Electronic Supplementary Information

A direct access to bioactive fused *N*-heterocyclic acetic acid derivatives

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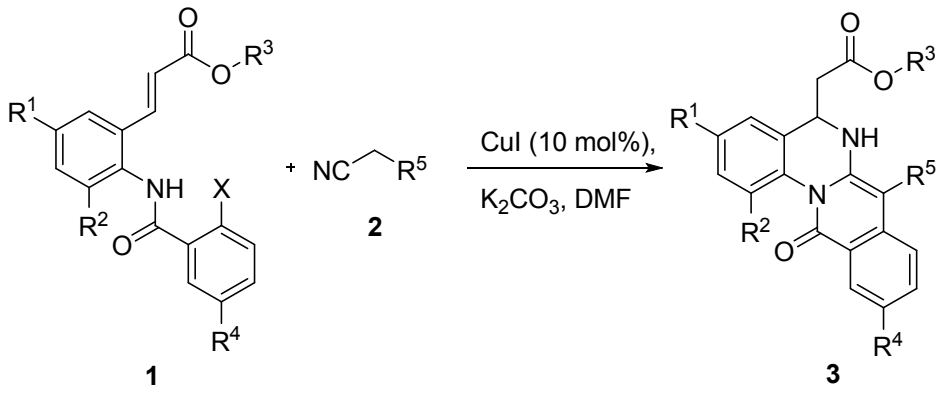
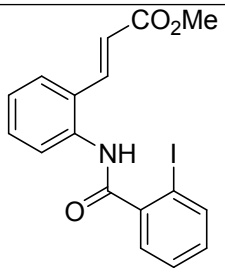
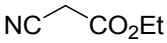
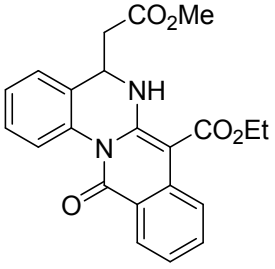
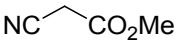
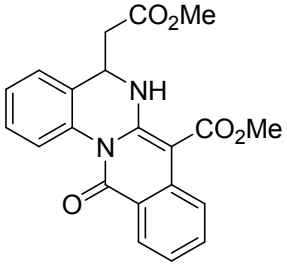
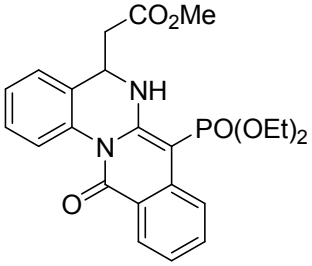
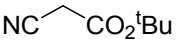
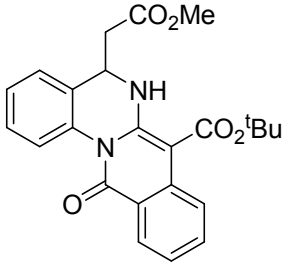
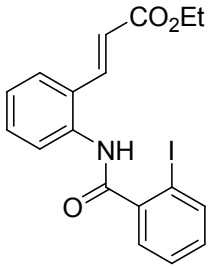
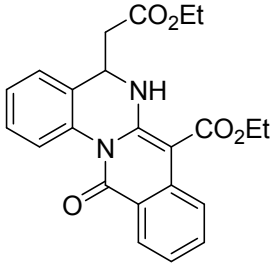
Experimental

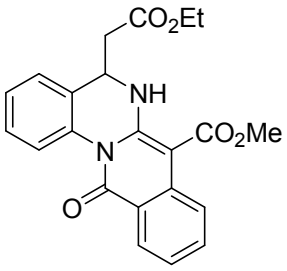
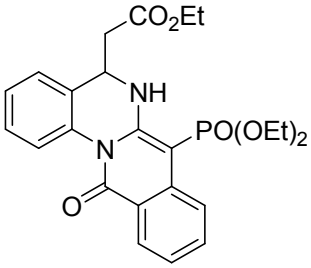
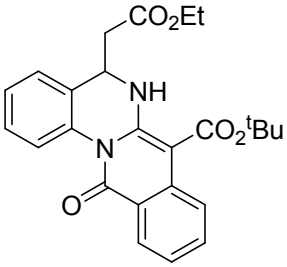
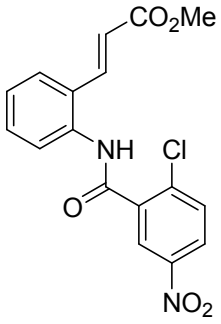
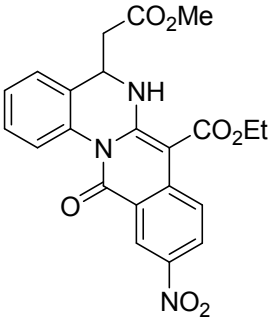
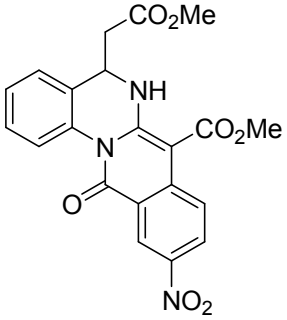
Chemistry

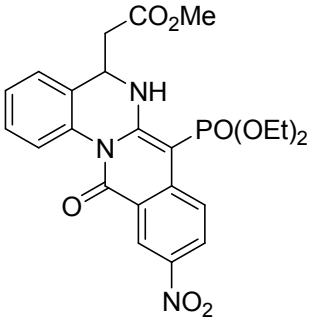
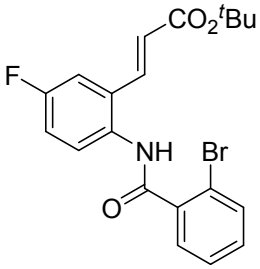
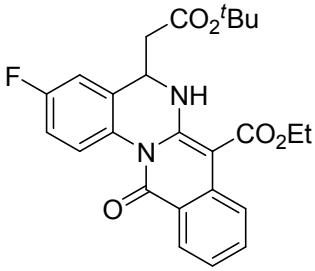
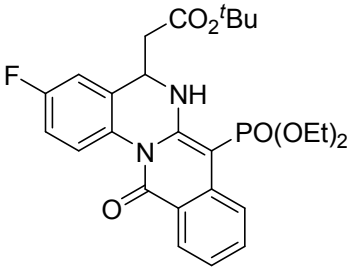
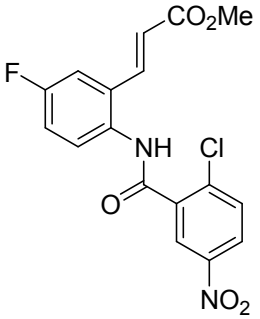
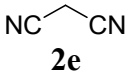
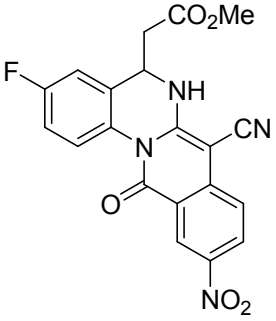
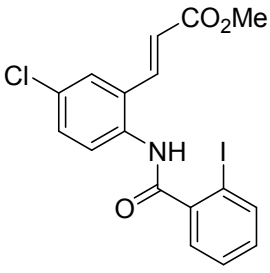
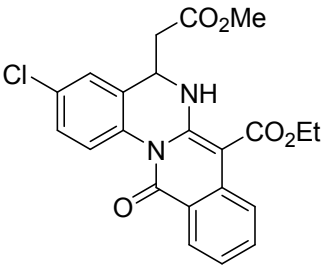
General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recodred in $CDCl_3$ or DMSO-d_6 solution by using a 400 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. MS spectra were obtained on a Agilent 6430 series Triple Quard LC-MS / MS spectrometer. Melting points (mp) were determined by using Buchi B-540 melting point appratus and are uncorrected. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times.

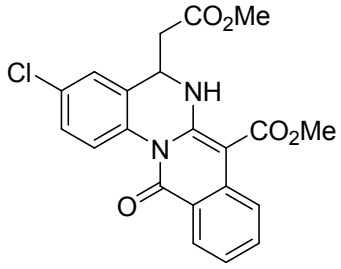
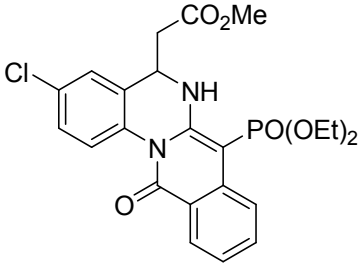
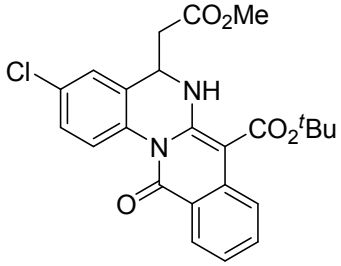
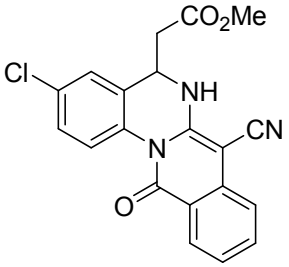
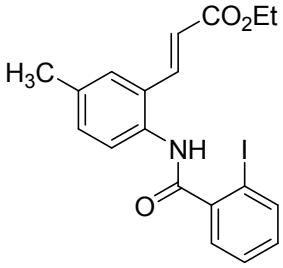
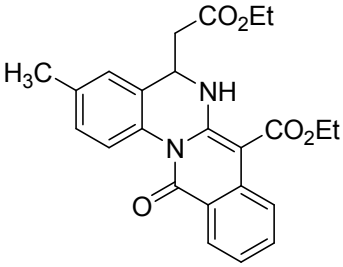
Table S-1: Cu catalyzed synthesis of 2-(12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (**3**)[a]

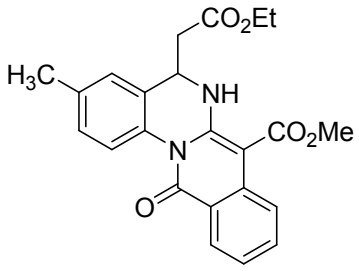
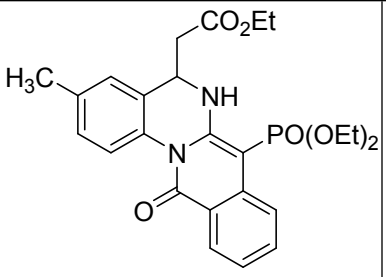
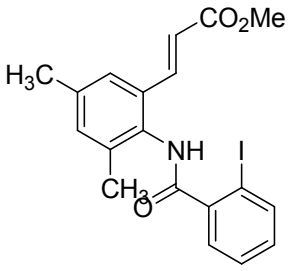
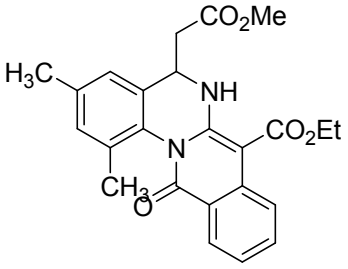
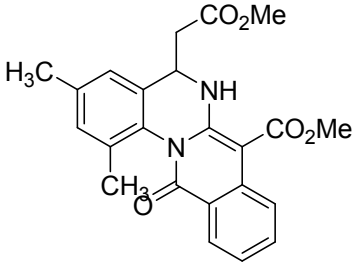
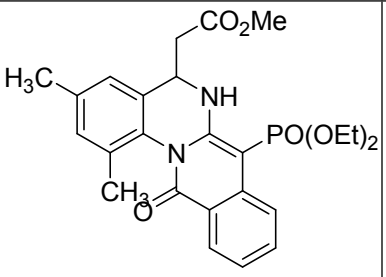


Entry	Halide (**1**)	Nitrile (**2**)	Time/ h	Product (**3**)	Yield (%)[b]
1	 **1a**	 **2a**	0.5	 **3a**	89
2	**1a**	 **2b**	0.5	 **3b**	84
3	**1a**	 **2c**	2.0	 **3c**	81
4	**1a**	 **2d**	0.5	 **3d**	81
5	 **1b**	**2a**	0.5	 **3e**	87

6	**1b**	**2b**	0.5	 **3f**	83
7	**1b**	**2c**	1.5	 **3g**	79
8	**1b**	**2d**	0.5	 **3h**	81
9	 **1c**	**2a**	1.5	 **3i**	76
10	**1c**	**2b**	1.5	 **3j**	73

11	**1c**	**2c**	2.5	 **3k**	73
12	 **1d**	**2a**	2.0	 **3l**	80
13	**1d**	**2c**	2.5	 **3m**	75
14	 **1e**	 **2e**	2.5	 **3n**	68
15	 **1f**	**2a**	0.5	 **3o**	85

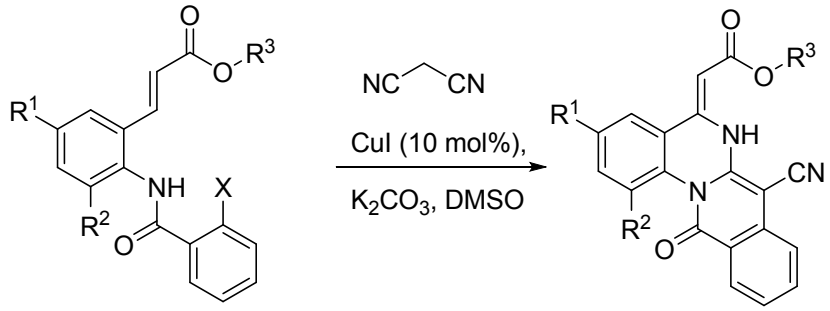
16	**1f**	**2b**	0.5	 **3p**	81
17	**1f**	**2c**	1.5	 **3q**	78
18	**1f**	**2d**	1.0	 **3r**	77
19	**1f**	**2e**	1.0	 **3s**	72
20	 **1g**	**2a**	0.5	 **3t**	87

21	**1g**	**2b**	0.5	 **3u**	84
22	**1g**	**2c**	2.0	 **3v**	82
23	 **1h**	**2a**	0.5	 **3w**	86
24	**1h**	**2b**	0.5	 **3x**	81
25	**1h**	**2c**	1.5	 **3y**	78

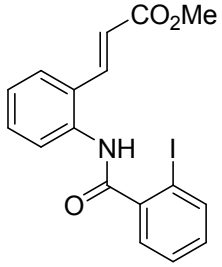
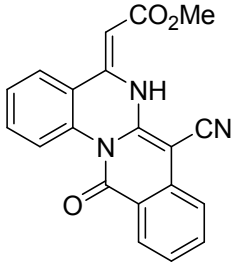
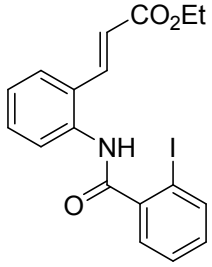
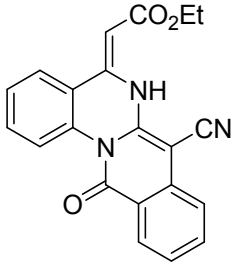
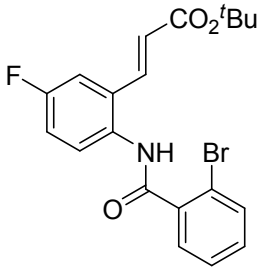
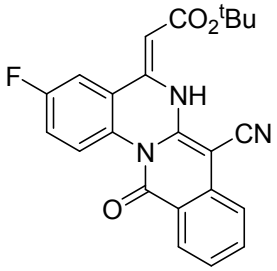
[a]Reactions were carried out using **1** (1 mmol), **2** (1.2 mmol), CuI (0.1 mmol) and K_2CO_3 (3 mmol) in DMF (2 mL) at 80 ºC under anhydrous conditions (no inert atmosphere).

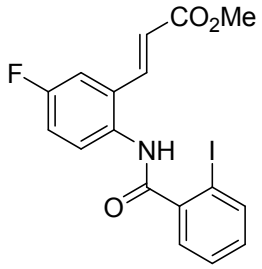
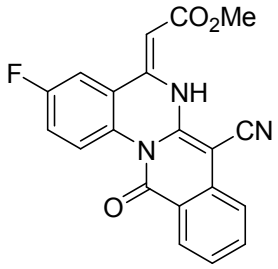
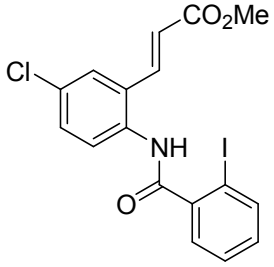
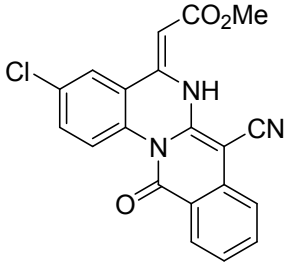
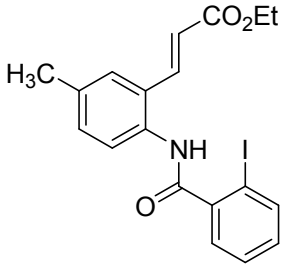
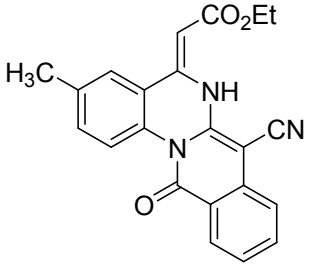
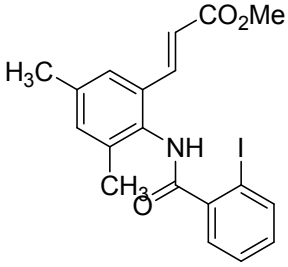
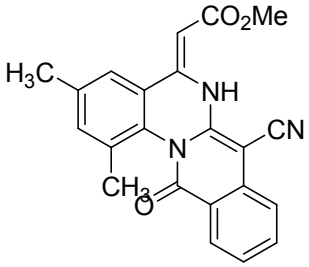
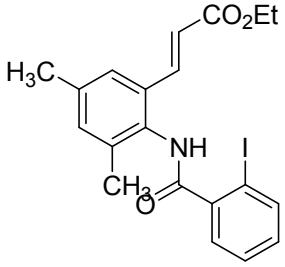
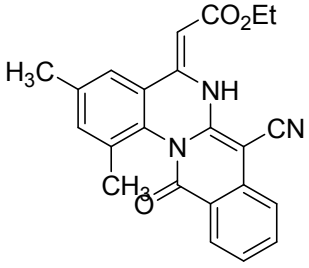
[b]Isolated yield.

Table S-2: Cu catalyzed synthesis of (Z)-alkyl 2-(7-cyano-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (**4**)[a]



1 **4**

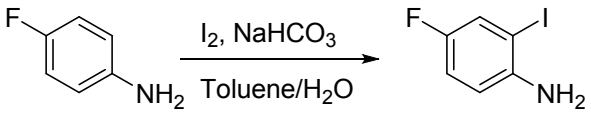
Entry	Halide (**1**)	Time/h	Product (**4**)	Yield (%)[b]
1	 **1a**	4.0	 **4a**	72
2	 **1b**	4.0	 **4b**	71
3	 **1d**	5.0	 **4c**	49

4	 **1i**	6.0	 **4d**	56
5	 **1f**	5.0	 **4e**	48
6	 **1g**	4.0	 **4f**	65
7	 **1h**	4.0	 **4g**	73
8	 **1j**	6.0	 **4h**	72

[a]Reactions were carried out using **1** (1 mmol), malononitrile (1.2 mmol), CuI (0.1 mmol) and K_2CO_3 (3 mmol) in DMSO (2 mL) at 80 ºC under anhydrous conditions (no inert atmosphere).

[b]Isolated yield.

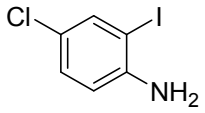
Typical procedure for preparation of 4-Fluoro-2-iodoaniline (S-1a)[1]



S-1a

A mixture of 4-fluoro aniline (1.0 g, 9.0 mmol), iodine (2.28 g, 9.0 mmol) and sodium bicarbonate (1.13 g, 13.5 mmol) in toluene, H_2O (10 mL, 9:1) was stirred at room temperature for 3 hours. After completion of the reaction, the mixture was diluted with ethyl acetate (30 mL), washed with sodium thiosulphate solution (2 x 20 mL), followed by brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexane to give the desired compound **S-1a**; Yield: 85% (1.8 g); dark brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (dd, *J* = 7.8, 2.2 Hz, 1H), 6.90 (tb, *J* = 8.1, 2.4 Hz, 1H), 6.69 (dd, *J* = 8.6, 4.9 Hz, 1H), 3.92 (bs, 2H).

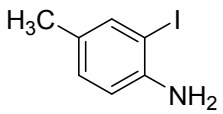
4-Chloro-2-iodoaniline (S-1b)[2]



Compound **S-1b** was synthesized from 4-chloro aniline following a procedure similar to that of compound **S-1a**.

Yield: 88% (1.7 g); dark brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 2.3 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 4.15 (bs, 2H).

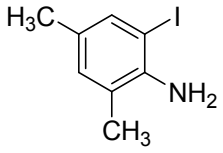
2-Iodo-4-methyl aniline (S-1c)[1]



Compound **S-1c** was synthesized from 4-methyl aniline following a procedure similar to that of compound **S-1a**.

Yield: 89% (1.9 g); dark brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (s, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.23 (bs, 2H), 2.22 (s, 3H).

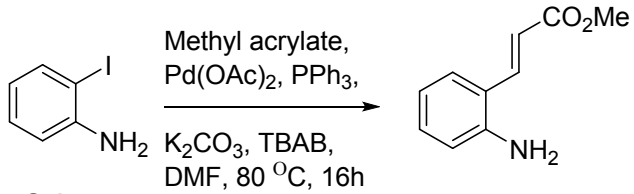
2-Iodo-4,6-dimethylaniline (S-1d)



Compound **S-1d** was synthesized from 2,4-dimethyl aniline following a procedure similar to that of compound **S-1a**.

Yield: 89% (1.8 g); light brown solid; mp: 62-64 °C (lit[3] 64-65 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (s, 1H), 6.85 (s, 1H), 3.98 (bs, 2H), 2.22 (s, 3H), 2.21 (s, 3H).

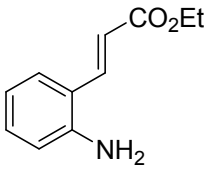
Typical procedure for preparation of (E)-Methyl 3-(2-aminophenyl)acrylate (S-2a)



The reaction vessel was charged with 2-iodo aniline (1.0 g, 4.58 mmol), methyl acrylate (0.83 mL, 9.17 mmol), K_2CO_3 (1.26 g, 9.17 mmol), palladium acetate (10 mg, 0.04 mmol), triphenyl phoshine (17 mg, 0.09 mmol) and tetra butyl ammonium bromide (74 mg, 0.23 mmol) in *N*,*N*-dimethylformamide (8 mL). The reaction mixture was stirred at 80 °C for 16 hours under nitrogen. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (30 mL), washed with water (3 x 15 mL) followed by brine solution (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane to give desired compound **S-2a**.

Yield: 78% (630 mg); light yellow solid; mp: 70-72 °C (lit[4] 65-67 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 15.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 3.97 (bs, 2H), 3.80 (s, 3H).

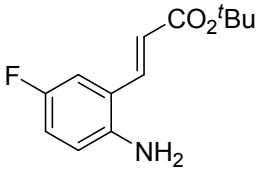
(*E*)-Ethyl-3-(2-aminophenyl)acrylate (S-2b)



Compound **S-2b** was synthesized from the reaction of 2-iodo aniline and ethyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 80% (700 mg); light yellow solid; mp: 67-69 °C (lit[5] 68-69 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 15.8 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.23-7.12 (m, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.97 (bs, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

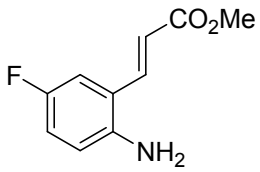
(*E*)-^{t}Butyl-3-(2-amino-5-fluorophenyl)acrylate (S-2c)



Compound **S-2c** was synthesized from the reaction of **S-1a** and *tert*-butyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 89% (895 mg); brown solid; mp: 94-96 °C; R_f = 0.2 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3361, 3332, 2983, 1699, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 15.7, 1.1 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.89 (tb, *J* = 8.4, 3.2 Hz, 1H), 6.65 (dd, *J* = 8.5, 4.6 Hz, 1H), 6.27 (d, *J* = 15.7 Hz, 1H), 3.80 (bs, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 157.3 (C-F *J* = 235.6 Hz), 141.5 (C-F *J* = 1.7 Hz), 137.8 (C-F *J* = 2.3 Hz), 121.3, 121.1 (C-F *J* = 7.2 Hz), 117.9 (C-F *J* = 18.6 Hz), 117.6 (C-F *J* = 2.4 Hz), 113.4 (C-F *J* = 25.4 Hz), 80.7, 28.1 (3C); MS (ES mass): 238.1 (M+1);

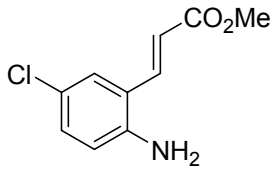
(*E*)-Methyl-3-(2-amino-5-fluorophenyl)acrylate (S-2d)[6]



Compound **S-2d** was synthesized from the reaction of **S-1a** and methyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 72% (590 mg); yellow solid; mp: 93-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 15.7 Hz, 1H), 7.08 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.91 (tb, *J* = 8.4, 2.9 Hz, 1H), 6.66 (dd, *J* = 8.8, 4.7 Hz, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 3.84 (bs, 2H), 3.82 (s, 3H).

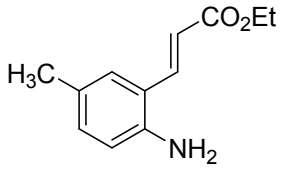
(*E*)-Methyl-3-(2-amino-5-chlorophenyl)acrylate (S-2e)[7]



Compound **S-2e** was synthesized from the reaction of **S-1b** and methyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 62% (520 mg); yellow solid; mp: 67-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 15.7 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.12 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 3.92 (bs, 2H), 3.81 (s, 3H).

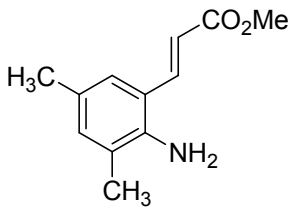
(*E*)-Ethyl-3-(2-amino-5-methylphenyl)acrylate (S-2f)



Compound **S-2f** was synthesized from the reaction of **S-1c** and ethyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 72% (635 mg); yellow solid; mp: 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 15.8 Hz, 1H), 7.20 (s, 1H), 6.99 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.85 (bs, 2H), 2.24 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

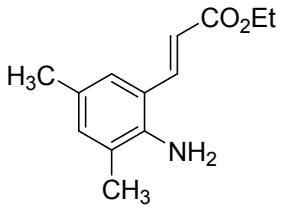
(*E*)-Methyl-3-(2-amino-3,5-dimethylphenyl)acrylate (S-2g)



Compound **S-2g** was synthesized from the reaction of **S-1d** and methyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 72% (600 mg); brown solid; mp: 92-94 °C; R_f = 0.7 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3391, 3336, 2953, 1715, 1621; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 15.7 Hz, 1H), 7.09 (s, 1H), 6.93 (s, 1H), 6.34 (d, *J* = 15.7 Hz, 1H), 3.84 (bs, 2H), 3.80 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 141.6, 140.7, 133.5, 127.3, 125.9, 123.3, 119.3, 117.4, 51.6, 20.3, 17.6; MS (ES mass): 206.2 (M+1);

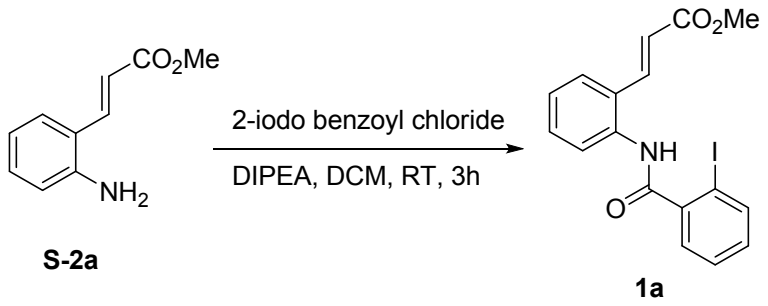
(*E*)-Methyl-3-(2-amino-3,5-dimethylphenyl)acrylate (S-2h)



Compound **S-2h** was synthesized from the reaction of **S-1d** and ethyl acrylate following a procedure similar to that of compound **S-2a**.

Yield: 69% (610 mg); yellow solid; mp: 68-70 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3364, 2965, 1705, 1625; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 15.7 Hz, 1H), 7.09 (s, 1H), 6.93 (s, 1H), 6.34 (d, *J* = 15.7 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 2.22 (s, 3H), 2.16 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 141.5, 140.5, 133.4, 127.3, 125.9, 123.3, 119.4, 117.9, 60.4, 20.3, 17.6, 14.4; MS (ES mass): 219.7 (M+1).

Typical procedure for preparation of (E)-Methyl-3-(2-(2-iodobenzamido)phenyl)acrylate (1a)

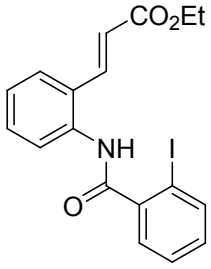


S-2a **1a**

To a solution of compound **S-2a** (500 mg, 2.82 mmol) in dry DCM (20 mL) was added DIPEA (0.73 mL, 4.23 mmol) at 0 ºC under a nitrogen atmosphere. To this 2-iodo benzoyl chloride[8] (0.48 mL, 3.38 mmol) was slowly added and the reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the mixture was diluted with DCM (25 mL), washed with saturated $NaHCO_3$ solution (2 x 30 mL) and water (30 mL) followed by brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexane to give the desired compound **1a**.

Yield: 52% (590 mg); white solid; mp: 155-157 °C; R_f = 0.5 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3204, 2948, 1711, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 15.9 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.66-7.51 (m, 3H), 7.52-7.39 (m, 2H), 7.33-7.24 (m, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 167.1, 141.8, 139.9, 139.6, 135.4, 131.5, 130.9, 128.5, 128.3, 128.2, 127.1, 126.4, 125.4, 120.0, 92.3, 51.8; MS (ES mass): 408.1 (M+1); HPLC: 99.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.44 min.

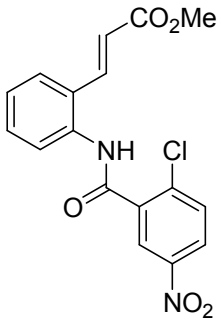
(*E*)-Ethyl-3-(2-(2-iodobenzamido)phenyl)acrylate (1b)



Compound **1b** was synthesized from the reaction of **S-2b** and 2-iodo benzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 58% (640 mg); white solid; mp: 136-138 °C; R_f = 0.5 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3246, 2982, 1711, 1656; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.03-7.90 (m, 3H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.60-7.52 (m, 2H), 7.51-7.38 (m, 2H), 7.30-7.27 (m, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 166.7, 141.9, 139.9, 139.3, 135.3, 131.5, 130.8, 128.5, 128.3, 128.2, 127.1, 126.4, 125.3, 120.8, 92.2, 60.7, 14.3; MS (ES mass): 422.1 (M+1); HPLC: 96.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.68 min.

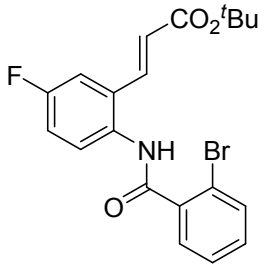
(*E*)-Methyl-3-(2-(2-chloro-5-nitrobenzamido)phenyl)acrylate (1c)



Compound **1c** was synthesized from the reaction of **S-2a** and 2-chloro-5-nitrobenzoyl chloride[9] following a procedure similar to that of compound **1a**.

Yield: 56% (570 mg); white solid; mp: 191-193 °C; R_f = 0.6 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3183, 2949, 1716, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 2.5 Hz, 2H), 8.19 (dd, *J* = 8.8, 2.6 Hz, 2H), 8.07 (d, *J* = 15.9 Hz, 1H), 7.69-7.74 (m, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.48-7.44 (m, 1H), 7.42-7.39 (m, 2H), 6.50 (d, *J* = 15.9 Hz, 1H), 3.91 (s, 3H) (extra protons due to rotamers);; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 166.2, 145.9, 137.9, 137.2, 136.1, 135.2, 133.3, 131.2, 130.9, 130.6, 129.3, 127.6, 125.8, 123.2, 122.8, 52.1; MS (ES mass): 358.4 (M-1); HPLC: 93.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 270 nm, retention time 5.14 min.

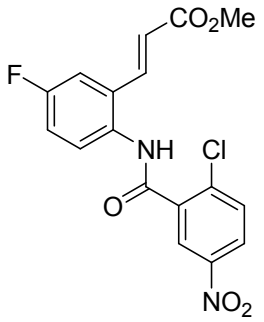
(*E*)-^{t}Butyl-3-(2-(2-bromobenzamido)-5-fluorophenyl)acrylate (1d)



Compound **1d** was synthesized from the reaction of **S-2c** and 2-bromo benzoyl chloride[8] following a procedure similar to that of compound **1a**.

Yield: 62% (550 mg); light brown solid; mp: 142-144 °C; R_f = 0.3 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3212, 2982, 1742, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (dd, *J* = 8.9, 5.2 Hz, 1H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.71 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67-7.64 (m, 2H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.36 (tb, *J* = 7.7, 1.6 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.15 (tb, *J* = 8.7, 2.8 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 165.5, 161.8 (C-F *J* = 245.1 Hz), 137.2, 136.9 (C-F *J* = 2.1 Hz), 133.4, 131.8, 131.2 (C-F *J* = 2.8 Hz), 130.8 (C-F *J* = 8.0 Hz), 129.9, 127.7, 127.6 (C-F *J* = 8.4 Hz), 123.9, 119.2, 117.5 (C-F *J* = 22.6 Hz), 113.3 (C-F *J* = 23.3 Hz), 81.1, 28.1 (3C); MS (ES mass): 419.4 (M-1); HPLC: 99.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.08 min.

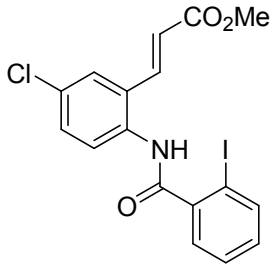
(*E*)-Methyl-3-(2-(2-chloro-5-nitrobenzamido)-5-fluorophenyl)acrylate (1e)



Compound **1e** was synthesized from the reaction of **S-2d** and 2-chloro-5-nitrobenzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 56% (540 mg); light yellow solid; mp: 154-156 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3212, 2998, 1704, 1648; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 2.2 Hz, 2H), 8.18 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.98 (d, *J* = 15.9 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.45 (dd, *J* = 8.7, 5.0 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.10 (tb, *J* = 8.7, 2.6 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 3.90 (s, 3H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 165.9, 164.2 (C-F *J* = 251.3 Hz), 146.0, 137.2, 136.9 (C-F *J* = 2.0 Hz), 136.0, 135.7 (C-F *J* = 8.4 Hz), 131.4 (C-F *J* = 9.1 Hz), 131.2, 131.1, 125.9, 123.9, 123.2, 118.5 (C-F *J* = 23.1 Hz), 114.5 (C-F *J* = 23.5 Hz), 52.3; MS (ES mass): 376.7 (M-1); HPLC: 93.4%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 270 nm, retention time 5.20 min.

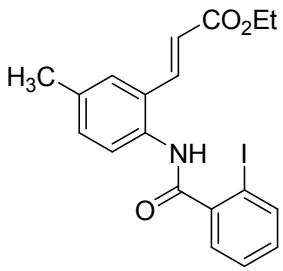
(*E*)-Methyl-3-(5-chloro-2-(2-iodobenzamido)phenyl)acrylate (1f)



Compound **1f** was synthesized from the reaction of **S-2e** and 2-iodo benzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 74% (770 mg); white solid; mp: 141-143 °C; R_f = 0.6 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3212, 3011, 1721, 1658; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97-7.90 (m, 3H), 7.63-7.55 (m, 2H), 7.54-7.41 (m, 3H), 7.20 (t, *J* = 7.1 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 166.8, 141.8, 140.0, 138.2, 133.8, 131.8, 131.7, 130.7, 128.6, 128.5, 127.9, 126.9, 126.4, 121.8, 92.1, 52.0; MS (ES mass): 439.5 (M-1); HPLC: 94.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.82 min.

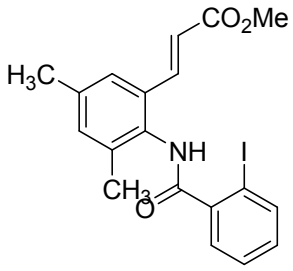
(*E*)-Ethyl-3-(2-(2-iodobenzamido)-5-methylphenyl)acrylate (1g)



Compound **1g** was synthesized from the reaction of **S-2f** and 2-iodo benzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 66% (700 mg); white solid; mp: 166-168 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3196, 2988, 1708, 1647; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 15.8 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 6.6 Hz, 1H), 7.43 (bs, 1H), 7.37-7.34 (m, 2H), 7.20-7.19 (m, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 166.8, 141.9, 139.8, 139.5, 136.3, 132.8, 131.6, 131.4, 128.5, 128.4, 128.3, 127.3, 125.6, 120.2, 92.3, 60.6, 21.0, 14.3; MS (ES mass): 436.1 (M+1); HPLC: 94.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.86 min.

(E)-Methyl-3-(2-(2-iodobenzamido)-3,5-dimethylphenyl)acrylate (1h)

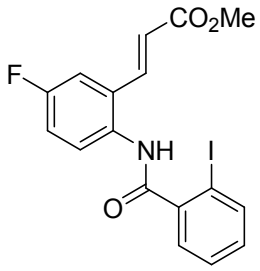


Compound **1h** was synthesized from the reaction of **S-2g** and 2-iodo benzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 64% (680 mg); white solid; mp: 171-173 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3222, 2948, 1718, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 15.9 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.34 (s, 1H), 7.23-7.13 (m, 3H), 6.41 (d, *J* = 15.9 Hz, 1H), 3.78 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 168.2, 167.2, 141.9, 141.0, 140.1, 137.8, 136.5, 133.5, 132.2, 131.4, 130.9, 128.5, 128.2, 125.1, 119.6, 92.1, 51.7, 21.0, 18.9; MS (ES mass): 436.2 (M+1); HPLC: 98.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.73 min.

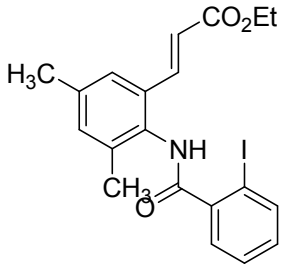
(E)-Methyl-3-(5-fluoro-2-(2-iodobenzamido)phenyl)acrylate (1i)



Compound **1i** was synthesized from the reaction of **S-2c** and 2-iodo benzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 67% (730 mg); light brown solid; mp: 118-120 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3173, 2987, 1721, 1657; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 5.4 Hz, 1H), 7.91 (bs, 1H), 7.86 (dd, *J* = 8.4, 5.4 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.48-7.42 (m, 2H), 7.31 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.23-7.14 (m, 2H), 6.42 (d, *J* = 15.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 166.8, 161.9 (C-F *J* = 245.4 Hz), 141.6, 139.9, 138.6, 131.6, 131.4 (C-F *J* = 2.4 Hz), 130.8 (C-F *J* = 8.0 Hz), 128.5, 128.3, 127.9 (C-F *J* = 8.3 Hz), 121.1, 117.9 (C-F *J* = 22.5 Hz), 113.3 (C-F *J* = 23.2 Hz), 92.3, 51.9; MS (ES mass): 425.5 (M+1); HPLC: 98.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.54 min.

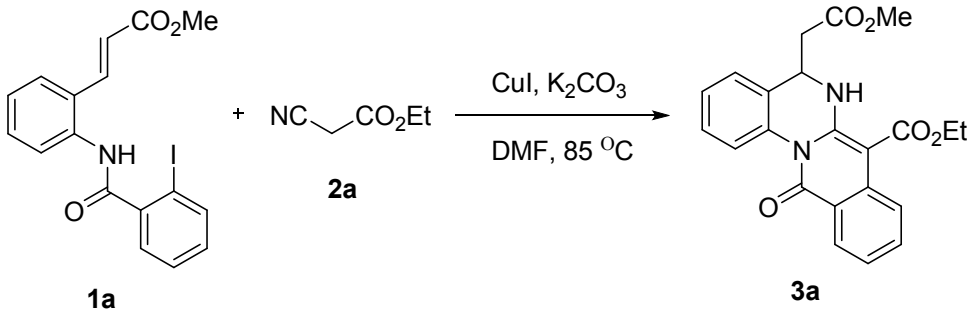
(E)-Ethyl-3-(2-(2-iodobenzamido)-3,5-dimethylphenyl)acrylate (1j)



Compound **1j** was synthesized from the reaction of **S-2h** and 2-iodo benzoyl chloride following a procedure similar to that of compound **1a**.

Yield: 63% (645 mg); light brown solid; mp: 171-173 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3215, 2948, 1708, 1645; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.37 (s, 1H), 7.24-7.13 (m, 3H), 6.44 (d, *J* = 15.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 2.37 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 166.8, 142.0, 140.6, 140.1, 137.8, 136.5, 133.5, 132.3, 131.4, 130.9, 128.5, 128.2, 125.1, 120.1, 92.2, 60.5, 21.1, 18.9, 14.4; MS (ES mass): 449.5 (M+1); HPLC: 96.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.93 min.

Typical procedure for preparation of Ethyl-5-(2-methoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3a)

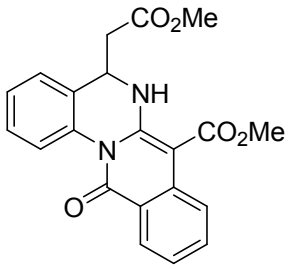


A mixture of compound **1a** (50 mg, 0.12 mmol), K_2CO_3 (50 mg, 0.36 mmol), ethyl cyano acetate (**2a**) (0.016 mL, 0.14 mmol) and CuI (2.3 mg, 0.012 mmol) in DMF (2 mL) was heated to 85 °C under anhydrous conditions ($CaCl_2$ filled guard tube) for 0.5 h. After completion of the reaction, the mixture was cooled to room temp, diluted with ethyl acetate (15 mL) and passed through celite. The resulting solution was washed with water (3 x 15 mL) followed by brine solution (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane to give desired compound **3a**.

Yield: 89% (44 mg); brown solid; mp: 131-133 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3227, 2983, 1725, 1684, 1632; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.43 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.58 (tb, *J* = 7.6, 1.4

Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.30-7.22 (m, 3H), 4.95-4.86 (m, 1H), 4.49-4.34 (m, 2H), 3.71 (s, 3H), 2.86-2.71 (m, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 169.1, 162.0, 151.6, 135.8, 133.2, 132.3, 129.5, 128.5, 127.9, 126.9, 125.3, 125.1, 123.4, 122.9, 121.8, 85.5, 60.6, 52.0, 48.9, 40.4, 14.4; MS (ES mass): 392.5 (M+1); HPLC: 96.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.14 min. Elemental analysis found C, 67.55; H, 5.17; N, 7.01; $C_{22}H_{20}N_2O_5$ requires C, 67.34; H, 5.14; N, 7.14.

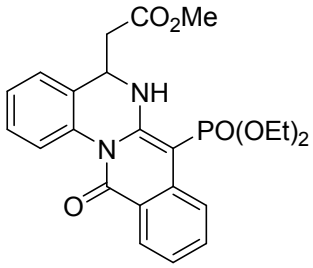
Methyl-5-(2-methoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3b)



Compound **3b** was synthesized from the reaction of **1a** and methyl cyano acetate (**2b**) following a procedure similar to that of compound **3a**.

Yield: 84% (39 mg); brown semi solid; R_f = 0.6 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3212, 2983, 1728, 1674, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.41 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.59 (tb, *J* = 8.0, 1.2 Hz, 1H), 7.37 (tb, *J* = 8.4, 1.5 Hz, 1H), 7.30-7.23 (m, 3H), 4.96-4.86 (m, 1H), 3.94 (s, 3H), 3.70 (s, 3H), 2.82-2.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 169.5, 162.0, 151.7, 135.7, 133.3, 132.3, 129.4, 128.5, 127.9, 126.9, 125.3, 125.1, 123.5, 122.9, 121.7, 85.3, 52.0, 51.5, 48.9, 40.4; MS (ES mass): 379.3 (M+1); HPLC: 93.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 4.50 min.

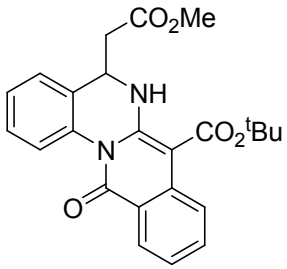
Methyl-2-(7-(diethoxyphosphoryl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3c)



Compound **3c** was synthesized from the reaction of **1a** and diethyl cyano methyl phosphonate (**2c**) following a procedure similar to that of compound **3a**.

Yield: 81% (45 mg); brown liquid; R_f = 0.3 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2951, 2925, 1738, 1679, 1590; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.80 (d, *J* = 2.7 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.3, 1.2 Hz, 1H), 7.37 (d, *J* = 8.4, 1.5 Hz, 1H), 7.32-7.21 (m, 3H), 4.86-4.82 (m, 1H), 4.22-3.99 (m, 3H), 3.96-3.84 (m, 1H), 3.75 (s, 3H), 2.84-2.71 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 162.3, 152.9 (C-P *J* = 22.0 Hz), 136.7 (C-P *J* = 7.1 Hz), 133.3, 132.5, 130.2, 128.7, 127.8, 126.8, 125.3, 123.5 (C-P *J* = 3.2 Hz), 123.3, 122.9, 121.4 (C-P *J* = 12.1 Hz), 74.7, 61.8, 61.7, 52.1, 49.3, 40.3, 16.3 (C-P *J* = 7.0 Hz), 16.2 (C-P *J* = 7.2 Hz); MS (ES mass): 457.3 (M+1); HPLC: 94.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 4.33 min.

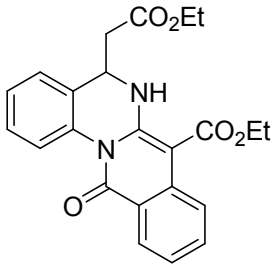
^{t}Butyl-5-(2-methoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3d)



Compound **3d** was synthesized from the reaction of **1a** and *tert*-butyl cyano acetate (**2d**) following a procedure similar to that of compound **3a**.

Yield: 81% (42 mg); brown solid; mp: 119-121 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2955, 2923, 1738, 1682, 1644; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.31 (d, *J* = 2.8 Hz, 1H), 8.35 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.57 (td, *J* = 7.9, 1.6 Hz, 1H), 7.37 (td, *J* = 8.3, 2.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.27-7.22 (m, 2H), 4.92-4.87 (m, 1H), 3.71 (s, 3H), 2.85-2.71 (m, 2H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 168.4, 162.1, 151.1, 136.1, 132.9, 132.4, 129.8, 128.4, 127.9, 126.8, 125.2, 125.1, 123.3, 123.0, 121.8, 86.9, 81.7, 52.0, 48.9, 40.4, 28.6 (3C); MS (ES mass): 421.3 (M+1); HPLC: 93.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.21 min.

Ethyl-5-(2-ethoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3e)

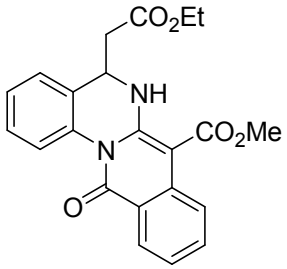


Compound **3e** was synthesized from the reaction of **1b** and **2a** following a procedure similar to that of compound **3a**.

Yield: 87% (42 mg); brown solid; mp: 125-127 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2969, 2931, 1720, 1676, 1632; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.43 (d, *J* = 2.5 Hz, 1H), 8.35 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.58 (tb, *J* = 8.4, 1.2 Hz, 1H), 7.37 (tb, *J* = 8.4, 1.1 Hz, 1H), 7.32-7.22 (m, 3H), 4.95-4.87 (m, 1H), 4.51-4.32 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.84-2.70 (m, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.1, 162.1, 151.7, 135.9, 133.3, 132.4, 129.6, 128.5, 127.9, 126.9, 125.3, 125.1, 123.4, 122.9, 121.8, 85.4, 61.2, 60.6, 48.9, 40.6, 14.5, 14.1; MS (ES mass): 407.2 (M+1); HPLC: 99.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.65 min.

Elemental analysis found C, 67.79; H, 5.45; N, 6.99; $C_{23}H_{22}N_2O_5$ requires C, 67.97; H, 5.46; N, 6.89.

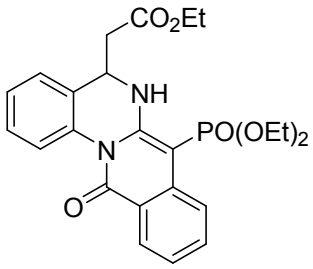
Methyl-5-(2-ethoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3f)



Compound **3f** was synthesized from the reaction of **1b** and **2b** following a procedure similar to that of compound **3a**.

Yield: 83% (38 mg); light brown solid; mp: 105-107 °C; R_f = 0.3 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2968, 2942, 1721, 1682, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.43 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.32-7.25 (m, 3H), 4.94-4.90 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 2.82-2.73 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.5, 162.1, 151.8, 135.7, 133.3, 132.4, 129.5, 128.6, 127.9, 126.9, 125.3, 125.1, 123.5, 122.9, 121.7, 85.3, 61.2, 51.5, 48.9, 40.7, 14.1; MS (ES mass): 392.6 (M+1); HPLC: 91.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.05 min.

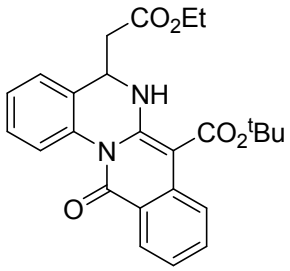
Ethyl-2-(7-(diethoxyphosphoryl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3g)



Compound **3g** was synthesized from the reaction of **1b** and **2c** following a procedure similar to that of compound **3a**.

Yield: 79% (44 mg); brown liquid; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2971, 2923, 1731, 1685, 1642; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.80 (d, *J* = 2.3 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.37 (tb, *J* = 8.3, 2.7 Hz, 1H), 7.32-7.22 (m, 3H), 4.89-4.81 (m, 1H), 4.26-4.13 (m, 3H), 4.12-4.00 (m, 2H), 3.95-3.84 (m, 1H), 2.84-2.70 (m, 2H), 1.33-1.26 (m, 6H), 1.25-1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 162.3, 153.0 (C-P *J* = 28.9 Hz), 136.7 (C-P *J* = 7.3 Hz), 133.3, 132.5, 130.3, 128.7, 127.8, 126.8, 125.4, 123.5 (C-P *J* = 3.2 Hz), 123.3, 122.9, 121.4 (C-P *J* = 11.2 Hz), 74.6, 61.8, 61.7, 61.1, 49.2, 40.5, 16.3 (C-P *J* = 7.1 Hz), 16.2 (C-P *J* = 7.2 Hz), 14.1; MS (ES mass): 470.6 (M+1); HPLC: 93.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 4.87 min.

^{t}Butyl-5-(2-ethoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3h)

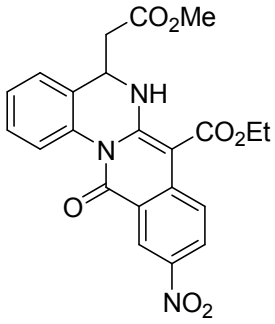


Compound **3h** was synthesized from the reaction of **1b** and **2d** following a procedure similar to that of compound **3a**.

Yield: 81% (41 mg); brown liquid; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2968, 2931, 1721, 1678, 1633; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.32 (d, *J* = 2.6 Hz, 1H), 8.34 (dd, *J* = 7.9, 1.1 Hz, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.56 (tb, *J* = 8.2, 1.2 Hz, 1H), 7.36 (tb, *J* = 8.4, 1.2 Hz, 1H), 7.29-7.27 (m, 1H), 7.26-7.20 (m, 2H), 4.93-4.85 (m, 1H), 4.20-4.11 (m, 2H), 2.81-2.69 (m, 2H), 1.64 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 168.4, 162.1, 151.2, 136.2, 132.9, 132.5, 129.8, 128.4, 127.9, 126.8, 125.3, 125.1, 123.3, 123.0, 121.8, 86.8, 81.7, 61.1, 48.9, 40.6, 28.6 (3C), 14.1; MS (ES mass):

434.7 (M+1); HPLC: 95.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.65 min.

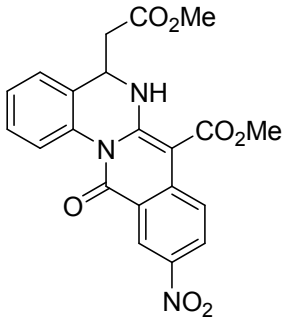
Ethyl-5-(2-methoxy-2-oxoethyl)-10-nitro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3i)



Compound **3i** was synthesized from the reaction of **1c** and **2a** following a procedure similar to that of compound **3a**.

Yield: 76% (46 mg); yellow solid; mp: 142-144 °C; R_f = 0.3 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2926, 2854, 1736, 1687, 1649; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.90 (d, *J* = 2.9 Hz, 1H), 9.22 (d, *J* = 2.5 Hz, 1H), 8.48 (d, *J* = 9.4 Hz, 1H), 8.35 (dd, *J* = 9.4, 2.6 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.44 (tb, *J* = 8.4, 1.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.30-7.28 (m, 1H), 5.03-4.99 (m, 1H), 4.51-4.42 (m, 2H), 3.75 (s, 3H), 2.89-2.80 (m, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 168.5, 160.8, 153.3, 142.8, 141.2, 131.7, 128.4, 128.3, 127.7, 127.0, 125.9, 125.5, 125.1, 122.5, 120.7, 85.7, 61.2, 52.2, 48.9, 40.7, 14.4; MS (ES mass): 435.7 (M-1); HPLC: 91.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.62 min.

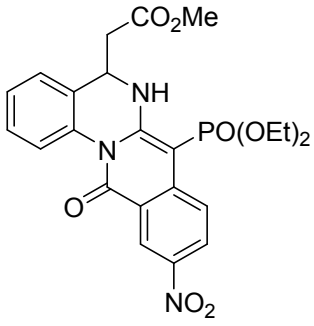
Methyl-5-(2-methoxy-2-oxoethyl)-10-nitro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3j)



Compound **3j** was synthesized from the reaction of **1c** and **2b** following a procedure similar to that of compound **3a**.

Yield: 73% (42 mg); brown solid; mp: 170-172 °C; R_f = 0.3 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2925, 2799, 1722, 1681, 1639; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.89 (d, *J* = 2.3 Hz, 1H), 9.22 (d, *J* = 2.5 Hz, 1H), 8.44 (d, *J* = 9.3 Hz, 1H), 8.35 (dd, *J* = 9.4, 2.6 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.44 (tb, *J* = 8.3, 1.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.29-7.27 (m, 1H), 5.04-5.00 (m, 1H), 3.99 (s, 3H), 3.75 (s, 3H), 2.88-2.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 168.9, 160.8, 153.3, 142.8, 141.1, 131.7, 128.4, 128.3, 127.7, 127.1, 125.9, 125.5, 125.1, 122.5, 120.7, 85.6, 52.2, 51.9, 48.9, 40.7; MS (ES mass): 423.6 (M+1); HPLC: 92.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.31 min.

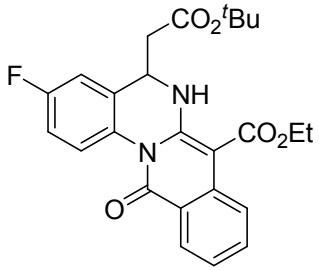
Methyl-2-(7-(diethoxyphosphoryl)-10-nitro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3k)



Compound **3k** was synthesized from the reaction of **1c** and **2c** following a procedure similar to that of compound **3a**.

Yield: 73% (50 mg); brown solid; mp: 166-168 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2931, 2892, 1739, 1642; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.27 (d, *J* = 3.0 Hz, 1H), 9.19 (d, *J* = 2.0 Hz, 1H), 8.30 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.42 (tb, *J* = 8.4, 1.4 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.28-7.27 (m, 1H), 4.96-4.89 (m, 1H), 4.28-4.01 (m, 3H), 4.02-3.90 (m, 1H), 3.75 (s, 3H), 2.83-2.75 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 161.1, 154.5 (C-P *J* = 21.1 Hz), 142.7, 142.4 (C-P *J* = 7.0 Hz), 131.8, 129.0, 128.2, 127.5, 127.1, 125.5, 125.4, 124.2 (C-P *J* = 3.2 Hz), 122.5, 120.4 (C-P *J* = 2.3 Hz), 75.7, 62.3, 62.2 (C-P *J* = 3.4 Hz), 52.2, 49.2, 40.8, 16.1 (C-P *J* = 7.0 Hz, 2C); MS (ES mass): 501.6 (M+1); HPLC: 95.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm, retention time 5.01 min. Elemental analysis found C, 55.19; H, 4.85; N, 8.23; $C_{23}H_{24}N_3O_8P$ requires C, 55.09; H, 4.82; N, 8.38.

Ethyl-5-(2-tert-butoxy-2-oxoethyl)-3-fluoro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3l)

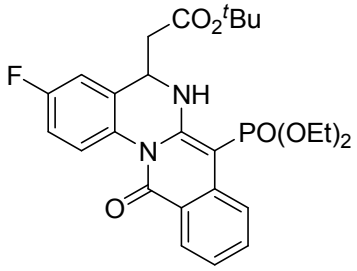


Compound **3l** was synthesized from the reaction of **1d** and **2a** following a procedure similar to that of compound **3a**.

Yield: 80% (38 mg); light brown solid; mp: 120-122 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2980, 2920, 1731, 1671, 1627; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.37 (d, *J* = 2.8 Hz, 1H), 8.34 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.08 (dd, *J* = 8.8, 4.9 Hz, 1H), 7.59 (tb, *J* = 8.4, 1.6 Hz, 1H), 7.29-7.27 (m, 1H), 7.07 (tb, *J* = 8.4, 2.9 Hz, 1H), 6.97 (dd, *J* = 7.9, 2.8 Hz, 1H), 4.89-4.80 (m, 1H), 4.50-4.30 (m, 2H), 2.72-2.64 (m, 2H), 1.48-1.41 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 168.9, 161.9, 161.7 (C-F *J* = 247.2 Hz), 151.3, 135.8, 133.3, 132.0 (C-F *J* = 7.8 Hz), 128.5, 128.4 (C-F *J* = 3.2 Hz), 125.1, 125.1 (C-F *J* = 8.4 Hz), 123.5,

121.7, 115.0 (C-F J = 22.7 Hz), 112.0 (C-F J = 23.3 Hz), 85.6, 82.0, 60.6, 48.9, 41.3, 27.9 (3C), 14.4; MS (ES mass): 453.3 (M+1); HPLC: 99.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.93 min. Elemental analysis found C, 66.20; H, 5.56; N, 6.33; $C_{25}H_{25}FN_2O_5$ requires C, 66.36; H, 5.57; N, 6.19.

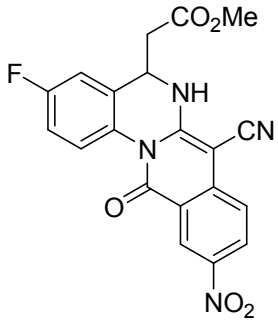
^{t}Butyl-2-(7-(diethoxyphosphoryl)-3-fluoro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3m)



Compound **3m** was synthesized from the reaction of **1d** and **2c** following a procedure similar to that of compound **3a**.

Yield: 75% (41 mg); light brown semi solid; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2982, 2914, 1735, 1611; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.77 (d, J = 3.0 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.12 (dd, J = 8.8, 4.9 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.55 (td, J = 8.6, 1.6 Hz, 1H), 7.26-7.22 (m, 1H), 7.06 (tb, J = 8.6, 2.7 Hz, 1H), 6.99 (dd, J = 8.0, 2.8 Hz, 1H), 4.79-4.74 (m, 1H), 4.25-3.99 (m, 3H), 3.97-3.83 (m, 1H), 2.73-2.61 (m, 2H), 1.47 (s, 9H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 162.2, 161.6 (C-F J = 247.0 Hz), 152.8 (C-P J = 21.9 Hz), 136.6 (C-P J = 7.0 Hz), 133.4, 132.8 (C-F J = 7.7 Hz), 128.7, 128.5 (C-F J = 3.4 Hz), 124.9 (C-P J = 8.3 Hz), 123.5 (C-F J = 3.1 Hz), 123.4, 121.3 (C-P J = 12.1 Hz), 114.8 (C-F J = 22.6 Hz), 112.2 (C=F J = 23.2 Hz), 81.8, 74.9, 61.8, 61.7, 49.1, 41.1, 28.0 (3C), 16.2 (C-P J = 7.0 Hz), 16.1 (C-P J = 7.3 Hz); MS (ES mass): 517.3 (M+1); HPLC: 91.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.27 min.

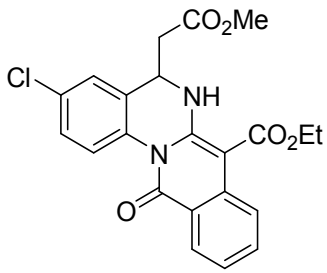
Methyl-2-(7-cyano-3-fluoro-10-nitro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3n)



Compound **3n** was synthesized from the reaction of **1e** and malononitrile (**2e**) following a procedure similar to that of compound **3a**.

Yield: 68% (36 mg); brown solid; mp: 115-117 °C; R_f = 0.1 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2978, 2923, 2221, 1731, 1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.16 (d, *J* = 2.0 Hz, 1H), 8.45 (dd, *J* = 8.8, 2.3 Hz, 1H), 8.34 (dd, *J* = 9.1, 4.8 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.18 (tb, *J* = 7.6, 2.8 Hz, 1H), 6.99 (dd, *J* = 7.6, 2.6 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 4.93 (tb, *J* = 6.9, 3.0 Hz, 1H), 3.81 (s, 3H), 2.87 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 166.3 (C-F *J* = 259.1 Hz), 160.0, 152.4, 143.4, 140.7, 130.6 (C-F *J* = 8.0 Hz), 128.1, 127.3, 125.5, 124.1 (C-F *J* = 8.2 Hz), 122.5, 119.3 (C-F *J* = 2.2 Hz), 115.7, 115.5 (C-F *J* = 25.1 Hz), 113.0 (C-F *J* = 22.7 Hz), 68.6, 52.1, 49.1, 40.3; MS (ES mass): 406.7 (M-1); HPLC: 95.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 225 nm, retention time 3.93 min. Elemental analysis found C, 58.79; H, 3.25; N, 13.93; $C_{20}H_{13}FN_4O_5$ requires C, 58.83; H, 3.21; N, 13.72.

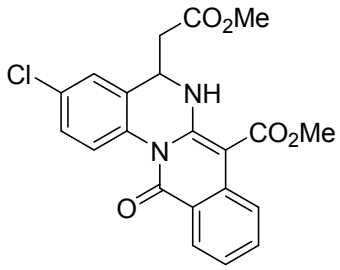
Ethyl-3-chloro-5-(2-methoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3o)



Compound **3o** was synthesized from the reaction of **1f** and **2a** following a procedure similar to that of compound **3a**.

Yield: 85% (41 mg); light yellow solid; mp: 151-153 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2947, 2843, 1731, 1676, 1654; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.39 (d, *J* = 3.0 Hz, 1H), 8.32 (t, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.60 (tb, *J* = 8.2, 1.6 Hz, 1H), 7.34 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.30-7.27 (m, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 4.90-4.83 (m, 1H), 4.50-4.34 (m, 2H), 3.71 (s, 3H), 2.83-2.71 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.0, 161.9, 151.2, 135.7, 133.4, 132.2, 131.2, 130.9, 128.5, 128.1, 125.1 (2C), 124.5, 123.7, 121.6, 85.9, 60.8, 52.1, 48.7, 40.1, 14.4; MS (ES mass): 426.6 (M+1); HPLC: 98.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.22 min. Elemental analysis found C, 61.79; H, 4.45; N, 6.83; $C_{22}H_{19}ClN_2O_5$ requires C, 61.90; H, 4.49; N, 6.56.

Methyl-3-chloro-5-(2-methoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3p)

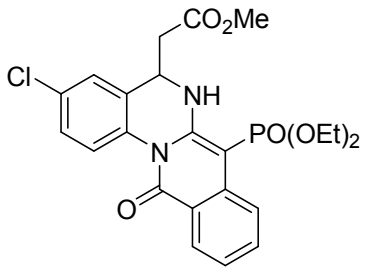


Compound **3p** was synthesized from the reaction of **1f** and **2b** following a procedure similar to that of compound **3a**.

Yield: 81% (37 mg); light brown solid; mp: 175-177 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2950, 2835, 1726, 1672, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.37 (d, *J* = 2.9 Hz, 1H), 8.34 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.60 (tb, *J* = 8.5, 1.5 Hz, 1H), 7.34 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.29-7.24 (m, 2H), 4.91-4.83 (m, 1H), 3.94 (s, 3H), 3.72 (s, 3H), 2.83-2.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.4, 161.8, 151.3, 135.6, 133.5, 132.3, 131.2, 130.9, 128.6, 128.1, 125.2, 125.1, 124.5, 123.7, 121.6, 85.7, 52.1, 51.6, 48.7, 40.2; MS (ES mass): 412.6 (M+1); HPLC: 95.8%, column: Symmetry C-18 75 x 4.6

mm 3.5μ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.92 min.

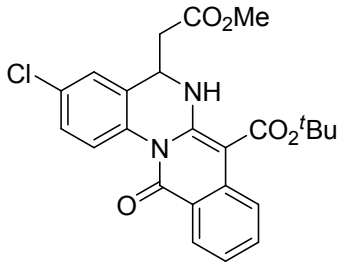
Methyl-2-(3-chloro-7-(diethoxyphosphoryl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3q)



Compound **3q** was synthesized from the reaction of **1f** and **2c** following a procedure similar to that of compound **3a**.

Yield: 78% (43 mg); brown liquid; mp: 121-123 °C; R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2953, 2834, 1732, 1686; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.79 (d, *J* = 2.3 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.37-7.32 (m, 1H), 7.30-7.23 (m, 2H), 4.85-4.77 (m, 1H), 4.22-4.01 (m, 3H), 3.96-3.87 (m, 1H), 3.76 (s, 3H), 2.82-2.71 (m, 2H), 1.35-1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 162.1, 152.5 (C-P *J* = 22.0 Hz), 139.2, 136.5 (C-P *J* = 6.3 Hz), 133.5, 132.1, 131.9, 128.7, 127.9, 125.2, 124.5, 123.6 (C-P *J* = 3.2 Hz), 123.5, 121.4 (C-P *J* = 12.0 Hz), 80.1, 61.9, 61.8, 52.2, 49.1, 40.0, 16.3 (C-P *J* = 6.9 Hz), 16.2 (C-P *J* = 7.1 Hz); MS (ES mass): 490.6 (M+1); HPLC: 89.9%, column: Symmetry C-18 75 x 4.6 mm 3.5μ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.59 min.

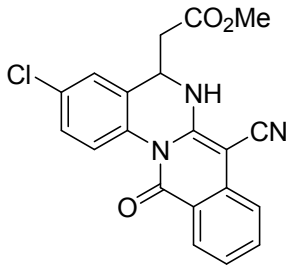
^{t}Butyl-3-chloro-5-(2-methoxy-2-oxoethyl)-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3r)



Compound **3r** was synthesized from the reaction of **1f** and **2d** following a procedure similar to that of compound **3a**.

Yield: 77% (39 mg); brown solid; mp: 150-152 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2953, 2797, 1730, 1673, 1624; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.26 (d, *J* = 2.9 Hz, 1H), 8.31 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.56 (tb, *J* = 8.2, 1.2 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.28-7.21 (m, 2H), 4.87-4.80 (m, 1H), 3.70 (s, 3H), 2.81-2.67 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 168.3, 161.9, 150.6, 135.9, 133.1, 132.2, 131.5, 130.9, 128.5, 128.1, 125.2, 125.1, 124.6, 123.5, 121.7, 87.3, 81.9, 52.2, 48.8, 40.1, 28.6 (3C); MS (ES mass): 454.6 (M+1); HPLC: 97.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 7.09 min.

Methyl-2-(3-chloro-7-cyano-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3s)

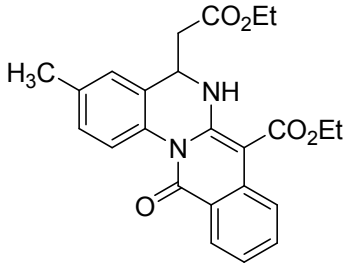


Compound **3s** was synthesized from the reaction of **1f** and **2e** following a procedure similar to that of compound **3a**.

Yield: 72% (31 mg); light yellow solid; mp: 214-216 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2959, 2878, 2217, 1723, 1686; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.32-8.29 (m, 2H), 7.70 (tb, *J* = 7.9, 1.2 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.36 (t, *J*

= 7.2 Hz, 1H), 7.27-7.24 (m, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 4.85-4.80 (m, 1H), 3.81 (s, 3H), 2.86-2.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 161.0, 150.3, 134.6, 134.4, 132.7, 130.4, 130.3, 129.0, 128.6, 125.5, 125.0, 124.2, 122.1, 120.8, 116.3, 70.5, 52.6, 49.4, 39.3; MS (ES mass): 377.6 (M-1); HPLC: 98.2%, column: X TERRA C-18 250 x 4.6 mm 5µ, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 3/20, 15/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 4.36 min.

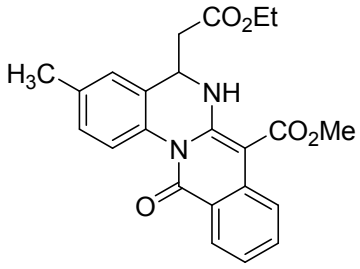
Ethyl-5-(2-ethoxy-2-oxoethyl)-3-methyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3t)



Compound **3t** was synthesized from the reaction of **1g** and **2a** following a procedure similar to that of compound **3a**.

Yield: 87% (42 mg); light brown solid; mp: 114-116 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3235, 2968, 1726, 1681, 1627; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.35 (d, *J* = 2.9 Hz, 1H), 8.30-8.23 (m, 2H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.50 (tb, *J* = 7.0, 1.2 Hz, 1H), 7.21-7.16 (m, 1H), 7.10 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.97 (s, 1H), 4.81-4.77 (m, 1H), 4.42-4.25 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.72-2.61 (m, 2H), 2.30 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.18-1.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.1, 162.0, 151.7, 136.9, 135.8, 133.1, 129.8, 129.4, 128.6, 128.5, 125.6, 125.0, 123.3, 122.7, 121.7, 85.3, 61.1, 60.6, 48.9, 40.7, 20.9, 14.4, 14.1; MS (ES mass): 421.3 (M+1); HPLC: 97.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 245 nm, retention time 5.19 min. Elemental analysis found C, 68.79; H, 5.74; N, 6.43; $C_{24}H_{24}N_2O_5$ requires C, 68.56; H, 5.75; N, 6.66.

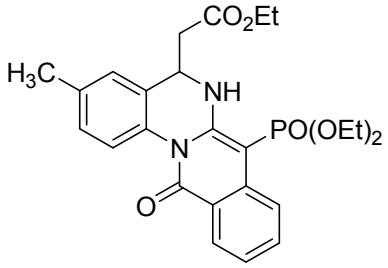
Methyl-5-(2-ethoxy-2-oxoethyl)-3-methyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3u)



Compound **3u** was synthesized from the reaction of **1g** and **2b** following a procedure similar to that of compound **3a**.

Yield: 84% (39 mg); light brown solid; mp: 112-114 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3185, 2952, 1730, 1680, 1641; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.33 (d, *J* = 2.9 Hz, 1H), 8.27 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.50 (tb, *J* = 7.8, 1.2 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.10 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.96 (s, 1H), 4.83-4.76 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 2.73-2.61 (m, 2H), 2.30 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.5, 161.9, 151.7, 136.9, 135.7, 133.2, 129.8, 129.3, 128.6, 128.5, 125.6, 125.0, 123.4, 122.7, 121.7, 85.2, 61.1, 51.4, 48.9, 40.7, 20.9, 14.1; MS (ES mass): 407.2 (M+1); HPLC: 97.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.66 min.

Ethyl-2-(7-(diethoxyphosphoryl)-3-methyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3v)

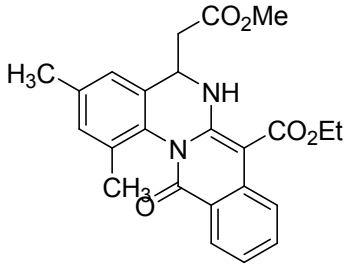


Compound **3v** was synthesized from the reaction of **1g** and **2c** following a procedure similar to that of compound **3a**.

Yield: 82% (45 mg); brown liquid; R_f = 0.1 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2978, 2926, 1732, 1679, 1599; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.78 (d, *J* = 2.7 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.54 (tb, *J* = 8.4, 1.5 Hz, 1H),

7.24 (t, J = 7.5 Hz, 1H), 7.17 (dd, J = 8.5, 1.4 Hz, 1H), 7.06 (s, 1H), 4.84-4.77 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.14-3.98 (m, 3H), 3.95-3.82 (m, 1H), 2.78-2.69 (m, 2H), 2.37 (s, 3H), 1.33-1.27 (m, 6H), 1.25-1.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 162.3, 153.0 (C-P J = 28.9 Hz), 136.7, 136.6 (C-P J = 7.1 Hz), 133.2, 130.1, 129.9, 128.7, 128.5, 125.7, 123.4 (C-P J = 3.2 Hz), 123.2, 122.7, 121.4 (C-P J = 12.2 Hz), 74.5, 61.7, 61.8, 61.1, 49.2, 40.6, 20.9, 16.2 (C-P J = 7.3 Hz), 16.1 (C-P J = 7.3 Hz), 14.1; MS (ES mass): 485.3 (M+1); HPLC: 89.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.40 min.

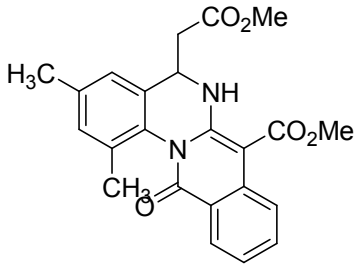
Ethyl-5-(2-methoxy-2-oxoethyl)-1,3-dimethyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3w)



Compound **3w** was synthesized from the reaction of **1h** and **2a** following a procedure similar to that of compound **3a**.

Yield: 86% (41 mg); light brown solid; mp: 176-178 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2943, 2834, 1732, 1688, 1642; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (d, J = 3.1 Hz, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.60 (tb, J = 8.4, 1.2 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.07 (s, 1H), 6.93 (s, 1H), 4.88-4.80 (m, 1H), 4.50-4.41 (m, 1H), 4.38-4.30 (m, 1H), 3.67 (s, 3H), 2.80-2.69 (m, 2H), 2.36 (s, 3H), 2.05 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 168.8, 161.3, 153.0, 136.9, 135.6, 132.9, 132.5, 132.4, 132.0, 129.1, 127.8, 125.5, 123.6, 123.5, 122.8, 86.5, 60.5, 51.9, 50.2, 40.1, 20.8, 20.5, 14.5; MS (ES mass): 420.6 (M+1); HPLC: 99.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.29 min.

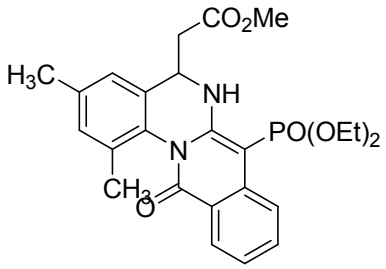
Methyl-5-(2-methoxy-2-oxoethyl)-1,3-dimethyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3x)



Compound **3x** was synthesized from the reaction of **1h** and **2b** following a procedure similar to that of compound **3a**.

Yield: 81% (37 mg); light yellow solid; mp: 135-137 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2941, 2823, 1731, 1685, 1638; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (d, *J* = 2.9 Hz, 1H), 8.27-8.24 (m, 2H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 6.93 (s, 1H), 4.89-4.79 (m, 1H), 3.93 (s, 3H), 3.67 (s, 3H), 2.79-2.69 (m, 2H), 2.36 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 169.2, 161.3, 153.1, 136.9, 135.5, 132.9, 132.5, 132.4, 132.0, 129.0, 127.8, 125.4, 123.6, 123.5, 122.8, 86.3, 51.9, 51.4, 50.2, 40.1, 20.8, 20.5; MS (ES mass): 406.6 (M+1); HPLC: 97.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.67 min.

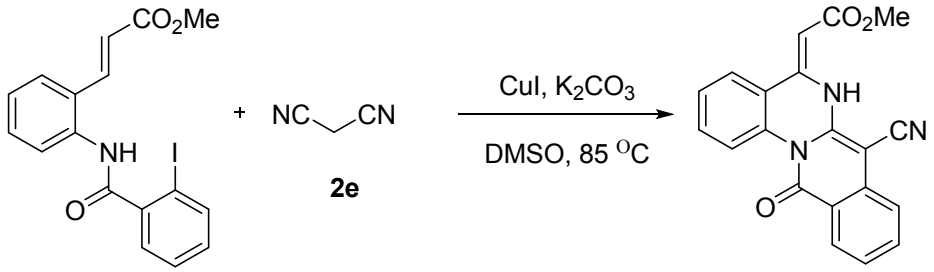
Methyl-2-(7-(diethoxyphosphoryl)-1,3-dimethyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-yl)acetate (3y)



Compound **3y** was synthesized from the reaction of **1h** and **2c** following a procedure similar to that of compound **3a**.

Yield: 78% (43 mg); light brown semi solid; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2921, 2834, 1731, 1682, 1639; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.45 (d, *J* = 2.6 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.26-7.21 (m, 1H), 7.08 (s, 1H), 6.94 (s, 1H), 4.80-4.76 (m, 1H), 4.25-4.14 (m, 1H), 4.14-3.99 (m, 2H), 3.84-3.76 (m, 1H), 3.73 (s, 3H), 2.80-2.69 (m, 2H), 2.36 (s, 3H), 2.07 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 161.4, 154.2 (C-P *J* = 21.4 Hz), 136.8, 136.5 (C-P *J* = 7.0 Hz), 133.0, 132.9, 132.4, 131.9, 129.2, 128.1, 123.7 (C-P *J* = 3.1 Hz), 123.5, 123.4, 122.3 (C-P *J* = 11.7 Hz), 74.8, 61.8, 61.7, 52.1, 50.4, 39.9, 20.8, 20.6, 16.3 (C-P *J* = 6.9 Hz), 16.1 (C-P *J* = 7.2 Hz); MS (ES mass): 484.7 (M+1); HPLC: 97.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 6/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.44 min. Elemental analysis found C, 61.69; H, 6.05; N, 5.93; $C_{25}H_{29}N_2O_6P$ requires C, 61.98; H, 6.03; N, 5.78.

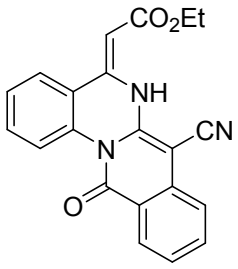
Typical procedure for preparation of (Z)-Methyl-2-(7-cyano-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4a)



A mixture of compound **1a** (50 mg, 0.12 mmol), K_2CO_3 (50 mg, 0.36 mmol), malononitrile (**2e**) (9.4 mg, 0.14 mmol) and CuI (2.3 mg, 0.012 mmol) in DMSO (2 mL) was heated to 85 °C under anhydrous conditions ($CaCl_2$ filled guard tube) for 4 h. After completion of the reaction, reaction mixture was cooled to RT, diluted with ethyl acetate (15 mL) and passed through celite. The resulting solution was washed with water (3 x 15 mL) followed by brine solution (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane to give desired compound **4a**.

Yield: 72% (30 mg); yellow solid; mp: 205-207 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2969, 2853, 2221, 1681, 1642; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.70 (s, 1H), 8.87 (d, *J* = 8.7 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.80-7.66 (m, 3H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.43-7.38 (m, 2H), 5.77 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 161.3, 144.0, 143.8, 134.7, 133.6, 132.9, 132.4, 129.1, 127.4, 125.7, 124.1, 122.5, 122.2, 121.2, 119.0, 115.4, 85.8, 71.3, 51.9; MS (ES mass): 341.5 (M-1); HPLC: 95.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.72 min.

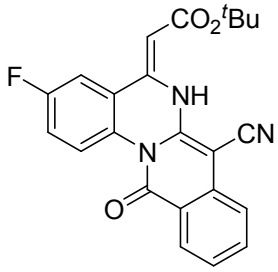
(Z)-Ethyl-2-(7-cyano-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4b)



Compound **4b** was synthesized from the reaction of **1b** and **2e** following a procedure similar to that of compound **4a**.

Yield: 71% (30 mg); yellow solid; mp: 214-216 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2972, 2855, 2214, 1676, 1638; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.75 (s, 1H), 8.86 (d, *J* = 8.7 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.73-7.68 (m, 2H), 7.61 (tb, *J* = 8.6, 1.4 Hz, 1H), 7.43-7.38 (m, 2H), 5.77 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 161.3, 144.1, 143.7, 134.7, 133.6, 132.9, 132.3, 129.1, 127.4, 125.7, 124.1, 122.5, 122.2, 121.2, 119.1, 115.4, 86.2, 71.2, 60.7, 14.4; MS (ES mass): 357.6 (M+1); HPLC: 93.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.24 min.

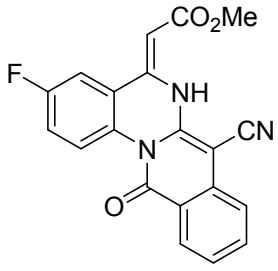
(Z)-^{t}Butyl-2-(7-cyano-3-fluoro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4c)



Compound **4c** was synthesized from the reaction of **1d** and **2e** following a procedure similar to that of compound **4a**.

Yield: 49% (23 mg); brown solid; mp: 175-177 °C; R_f = 0.7 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2958, 2854, 2221, 1698, 1643; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.75 (s, 1H), 8.89 (dd, *J* = 9.3, 4.9 Hz, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 7.75-7.68 (m, 2H), 7.41-7.38 (m, 2H), 7.34-7.27 (m, 1H), 5.63 (s, 1H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.3, 169.5, 161.7 (C-F *J* = 248.4 Hz), 161.3, 143.9, 142.0 (C-F *J* = 2.7 Hz), 134.8, 133.8, 129.0, 125.7, 124.8 (C-F *J* = 8.1 Hz), 122.5, 121.8 (C-F *J* = 8.1 Hz), 121.0, 119.3 (C-F *J* = 22.3 Hz), 115.2, 110.3 (C-F *J* = 14.2 Hz), 89.1, 81.7, 71.2, 28.3 (3C); MS (ES mass): 401.7 (M-1); HPLC: 90.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.79 min.

(Z)-Methyl-2-(7-cyano-3-fluoro-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4d)

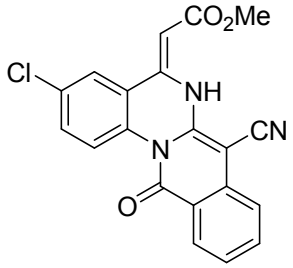


Compound **4d** was synthesized from the reaction of **1i** and **2e** following a procedure similar to that of compound **4a**.

Yield: 56% (23 mg); light yellow solid; mp: 172-174 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2963, 2845, 2216, 1692, 1645; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.69 (s, 1H), 8.96

(dd, *J* = 9.3, 5.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.80-7.65 (m, 2H), 7.47-7.39 (m, 2H), 7.35-7.33 (m, 1H), 5.70 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 168.2, 161.7 (C-F *J* = 258.9 Hz), 161.2, 143.6, 142.9 (C-F *J* = 2.7 Hz), 134.8, 133.4, 129.0, 125.8, 124.8 (C-F *J* = 8.0 Hz), 122.6, 121.2 (C-F *J* = 8.4 Hz), 121.1, 119.7 (C-F *J* = 22.2 Hz), 115.3, 110.4 (C-F *J* = 24.6 Hz), 86.6, 71.5, 52.1; MS (ES mass): 359.6 (M-1); HPLC: 92.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.42 min.

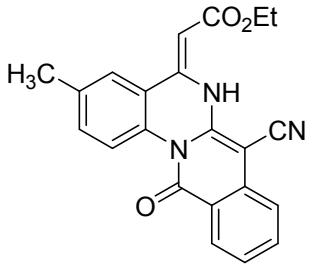
(Z)-Methyl-2-(3-chloro-7-cyano-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4e)



Compound **4e** was synthesized from the reaction of **1f** and **2e** following a procedure similar to that of compound **4a**.

Yield: 48% (20 mg); yellow solid; mp: 205-207 °C; R_f = 0.6 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2943, 2851, 2220, 1682, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.69 (s, 1H), 8.89 (d, *J* = 9.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.76-7.69 (m, 3H), 7.56 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 5.74 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 161.2, 143.6, 142.6, 134.9, 133.4, 133.2, 132.2, 131.5, 129.1, 125.9, 123.8, 123.7, 122.6, 121.1, 120.7, 115.2, 86.6, 71.7, 52.1; MS (ES mass): 375.4 (M-1); HPLC: 94.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.72 min. Elemental analysis found C, 63.39; H, 3.25; N, 11.33; $C_{20}H_{12}ClN_3O_3$ requires C, 63.59; H, 3.20; N, 11.12.

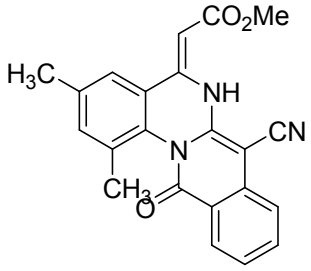
(Z)-Ethyl-2-(7-cyano-3-methyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4f)



Compound **4f** was synthesized from the reaction of **1g** and **2e** following a procedure similar to that of compound **4a**.

Yield: 65% (27 mg); brown solid; mp: 189-191 °C; R_f = 0.6 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2920, 2853, 2208, 1682, 1643; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.74 (s, 1H), 8.79 (d, *J* = 8.6 Hz, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.73-7.68 (m, 2H), 7.56 (s, 1H), 7.42-7.37 (m, 2H), 5.75 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 161.3, 143.9, 143.8, 137.5, 134.5, 133.6, 133.2, 128.9 (2C), 125.5, 124.1, 122.5, 122.0, 121.1, 118.8, 109.9, 85.9, 71.0, 60.6, 20.9, 14.4; MS (ES mass): 372.2 (M+1); HPLC: 91.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.65 min.

(Z)-Methyl-2-(7-cyano-1,3-dimethyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4g)

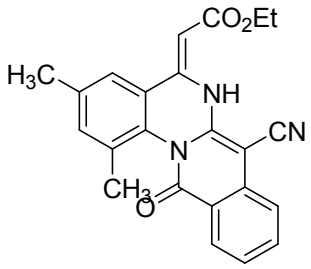


Compound **4g** was synthesized from the reaction of **1h** and **2e** following a procedure similar to that of compound **4a**.

Yield: 73% (31 mg); brown solid; mp: 178-180 °C; R_f = 0.6 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2931, 2855, 2212, 1679, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.37 (s, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.74-7.68 (m, 2H), 7.43-7.36 (m, 2H), 7.29 (s, 1H), 5.81 (s, 1H), 3.86 (s, 3H), 2.42

(s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 160.2, 145.7, 144.9, 137.3, 136.1, 134.4, 133.9, 132.7, 128.8, 128.4, 125.5, 122.8, 122.4, 122.2, 121.8, 115.5, 87.3, 70.5, 51.9, 21.5, 20.9; MS (ES mass): 371.7 (M+1); HPLC: 98.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.31 min.

(Z)-Ethyl-2-(7-cyano-1,3-dimethyl-12-oxo-6,12-dihydro-5*H*-isoquinolino[2,3-*a*]quinazolin-5-ylidene)acetate (4h)



Compound **4h** was synthesized from the reaction of **1j** and **2e** following a procedure similar to that of compound **4a**.

Yield: 72% (31 mg); light brown solid; mp: 188-190 °C; R_f = 0.5 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2935, 2843, 2209, 1672, 1644; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.41 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.74-7.68 (m, 2H), 7.42-7.36 (m, 2H), 7.29 (s, 1H), 5.81 (s, 1H), 4.33 (m, *J* = 7.0, 2.3 Hz, 2H), 2.41 (s, 3H), 2.15 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 160.2, 145.8, 144.8, 137.3, 136.1, 134.3, 134.0, 132.7, 128.7, 128.4, 125.5, 122.8, 122.5, 122.2, 121.8, 115.5, 87.8, 70.5, 60.7, 21.5, 20.9, 14.4; MS (ES mass): 385.7 (M+1); HPLC: 98.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.61 min. Elemental analysis found C, 71.39; H, 5.05; N, 11.01; $C_{23}H_{19}N_3O_3$ requires C, 71.67; H, 4.97; N, 10.90.

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Docking studies

The following molecular docking Simulation was done with Chemical Computing Group's Molecular Operating Environment (MOE) software 2008.10 Version, "DOCK" application Module. The compound **3e** and **3u** were docked in the PDE4B protein and their respective Docking scores and interactions were observed.

The following Dock scores were obtained after docking with PDE4B and PDE4D proteins:-

Table S-3:

	MOE Dock score (K.cal/mol)
Compounds	PDE4B
Rolipram	-24.61
3e	-23.05
3u	-22.05

Molecular docking studies of **3e** and **3u** were performed to define its binding mode in PDE4B isoform of Phosphodiesterases.

The purpose of Docking is to search for favorable binding configurations in macromolecular target, which is usually a protein. For each ligand, a number of configurations called *poses* are generated and scored in an effort to determine favorable binding modes.

The Dock workflow involves Conformational Analysis, Placement, scoring, and Force field method of Refinement.

Docking procedure: The PDE4B receptor in complex with Rolipram (PDB code-1XMY) was used for docking. The original PDB file contained crystallized Zn and Mn metal ions. The PDE Protein's were retrieved from PDB and Protonated (Addition of Hydrogen atoms) with Protonation 3D application in MOE, Connolly Molecular surface was generated around the ligand site of the protein, Gasteiger Partial charges was added to the protein and finally energy minimized to relieve bad crystallographic contacts. "Active site finder" function of the MOE software is used to denote potential docking pockets within the Protein crystal structure. Compounds **3e** and **3u** were placed in the Active site pocket of the protein by the "Triangle Matcher" Method, which generates poses by aligning the ligand triplet of atoms with the triplet of alpha spheres in cavities of tight atomic packing. The dock scoring was done with London dG method and then finally retaining and scoring the best 10 poses of molecules .The Preparation of the Ligands for Docking Simulation involves the Energy minimization with Molecular Mechanics Force-field MMFF94x (Merck Molecular Force Field 94×) and then molecules were subjected to conformational search in MOE using the Conformations Stochastic search module to find the lowest Energy Conformers.

The docking results were appeared as Docking Score in which the docking poses are ranked by the Molecular Mechanics and Generalized Born solvation model (MM/GBVI)_ binding free energy.

For all scoring functions, lower scores indicate more favorable poses. The unit for all scoring functions is k.cal/mol. The final energy was calculated using the Generalized Born solvation model. Poses for each ligand were scored based on complementarity with binding pocket.

The London dG scoring function estimates the free energy of binding of the ligand from a given pose. The functional form is a sum of terms:

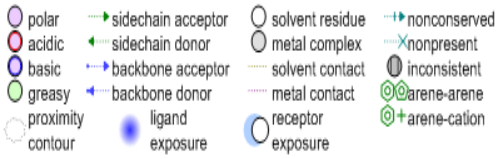
$$\Delta G = c + E_{flex} + \sum_{h-bonds} c_{HB} f_{HB} + \sum_{m-lig} c_M f_M + \sum_{atoms\ i} \Delta D_i$$

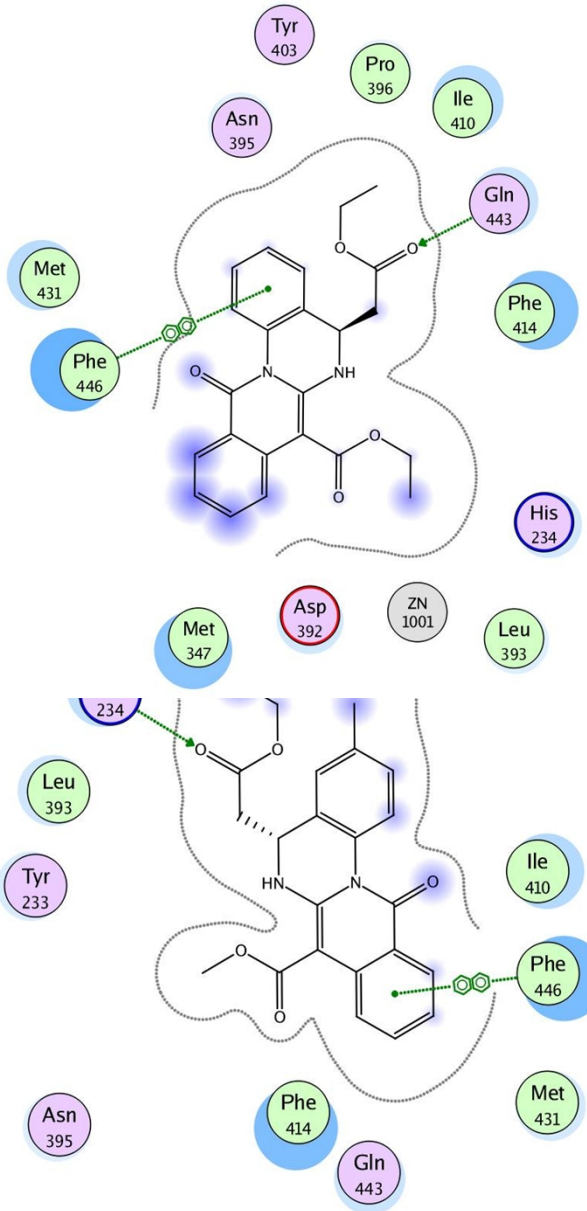
where c represents the average gain/loss of rotational and translational entropy; E_{flex} is the energy due to the loss of flexibility of the ligand (calculated from ligand topology only); f_{HB} measures geometric imperfections of hydrogen bonds and takes a value in [0,1]; c_{HB} is the energy of an ideal hydrogen bond; f_M measures geometric imperfections of metal ligations and takes a value in [0,1]; c_M is the energy of an ideal metal ligation; and D_i is the desolvation energy of atom i.

To validate the Docking accuracy of the program used, the native co-crystallized Rolipram ligand was docked back into its binding site of PDE4B Protein.

Protein-Molecular Interactions in Docking Pose

Fig S-1: Docking of **3e** into the PDE4B protien:-





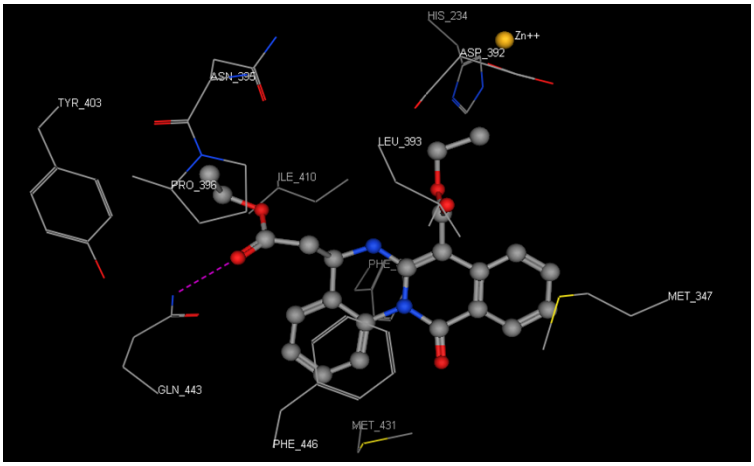


Fig S-2: Docking of **3u** into the PDE4B protien:-

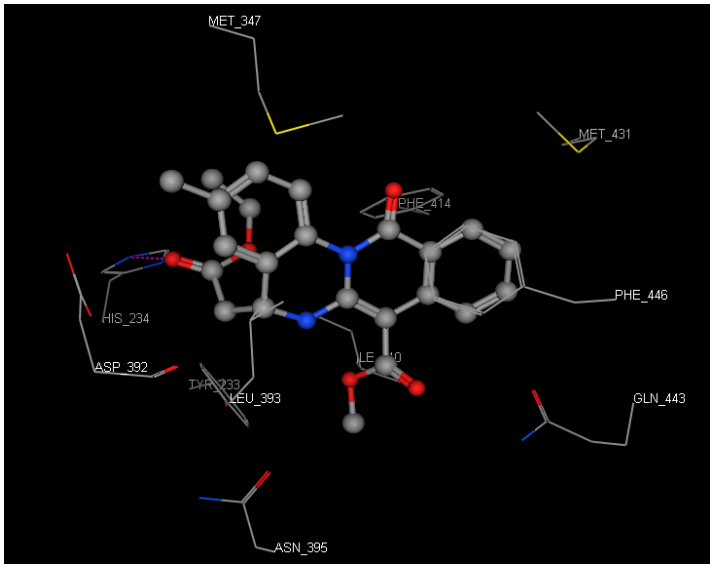
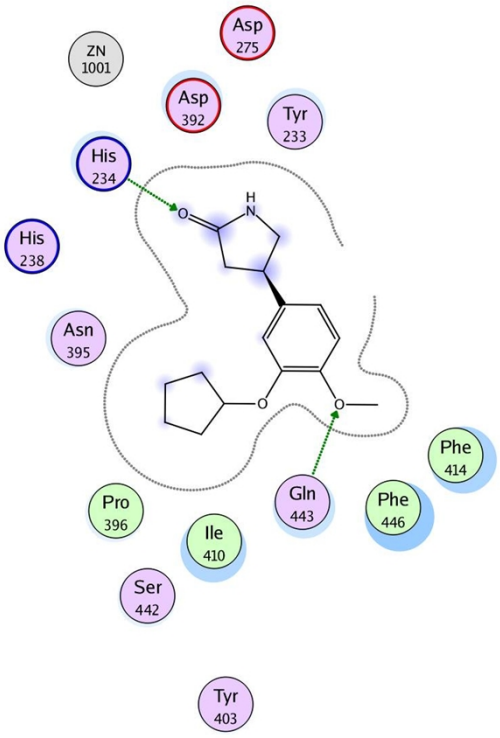
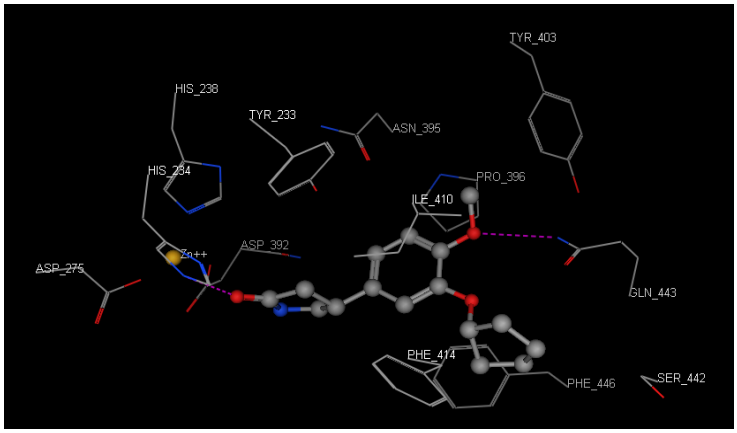


Fig S-3: Docking of Rolipram into PDE4B Protein:-





Molecular interactions Summary of top-ranked docking poses of 3e and 3u

Table S-4:

H-bond interactions

Compounds	PDE4B
Rolipram	His234, Gln443
3e	Gln443
3u	His234

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Pharmacology

PDE4B protein production and purification

PDE4B1 cDNA was sub-cloned into pFAST Bac HTB vector (Invitrogen) and transformed into DH10Bac (Invitrogen) competent cells. Recombinant bacmids were tested for integration by PCR analysis. Sf9 cells were transfected with bacmid using Lipofectamine 2000 (Invitrogen) according to manufacturer's instructions. Subsequently, P3 viral titer was amplified, cells were infected and 48 h post infection cells were lysed in lysis buffer (50 mM Tris-HCl pH 8.5, 10 mM 2-mercaptoethanol, 1 % protease inhibitor cocktail (Roche), 1 % NP40). Recombinant His-tagged PDE4B protein was purified as previously described elsewhere.[19a] Briefly, lysate was centrifuged at 10,000 rpm for 10 min at 4 ºC and supernatant was collected. Supernatant was mixed with Ni-NTA resin (GE Life Sciences) in a ratio of 4:1 (v/v) and equilibrated with binding buffer (20 mM Tris-HCl pH 8.0, 500 mM-KCl, 5 mM imidazole, 10 mM 2-mercaptoethanol and 10 % glycerol) in a ratio of 2:1 (v/v) and mixed gently on rotary shaker for 1 hour at 4 ºC. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4 ºC and the supernatant was collected as the flow-through fraction. Resin was washed twice with wash buffer (20 mM Tris-HCl pH 8.5, 1 M KCl, 10 mM 2-mercaptoethanol and 10% glycerol). Protein was eluted sequentially twice using elution buffers (Buffer I: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 250 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol, Buffer II: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 500 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol). Eluates were collected in four fractions and analyzed by SDS-PAGE. Eluates containing PDE4B protein were pooled and stored at -80 ºC in 50% glycerol until further use.

PDE4 enzymatic assay

The inhibition of PDE4 enzyme was measured using PDElight HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer's recommendations. Briefly, 10 ng of in house purified PDE4B1 or 0.5 ng commercially procured PDE4D2 enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 µM) for 1 hour. The reaction was halted with stop solution and reaction mix was incubated with detection reagent for 10 minutes in dark. Dose response studies were performed at 13 different concentrations ranging from 200 µM to 0.001 µM. Luminescence values (RLUs) were measured by a Multilabel Plate Reader (PerklinElmer 1420 Multilabel Counter). The percentage of inhibition was calculated using the following formula and the IC_{50} values were determined by a nonlinear regression analysis from dose response curve using Graphpad Prism software (San Diego, U.S.A). IC_{50} values are presented as mean ± SD.

$$\%\ inhibition = \frac{(RLU\ of\ vehicle\ control\ -\ RLU\ of\ inhibitior)}{RLU\ of\ vehicle\ control} X\ 100$$

Some of the synthesized compounds were tested for their PDE4B inhibitory potential *in vitro* at 30 μM using PDE4B enzyme and rolipram as a reference compound.

Table S-5. In vitro PDE4B inhibition by compound **3**.

S. No	Compound	%inhibition of PDE4B @ 30 µM
1	**3b**	70.61±0.75
2	**3e**	92.72±3.22
3	**3f**	86.45±2.19
4	**3i**	65.52±1.18
5	**3j**	66.20±3.18
6	**3k**	77.97±1.27
7	**3l**	42.47±3.13
8	**3o**	61.65±3.93
9	**3p**	62.30±0.53
10	**3r**	32.28±2.84

11	**3s**	59.16±0.68
12	**3t**	83.31±5.81
13	**3u**	92.90±3.54
14	**3w**	70.79±0.65 (16 μM)
15	**3x**	87.62±0.06

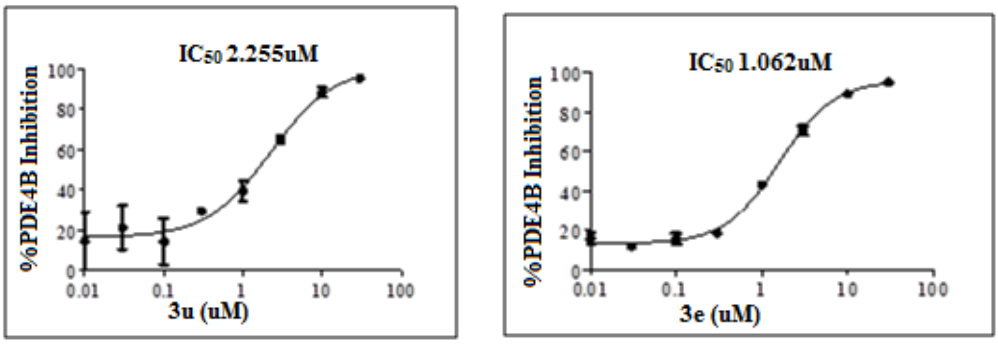

Figure S-4. Dose dependent inhibition of PDE4B by compounds **3u** and **3e**.