Design, Synthesis and Biological Evaluation of Novel Imidazo[1,2-*a*]pyridine Derivatives as Potent c-Met Inhibitors

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HPLC analysis data of all final compounds

Table S1. HPLC analysis data of all tested compounds. HPLC analysis was conducted according to different eluent. The retention time (t_R) is expressed in min at UV detection of 254 nM. HPLC analysis was performed on an Agilent Extend-C18 (4.6 × 150 mm, 5 μm) at 23 °C. Flow rate: 1 mL/min.

Equipment	Agilent 1260 with binary pump and photodiode array detector (DAD)	
Column	Agilent Extend-C18 (150×4.6 mm, 5 μm)	
Compound	Results	
	Retention time (min)	Relactive purity (%)
15a	2.596 [a]	> 99
15b	2.711 [a]	96.58
15c	2.729 [a]	97.13
15d	2.840 [a]	96.55
15e	2.030 [a]	95.92
15f	18.822 [b]	98.38
15g	2.266 [a]	98.99
15h	1.937 [a]	95.57
15i	9.982 [c]	97.10
16a	5.677 [a]	> 99
16b	19.977 [b]	98.32
16c	3.775 [a]	> 99
16d	3.543 [a]	96.98
16e	8.235 [a]	> 99
16f	3.940 [a]	> 99
16g	5.965 [a]	> 99
16h	7.845 [a]	95.40
22a	2.583 [a]	97.10
22b	2.920 [a]	> 99

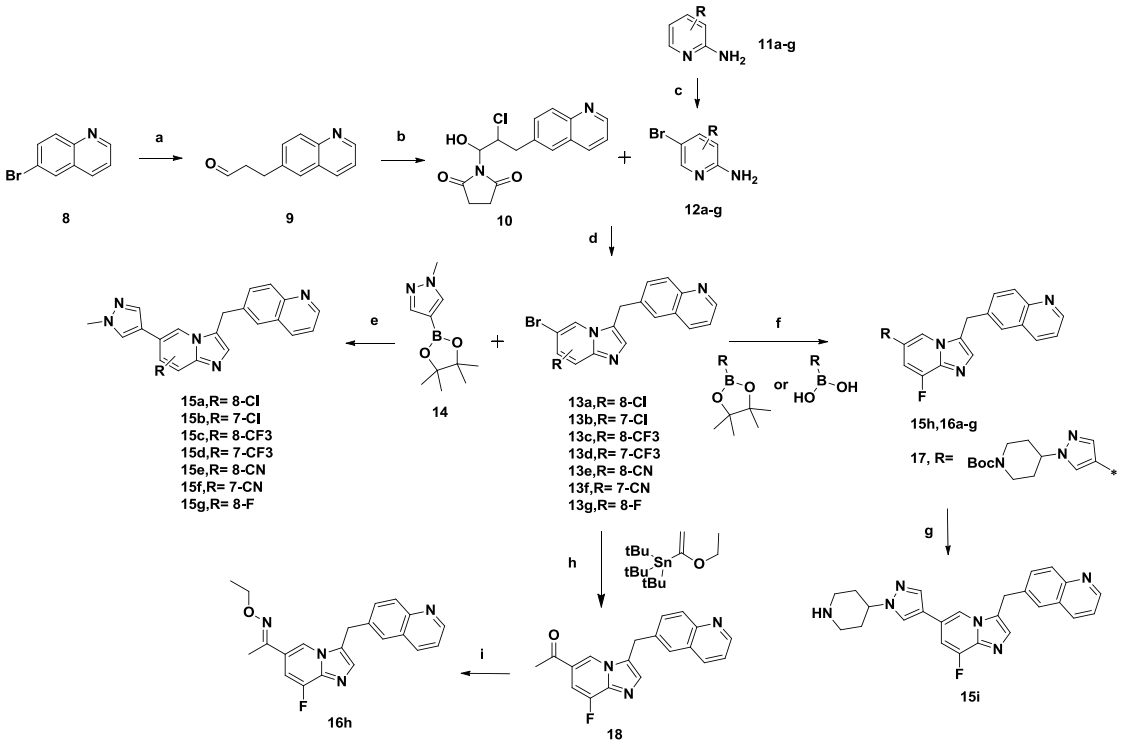
22c	2.448 [a]	> 99
22d	2.619 [a]	> 99
22e	2.408 [a]	> 99
22f	20.045 [b]	95.45
22g	2.557 [a]	98.48
22h	2.696 [a]	96.15
22i	12.009 [c]	> 99
22j	17.813 [b]	96.17
22k	18.197 [b]	95.66
22l	18.034 [b]	97.05
22m	2.884 [a]	> 99
22n	6.655 [a]	> 99
22o	2.760 [a]	95.75
33	1.960 [a]	95.72
42	2.989 [a]	> 99

[a] CH_3OH/H_2O (70/30, v/v); [b] solvent A: water (5 mM NH_4OAc, 0.1% HCOOH); solvent B: CH_3OH; gradient: 10−25%B (10 min), 25−70%B (15 min); [c] solvent A: water (5 mM NH_4OAc, 0.1% HCOOH); solvent B: MeCN; gradient: 3−25%B (10 min), 25−70%B (10 min), 70%B (5 min).

General information. The reagents (chemicals) were purchased and used without further purification. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker AMX-400 and AMX-300 NMR (IS as TMS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were given with electric, electrospray, and matrix-assisted laser desorption ionization (EI, ESI, and MALDI) produced by a Finnigan MAT-95, LCQ-DECA spectrometer and IonSpec 4.7 T.

Experimental Procedures and Compound Characterization Data

Scheme 1. Synthesis of Compounds 15a-15i, and 16a-h[a]



[a]Reagents and conditions: (a) 2-propene-1-ol, $Pd_2(dba)_3$, Tri-tert-butylphosphine tetrafluoroborate, *N,N′*-Dicyclohexylmethylamine,1,4-dioxane, rt, 24h; (b) NCS, *L*-Pro, $CHCl_3$, 0 ^{0}C-rt (c) NBS,CH_3CN,0 ^{0}C -rt; (d) EtOH, Ar, reflux; (e) $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, Na_2CO_3, DMF/H_2O (4:1), 80, overnight; (f) For **13g**, $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, Na_2CO_3, DMF/H_2O (4:1), 80 ^{0}C, overnight; (g) For

17, CH_2Cl_2/TFA (4:1), rt; (h) For **13g**, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Ar, 80 ^{0}C, overnight, then 3N HCl, rt; (i) *O*-ethylhydroxylamine hydrochloride, Et_3N, PH= 5-6, rt, overnight.

3-(Quinolin-6-yl)propanal (9). $Pd_2(dba)_3$ (333 mg, 0.36 mmol) and tri-tert-butyl-phosphoniumtetrafluoroborate (199 mg, 0.72 mmol) in a flask was evacuated and refilled with nitrogen (3 times). 1,4-Dioxane (30 mL) was added followed by consecutive addition of 6-bromoquinoline (5 g, 24.03 mmol) , 2-propen-1-ol (2.79 g, 48.06 mmol) and *N,N'*-Dicyclohexylmethylamine (6.18 mL, 28.84 mmol). The reaction vessel was evacuated and refilled with nitrogen (3 times). The reaction mixture was stirred at 30° C for 24 h. Diethyl ether (30 mL) was added to the reaction mixture and then filtered and washed with diethyl ether. The organic extract was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in hexanes (0-50%) to afford the desired product (2.2 g, 49.4 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.89–8.76 (m, 1H), 8.03 (dd, J = 13.1, 8.6 Hz, 2H), 7.61 – 7.48 (m, 2H), 7.40–7.28 (m, 1H), 3.10 (t, J = 7.4 Hz, 2H), 2.85 (t, J = 7.4 Hz, 2H); MS (ESI, m/z): 186.0 $[M+H]^+$.

1-(2-Chloro-1-hydroxy-3-(quinolin-6-yl)propyl)pyrrolidine-2,5-dione (10). To a solution of **9** (2.67 g, 14.42 mmol) in chloroform (5 mL) cooled at 0°C was added L-proline (332 mg, 2.88 mmol). To the mixture was then added N-chlorosuccinimide (2.02 g, 15.14 mmol) at 0° C. The reaction was warmed to r.t. and stirred overnight. Solid was filtered and was washed with chloroform to give the pure product (2 g, 43.53% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.90 (dd, J = 4.0, 2.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.65 (dd, J = 8.0, 2.0 Hz, 1H),

7.40 (dd, *J* = 8.4, 4.0 Hz, 1H), 5.46 (d, *J* = 9.4 Hz, 1H), 4.95 (ddd, *J* = 9.4, 8.0, 3.1 Hz, 1H), 3.73 (dd, *J* = 14.3, 3.1 Hz, 1H), 3.19 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.75 (s, 4H).

5-Bromo-3-chloropyridin-2-amine (12a). To the mixture of 3-chloropyridin-2-amine (10.0 g, 106 mmol) in acetonitrile (200 mL), was added NBS (22.6 g, 127 mmol) portionwise at 0 °C. The mixture was warmed to room temperature and stirred at room temperature for 2 h. Solvent was evaporated in vacuum. The residue was purified by silica gel column (PE/EA, 4/1) to afford 18 g (yield: 98%) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.9 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 4.91 (s, 2H); MS (ESI, m/z): 206.9 $[M+H]^+$, 208.9 $[M+H+2]^+$.

5-Bromo-4-chloropyridin-2-amine (12b). Compound **12b** was prepared in a similar manner as described for compound **12a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.63 (s, 1H), 4.53 (s, 2H); MS (ESI, m/z): 206.9 $[M+H]^+$, 208.9 $[M+H+2]^+$.

5-Bromo-3-(trifluoromethyl)pyridin-2-amine (12c). Compound **12c** was prepared in a similar manner as described for compound **12a**. ^{1}H NMR (400 MHz, CDCl3) δ 8.26 (s, 1H), 7.79 (d, J = 1.8 Hz, 1H), 5.02 (s, 2H); MS (ESI, m/z): 240.9 $[M+H]^+$, 242.9 $[M+H+2]^+$.

5-Bromo-4-(trifluoromethyl)pyridin-2-amine (12d). Compound **12d** was prepared in a similar manner as described for compound **12a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 6.78 (s, 1H), 4.74 (s, 2H).

2-Amino-5-bromonicotinonitrile (12e). Compound **12e** was prepared in a similar manner as described for compound **12a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 2.3 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 5.24 (s, 2H); MS (ESI, m/z): 197.9 $[M+H]^+$, 199.9 $[M+H+2]^+$.

2-Amino-5-bromoisonicotinonitrile (12f). Compound **12f** was prepared in a similar manner as described for compound **12a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 6.74 (s, 1H), 4.73 (s, 2H); MS (ESI, m/z): 198.0 $[M+H]^+$, 199.9 $[M+H+2]^+$.

5-Bromo-3-fluoropyridin-2-amine (12g). Compound **12g** was prepared in a similar manner as described for compound **12a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 1.4 Hz, 1H), 7.36 (dd, J = 9.8, 1.8 Hz, 1H), 4.65 (s, 2H); MS (ESI, m/z): 191.0 $[M+H]^+$, 192.9 $[M+H+2]^+$.

6-((6-Bromo-8-chloroimidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (13a). 1-(2-chloro-1-hydroxy-3-(quinolin-6-yl)propyl)pyrrolidine-2,5-dione **9** (500mg, 1.57 mmol) and 5-bromo-3-chloropyridin-2-amine **12a** (358 mg, 1.73 mmol) were dissolved in 20 mL of EtOH. The mixture was then heated to reflux for 36 h. The reaction solution was concentrated under reduced pressure and then the saturated sodium carbonate solution was added. The mixture was extracted with ethyl acetate (EA). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1/50) to afford compound **13a** as a yellow solid (340 mg, 58.13% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.86 (d, J = 4.1 Hz, 1H), 8.67

(s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.80 (s, 1H), 7.69 (d, *J* = 10.2 Hz, 2H), 7.55–7.47 (m, 2H), 4.56 (s, 2H); MS (ESI, m/z): 371.9 $[M+H]^+$, 373.9 $[M+H+2]^+$.

6-((6-Bromo-7-chloroimidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (13b). Compound **13b** was prepared in a similar manner as described for compound **13a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 3.0 Hz, 1H), 8.20–8.03 (m, 3H), 7.84 (s, 1H), 7.65–7.50 (m, 3H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.43 (s, 2H); MS (ESI, m/z): 371.9 $[M+H]^+$, 373.9 $[M+H+2]^+$.

6-((6-Bromo-8-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (13c). Compound **13c** was prepared in a similar manner as described for compound **13a**; MS (ESI, m/z): 405.9 $[M+H]^+$, 407.9 $[M+H+2]^+$.

6-((6-Bromo-7-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (13d). Compound **13d** was prepared in a similar manner as described for compound **13a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.19–8.02 (m, 4H), 7.72 (s, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.56 (s, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.47 (s, 2H).

6-Bromo-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (13e). Compound **13e** was prepared in a similar manner as described for compound **13a**. 1H NMR (400 MHz, DMSO) δ 9.02 (s, 1H), 8.86 (d, J = 4.0 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H), 8.22 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.80 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.61 (s, 1H), 7.51 (dd, J = 8.1, 4.1 Hz, 1H), 4.58 (s, 2H); MS (ESI, m/z): 363.0 $[M+H]^+$, 364.9 $[M+H+2]^+$.

6-Bromo-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridine-7-carbonitrile (13f). Compound **13f** was prepared in a similar manner as described for compound **13a**. ^{1}H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 8.2, 4.0 Hz, 1H), 4.59 (s, 2H); MS (ESI, m/z): 362.9 $[M+H]^+$, 365.0 $[M+H+2]^+$.

6-((6-Bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (13g). Compound **13g** was prepared in a similar manner as described for compound **13a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 3.2 Hz, 1H), 8.09 (t, J = 9.3 Hz, 2H), 7.77 (s, 1H), 7.59 (dd, J = 8.6, 2.0 Hz, 1H), 7.54 (s, 2H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.02 (dd, J = 9.5, 1.5 Hz, 1H), 4.42 (s, 2H); MS (ESI, m/z): 355.9 $[M+H]^+$, 358.0 $[M+H+2]^+$.

6-((8-Chloro-6-(1-methyl-1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (15a). To a solution of 6-((6-bromo-8-chloroimidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone **12a** (250 mg, 0.67 mmol) and 1-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (195 mg, 0.94 mmol) in 5.36 mL of DMF was added 1.34 mL of sodium carbonate (1 M) solution , followed by $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ (55 mg, 0.067 mmol). The resulting reaction medium was evacuated and refilled with argon three times. Then the reaction medium was heated at 80°C for 16 h and was extracted with EA. After washing with brine, the solution was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$,

1/50) to afford compound **15a** (130 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, J = 4.2, 1.7 Hz, 1H), 8.07 (dd, J = 16.7, 8.5 Hz, 2H), 7.76 (d, J = 1.4 Hz, 1H), 7.62 (dd, J = 8.7, 2.0 Hz, 1H), 7.57 (s, 1H), 7.54 (s, 2H), 7.46 (s, 1H), 7.42–7.34 (m, 2H), 4.46 (s, 2H), 3.90 (s, 3H); MS (ESI, m/z): 374.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{21}H_{17}N_5Cl$ ($[M+H]^+$): 374.1172; found: 374.1164.

6-((7-Chloro-6-(1-methyl-1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (15b). Compound **15b** was prepared in a similar manner as described for compound **15a**. Yield: 45%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.08 (t, J = 8.3 Hz, 2H), 7.85 (s, 1H), 7.78 (s, 1H), 7.57 (dd, J = 13.4, 7.9 Hz, 4H), 7.48 (s, 1H), 7.41 (dd, J = 8.4, 4.0 Hz, 1H), 4.45 (s, 2H), 3.93 (s, 3H); MS (ESI, m/z): 374.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{21}H_{17}N_5Cl$ ($[M+H]^+$): 374.1172; found: 374.1169.

6-((6-(1-Methyl-1*H*-pyrazol-4-yl)-8-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (15c). Compound **15c** was prepared in a similar manner as described for compound **15a**. Yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 4.1, 1H), 8.11 (dd, J = 17.7, 8.5 Hz, 2H), 7.96 (s, 1H), 7.69–7.59 (m, 3H), 7.57 (s, 2H), 7.50 (s, 1H), 7.42 (dd, J = 8.3 Hz, 4.4, 1H), 4.50 (s, 2H), 3.92 (s, 3H); MS (ESI, m/z): 408.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{22}H_{17}N_5F_3$ ($[M+H]^+$): 408.1436; found: 408.1425.

6-((6-(1-Methyl-1*H*-pyrazol-4-yl)-7-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (15d). Compound **15d** was prepared in a similar manner as described for compound **15a**. Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, J

= 4.2, 1.6, 1H), 8.17 (s, 1H), 8.09 (t, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 16.7 Hz, 2H), 7.62–7.54 (m, 2H), 7.46–7.39 (m, 2H), 7.37 (s, 1H), 4.46 (s, 2H), 3.92 (s, 3H); MS (ESI, m/z): 408.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{22}H_{17}N_5F_3$ ($[M+H]^+$): 408.1436; found: 408.1448.

6-(1-Methyl-1*H*-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (15e). Compound **15e** was prepared in a similar manner as described for compound **15a**. Yield: 63%; ^{1}H NMR (400 MHz, DMSO) δ 8.89 (d, *J* = 1.5 Hz, 1H), 8.85 (dd, *J* = 4.1 Hz, 1.6, 1H), 8.34–8.28 (m, 2H), 8.27 (s, 1H), 7.99 (d, *J* = 10.4 Hz, 2H), 7.86 (s, 1H), 7.74 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.55–7.47 (m, 3H), 4.61 (s, 2H), 3.86 (s, 3H); MS (ESI, m/z): 365.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{22}H_{17}N_6$ ($[M+H]^+$): 365.1515; found: 365.1524.

6-(1-Methyl-1*H*-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridine-7-carbonitrile (15f). Compound **15f** was prepared in a similar manner as described for compound **15a**. Yield: 50%; ^{1}H NMR (400 MHz, DMSO) δ 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.58 (s, 1H), 8.44 (s, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 8.12 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.74–7.69 (m, 2H), 7.50 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.62 (s, 2H), 3.91 (s, 3H); MS (ESI, m/z): 365.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{22}H_{17}N_6$ ($[M+H]^+$): 365.1515; found: 365.1508.

6-((8-Fluoro-6-(1-methyl-1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (15g). Compound **15g** was prepared in a similar manner as described for compound **15a**. Yield: 66%; ^{1}H NMR (400 MHz, DMSO) δ 9.19 (d, *J* = 4.4, 1H),

8.90–8.80 (m, 2H), 8.38 (s, 1H), 8.19 (dd, *J* = 19.1, 9.6 Hz, 3H), 8.12–8.03 (m, 2H), 8.00 (s, 1H), 7.92 (dd, *J* = 8.1, 5.0 Hz, 1H), 4.77 (s, 2H), 3.88 (s, 3H); MS (ESI, m/z): 358.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{21}H_{17}N_5F$ ($[M+H]^+$): 358.1468; found: 358.1461.

2-(4-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-1*H*-pyrazol-1-yl)ethanol (15h). Compound **15h** was prepared in a similar manner as described for compound **15a**. Yield: 46%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (d, *J* = 4.2 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.17 (s, 1H), 8.03–7.94 (m, 2H), 7.79 (d, *J* = 6.6 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.47 (dd, *J* = 6.9, 4.3 Hz, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 11.7 Hz, 1H), 4.52 (s, 2H), 4.22 (t, *J* = 5.2 Hz, 2H), 3.88 (t, *J* = 5.3 Hz, 2H); MS (ESI, m/z): 388.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{22}H_{19}N_5OF$ ($[M+H]^+$): 388.1574; found: 388.1564.

6-((8-Fluoro-6-(thiophen-3-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (16a). Compound **16a** was prepared in a similar manner as described for compound **15a**. Yield: 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 4.2 Hz, 1.6, 1H), 8.11 (dd, *J* = 13.8, 8.4 Hz, 2H), 7.84 (d, *J* = 1.0 Hz, 1H), 7.66 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 7.42 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.28 (d, *J* = 1.0 Hz, 1H), 7.14 (ddd, *J* = 7.3, 4.7, 1.2 Hz, 2H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.48 (s, 2H); MS (ESI, m/z): 360.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{21}H_{15}N_3FS$ ($[M+H]^+$): 360.0971; found: 360.0962.

5-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)picolinonitrile

(16b). Compound **16b** was prepared in a similar manner as described for compound **15a**. Yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, J = 4.2, 1.5 Hz, 1H), 8.75 (d, J = 2.2 Hz, 1H), 8.14–8.05 (m, 2H), 7.88–7.80 (m, 2H), 7.73 (d, J = 8.1 Hz, 1H), 7.67–7.56 (m, 3H), 7.42 (dd, J = 8.3, 4.3 Hz, 1H), 7.11 (dd, J = 10.7, 1.2 Hz, 1H), 4.53 (s, 2H); MS (ESI, m/z): 380.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{23}H_{15}N_5F$ ($[M+H]^+$): 380.1311; found: 380.1302.

4-(5-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)pyridin-2-yl) morpholine (16c). Compound **16c** was prepared in a similar manner as described for compound **15a**. Yield: 42%; ^{1}H NMR (400 MHz, DMSO) δ 8.89–8.82 (m, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.44 (s, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.91 (dd, J = 8.8, 2.4 Hz, 1H), 7.86 (s, 1H), 7.73 (dd, J = 8.6, 1.7 Hz, 1H), 7.61–7.45 (m, 3H), 6.93 (d, J = 8.9 Hz, 1H), 4.62 (s, 2H), 3.77–3.64 (m, 4H), 3.56–3.43 (m, 4H); MS (ESI, m/z): 440.4 $[M+H]^+$; HRMS (ESI) cacld for $C_{26}H_{23}N_5OF$ ($[M+H]^+$): 440.1887; found: 440.1884.

3-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzonitrile (16d). Compound **16d** was prepared in a similar manner as described for compound **15a**. Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, J = 4.2, 1.7 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 1.4 Hz, 1H), 7.70–7.57 (m, 6H), 7.53 (t, J = 7.8 Hz, 1H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 7.12 (dd, J = 11.0, 1.4 Hz, 1H), 4.53 (s, 2H); MS (ESI, m/z): 378.8 $[M]^+$; HRMS (ESI) cacld for $C_{24}H_{16}N_4F$ ($[M+H]^+$): 379.1359; found: 379.1369.

6-((6-(3,5-Difluorophenyl)-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)methyl)quinolone (16e). Compound **16e** was prepared in a similar manner as described for compound **15a**. Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 3.0 Hz, 1H), 8.12 (dd, J = 14.7, 8.5 Hz, 2H), 7.79 (s, 1H), 7.67–7.57 (m, 3H), 7.43 (dd, J = 8.3, 4.3 Hz, 1H), 7.11 (dd, J = 11.0, 1.2 Hz, 1H), 6.94–6.85 (m, 2H), 6.81 (tt, J = 8.7, 2.2 Hz, 1H), 4.51 (s, 2H); MS (ESI, m/z): 390.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{23}H_{15}N_3F_3$ ($[M+H]^+$): 390.1218; found: 390.1212.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzonitrile (16f). Compound **16f** was prepared in a similar manner as described for compound **15a**. Yield: 68%; ^{1}H NMR (400 MHz, DMSO) δ 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.78 (t, J = 4.9 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.07-7.98 (m, 3H), 7.91–7.83 (m, 2H), 7.77–7.70 (m, 2H), 7.49 (dd, J = 7.4, 3.3 Hz, 2H), 4.66 (s, 2H); MS (ESI, m/z): 397.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{24}H_{15}N_4F_2$ ($[M+H]^+$): 397.1265; found: 397.1254.

6-((8-Fluoro-6-(3-fluoro-4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl) quinolone (16g). Compound **16g** was prepared in a similar manner as described for compound **15a**. Yield: 60%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, J = 3.6 Hz, 1H), 8.16–8.05 (m, 2H), 7.71 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.57 (s, 2H), 7.41 (dd, J = 8.1, 4.0 Hz, 1H), 7.10 (dd, J = 11.2, 7.6 Hz, 3H), 6.97 (t, J = 8.5 Hz, 1H), 4.49 (s, 2H), 3.90 (s, 3H); MS (ESI, m/z): 402.4 $[M+H]^+$; HRMS (ESI) cacld for $C_{24}H_{18}N_3OF_2$ ($[M+H]^+$): 402.1418; found: 402.1425.

***tert*-Butyl 4-(4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (17)**. Compound **17** was prepared in a similar manner as described for compound **15a.** Yield: 53%; ^{1}H NMR (400 MHz, DMSO) δ 8.88–8.82 (m, 1H), 8.47 (s, 1H), 8.35 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.99 (t, *J* = 4.3 Hz, 2H), 7.89 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 12.3 Hz, 2H), 7.42 (s, 1H), 4.56 (s, 2H), 4.35 (t, *J* = 11.4 Hz, 1H), 4.04 (d, *J* = 7.1 Hz, 2H), 2.92 (s, 2H), 2.01 (t, *J* = 12.1 Hz, 2H), 1.76 (qd, *J* = 12.1, 4.1 Hz, 2H), 1.41 (d, *J* = 1.5 Hz, 9H).

6-((8-Fluoro-6-(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl) methyl)quinolone (15i). To the solution of **17** (100 mg, 0.19 mmol) in 10 mL of CH_2Cl_2 was added 2 mL of TFA. The resulting medium was stirred at room temperature for 1 h. After concentration, the residue was dissolved in CH_2Cl_2/MeOH (10:1). The solution was neutralized with saturated $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compound **15i** (65 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO) δ 8.87 (d, *J* = 2.8 Hz, 1H), 8.52 (s, 2H), 8.34 (s, 2H), 8.05 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.89 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.62-7.46 (m, 3H), 4.59 (s, 2H), 4.54-4.44 (m, 1H), 3.55-3.35 (m, 2H), 3.11 (d, *J* = 10.5 Hz, 3H), 2.27-2.17 (m, 2H), 2.16-2.05 (m, 2H); MS (ESI, m/z): 427.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{25}H_{24}N_6F$ ($[M+H]^+$): 427.2046; found: 427.2055.

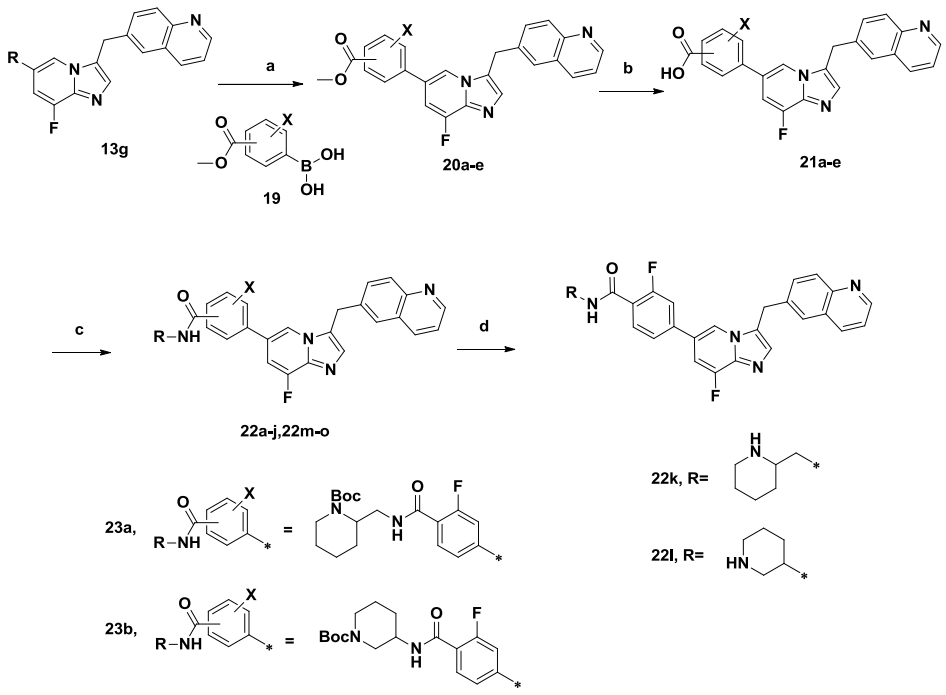
1-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)ethanone (18). A flask was charged with **13g** (658 mg, 1.85 mmol),

tributyl-(1-ethoxy-vinyl)-stannane (1 g, 2.77 mmol), $Pd(PPh_3)_2Cl_2$ (130 mg, 0.18 mmol) and 15 mL of 1,4-dioxane. The resulting reaction medium was evacuated and refilled with argon three times. The temperature was increased to 100 °C and stirred overnight. The reaction mixture was then cooled to room temperature, 5 mL of 3N HCl was added and the mixture was stirred for additional 2 h. Saturated $NaHCO_3$ was added and the product was extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EA to 3%MeOH in EA) to afford compound **18** as a yellow solid (509 mg, 86% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.94 (s, 1H), 8.86 (s, 1H), 8.30 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.57 (s, 1H), 7.53–7.42 (m, 2H), 4.67 (s, 2H), 2.58 (s, 3H); MS (ESI, m/z): 320.0 $[M+H]^+$.

(*E*)-1-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)ethanone *O*-ethyl oxime (16h). To a solution of **18** (50 mg, 0.16 mmol) in methanol (10 mL) was added *O*-ethylhydroxylamine hydrochloride (46 mg, 0.47 mmol). Triethyl amine was added dropwise to adjust the pH to 5-6. The reaction mixture was stirred at rt overnight. The solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to afford 30 mg (53%) of the title compound as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (dd, J = 11.3, 9.4 Hz, 2H), 7.76 (d, J = 1.4 Hz, 1H), 7.62 (dd, J = 8.7, 1.9 Hz, 1H), 7.55 (d, J = 14.6 Hz, 2H), 7.44–7.36 (m, 2H), 4.46 (s, 2H), 4.20 (q, J = 7.1

Hz, 2H), 2.04 (d, *J* = 1.3 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); MS (ESI, m/z): 363.2 $[M+H]^+$; HRMS (ESI) cacld for $C_{21}H_{20}N_4OF$ ($[M+H]^+$): 363.1621; found: 363.1635

Scheme 2. Synthesis of Compounds 22a-22o[a]



[a]Reagents and conditions: (a) $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$, Na_2CO_3, DMF/H_2O (4:1), 80^0C, overnight; (b) $LiOH \cdot H_2O$, MeOH/THF/H_2O (2:1:1), rt; (c) HATU, DIPEA, DMF, 0 ^{0}C -rt; (d) For **23a** and **23b**, CH_2Cl_2/TFA (4:1), rt.

Methyl 3-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoate (20a). Compound **20a** was prepared in a similar manner as described for compound **15a.** Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09–7.99 (m, 3H), 7.99–7.91 (m, 1H), 7.81 (d, *J* = 1.3 Hz, 1H), 7.60–7.53 (m, 2H), 7.53–7.46 (m, 2H), 7.41 (ddd, *J* = 7.7, 3.2, 0.9 Hz, 1H), 7.33 (ddd, *J* = 8.1, 4.2, 1.6 Hz, 1H), 7.10 (dd, *J* = 11.2, 1.4 Hz, 1H), 4.43 (s, 2H), 3.92–3.79 (m, 3H).

Methyl 2-fluoro-5-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoate (20b). Compound **20b** was prepared in a similar manner as described for compound **15a.** Yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92–8.85 (m, 1H), 8.07 (t, J = 9.3 Hz, 2H), 7.96 (dd, J = 6.6, 2.5 Hz, 1H), 7.77 (s, 1H), 7.65–7.59 (m, 1H), 7.57 (d, J = 5.0 Hz, 2H), 7.50 (ddd, J = 8.5, 4.3, 2.6 Hz, 1H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H), 7.21–7.13 (m, 1H), 7.10 (d, J = 11.1 Hz, 1H), 4.49 (s, 2H), 3.92 (s, 3H); MS (ESI, m/z): 430.0 $[M+H]^+$.

Methyl 2-chloro-5-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoate (20c). Compound **20c** was prepared in a similar manner as described for compound **15a.** Yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (dd, J = 4.3, 1.7 Hz, 1H), 8.12 (dd, J = 15.8, 8.2 Hz, 2H), 7.84 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 1.4 Hz, 1H), 7.65 (dd, J = 8.7, 2.0 Hz, 1H), 7.59 (s, 2H), 7.49 (d, J = 8.3 Hz, 1H), 7.42 (ddd, J = 8.4, 6.5, 3.3 Hz, 2H), 7.12 (dd, J = 11.0, 1.4 Hz, 1H), 4.50 (s, 2H), 3.93 (s, 3H).

Methyl 4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-2-methoxybenzoate (20d). Compound **20d** was prepared in a similar manner as described for compound **15a.** Yield: 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95–8.88 (m, 1H), 8.13 (dd, J = 17.3, 8.3 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.67–7.58 (m, 3H), 7.44 (dd, J = 8.3, 4.3 Hz, 1H), 7.14 (d, J = 10.6 Hz, 1H), 7.00–6.95 (m, 1H), 6.78 (s, 1H), 4.53 (s, 2H), 3.89 (s, 3H), 3.76 (s, 3H).

Methyl 2-fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoate (20e). Compound **20e** was prepared in a similar manner as described for compound **15a.** Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94–8.87 (m, 1H), 8.08 (t, J = 9.3 Hz, 2H), 7.96 (t, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.64–7.57 (m, 3H), 7.40 (dd, J = 8.2, 4.2 Hz, 1H), 7.21 (dd, J = 8.2, 1.6 Hz, 1H), 7.18–7.11 (m, 2H), 4.50 (s, 2H), 3.93 (s, 3H); MS (ESI, m/z): 430.0 $[M+H]^+$.

3-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoic acid (21a). **20a** (200 mg, 0.49 mmol) was suspended in 8 mL of MeOH/THF/H_2O (2:1:1). To this suspension was added $LiOH{\cdot}H_2O$ (102 mg, 2.43 mmol). The resulting mixture was stirred at room temperature for 10 h. After concentration, the residue was acidified to PH 2–3 by adding concentrated HCl. The precipitate was filtered and dried to afford **21a** as a yellow solid (150 mg, 78% yield). MS (ESI, m/z): 396.1 $[M-H]^-$.

2-Fluoro-5-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoic acid (21b). Compound **21b** was prepared in a similar manner as described for compound **21a**. Yield: 80%; MS (ESI, m/z): 414.1 $[M-H]^-$.

2-Chloro-5-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoic acid (21c). Compound **21c** was prepared in a similar manner as described for compound **21a**. Yield: 76%; MS (ESI, m/z): 430.1 $[M-H]^-$.

4-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-2-methoxybenz

oic acid (21d). Compound **21d** was prepared in a similar manner as described for compound **21a**. Yield: 83%; MS (ESI, m/z): 426.1 $[M-H]^-$.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzoi c acid (21e). Compound **21e** was prepared in a similar manner as described for compound **21a**. Yield: 79%; MS (ESI, m/z): 414.1 $[M-H]^-$.

3-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-methylbenza mide (22a). **21a** (100 mg, 0.25 mmol) was dissolved in 5 mL of DMF and the solution was cooled in an ice bath. To the solution was successively added HATU (105 mg, 0.28 mmol), DIPEA (50 μL, 0.3 mmol) and methylamine (150 μL, 0.3 mmol, 2M in THF). The resulting medium was stirred at room temperature for 1h and quenched with 2 mL of saturated $NaHCO_3$. The mixture was extracted with 50 mL of EA. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1/20) to afford the desired product **22a** (72 mg, 70% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 4.2, 1.6 Hz, 1H), 8.09 (dd, J = 8.0, 4.1 Hz, 2H), 7.92–7.82 (m, 2H), 7.70 (d, J = 7.3 Hz, 1H), 7.65–7.57 (m, 2H), 7.53 (s, 1H), 7.51–7.43 (m, 2H), 7.42–7.37 (m, 1H), 7.16–7.10 (m, 1H), 6.45 (s, 1H), 4.48 (s, 2H), 3.02 (d, J = 4.8 Hz, 3H); MS (ESI, m/z): 411.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{25}H_{20}N_4OF$ ($[M+H]^+$): 411.1621; found: 411.1611.

2-Fluoro-5-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-met hylbenzamide (22b). Compound **22b** was prepared in a similar manner as described

for compound **22a**. Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89–8.83 (m, 1H), 8.06 (t, J = 8.0 Hz, 2H), 7.95–7.87 (m, 2H), 7.81–7.74 (m, 1H), 7.58 (d, J = 6.4 Hz, 2H), 7.49 (s, 1H), 7.38 (dd, J = 8.3, 4.3 Hz, 1H), 7.17–7.06 (m, 2H), 7.03 (d, J = 11.2 Hz, 1H), 4.44 (s, 2H), 2.99 (d, J = 4.7 Hz, 3H); MS (ESI, m/z): 429.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{25}H_{19}N_4OF_2$ ($[M+H]^+$): 429.1527; found: 429.1533.

2-Chloro-5-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-methylbenzamide (22c). Compound **22c** was prepared in a similar manner as described for compound **22a**. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 2.8 Hz, 1H), 8.12 (d, J = 8.6 Hz, 2H), 7.80 (s, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.66–7.57 (m, 2H), 7.54 (s, 1H), 7.42 (dd, J = 8.3, 4.2 Hz, 2H), 7.34 (dd, J = 8.4, 2.3 Hz, 1H), 7.09 (d, J = 11.0 Hz, 1H), 6.43 (s, 1H), 4.48 (s, 2H), 3.04 (d, J = 4.9 Hz, 3H); MS (ESI, m/z): 445.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{25}H_{18}N_4ONaClF$ ($[M+Na]^+$): 467.1051; found: 467.1061.

4-(8-Fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-2-methoxy-*N*-methylbenzamide (22d). Compound **22d** was prepared in a similar manner as described for compound **22a**. Yield: 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, J = 4.3, 1.7 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.12 (t, J = 9.5 Hz, 2H), 7.75 (dd, J = 9.6, 2.8 Hz, 2H), 7.63 (dd, J = 11.2, 3.8 Hz, 3H), 7.43 (dd, J = 8.3, 4.3 Hz, 1H), 7.14 (dd, J = 11.1, 1.3 Hz, 1H), 7.07 (dd, J = 8.1, 1.7 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 4.52 (s, 2H), 3.82 (s, 3H), 3.00 (d, J = 4.8 Hz, 3H); MS (ESI, m/z): 441.4 $[M+H]^+$; HRMS (ESI) cacld for $C_{26}H_{22}N_4O_2F$ ($[M+H]^+$): 441.1727; found: 441.1721.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-methylbenzamide (22e). Compound **22e** was prepared in a similar manner as described for compound **22a**. Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99–8.81 (m, 1H), 8.15–8.03 (m, 3H), 7.83 (s, 1H), 7.59 (t, *J* = 8.3 Hz, 3H), 7.40 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.25 (dd, *J* = 7.4, 2.4 Hz, 1H), 7.12 (d, *J* = 11.3 Hz, 2H), 6.76 (d, *J* = 7.2 Hz, 1H), 4.49 (s, 2H), 3.03 (d, *J* = 4.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.36, 160.86 (d, *J* = 248.0 Hz), 151.77 (d, *J* = 255.4 Hz), 150.68, 147.60, 141.71 (d, *J* = 9.3 Hz), 137.84 (d, *J* = 28.4 Hz), 135.82, 134.38, 134.01, 133.12 (d, *J* = 2.7 Hz), 130.47, 130.22, 128.47, 126.72, 124.81, 124.36 (d, *J* = 6.6 Hz), 123.07 (d, *J* = 2.4 Hz), 121.79, 120.55 (d, *J* = 12.1 Hz), 117.41 (d, *J* = 4.4 Hz), 114.39 (d, *J* = 26.6 Hz), 106.84 (d, *J* = 17.5 Hz), 30.58, 26.99; MS (ESI, m/z): 429.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{25}H_{19}N_4OF_2$ ($[M+H]^+$): 429.1527; found: 429.1530.

(2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)phenyl)(2-oxa-6-azaspiro[3.4]octan-6-yl)methanone (22f). Compound **22f** was prepared in a similar manner as described for compound **22a**. Yield: 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, *J* = 4.3 Hz, 1H), 8.19 (dd, *J* = 17.6, 8.4 Hz, 2H), 7.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72–7.58 (m, 3H), 7.51–7.42 (m, 2H), 7.22 (td, *J* = 7.7, 1.6 Hz, 1H), 7.17–7.08 (m, 2H), 4.75 (d, *J* = 6.2 Hz, 1H), 4.61 (d, *J* = 6.2 Hz, 2H), 4.51 (d, *J* = 6.4 Hz, 3H), 3.88 (s, 1H), 3.67 (t, *J* = 7.3 Hz, 1H), 3.59 (s, 1H), 3.37 (t, *J* = 6.9 Hz, 1H), 2.30–2.19 (m, 2H); MS (ESI, m/z): 511.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{30}H_{25}N_4O_2F_2$ ($[M+H]^+$): 511.1946; found: 511.1939.

(2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)phenyl)(4-methylpiperazin-1-yl)methanone (22g). Compound **22g** was prepared in a similar manner as described for compound **22a**. Yield: 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, J = 4.2, 1.5 Hz, 1H), 8.08 (t, J = 9.0 Hz, 2H), 7.78 (d, J = 1.4 Hz, 1H), 7.61 (dd, J = 12.0, 2.8 Hz, 3H), 7.45–7.37 (m, 2H), 7.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.14–7.07 (m, 2H), 4.50 (s, 2H), 3.82 (s, 2H), 3.36 (s, 2H), 2.50 (t, J = 4.9 Hz, 2H), 2.37 (s, 2H), 2.33 (s, 3H); MS (ESI, m/z): 498.4 $[M+H]^+$; HRMS (ESI) cacld for $C_{29}H_{26}N_5OF_2$ ($[M+H]^+$): 498.2105; found: 498.2106.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-(2-morpholinoethyl)benzamide (22h). Compound **22h** was prepared in a similar manner as described for compound **22a**. Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92–8.86 (m, 1H), 8.09 (dd, J = 19.4, 9.1 Hz, 3H), 7.83 (s, 1H), 7.65–7.56 (m, 3H), 7.47–7.36 (m, 2H), 7.26 (dd, J = 5.8, 2.4 Hz, 1H), 7.18–7.09 (m, 2H), 4.50 (s, 2H), 3.80–3.64 (m, 4H), 3.57 (d, J = 5.2 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.51 (s, 4H); MS (ESI, m/z): 528.2 $[M+H]^+$; HRMS (ESI) cacld for $C_{30}H_{28}N_5O_2F_2$ ($[M+H]^+$): 528.2211; found: 528.2212.

***N*-(2-(Dimethylamino)ethyl)-2-fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzamide (22i)**. Compound **22i** was prepared in a similar manner as described for compound **22a**. Yield: 55%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (dd, J = 4.3, 1.6 Hz, 1H), 8.36 (s, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.83 (dd, J = 14.8, 6.3 Hz, 2H), 7.75 (dd, J = 8.8, 1.8 Hz, 1H), 7.54–7.44 (m, 5H), 4.63 (s, 2H), 3.58 (d, J = 5.7 Hz, 2H), 2.72 (d, J = 18.2 Hz, 2H), 2.43 (d, J = 14.9

Hz, 6H); MS (ESI, m/z): 486.2 $[M+H]^+$; HRMS (ESI) cacld for $C_{28}H_{26}N_5OF_2$ ($[M+H]^+$): 486.2105; found: 486.2112.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-(3-(pyrrolidin-1-yl)propyl)benzamide (22j). Compound **22j** was prepared in a similar manner as described for compound **22a**. Yield: 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13–7.99 (m, 3H), 7.91 (s, 1H), 7.83 (d, *J* = 1.3 Hz, 1H), 7.61 (dd, *J* = 10.2, 2.6 Hz, 3H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.23 (d, *J* = 1.7 Hz, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 4.50 (s, 2H), 3.64 (dd, *J* = 11.8, 5.8 Hz, 2H), 3.03–2.89 (m, 6H), 2.03 (dd, *J* = 13.3, 7.3 Hz, 7H); MS (ESI, m/z): 526.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{31}H_{30}N_5OF_2$ ($[M+H]^+$): 526.2418; found: 526.2421.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-(pyridin-2-ylmethyl)benzamide (22m). Compound **22m** was prepared in a similar manner as described for compound **22a**. Yield: 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.58 (d, *J* = 4.9 Hz, 1H), 8.21–7.99 (m, 4H), 7.85 (d, *J* = 1.4 Hz, 1H), 7.73–7.57 (m, 4H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.15 (ddd, *J* = 6.3, 5.6, 1.6 Hz, 2H), 4.80 (d, *J* = 4.4 Hz, 2H), 4.51 (s, 2H); MS (ESI, m/z): 506.1 $[M+H]^+$; HRMS (ESI) cacld for $C_{30}H_{22}N_5OF_2$ ($[M+H]^+$): 506.1792; found: 506.1782.

***N*-(3,5-Difluorobenzyl)-2-fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzamide (22n)**. Compound **22n** was prepared in a similar manner

as described for compound **22a**. Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 4.1 Hz, 1H), 8.14 (t, J = 8.2 Hz, 1H), 8.08 (t, J = 8.8 Hz, 2H), 7.84 (s, 1H), 7.61 (d, J = 9.8 Hz, 3H), 7.40 (dd, J = 8.3, 4.3 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.20–7.10 (m, 3H), 6.86 (d, J = 6.7 Hz, 2H), 6.71 (t, J = 8.9 Hz, 1H), 4.65 (d, J = 5.9 Hz, 2H), 4.50 (s, 2H); MS (ESI, m/z): 541.0 $[M+H]^+$; HRMS (ESI) cacld for $C_{31}H_{21}N_4OF_4$ ($[M+H]^+$): 541.1651; found: 541.1642.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide (22o). Compound **22o** was prepared in a similar manner as described for compound **22a**. Yield: 77%; ^{1}H NMR (300 MHz, CD_3OD) δ 8.80 (dd, J = 4.3, 1.7 Hz, 1H), 8.35 (d, J = 1.4 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.85 (s, 1H), 7.78–7.66 (m, 2H), 7.55–7.41 (m, 5H), 4.63 (s, 2H), 4.17–4.04 (m, 1H), 3.96 (d, J = 10.6 Hz, 2H), 3.52 (td, J = 11.6, 2.0 Hz, 2H), 1.97–1.86 (m, 2H), 1.63 (ddd, J = 16.0, 12.2, 4.4 Hz, 2H); MS (ESI, m/z): 499.4 $[M+H]^+$; HRMS (ESI) cacld for $C_{29}H_{25}N_4O_2F_2$ ($[M+H]^+$): 499.1946; found: 499.1957.

***tert*-Butyl 2-((2-fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzamido)methyl)piperidine-1-carboxylate (23a)**. Compound **23a** was prepared in a similar manner as described for compound **22a**. Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95–8.88 (m, 1H), 8.10 (dd, J = 15.9, 8.1 Hz, 3H), 7.83 (s, 1H), 7.61 (t, J = 9.7 Hz, 3H), 7.43 (dd, J = 8.2, 4.3 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.16–7.08 (m, 2H), 4.51 (s, 3H), 3.96 (s, 2H), 3.41 (d, J = 13.3 Hz, 1H), 2.88 (t, J = 12.9 Hz, 1H),

1.66 (d, *J* = 8.5 Hz, 5H), 1.42 (d, *J* = 15.6 Hz, 1H), 1.36 (s, 9H); MS (ESI, m/z): 612.1$[M+H]^+$.

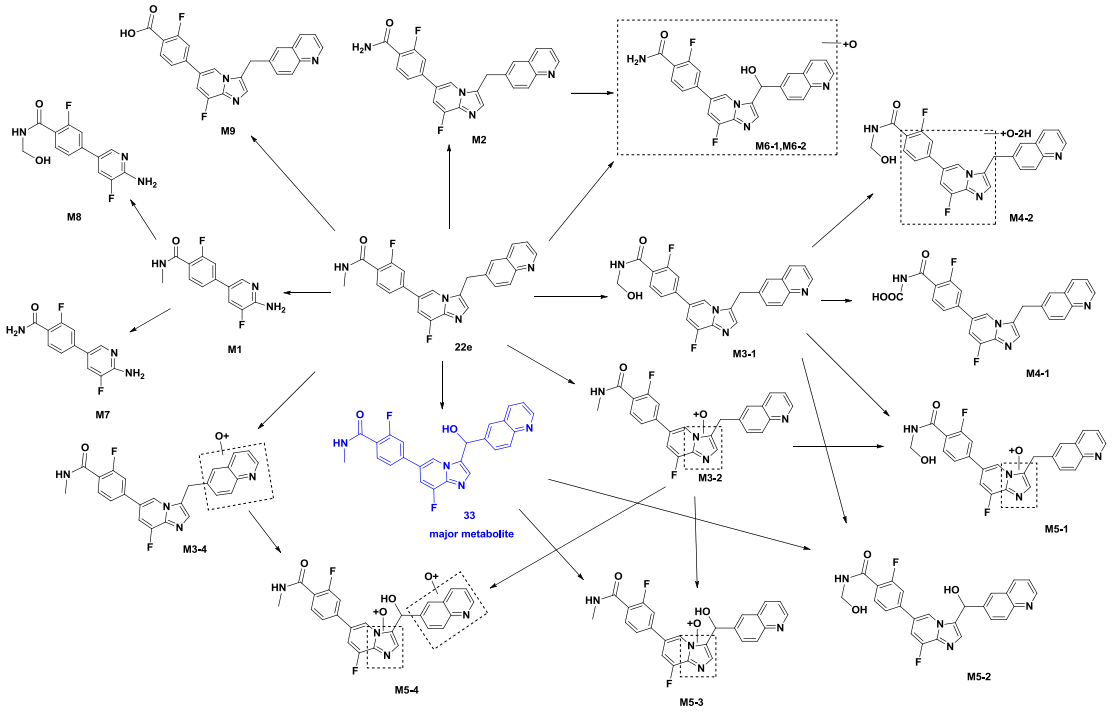
***tert*-Butyl 3-(2-fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)benzamido)piperidine-1-carboxylate (23b)**. Compound **23b** was prepared in a similar manner as described for compound **22a**. Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90–8.83 (m, 1H), 8.05 (dd, *J* = 8.5, 3.6 Hz, 3H), 7.83 (s, 1H), 7.63–7.49 (m, 3H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.29–7.21 (m, 1H), 7.10 (dd, *J* = 11.8, 5.4 Hz, 2H), 6.85 (s, 1H), 4.48 (s, 2H), 4.16 (s, 1H), 3.61–3.45 (m, 3H), 3.30–3.20 (m, 1H), 1.90–1.73 (m, 2H), 1.72–1.61 (m, 1H), 1.57 (s, 1H), 1.41 (s, 9H); MS (ESI, m/z): 598.1 $[M+H]^+$.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-(piperidin-2-ylmethyl)benzamide (22k). Compound **22k** was prepared in a similar manner as described for compound **15i**. Yield: 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96–8.86 (m, 1H), 8.08 (t, *J* = 8.6 Hz, 3H), 7.82 (s, 1H), 7.61 (d, *J* = 13.8 Hz, 3H), 7.41 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.29–7.23 (m, 2H), 7.14 (t, *J* = 16.2 Hz, 3H), 4.50 (s, 2H), 3.53 (d, *J* = 13.6 Hz, 1H), 3.39–3.25 (m, 1H), 3.09 (d, *J* = 10.9 Hz, 1H), 2.82 (s, 1H), 2.64 (t, *J* = 10.7 Hz, 1H), 1.82 (s, 1H), 1.70 (d, *J* = 12.3 Hz, 1H), 1.60 (s, 1H), 1.39 (t, *J* = 9.9 Hz, 2H), 1.23 (dd, *J* = 29.3, 15.1 Hz, 3H). MS (ESI, m/z): 512.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{30}H_{28}N_5OF_2$ ($[M+H]^+$): 512.2262; found: 512.2266.

2-Fluoro-4-(8-fluoro-3-(quinolin-6-ylmethyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-(pi

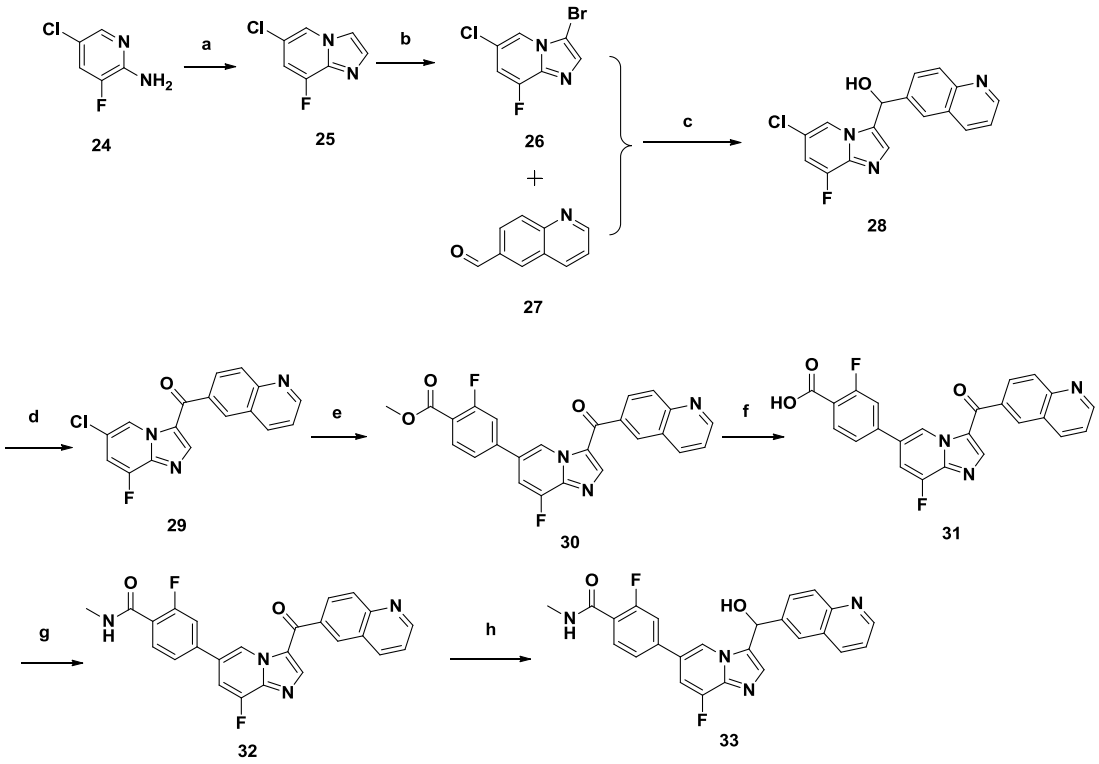
peridin-3-yl)benzamide (22l). Compound **22l** was prepared in a similar manner as described for compound **15i**. Yield: 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (t, J = 8.2 Hz, 3H), 7.83 (d, J = 1.3 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.40 (dd, J = 8.2, 4.2 Hz, 1H), 7.24 (d, J = 1.7 Hz, 1H), 7.15 – 7.09 (m, 2H), 4.52 – 4.47 (m, 2H), 4.20 (brs, 1H), 3.11 (dd, J = 11.8, 2.7 Hz, 1H), 2.84 (s, 2H), 2.50 (brs, 2H), 1.90 – 1.68 (m, 3H), 1.64 – 1.53 (m, 1H); MS (ESI, m/z): 498.3 $[M+H]^+$; HRMS (ESI) cacld for $C_{29}H_{26}N_5OF_2$ ($[M+H]^+$): 498.2105; found: 498.2106.

Scheme 3a. Proposed pathways of active metabolite of 22e[a]



[a]Proposed pathways of active metabolite via in vitro metabolic activation of **22e** upon incubation with liver microsomes of different species (e.g., rats, mouse, monkeys, dogs and human) in the presence of NADPH.

Scheme 3b. Synthesis of Compound 33[a]



[a]Reagents and conditions: (a) Chloroacetaldehyde (40%), EtOH, reflux, 8h; (b) NBS, CH_3CN, Ar, 0 ^{0}C-rt; (c) EtMgBr, THF, 0 ^{0}C-rt; (d) MnO_2, 1,4-dioxane, reflux, 2h; (e) $Pd(OAc)_2$, Xantphos, K_3PO_4, 1,4-dioxane/H_2O (3:1), 100 ^{0}C, overnight; (f) $LiOH·H_2O$, MeOH/THF/H_2O (2:1:1), rt ; (g) HATU, DIPEA, DMF, 0 ^{0}C-rt; (h) $NaBH_4$, MeOH, rt.

6-Chloro-8-fluoroimidazo[1,2-*a*]pyridine (25). **24** (500 mg, 3.41 mmol) was dissolved in 10 mL of ethanol. To the solution was added 40% chloroacetaldehyde (1.13 mL, 17.06 mmol). The mixture was stirred overnight under reflux. Then the reaction mixture was gradually cooled to room temperature, to which was added saturated $NaHCO_3$ aqueous solution. The mixture was extracted with EA for two times. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography eluting with ethyl acetate in hexanes (0-25%) to afford the desired product (452 mg, 78 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.65 (d, J = 18.0 Hz, 2H), 6.92 (dd, J = 9.7, 1.5 Hz, 1H); MS (ESI, m/z): 171.0 $[M+H]^+$.

3-Bromo-6-chloro-8-fluoroimidazo[1,2-*a*]pyridine (26). To the mixture of **25** (450 mg, 2.64 mmol) in acetonitrile (10 mL), was added NBS (517 mg, 2.9 mmol) portionwise at 0°C. The resulting reaction medium was evacuated and refilled with argon three times. The mixture was warmed to room temperature and stirred at room temperature for 2 h. Solvent was evaporated in vacuum. The residue was purified by silica gel column (PE/EA, 4/1) to afford 595 mg (yield: 90%) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.02 (m, 1H), 7.66 (s, 1H), 7.02 (dd, J = 9.6, 1.6 Hz, 1H); MS (ESI, m/z): 248.9 $[M+H]^+$, 250.9 $[M+H+2]^+$.

(6-Chloro-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)(quinolin-6-yl)methanol (28). To a solution of 3-bromo-6-chloro-8-fluoroimidazo[1,2-*a*]pyridine (200 mg, 0.8 mmol) in 6 ml of THF was added EtMgBr (0.96 mL, 0.96 mmol) solution dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h and a suspension of quinoline-6-carbaldehyde (126 mg, 0.8 mmol) in 5 mL of THF was added. The resulting mixture was stirred at room temperature for 3 h and quenched with 10 ml of water. The precipitate was collected by filtration and purified by silica gel column ($MeOH/CH_2Cl_2$, 1/15) to afford 54 mg (yield: 21%) desired product as a off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 8.96–8.86 (m, 1H), 8.52 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.55 (dd, J = 8.3, 4.2 Hz, 1H), 7.49 (d, J = 10.8 Hz, 1H), 7.25 (s, 1H), 6.55 (d, J = 5.3 Hz, 1H), 6.46 (d, J = 5.2 Hz, 1H); MS (ESI, m/z): 327.9 $[M+H]^+$.

(6-Chloro-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)(quinolin-6-yl)methanone (29). To a solution of

(6-chloro-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)(quinolin-6-yl)methanol (80 mg, 0.24 mmol) in 5 mL of 1,4-dioxane was added MnO_2 (106 mg, 1.22 mmol) at room temperature. The reaction mixture was heated to reflux for 1h. The resulting solution was filtered over celite, and washed with CH_2Cl_2. The filtrate was concentrated under vacuum. The residue was purified by silica gel column (MeOH/CH_2Cl_2, 1/25) to afford 45 mg (yield: 57%) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 9.06 (d, J = 2.7 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.35–8.25 (m, 3H), 8.19 (dd, J = 8.7, 1.8 Hz, 1H), 7.55 (dd, J = 8.3, 4.2 Hz, 1H), 7.34 (dd, J = 9.2, 1.6 Hz, 1H); MS (ESI, m/z): 325.9 $[M+H]^+$.

Methyl 2-fluoro-4-(8-fluoro-3-(quinoline-6-carbonyl)imidazo[1,2-*a*]pyridin-6-yl)benzoate (30). To a seal tube was added compound **29** (150 mg, 0.46 mmol), 3-fluoro-4-(methoxycarbonyl)phenyl)boronic acid (182 mg, 0.92 mmol), $Pd(OAc)_2$ (10 mg, 0.046 mmol), Xantphos (13 mg, 0.023 mmol), tripotassium phosphate (293 mg, 1.38 mmol), dioxane (4 mL) and water (1 mL). The reaction mixture was degassed and filled with Ar. The reaction mixture was heated at 100 °C overnight. After this time, the mixture was filtered through celite and the filter cake washed with a mixture of 1:20 MeOH/CH_2Cl_2. The filtrate was washed with water (10 mL), then brine and dried over sodium sulfate. The crude product was purified by silica gel column (MeOH/CH_2Cl_2, 1/20) to afford 112 mg (yield: 55%) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 9.11 (d, J = 2.9 Hz, 1H), 8.41 (s, 1H), 8.39–8.31 (m, 3H), 8.22 (dd, J = 8.7, 1.7 Hz, 1H), 8.11 (t, J = 7.8 Hz, 1H),

7.61–7.50 (m, 3H), 7.46 (d, *J* = 11.4 Hz, 1H), 3.98 (s, 3H).

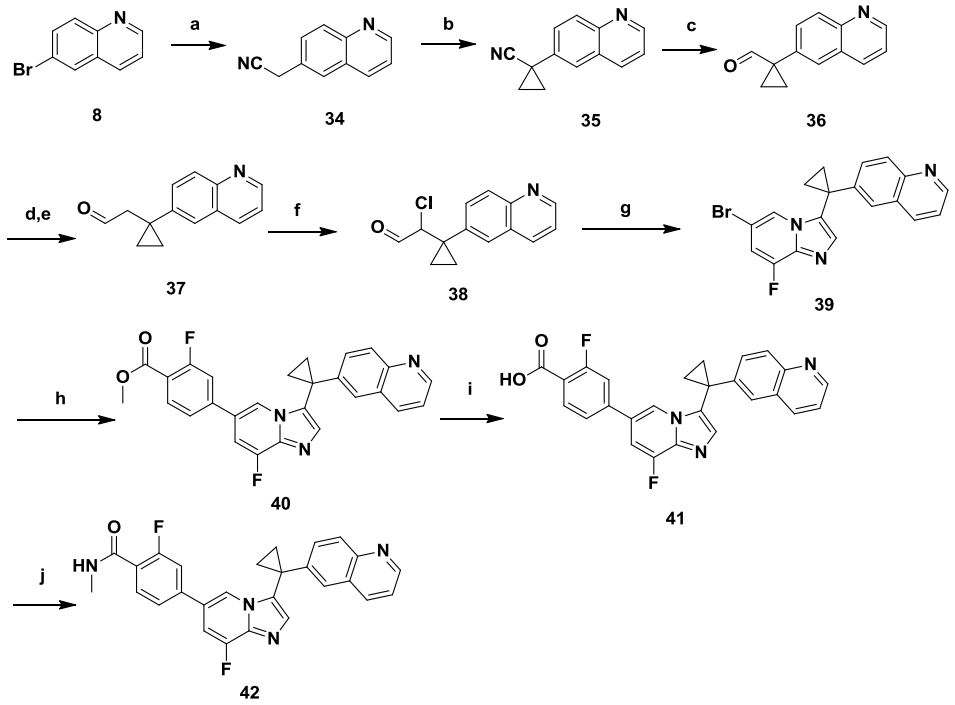
2-Fluoro-4-(8-fluoro-3-(quinoline-6-carbonyl)imidazo[1,2-*a*]pyridin-6-yl)benzoic acid (31). Compound **31** was prepared in a similar manner as described for compound **21a**. Yield: 65%; MS (ESI, m/z): 442.0 $[M-H]^-$.

2-Fluoro-4-(8-fluoro-3-(quinoline-6-carbonyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-methylbenzamide (32). Compound **32** was prepared in a similar manner as described for compound **22a**. Yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (d, *J* = 1.5 Hz, 1H), 9.08 (d, *J* = 2.7 Hz, 1H), 8.41 (d, *J* = 1.8 Hz, 1H), 8.36–8.29 (m, 4H), 8.22 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.60–7.55 (m, 3H), 7.45 (dd, *J* = 12.8, 1.7 Hz, 1H), 6.82 (s, 1H), 3.11–3.06 (m, 3H); MS (ESI, m/z): 443.0 $[M+H]^+$.

2-Fluoro-4-(8-fluoro-3-(hydroxy(quinolin-6-yl)methyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-methylbenzamide (33). 32 (20 mg, 0.045 mmol) was dissolved in 4 mL of methanol. To the solution was added $NaBH_4$ (1.7 mg, 0.045 mmol). The reaction mixture was stirred at room temperature for 2h and quenched with water. The mixture was extracted with CH_2Cl_2 for two times. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column (MeOH/CH_2Cl_2, 1/20) to afford 10 mg (yield: 50%) desired product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.87 (d, *J* = 4.0 Hz, 1H), 8.64 (s, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.20 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.94–7.80 (m, 2H), 7.62–7.47 (m, 4H), 7.22 (s, 1H), 6.56 (s, 1H), 2.94 (s, 3H); MS (ESI, m/z): 445.0 $[M+H]^+$; HRMS (ESI) cacld for $C_{25}H_{18}N_4O_2F_2Na$ ($[M+Na]^+$):

467.1296; found: 467.1302.

Scheme 4. Synthesis of Compound 42[a]



[a]Reagents and conditions: (a) trimethylsilanyl-acetonitrile, $Pd_2(dba)_3$, ZnF_2, Xantphos, DMF, 105 ^{0}C, 20h; (b) 1-bromo-2-chloroethane, TEBA, 50% NaOH aq, 50 ^{0}C, 3h; (c) DIBAL-H, toluene, -78 - 0 ^{0}C, 4h; (d) (Methoxymethyl)triphenylphosphonium chloride, t-BuOK, 0 ^{0}C-rt; (e) 10% HCl aq, THF, 2h; (f) NCS, L-Pro, CHCl3, 0 ^{0}C - rt, 3h; (g) 2-amino-5-bromo-3-fluoropyridine, EtOH, reflux, 24h; (h) $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, Na_2CO_3, DMF/H_2O (4:1), 80, overnight; (i) $LiOH{\cdot}H2O$, MeOH/THF/H_2O (2:1:1), rt; (j) HATU, DIPEA, DMF, 0 ^{0}C - rt.

2-(Quinolin-6-yl)acetonitrile (34). To a mixture of (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (112 mg, 0.19 mmol), tris(dibenzylideneacetone)dipalladium(0) (167 mg, 0.19 mol), 6-bromoquinoline (2 g, 9.61 mmol) in DMF (10 mL) in a 2-neck round bottom flask with stirring under an atmosphere of argon was added (trimethylsilyl)acetonitrile (1.65 mL, 12.02 mmol), followed by zinc difluoride (696 mg, 6.73 mmol). The flask was sealed under an atmosphere of argon. The reaction was stirred at 105 °C for 20 h. After cooling the

solution to room temperature, the reaction mixture was quenched with aqueous ammonia solution and extracted with ethyl acetate (3*30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column (ethyl acetate in hexanes: 0-65%) to afford 1.1 g (yield: 68%) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 4.1 Hz, 1H), 8.20–8.08 (m, 2H), 7.83 (d, J = 6.0 Hz, 1H), 7.65–7.56 (m, 1H), 7.48–7.40 (m, 1H), 3.95 (d, J = 4.5 Hz, 2H); MS (ESI, m/z): 169.1 $[M+H]^+$.

1-(Quinolin-6-yl)cyclopropanecarbonitrile (35). 5 mL of 50% aqueous sodium hydroxide was added to a mixture of 1 -bromo-2-chloroethane (1.98 mL, 23.78 mmol), quinolin-6-ylacetonitrile (1 g, 5.95 mmol), and benzyltriethylammonium chloride (81 mg, 0.36 mmol) at 50 ^{0}C. The reaction mixture was stirred at 50 ^{0}C for 3 h. After cooling to RT, the reaction mixture was poured into 10 mL water, and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column (ethyl acetate in dichloromethane: 0-20%) to afford 967 mg (yield: 84%) desired product. ^{1}H NMR (400 MHz, DMSO) δ 8.93–8.87 (m, 1H), 8.38 (d, J = 8.2 Hz, 1H), 8.07–7.96 (m, 2H), 7.64 (d, J = 8.8 Hz, 1H), 7.55 (dd, J = 8.2, 4.1 Hz, 1H), 1.86 (t, J = 6.3 Hz, 2H), 1.66 (t, J = 6.3 Hz, 2H); MS (ESI, m/z): 195.1 $[M+H]^+$.

1-(Quinolin-6-yl)cyclopropanecarbaldehyde (36). Diisobutylaluminum hydride in THF (1.0 M, 6.18 mL, 6.18 mmol) was added to a solution of

1-quinolin-6-ylcyclopropanecarbonitrile (800 mg, 4.12 mmol) in toluene (10 mL) at -78 °C. under an atmosphere of argon. The reaction mixture was allowed to warm to -5 to 0 °C, and stirred at that temperature for 3 h. The mixture was re-cooled to -60 °C. Isopropyl alcohol (3 mL) was carefully added dropwise. After stirring for 30 min, the mixture was warmed to -5 to 0 °C. The mixture was diluted with ethyl acetate, quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The crude product was purified by silica gel column (ethyl acetate in hexanes: 0-40%) to afford 698 mg (yield: 86%) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28–9.18 (m, 1H), 8.89 (d, J = 4.2 Hz, 1H), 8.10 (t, J = 7.5 Hz, 2H), 7.72 (s, 1H), 7.69–7.61 (m, 1H), 7.39 (dd, J = 8.2, 4.1 Hz, 1H), 1.66 (dd, J = 6.7, 4.1 Hz, 2H), 1.51 (dd, J = 6.9, 4.1 Hz, 2H); MS (ESI, m/z): 198.1 $[M+H]^+$.

2-(1-(Quinolin-6-yl)cyclopropyl)acetaldehyde (37). To a suspension of chloro(methoxymethyl)triphenylphosphorane (3.5 g, 10 mmol) in tetrahydrofuran (10 mL) at -10 °C was added dropwise a solution of 1.0 M potassium tert-butoxide in tetrahydrofuran (10 mL). After the reaction mixture was stirred at RT for 1 hour, the reaction mixture was cooled to 0 °C and a solution of 1-(quinolin-6-yl)cyclopropanecarbaldehyde (500 mg, 2.5 mmol) in THF (5 mL) was added. The mixture was stirred at ambient temperature for 1 h. The mixture was diluted with ethyl acetate, quenched with water and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered through a pad of silica gel eluting with 50% ethyl acetate in dichloromethane. The filtrate was

concentrated and dissolved in 15 mL THF. To the solution was added 6 mL of 10% aqueous HCl solution at ambient temperature with stirring. The reaction mixture was stirred at ambient temperature for 2 h, and then neutralized with saturated sodium bicarbonate. The mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column (ethyl acetate in hexanes: 0-40%) to afford 380 mg (yield: 71% two steps) desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 2.4 Hz, 1H), 8.86 (dd, J = 4.2, 1.7 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.63 (dd, J = 8.8, 2.1 Hz, 1H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 2.74 (d, J = 2.3 Hz, 2H), 1.15 (q, J = 5.0 Hz, 2H), 1.00 (t, J = 5.5 Hz, 2H); MS (ESI, m/z): 212.1 $[M+H]^+$; 244.1 $[M+MeOH+H]^+$.

2-Chloro-2-(1-(quinolin-6-yl)cyclopropyl)acetaldehyde (38). To a mixture of **37** (300 mg, 1.42 mmol), D-proline (33 mg, 0.28 mmol) in dichloromethane (10 mL) cooled (0 ^{0}C) was added N-chlorosuccinimide (228 mg, 1.70 mmol) with stirring. The reaction mixture was stirred at 0 °C for 1 h, then gradually warmed to RT. The reaction mixture was quenched with water, extracted with dichloromethane. The combined organic extracts were concentrated and the residue purified by flash chromatography eluting with ethyl acetate in hexanes (0-25%) to afford the desired product (201 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, J = 3.3 Hz, 1H), 8.89 (dd, J = 4.1, 1.5 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.81 (t, J = 3.2 Hz, 1H), 7.73 (dd, J = 8.7, 2.0 Hz, 1H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H), 3.94 (d, J = 3.3 Hz, 1H), 1.32–1.22 (m, 2H), 1.21–1.10 (m, 2H); MS (ESI, m/z): 246.1 $[M+H]^+$;

278.0 $[M+MeOH+H]^+$.

6-(1-(6-Bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)cyclopropyl)quinoline (39). Compound **39** was prepared in a similar manner as described for compound **13a**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 4.0 Hz, 1H), 8.00 (dd, J = 16.6, 8.6 Hz, 2H), 7.90 (s, 1H), 7.72 (s, 1H), 7.36 (dd, J = 8.5, 2.9 Hz, 2H), 7.30 (s, 1H), 7.03 (d, J = 9.5 Hz, 1H), 1.67 (t, J = 5.6 Hz, 2H), 1.49 (t, J = 5.6 Hz, 2H).

Methyl 2-fluoro-4-(8-fluoro-3-(1-(quinolin-6-yl)cyclopropyl)imidazo[1,2-*a*]pyridin-6-yl)benzoate (40). Compound **40** was prepared in a similar manner as described for compound **15a.** Yield: 52%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 4.1 Hz, 1H), 8.08–7.89 (m, 4H), 7.79 (s, 1H), 7.48–7.33 (m, 3H), 7.22–7.07 (m, 3H), 3.92 (s, 3H), 1.71 (t, J = 5.6 Hz, 2H), 1.54 (t, J = 5.6 Hz, 2H); MS (ESI, m/z): 456.0 $[M+H]^+$.

2-Fluoro-4-(8-fluoro-3-(1-(quinolin-6-yl)cyclopropyl)imidazo[1,2-*a*]pyridin-6-yl)benzoic acid (41). Compound **41** was prepared in a similar manner as described for compound **21a**. Yield: 75%; MS (ESI, m/z): 440.2 $[M-H]^-$.

2-Fluoro-4-(8-fluoro-3-(1-(quinolin-6-yl)cyclopropyl)imidazo[1,2-*a*]pyridin-6-yl)-*N*-methylbenzamide (42). Compound **42** was prepared in a similar manner as described for compound **22a**. Yield: 69%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.94–8.76 (m, 1H), 8.11 (t, J = 8.2 Hz, 1H), 8.01 (dd, J = 15.3, 8.2 Hz, 3H), 7.78 (s, 1H), 7.39 (ddd, J = 19.7, 9.6, 3.1 Hz, 3H), 7.23 (dd, J = 8.2, 1.5 Hz, 1H), 7.12 (dd, J = 22.9, 12.0 Hz, 2H), 6.73 (s, 1H), 3.02 (d, J = 4.6 Hz, 3H), 1.71 (q, J = 4.8 Hz, 2H), 1.54 (q,

J = 4.7 Hz, 2H); MS (ESI, m/z): 455.0 $[M+H]^+$; HRMS (ESI) cacld for $C_{27}H_{20}N_4OF_2Na$ ($[M+Na]^+$): 477.1503; found: 477.1502.

Biological Assay Methods:

ELISA kinase assay. The effects of **22e** on the activities of various tyrosine kinases were determined using enzyme-linked immunosorbent assays (ELISAs) with purified recombinant proteins. Briefly, 20 μg/mL poly (Glu,Tyr)4:1 (Sigma, St Louis, MO, USA) was pre-coated in 96-well plates as a substrate. A 50-μL aliquot of 10 μM ATP solution diluted in kinase reaction buffer (50 mM HEPES [pH 7.4], 50 mM $MgCl_2$, 0.5 mM $MnCl_2$, 0.2 mM Na_3VO_4, and 1 mM DTT) was added to each well; 1 μL of various concentrations of indicated compound diluted in 1% DMSO (v/v) (Sigma, St Louis, MO, USA) were then added to each reaction well. DMSO (1%, v/v) was used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins diluted in 49 μL of kinase reaction buffer. After incubation for 60 min at 37 °C, the plate was washed three times with phos-phate-buffered saline (PBS) containing 0.1% Tween 20 (T-PBS). Anti-phosphotyrosine (PY99) antibody (100 μL; 1:500, diluted in 5 mg/mL BSA T-PBS) was then added. After a 30-min incubation at 37 °C, the plate was washed three times, and 100 μL horseradish peroxidase-conjugated goat anti-mouse IgG (1:1000, diluted in 5 mg/mL BSA T-PBS) was added. The plate was then incubated at 37 °C for 30 min and washed 3 times. A 100-μL aliquot of a solution containing

0.03% H_2O_2 and 2 mg/mL o-phenylenediamine in 0.1 M citrate buffer (pH 5.5) was added. The reaction was terminated by the addition of 50 μL of 2 M H_2SO_4 as the color changed, and the plate was analyzed using a multi-well spectrophotometer (SpectraMAX 190, from Molecular Devices, Palo Alto, CA, USA) at 490 nm. The inhibition rate (%) was calculated using the following equation: [1-(A490/A490 control)]×100%. The IC_{50} values were calculated from the inhibition curves in two separate experiments.

Table S1 Kinase-selectivity profile of 22e

Kinase	IC_{50} (nM)[a]
c-Met	3.9±0.7
RON	>10000
Axl	>10000
Tyro-3	>10000
c-Mer	>10000
IGF1R	>10000
ALK	>10000
Flt-1	>10000
KDR	>10000
c-Kit	>10000
PDGFRα	>10000
PDGFRβ	>10000
RET	>10000
FGFR1	>10000
ErbB2	>10000
ErbB4	>10000
c-Src	>10000
EPH-A2	>10000
EPH-B2	>10000
EGFR	>10000
EGFR/T790M-L858R	>10000
ABL	>10000

[a] IC_{50} values are shown as the mean±SD (nM) or estimated values from two separate experiments.

Western blot analysis. EBC-1, MKN-45, and BaF3/TPR-Met cells were treated

with the indicated dose of **22e** for 2 h at 37 °C and then lysed in 1×SDS sample buffer. The cell lysates were subsequently resolved by 10% SDS-PAGE and transferred to nitrocellulose membranes. The membranes were probed with the appropriate primary antibodies [c-Met (Santa Cruz, CA, USA), phospho-c-Met, phospho-ERK1/2, ERK1/2, phospho-AKT, and AKT (all from Cell Signaling Technology, Beverly, MA, USA), and GAPDH (KangChen Biotech, Shanghai, China)] and then with horseradish peroxidase-conjugated anti-rabbit or anti-mouse IgG. The immunoreactive proteins were detected using an enhanced chemiluminescence detection reagent (Thermo Fisher Scientific, Rockford, IL, USA).

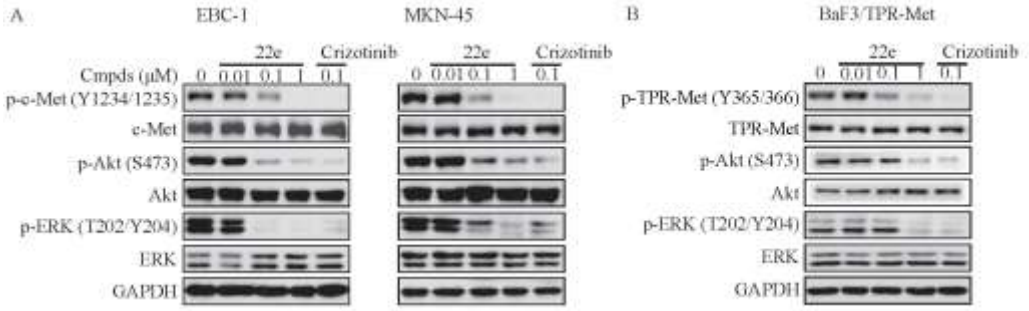


Figure S1. 22e suppresses c-Met phosphorylation and downstream signaling in various cells. (**A**，**B**) **22e** effectively inhibits the phosphorylation of c-Met and the c-Met pathway downstream effectors Erk1/2 and Akt in EBC-1, MKN-45 (**A**), and BaF3/TPR-Met cells (**B**) Cells treated for 2 h with **22e** at the indicated concentrations were lysed and subjected to Western blot analysis.

Cell proliferation assay. Cells were seeded in 96-well tissue culture plates. On the next day, the cells were exposed to various concentrations of compounds and further cultured for 72 h. Cell proliferation was then determined using sulforhodamine B (SRB, from Sigma-Aldrich, St Louis, MO, USA) or the thiazolyl blue tetrazolium bromide (MTT, from Sigma-Aldrich, St Louis, MO, USA) assay. The IC_{50} values

were calculated by concentration-response curve fitting using the four-parameter method.

Cell cycle distribution assay. EBC-1 cells (1×10^5) were seeded in 6-well plates overnight and treated with different concentrations of **22e** on the following day. After 24 h, the cells were collected by EDTA-free trypsinization, centrifuged at 1000×g, and fixed in 70% ethanol at -20 °C for 1 h. The cells were then centrifuged at 1000×g, resuspended in 500 μL PBS containing 20 ng/mL RNase and 10 ng/mL propidium iodide, incubated in the dark for 30 min at room temperature, and analyzed using flow cytometry (FACsCalibur, from BD bioscience, San Jose, CA, USA). The data were analyzed using Modifit LT.

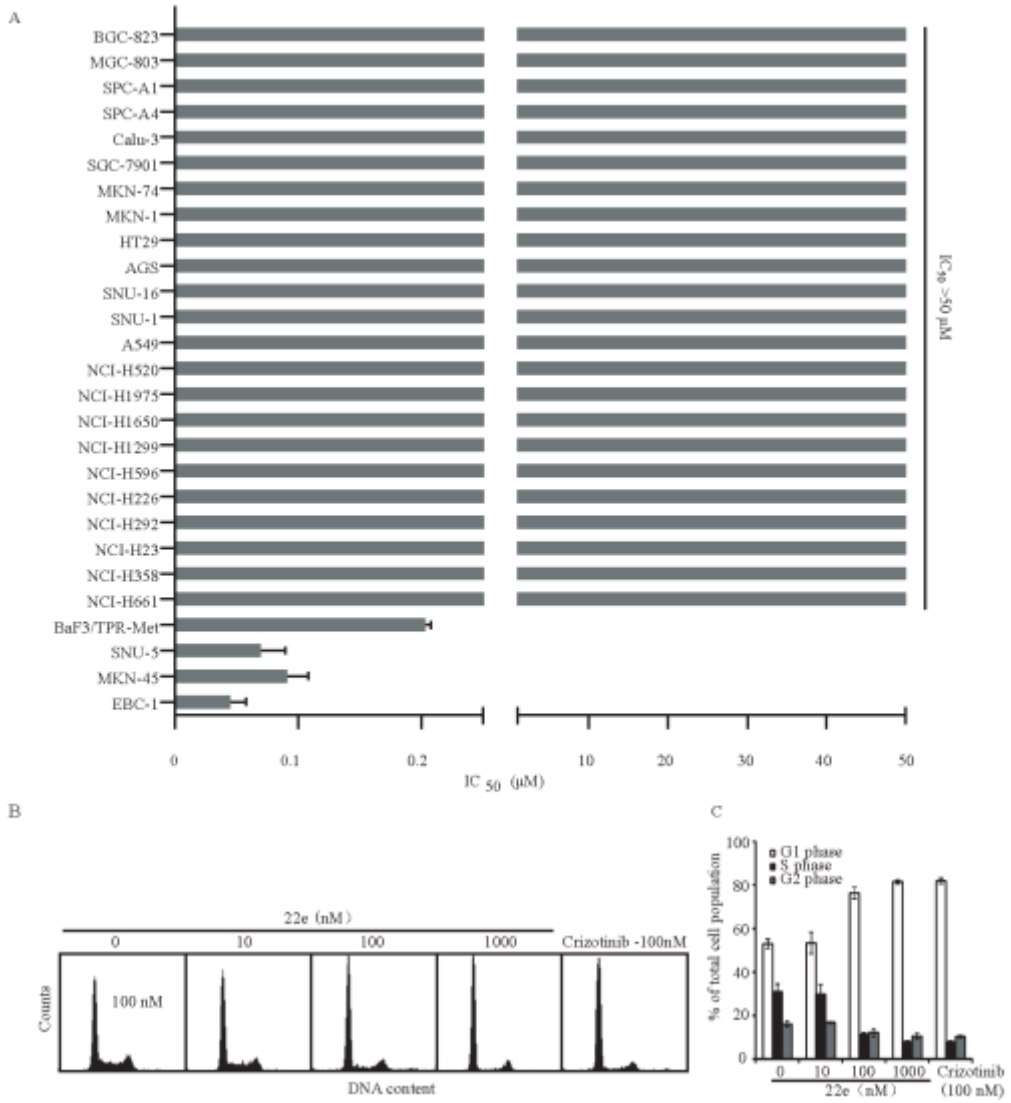


Figure S2. 22e specifically inhibits c-Met-driven proliferation via inducing G1/S arrest. (**A**) The anti-proliferation activity of **22e** against a panel of tumor cell lines originating from different tissue types was determined by a sulforhodamine B (SRB) or an MTT assay. The IC_{50} values were plotted as the mean±SD (μM) or estimated values from three separate experiments. (**B**) **22e** induces G1 phase arrest in EBC-1 cells. EBC-1 cells were treated with increasing concentrations of **22e** or vehicle for 24 h. The DNA content was measured by FACS analysis. (**C**) The percentage of EBC-1cells in different cell cycle phases determined by FACS and analyzed with Modifit LT was plotted. The data shown are the mean±SD from two independent experiments, and representative images are shown.

Migration assay and invasion assay. For the migration assay, NCI-H441 cells suspended in serum-free medium (1.5×10^5 cells per well) were seeded in 24-well Transwell plates (pore size, 8 μm; Corning). The bottom chambers were filled with

serum-free medium supplemented with HGF (100 ng/mL), and 100nM, 500nM, and 1000 nM of **22e** was added to both sides of the membrane. The cultures were maintained for 24 h, followed by the removal of non-motile cells at the top of the filter using a cotton swab. The migrating cells were fixed in paraformaldehyde (4%) and stained with crystal violet (0.1%) for 15 min at room temperature. The dye that was taken up by the cells bound to the membrane was released by the addition of 100 μL 10% acetic acid, and the absorbance of the resulting solution was measured at 595 nm using a multiwell spectrophotometer (SpetraMAX 190, from Molecular Devices, Palo Alto, CA, USA). The assay was performed in triplicate.

For the invasion assay, NCI-H441 cells were cultured in the top chambers containing Matrigel-coated membrane inserts (Matrigel, BD). The ensuing procedure was identical to the migration assay. The assay was performed in triplicate. Images were obtained using an Olympus BX51 microscope.

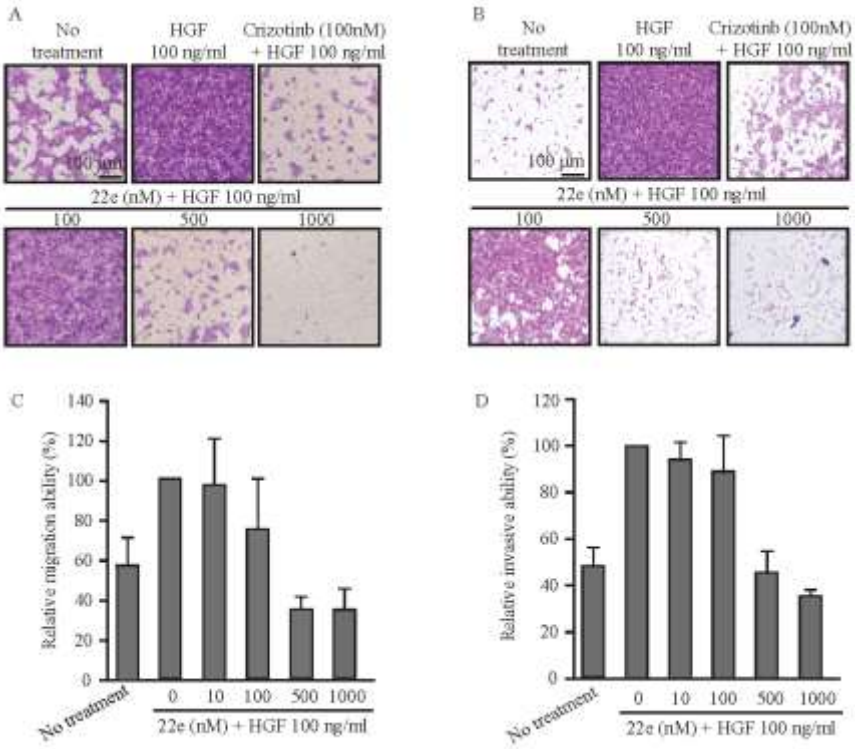


Figure S3. 22e inhibits HGF-induced cell migration and invasion. The migratory ability (**A**) and invasive ability (**B**) of NCI-H441 cells induced by 100 ng/mL.HGF were impaired by **22e**. Representative images from three separate experiments are shown (scale bars, 100 μm). (**C, D**) The relative migration (**C**) and invasion (**D**) were plotted. The data shown are the mean±SD from three independent experiments, assuming 100% migration or invasion of cells stimulated with HGF.

Cell-scatter assay. MDCK cells (3×10^3 cells per well) were plated in 24-well plates and grown overnight. Increasing concentrations of **22e** and HGF (100 ng/mL) were added to the appropriate wells, and the plates were incubated at 37 °C and 5% CO_2 for 24 h. The cells were fixed with 4% paraformaldehyde for 15 min at room temperature and then stained with 0.2% crystal violet, washed with water, and dried. Images were obtained using an Olympus IX51 microscope.

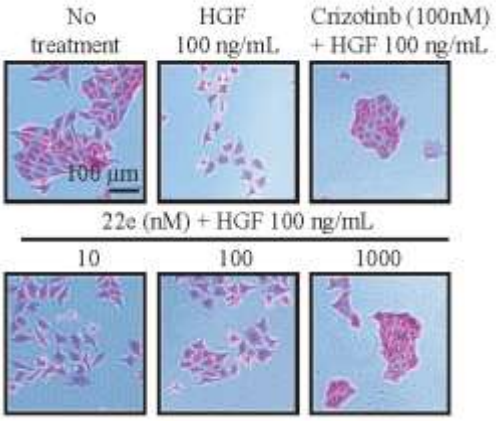


Figure S4. 22e inhibits HGF-induced cell scattering. Cell scattering by MDCK cells induced by HGF were dose-dependently inhibited by **22e**. Representative images from two separate experiments are shown (scale bars, 100 μm).

Cell branching morphogenesis assay. MDCK cells at a density of 2×10^4 cells/mL in DMEM medium were mixed with an equal volume of collagen I solution and plated at 0.1 mL/well in a 96-well culture plate. After incubation for 45 min at 37 °C and 5% CO_2 to allow the collagen to gel, HGF (100 ng/mL) with or without **22e** at various concentrations dissolved in 100 μL of growth medium was added to each well. The medium was replaced with fresh growth medium every 2 d. Images were obtained using an Olympus IX51 microscope after 4 d.

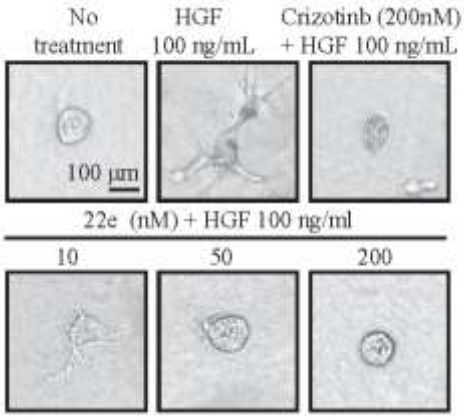


Figure S5. 22e inhibits HGF-induced invasive cell growth. The MDCK branching morphogenesis on collagen induced by HGF was inhibited by **22e**. Images were obtained 4 d after treatment. Representative images from two separate experiments

are shown (scale bars, 100 μm).

In vivo anti-tumor activity assay. Female nude mice (4–6 weeks) were housed at five or six mice per cage in a specific pathogen-free room with a 12-h light/ dark schedule at 25±1 °C; the animals were fed an autoclaved chow diet and water ad libitum. All the animal experiments were performed according to the institutional ethical guidelines of animal care.

EBC-1 cells at a density of (5–10)×10^6 in 200 μL were first implanted sc into the right flank of each mouse and then allowed to grow to 700–800 mm^3, which was defined as a well-developed tumor. The well-developed tumors were cut into 1-mm^3 fragments and transplanted sc into the right flank of nude mice using a trocar. When the tumor volume reached 100–150 mm^3, the mice were randomly assigned into control and treatment groups (drug-treated group, n = 6; vehicle group, n=12). The control groups were given vehicle alone, and the treatment groups received **22e** (methanesulfonic salt) or JNJ38877605 formulated in 0.5% CMC-Na at the indicated doses via oral administration once daily for 3 weeks. The sizes of the tumors were measured twice per week using microcalipers. The tumor volume (TV) was calculated as follows: TV=(length×$width^2$)/^{2}. The tumor volume shown was obtained on the indicated days as the median tumor volume±SEM for indicated groups of mice. The percent (%) inhibition values were measured on the final day of the study for the drug-treated compared with the vehicle-treated mice and were calculated as 100%×{1–[(treated final day–treated d $_0$)/(control final day–control day $_0$)]}. Significant differences between the treated versus the control groups ($P \leq 0.05$) were

determined using Student's test.

Pharmacokinetic profiles in SD rats. Compound **22e** (5% DMSO + 5% Tween-80 in 90% saline) was subjected to PK studies on SD rats. p. Test compound was administered via the oral route at 20 mg/kg or administered via the intravenous route at 10 mg/kg. After oral and intravenous administration, blood samples were collected. The blood samples were centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with methanol containing an internal standard. After centrifugation, the supernatant was diluted with methanol and centrifuged again. The compound concentrations in the supernatant were measured by LC/MS/MS.

Table S2. In vivo rat pharmacokinetic properties of 22e

in vivo rat PK						
i.v.				p.o.		
dose (mg/kg)	CL (L/kg/h)	Vss (L/kg)	$T_{1/2}$ (h)	dose (mg/kg)	%F	$AUC_{0-\infty}$ (ng/mL*h)
10	2.671	3.814	1.17	20	29.4	3176

p.o., oral administration; i.v., intravenous injection

hERG testing using FluxOR™ thallium assay. Step1: Growing cells. CHO-hERG-ZG cells are grown in 75 cm^2 flask with complete medium with 100 μg/mL G418 and 100 μg/mL Hygromycin B until 80–90% confluency. Wash cells with PBS once. Incubate cells with 1 mL 0.25% Trypsin until all cells are rounded and can be easily dislodged from the surface. Add 10 mL complete medium to stop Trypsin activity. Disassociate cells by thoroughly, repetitively pipetting.

Transfer them to 50 mL Falcon tube and spin down at 1000 rpm for 5 min. Aspirate medium and resuspend cells using a small volume of complete medium, like 0.5 mL. Count cell density. Step 2: Cell seeding. CHO-hERG-ZG cells are plated into 96-well plates and after plating, tap plates on sides to separate cells and let plates sit in the dark at RT for 30 min before incubation at 37 °C for 16–18 h. Cells will reach 80% confluency. After overnight incubation the cells are media changed in loading buffer (old media is tapped out) and incubated in the dark at RT for 90 min. Remove the loading buffer and replace with assay buffer. Compound **22e** was added to the cell plate. The cell plate is incubated with compound for 20 min in the dark at RT. Load the cell plates on FDSS. Fluorescent signals will be recorded every 2 s till 10 s. At 10 s, stimulus buffer will be added to cells. Then fluorescent signals will be recorded every second till 180 s, data QC on FDSS.

In vitro metabolic studys. *Materials.* Chromatography-grade H_2O, CH_3CN, NH_4OAc and formic acid were all purchased from Sigma-Aldrich, Tieda and Fluka. NADPH was purchased from Roche (Germany). Liver microsomes (humans, beagle dogs, SD rats, CD-1 mice and Stump-tailed monkey) were purchased from BD Gentest Corporation, USA.

Protocol. Each in vitro incubation mixture contains 1.0 mg/mL liver microsomes (humans, beagle dogs, SD rats, CD-1 mice and Stump-tailed monkey), 1.0 mM NADPH, 3 μM **22e** in a final volume of 200 μL of potassium phosphate (100 mM) buffer (pH 7.4). All the samples were incubated in a 37 °C water bath for 60 min. All the in vitro metabolism incubations were terminated by the addition of ice-cold

acetonitrile. After mixing, samples were centrifuged at 14000 rpm for 5 min, and the resulting supernatants were analyzed by UPLC/Q-TOF MS. MS Analysis of Metabolite profile.

Conditions. Chromatographic analysis of the supernatant resulting from the above incubation was conducted on a Waters Synapt UPLC/Q-TOF MS using a ACQUITY^{TM} HSS T3 C_{18} column (2.1 × 100 mm I.D., 1.8 μm, Waters Corporation, Milford, MA, USA). The column temperature was maintained at 40°C. The mobile phase consisted of H_2O (solvent A, 5mM NH_4OAc, containing 0.1% formic acid) and CH_3CN (solvent B) and was delivered at 400 μL/min. The initial composition of solvent B was maintained at 5% for 2 min and then increased in a linear manner to 30% at 15 min and 99% at 16 min. It was then maintained at 99% solvent B for 0.5 min and finally decreased to 5% at 17 min. The column was allowed to equilibrate at 5% solvent B for 3 min before the ending of the 20 min gradient elution program for next injection. The eluent was introduced into the mass spectrometer (Waters). MS analysis was conducted using a standard electrospray ionization (ESI) source operating in positive ionization mode. Source parameters were as follows: capillary voltage, 3.0 kV; desolvation gas flow, 700 $L•h^{-1}$; source temperature: 120°C; desolvation temperature, 500°C. To ensure mass accuracy and reproducibility, leucine-enkephalin was used as the reference lock mass (m/z 554.2615) with the LockSpray interface.

Table S3. In vitro metabolic activation studies on 22e in liver microsomes of different species[a]

Compd	*m/z*	Formula	Retention time (min)	Relative peak areas %				
				human	monkey	dog	rat	mice
22e	429.1515	$C_{25}H_{18}F_2N_4O$	13.3	19.6	0.9	13.7	2.1	13.2
M1	264.0954	$C_{13}H_{11}F_2N_3O$	9.4	5.3	5.2	16.8	6.2	2.6
M2	415.1354	$C_{24}H_{16}F_2N_4O$	11.9	0.8	0.5	4.1	–	0.3
M3-1	445.1496	$C_{25}H_{18}F_2N_4O_2$	11.4	1.7	–	2.4	–	0.7
M3-2	445.1454	$C_{25}H_{18}F_2N_4O_2$	11.8	19.1	12.7	12.5	27.5	11.2
33	445.1424	$C_{25}H_{18}F_2N_4O_2$	12.1	41.7	37.9	35.8	11.7	39.8
M3-4	445.1473	$C_{25}H_{18}F_2N_4O_2$	13.5	1.6	–	4.1	3.7	2.1
M4-1	459.1228	$C_{25}H_{16}F_2N_4O_3$	14.4	1.3	14.9	2.4	12.1	2.9
M4-2	459.1281	$C_{25}H_{16}F_2N_4O_3$	15.7	0.6	2.9	–	2.0	4.6
M5-1	461.1461	$C_{25}H_{18}F_2N_4O_3$	10.2	2.0	2.1	1.3	2.1	0.7
M5-2	461.1424	$C_{25}H_{18}F_2N_4O_3$	10.5	1.1	0.8	0.7	–	0.4
M5-3	461.1407	$C_{25}H_{18}F_2N_4O_3$	10.9	3.6	19.7	3.0	27.7	19.2
M5-4	461.1433	$C_{25}H_{18}F_2N_4O_3$	11.9	1.6	–	0.6	1.9	2.1
M6-1	447.1321	$C_{24}H_{16}F_2N_4O_3$	9.5	–	0.4	–	–	–
M6-2	447.1281	$C_{24}H_{16}F_2N_4O_3$	9.7	–	2.0	–	–	–
M7	250.0797	$C_{12}H_9F_2N_3O$	7.6	–	–	0.5	–	–
M8	280.0847	$C_{13}H_{11}F_2N_3O_2$	7.5	–	–	1.1	–	0.3
M9	416.1239	$C_{24}H_{15}F_2N_3O_2$	13.0	–	–	0.7	–	–

[a] The in vitro metabolism of **22e** by liver microsomes from rats, mouse, dogs, monkeys, and humans in the presence of NADPH. **22e** (3 μM) was incubated at 37°C with liver microsomes from various species (1 mg of protein/mL) and potassium phosphate buffer (100 mM, pH 7.4) with NADPH (1.0 mM). Incubations were terminated with organic, centrifuged, and the resulting supernatants analyzed by UPLC/Q-TOF MS.

Docking studies

The c-Met protein was extracted from RCSB Protein Data Bank (PDB ID: 3ZXZ). Compounds were generated using ChemDraw program. Docking studies were

performed using Glide program. The c-Met protein was processed by minimal minimization with OPLS2005 force field. The grid was sized to 15 Å in each direction at the center of the binding pocket. Compounds were prepared for docking using Ligprep. Ligand docking was performed in SP mode and flexible option. Glide score was consulted for results analyzing.