 7.19 - 7.36 (m, 6 H), 7.41-7.48 (m, 4H) 9.77 (s, 1H), 12.26 (s, 1H); HRMS (ESI): m/z calcd for $C_{31}H_{29}N_3O_5$ $[M+ H]^+$ 524.2189, found 524.2184.

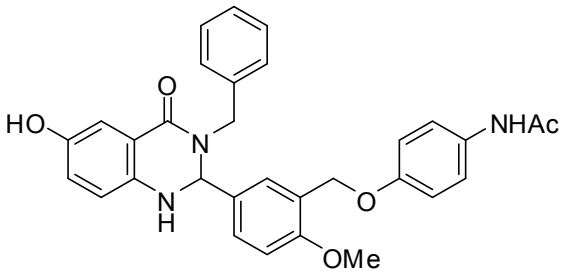
N-(4-(5-(3-Benzyl-5-methoxy-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1c).



1c was synthesized following the general procedures for the synthesis of **1** starting with 2-amino-N-benzyl-6-methoxybenzamide (prepared according to the procedure described in Neumann et al, *PNAS*, 2009, 12471) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1c**

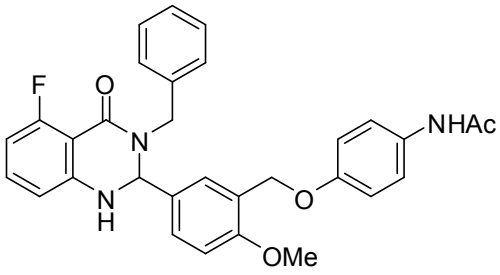
as a solid (54 mg, 36% yield). HPLC: t_R = 5.34 min, UV_{254} = 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 3.80 (d, *J*=15.3 Hz, 1H), 4.92 (s, 2H), 5.22 (d, *J*=15.3 Hz, 1H), 5.58 (d, *J*=2.0 Hz, 1H), 6.26 (t, *J*=7.0 Hz, 2H), 6.88 (d, *J*=9.0 Hz, 2H), 6.98 (d, *J*=8.6 Hz, 1H), 7.10 (t, *J*=8.2 Hz, 1H), 7.16 - 7.57 (m, 9 H), 9.77 (s, 1H); HRMS (ESI): m/z calcd for $C_{32}H_{31}N_3O_5$ $[M+H]^+$ 538.2340, found 538.2339.

N-(4-(5-(3-Benzyl-6-hydroxy-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1d).



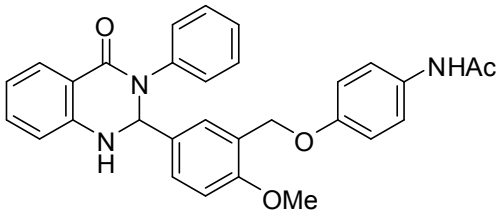
1d was synthesized following the general procedures for the synthesis of **1** from 2-amino-N-benzyl-5-hydroxybenzamide and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1d** as a solid (35 mg, 32% yield). HPLC: t_R = 5.21 min, UV_{254} = 95%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3H), 3.76 (d, *J*=15.6 Hz, 1H), 3.78 (s, 3H), 4.93 (s, 2H), 5.23 (d, *J*=15.3 Hz, 1H), 5.60 (d, *J*=2.0 Hz, 1H), 6.52 (d, *J*=8.6 Hz, 1H), 6.66 - 6.79 (m, 2H), 6.89 (d, *J*=9.0 Hz, 2H), 6.97 (d, *J*=8.6 Hz, 1H), 7.11 - 7.43 (m, 9H), 7.48 (d, *J*=9.0 Hz, 2H), 8.86 (s, 1H), 9.78 (s, 1H); HRMS (ESI): m/z calcd for $C_{31}H_{29}N_3O_5$ $[M+H]^+$ 524.2189, found 524.2190.

N-(4-(5-(3-Benzyl-5-fluoro-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1e).



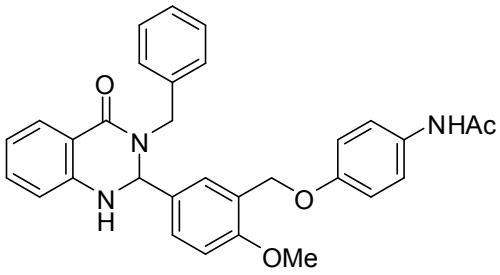
1e was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and 6-fluroisatoic) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1e** (15 mg, 17% yield) as a solid. For full experimental data, please refer to reference 27.

N-(4-(2-Methoxy-5-(4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)benzyloxy)phenyl)acetamide (1f).



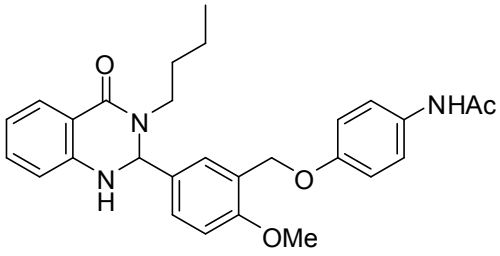
1f was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with 2-amino-N-phenylbenzamide and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1f** as a solid (68 mg, 42% yield). HPLC: t_R = 5.37 min, UV_{254} = 95%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3H), 3.76 (s, 3H), 4.92 (s, 2H), 6.23 (d, *J*=2.3 Hz, 1H), 6.65 - 6.77 (m, 2H), 6.84 (d, *J*=9.0 Hz, 2H), 6.95 (d, *J*=8.4 Hz, 1H), 7.11 - 7.36 (m, 7H), 7.39 - 7.51 (m, 3H), 7.55 (d, *J*=2.3 Hz, 1H), 7.65 - 7.73 (m, 1H), 9.77 (s, 1H); HRMS (ESI): m/z calcd for $C_{30}H_{27}N_3O_4$ $[M+H]^+$ 494.2091, found 494.2092.

N-(4-(5-(3-Benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1g).



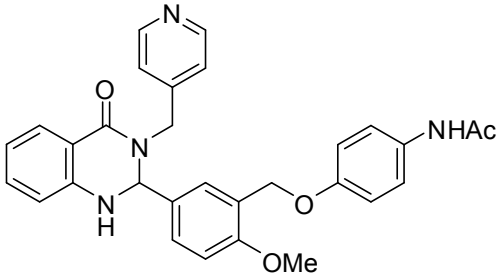
1g was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1g** (175 mg, 62% yield) as a solid. HPLC: t_R = 5.69 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.66 (d, *J*=15.3 Hz, 1H), 3.83 (s, 3H), 5.00 (s, 2H), 5.48 (d, *J*=15.3 Hz, 1H), 5.57 (s, 1H), 6.49 (d, *J*=7.8 Hz, 1H), 6.67 - 7.00 (m, 4H), 7.05 - 7.57 (m, 12H), 7.99 (d, *J*=7.8 Hz, 1H); HRMS (ESI): *m/z* calcd for $C_{31}H_{29}N_3O_4$ $[M+ H]^+$ 508.2242, found 508.2233.

N-(4-(5-(3-Butyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1h).



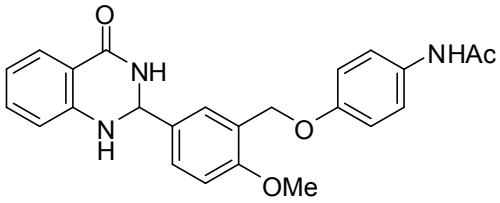
1h was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with butylamine and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1h** as a solid (343 mg, 68% yield). HPLC: t_R = 5.15 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.74 - 0.87 (m, 3H), 1.14 - 1.27 (m, 2H), 1.33 - 1.52 (m, 2H), 1.96 (s, 3H), 2.58 - 2.69 (m, 1H), 3.71 - 3.84 (m, 1H), 3.78 (s, 3H), 4.91 (s, 2H), 5.78 (d, *J*=1.6 Hz, 1H), 6.54 - 6.70 (m, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 7.00 (d, *J*=8.6 Hz, 1H), 7.09 - 7.31 (m, 3H), 7.36 - 7.52 (m, 3H), 7.62 (d, *J*=7.6 Hz, 1H), 9.76 (s, 1H); HRMS (ESI): *m/z* calcd for $C_{28}H_{31}N_3O_4$ $[M+H]^+$ 474.2399, found 474.2394.

N-(4-(2-Methoxy-5-(4-oxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydroquinazolin-2-yl)benzyloxy)phenyl)acetamide (1i).



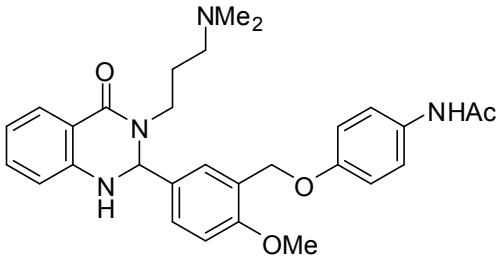
1i was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with pyridin-4-ylmethanamine and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1i** as a solid (438 mg, 81% yield). HPLC: t_R = 4.08 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 3.78 (s, 3H), 3.97 (d, *J*=16.2 Hz, 1H), 4.93 (s, 2H), 5.04 (d, *J*=16.4 Hz, 1H), 5.72 (s, 1H), 6.58 - 6.75 (m, 2H), 6.86 (d, *J*=9.0 Hz, 2H), 6.99 (d, *J*=8.6 Hz, 1H), 7.14 - 7.32 (m, 4H), 7.32 - 7.54 (m, 4H), 7.67 (d, *J*=7.6 Hz, 1H), 8.46 (d, *J*=5.7 Hz, 2H), 9.77 (s, 1H); HRMS (ESI): *m/z* calcd for $C_{30}H_{28}N_4O_4$ $[M+H]^+$ 509.2183, found 509.2179.

N-(4-(2-Methoxy-5-(4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzyloxy)phenyl)acetamide (1j).



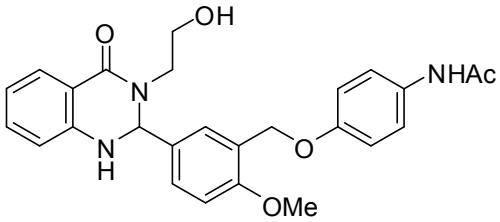
1j was synthesized following the general procedures for the synthesis of **1** from 2-aminobenzamide and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1j** as a solid (28 mg, 34% yield). HPLC: t_R = 4.69 min, UV_{254} = 95%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 3.82 (s, 3H), 4.98 (s, 2H), 5.72 (s, 1H), 6.59 - 6.78 (m, 2H), 6.92 (d, *J*=9.0 Hz, 2H), 6.99 - 7.11 (m, 2H), 7.23 (t, *J*=7.6 Hz, 1H), 7.38 - 7.51 (m, 3H), 7.53 - 7.64 (m, 2H), 8.19 (s, 1H), 9.77 (s, 1H); HRMS (ESI): *m/z* calcd for $C_{24}H_{23}N_3O_4$ $[M+H]^+$ 418.1773, found 418.1775.

N-(4-(5-(3-(3-(Dimethylamino)propyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1k).



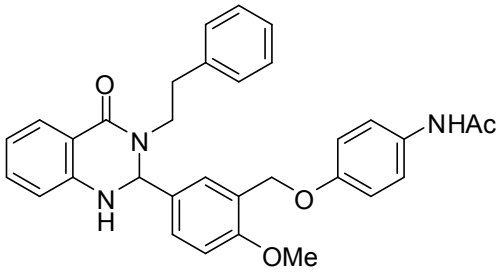
1k was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with N',N'-dimethylpropane-1,3-diamine and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1k** as a solid (170 mg, 32% yield). HPLC: t_R = 4.05 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74 - 1.88 (m, 2H), 2.00 (s, 3H), 2.72 (s, 6H), 2.82-2.87 (m, 1H), 2.92-3.03 (m, 2H), 3.79 (s, 3H), 4.06-4.10 (m, 1H), 4.96 (s, 2H), 5.86 (s, 1H), 6.57 - 6.72 (m, 2H), 6.87 (d, *J*=9.0 Hz, 2H), 7.03 (d, *J*=8.4 Hz, 1H), 7.13 - 7.36 (m, 3H), 7.46 (dd, *J*=5.7, 3.1 Hz, 3H), 7.65 (d, *J*=7.6 Hz, 1H), 9.77 (s, 1H); HRMS (ESI): *m/z* calcd for $C_{29}H_{34}N_4O_4$ $[M+H]^+$ 503.2653, found 503.2660.

N-(4-(5-(3-(2-Hydroxyethyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1l).



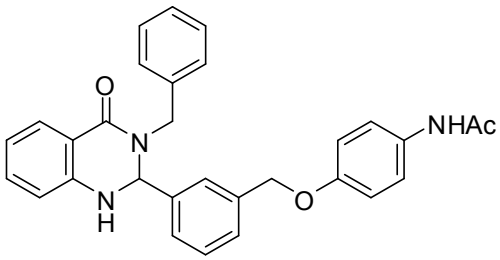
1l was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with 2-aminoethanol and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1l** as a solid (272 mg, 55% yield). HPLC: t_R = 4.50 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 2.79 (dt, *J*=13.5, 6.8 Hz, 1H) 3.38 - 3.60 (m, 2H), 3.78 (s, 3H), 3.81 - 3.94 (m, 1H), 4.74 (t, *J*=5.4 Hz, 1H), 4.94 (s, 2H), 5.89 (d, *J*=1.8 Hz, 1H), 6.52 - 6.69 (m, 2H) 6.87 (d, *J*=8.8 Hz, 2H) 7.01 (d, *J*=8.6 Hz, 1H) 7.11 - 7.33 (m, 3H) 7.38 - 7.52 (m, 3H) 7.63 (d, *J*=7.6 Hz, 1H) 9.77 (s, 1H); HRMS (ESI): *m/z* calcd for $C_{26}H_{27}N_3O_5$ $[M+Na]^+$ 484.1868, found 484.1865.

N-(4-(2-Methoxy-5-(4-oxo-3-phenethyl-1,2,3,4-tetrahydroquinazolin-2-yl)benzyloxy)phenyl)acetamide (1m).



1m was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with phenylethylamine and isatoic anhydride) and N-(4-(5-formyl-2-methoxybenzyloxy)phenyl)acetamide to afford **1m** as a solid (381mg, 68% yield). HPLC: t_R = 5.75 min, UV_{254} = 96%; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.96 (s, 3H), 2.64 (d, *J*=7.6 Hz, 1H), 2.77 - 2.95 (m, 2H), 3.75 (s, 3H), 3.90 (d, *J*=9.0 Hz, 1H), 4.92 (s, 2H), 5.76 (d, *J*=1.6 Hz, 1H), 6.53 - 6.68 (m, 2H), 6.83 (d, *J*=9.0 Hz, 2H), 6.99 (d, *J*=8.8 Hz, 1H), 7.06 - 7.30 (m, 8H), 7.38 - 7.47 (m, 3H), 7.61 (d, *J*=7.6 Hz, 1H), 9.72 (s, 1H); HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_3O_4$ $[M+ H]^+$ 522.2387, found 522.2385.

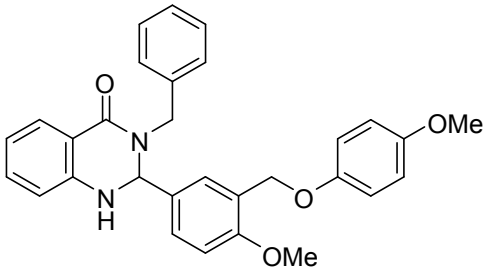
N-(4-(3-(3-Benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzyloxy)phenyl)acetamide (1n).



1n was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzyl amine and isatoic anhydride) and **7** (following general procedure with 3-bromomethylbenzaldehyde and N-(4-hydroxyphenyl)acetamide) to afford **1n** as a solid (70 mg, 14% yield). HPLC: t_R = 5.60 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H),

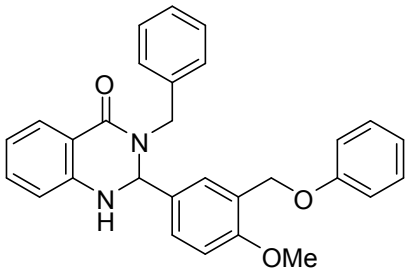
3.82 (d, *J*=15.5 Hz, 1H), 5.00 (s, 2H), 5.29 (d, *J*=15.5 Hz, 1H), 5.75 (s, 1H), 6.60 - 6.73 (m, 2H), 6.89 (d, *J*=9.0 Hz, 2H), 7.17 - 7.42 (m, 11H), 7.46 (d, *J*=9.0 Hz, 2H), 7.66 - 7.74 (m, 1H), 9.77 (s, 1H); HRMS (ESI): m/z calcd for $C_{30}H_{27}N_3O_3$ $[M+H]^+$ 478.2137, found 478.2129.

3-Benzyl-2-(4-methoxy-3-((4-methoxyphenoxy)methyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (1o).



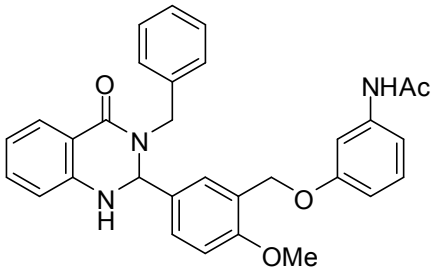
1o was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and isatoic anhydride) and **7** (following general procedure with 4-methoxyphenol and 3-(chloromethyl)-4-methoxybenzaldehyde) to afford **1o** as a solid (53 mg, 41% yield). HPLC: t_R = 6.41 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.69 (s, 3H), 3.73 (d, *J*=15.3 Hz, 1H), 3.78 (s, 3H), 4.92 (s, 2H), 5.26 (d, *J*=15.3 Hz, 1H), 5.67 (d, *J*=1.4 Hz, 1H), 6.56 - 6.73 (m, 2H), 6.78 - 6.92 (m, 4 H), 6.99 (d, *J*=8.6 Hz, 1H), 7.14 - 7.36 (m, 8H), 7.38 (s, 1H), 7.69 (d, *J*=7.6 Hz, 1H); HRMS (ESI): m/z calcd for $C_{30}H_{28}N_2O_4$ $[M+ H]^+$ 481.2131, found 481.2124.

3-Benzyl-2-(4-methoxy-3-(phenoxymethyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (1p).



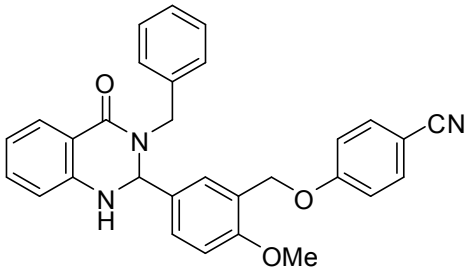
1p was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and isatoic anhydride) and **7** (following general procedure with phenol and 3-(chloromethyl)-4-methoxybenzaldehyde) to afford **1p** as a solid (62 mg, 51% yield). HPLC: t_R = 6.53 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (d, 1H, *J*=15.3 Hz), 3.84 (s, 3H), 4.38 (s, 1H), 5.05 (s, 2H), 5.51 (d, *J*=15.3 Hz, 1H), 5.58 (d, *J*=1.4 Hz, 1H), 6.48 (d, *J*=8.0 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 6.83 - 6.88 (m, 1H), 6.92 - 6.99 (m, 3H), 7.15 - 7.19 (m, 2H), 7.20 - 7.32 (m, 8H), 7.36 (d, *J*=2.2 Hz, 1H), 8.02 (d, *J*=7.8 Hz, 1H); HRMS (ESI): m/z calcd for $C_{29}H_{26}N_2O_3$ $[M+ H]^+$ 451.2028, found 451.2028.

N-(3-(5-(3-Benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (1q).



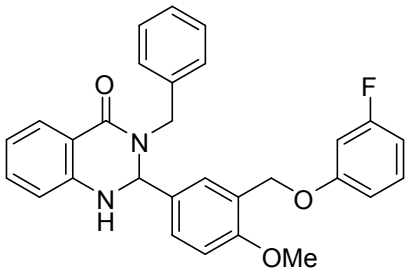
1q was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and isatoic anhydride) and **7** (following general procedure with 4-acetamidophenol and 3-(chloromethyl)-4-methoxybenzaldehyde) to afford **1q** as a solid (91 mg, 29% yield). HPLC: t_R = 5.78 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.02 (s, 3H), 3.75 (d, *J*=15.5 Hz, 1H), 3.79 (s, 3H), 4.94 (s, 2H), 5.25 (d, *J*=15.5 Hz, 1H), 5.68 (d, *J*=2.4 Hz, 1H), 5.75 (s, 1H), 6.63 (s, 2H), 6.68 (s, 1H), 7.00 (d, *J*=8.4 Hz, 1H), 7.08 - 7.13 (m, 1H), 7.18 (t, *J*=7.9 Hz, 1H), 7.21 - 7.26 (m, 4 H), 7.26 - 7.34 (m, 4 H), 7.39 (d, *J*=2.2 Hz, 1H), 7.69 (d, *J*=7.8 Hz, 1H), 9.90 (s, 1H); HRMS (ESI): m/z calcd for $C_{31}H_{29}N_3O_4$ $[M+H]^+$ 508.2242, found 508.2244

4-(5-(3-Benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzyloxy)benzonitrile (1r)



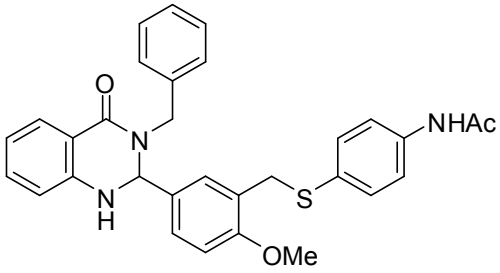
1r was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and isatoic anhydride) and **7** (following general procedure with 4-cyanophenol and 3-(chloromethyl)-4-methoxybenzaldehyde) to afford **1r** as a solid (69 mg, 54% yield). HPLC: t_R = 6.27 min, UV_{254} = 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (d, *J*=15.6 Hz, 1H), 3.80 (s, 3H), 5.09 (s, 2H), 5.25 (d, *J*=15.7 Hz, 1H), 5.68 (d, *J*=2.3 Hz, 1H), 6.61 (d, *J*=7.8 Hz, 1H), 6.67 (t, *J*=7.4 Hz, 1H), 6.95 - 7.14 (m, 3H), 7.14 - 7.42 (m, 9 H), 7.66 (d, *J*=6.7 Hz, 1H), 7.75 (d, *J*=8.6 Hz, 2H), HRMS (ESI): m/z calcd for $C_{30}H_{25}N_3O_3$ $[M+H]^+$ 476.1969, found 476.1970.

3-Benzyl-2-(3-((3-fluorophenoxy)methyl)-4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (1s)



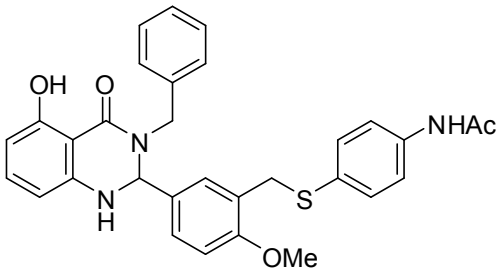
1s was synthesized following the general procedures for the synthesis of **1** from **3** (*Method 1* with benzylamine and isatoic anhydride) and **7** (following general procedure with 3-flurophenol and 3-(chloromethyl)-4-methoxybenzaldehyde) to afford **1s** as a solid (79 mg, 47% yield). HPLC: t_R = 6.59 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (d, *J*=15.6 Hz, 1H), 3.79 (s, 3H), 5.00 (s, 2H), 5.26 (d, *J*=15.3 Hz, 1H), 5.68 (d, *J*=2.0 Hz, 1H), 6.56 - 6.72 (m, 2H), 6.72 - 6.88 (m, 3H), 7.01 (d, *J*=8.6 Hz, 1H), 7.16 - 7.47 (m, 10 H), 7.68 (d, *J*=6.7 Hz, 1H); HRMS (ESI): m/z calcd for $C_{29}H_{25F}N_2O_3$ $[M+H]^+$ 469.1933, found 469.1932.

N-(4-(5-(3-Benzyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzylthio)phenyl)acetamide (8a)



The general procedure for the synthesis of **1g** was followed with the substitution of 4-acetamidothiophenol for 4-acetamidophenol in the synthesis of **7** to afford **8a** as a solid (32 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.50 (d, *J*=15.4 Hz, 1H), 3.83 (s, 3H), 3.88 (d, *J*=13.1 Hz, 1H), 4.00 (d, *J*=13.1 Hz, 1H), 5.42 (d, *J*=15.3 Hz, 1H), 5.45 (s, 1H), 6.52 (d, *J*=8.2 Hz, 1H), 6.74 (d, *J*=8.6 Hz, 1H), 6.79 (d, *J*=2.0 Hz, 1H), 6.84 (t, *J*=7.4 Hz, 1H), 7.06 (dd, *J*=8.4, 2.2 Hz, 1H), 7.10 - 7.33 (m, 9 H), 7.37 (d, *J*=8.6 Hz, 2H), 7.68 (br. s., 1H), 7.96 (d, *J*=6.6 Hz, 1H); HPLC: t_R = 5.88 min, UV_{254} = 98%; HRMS (ESI): *m/z* calcd for $C_{31}H_{29}N_3O_3S$ $[M+H]^+$ 524.2002, found 524.2002.

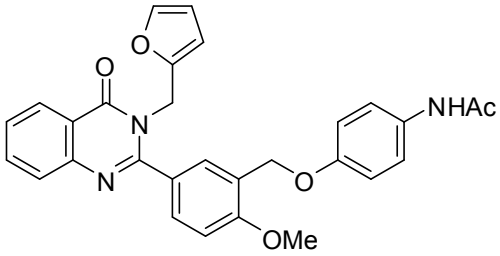
N-(4-(5-(3-Benzyl-5-hydroxy-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2-methoxybenzylthio)phenyl)acetamide (8b).



The general procedure for the synthesis of **1b** was followed with the substitution of 4-acetamidothiophenol for 4-acetamidophenol in the synthesis of **7** to afford **8b** as a solid (15 mg, 23% yield). HPLC: t_R = 6.27 min, UV_{254} = 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H), 3.65 (d, *J*=15.3 Hz, 1H), 3.76 (s, 3H), 4.00 (d, *J*=13.3 Hz, 1H), 4.04 (d, *J*=13.3 Hz, 1H), 5.09 (d, *J*=15.3 Hz, 1H), 5.64 (d, *J*=2.0 Hz, 1H), 6.06 (dd, *J*=8.0, 3.3 Hz, 2H), 6.96 (d, *J*=8.2 Hz, 1H), 7.07 (t, *J*=8.0 Hz, 1H), 7.12 - 7.39 (m, 10 H), 7.52 (d, *J*=8.6 Hz, 2H), 9.95 (s, 1H), 12.26 (s, 1H); HRMS (ESI): m/z calcd for $C_{31}H_{29}N_3O_{4S}$ $[M+H]^+$ 540.1963, found 540.1961

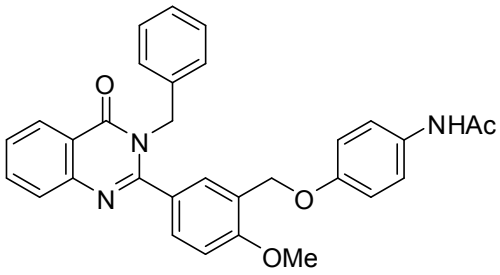
Procedure for the synthesis of quinazolin-4-ones 9:

N-(4-(5-(3-(Furan-2-ylmethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (9a).



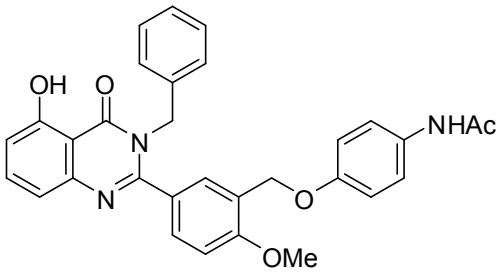
To a solution of **1a** (99 mg, 200 µmol) in EtOH (5 mL) was added DDQ (54.5 mg, 240 µmol, in 4 mL of acetonitrile). After stirring at r.t. for 4 h, the mixture was concentrated under reduced pressure and purified *via* column chromatography on silica gel using 7-50% EtOAc/Hexanes gradient elution to afford **9a** as a solid (56 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3 H), 3.95 (s, 3 H), 5.12 (s, 2H), 5.19 (s, 2H), 6.12 (d, *J*=2.7 Hz, 1H), 6.22 - 6.28 (m, 1H), 6.93 (d, *J*=9.0 Hz, 2H), 7.00 (d, *J*=8.6 Hz, 1H), 7.12 (br. s., 1H), 7.24 (s, 1H), 7.39 (d, *J*=9.0 Hz, 2H), 7.46 - 7.56 (m, 2H), 7.64 - 7.82 (m, 3 H), 8.33 (d, *J*=8.2 Hz, 1H); HPLC: t_R = 5.49 min, UV_{254} = 95%; HRMS (ESI): m/z calcd for $C_{29}H_{25}N_3O_5$ $[M+H]^+$ 496.1872, found 496.1873.

N-(4-(5-(3-Benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (9b).



To a solution of **1g** (102 mg, 200 µmol) in EtOH (5 mL) was added DDQ (55 mg, 240 µmol in 4 mL of acetonitrile). After stirring at r.t. for 4 h, the mixture was concentrated under reduced pressure and purified *via* column chromatography on silica gel using 7-50% EtOAc/Hexanes gradient elution to afford **9b** as a solid (49 mg, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3 H), 3.91 (s, 3 H), 5.04 (s, 2H), 5.26 (s, 2H), 6.81 - 7.04 (m, 5 H), 7.11 - 7.26 (m, 5 H), 7.38 (d, *J*=9.0 Hz, 2H), 7.46 - 7.58 (m, 2H), 7.71 - 7.83 (m, 2H), 8.36 (d, *J*=7.8 Hz, 1H); HPLC: t_R = 5.69 min, UV_{254} = 98%; HRMS (ESI): m/z calcd for $C_{31}H_{27}N_3O_4$ $[M+H]^+$ 506.2086, found 506.2082.

N-(4-(5-(3-Benzyl-5-hydroxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methoxybenzyloxy)phenyl)acetamide (9c).



To a solution of **1b** (15.0 mg, 29 µmol) in 2 mL of DMSO was added MnO_2 (87 mg, 0.29 mmol). The mixture was heated at 80 °C for 12 h. The solid was filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (7-60% EtOAc in hexanes) to afford **9c** (8.1 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3 H), 3.90 (s, 3 H), 5.04 (s, 2H), 5.20 (s, 2H), 6.79 - 7.01 (m, 6 H), 7.08 (br. s., 1H), 7.20 - 7.25 (m, 4 H), 7.27 - 7.42 (m, 3 H), 7.52 (d, *J*=2.0 Hz, 1H), 7.64 (t, *J*=8.1 Hz, 1H), 11.69 (s, 1H); HPLC: t_R = 6.23 min, UV_{254} = 98%; HRMS (ESI): m/z calcd for $C_{31}H_{27}N_3O_5$ $[M+H]^+$ 522.2027, found 522.2028.