CHAPTER 2

EXPERIMENTAL

General Experimental Procedures

Melting points were measured using a Kofler hot-stage apparatus or Reichert hot-stage microscope and are uncorrected. The IR spectra were obtained on a Perkin-Elmer FT-IR spectrometer as thin film on sodium chloride discs. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker DPX300 and Bruker DRX500 instruments and recorded as δ values in ppm down field from TMS (internal standard δ= 0.00) and coupling constants are given in hertz (Hz). HRESIMS was recorded on a Bruker HCT-ultra (ESI^{+}), and accurate masses were obtained using a Bruker Daltonics micrOTOF mass spectrometer. Pre-coated TLC aluminium sheets of silica gel $60F_{254}$ (E. Merck) was used for analytical proposes and compounds were visualized under ultraviolet light (at 254 nm). Column chromatography was performed using silica gel 60 (230-400 mesh). Reagents were obtained from commercial supplier.

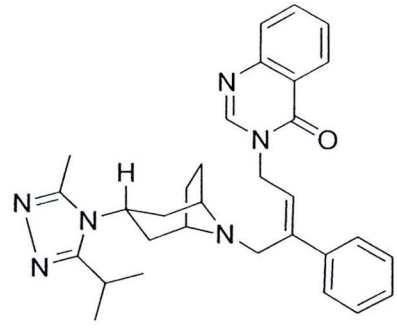
All compounds were named according to the IUPAC system using the ACD/ILAB (ACD/IUPAC v.12.0 programme) web service (http:/www.acdlabs.com).

Experimental Data

General procedure A: Palladium catalysed-3-component cascade

$Pd(OAc)_2$ (0.0056 g, 5 mol %) and tri(2-furyl)phosphine (0.0116 g, 10 mol%) were added to a stirred solution of the allene (0.5 mmol), aryl iodide (0.5 mmol), *N*-heterocycle (0.6 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 2 h, then cooled, filtered and the filtrate evaporated. The residue was purified by flash column chromatography to yield the product.

3-{(2Z)-4-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo [3.2.1]oct-8-yl]-3-phenylbut-2-en-1-yl}quinazolin-4(3H)-one

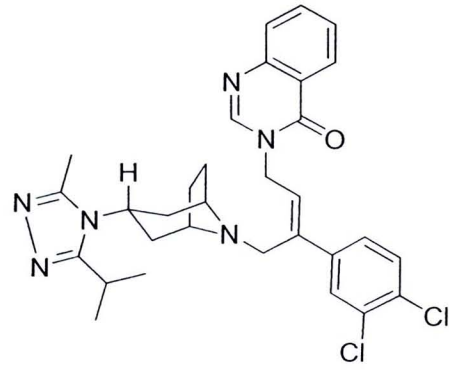


2.24

Prepared by general procedure A from $Pd(OAc)_2$ (0.0056 g, 5 mol %), tri(2-furyl)phosphine (0.0116 g, 10 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), iodobenzene (0.1020 g, 0.5 mmol), 1,3,4-triazole-subtituted tropane (0.1400 g, 0.6 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80°C for 2 h. Work up followed by chromatography eluting with MeOH-Et_2O 1:20, afforded

the product (239 mg, 96%). as a yellow amorphous solid, m.p. 103-105 °C; R_f 0.22 (MeOH-Et_2O 1:4); FT-IR (film) ν_{max}/cm^{-1}; 2965, 1673, 1609, 1366, 1322, 1290, 1253; ^1H NMR ($CDCl_3$, 300 MHz); δ_H 8.33 (1H, d, J = 0.5 Hz, ArH), 8.22 (1H, s, ArH), 7.81 (1H, ddd, J = 8.2 , 6.8, 1.4 Hz, ArH), 7.74 (1H, app t, J = 8.2 Hz, ArH), 7.54 (1H, J = 7.4, 1.2 Hz, ArH), 7.43-7.34 (2H, m, ArH), 7.35-7.26 (3H, m, ArH), 5.92 (1H, t, J = 7.0 Hz, CH=) 4.96 (2H, d, J = 7.0 Hz, NCH_2CH=), 4.25 (1H, heptet, J = 6.1 Hz, CHN), 3.68 (2H, s, NCH_2CH=), 3.43 (2H, brs, NCHCH_2), 2.92 (1H, q, J = 6.9 Hz, CH(CH_3)$_2$), 2.36 (3H, s, CH_3), 2.19 (2H, m, CH_2) 2.06 (2H, t, J = 11.2 Hz, CH_2), 1.72-1.61 (4H, m, CH_2), 1.32 (6H, d, J = 6.8 Hz, CHCH_3); ^{13}C NMR δ_C (75 MHz, $CDCl_3$); 161.5 (CO), 159.6 (ArC), 151.1 (ArC), 148.4 (ArC), 146.6 (ArCH), 143.6 (C=CH), 142.0 (ArC), 134.9 (ArCH), 128.6 (2 × ArCH), 128.1 (ArCH), 127.9 (2 × ArCH), 127.2 (2×ArCH), 127.1 (ArCH), 125.6 (CH=), 122.5 (ArC), 59.2 (2 × CHN), 51.6 (CH$_2$CH=), 49.7 (CHN), 44.7 (CH$_2$C=), 37.5 (2 × CH_2), 27.0 (2 × CH_2), 26.2 (CH(CH_3)$_2$), 22.0 (2 × CH_3), 13.1 (CH_3); HRESIMS *m/z* $[M + H]^+$ 509.3024 (calcd for $C_{31}H_{37}N_6O$, 509.3023); Elemental anal: C, 67.7; H, 6.95; N, 15.6%, calcd for $C_{31}H_{40.5}N_6O_{3.25}$, C, 67.8; H, 7.43; N, 15.3%.

3-{(2Z)-3-(3,4-Dichlorophenyl)-4-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]but-2-en-1-yl}quinazolin-4(3H)-one

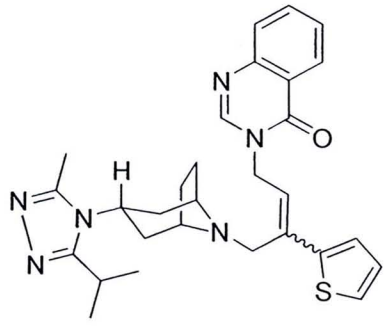


2.25

Prepared by general procedure A from $Pd(OAc)_2$ (0.0056 g, 5 mol %), tri(2-furyl)phosphine (0.0116 g, 10 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 3,4-dichlorobenzene (0.1360 g, 0.5 mmol), 1,3,4-triazole-subtituted tropane (0.1400 g, 0.6 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 3 h. Work up followed by chromatography eluting with MeOH-EtOAc 3:17, afforded the product (266 mg, 92%) as a pale yellow amorphous solid, m.p. 96-98 °C; R_f 0.18 (MeOH-EtOAc 3:17); FT-IR (film) ν_{max} 2968, 1668, 1611, 1564, 1517, 1474, 1417, 1367, 1323, 1291, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz); δ_H 8.32 (1H, dd, J = 8.0, 0.9 Hz, ArH), 8.15 (1H, s, ArH), 7.80 (1H, dt, J = 6.8, 1.38 Hz, ArH), 7.74 (1H, J = 8.1, 0.9 Hz, ArH), 7.66 (1H, d, J = 2.0 Hz, ArH), 7.54 (1H, ddd, J = 8.1, 6.8, 1.3 Hz, ArH), 7.38 (1H, d, J = 8.4 Hz, ArH), 7.26 (1H, dd, J = 8.4, 2.12 Hz, ArH), 5.94 (1H, t, J = 6.9 Hz, CH=), 4.90 (2H, d, J = 6.9 Hz, NCH_2CH=), 4.25 (1H, heptet, J = 6.1 Hz, CHN), 3.62 (2H, s, NCH_2C=), 3.42 (2H, brs, CHN), 2.92 (1H, q, J = 6.9 Hz, $CH(CH_3)_2$),

in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 2 h. Work up followed by chromatography eluting with MeOH-EtOAc 3:17 afforded the product (266 mg, 92%) as a pale yellow amorphous solid, m.p. 92-95 °C; R_f 0.18 (MeOH-EtOAc 3:17); FT-IR (film) ν_{max} 2964, 1673, 1609, 1563, 1514, 1473,1366, 1321, 1289,1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.70 (1H, d, J = 2.1 Hz, ArH), 8.53 (1H, dd, J = 4.8, 1.5 Hz, ArH), 8.37 (1H, dd, J = 8.0, 0.8 Hz, ArH), 8.17 (1H, s, ArH), 7.72-7.80 (3H, m, ArH), 7.54 (1H, ddd, J = 8.1, 6.8, 1.4 Hz, ArH), 7.26 (1H, dd, J = 7.9, 4.0 Hz, ArH), 5.96 (1H, t, J = 6.9 Hz, CH=), 4.94 (2H, d, J = 6.9 Hz, NCH_2CH=), 4.24 (1H, heptet, J = 6.1 Hz, CHN), 3.69 (2H, s, NCH_2C=), 3.42 (2H, brs, CHN), 2.90 (1H, q, J = 6.9 Hz, C$H(CH_3)_2$), 2.34 (3H, s, CH_3), 2.24-2.21 (2H, m, CH_2), 2.03 (2H, dt, J = 12.4, 2.6 Hz, CH_2), 1.76-1.63 (4H, m, CH_2), 1.34 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.4 (CO), 159.5 (ArC), 151.0 (ArC), 149.2 (ArCH), 148.6 (ArCH), 148.5 (ArC), 146.2 (ArCH), 140.6 (*C*=CH), 137.1 (ArC), 134.9 (ArCH), 134.7 (ArCH), 128.6 (ArCH), 128.0 (ArC), 128.0 (ArCH), 127.1 (ArCH), 126.8 (CH=), 123.2 (ArCH), 122.5 (ArC), 59.4 (2 × CHN), 51.6 (NCH_2C=), 47.4 (CHN), 44.6 (NCH_2CH=), 37.9 (2 × CH_2), 27.0 (2 × CH_2), 26.3 (CHN), 22.1 (2 × CH_3), 13.3 (CH_3); HRESIMS *m/z* 510.2962 $[M + H]^+$ (calcd for $C_{30}H_{36}N_7O$, 510.2976); Elemental anal: C, 66.9; H, 6.80; N, 18.0%, calcd for $C_{30}H_{38}N_7O_{2.5}$, C, 67.1; H, 7.14; N, 18.3%.

3-[(2E)-4-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo [3.2.1]oct-8-yl]-3-(2-thienyl)but-2-en-1-yl]quinazolin-4(3H)-one



2.27

Prepared by general procedure A from $Pd(OAc)_2$ (0.0056 g, 5 mol %), tri(2-furyl)phosphine (0.0116 g, 10 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 2-iodothiophene (0.1050 g, 0.5 mmol), 1,3,4-triazole-subtituted tropane (0.1400 g, 0.6 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 2 h. Work up followed by chromatography eluting with MeOH-Et_2O 1:4 afforded a 2.6:1 mixture of *E*- and *Z*-isomer (202 mg, 80%). The major *E*-isomer was a pale yellow amorphous solid, m.p. 98-100 °C; R_f 0.21 (MeOH-Et_2O 1:4); FT-IR (film) ν_{max} 2965, 1670, 1610, 1517, 174, 1365, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.32 (1H, dd, J = 8.0, 0.8 Hz, ArH), 8.18 (1H, s, ArH), 7.79 (1H, ddd, J = 8.2, 6.8, 1.5 Hz, ArH), 7.74 (1H, dt, J = 6.5, 5.9, 1.4 Hz, ArH), 7.53 (1H, ddd, J = 8.1, 6.7, 1.4 Hz, ArH), 7.53 (2H, app t, J = 4.5 Hz, ArH), 6.98 (1H, dd, J = 5.1, 3.8 Hz, ArH), 6.12 (1H, t, J = 7.0 Hz, CH=), 4.93 (2H, d, J = 7.1 Hz, NCH_2CH=), 4.32 (1H, heptet, J = 6.1 Hz, CHN), 3.58 (2H, s, NCH_2C=), 3.52 (2H, brs, CHN), 3.05 (1H, q, J =6.8 Hz, $CH(CH_3)_2$), 2.52 (3H, s, CH_3), 2.39-2.27 (4H, m, CH_2), 1.80-1.70 (4H, m, CH_2), 1.39 (6H,

(4H, m, CH_2), 1.39 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 160.40 (CO), 159.6 (ArC), 151.0 (ArC), 148.5 (ArCH), 146.3 (ArCH), 144.7 (ArC), 136.4 (*C*=CH), 134.8 (ArCH), 128.0 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 126.2 (ArCH), 125.9 (ArC), 124.8 (ArCH), 123.5 (CH=), 122.5 (ArC), 59.5 (2 × CHN), 52.4 (N*C*H_2C=), 47.7 (CHN), 44.5 (N*C*H_2CH=), 37.7 (2 × CH_2), 27.1 (2 × CH_2), 26.3 (C*H*(CH_3)$_2$), 22.1 (2 × CH_3), 13.4 (CH_3); HRESIMS *m/z* 515.2582 $[M + H]^+$ (calcd for $C_{29}H_{35}N_6OS$, 515.2588); Elemental anal: C, 66.8; H, 6.65; N, 16.2%, calcd for $C_{29}H_{35}N_6O_{1.5}S$, C, 66.5; H, 6.74; N, 16.1%.

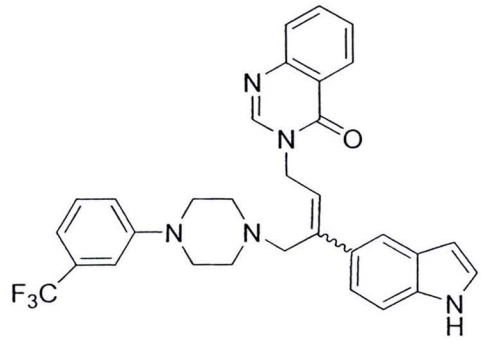
Minor *Z*-isomer was a yellow gum, FT-IR (film) ν_{max} 2964, 1674, 1607, 1563, 1519, 1473,1366, 1291, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.32 (1H, dd, J = 8.0, 0.9 Hz, ArH), 7.93 (1H, s, ArH), 7.78 (1H, ddd, J = 8.3, 7.0, 1.5 Hz, ArH), 7.71 (1H, dd, J = 8.2, 0.6 Hz, ArH), 7.56 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.41 (1H, dd, J = 5.0, 1.1 Hz, ArH), 7.12 (1H, dd, J = 5.1, 3.6 Hz, ArH), 7.08 (1H, dd, J = 3.5, 1.1 Hz, ArH), 5.83 (1H, t, J = 6.4 Hz, CH=), 4.89 (1H, d, J = 6.4 Hz, NC*H*$_2$CH=), 4.29 (1H, heptet, J = 6.1 Hz, CHN), 3.42 (2H, brs, NC*H*CH_2), 3.19 (1H, s, NCH_2C=), 3.05 (1H, q, J = 6.9 Hz, C*H*(CH_3)$_2$), 2.94 (3H, s, CH_3), 2.26 (2H, dt, J = 12.3, 12.2, 2.4 Hz, CH_2), 2.11-2.08 (2H, m, CH_2), 1.74-1.63 (2H, m, CH_2), 1.67 (2H, d, J = 8.4 Hz, CH_2),1.35 (6H, d, J = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.1 (CO), 159.4 (ArC), 150.9 (ArC), 147.9 (ArC), 146.2 (ArCH), 139.0 (ArC), 136.3 (*C*=CH), 134.6 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 126.8 (ArCH), 126.7 (2 × ArCH), 124.7 (CH=), 122.0 (ArC), 60.7 (N*C*H_2C=), 59.5 (2 × CHN), 47.7 (CHN), 45.4 (N*C*H_2CH=), 37.3 (2 × CH_2), 26.7 (2 × CH_2), 25.8 (C*H*(CH_3)$_2$),

21.9 (2 × CH_3), 12.8 (CH_3); HRESIMS *m/z* 515.2609 $[M + H]^+$ (calcd for $C_{29}H_{35}N_6OS$, 515.2588).

General procedures B: Palladium Catalyzed-3-Component Cascade

As for general procedure A except that $Pd(OAc)_2$ (0.0122 g, 10 mol %) and tri(2-furyl)phosphine (0.0232 g, 20 mol%) were used.

3-[(2Z)-3-(1H-Indol-5-yl)-4-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}but-2-en-1-yl]quinazolin-4(3H)-one



2.28

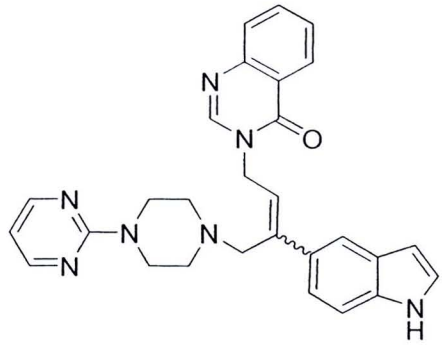
Prepared by general procedure B from $Pd(OAc)_2$ (0.0122 g, 10 mol %), tri(2-furyl)phosphine (0.0232 g, 20 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 1-(3-trifluoromethylphenyl) piperazine (0.1381 g, 0.6 mmol), 5-iodoindole (0.1210 g, 0.5 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 2 h. Work up followed by chromatography eluting with Et_2O-Hexanes 9:1 afforded a 5.4:1 mixture of *Z*- and *E*-isomer (179 mg, 66%). The major *Z*-isomer as a yellow amorphour solid; m.p. 79-81 °C; R_f 0.23 (EtOAc-hexanes

1:1); FT-IR (film) ν_{max} 3315, 2924, 2828, 1671, 1610, 1564, 1496, 1474, 1449, 1319, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.36 (1H, brs, NH), 8.33 (1H, s, ArH), 8.34 (1H, d, J = 8.8 Hz, ArH), 7.78-7.7 (1H, 3H, m, ArH), 7.51 (1H, ddd, J = 8.2, 6.2, 1.7 Hz, ArH), 7.31 (1H, t, J = 6.8 Hz, ArH), 7.30 (1H, d, J = 7.7 Hz, ArH), 7.25 (1H, dd, J = 8.54, 1.54 Hz, ArH), 7.20 (1H, t, J = 2.8 Hz, ArH), 7.06 (1H, s, ArH), 7.05 (1H,d, J = 7.1 Hz, ArH), 7.01 (1H, d, J = 8.9 Hz, ArH), 6.53 (1H, app t, J = 2.14 Hz, ArH), 6.04 (1H, t, J = 7.1 Hz, CH=), 5.01 (2H, d, J = 7.08 Hz, NCH_2CH=), 5.02 (2H, d, J = 7.1 Hz, NCH_2C=), 3.19 (4H, t, J = 4.7 Hz, CH_2N), 2.96 (4H, t, J = 4.5, Hz CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.2 (CO), 151.3 (ArC), 148.1 (ArC), 145.7 (ArCH), 142.2 (*C*=CH), 135.4 (ArC), 134.2 (ArCH), 134.0 (ArC),131.4 (q, J = 31.8 Hz, *C*-CF_3), 129.5 (ArCH), 127.9 (ArCH), 127.5 (ArCH), 127. 3 (ArCH), 126.7 (ArCH), 124.9 (ArCH), 124.8 (CH=), 124.3 (q, J = 272.4 Hz, CF_3), 122.2 (ArC), 121.1 (ArCH), 118.8 (ArCH), 118.7 (ArC), 115.7 (q, J = 4.1 Hz, *C*H=C-CF_3), 112.1 (q, J = 3.6 Hz, *C*H=C-CF_3), 110.8 (ArCH), 103.0 (ArCH), 58.3 (NCH_2C=), 53.0 (2 × CH_2N), 48.6 (2 × CH_2N), 44.6 (NCH_2CH=); HRESIMS m/z 544.2318 $[M + H]^+$ (calcd for $C_{31}H_{29}F_3N_5O$, 544.2319).

Minor *E*-isomer was a yellow amorphous solid; FT-IR (film) ν_{max} 3318, 2924, 2853, 1673, 1610, 1495, 1451, 1365, 1320, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.33 (1H, s, NH), 8.32 (1H, dd, J = 7.9, 0.7 Hz, ArH), 7.74 (1H, t, J = 7.6, ArH), 7.75 (1H, s, ArH), 7.58 (1H, d, J = 8.1 Hz, ArH), 7.53 (1H, s, ArH), 7.51 (1H, t, J = 7.06 Hz, ArH), 7.44 (1H, d, J = 8.3 Hz, ArH), 7.33 (1H, t, J = 7.8 Hz, ArH), 7.27 (1H, t, J = 2.5 Hz, ArH), 7.11-7.01 (4H, m, ArH), 6.60-6.58 (1H, m, ArH), 5.95 (1H, t, J = 6.9 Hz, CH=), 4.67 (2H, d, J = 4.7

Hz, ArH), 3.35 (2H, s, NCH_2C=), 3.20 (4H, t, J = 4.9 Hz, CH_2N), 2.65 (4H, t, J = 4.9 Hz, CH_2N), ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.1 (CO), 151.4 (ArC), 148.1 (ArC), 146.4 (ArCH), 144.0 (*C*=CH), 135.3 (ArC), 134.2 (ArCH), 131.4 (q, J 25.3, *C*—CF_3), 130.2 (ArC), 129.5 (ArCH), 127.9 (ArC), 127.4 (ArCH), 127.2 (ArCH), 126.7 (ArCH), 125.0 (ArCH), 124.5 (q, J = 272.4 Hz, CF_3), 122.8 (CH=), 122.4 (ArCH), 122.2 (ArC), 120.4 (ArCH), 118.7 (ArCH), 115.7 (q, J = 3.6 Hz, *C*H=CCF_3), 112.1 (q, J = 3.0 Hz, *C*H=CCF_3) 111.2 (ArCH), 102.8 (ArCH), 65.9 (N*C*H_2CH=), 52.9 (2 × CH_2N), 48.6 (2 × CH_2N), 44.7 (N*C*H_2C=); HRESIMS m/z 544.2318 $[M + H]^+$ (calcd for $C_{31}H_{29}F_3N_5O$, 544.2319).

3-{(2Z)-3-(1H-Indol-5-yl)-4-[4-(pyrimidin-2-yl)piperazin-1-yl]but-2-en-1-yl}quinazolin-4(3H)-one



2.29

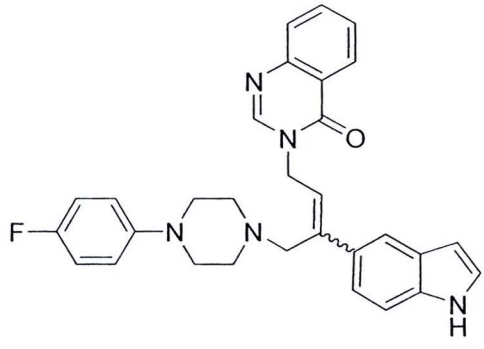
Prepared by general procedure B from $Pd(OAc)_2$ (0.0122 g, 10 mol %), tri(2-furyl)phosphine (0.0232 g, 20 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 1,2-pyrimidyl piperazine (0.0980 g, 0.6 mmol), 5-iodoindole (0.1210 g, 0.5 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 3 h. Work up followed by chromatography eluting with MeOH-Et_2O 1:100 afforded a

6.8:1 mixture of *Z*- and *E*-isomer (189 mg, 79%). The major *Z*-isomer was a pale yellow needles, m.p. 145-148 °C (from Et_2O-CH_2Cl_2), R_f 0.11 (MeOH-Et_2O 1:100); FT-IR (film) ν_{max} 3401, 2948, 1667, 1610, 1586, 1547, 1475, 1448, 1392, 1359, 1308, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.43 (1H, brs, NH), 8.349 (1H, d, J = 9.0 Hz, ArH), 8.36 (1H, s, ArH), 8.29 (1H, d, J = 4.7 Hz, ArH), 7.79 (3H, m, ArH), 7.51 (1H, ddd, J = 8.2, 6.6, 1.8 Hz, ArH), 7.30 (1H, t, J = 8.5 Hz, ArH), 7.26 (1H, t, J = 8.4 Hz, ArH), 7.19 (1H, t, J = 2.8 Hz, ArH), 6.51 (1H, app t, J = 2.6 Hz, ArH), 6.46 (1H, t, J = 4.7 Hz, ArH), 6.04 (1H, t, J = 7.1 Hz, CH=), 5.02 (2H, d, J = 7.0 Hz, NCH_2CH=), 3.83 (4H, t, J = 4.8 Hz, CH_2N), 3.65 (2H, s, NCH_2C=), 2.6 (4H, t, J = 4.9 Hz, CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.6 (ArC), 161.2 (CO), 157.7 (2 × ArCH), 148.2 (ArC), 146.7 (ArCH), 142.2 (C=CH), 135.4 (ArC), 134.2 (ArCH), 134.0 (ArC), 127.8 (ArC), 127.5 (ArCH), 127.2 (ArCH), 126.7 (ArCH), 125.5 (ArC), 124.9 (ArCH), 124.6 (CH=), 122.2 (ArCH), 121.1 (ArCH), 118.7 (ArCH), 111.8 (ArCH), 109. 8 (ArCH), 102.9 (ArCH), 58.5 (NCH_2C=), 53.1 (2 × CH_2N), 44.7 (NCH_2CH=), 43.8 (2 × CH_2N); HRESIMS *m/z* 478.2350 $[M + H]^+$ (calcd for $C_{28}H_{28}N_7O$, 478.2350).

Minor *E*-isomer, FT-IR (film) ν_{max} 3319, 2949, 1673, 1609, 1586, 1548, 1474, 1448, 1359, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8. 53 (1H, brs, NH), 8.29 (2H, dd, J = 8.0, 1.3 Hz, ArH), 7.71 (1H, s, ArH), 7.69-1.773 (1H, m, ArH), 7.65 (1H, dd , J = 8.1, 0.7 Hz, ArH), 7.49 (1H, br s, ArH), 7.47 (1H, t, J = 8.2 Hz, ArH), 7.38 (1H, d, J = 8.3 Hz, ArH), 7.22 (1H, t, J = 2.76 Hz, ArH), 7.05 (1H, dd, J = 8.3, 1.5 Hz, ArH), 6.54 (1H, t, J = 2.1 Hz, ArH), 6.44(1H, t, J = 4.8 Hz, ArH), 5.93 (1H, t, J = 6.9 Hz, CH=), 4.64 (2H, d, J =

6.9 Hz, NCH_2CH=), 3.75 (1H, t, J = 4.8 Hz, CH_2N), 3.75 (4H, t, J = 4.8 Hz, CH_2N), 3.31 (2H, s, NCH_2C=), 2.51 (4H, t, J = 5.0 Hz, CH_2N), ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 161.7 (ArC), 161.0 (CO), 157.6 (2 × ArCH), 148.1 (ArC), 146.3 (ArCH), 144.1 (C=CH), 135.3 (ArC), 134.1 (ArCH), 130.1 (ArC), 127.9 (ArC), 127.4 (2×ArCH), 126.7 (ArCH), 125.0 (ArCH), 122.3 (ArCH and CH=), 122.1 (ArC), 120.3 (ArCH), 111.2 (ArCH), 109.7 (ArCH), 102.7 (ArCH), 66.0 (NCH_2C=), 53.0 (2 × CH_2N), 44.7 (NCH_2CH=), 43.7 (2 × CH_2N); HRESIMS m/z 478.2346 $[M + H]^+$ (calcd for $C_{28}H_{28}N_7O$, 478.2350).

3-[(2Z)-4-[4-(4-Fluorophenyl)piperazin-1-yl]-3-(1H-indol-5-yl)but-2-en-1-yl]quinazolin-4(3H)-one



2.30

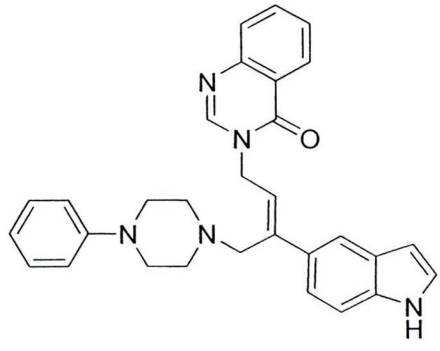
Prepared by general procedure B from $Pd(OAc)_2$ (0.0122 g, 10 mol %), tri(2-furyl)phosphine (0.0232 g, 20 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 1-(4-fluorophenyl)piperazine (0.1289 g, 0.6 mmol), 5-iodoindole (0.1210 g, 0.5 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 2 h. Work up followed by chromatography eluting with Et_2O afforded a 5:1 mixture of *Z*- and *E*-isomer (165 mg, 67%). The major *Z*-isomer was a pale

yellow amorphous solid; m.p. 93-95 °C; R_f 0.10 (Et_2O); FT-IR (film) ν_{max} 3314, 2823, 1668, 1609, 1508, 1473, 1369, 1321, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.32 (1H, brs, NH), 8.34 (1H, d, J = 7.7 Hz, ArH), 8.34 (1H, s, ArH), 7.79 (3H, m, ArH), 7.51(1H, ddd, J = 8.1, 6.7, 1.6 Hz, ArH), 7.31(1H, t, J = 8.6 Hz, ArH), 7.27 (1H, dt, J = 8.5, 1.4 Hz, ArH), 7.20 (3H, app t, J = 2.8 Hz, ArH), 6.95 (1H, t, J = 8.7 Hz, ArH), 6.83 (1H, dd, J 9.2, 4.6 Hz, ArH), 6.52 (1H, app t, J = 2.2 Hz, ArH), 6.03 (1H, t, J = 7.1 Hz, CH=), 5.02 (2H, d, J = 7.1 Hz, NCH_2CH=), 3.68 (2H, s, NCH_2C=), 3.10 (4H, t, J = 4.3 Hz, CH_2N), 2.71 (4H, brs, CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.2(CO), 157.1 (d, J = 238.0 Hz, C-F), 148.2 (ArC), 147.9 (ArC), 146.7 (ArCH), 142.2 (*C*=CH), 135.4 (ArC), 134.2 (ArCH), 134.0 (ArC), 127.8 (ArC), 127.4 (ArCH), 127.3(ArCH), 126.7 (ArCH), 124.9 (ArC and CH=), 122.2 (ArC), 121.1 (ArCH), 118.7 (ArCH), 117.8 (d, J = 7.7 Hz, 2 × *C*H=CH—C—F), 115.4 (d, J = 22.0 Hz, 2 × *C*H-C-F), 111.1 (ArCH), 110.8 (ArCH), 102.9 (ArCH), 58.3 (NCH_2C=), 53.2 (2 × CH_2N), 50.11 (2 × CH_2N), 44.7 (NCH_2CH=); HRESIMS *m/z* 494.2352 $[M + H]^+$ (cacld for $C_{30}H_{29}FN_5O$, 494.2351); Elemental anal: C, 70.0; H, 5.55; N, 13.4%, calcd for $C_{30}H_{30}FN_5O_2$, C, 70.4; H, 5.91; N, 13.7%.

Minor *E*-isomer, FT-IR (film) ν_{max} 2953, 1673, 1609, 1509, 1473, 1367, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (300 MHz, $CDCl_3$); 9.05 (1H, brs, NH), 8.30 (1H, dd, J = 8.3, 0.8 Hz, ArH), 7.77 (1H, t, J = 8.3 Hz, ArH), 7.72 (1H, s, ArH), 7.67 (1H, d, J = 8.2 Hz, ArH), 7.51 (1H, *t*, J = 7.3 Hz, ArH), 7.51 (1H, s, ArH), 7.45 (1H, d, J = 8.3 Hz, ArH), 7.27 (1H, app t, J = 2.5 Hz, ArH), 7.07 (1H, dd, J = 8.3, 1.3 Hz, ArH), 6.94 (2H, dd, J = 6.7, 15.4 Hz, ArH), 6.85 (2H, dd, J = 9.2, 4.6 Hz, ArH), 6.56 (1H, brs, ArH), 5.93 (1H, t, J

= 7.1 Hz, CH=), 4.67 (2H, d, J = 6.9 Hz, NCH_2CH=), 3.37 (2H, s, NCH_2C=), 3.07 (4H, t, J = 4.8 Hz, CH_2N), 2.64 (4H, t, J = 4.9 Hz, CH_2N); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 161.2 (CO), 157.3 (d, J = 238.3 Hz, C-F), 148.0 (d, J = 2.7 Hz, =*C*-CH=CH-C-F), 147.8 (ArC), 146.6 (ArCH), 144.4 (*C*=CH), 135.4 (ArC), 134.4 (ArCH), 129.7 (ArC), 128.0 (ArC), 127.5 (ArCH), 127.1 (ArCH), 126.7 (ArCH), 125.5 (ArC), 125.2 (ArC), 122.6 (ArC), 122.0 (ArCH and ArC), 120.2 (ArCH), 118.0 (d, J = 7.8 Hz, 2 × *C*H=CH-C-F), 115.5 (d, J = 22.3 Hz, 2 × *C*H-C-F), 111.4 (ArCH), 102.2 (ArCH), 65.9 (N*C*H_2C=), 53.0 (2 × CH_2N), 49.8 (2 × CH_2N), 44.9 (N*C*H_2CH=); HRESIMS *m/z* 494.2370 $[M + H]^+$ (calcd for $C_{30}H_{29}FN_5O$, 494.2351).

3-[(2Z)-3-(1H-Indol-5-yl)-4-(4-phenylpiperazin-1-yl)but-2-en-1-yl]quinazolin-4(3H)-one



2.31

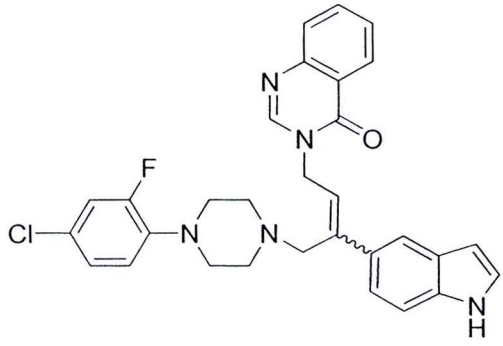
Prepared by general procedure B from $Pd(OAc)_2$ (0.0122 g, 10 mol %), tri(2-furyl)phosphine (0.0232 g, 20 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 1-phenylpiperazine (0.0973 g, 0.6 mmol), 5-iodoindole (0.1210 g, 0.5 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 4 h. Work up

followed by chromatography eluting with Et_2O-hexanes 7:1 afforded a 7:1 mixture of *Z*- and *E*-isomer (146 mg, 62%). The major *Z*-isomer was colourless needles, m.p. 196-197 °C (from DCM-Et_2O); R_f 0.04 (Et_2O-hexanes 7:1); FT-IR (film) ν_{max} 3314, 2823, 1668, 1609, 1495, 1473, 1370, 1321, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.39 (1H, brs, NH), 8.35 (1H, dd, J = 6.0, 1.0 Hz, ArH), 8.36 (1H, s, ArH), 7.78-7.70 (3H, m, ArH), 7.51 (1H, ddd, J = 8.1, 6.6, 1.7 Hz, ArH), 7.32-7.22 (4H, m, ArH), 7.20 (1H, J = 2.77 Hz, ArH), 6.90 (2H, d, J = 8.0 Hz, ArH), 6.84 (1H, t, J = 7.3 Hz, ArH), 6.52 (1H, app t, J = 2.2 Hz, ArH), 6.03 (1H, t, J = 7.1 Hz, CH=), 5.02 (2H, d, J = 7.1 Hz, NCH_2CH=), 3.66 (2H, s, NCH_2C=), 3.18 (4H, t, J = 4.7 Hz, CH_2N), 2.70 (4H, t, J = 4.7 Hz, CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.6 (CO), 151.6 (ArC), 148.6 (ArC), 147.2 (ArCH), 142.7 (*C*=CH), 135.8 (ArC), 134.5 (ArCH), 134.5 (ArC), 129.5 (2 × ArCH), 128.3 (ArC), 127.9 (ArCH), 127.7 (ArCH), 127.1 (ArCH), 125.3 (ArCH), 125.1 (CH=), 122.7 (ArC), 121.5 (ArCH), 120.0 (ArCH), 119.2 (ArCH), 116.5 (2 × ArCH), 111.3 (ArCH), 103.4 (ArCH), 58.8 (NCH_2C=), 53.7 (2 × CH_2N), 49.6 (2 × CH_2N), 45.1 (NCH_2CH=); HRESIMS 476.2443 $[M + H]^+$ (calcd for $C_{30}H_{30}N_5O$, 476.2445). Elemental anal: C, 74.9; H, 6.10; N, 14.6%, calcd for $C_{30}H_{29.5}N_5O_{1.25}$, C, 75.1; H, 6.19; N, 14.6%.

Minor *E*-isomer, FT-IR (film) ν_{max} 3312, 2926, 2820, 1673, 1609, 1495, 1473, 1368, 1323, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.56 (1H, brs, NH), 8.30 (1H, d, J = 8.0 Hz, ArH), 7.73 (1H, s, ArH), 7.72 (1H, t, J = 8.4 Hz, ArH), 7.66 (1H, d, J = 8.0 Hz, ArH), 7.50 (1H, s, ArH), 7.47 (1H, t, J = 7.0 Hz, ArH), 7.37 (1H, d, J = 8.3 Hz, ArH), 7.24-7.20 (3H, m, ArH), 7.05 (1H, dd, J = 8.3, 1.3 Hz, ArH), 6.87 (2H, d, J = 8.1 Hz, ArH), 6.81 (1H, t, J = 7.2 Hz,

ArH), 6.54 (1H, brs, ArH), 5.92 (1H, t, J = 6.9 Hz, CH=), 4,64 (2H, d, J = 6.9 Hz, NCH_2CH=), 3.33 (2H, s, NCH_2C=), 3.13 (4H, t, J = 4.8 Hz, CH_2N), 2.60 (4H, t, J = 4.8 Hz, CH_2N); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_c 161.0 (CO), 151.4 (ArC), 148.1 (ArC), 146.4 (ArCH), 142.2 (*C*=CH), 135.3 (ArC), 134.1 (ArCH), 130.2 (ArC), 129.1 (2×ArCH), 127.9 (ArC), 127.4 (ArCH), 127.2 (ArCH), 126.7 (ArCH), 125.1 (ArCH), 122.6 (CH=), 122.3 (ArCH), 122.2 (ArC), 120.3 (ArCH), 119.5 (ArCH), 116.0 (2 × ArCH), 111.3 (ArCH), 102.7 (ArCH), 66.0 (N*C*H_2C=), 53.2 (2 × CH_2N), 49.1 (2 × CH_2N), 44.7 (N*C*H_2CH=); HRESIMS *m/z* 476.2453 $[M + H]^+$ (calcd for $C_{30}H_{30}N_5O$, 476.2445).

3-[(2Z)-4-[4-(4-Chloro-2-fluorophenyl)piperazin-1-yl]-3-(1H-indol-5-yl) but-2-en-1-yl]quinazolin-4(3H)-one



2.32

Prepared by general procedure B from $Pd(OAc)_2$ (0.0122 g, 10 mol %), tri(2-furyl)phosphine (0.0232 g, 20 mol%), 3-(buta-2,3-dienyl)quinazolin-4(3H)-one (0.0990 g, 0.5 mmol), 1-(4-chloro-2-fluorophenyl)piperazine (0.1288 g, 0.6 mmol), 5-iodoindole (0.1210 g, 0.5 mmol) and cesium carbonate (0.3250 g, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred and heated at 80 °C for 2 h.

Work up followed by chromatography eluting with Et_2O afforded a 6.2:1 mixture of *Z*- and *E*-isomer (165 mg, 62%). The major *Z*-isomer as pale yellow amorphous solid; m.p. 63-66 °C; R_f 0.11 (Et_2O); FT-IR (film) ν_{max} 3252, 2939, 2826, 1668, 1609, 1564, 1495, 1473, 1413, 1370, 1322, 1258, 1234, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.42 (1H, brs, NH), 8.35 (1H, dd, *J* = 8.4 Hz, ArH), 8.34 (1H, s, ArH), 7.78 (1H, ddd, *J* = 8.2, 6.8, 1.4 Hz, ArH), 7.74-7.71 (2H, m, ArH), 7.53 (1H, ddd, *J* = 8.1, 6.6, 1.7 Hz, ArH), 7.30 (1H, t, *J* = 8.5 Hz, ArH), 7.30-7.24 (1H, m, ArH), 7.20 (1H, t, *J* = 2.8 Hz, ArH), 7.03 (1H, app t, *J* = 3.9 Hz, ArH), 7.00 (1H, d, *J* = 3.2 Hz, ArH), 6.79 (1H, t, *J* = 9.0 Hz, ArH), 6.53-6.52 (1H, m, ArH), 6.03 (1H, t, *J* = 7.1 Hz, CH=), 5.06 (1H, d, *J* = 6.9 Hz, NCH_2CH=), 3.67 (2H, s, NCH_2C=), 3.03 (4H, t, *J* = 4.2 Hz, CH_2N), 2.72 (4H, app brs, CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 160.1 (CO), 154.1 (d, *J* = 255.4 Hz, C-F, $^1J_{CF}$), 147.1 (ArC), 145.7 (ArCH), 141.2 (*C*=CH), 137.8 (d, *J* = 8.8 Hz, CH=*C*-C-F, $^2J_{CF}$), 134.4 (ArCH), 132.9 (ArC), 126.8 (ArC), 126.4 (ArCH), 126.2 (ArCH), 125.7 (ArCH), 125.5 (d, *J* = 12.5 Hz, Cl-*C*-CH=C-F, $^3J_{CF}$), 124.5 (ArCH), 123.6 (CH=), 123.4 (d, *J* = 3.6 Hz, Cl-*C*H-C-CH=C-F, $^4J_{CF}$), 122.4 (ArC), 121.2 (ArC), 120.0 (ArCH), 118.5 (d, *J* = 3.7 Hz, *C*H=C-C-F, $^3J_{CF}$), 117.7 (ArCH), 115.7 (d, *J* = 24.3 Hz, Cl-C-*C*H=C-F, $^2J_{CF}$), 109.8 (ArCH), 101.9(ArCH), 57.3 (NCH_2C=), 52.1 (2 × CH_2N), 49.4 (d, *J* = 3.1 Hz, 2 × CH_2N), 43.6 (N*C*H_2CH=); HRESIMS *m/z* 528.1965 $[M + H]^+$ (calcd for $C_{30}H_{28}FN_5O$, 528.1961); Elemental anal: C, 67.0; H, 5.20; N 12.2%, calcd for $C_{30}H_{28}ClFN_5O_{1.5}$, C, 67.1; H, 5.26; N, 13.0%.

Minor *E*-isomer, ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.29 (1H, d, *J* = 7.0 Hz, ArH), 7.74-7.70 (2H, m, ArH), 7.65 (1H, d, *J* = 7.9 Hz, ArH), 7.51 (1H, s,

ArH), 7.49 (1H, t, J = 7.6 Hz, ArH), 7.43 (1H, d, J = 8.3 Hz, ArH), 7.26-7.240 (1H, obscured by solvent signal, ArH), 7.07 (1H, d, J = 8.2 Hz, ArH), 7.09-6.98 (2H, m, ArH), 6.79 (1H, t, J = 9.0 Hz, ArH), 6.56 (1H, brs, ArH), 5.94 (1H, brs, CH=), 4.65 (2H, d, J = 6.6 Hz, NCH_2CH=), 3.36 (2H, s, NCH_2C=), 3.04 (4H, app brs, CH_2N), 2.67 (4H, app brs, CH_2N).