Supporting Information

Novel 3-Trifluoromethyl-1,2,4-Oxadiazole Analogues of Astemizole with Multi-Stage Antiplasmodium Activity and In vivo Efficacy in a *Plasmodium berghei* Mouse Malaria Infection Model

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Characterization data for compounds not shown in the main manuscript

***N'*-hydroxypivalimidamide (31b)**. Following general procedure 1, obtained from pivalonitrile (0.500 g, 6.01 mmol) as a yellow solid (0.7 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 6.55 (s, 2H), 1.43 (s, 9H).

***N'*-hydroxycyclopropanecarboximidamide (31c)**. Following general procedure 1, obtained from cyclopropane carbonitrile (0.3 g, 4.47 mmol) as a white solid (0.4 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 6.49 (s, 2H) 0.71 – 0.52 (m, 2H), 0.46 – 0.28 (m, 2H), 0.20 (p, J = 4.8 Hz, 1H).

***N'*-hydroxy-2-(methylthio) acetimidamide (31d)**. Following general procedure 1, obtained from 2-(methylthio) acetonitrile (0.400 g, 4.60 mmol) as a pale-yellow solid (0.440 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 6.55 (s, 2H), 3.43 (s, 2H), 2.13 (s, 3H).

2-(dimethylamino)-N'-hydroxyacetimidamide (31e). Following general procedure 1, obtained from 2-(dimethylamine) acetonitrile (0.2 g, 2.37 mmol) as a dark brown solid (0.190 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 6.53 (s, 2H), 3.35 (s, 2H), 2.24 (s, 6H).

***(R)*-4-(2-bromoethyl)-N-(2-hydroxypropyl)benzamide (3b)**. Following general procedure 2, obtained from *(R)*-1-aminopropan-2-ol (0.055 g, 0.73 mmol) as a white solid (0.191 g, 91%). ^{1}HNMR (300 MHz, Methanol-d_4) δ 8.12 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.71 (qt, J = 6.8, 6.1 Hz, 1H), 3.51 (t, J = 7.2 Hz, 2H), 3.12 (d, J = 6.1 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 1.22 (d, J = 6.8 Hz, 3H). LC-MS (APCI$^+$/ESI): found m/z = 286.0, 288.0 [M+H] $^+$ (cal. for $C_{12}H_{16}BrNO_2$, 285.04, 287.03). HPLC Purity: 98%, retention time (t_r) = 2.508 min.

***N'*-acetyl-4-(2-bromoethyl)benzohydrazide (3c)**. Following general procedure 2, obtained from acetyl hydrazide (0.089 g, 1.20 mmol) as a white solid (0.180 g, 65%). ^{1}HNMR (300 MHz, Methanol-d_4) δ 7.83 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 3.66 (t, J = 7.1 Hz, 2H), 3.23 (t, J = 7.1 Hz, 2H), 2.06 (s, 3H). HPLC Purity: 96%, t_R = 2.501 min.

N-((4-(2-bromoethyl)benzoyl)oxy)acetimidamide (3d). Following general procedure 2, obtained from *N*-hydroxyacetimidamide (0.89 g, 12.0 mmol) as a white solid (2.80 g, 90%). ^{1}HNMR (300 MHz, Methanol-d_4) δ 8.05 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 3.67 (t, J = 7.1 Hz, 2H), 3.24 (t, J = 7.1 Hz, 2H), 1.95 (s, 3H). LC-MS (APCI/ESI): found m/z = 284.8, 286.8 [M+H] $^+$ (cal. for $C_{11}H_{13}BrN_5O_2$, 284.8, 286.8). HPLC Purity: 85%, t_R = 3.003 min.

N-((4-(2-bromoethyl)benzoyl)oxy)-2,2,2-trifluoroacetimidamide (3e). Following general procedure 2, obtained from 2,2,2-trifluoro-*N*-hydroxyacetimidamide (0.615 g, 4.80 mmol) as a white solid (1.16 g, 78%). ^{1}HNMR (300 MHz, DMSO-d_6) δ 8.10 (d, *J* = 8.1 MHz, 2H), 7.71 (s, 1H), 7.45 (d, *J* = 8.1 MHz, 2H), 3.80 (d, *J* = 7.0 Hz, 2H), 3.24 (t, *J* = 7.0 Hz, 2H). LC-MS (APCI/ESI): found *m/z* = 337.99, 339.99 $[M+H]^+$ (cal. for $C_{11}H_{10}BrF_3N_2O_2$, 338.99, 340.99). HPLC Purity: 98%, t_R = 3.466 min.

***(S)*-2-(4-(2-bromoethyl)phenyl)-4-methyl-4,5-dihydrooxazole (4b)**. Following general procedure 3, obtained from **3b** (0.11 g, 0.38 mmol) as a white solid (0.088 g, 85%). ^{1}HNMR (300 MHz, Methanol-d_4) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.25 (dd, *J* = 14.1, 8.9 Hz, 1H), 4.00 (ddq, *J* = 14.1, 6.3, 6.6 Hz, 1H), 3.65 (t, *J* = 7.3 Hz, 2H), 3.33, (dd, *J* = 8.9, 6.3 Hz, 1H), 3.29 (t, *J* = 7.3 Hz, 2H), 1.95 (d, *J* = 6.6 Hz, 3H). LC-MS ($APCI^+$/ESI): found *m/z* = 268.0, 270.0 $[M+H]^+$ (cal. for $C_{12}H_{14}BrNO$, 267.03, 267.02). HPLC Purity: 98%, t_R = 2.807 min.

2-(4-(2-bromoethyl)phenyl)-5-methyl-1,3,4-oxadiazole (4c). Following general procedure 3, obtained from **3d** (0.15 g, 0.50 mmol) as a yellow crystalline solid (0.134 g, 88%). ^{1}HNMR (300 MHz, Methanol-d_4) δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 3.69 (t, *J* = 7.1 Hz, 2H), 3.28 (t, *J* = 7.1 Hz, 2H), 1.99 (s, 3H). LC-MS (APCI/ESI): found *m/z* = 266.9, 268.9 $[M+H]^+$ (cal. for $C_{11}H_{11}BrN_2O$, 266.01, 268.00). HPLC Purity: 97%, t_R = 2.747min.

***Tert*-butyl (R)-3-((1-(4-cyanobenzyl)-1H-benzo[*d*]imidazol-2-yl) amino) pyrrolidine-1-carboxylate (26b**). Following general procedure 5, obtained obtained from **25** (0.200 g, 0.75 mmol) and *tert*-butyl *(R)*-3-aminopyrrolidine-1-carboxylate (192 µl, 1.12 mmol) as a light brown solid (0.243 g, 78%). R_f (10% MeOH/DCM), 0.50. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.43 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.30 (ddd, *J* = 7.8, 7.0, 1.2 Hz, 1H), 7.26 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.21 (ddd, *J* = 8.0, 7.0, 1.4 Hz, 1H), 5.63 (s, 2H), 4.66 (tt, *J* = 7.1, 4.0 Hz, 1H), 3.70 (dd, *J* = 12.5, 7.1 Hz, 1H), 3.57 – 3.48 (m, 2H), 3.35 (ddd, *J* = 10.5, 8.9, 5.0 Hz, 1H), 2.53 (ddd, *J* = 15.0, 8.9, 7.1 Hz, 1H), 2.21 (ddd, *J* = 11.5, 8.9, 4.0 Hz, 1H), 1.46 (s, 9H). LC-MS ($APCI^+$/ESI): found *m/z* = 418.2 $[M+H]^+$ (cal. for $C_{24}H_{27}N_5O_2$, 417.22). Purity: 98%, t_R = 2.876 min.

***Tert*-butyl-6-(1-(4-cyanobenzyl)-1-benzo[*d*]imidazol-2-yl)-2,6-diazaspiro[3.4]octane-2-carboxylate (26c)**. Following general procedure 5, obtained from **25** (0.151 g, 0.57 mmol) and tert-butyl 2,6-diazaspiro [3.4] octane-2-carboxylate (181 g, 0.85 mmol) after irradiation under

microwave for 6 min, as a white crystal (0.173 g, 55%). R_f (7% MeOH/DCM), 0.63. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.40 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.13 (ddd, *J* = 7.9, 7.4, 1.2 Hz, 1H), 7.10 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.4, 1.2 Hz, 1H), 5.49 (s, 2H), 3.84 (br-s, 4H), 3.69 (s, 2H), 3.58 (t, *J* = 6.9 Hz, 2H), 2.15 (t, *J* = 6.9 Hz, 2H), 1.43 (s, 9H). LC-MS (APCI$^+$/ESI): found *m/z* = 444.2 [M+H] $^+$ (cal. for $C_{26}H_{29}N_5O_2$, 443.23). Purity: 99%, t_R = 2.409 min

(S)-4-((2-(pyrrolidin-3-ylamino)-1H-benzo[*d*]imidazol-1-yl) methyl) benzonitrile (27b). Following general procedure 6, obtained obtained from **26b** (0.200 g, 0.47 mmol) as a pale-yellow solid (0.114 g, 75%). R_f (10% MeOH/DCM), 0.11. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.41 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.29 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.2, 1.4 Hz, 1H), 5.64 (s, 2H), 4.62 (tt, *J* = 7.0, 4.1 Hz, 1H), 3.66 (dd, *J* = 12.3, 7.0 Hz, 1H), 3.55 – 3.46 (m, 2H), 3.30 (ddd, *J* = 10.9, 8.5, 5.1 Hz, 1H), 2.52 (ddd, *J* = 15.0, 8.5, 7.0 Hz, 1H), 2.19 (ddd, *J* = 11.5, 8.5, 4.1 Hz, 1H). LC-MS (APCI$^+$/ESI): found *m/z* = 318.2 [M+H] $^+$ (cal. for $C_{19}H_{19}N_5$, 317.16). Purity: 97%, t_R = 2.401 min.

4-((2-(2,6-diazaspiro[3.4]octan-6-yl)-1H-benzo[*d*]imidazol-1-yl) methyl) benzonitrile (27c). Following general procedure 6, obtained obtained from **26c** (0.160 g, 0.36 mmol) as a pale-yellow solid (0.121 g, 98%). R_f (10% MeOH/DCM), 0.10. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.38 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.10 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.02 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 5.45 (s, 2H), 3.77 (br-s, 4H), 3.71 (s, 2H), 3.50 (t, *J* = 6.8 Hz, 2H), 2.11 (t, *J* = 6.8 Hz, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 344.1 [M+H] $^+$ (cal. for $C_{21}H_{21}N_5$, 343.18). Purity: 99%, t_R = 0.426 min.

5,6-dichloro-1-methyl-N-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (60b). Following general procedure 6, obtained from **59b** (0.130 g, 0.33 mmol) as a brown solid (0.084 g, 86%). R_f (5% MeOH/DCM), 0.14. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (s, 1H), 8.04 (s, 1H), 3.92 (tt, *J* = 10.9, 4.1 Hz, 1H), 3.51 (s, 3H), 3.21 – 3.12 (m, 2H), 3.09 – 3.01 (m, 2H), 2.09 – 2.00 (m, 2H), 1.48 – 1.37 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 299.1, 301.1 [M+H] $^+$ (cal. for $C_{13}H_{16}Cl_2N_4$, 298.08, 300.07). Purity: 99%, t_R = 0.811 min.

1,5,6-trimethyl-N-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (60c). Following general procedure 6, obtained from **59c** (0.200 g, 0.56 mmol) as a light brown solid (0.127 g, 88%). R_f (5% MeOH/DCM) 0.12. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 (s, 1H), 7.28 (s, 1H), 3.91 (tt, *J* =

10.9, 4.1 Hz, 1H), 3.51 (s, 3H), 3.20 – 3.11 (m, 2H), 3.06 – 2.98 (m, 2H), 2.26 (s, 3H), 2.20 (s, 3H), 2.09 – 1.98 (m, 2H), 1.50 – 1.39 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 259.2 [M+H] $^+$ (cal. For $C_{15}H_{22}N_4$, 258.18). Purity: 98%, t_R = 0.733 min.

1-methyl-N-(piperidin-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine (60e). Following general procedure 6, obtained from **59e** (0.480 g, 1.21 mmol) as a white solid (0.348 g, 97%). R_f (5% MeOH/DCM), 0.17. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46 (d, *J* = 1.3 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.25 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 4.12 – 3.93 (m, 1H), 3.56 (s, 3H), 3.44 – 3.25 (m, 2H), 3.05 (td, *J* = 12.5, 3.0 Hz, 2H), 2.24 – 2.08 (m, 2H), 1.87 – 1.66 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 299.1 [M+H] $^+$ (cal. for $C_{14}H_{17}F_3N_4$, 298.14). Purity: 99%, t_R = 0.813 min.

5-methoxy-1-methyl-N-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (60f). Following general procedure 6, obtained from **59f** (0.470 g, 1.31 mmol) as a light brown solid (0.322 g, 95%). R_f (5% MeOH/DCM), 0.10. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (d, *J* = 1.1 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 3.92 (tt, *J* = 11.0, 4.1 Hz, 1H), 3.85 (s, 3H), 3.52 (s, 3H), 3.19 – 3.11 (m, 2H), 3.07 – 2.98 (m, 2H), 2.10 – 2.01 (m, 2H), 1.53 – 1.41 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 261.2 [M+H] $^+$ (cal. for $C_{14}H_{20}N_4O$, 260.16). Purity: 99%, t_R = 0.690 min.

1-methyl-5-(methylsulfonyl)-N-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (60g). Following general procedure 6, obtained from **59g** (0.490 g, 1.20 mmol) as a light brown solid (0.314 g, 85%). R_f (5% MeOH/DCM), 0.09. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 (d, *J* = 1.3 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.40 (dd, *J* = 7.8, 1.3 Hz, 1H), 3.91 (tt, *J* = 10.9, 4.1 Hz, 1H), 3.52 (s, 3H), 3.38 (s, 3H), 3.19 – 3.12 (m, 2H), 3.07 – 2.98 (m, 2H), 2.09 – 2.00 (m, 2H), 1.51 – 1.43 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 309.1 [M+H] $^+$ (cal. for $C_{14}H_{20}N_4O_2S$, 308.13). Purity: 97%, t_R = 0.643 min.

Methyl 1-methyl-2-(piperidin-4-ylamino)-1H-benzo[d]imidazole-5-carboxylate (60h). Following general procedure 6, obtained from **59h** (0.495 g, 1.28 mmol) as an off-white solid (0.341 g, 93%). R_f (5% MeOH/DCM), 0.08. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.12 (d, *J* = 1.3 Hz, 1H), 7.90 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 3.90 (tt, *J* = 10.9, 4.2 Hz, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 3.20 – 3.13 (m, 2H), 3.09 – 3.01 (m, 2H), 2.08 – 2.02 (m, 2H), 1.51 –

1.43 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 289.2 [M+H] $^+$ (cal. for $C_{15}H_{20}N_4O_2$, 288.16). Purity: 98%, t_R = 0.661 min.

5-fluoro-1-methyl-N-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (60i). Following general procedure 6, obtained from **59i** (0.490 g, 1.41 mmol) as a light brown solid (0.342 g, 98%). R_f (5% MeOH/DCM), 0.11. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.51 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.87 (ddd, *J* = 8.0, 7.9, 1.3 Hz, 1H), 3.92 (tt, *J* = 11.2, 4.1 Hz, 1H), 3.52 (s, 3H), 3.19 – 3.10 (m, 2H), 3.04 – 2.93 (m, 2H), 2.09 – 2.00 (m, 2H), 1.50 – 1.39 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 249.2 [M+H] $^+$ (cal. for $C_{13}H_{17}FN_4$, 248.14). Purity: 97%, t_R = 0.802 min.

5-bromo-1-methyl-N-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (60j). Following general procedure 6, obtained from **59j** (0.380 g, 0.93 mmol) as a brown solid (0.273 g, 95%). R_f (5% MeOH/DCM), 0.12. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35 (d, *J* = 1.3 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.13 (dd, *J* = 7.8, 1.3 Hz, 1H), 3.92 (tt, *J* = 10.9, 4.0 Hz, 1H), 3.51 (s, 3H), 3.20 – 3.12 (m, 2H), 3.07 – 2.99 (m, 2H), 2.10 – 2.00 (m, 2H), 1.49 – 1.38 (m, 2H). LC-MS (APCI$^+$/ESI): found *m/z* = 309.1 [M+H] $^+$ (cal. for $C_{13}H_{17}BrN_4$, 308.06, 310.06). Purity: 98%, t_R = 0.856 min.

2,5,6-trichloro-1H-benzo[d]imidazole (54b). Following general procedure 7, obtained from 4,5-dichlorobenzene-1,2-diamine, **52b** (0.250g, 1.41 mmol) as a light green solid (0.215 g, 69%). R_f (5% MeOH/DCM), 0.81. ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.51 (s, 2H). LC-MS (APCI$^+$/ESI): found m/z = 221.0, 223.0 $[M+H]^+$ (cal. For $C_7H_3ClF_2N_2$, 219.94, 221.93). Purity: 97%, t_R = 2.687 min.

2-chloro-5,6-dimethyl-1H-benzo[d]imidazole (54c). Following general procedure 7, obtained from 4,5-dimethylbenzene-1,2-diamine, **52c** (0.250g, 1.83 mmol) as a brown solid (0.259 g, 77%). R_f (5% MeOH/DCM), 0.48. ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.23 (s, 2H), 2.68 (s, 6H). LC-MS (APCI$^+$/ESI): found m/z = 181.0, 183.0 $[M+H]^+$ (cal. For $C_9H_9ClN_2$, 180.05, 182.04). Purity: 97%, t_R = 2.568 min.

2,5,6-trichloro-1-methyl-1H-benzo[d]imidazole (55b). Following general procedure 8, obtained from **54b** (0.200 g, 0.90 mmol) and methyl iodide (67 µl, 1.08 mmol), as a light purple solid (0.147 g, 69%). R_f (5% MeOH/DCM), 0.90. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.51 (s, 1H), 7.38 (s,

1H), 3.83 (s, 3H). LC-MS (APCI$^+$/ESI): found m/z = 234.9, 236.9 $[M+H]^+$ (cal. for $C_8H_5Cl_3N_2$, 233.95, 235.95). Purity: 98%, t_R = 2.501min.

2-chloro-1,5,6-trimethyl-1H-benzo[d]imidazole (55c). Following general procedure 8, obtained from **54c** (0.240 g, 1.31 mmol) and methyl iodide (99 µl, 1.58 mmol), as a pale-yellow solid (0.195 g, 76%). R_f (5% MeOH/DCM), 0.83. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.28 (s, 1H), 7.19 (s, 1H), 3.83 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H). LC-MS (APCI$^+$/ESI): found m/z = 195.0, 197.0 $[M+H]^+$ (cal. For $C_{10}H_{11}ClN_2$, 194.06, 196.06). Purity: 97%, t_R = 2.444 min.

Ethyl 4-((5,6-dichloro-1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59b). Following general procedure 9, obtained from **55b** (0.130 g, 0.55 mmol) and *tert*-butyl 4-aminopiperidine-1-carboxylate (0.166 g, 0.83 mmol), as a light brown solid (0.143 g, 65%). R_f (5% MeOH/DCM), 0.79. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.03 (s, 1H), 6.70 (d, J = 7.3 Hz, 1H), 4.51 – 4.46 (m, 2H), 3.92 (tt, J = 10.9, 4.1 Hz, 1H), 3.52 (s, 3H), 3.10 – 3.02 (m, 2H), 2.09 – 2.00 (m, 2H), 1.52 – 1.47 (m, 2H), 1.39 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 399.1, 401.1 $[M+H]^+$ (cal. for $C_{18}H_{24}Cl_2N_4O_2$, 398.13, 400.12). Purity: 96%, t_R = 2.530 min.

Ethyl 4-((1,5,6-trimethyl-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59c). Following general procedure 9, obtained from **55c** (0.180 g, 0.91 mmol) and *tert*-butyl 4-aminopiperidine-1-carboxylate (0.276 g, 1.38 mmol), as a light brown solid (0.225 g, 69%). R_f (5% MeOH/DCM), 0.69. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (s, 1H), 7.22 (s, 1H), 6.65 (d, J = 7.2 Hz, 1H), 4.54 – 4.46 (m, 2H), 3.92 (tt, J = 10.9, 4.2 Hz, 1H), 3.51 (s, 3H), 3.07 – 2.99 (m, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 2.11 – 1.10 (m, 2H), 1.51 – 1.44 (m, 2H), 1.32 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 359.2 $[M+H]^+$ (cal. for $C_{20}H_{30}N_4O_2$, 358.24). Purity: 98%, t_R = 2.499 min.

***N*1-methyl-4-(trifluoromethyl)benzene-1,2-diamine (58b)**. Following general procedure 10, obtained from 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (0.500 g, 2.39 mmol) and methylamine (2M solution in THF, 1.43 ml, 2.86 mmol), as a dark brown solid (0.395 g, 87% over two steps). R_f (20% EtOAc/Hexane) 0.36. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.86 – 6.80 (m, 2H), 6.43 (d, J = 8.0 Hz, 1H), 5.00 (s, 2H), 2.76 (s, 3H). Purity: 98%, t_R = 0.212 min.

4-methoxy-N1-methylbenzene-1,2-diamine (58c). Following general procedure 10, obtained from 1-fluoro-4-methoxy-2-nitrobenzene (0.500 g, 2.92 mmol) and methylamine (2M solution in THF, 1.75 ml, 3.50 mmol), as a blackish solid (0.293 g, 66% over two steps). R_f (40%

EtOAc/Hexane) 0.31. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.80 (d, J = 1.2 Hz, 1H), 6.48 (dd, J = 8.3, 1.2 Hz, 1H), 6.23 (d, J = 8.3 Hz, 1H), 5.05 (s, 2H), 3.91 (s, 3H), 2.69 (s, 3H). Purity: 97%, t_R = 0.182 min.

***N*1-methyl-4-(methylsulfonyl)benzene-1,2-diamine (58d)**. Following general procedure 10, obtained from 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (0.500 g, 2.28 mmol) and methylamine (2M solution in THF, 1.37 ml, 2.73 mmol), as a brown solid (0.388 g, 85% over two steps). R_f (40% EtOAc/Hexane) 0.45. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40 – 7.38 (m, 2H), 6.82 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 3.01 (s, 3H), 2.75 (s, 3H). Purity: 97%, t_R = 0.220 min.

Methyl 3-amino-4-(methylamino)benzoate (58e). Following general procedure 10, obtained from methyl 4-fluoro-3-nitrobenzoate (0.500 g, 2.51 mmol) and methylamine (2M solution in THF, 1.50 ml, 3.01 mmol), as a yellow solid (0.348 g, 77% over two steps). R_f (40% EtOAc/Hexane) 0.39. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (d, J = 1.1 Hz, 1H), 7.68 (dd, J = 8.2, 1.0 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 4.99 (s, 2H), 3.88 (s, 3H), 2.70 (s, 3H). Purity: 99%, t_R = 0.197 min.

4-fluoro-N1-methylbenzene-1,2-diamine (58f). Following general procedure 10, obtained from 1,4-difluoro-2-nitrobenzene (0.500 g, 3.14 mmol) and methylamine (2M solution in THF, 1.88 ml, 3.77 mmol), as a dark oil (0.347 g, 79% over two steps). R_f (20% EtOAc/Hexane) 0.42. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.98 (d, J = 1.2 Hz, 1H), 6.25 – 6.49 (m, 2H), 5.03 (s, 2H), 2.68 (s, 3H). Purity: 99%, t_R = 0.283 min.

4-bromo-N1-methylbenzene-1,2-diamine (58g). Following general procedure 10, obtained from 4-bromo-1-fluoro-2-nitrobenzene (0.500 g, 2.30 mmol) and methylamine (2M solution in THF, 1.38 ml, 2.76 mmol), as a dark brown solid (0.370 g, 81% over two steps). R_f (20% EtOAc/Hexane) 0.38. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.01 (d, J = 1.0 Hz, 1H), 6.78 – 6.71 (m, 2H), 5.05 (s, 2H), 2.69 (s, 3H). Purity: 99%, t_R = 0.291 min.

Tert-butyl 4-((1-methyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59e). Following general procedure 11, obtained from **58b** (0.300 g, 1.57 mmol) and **52** (0.420 g, 1.73 mmol), as an off-white solid (0.520 g, 83%). R_f (5% MeOH/DCM), 0.73. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47 (d, J = 1.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.23 (dd, J = 8.2, 1.6 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 4.04 – 3.84 (m, 3H), 3.54 (s, 3H), 3.00 – 2.72 (m, 2H), 2.09

– 1.86 (m, 2H), 1.57 – 1.32 (m, 11H). LC-MS (APCI$^+$/ESI): found m/z = 399.2 $[M+H]^+$ (cal. For $C_{17}H_{21}F_3N_4O_2$, 398.19). Purity: 99%, t_R = 2.588 min.

Tert-butyl 4-((5-methoxy-1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59f). Following general procedure 11, obtained from **58c** (0.250 g, 1.64 mmol) and **52** (0.437 g, 1.81 mmol), as a light brown solid (0.501 g, 85%). R_f (5% MeOH/DCM), 0.51. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (d, *J* = 1.4 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 4.50 – 4.43 (m, 2H), 3.91 (tt, *J* = 11.0, 4.1 Hz, 1H), 3.86 (s, 3H), 3.51 (s, 3H), 3.07 – 2.96 (m, 2H), 2.10 – 1.99 (m, 2H), 1.51 – 1.45 (m, 2H), 1.41 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 361.2 $[M+H]^+$ (cal. For $C_{19}H_{28}N_4O_3$, 360.22). Purity: 97%, t_R = 2.393 min.

Tert-butyl 4-((1-methyl-5-(methylsulfonyl)-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59g). Following general procedure 11, obtained from **58d** (0.300 g, 1.50 mmol) and **52** (0.400 g, 1.64 mmol), as a light brown solid (0.538 g, 88%). R_f (5% MeOH/DCM), 0.57. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, *J* = 1.1 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 4.50 – 4.43 (m, 2H), 3.92 (tt, *J* = 10.9, 4.1 Hz, 1H), 3.61 (s, 3H), 3.49 (s, 3H), 3.10 – 3.01 (m, 2H), 2.10 – 2.00 (m, 2H), 1.51 – 1.44 (m, 2H), 1.44 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 409.2 $[M+H]^+$ (cal. For $C_{19}H_{28}N_4O_2S$, 408.18). Purity: 96%, t_R = 2.492 min.

Methyl 2-((1-(tert-butoxycarbonyl) piperidin-4-yl) amino)-1-methyl-1H-benzo[d]imidazole-5-carboxylate (59h). Following general procedure 11, obtained from **58e** (0.250 g, 1.38 mmol) and **52** (0.370 g, 1.53 mmol), as an off-white solid (0.434 g, 81%). R_f (5% MeOH/DCM), 0.55. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J* = 1.3 Hz, 1H), 7.89 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 4.49 – 4.42 (m, 2H), 3.91 (tt, *J* = 10.9, 4.2 Hz, 1H), 3.78 (s, 3H), 3.51 (s, 3H), 3.08 – 2.98 (m, 2H), 2.08 – 2.01 (m, 2H), 1.50 – 1.42 (m, 2H), 1.40 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 389.2 $[M+H]^+$ (cal. for $C_{20}H_{28}N_4O_4$, 388.21). Purity: 98%, t_R = 2.403 min.

Tert-butyl 4-((5-fluoro-1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59i). Following general procedure 11, obtained from **58f** (0.250 g, 1.78 mmol) and **52** (0.475 g, 1.96 mmol), as a light brown solid (0.545 g, 88%). R_f (5% MeOH/DCM), 0.53. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.39 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.85

(ddd, *J* = 8.0, 7.9, 1.3 Hz, 1H), 6.68 (d, *J* = 7.1 Hz, 1H), 4.54 – 4.46 (m, 2H), 3.93 (tt, *J* = 11.2, 4.1 Hz, 1H), 3.52 (s, 3H), 3.01 – 2.93 (m, 2H), 2.15 – 2.08 (m, 2H), 1.56 – 1.49 (m, 2H), 1.38 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 349.2 $[M+H]^+$ (cal. for $C_{18}H_{25}FN_4O_2$, 348.20). Purity: 99%, t_R = 2.553 min.

Tert-butyl 4-((5-bromo-1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidine-1-carboxylate (59j). Following general procedure 11, obtained from **58g** (0.250 g, 1.24 mmol) and **52** (0.331 g, 1.37 mmol), as a dark brown solid (0.422 g, 83%). R_f (5% MeOH/DCM), 0.62. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, *J* = 1.3 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.13 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.71 (d, *J* = 7.1 Hz, 1H), 4.51 – 4.43 (m, 2H), 3.92 (tt, *J* = 10.9, 4.0 Hz, 1H), 3.51 (s, 3H), 3.07 – 2.98 (m, 2H), 2.10 – 2.01 (m, 2H), 1.59 – 1.51 (m, 2H), 1.42 (s, 9H). LC-MS (APCI$^+$/ESI): found m/z = 409.1, 411.1 $[M+H]^+$ (cal. For $C_{18}H_{25}BrN_4O_2$, 408.12, 410.11). Purity: 98%, t_R = 2.591 min.

4-((2-((1-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl) phenethyl) piperidin-4-yl) amino)-1H-benzo[*d*]imidazol-1-yl) methyl) benzonitrile (8). Following general procedure 12, obtained from **5** (0.080 g, 0.24 mmol) and **2d** (0.093 g, 0.29 mmol) as a pale-yellow solid (0.107 g, 78%); m.p.: 125 – 126 °C; R_f (10% MeOH/DCM) 0.58. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.06 (ddd, *J* = 7.8, 7.3, 1.0 Hz, 1H), 7.01 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.95 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H), 5.38 (s, 2H), 3.85 (tt, *J* = 10.9, 4.1 Hz, 1H), 3.12 – 3.05 (m, 2H), 2.97 – 2.91 (m, 2H), 2.77 – 2.70 (m, 2H), 2.41 – 2.33 (m, 2H), 2.14 – 2.09 (m, 2H), 1.68 – 1.62 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 169.1, 160.0 (q, *J* = 23.9 Hz), 154.0, 144.8, 142.3, 141.6, 133.9, 132.3 (2C), 129.3 (2C), 127.5 (2C), 127.1 (2C), 123.0, 121.3, 119.6, 118.0, 117.1, 115.3, 111.0, 107.6, 59.3, 52.1 (2C), 49.8, 44.2, 32.6, 31.3 (2C). LC-MS (APCI$^+$/ESI): found *m/z* = 572.2 $[M+H]^+$ (cal. For $C_{31}H_{28}F_3N_7O$, 571.23). Purity: 97%, t_R = 2.732 min.

4-((2-((1-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenethyl)piperidin-4-yl)amino)-1H-benzo[d]imidazol-1-yl)methyl)benzonitrile (9). Following general procedure 12, obtained from **5** (0.100 g, 0.30 mmol) and **3d** (0.103 g, 0.36 mmol) as a pale-yellow solid (0.100 g, 65%). m.p.: 147 – 149 °C; R_f (10% MeOH/DCM), 0.56. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.08 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.02 – 6.91 (m, 1H), 5.39 (s, 2H), 3.90 – 3.78 (m, 2H), 3.07 – 2.98 (m, 2H), 2.95 – 2.88 (m, 2H), 2.71 – 2.63 (m, 2H), 2.43 (s, 3H), 2.34 – 2.36 (m,

2H), 2.11 – 2.06 (m, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 175.4, 164.4, 154.0, 144.6, 142.3, 141.6, 133.9, 132.3 (2C), 129.3 (2C), 127.2 (2C), 126.6 (2C), 121.3, 119.6, 118.0, 114.9, 112.0, 111.1, 107.5, 59.3, 52.1 (2C), 49.9, 44.3, 32.6, 31.4 (2C), 9.1. LC-MS (APCI+/ESI): found *m/z* = 517.9 $[M+H]^+$ (cal. For $C_{31}H_{31}N_7O$, 517.24). HPLC Purity: 98%, t_R = 2.453 min.

4-((2-((1-(4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)phenethyl)piperidin-4-yl)amino)-1-benzimidazol-1-yl)methyl)benzonitrile (10). Following general procedure 12, obtained from **5** (0.100 g, 0.30 mmol) and **3e** (0.122 g, 0.36 mmol) as a white solid (0.128 g, 75%). m.p.: 117 – 119 °C; R_f (10% MeOH/DCM), 0.67. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.05 (dd, *J* = 7.9, 1.2, 1H), 7.01 – 6.92 (m, 1H), 5.39 (s, 2H), 3.86 (tt, *J* = 10.9, 3.8 Hz, 1H), 3.05 – 2.97 (m, 2H), 2.97 – 2.89 (m, 2H), 2.72 – 2.67 (m, 2H), 2.33 – 2.25 (m, 2H), 2.10 – 2.02 (m, 2H), 1.72 – 1.55 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 168.9, 165.3 (q, *J* = 24.0 Hz), 154.0, 144.8, 142.5, 142.0, 134.0, 132.5 (2C), 129.5 (2C), 127.9 (2C), 127.6 (2C), 123.0, 121.7, 120.0, 118.1, 117.0, 115.3, 111.1, 107.6, 59.3, 52.2 (2C), 50.0, 44.4, 32.6, 31.2 (2C). LC-MS (APCI+/ESI): found *m/z* = 571.9 $[M+H]^+$ (cal. For $C_{31}H_{28}F_3N_7O$, 571.23). HPLC Purity: 97%, t_R = 2.699 min.

4-((2-((1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenethyl)piperidin-4-yl)amino)-1H-benzo[d]imidazol-1-yl)methyl)benzonitrile (11). Following general procedure 12, obtained from **5** (0.100 g, 0.30 mmol) and **4c** (0.096 g, 0.36 mmol) as a white solid (0.074 g, 48%). M.p.: 125 – 127 °C; R_f (10% MeOH/DCM), 0.56. ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.34 (dd, *J* = 7.9, 1.2, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.06 (td, *J* = 7.5, 1.6 Hz, 1H), 7.03 – 6.92 (m, 2H), 5.38 (s, 2H), 3.84 (tt, *J* = 10.8, 3.9 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.93 – 2.86 (m, 2H), 2.71 – 2.63 (m, 2H), 2.61 (s, 3H), 2.35 – 2.27 (m, 2H), 2.11 – 2.03 (m, 2H), 1.73 – 1.55 (m, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 164.4, 154.0, 144.6, 142.3, 141.6, 138.4, 133.9, 132.3 (2C), 129.3 (2C), 127.2 (2C), 126.6 (2C), 121.3, 119.6, 118.0, 114.9, 112.3, 111.1, 107.5, 59.3, 52.1 (2C), 49.9, 44.3, 32.6, 31.4 (2C), 9.3. LC-MS (APCI+/ESI): found *m/z* = 517.9 $[M+H]^+$ (cal. For $C_{31}H_{31}N_7O$, 517.24). HPLC Purity: 97%, t_R = 2.514 min.

(S)-4-((2-((1-(4-(4-methyl-4,5-dihydrooxazol-2-yl) phenethyl) piperidin-4-yl) amino)-1H-benzo[*d*]imidazol-1-yl) methyl) benzonitrile (12). Following general procedure 12, obtained from **5** (0.047 g, 0.14 mmol) and **4a** (0.047 g, 0.17 mmol) as a pale pale-yellow solid (0.061 g,

81%); m.p.: 104 – 106 °C; R_f (10% MeOH/DCM), 0.34. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.32 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.06 (ddd, *J* = 7.7, 7.2, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.95 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H), 5.38 (s, 2H), 4.57 (dd, *J* = 9.3, 8.0 Hz, 1H), 4.35 (ddq, *J* = 9.3, 7.5, 6.6 Hz, 1H), 4.01 (dd, *J* = 8.0, 7.5 Hz, 1H), 3.86 (tt, *J* = 10.9, 4.1 Hz, 1H), 3.12 – 3.08 (m, 2H), 2.93 – 2.89 (m, 2H), 2.76 – 2.72 (m, 2H), 2.44 – 2.37 (m, 2H), 2.14 – 2.09 (m, 2H), 1.70 – 1.62 (m, 2H), 1.33 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 164.5, 153.9, 143.9, 142.3, 141.5, 133.9, 132.3 (2C), 128.6 (2C), 128.1 (2C), 127.1 (2C), 125.3, 121.4, 119.6, 118.0, 114.8, 111.0, 107.6, 74.0, 61.2, 59.2, 52.1 (2C), 49.7, 44.3, 32.4, 31.1 (2C), 20.1. LC-MS (APCI$^+$/ESI): found *m/z* = 519.2 $[M+H]^+$ (cal. For $C_{32}H_{34}N_6O$, 518.28). Purity: 98%, t_R = 2.700 min. Specific rotation, $[\alpha]^{25}_D$ = +7.78°.

(S)-4-((2-((1-(4-(5-methyl-4,5-dihydrooxazol-2-yl) phenethyl) piperidin-4-yl) amino)-1H-benzo[*d*]imidazol-1-yl) methyl) benzonitrile (13). Following general procedure 12, obtained from **5** (0.050 g, 0.15 mmol) and **4b** (0.049 g, 0.18 mmol) as a pale-yellow solid (0.045 g, 58%); m.p.: 67 – 69 °C; R_f (10% MeOH/DCM), 0.33. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.30 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.06 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.96 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 5.38 (s, 2H), 4.91 (ddq, *J* = 14.3, 9.3, 6.3 Hz, 1H), 4.11 (dd, *J* = 14.3, 7.4 Hz, 1H), 3.85 (tt, *J* = 11.0, 5.5 Hz, 1H), 3.57 (dd, *J* = 9.3, 7.4 Hz, 1H), 3.11 – 3.03 (m, 2H), 2.95 – 2.85 (m, 2H), 2.76 – 2.66 (m, 2H), 2.42 – 2.32 (m, 2H), 2.15 – 2.06 (m, 2H), 1.71 – 1.58 (m, 2H), 1.42 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 164.8, 153.9, 144.0, 142.3, 141.6, 133.9, 132.3 (2C), 128.5 (2C), 128.0 (2C), 127.1 (2C), 125.5, 121.3, 119.6, 118.0, 114.8, 111.0, 107.6, 76.7, 60.3, 59.3, 52.1 (2C), 49.8, 44.3, 32.5, 31.3 (2C), 19.8. LC-MS (APCI$^+$/ESI): found *m/z* = 519.2 $[M+H]^+$ (cal. For $C_{32}H_{34}N_6O$, 518.28). Purity: 98%, t_R= 2.676 min. Specific rotation, $[\alpha]^{25}_D$ = +8.11°.

1-Methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[*d*]imidazol-2-amine (16). Following general procedure 12, obtained from **14b** (0.150 g, 0.65 mmol) and **3d** (0.223 g, 0.78 mmol) as a pale-yellow solid (0.203 g, 75%); m.p.: 134 – 136 °C; R_f (10% MeOH/DCM), 0.34. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.28 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.12 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.03 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1H), 7.00 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 3.79 (tt, *J* = 11.1, 4.2 Hz, 1H), 3.52 (s, 3H), 3.14 – 3.07 (m, 2H), 2.98 – 2.92 (m, 2H), 2.75 – 2.70 (m, 2H), 2.42 (s, 3H), 2.37 – 2.30 (m, 2H), 2.17 – 2.10 (m, 2H), 1.74 – 1.65 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.5,

167.6, 154.2, 145.8, 141.2, 134.6, 129.4 (2C), 127.8 (2C), 121.9, 120.7, 119.3, 114.4, 107.0, 59.3, 52.3 (2C), 49.9, 32.8, 31.6 (2C), 27.2, 10.0. LC-MS (APCI$^+$/ESI): found *m/z* = 417.2 [M+H] $^+$ (cal. For $C_{24}H_{28}N_6O$, 416.23). Purity: 99%, t_R = 2.530 min.

1-Isopropyl-*N*-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[*d*]imidazol-2-amine (17). Following general procedure 12, obtained from **14c** (0.030 g, 0.12 mmol) and **3d** (0.040 g, 0.14 mmol) as a pale-yellow solid (0.047 g, 91%); m.p.: 183 – 185 °C; R_f (10% MeOH/DCM), 0.37. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.35 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.02 (ddd, *J* = 7.6, 7.1, 1.1 Hz, 1H), 6.96 (ddd, *J* = 7.9, 7.1, 1.2 Hz, 1H), 4.61 (hept, *J* = 6.9 Hz, 1H), 3.80 (tt, *J* = 11.1, 4.2 Hz, 1H), 3.16 – 3.09 (m, 2H), 3.00 – 2.93 (m, 2H), 2.77 – 2.73 (m, 2H), 2.43 (s, 3H), 2.39 – 2.32 (m, 2H), 2.17 – 2.10 (m, 2H), 1.73 – 1.66 (m, 2H), 1.57 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.5, 167.6, 153.0, 145.8, 141.7, 132.1, 129.4 (2C), 127.8 (2C), 121.9, 120.5, 119.0, 114.8, 109.9, 59.3, 52.3 (2C), 50.0, 45.9, 32.7, 31.5 (2C), 19.4 (2C), 10.0. LC-MS (APCI$^+$/ESI): found *m/z* = 445.2 [M+H] $^+$ (cal. For $C_{26}H_{32}N_6O$, 444.26). Purity: 97%, t_R = 2.581 min.

(S)-4-((2-((1-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenethyl) pyrrolidine-3-yl) amino)-1H-benzo[*d*]imidazol-1-yl)methyl)benzonitrile (29). Following general procedure 12, obtained from **27b** (0.070 g, 0.22 mmol) and **3d** (0.075 g, 0.26 mmol) as a pale-yellow solid (0.089 g, 80%); m.p.: 75 – 77 °C; R_f (10% MeOH/DCM), 0.36. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.32 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.05 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 7.01 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.96 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.36 (s, 2H), 4.49 (tt, *J* = 7.0, 4.1 Hz, 1H), 3.09 – 2.98 (m, 2H), 2.98 – 2.80 (m, 5H), 2.69 – 2.61 (m, 1H), 2.48 – 2.38 (m, 4H), 1.91 – 1.80 (m, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.3, 168.5, 154.8, 146.2, 143.0, 142.2, 134.8, 133.2 (2C), 130. (2C), 128.7 (2C), 128.0 (2C), 122.9, 122.3, 120.8, 118.9, 115.9, 111.9, 108.6, 61.0, 57.4, 53.7, 52.8, 45.2, 35.0, 32.1, 10.9. LC-MS (APCI$^+$/ESI): found *m/z* = 504.2 [M+H] $^+$ (cal. For $C_{30}H_{29}N_7O$, 503.24). Purity: 97%, t_R = 2.745 min. Specific rotation, $[\alpha]^{25}_D$ = +4.58°.

4-((2-(2-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenethyl)-2,6-diazaspiro[3.4]octan-6-yl)-1H-benzo[*d*]imidazol-1-yl)methyl)benzonitrile (30). Following general procedure 12, obtained from **27c** (0.055 g, 0.16 mmol) and **3d** (0.055 g, 0.19 mmol) as a pale-yellow solid (0.065 g, 77%); m.p.: 113 – 115 °C; R_f (10% MeOH/DCM), 0.40. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.02 (d, *J* = 8.2

Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.39 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.12 (ddd, *J* = 7.9, 7.5, 1.0 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.02 (ddd, *J* = 8.1, 7.5, 1.0 Hz, 1H), 5.47 (s, 2H), 3.64 (s, 2H), 3.54 (t, *J* = 6.9 Hz, 2H), 3.26 (m, 4H), 2.82 – 2.77 (m, 2H), 2.77 – 2.73 (m, 2H), 2.42 (s, 3H), 2.12 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.4, 167.6, 155.9, 145.3, 142.8, 141.3, 135.4, 132.4 (2C), 129.4 (2C), 127.7 (2C), 126.7 (2C), 121.9, 120.4, 118.0, 115.5, 111.1, 108.3, 63.0, 59.9, 59.1, 48.6, 46.8, 40.6, 35.3, 33.5, 29.3, 10.0. LC-MS (APCI$^+$/ESI): found *m/z* = 530.2 [M+H] $^+$ (cal. For $C_{32}H_{31}N_7O$, 529.26). Purity: 97%, t_R = 2.340 min.

5,6-difluoro-1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (62). Following general procedure 12, obtained from **60a** (0.080 g, 0.30 mmol) and **3d** (0.103 g, 0.36 mmol) as a pale-yellow solid (0.072 g, 53%). M.p.: 175 – 177 °C; R_f (10% MeOH/DCM), 0.38. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.45 (dd, *J* = 7.4, 5.3 Hz, 1H), 7.36 (dd, *J* = 7.5, 5.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.85 (tt, *J* = 11.1, 4.2 Hz, 1H), 3.51 (s, 3H), 3.20 – 3.12 (m, 2H), 2.97 – 2.91 (m, 2H), 2.75 – 2.69 (m, 2H), 2.41 (s, 3H), 2.35 – 2.28 (m, 2H), 2.18 – 2.01 (m, 2H), 1.73 – 1.65 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.2, 163.5, 144.0, 143.9, 141.9, 139.3, 138.0, 133.9, 128.8 (2C), 127.9 (2C), 119.3, 108.2, 107.9, 59.5, 56.5, 52.3 (2C), 34.9, 32.7, 31.8 (2C), 16.9. LC-MS (APCI$^+$/ESI): found m/z = 453.2 [M+H]$^+$ (cal. For $C_{24}H_{26}F_2N_6O$, 452.21). Purity: 99%, t_R = 2.223 min.

5,6-dichloro-1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (63). Following general procedure 12, obtained from **60b** (0.080 g, 0.27 mmol) and **3d** (0.089 g, 0.32 mmol) as a cream white solid (0.060 g, 46%). m.p.: 188 – 190 °C; R_f (10% MeOH/DCM), 0.39. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.28 (s, 1H), 3.79 (tt, *J* = 11.2, 4.2 Hz, 1H), 3.50 (s, 3H), 3.20 – 3.11 (m, 2H), 3.01 – 2.90 (m, 2H), 2.81 – 2.73 (m, 2H), 2.45 – 2.31 (m, 5H), 2.19 – 2.06 (m, 2H), 1.79 – 1.63 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) ^{13}C NMR (101 MHz, Methanol-d_4) δ 174.1, 166.2, 154.5, 144.2, 140.1, 133.1, 127.9 (2C), 126.4 (2C), 122.5, 120.7, 120.5, 113.9, 107.1, 57.2, 50.8 (2C), 47.9, 31.2, 29.9 (2C), 26.1, 8.6. LC-MS (APCI$^+$/ESI): found m/z = 485.2, 487.2 [M+H]$^+$ (cal. for $C_{24}H_{26}Cl_2N_6O$, 484.15, 486.15). Purity: 99%, t_R = 2.400 min.

1-methyl-2-((1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl) amino)-1H-benzo[d]imidazole-5-carbonitrile (64). Following general procedure 12, obtained from **60d** (0.080 g, 0.32 mmol) and **3d** (0.108 g, 0.38 mmol) as a cream white solid (0.095 g, 69%). m.p.:

97 – 99 °C; R_f (10% MeOH/DCM), 0.21. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 1.4 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.85 (tt, *J* = 10.8, 4.0 Hz, 1H), 3.51 (s, 3H), 3.21 – 3.13 (m, 2H), 3.01 – 2.93 (m, 2H), 2.74 – 2.69 (m, 2H), 2.41 (s, 3H), 2.38 – 2.29 (m, 2H), 2.17 – 2.09 (m, 2H), 1.74 – 1.64 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.4, 159.2, 141.5, 139.3, 137.7, 133.8, 128.6 (2C), 127.9 (2C), 125.9, 121.3, 119.8, 118.4, 115.1, 106.3, 59.5, 56.7, 52.0 (2C), 34.6, 32.3, 31.6 (2C), 16.8. LC-MS (APCI$^+$/ESI): found m/z = 442.2 $[M+H]^+$ (cal. for $C_{25}H_{27}N_7O$, 441.23). Purity: 98%, t_R = 2.201 min.

1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine (65). Following general procedure 12, obtained from **60e** (0.080 g, 0.27 mmol) and **3d** (0.092 g, 0.32 mmol) as an off-white solid (0.081 g, 62%). m.p.: 156 – 157 °C; R_f (10% MeOH/DCM), 0.29. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.47 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 3.81 (m, 1H), 3.55 (s, 3H), 3.11 – 3.04 (m, 2H), 2.96 – 2.88 (m, 2H), 2.77 – 2.68 (m, 2H), 2.44- 2.38 (m, 2H), 2.08 (s, 3H), 2.04 – 2.00 (m, 2H), 1.68 – 1.59 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 175.9, 162.2, 141.7, 139.2, 137.7, 133.8, 128.6 (2C), 127.9 (2C), 125.6, 124.2 (q, *J* = 27.3 Hz), 122.2, 119.2, 112.2, 107.4, 59.6, 56.7, 52.3 (2C), 34.9, 32.9, 29.4 (2C), 11.9. LC-MS (APCI$^+$/ESI): found m/z = 485.2 $[M+H]^+$ (cal. for $C_{25}H_{27}F_3N_6O$, 484.22). Purity: 99%, t_R = 2.382 min.

5-methoxy-1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (66). Following general procedure 12, obtained from **60f** (0.080 g, 0.31 mmol) and **3d** (0.106 g, 0.37 mmol) as a light brown solid (0.074 g, 54%). m.p.: 109 – 111 °C; R_f (10% MeOH/DCM), 0.22. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 1.4 Hz, 1H), 7.30 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.86 (tt, *J* = 10.7, 3.9 Hz, 1H), 3.86 (s, 3H), 3.51 (s, 3H), 3.20 – 3.12 (m, 2H), 2.96 – 2.88 (m, 2H), 2.74 – 2.68 (m, 2H), 2.41 (s, 3H), 2.37 – 2.29 (m, 2H), 2.09 – 1.99 (m, 2H), 1.71 – 1.63 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.3, 162.4, 156.9, 142.0, 139.4, 137.7, 133.9, 128.9 (2C), 127.9 (2C), 126.3, 113.2, 112.4, 100.2, 59.6, 56.8, 52.4 (2C), 34.5, 32.2, 31.1 (2C), 56.8, 16.9. LC-MS (APCI$^+$/ESI): found m/z = 447.2 $[M+H]^+$ (cal. For $C_{25}H_{30}N_6O_2$, 446.24). Purity: 97%, t_R = 2.214 min.

1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-5-(methylsulfonyl)-1H-benzo[d]imidazol-2-amine (67). Following general procedure 12, obtained from **60g** (0.080 g, 0.26 mmol) and **3d** (0.089 g, 0.31 mmol) as an off white solid (0.082 g, 64%). m.p.: 202 – 204 °C; R_f (10% MeOH/DCM), 0.19. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 1.3 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 3.88 (tt, *J* = 10.9, 4.0 Hz, 1H), 3.53 (s, 3H), 3.39 (s, 3H), 3.19 – 3.12 (m, 2H), 2.98 – 2.92 (m, 2H), 2.75 – 2.70 (m, 2H), 2.42 (s, 3H), 2.37 – 2.99 (m, 2H), 2.15 – 2.07 (m, 2H), 1.69 – 1.60 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.8, 161.1, 141.6, 139.4, 138.1, 133.8, 132.0, 128.5 (2C), 127.8 (2C), 120.1, 119.3, 116.2, 112.4, 59.6, 56.7, 52.4 (2C), 47.1, 34.9, 32.7, 31.7 (2C), 16.9. LC-MS (APCI$^+$/ESI): found m/z = 495.2 $[M+H]^+$ (cal. for $C_{25}H_{30}N_6O_3S$, 494.21). Purity: 99%, t_R = 2.043 min.

5-fluoro-1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (70). Following general procedure 12, obtained from **60i** (0.080 g, 0.32 mmol) and **3d** (0.109 g, 0.38 mmol) as a light brown solid (0.091 g, 65%). m.p.: 72 – 74 °C; R_f (10% MeOH/DCM), 0.25. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.54 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.88 (ddd, *J* = 8.0, 7.6, 1.3 Hz, 1H), 3.91 (tt, *J* = 11.2, 4.1 Hz, 1H), 3.52 (s, 3H), 3.19 – 3.10 (m, 2H), 2.99 – 2.91 (m, 2H), 2.76 – 2.69 (m, 2H), 2.41 (s, 3H), 2.35 – 2.29 (m, 2H), 2.16 – 2.09 (m, 2H), 1.70 – 1.61 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.7, 160.2, 156.9 (d, *J* = 23.1 Hz), 141.5, 140.9, 138.2, 134.2, 128.5 (2C), 127.2 (2C), 120.1, 116.8, 110.5, 102.9, 59.3, 56.3, 52.3 (2C), 34.7, 32.3, 31.5 (2C), 16.9. LC-MS (APCI$^+$/ESI): found m/z = 435.2 $[M+H]^+$ (cal. for $C_{24}H_{27}FN_6O$, 434.22). Purity: 98%, t_R = 2.028 min.

5-bromo-1-methyl-N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (71). Following general procedure 12, obtained from **60j** (0.080 g, 0.26 mmol) and **3d** (0.089 g, 0.31 mmol) as a light brown solid (0.099 g, 77%). M.p.: 75 – 76 °C; R_f (10% MeOH/DCM), 0.30. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 1.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 3.86 (tt, *J* = 10.9, 4.0 Hz, 1H), 3.52 (s, 3H), 3.20 – 3.12 (m, 2H), 3.01 – 2.93 (m, 2H), 2.75 – 2.70 (m, 2H), 2.42 (s, 3H), 2.32 – 2.23 (m, 2H), 2.14 – 2.09 (m, 2H), 1.71 – 1.63 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.9, 160.1, 141.2, 141.1, 138.3, 134.1, 128.8 (2C), 127.8 (2C), 126.4, 119.0, 118.3, 116.1, 112.5, 59.7, 56.7, 52.3 (2C), 34.7, 32.9, 31.6 (2C), 16.9. LC-MS

(APCI$^+$/ESI): found m/z = 495.2, 457.2 $[M+H]^+$ (cal. For $C_{24}H_{27}BrN_6O$, 494.14, 496.14). Purity: 98%, t_R = 2.285 min.

1-(2-aminoethyl)-N-(1-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (72). Following general procedure 12, obtained from **60k** (0.300 g, 1.16 mmol) and **3e** (0.446 g, 1.39 mmol) as a pale-yellow solid (0.365 g, 63%). m.p.: 66 – 68 °C. R_f (10% MeOH/DCM), 0.18. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.61 – 8.00 (br-s, 2H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.26 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.98 (ddd, *J* = 7.9, 6.2, 1.2 Hz, 1H), 6.93 (ddd, *J* = 7.7, 6.2, 1.3 Hz, 1H), 6.69 (d, J = 6.5 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 3.82 (tt, *J* = 11.0, 4.2 Hz, 1H), 3.18 – 3.02 (m, 4H), 2.95 – 2.91 (m, 2H), 2.89 – 2.77 (m, 2H), 2.51 – 2.33 (m, 2H), 2.14 – 1.95 (m, 2H), 1.78 – 1.65 (m, 2H). LC-MS (APCI$^+$/ESI): found m/z = 500.2 $[M+H]^+$ (cal. for $C_{25}H_{28}F_3N_7O$, 499.23). Purity: 98%, t_R = 2.082 min.

1-((4,4-difluorocyclohexyl)methyl)-*N*-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[*d*]imidazol-2-amine (19). Following general procedure 13, obtained from **15** (0.080 g, 0.20 mmol) and 4-(bromomethyl)-1,1-difluorocyclohexane (0.051 g, 0.24 mmol) as a light brown solid (0.087 g, 68%); m.p.: 91 – 93 °C; R_f (10% MeOH/DCM), 0.66. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.30 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.01 (ddd, *J* = 8.1, 7.4, 1.1 Hz, 1H), 6.92 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 1H), 4.01 (d, *J* = 7.6 Hz, 2H), 3.77 (tt, *J* = 11.0, 4.1 Hz, 1H), 3.11 – 3.04 (m, 2H), 2.95 – 2.89 (m, 2H), 2.76 – 2.67 (m, 2H), 2.39 (s, 3H), 2.37 – 2.31 (m, 2H), 2.10 – 2.04 (m, 2H), 1.88 – 1.80 (m, 1H), 1.77 – 1.68 (m, 6H), 1.65 – 1.59 (m, 2H), 1.22 – 1.20 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.0, 167.5, 153.9, 147.9, 140.2, 134.0, 129.9 (2C), 128.1 (2C), 125.3, 121.7, 121.1, 119.9, 115.9, 107.9, 61.5, 53.1 (2C), 49.9, 38.7, 33.3, 32.0 (t, *J* = 24.5 Hz), 31.0, 25.9 (2C), 24.9 (2C), 11.0. LC-MS (APCI$^+$/ESI): found *m/z* = 537.3 $[M+H]^+$ (cal. For $C_{30}H_{36}F_2N_6O$, 534.29). Purity: 98%, t_R = 2.265 min.

N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenethyl)piperidin-4-yl)-1-(yridine-3-ylmethyl)-1H-benzo[*d*]imidazol-2-amine (20). Following general procedure 13, obtained from **15** (0.080 g, 0.20 mmol) and 3-(bromomethyl)pyridine hydrochloride (0.061 g, 0.24 mmol) as a brown solid (0.066 g, 67%); m.p.: 217 – 219 °C; R_f (10% MeOH/DCM), 0.51. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.44 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.54 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.37 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.33 (dd, *J* = 8.0, 0.9

Hz, 1H), 7.10 – 7.05 (m, 2H), 6.98 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 5.37 (s, 2H), 3.87 (tt, *J* = 11.0, 4.0 Hz, 1H), 3.16 – 3.09 (m, 2H), 2.99 – 2.94 (m, 2H), 2.81 – 2.76 (m, 2H), 2.43 (m, 5H), 2.17 – 2.11 (m, 2H), 1.73 – 1.64 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.4, 167.6, 153.8, 147.9, 147.3, 145.4, 141.3, 135.2, 133.7, 133.1, 129.4 (2C), 127.8 (2C), 123.9, 121.9, 121.4, 119.7, 114.8, 107.5, 59.0, 52.1 (2C), 49.7, 42.2, 32.5, 31.2 (2C), 9.9. LC-MS (APCI$^+$/ESI): found *m/z* = 494.2 [M+H] $^+$ (cal. For $C_{29}H_{31}N_7O$, 493.26). Purity: 98%, t_R = 2.333 min.

N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1-((6-(trifluoromethyl) pyridin-3-yl)methyl)-1H-benzo[*d*]imidazol-2-amine (21). Following general procedure 13, obtained from **15** (0.080 g, 0.20 mmol) and 5-(bromomethyl)-2-(trifluoromethyl)pyridine (0.058 g, 0.24 mmol) as a white solid (0.065g, 58%); m.p.: 90 – 92 °C; R_f (10% MeOH/DCM), 0.45. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.54 (br-s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.60 (m, 3H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.35 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.99 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H), 5.45 (s, 2H), 3.84 (tt, *J* = 11.0, 4.1 Hz, 1H), 3.08 – 3.02 (m, 2H), 2.95 – 2.88 (m, 2H), 2.72 – 2.66 (m, 2H), 2.37 – 2.30 (m, 2H), 2.20 (s, 3H), 2.14 – 2.08 (m, 2H), 1.68 – 1.59 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 177.1, 155.0, 149.1, 147.8 (q, *J* = 34.3 Hz), 144.9, 141.0, 137.5, 135.2, 133.1, 132.9 (2C), 128.4 (2C), 121.1, 120.2, 120.0, 119.8, 118.0, 115.9, 109.6, 107.4, 58.9, 51.1 (2C), 50.9, 41.1, 33.7, 31.5 (2C), 10.9. LC-MS (APCI$^+$/ESI): found *m/z* = 562.2 [M+H] $^+$ (cal. for $C_{30}H_{30}F_3N_7O$, 561.25). Purity: 97%, t_R = 2.708 min.

N-(1-(4-(3-methyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1-(4-(trifluoromethyl) benzyl)-1H-benzo[*d*]imidazol-2-amine (22). Following general procedure 13, obtained from **15** (0.080 g, 0.20 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.057 g, 0.24 mmol) as a pale-yellow solid (0.090 g, 80%); m.p.: 171 – 173 °C; R_f (10% MeOH/DCM), 0.31. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.19 (ddd, *J* = 7.8, 7.4, 1.2 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.89 (ddd, *J* = 8.1, 7.4, 1.1 Hz, 1H), 5.39 (s, 2H), 3.90 (tt, *J* = 10.9, 4.0 Hz, 1H), 3.11 – 3.03 (m, 2H), 2.95 – 2.82 (m, 2H), 2.71 – 2.66 (m, 2H), 2.43 (s, 3H), 2.34 – 2.26 (m, 2H), 2.11 – 2.01 (m, 2H), 1.64 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 176.9, 164.4, 153.9, 144.6, 142.3, 141.6, 133.9 (q, *J* = 33.0 Hz), 132.3 (2C), 129.3 (2C), 127.1 (2C), 126.6 (2C), 121.3, 119.6, 118.0, 114.9, 111.1, 107.5, 59.2, 52.1, 49.9, 44.3, 35.2, 32.6, 31.4, 9.0. LC-MS (APCI$^+$/ESI): found *m/z* = 562.2 [M+H] $^+$ (cal. for $C_{31}H_{31}F_3N_6O$, 561.25). Purity: 97%, t_R = 2.803 min.

N-(1-(4-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1-methyl-1H-benzo[d]imidazol-2-amine (36). Following general procedure 14, obtained from **31b** (0.021 g, 0.18 mmol) as a light brown solid (0.046 g, 66% over two steps). m.p.: 164 – 166 °C; R_f (10% MeOH/DCM), 0.45. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 7.8, 1.3 Hz, 1H), 7.13 (dd, J = 7.7, 1.3 Hz, 1H), 7.06 – 6.99 (m, 2H), 3.80 (tt, J = 11.0, 3.9 Hz, 1H), 3.52 (s, 3H), 3.16 – 3.06 (m, 2H), 2.99 – 2.92 (m, 2H), 2.79 – 2.71 (m, 2H), 2.37 (td, J = 11.9, 2.5 Hz, 2H), 2.15 (dt, J = 13.6, 3.5 Hz, 2H), 1.75 – 1.67 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 178.1, 175.3, 154.1, 145.5, 140.9, 134.5, 129.3 (2C), 127.8 (2C), 122.2, 120.8, 119.4, 114.3, 106.9, 59.1, 52.2 (2C), 49.8, 32.7, 32.1, 31.5 (2C), 27.4 (3C), 27.2. LC-MS (APCI$^+$/ESI): found m/z = 459.2 $[M+H]^+$ (cal. For $C_{27}H_{34}N_6O$, 458.28). Purity: 95%, t_R = 2.281 min.

N-(1-(4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1-methyl-1H-benzo[d]imidazol-2-amine (37). Following general procedure 14, obtained from **31c** (0.018 g, 0.18 mmol) as a pale-yellow solid (0.036 g, 56% over two steps). m.p.: 123 – 124 °C; R_f (10% MeOH/DCM), 0.39. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.34 (dd, J = 7.7, 1.2 Hz, 1H), 7.12 (dd, J = 8.2, 1.2 Hz, 1H), 7.05 (ddd, J = 7.7, 7.2, 1.2 Hz, 1H), 6.95 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 3.81 (tt, J = 10.8, 4.4 Hz, 1H), 3.52 (s, 3H), 3.08 – 3.02 (m, 2H), 2.98 – 2.90 (m, 2H), 2.75 – 2.66 (m, 2H), 2.36 – 2.25 (m, 3H), 2.20 – 2.10 (m, 2H), 1.76 – 1.65 (m, 2H), 1.25 (dd, J = 11.3, 6.7 Hz, 2H), 0.97 (dd, J = 11.3, 6.7, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 177.0, 169.1, 153.9, 145.0, 140.4, 132.8, 130.6 (2C), 127.5 (2C), 121.7, 120.9, 119.7, 114.9, 107.3, 60.3, 54.2 (2C), 50.4, 32.1, 31.2 (2C), 30.6, 9.9 (2C), 8.8. LC-MS (APCI$^+$/ESI): found m/z = 443.2 $[M+H]^+$ (cal. For $C_{26}H_{30}N_6O$, 442.25). Purity: 98%, t_R = 2.122 min.

1-methyl-N-(1-(4-(3-((methylthio)methyl)-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (38). Following general procedure 14, obtained from **31d** (0.022 g, 0.18 mmol) as a pale-yellow solid (0.036 g, 51% over two steps). m.p.: 66 – 68 °C; R_f (10% MeOH/DCM), 0.38. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.05 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.30 (dd, J = 7.8, 1.2 Hz, 1H), 7.11 (dd, J = 8.1, 1.2 Hz, 1H), 7.05 – 6.90 (m, 2H), 3.82 (tt, J = 10.9, 4.4 Hz, 1H), 3.68 (s, 2H), 3.52 (s, 3H), 3.14 – 3.10 (m, 2H), 3.00 – 2.92 (m, 2H), 2.77 – 2.69 (m, 2H), 2.35 – 2.30 (m, 2H), 2.16 – 2.03 (m, 5H), 1.72 – 1.66 (m, 2H). ^{13}C NMR (151

MHz, Methanol-d_4) δ 177.0, 159.3, 148.3, 142.5, 140.1, 134.3, 130.4 (2C), 127.8 (2C), 122.0, 120.9, 119.2, 114.3, 106.3, 59.9, 51.3 (2C), 49.9, 35.2, 32.8, 30.9 (2C), 27.9, 14.1. LC-MS (APCI$^+$/ESI): found m/z = 463.2 $[M+H]^+$ (cal. for $C_{25}H_{30}N_6OS$, 462.22). Purity: 98%, t_R = 2.034 min.

N-(1-(4-(3-((dimethylamino)methyl)-1,2,4-oxadiazol-5-yl) phenethyl) piperidin-4-yl)-1-methyl-1H-benzo[d]imidazol-2-amine (39). Following general procedure 14, obtained from **31e** (0.021 g, 0.18 mmol) as a pale-yellow solid (0.037 g, 53% over two steps). m.p.: 119 – 120 °C; R_f (10% MeOH/DCM), 0.24. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.33 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.13 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.04 (ddd, *J* = 7.8, 7.1, 1.2 Hz, 1H), 6.96 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 4.49 (s, 2H), 3.82 (tt, *J* = 10.9, 4.3 Hz, 1H), 3.53 (s, 3H), 3.09 – 3.00 (m, 2H), 2.98 – 2.89 (m, 2H), 2.75 – 2.65 (m, 2H), 2.37 – 2.26 (m, 3H), 2.20 – 2.09 (m, 8H), 1.71 – 1.59 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.9, 169.1, 153.8, 145.1, 140.7, 133.1, 130.9 (2C), 127.9 (2C), 121.9, 120.0, 119.1, 114.8, 107.2, 61.0, 58.0, 54.3 (2C), 50.3, 46.8 (2C), 33.0, 31.4 (2C), 30.0. LC-MS (APCI$^+$/ESI): found m/z = 460.2 $[M+H]^+$ (cal. for $C_{26}H_{33}N_7O$, 459.27). Purity: 95%, t_R = 0.155 min.

(5-(4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) phenyl)-1,2,4-oxadiazol-3-yl) methanol (40). Following general procedure 14, obtained from *N*-2-dihydroxyacetimidamide (0.016 g, 0.18 mmol) as a cream white solid (0.029 g, 44% over two steps). m.p.: 105 – 107 °C; R_f (10% MeOH/DCM), 0.24. ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.29 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.06 (ddd, *J* = 7.8, 7.2, 1.0 Hz, 1H), 6.96 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 5.03 (d, *J* = 4.8 Hz, 2H), 3.80 (tt, *J* = 10.8, 4.3 Hz, 1H), 3.53 (s, 3H), 3.14 – 3.09 (m, 2H), 3.00 – 2.90 (m, 2H), 2.76 – 2.65 (m, 2H), 2.34 – 2.29 (m, 2H), 2.17 – 2.11 (m, 2H), 1.73 – 1.64 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.9, 159.4, 148.6, 142.0, 139.8, 135.0, 130.3 (2C), 127.7 (2C), 121.9, 120.4, 119.0, 114.2, 105.7, 59.9, 52.9 (2C), 49.5, 35.1, 32.3, 30.5 (2C), 28.3. LC-MS (APCI$^+$/ESI): found m/z = 433.2 $[M+H]^+$ (cal. For $C_{24}H_{28}N_6O_2$, 432.23). Purity: 99%, t_R = 0.176 min.

N-(1-(hydroxymethyl) cyclopropyl)-4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) benzamide (44). Following general procedure 14, obtained from 1-(aminomethyl)cyclopropanol (0.016 g, 0.18 mmol) as a cream white solid (0.048 g, 71%). m.p.: 221 – 223 °C; R_f (10% MeOH/DCM), 0.26. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.15 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.08 – 6.98

(m, 2H), 3.80 (tt, *J* = 10.4, 4.2 Hz, 1H), 3.68 (s, 2H), 3.54 (s, 3H), 3.20 – 3.12 (m, 2H), 2.96 – 2.90 (m, 2H), 2.78 – 2.68 (m, 2H), 2.44 – 2.33 (m, 2H), 2.20 – 2.11 (m, 2H), 1.80 – 1.64 (m, 2H), 0.92 – 0.82 (m, 4H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 169.9, 154.1, 143.8, 140.9, 134.5, 132.3, 128.4 (2C), 127.30 (2C), 120.8, 119.4, 114.3, 107.0, 65.8, 59.4, 52.3 (2C), 49.7, 34.7, 32.4, 31.4 (2C), 27.2, 10.6 (2C). LC-MS (APCI$^+$/ESI): found m/z = 448.3 $[M+H]^+$ (cal. for $C_{26}H_{33}N_5O_2$, 447.26). Purity: 98%, t_R = 0.153 min.

N-(2-aminoethyl)-4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) benzamide (45). Following general procedure 14, obtained from tert-butyl (2-aminoethyl)carbamate (0.029 g, 0.18 mmol), followed by general procedure 7, as a white solid (0.045 g, 85%, over two steps). m.p.: 125 – 127 °C; R_f (10% MeOH/DCM), 0.28. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.21 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.09 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.99 (ddd, *J* = 8.1, 7.5, 1.3 Hz, 1H), 6.85 (ddd, *J* = 7.8, 7.5, 1.1 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.86 – 3.61 (m, 3H), 3.53 (s, 3H), 3.15 – 3.08 (m, 2H), 2.80 – 2.71 (m, 2H), 2.68 – 2.59 (m, 2H), 2.29 – 2.18 (m, 2H), 2.09 – 2.01 (m, 2H), 1.78 – 1.65 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 169.4, 144.7, 141.2, 139.4, 135.5, 129.4 (2C), 128.5 (2C), 123.3, 120.8, 119.2, 112.9, 105.3, 63.7, 62.1, 60.7, 52.2 (2C), 51.3, 42.6, 33.6 (2C), 27.4. LC-MS (APCI$^+$/ESI): found m/z = 421.2 $[M+H]^+$ (cal. for $C_{24}H_{32}N_6O$, 420.26). Purity: 99%, t_R = 0.120 min.

N-allyl-4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) benzamide (46). Following general procedure 14, obtained from prop-2-en-1-amine (0.010 g, 0.18 mmol) as an off white solid (0.042 g, 66%). m.p.: 128 – 129 °C; R_f (10% MeOH/DCM), 0.31. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.20 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.09 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.98 (ddd, *J* = 8.0, 7.5, 1.3 Hz, 1H), 6.87 (ddd, *J* = 7.8, 7.5, 1.1 Hz, 1H), 5.81 (dd, *J* = 15.2, 10.2 Hz, 1H), 5.33 (dd, *J* = 15.2, 3.2 Hz, 1H), 5.20 (dd, 10.2, 3.2 Hz, 1H), 3.57 (tt, *J* = 11.2, 4.2 Hz, 1H), 3.52 (s, 3H), 3.13 – 3.06 (m, 2H), 2.93 – 2.87 (m, 2H), 2.73 – 2.69 (m, 2H), 2.35 – 2.29 (m, 2H), 2.16 – 2.09 (m, 2H), 1.73 – 1.65 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 167.6, 143.1, 140.9, 138.8, 136.8, 134.4, 130.2 (2C), 129.9 (2C), 122.2, 120.3, 119.3, 117.5, 113.5, 105.7, 63.4, 60.2, 52.9 (2C), 51.4, 43.0, 34.1, 30.2 (2C). LC-MS (APCI$^+$/ESI): found m/z = 418.2 $[M+H]^+$ (cal. for $C_{25}H_{31}N_5O$, 417.25). Purity: 99%, t_R = 0.175 min.

(3-hydroxypyrrolidin-1-yl)(4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl)amino)piperidin-1-yl)ethyl)phenyl)methanone (47). Following general procedure 14, obtained from pyrrolidin-3-ol (0.016 g, 0.18 mmol) as a yellow solid (0.035 g, 62%). m.p.: 130 – 132 °C; R_f (10% MeOH/DCM), 0.24. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.92 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.20 (dd, J = 7.8, 1.4 Hz, 1H), 7.08 (dd, J = 7.9, 1.3 Hz, 1H), 6.98 (ddd, J = 7.8, 7.4, 1.3 Hz, 1H), 6.83 (ddd, J = 7.9, 7.4, 1.4 Hz, 1H), 3.82 – 3.61 (m, 5H), 3.55 (tt, J = 11.0, 4.1 Hz, 1H), 3.49 (s, 3H), 3.19 – 3.08 (m, 2H), 2.85 – 2.78 (m, 2H), 2.70 – 2.61 (m, 2H), 2.40 – 2.31 (m, 2H), 2.18 (ddd, J = 14.0, 9.2, 6.8 Hz, 1H), 2.16 – 2.00 (m, 3H), 1.66 – 1.58 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.4, 145.2, 139.4, 137.6, 129.2 (2C), 128.5 (2C), 122.2, 120.9, 119.0, 118.7, 113.8, 104.6, 64.1, 60.1, 53.3 (2C), 51.3, 49.3, 48.3, 34.5, 30.9 (2C), 23.7, 22.3. LC-MS (APCI$^+$/ESI): found m/z = 448.3 $[M+H]^+$ (cal. for $C_{26}H_{33}N_5O_2$, 447.26). Purity: 98%, t_R = 0.141 min.

(3-hydroxy-3-methylpyrrolidin-1-yl) (4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) phenyl) methanone (48). Following general procedure 14, obtained from 3-methylpyrrolidin-3-ol (0.012 g, 0.18 mmol) as a pale-yellow solid (0.054 g, 77%). m.p.: 119 – 121 °C; R_f (10% MeOH/DCM), 0.36. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.90 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.18 (dd, J = 7.8, 1.4 Hz, 1H), 7.09 (dd, J = 7.9, 1.3 Hz, 1H), 6.97 (ddd, J = 7.8, 7.4, 1.3 Hz, 1H), 6.84 (ddd, J = 7.9, 7.4, 1.4 Hz, 1H), 3.91 – 3.69 (m, 4H), 3.58 (tt, J = 11.2, 4.2 Hz, 1H), 3.52 (s, 3H), 3.24 – 3.11 (m, 2H), 2.88 – 2.82 (m, 2H), 2.78 – 2.62 (m, 3H), 2.38 – 2.29 (m, 2H), 2.23 (ddd, J = 14.0, 9.3, 7.2 Hz), 2.18 – 2.06 (m, 3H), 1.70 – 1.62 (m, 2H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 172.6, 145.2, 141.0, 139.3, 136.1, 129.8 (2C), 128.8 (2C), 122.7, 120.4, 119.1, 113.7, 105.8, 77.2, 70.0, 63.1, 60.3, 52.9 (2C), 51.4, 48.1, 43.3, 34.2, 30.3 (2C), 25.1. LC-MS (APCI$^+$/ESI): found m/z = 462.3 $[M+H]^+$ (cal. for $C_{27}H_{35}N_5O_2$, 461.28). Purity: 98%, t_R = 0.173 min.

(4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) phenyl) (morpholino) methanone (49). Following general procedure 14, obtained from morpholine (0.016 g, 0.18 mmol) as a pale-yellow solid (0.051 g, 76%). m.p.: 110 – 111 °C; R_f (10% MeOH/DCM), 0.39. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.93 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.19 (dd, J = 8.0, 1.3 Hz, 1H), 7.10 (dd, J = 7.9, 1.3 Hz, 1H), 7.04 (ddd, J = 8.0, 7.3, 1.3 Hz, 1H), 6.88 (ddd, J = 7.9, 7.3, 1.3 Hz, 1H), 3.83 – 3.78 (m, 4H), 3.75 – 3.71 (m, 4H), 3.61 (tt, J = 10.9, 4.3 Hz, 1H), 3.52 (s, 3H), 3.20 – 3.13 (m, 2H), 2.89 – 2.81 (m, 2H), 2.76 – 2.65 (m, 2H),

2.39 – 2.30 (m, 2H), 2.18 – 2.09 (m, 2H), 1.73 – 1.65 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 168.9, 145.6, 141.1, 138.9, 135.4, 130.1 (2C), 128.2 (2C), 122.8, 120.3, 119.2, 113.6, 105.3, 63.8, 60.1, 53.2 (2C), 52.8 (2C), 51.2, 45.2 (2C), 34.0, 30.5 (2C). LC-MS (APCI$^+$/ESI): found m/z = 448.2 $[M+H]^+$ (cal. for $C_{26}H_{33}N_5O_2$, 447.26). Purity: 99%, t_R = 0.125 min.

(4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) phenyl) (piperazin-1-yl) methanone (50). Following general procedure 14, obtained from *tert*-butyl piperazine-1-carboxylate (0.034 g, 0.18 mmol), followed by procedure 2, as an off white solid (0.030 g, 90%, over two steps). m.p.: 108 – 109 °C; R_f (10% MeOH/DCM), 0.28. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.18 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.09 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.99 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H), 6.86 (ddd, *J* = 7.7, 7.4, 1.3 Hz, 1H), 3.81 – 3.75 (m, 4H), 3.73 – 3.68 (m, 4H), 3.59 (tt, *J* = 10.9, 4.3 Hz, 1H), 3.52 (s, 3H), 3.20 – 3.11 (m, 2H), 2.88 – 2.81 (m, 2H), 2.75 – 2.65 (m, 2H), 2.38 – 2.29 (m, 2H), 2.18 – 2.05 (m, 2H), 1.73 – 1.64 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 169.8, 145.4, 141.2, 138.9, 136.8, 130.3 (2C), 128.5 (2C), 122.9, 120.4, 119.3, 113.6, 105.7, 63.4, 60.2, 53.3 (2C), 52.8 (2C), 51.8, 45.7 (2C), 34.1, 30.4 (2C). LC-MS (APCI$^+$/ESI): found m/z = 447.3 $[M+H]^+$ (cal. for $C_{26}H_{34}N_6O$, 446.28). Purity: 98%, t_R = 0.122 min.

(hexahydropyrrolo [1,2-a] pyrazin-2(1H)-yl) (4-(2-(4-((1-methyl-1H-benzo[d]imidazol-2-yl) amino) piperidin-1-yl) ethyl) phenyl) methanone (51). Following general procedure 14, obtained from octahydropyrrolo[1,2-a]pyrazine (0.023 g, 0.18 mmol) as an off white solid (0.054 g, 73%). m.p.: 85 – 87 °C; R_f (10% MeOH/DCM), 0.25. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.18 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.96 (ddd, *J* = 7.8, 7.3, 1.2 Hz, 1H), 6.87 (ddd, *J* = 8.0, 7.3, 1.3 Hz, 1H), 3.84 (tt, *J* = 10.9, 4.2 Hz, 1H), 3.52 (s, 3H), 3.31 – 3.20 (m, 4H), 3.12 – 3.05 (m, 2H), 3.00 – 2.81 (m, 5H), 2.77 – 2.65 (m, 2H), 2.46 – 2.24 (m, 2H), 2.18 – 2.11 (m, 2H), 1.77 – 1.61 (m, 4H), 1.54 – 1.41 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 168.9, 145.2, 141.0, 138.5, 135.0, 130.1 (2C), 127.3 (2C), 122.3, 120.3, 119.2, 113.8, 105.3, 67.3, 60.0, 55.1, 53.1 (2C), 51.2, 50.1, 46.2, 47.0, 36.0, 34.3, 30.3 (2C), 27.0, 22.3. LC-MS (APCI$^+$/ESI): found m/z = 487.3 $[M+H]^+$ (cal. for $C_{29}H_{38}N_6O$, 486.31). Purity: 98%, t_R = 0.193 min.

Kinetic solubility assay. The test compound was dissolved in DMSO to make a 10 mM stock solution. A pre-dilution plate was prepared by taking from each stock solution and serially diluting in triplicate to yield concentrations from 0.25 mM to 10.0 mM in 96 well plates. From each pre-

dilution solution, secondary dilutions of the compounds in both DMSO and 0.01M pH 7.4 PBS where prepared in a second 96-well plate, also in triplicate. Wells in columns 1-6 would contain compound in DMSO while those in columns 7 – 12 would contain samples in PBS at similar nominal concentrations as those in DMSO. The final volume of solvent in each assay plate was 200 µl, prepared by pipetting 4 µl each of solution from the pre-dilution plate to the corresponding well into both DMSO and PBS (both 196 µl). This ensures that the final concentration of DMSO in the PBS aqueous buffer does not exceed 2% v/v. The different concentrations in DMSO are prepared to serve as controls to determine potential false turbimetric absorbance readings arising from the compounds in solution absorbing incident radiation at the analysis wavelength. After making the assay plate preparation, the plate is covered and left to equilibrate for 2 hours at 25^{o}C. After incubation, Uv-vis absorbance readings from the plate was measured at 620 nm using a SpectraMax 340PC^{384} microplate reader. Using MS Excel, plots of corrected absorbance against compound concentration are computed for a graphical representation of the data. Reserpine and hydrocortisone were used as positive and negative controls respectively.

In vitro **antiplasmodium assay**. Compounds were tested using parasite lactate dehydrogenase assay as a marker for parasite survival.[1] All parasite strains were acquired from MR4 (Malaria Research and Reference Reagent Resource Center, Manassas, VA). Briefly, the respective stock solutions of CQ diphosphate and test compounds were prepared to 2 mg/ml in distilled H_2O (for CQ) and 100% DMSO for test compounds and then stored at – 20 °C, and further dilutions were prepared on the day of the experiment. The cultures were synchronized in the ring stage as described previously using 15 mL of 5% (w/v) D-sorbitol in H_2O. Synchronous cultures of *Pf*NF54 (CQ-S) and *Pf*K1 (MDR) in the late trophozoite stage were prepared to 2% parasitemia and 2% hematocrit. Compounds were tested at starting concentrations of 10 000 ng/mL (1000 ng/mL for CQ), which were then serially diluted two-fold in complete medium to give 10 concentrations with a final volume of 200 µl in each well. Parasites were incubated in the presence of the compounds at 37°C under normal hypoxic conditions [4% CO_2 and 3% O_2 in nitrogen (N_2)] for 48 h. Following incubation, 100 µl of MalStat reagent and 15 µl of resuspended culture were combined, followed by addition of 25 µl of nitro blue tetrazolium chloride (NBT). The plates were kept in the dark for about 10 min to fully develop, and absorbance was measured at 620 nm on a microplate reader. Raw data were exported to Microsoft Excel for dose-response analysis.

***In vitro* gametocytocidal activity assay**. Gametocytes were produced as per the method reported by Reader and co-workers.[2] The luciferase reporter assay was used to enable accurate, reliable and quantifiable investigations of the stage-specific action of gametocytocidal compounds for the early and late gametocyte marker cell line NF54-*Pf*S16-GFP-Luc. Assays were set up on day 5 and 10 (representing >90% of either early stage II/III or mature/late stage IV/V gametocytes, respectively). In each instance, assays were set up using a 2 – 3% gametocytemia, 1.5% hematocrit culture and 48 h drug pressure in a gas chamber (90% N_2, 5% O_2, and 5% CO_2) at 37ºC. Luciferase activity was determined in 30 µl parasite lysates by adding 30 µl luciferin substrate (Promega Luciferase Assay System) at room temperature and detection of resultant bioluminescence at an integration constant of 10s with the GloMax® Explorer Detection System with Instinct® Software. Methylene blue (5 µM) and internal project specific controls were included as controls. The dual point screens were performed as technical triplicates for a single biological assay.

Table S1: *In vitro* gametocytocidal activity of selected analogues (duo-point and IC_{50}'s).

Compound	Early Gametocytes (EG)[a]			Late Gametocytes (LG)[b]		
	% activity		*Pf*EG IC_{50} (µM)	% activity		*Pf*LG IC_{50} (µM)
	1.0 µM	5.0 µM		1.0 µM	5.0 µM	
AST	5	61	-	0 13[c]	11 52[c]	3.35[c]
6	2	0	-	2	20	-
7	0	14	-	10	41	-
8	36	77	-	43	62	-
10	31	54	-	49	76	-
11	1	14	-	14	45	-
12	1	46	-	27	58	-
15	12	14	-	43	63	-
16	0	0	-	10	36	-
17	8	3	-	14	33	-
21	2	15	-	7	43	-
22	0	75	-	0	70	-
23	29	**83**	1.52±0.3	17	45	-
23	19	**85**	1.67±0.3	0	0	-
28	5	0	-	14	62	-
29	10	1	-	11	42	-
35	8	70	-	0	0	-

Compound	Early Gametocytes (EG)[a]			Late Gametocytes (LG)[b]		
	% activity		*Pf*EG IC_{50} (µM)	% activity		*Pf*LG IC_{50} (µM)
	1.0 µM	5.0 µM		1.0 µM	5.0 µM	
36	17	**89**	1.18±0.3	0	31	-
37	6	43	-	0	0	
42	0	3	-	0	0	
61	8	49	-	0	16	

[a]*Pf*NF54 early-stages (I – III) and [b]late-stages (IV – V) gametocytes, obtained at 1.0 µM and 5.0 µM (n = 3, technical triplicates). Methylene blue (EG luc at 1.0 µM = 95% inhibition, EG IC_{50} = 0.2 µM; LG luc at 1.0 µM = 92% inhibition, LG IC_{50} = 0.14 µM).[c]Data generated using ATP bioluminescence assay. [d]n = 3, technical triplicates ± SEM. ND = not determined.

***In vitro* liver-stage assay (*P. berghei*-sporozoite infection)**. In a 24-well plate, HepG2 was seeded onto monolayers to a 5×10^3 cell number in 250 µl of RPMI medium. After 24 h of incubation, medium was replaced by a volume 250 µl of 5×10^4 *P. berghei*-GFP sporozoites per well. After 1 h, medium was replaced by 250 µl of medium containing drugs and further incubated for 48 h at 37 °C. Primaquine biphosphate (Sigma-Aldrich) and Astemizole (USP reference standard) were employed as reference drugs. Negative control wells received medium only. 48 h post-infection, cells were trypsinized and the percent (%) of infected cells was determined by flow cytometry (BD LSRFortessa) using at least 10000 events. For determining host cell viability, in a 96-well plate, HepG2 was seeded onto monolayers to a 5×10^3 cell number in 100 µl of RPMI medium. After 24 h of incubation, a volume 100 µl of medium containing drugs was added and further incubated at 37 °C. Negative control wells received medium only and positive wells received gentian violet. After 48 h of drug exposure, cell viability was measured using CellTiter Glo (Promega). Two independent experiments were performed. Drugs were tested in five different concentrations, each one in triplicate.

Table S2: The percent (%) and IC_{50} of infection reduction and functional viability (cell confluency) of HepG2 cells infected by *P. berghei* sporozoites.

Assay	IC_{50} (μM)				
	AST[d]	**15**	**23**	**24**	**36**
HepG2[a]	11.1 ± 2.5	4.4 ± 0.8	5.9 ± 1.2	20.8 ± 2.8	10.0 ± 1.1
Sporozoites[b]	79 ± 3.8	10 ± 20	79 ± 2.5	89 ± 1.9	55 ± 9.0
Sporozoites[c]	0.59 ± 0.21	N.D	0.49 ± 0.18	0.21 ± 0.09	N.D

[a]Activity was determined after 48 h of drug incubation in uninfected HepG2. Two independent experiments were performed; values are mean of one experiment, each concentration tested in triplicate. Values are mean±S.D. Reference drug gentian violet (IC_{50} of 3.9±0.2 μM).
[b]The percent (%) of parasite reduction at drug concentration of 1.0 μM in comparison to untreated control. Activity was determined after 48 h of drug incubation in infected HepG2 with *P. berghei* sporozoites. Values are mean of one experiment, each concentration tested in triplicate. Reference drug Primaquine (89±5.0 % at 10 μM).
[c]The IC_{50} values are the mean ± standard deviation from two experiments, each drug concentration tested in triplicate. Reference drug Primaquine (IC_{50} = 6.0±1.4 μM).
[d]AST = Astemizole. N.D. = not determined

***In vitro* hERG assay**. A QPatch hERG assay employing a four-point concentration response format was used to carry out hERG inhibition studies by the Metrion Biosciences Ltd, Cambridge, UK. The hERG gene was stably expressed in a CHO K1 cell line from the American Type Culture Collection (ATCC) which was grown and passaged under standard culture conditions. The external (e) and internal (i) recording solutions were of the following compositions (mM): NaCl – 140(e) : 0 (i); KCl – 2 (e): 70 (i); KF – 0 (e) : 60 (i); HEPES – 10 (e) : 10 (i); $MgCl_2$ – 1 (e) : 0 (i); $CaCl_2$ – 2 (e) : 0 (i); Glucose – 5 (e) : 0 (i); EGTA - 0 (e) : 5 (i); Mg_2ATP – 0 (e) : 5 (i) and pH – 7.4 (NaOH) (e) : 7.2 (KOH) (i). The external recording solution was regularly prepared and kept at 4°C until required and was maintained at room temperature during recording. The internal recording solution was prepared and kept at –20 °C until required.

The QPatch is a chip-based planar patch clamp which is automated. Using suction, cells added to each well are drawn across a small aperture creating a Giga-ohm seal between the membrane surface and a treated silicon surface. A small volume of bathing solution containing the test compound or control bathing solution is added to a reservoir on the chip which perfuses across the cell through quartz-lined microfluidic channels. The solution is removed by capillary action before the next sample is added. Using the industry +40/–40 voltage protocol, currents were triggered from a holding potential of –90 mV at a stimulus frequency of 0.1 Hz.

By cumulatively adding four escalating concentrations of the test compounds to an individual cell, the concentration response curves were established. This was done by firstly allowing the whole-cell configuration to be achieved followed by the addition of the vehicle (0.1% DMSO v/v in external recording solution) to each well in two bolus additions allowing a two-minute recording time between each addition. This was followed by the addition of four concentrations (0.3 – 10 μM) of test compounds in two bolus additions at 2-minute intervals. The effect on the hERG tail current amplitude was measured during the 4-minute recording time. The concentrations (0.3, 1, 3 and 10 μM) of the test samples were prepared in such a way to have a final concentration of 0.1% of DMSO v/v in the external recording solution. For each compound, the experiments at each concentration were done in triplicate and using a bioinformatics suite developed and running in Pipeline Pilot (Biovia, USA), the percent inhibition, as a reduction in mean peak current relative to the value measured at the end of the vehicle control period, was calculated. Such percent inhibition data were used to construct the concentration-response curves which enabled calculation of the IC_{50} values. For compounds which could not achieve 50% inhibition even at the highest tested concentration of 10 μM, extrapolated IC_{50} values for such are reported. In this regard, all IC_{50} values above 10 μM reported in this article were extrapolated and should be treated with caution.

***In vitro* β-Hematin formation inhibition assay**. Briefly, stock solutions of control (CQ and Pyrimethamine) and test compounds were made to 20 mM in 100% DMSO. A solution containing H_2O/305.5 μM NP40/DMSO at a v/v ratio of 70%/20%/10%, respectively, was added to every well in columns 1 – 11 of a 96–well plate while 140 μl of H_2O and 40 μl of 305.5 μM NP40 were added to column 12 to mediate the formation of β-hematin. Exactly 20 μl of control or test compound (20 mM) was added to column 12, and 100 μl of this solution was serially diluted to column 2, with column 1 left as a blank (0.0 μM compound). A 178.8 μl aliquot of hematin stock was suspended in 20 mL of a 1 M acetate buffer, pH 4.9, and 100 μl of this hematin suspension was added into each well. Plates were then incubated for ~5 h at 37 °C after which 32 μl of pyridine solution (20% H_2O, 20% acetone, 10% 2 M HEPES buffer, pH 7.4, 50% pyridine) was added followed by addition of 60 μl of acetone to all wells. Plates were read at 405 nm, and dose-response curves were plotted in GraphPad Prism v 6.01 (GraphPad Software Inc., La Jolla, California, USA) to obtain IC_{50} values.

Table S3: *In vitro* β-hematin inhibition results of selected analogues

Compound	β-HIA, IC_{50} (μM)[a]
AST	130.5
11	16.1
10	16.1
11	113.9
15	62.4
16	186.5
18	123.2
19	307.5
21	11.2

Compound	β-HIA, IC_{50} (μM)[a]
22	188.3
23	23.8
24	62
35	66.8
36	127.4
37	63.1
Chloroquine	24
Amodiaquine	9.23

[a]β-hematin inhibition, expressed as 50% inhibitory concentration, IC_{50} (n = 3, technical triplicates).

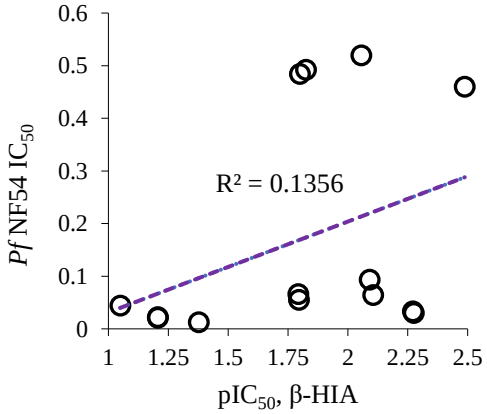

Figure S1: Linear correlation between βH inhibition and parasite growth IC_{50} values for *Pf*NF54.

***In vivo* antiplasmodium assay at Swiss TPH**. In vivo efficacy was assessed as previously described,[37] with the modification that mice (n = 3) were infected with a GFP-transfected P. berghei ANKA strain (donated by A. P. Waters and C. J. Janse, Leiden University, The Netherlands), and parasitemia was determined using standard flow cytometry techniques. The detection limit was 1 parasite in 1000 erythrocytes (that is, 0.1%). The activity was calculated as the difference between the mean percent parasitemia for the control and treated groups expressed as a percent relative to the control group. Compounds were dissolved or suspended in a vehicle consisting of 70% Tween-80 and 30% ethanol, followed by a 10-fold dilution in H2O and oral administration as four consecutive daily doses (4, 24, 48, and 72 h after infection). Blood samples for the quadruple-dose regimens were collected on day 4 (96 h after infection). The survival time

in days was also recorded up to 30 days after infection. A compound was considered curative if the animal survived to day 30 after infection with no detectable parasites by slide reading.

In vivo studies conducted at the Swiss TPH, Basel were approved by the veterinary authorities of the Canton Basel-Stadt (Permit No. 1731 and 2303) based on Swiss Cantonal (Verordnung Veterinäramt Basel-Stadt) and National Regulations (The Swiss Animal Protection Law, Tierschutzgesetz).

Dried blood spots PK analysis. Dried-blood spot (DBS) samples collected from infected *P. berghei* ANKA mice (whole blood at 1h, 4h, 24h post-administration) from the in vivo study at the Swiss TPH, Basel, Switzerland and shipped to the Drug Discovery and development Centre (H3D), Division of Clinical Pharmacology, Department of Medicine, University of Cape Town (UCT), where they were subjected to pharmacokinetics (PK) analysis. . DBS samples were reproducibly punched out of the Munktell cards and extracted by protein precipitation using acetonitrile containing 10ng/ml MMV902 as internal standard, and subsequently centrifuged. Calibration standards and quality controls were extracted following the same procedure. Supernatants were injected onto the column for LC-MS/MS analysis. Data processing conducted using graph. The total- and free-blood concentrations of front-runners are shown in Figure S2 below.

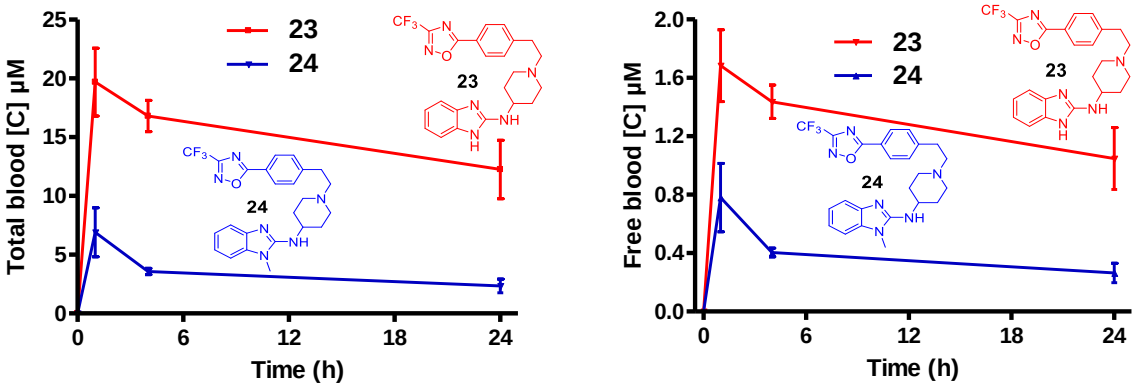

Figure S2: Total blood (left) and free-blood (right) concentrations of compound **23** and **24** in *P.berghei*-infected mice following oral administration at 4 × 50 mg•kg^{-1}

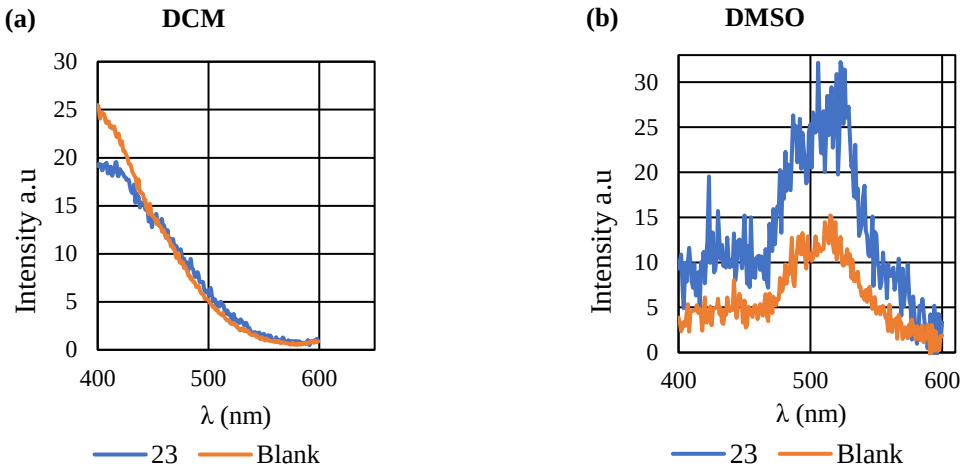

Figure S3: Emission spectra of **23** at 1.0 µM in (a) DCM and (b) DMSO

Parasite haem fractionation assay. This assay assesses the dose dependent effect of an inhibitor on the total haem in the parasite and was performed according to methods previously described by Combrinck et al.[3] Ring stage *Pf*NF54 parasites (5% parasitaemia and 2% haematocrit) were synchronized and incubated with varying concentrations of **23** as well as no compound, as a control, for 36 h, after which the mature trophozoites were isolated by saponin lysis. The isolated trophozoites were resuspended in 100 µl phosphate-buffered saline (PBS) and accurately transferred to a round-bottomed, 96-well 0.5 mL plate (Axygen Scientific) referred to as the "stock plate". A "counting plate" was prepared by adding 10 µl of the resuspended trophozoites to a fluorescence-activated cell sorting (FACS) diluent (PBS pH 7.5 containing 0.125% (v/v) glutaraldehyde and 0.5% (v/v) DNase) to a final volume of 200 µl and refrigerated at 4 °C. Cell counts were analysed using flow cytometry on a Becton Dickinson (BD) Accuri™ C6 Plus system with SSC/FL1530 nm using BD Accuri™ C6 Plus software. In a flat-bottomed, 96-well plate, samples were prepared by diluting 20 µl of the solution from the counting plate with 160 µl of 1× SYBR Green I in PBS. To this, 20 µl of Trucount™ beads (BD) were added such that a fixed number of beads was contained in a final volume of 200 µl. The plate was then incubated in the dark at 37 °C for 30 minutes and mixed well prior to reading on the flow cytometer.

The stock plate was stored at −20 °C. To determine the amount of haemoglobin, haem and hemozoin, a series of cellular fractionation steps were performed. The samples in the stock plate were thawed to promote cell membrane lysis; to this, 100 µl of water was added, and the samples

were sonicated for 5 min. A solution of HEPES buffer (50 µl, 0.02 M, pH 7.5) was added and the sample was centrifuged at 3600 rpm for 20 min. The supernatant of the solution was collected and transferred to an adjacent set of wells on the same plate. To the supernatant, 50 µl of 4% SDS was added, sonicated for 5 minutes, and incubated at room temperature for 30 minutes. Finally, to the supernatant, 50 µl of 0.3 M NaCl and 25% pyridine (v/v) in 0.2 M HEPES pH 7.5 were added and 200 µl of this was transferred to a flat-bottomed, 96-well plate termed the "reading plate". To the remaining pellet, 50 µl water and 50 µl of 4% SDS were added and resuspended well. The plate was then sonicated for 5 min and incubated at room temperature for 30 min to allow the free haem to be solubilised. Thereafter, 50 µl of 0.2 M HEPES pH 7.5, 50 µl of 0.3 M NaCl and 25% pyridine were added, and the plate was centrifuged at 3600 rpm for 20 min. The supernatant was transferred to an adjacent set of wells on the same plate and diluted to 400 µl with water. Of this solution, 200 µl was transferred to the reading plate. The remaining pellet was treated with 50 µl of water and 0.3 M NaOH and sonicated for 15 minutes to solubilise hemozoin. The plate was then incubated for 20 minutes at room temperature. Finally, 50 µl of 0.2 M HEPES buffer, 50 µl of 0.3 M HCl and 50 µl of 25% pyridine solution were added, and the supernatant was diluted with water to a final volume of 400 µl. Of this solution, 200 µl was transferred to the reading plate. The UV-visible spectra of these fractions were recorded between 400 nm and 415 nm on a multi-well plate reader (Spectramax 340PC, Molecular Devices). The percentages of the three fractions, haemoglobin, haem and hemozoin fractions, were determined from the absorbance values. The total haem in each of these samples was quantified using a standard curve. GraphPad Prism (v5) was used to analyse the final data set and perform the significance tests.

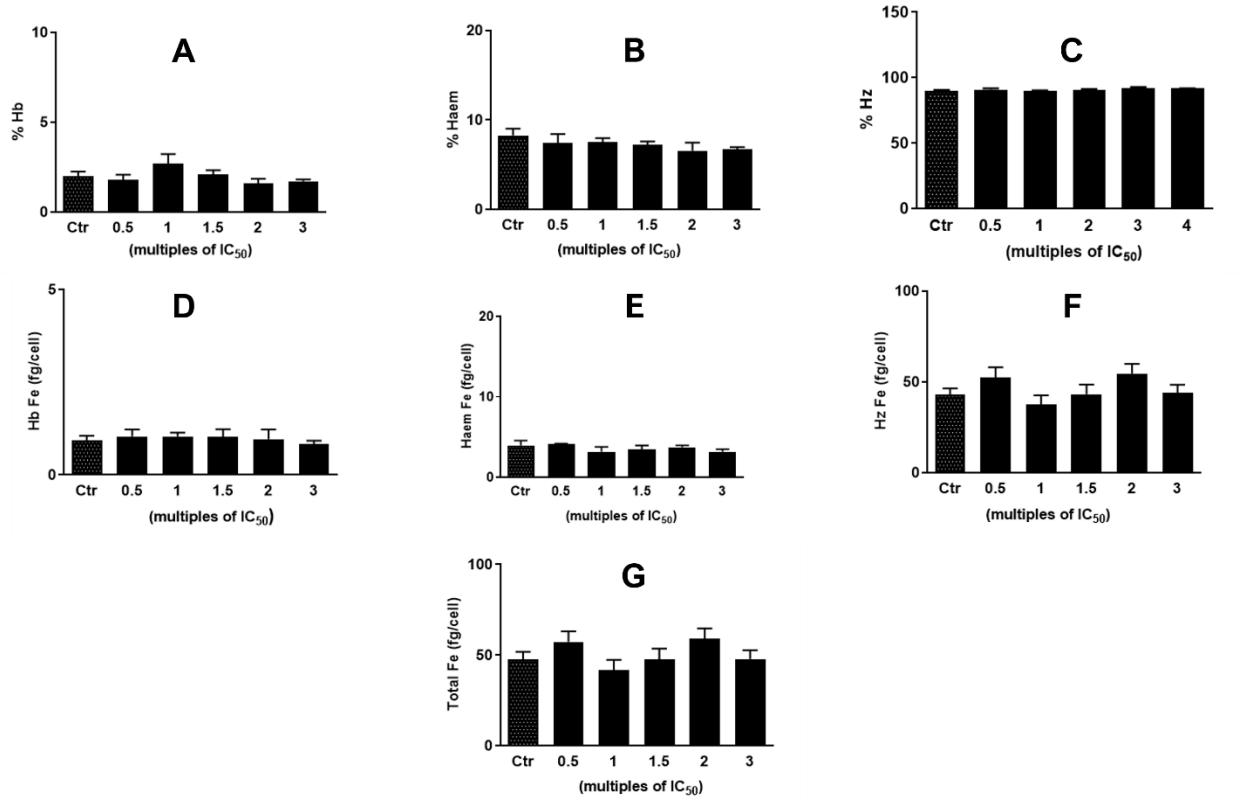

Figure S4: Haem species in synchronized control and compound **23** treated *Pf*NF54 parasites. Haem fractionation profile of **23** showing percent haemoglobin (**A**), haem (**B**) and hemozoin **(C**) at multiples of its IC_{50}. The absolute amount of haemoglobin (Hb) Fe, "free" haem Fe and hemozoin (Hz) Fe are depicted in (**D**), (**E**) and (**F**) at multiples of its IC_{50}. Plot (**G**) represents total Fe at multiples of its IC_{50}.

Optical polarimetry: Specific rotation was determined using the Rudolph Research Analytical AUTOPOL® I Automatic Polarimeter. For each compound, a 0.002 g sample was dissolved in 2 ml methanol (AR) and read using a 1 dm path length tube, at 22 °C (Na 'D' line 589 nm).

^{1}H NMR and ^{13}C NMR spectra of selected and key target compounds

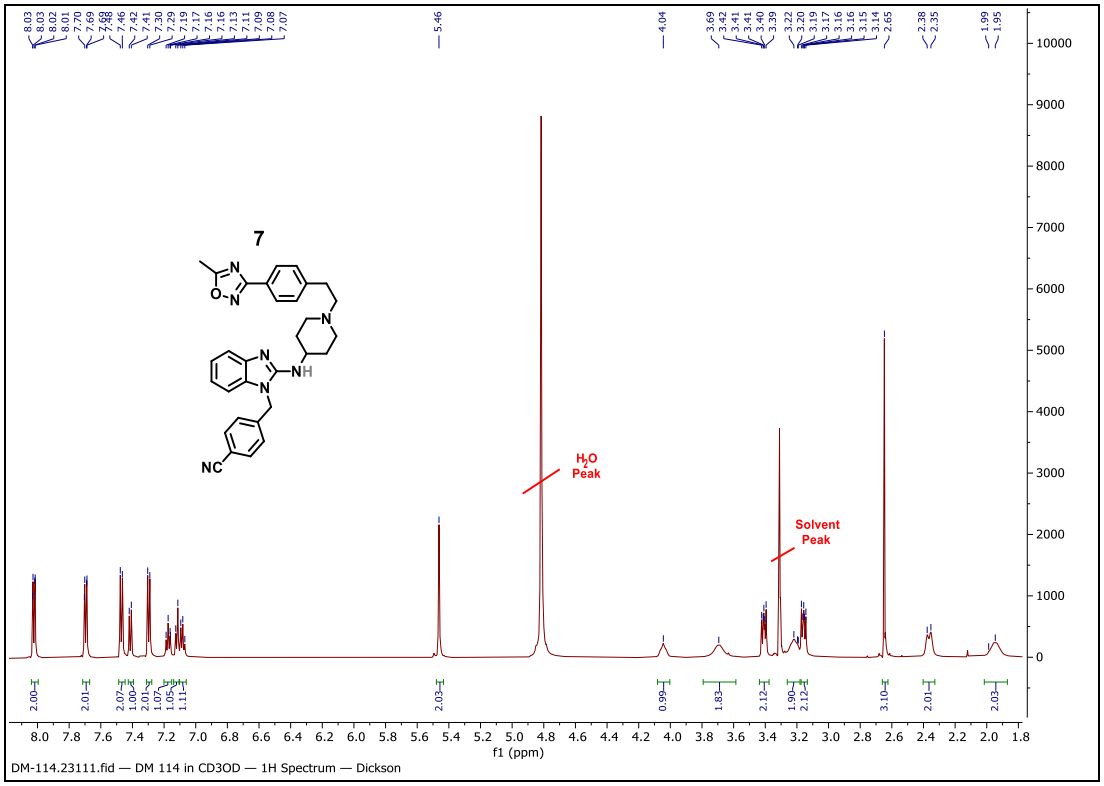

Figure S5: ^{1}H-NMR Spectrum of Compound **7** in Methanol-d_4 at 600 MHz

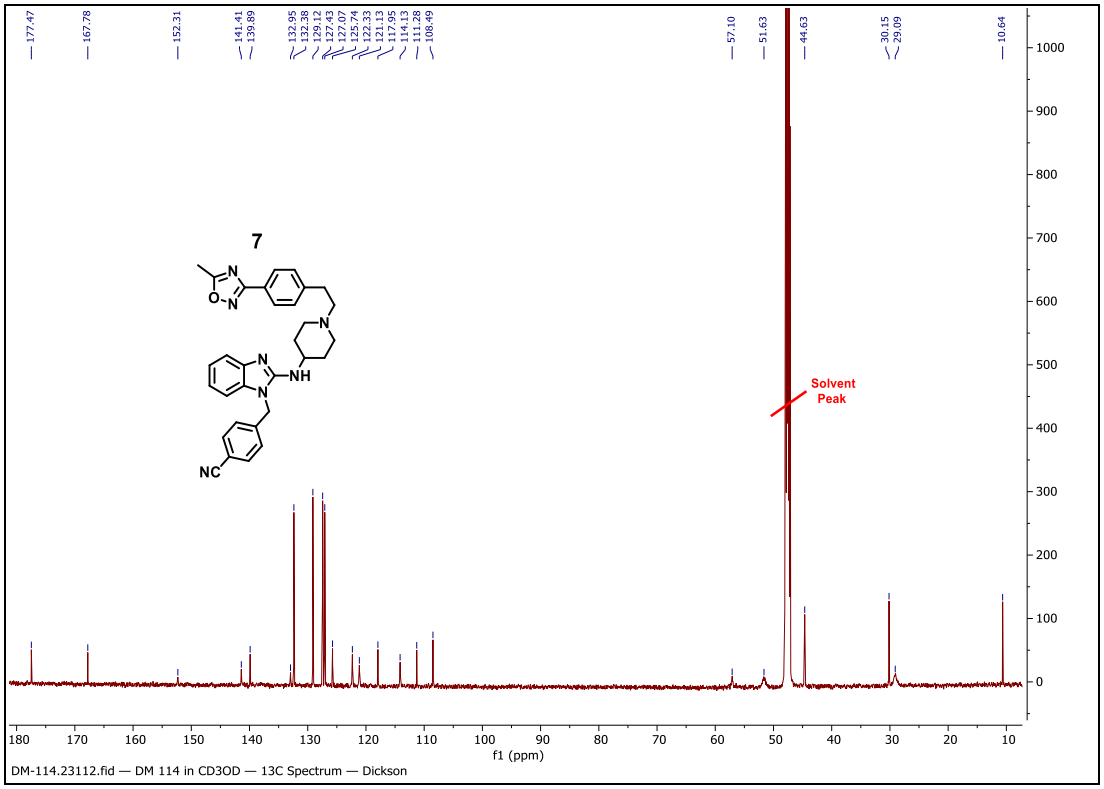

Figure S6: ^{13}C-NMR Spectrum of Compound **7** in Methanol-d_4 at 151 MHz

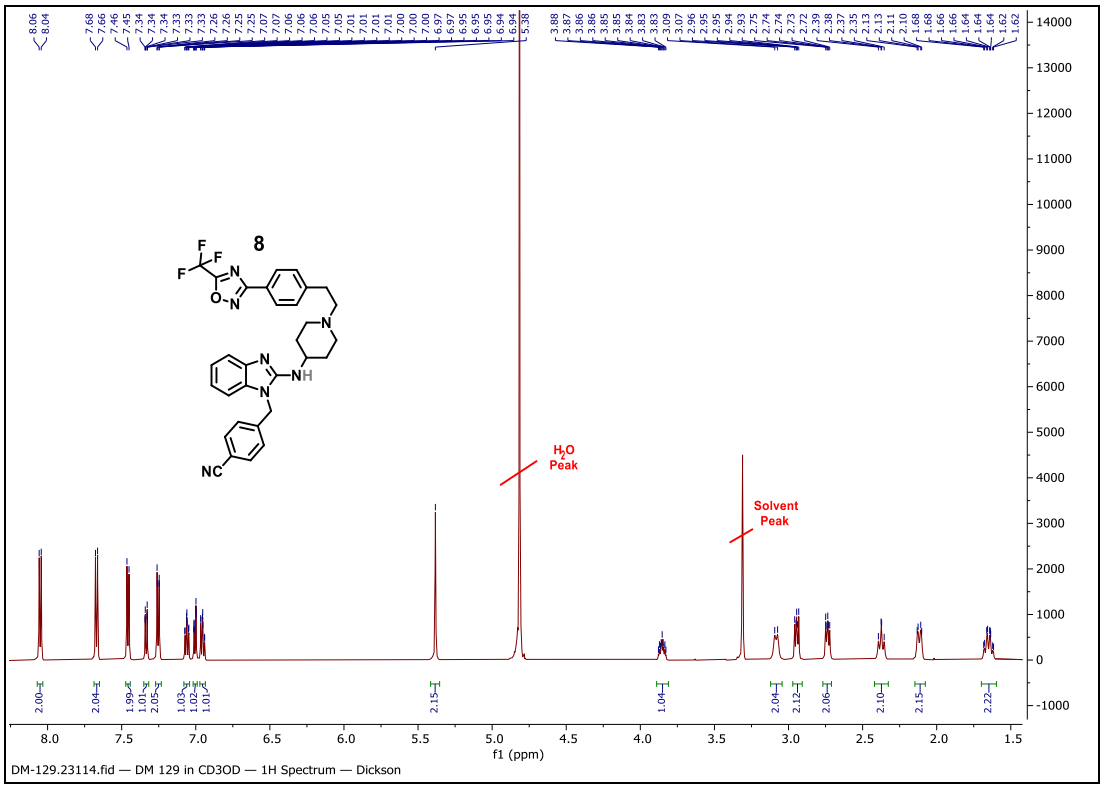

Figure S7: ^{1}H-NMR Spectrum of Compound **8** in Methanol-d_4 at 600 MHz

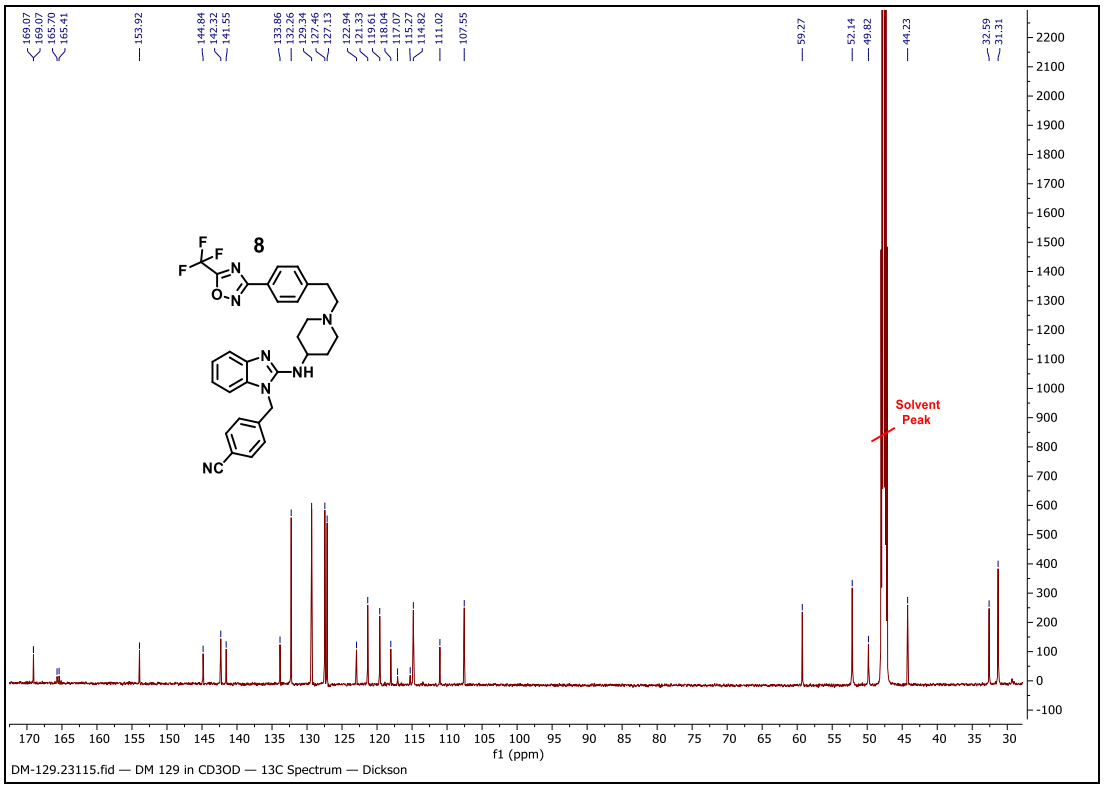

Figure S8: ^{13}C-NMR Spectrum of Compound **8** in Methanol-d_4 at 151 MHz

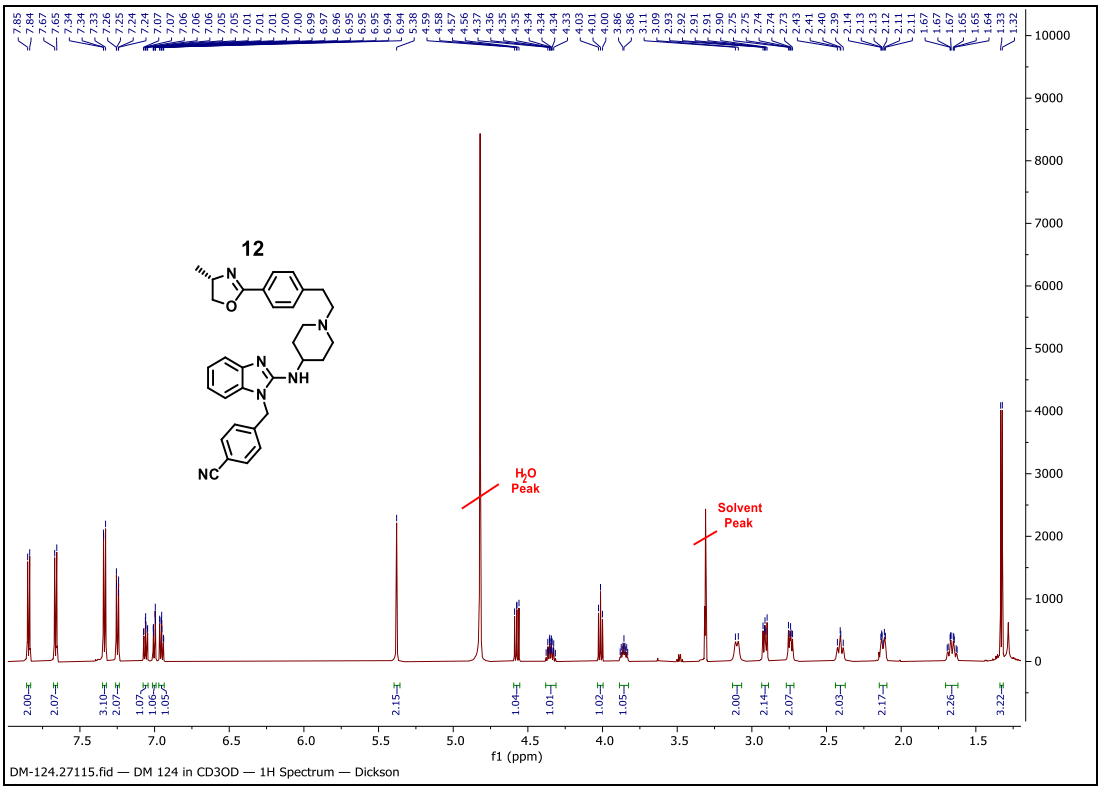

Figure S9: ^{1}H-NMR Spectrum of Compound **12** in Methanol-d_4 at 400 MHz

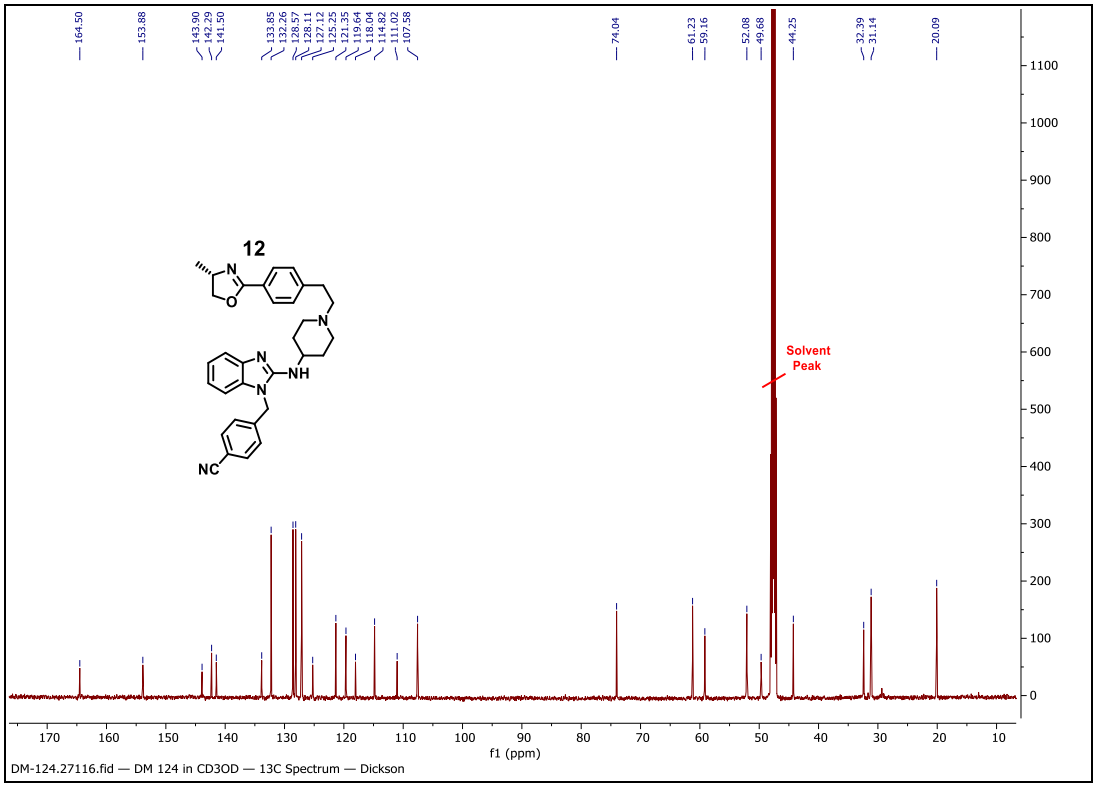

Figure S10: ^{13}C-NMR Spectrum of Compound **12** in Methanol-d_4 at 151 MHz

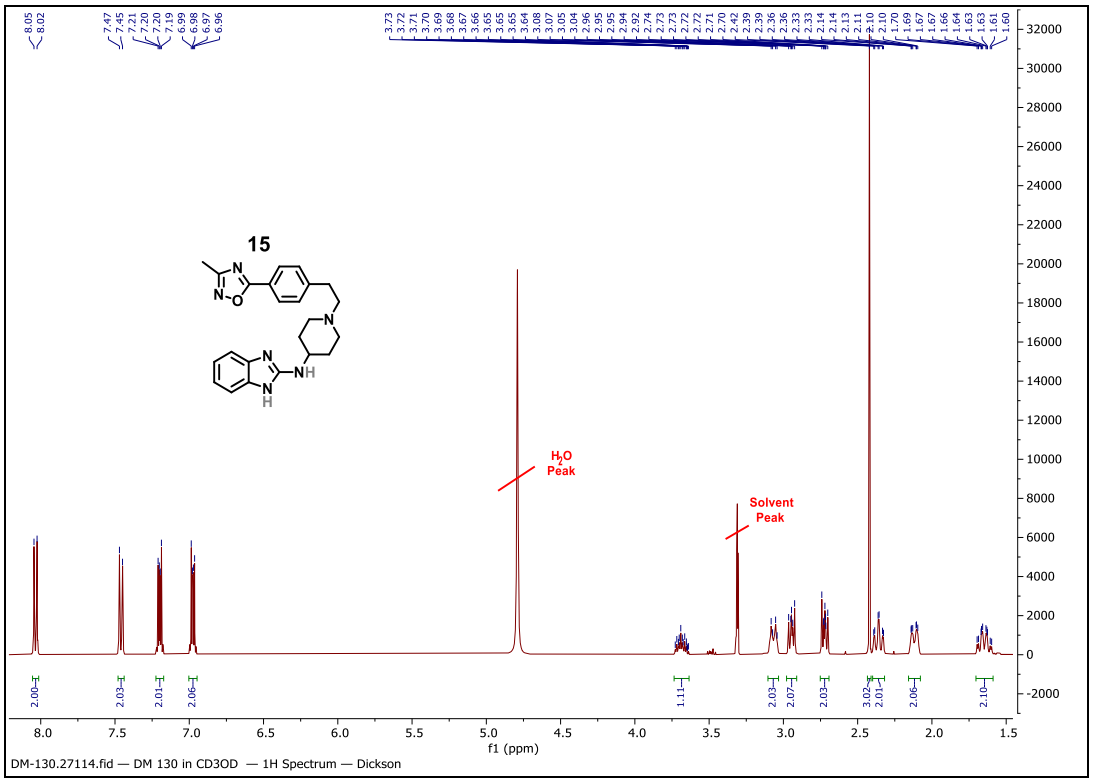

Figure S11: ^{1}H-NMR Spectrum of Compound **15** in Methanol-d_4 at 400 MHz

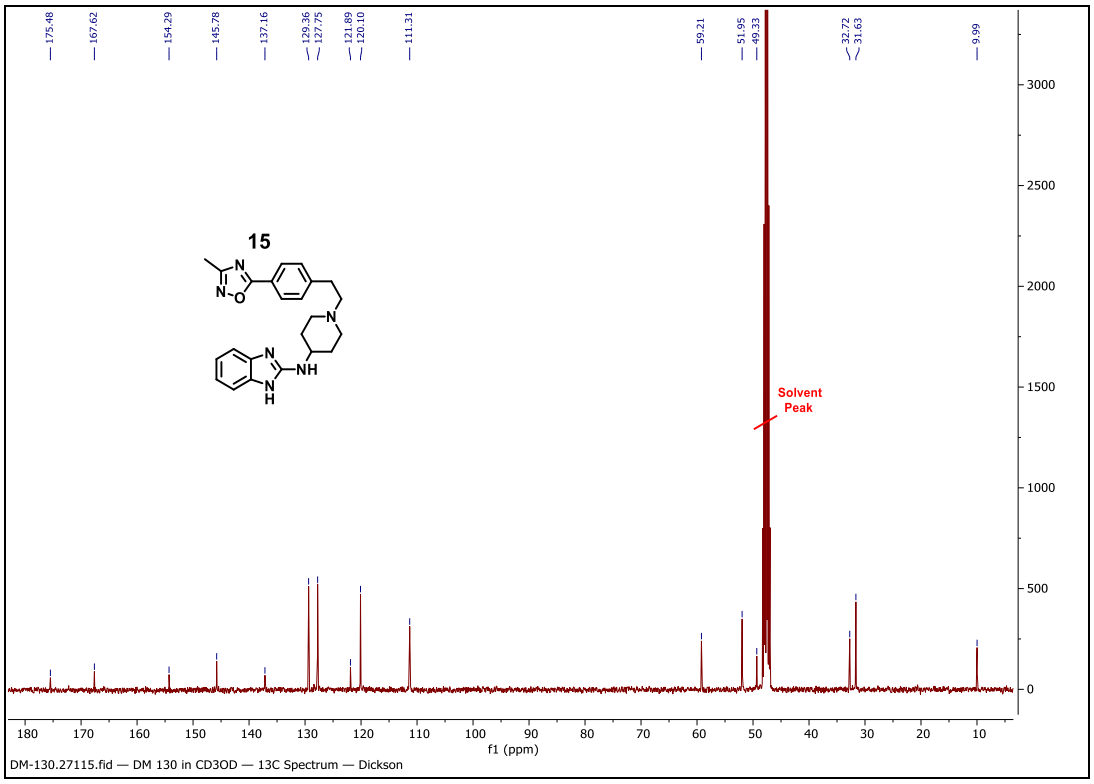

Figure S12: ^{13}C-NMR Spectrum of Compound **15** in Methanol-d_4 at 101 MHz

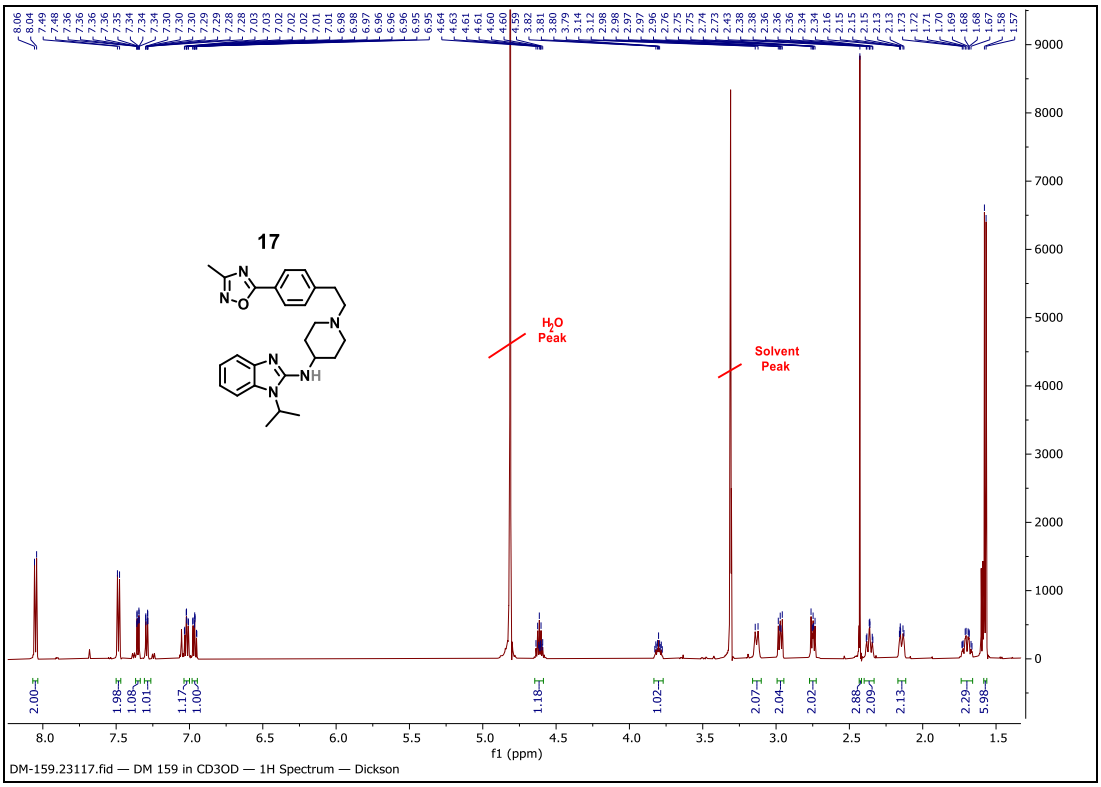

Figure S13: ^{1}H-NMR Spectrum of Compound **17** in Methanol-d_4 at 400 MHz

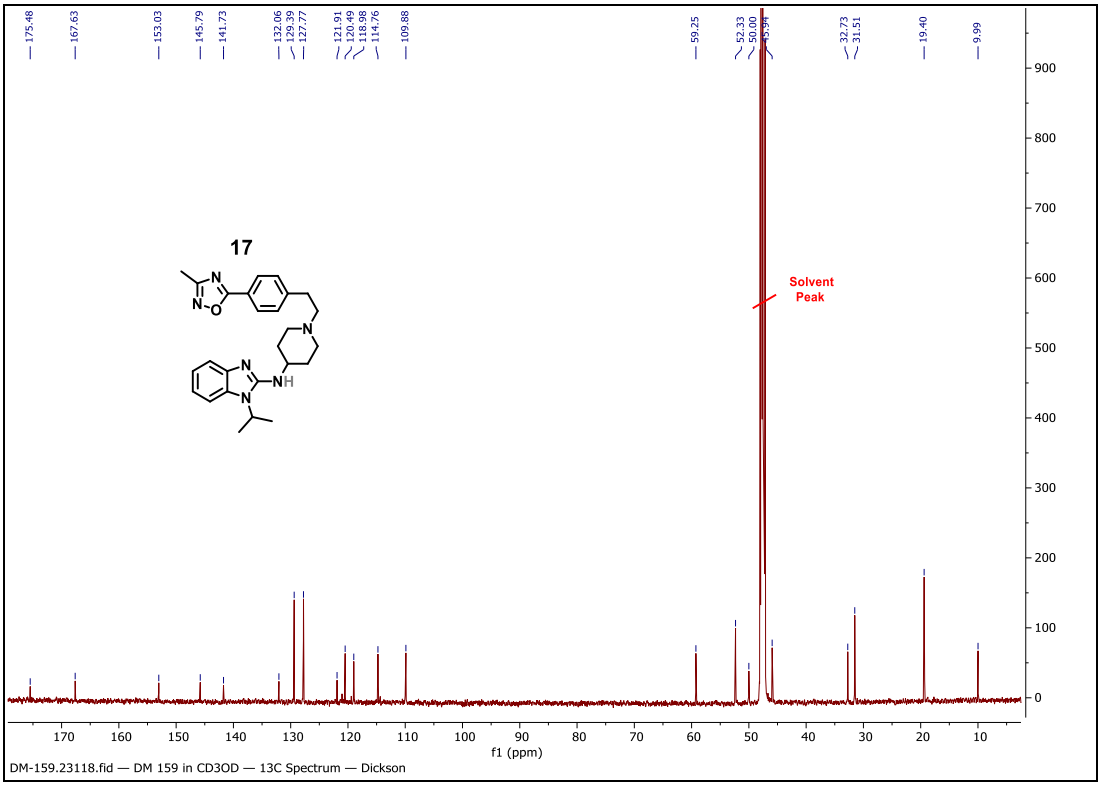

Figure S14: ^{13}C-NMR Spectrum of Compound **17** in Methanol-d_4 at 101 MHz

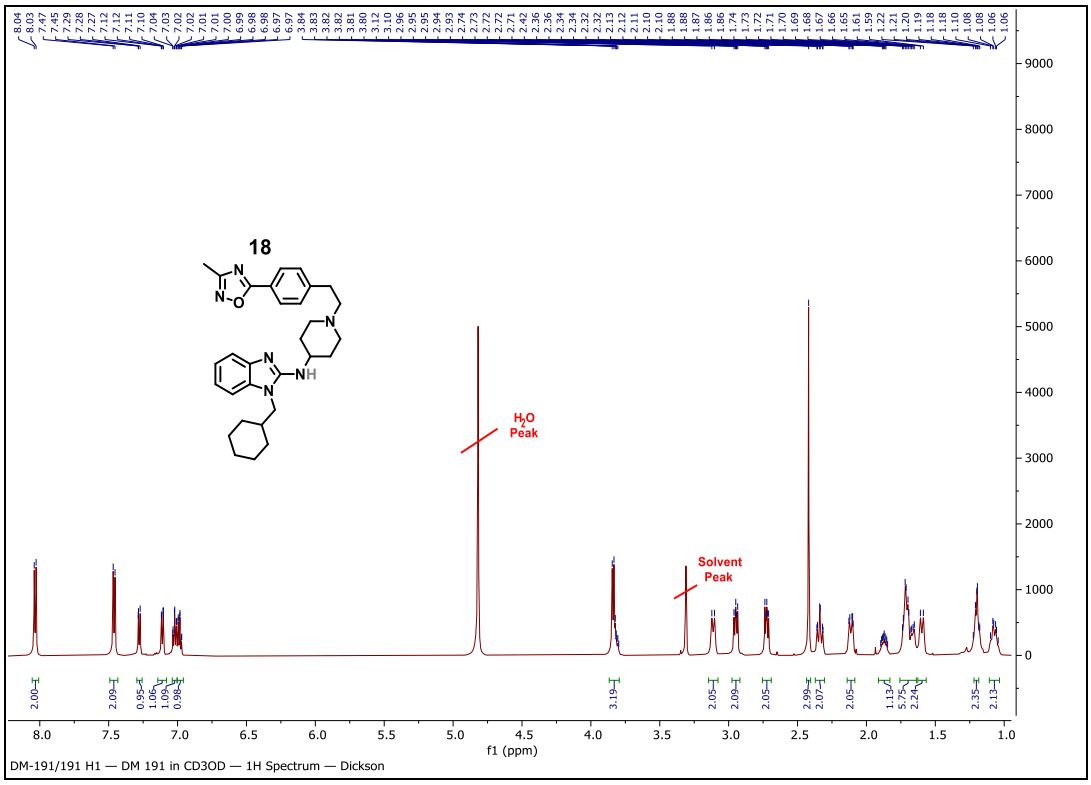

Figure S15: ^{1}H-NMR Spectrum of Compound **18** in Methanol-d_4 at 600 MHz

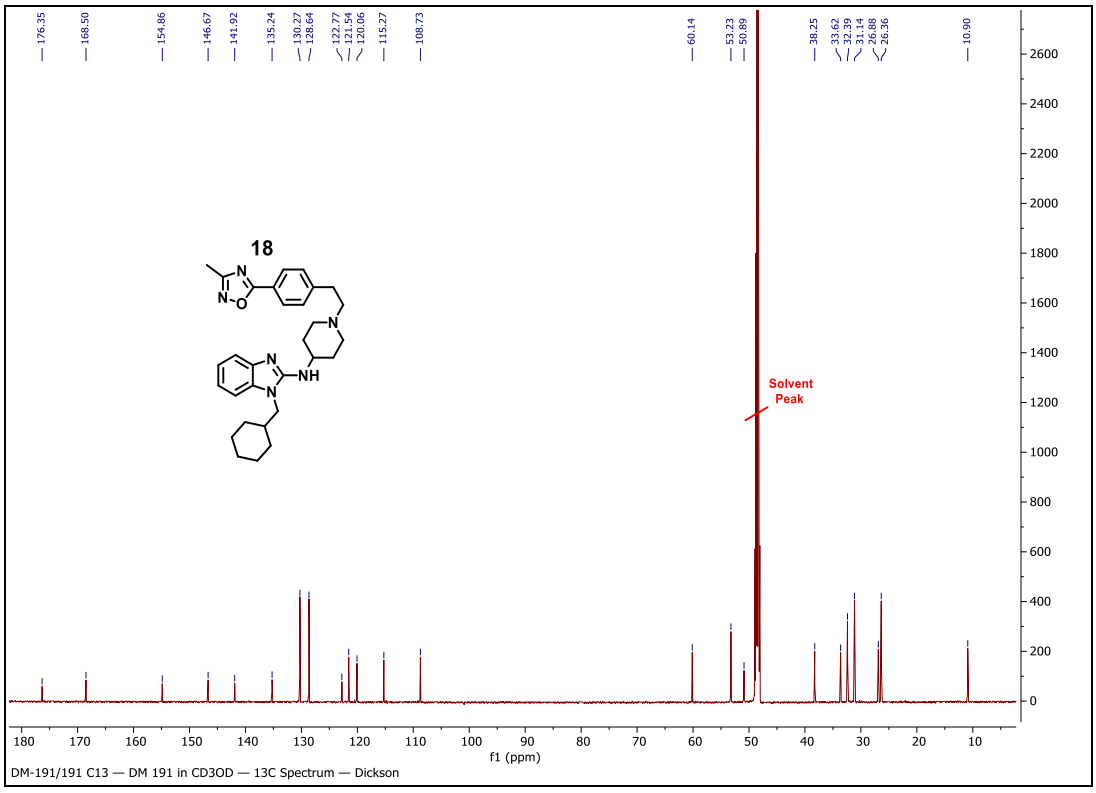

Figure S16: ^{13}C-NMR Spectrum of Compound **18** in Methanol-d_4 at 151 MHz

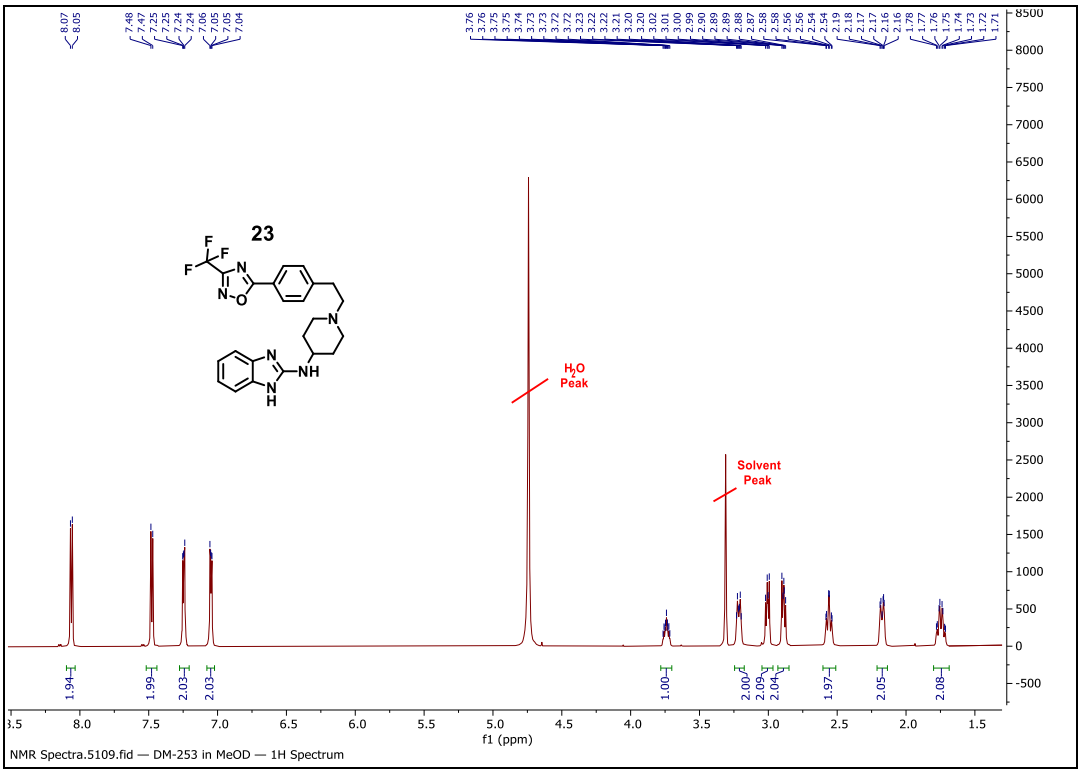

Figure S17: ^{1}H-NMR Spectrum of Compound **23** in Methanol-d_4 at 600 MHz

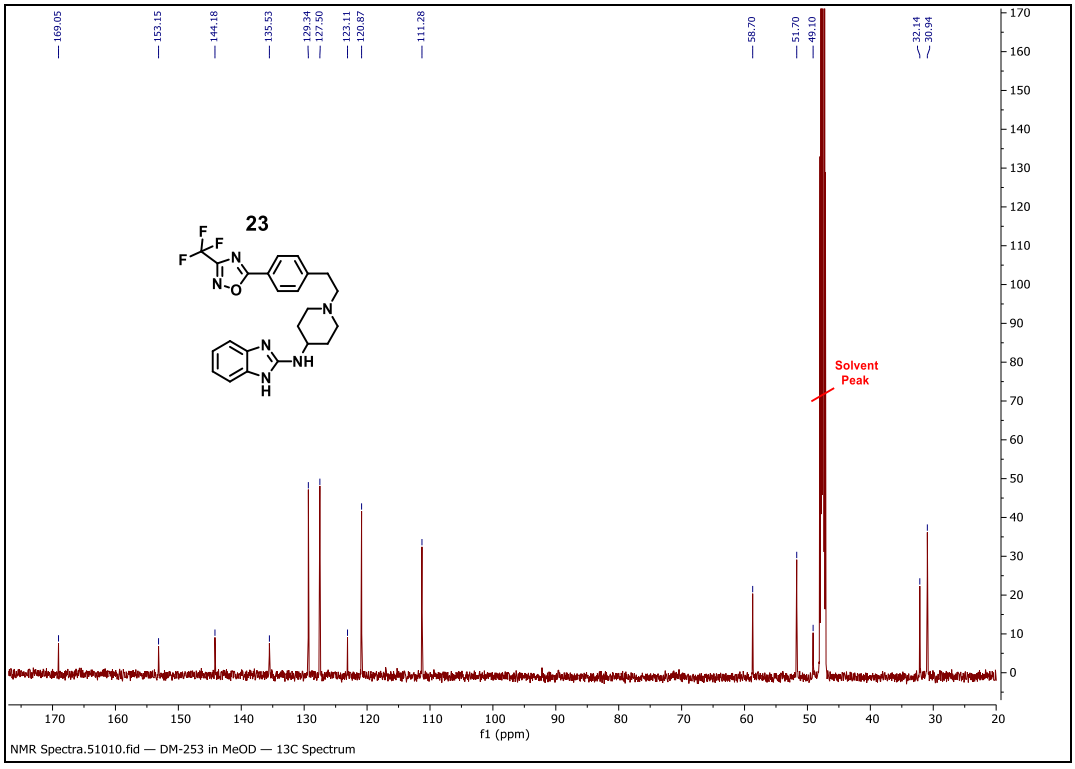

Figure S18: ^{13}C-NMR Spectrum of Compound **23** in Methanol-d_4 at 151 MHz

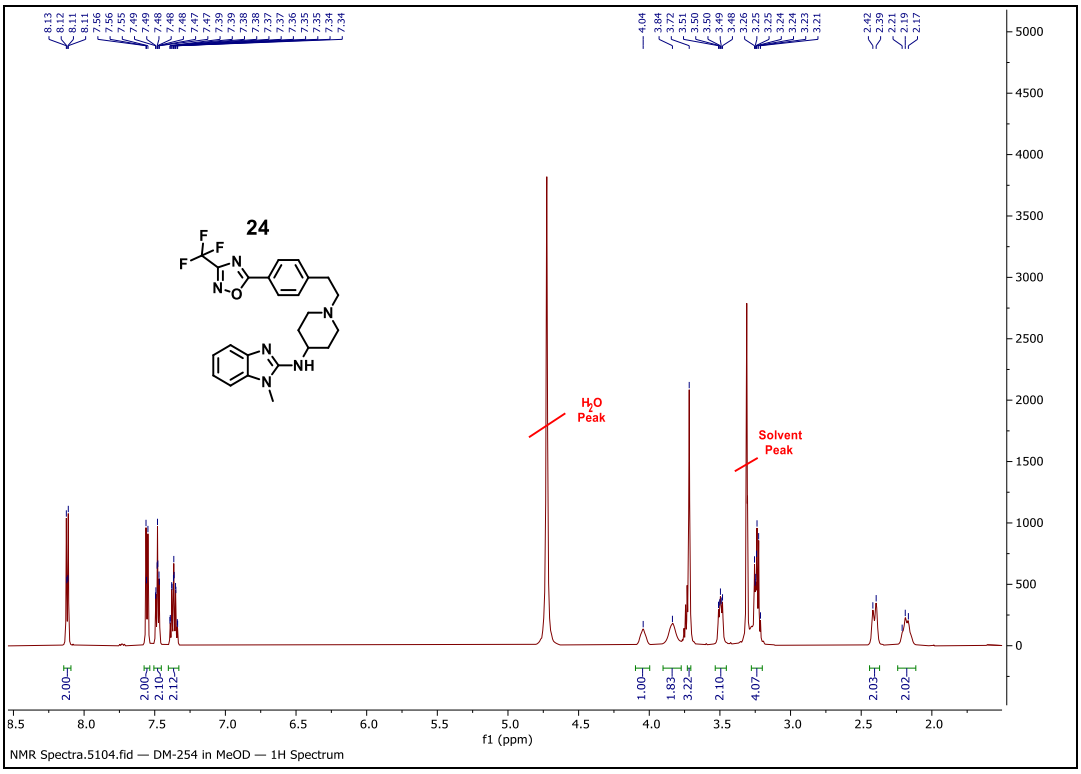

Figure S19: ^{1}H-NMR Spectrum of Compound **24** in Methanol-d_4 at 600 MHz

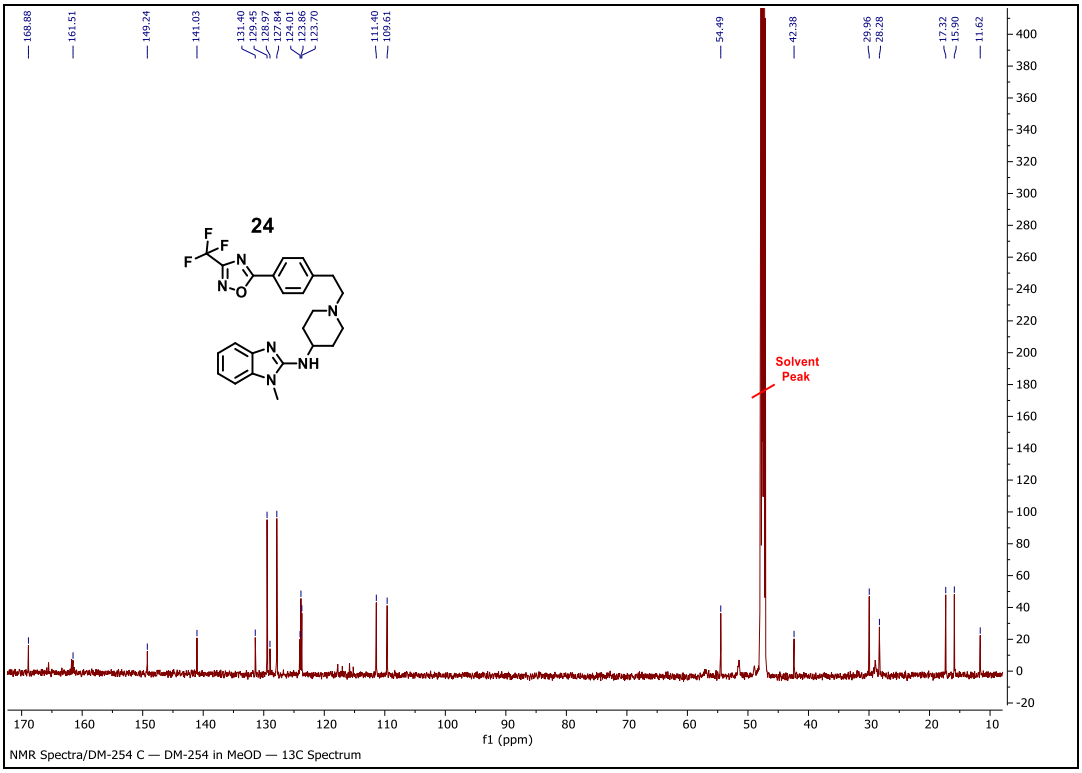

Figure S20: ^{13}C-NMR Spectrum of Compound **24** in Methanol-d_4 at 151 MHz

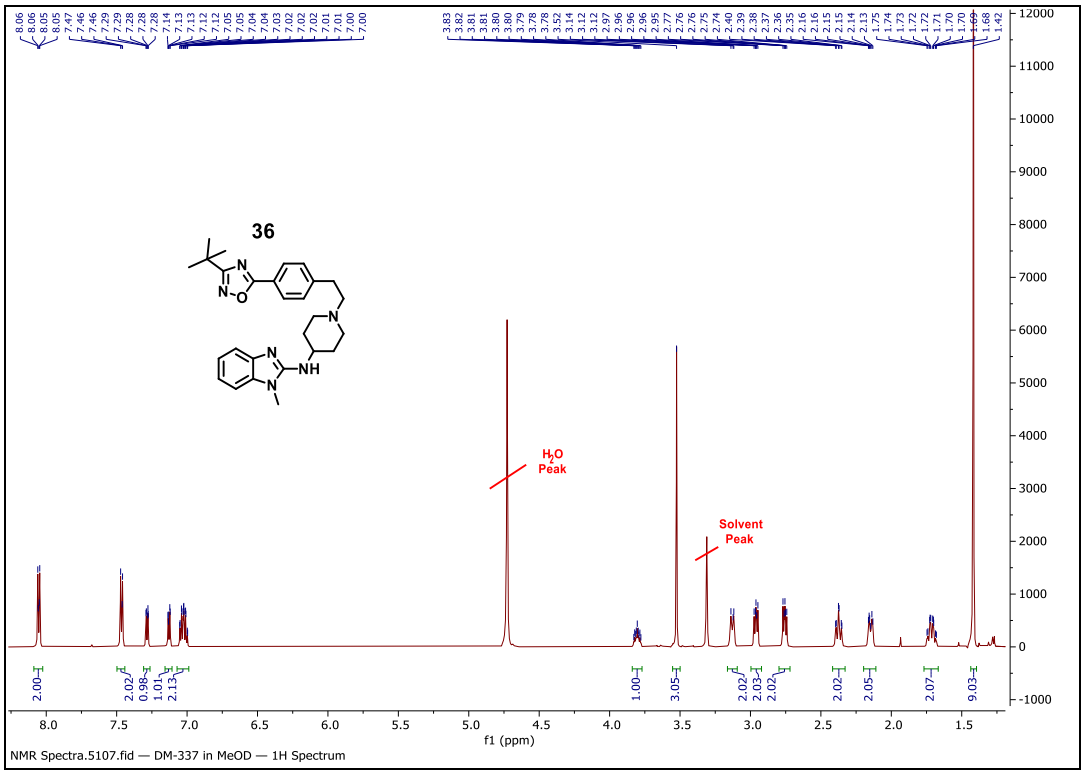

Figure S21: ^{1}H-NMR Spectrum of Compound **36** in Methanol-d_4 at 600 MHz

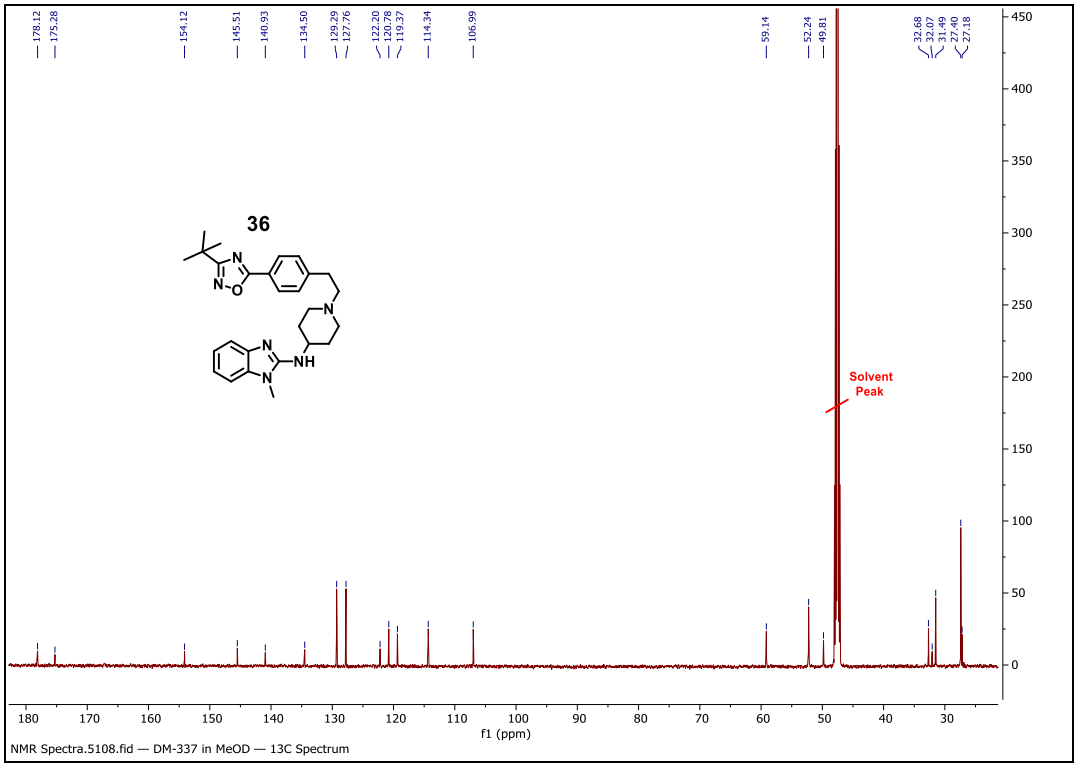

Figure S22: ^{13}C-NMR Spectrum of Compound **36** in Methanol-d_4 at 151 MHz

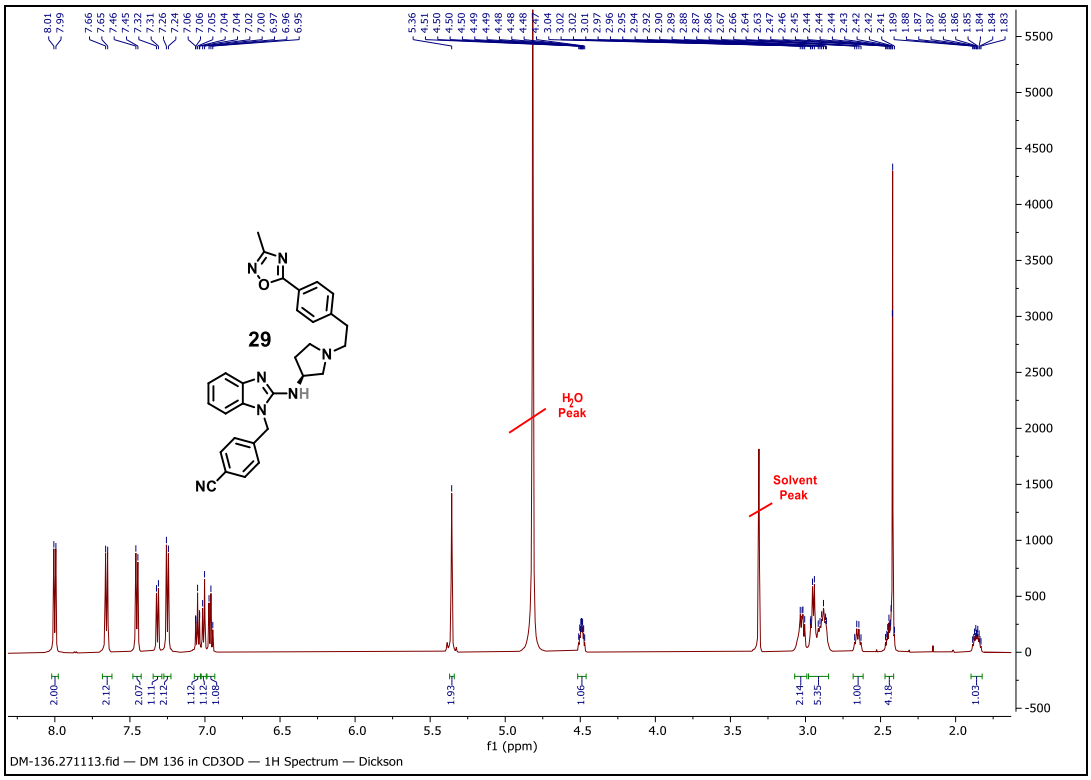

Figure S23: ^{1}H-NMR Spectrum of Compound **29** in Methanol-d_4 at 600 MHz

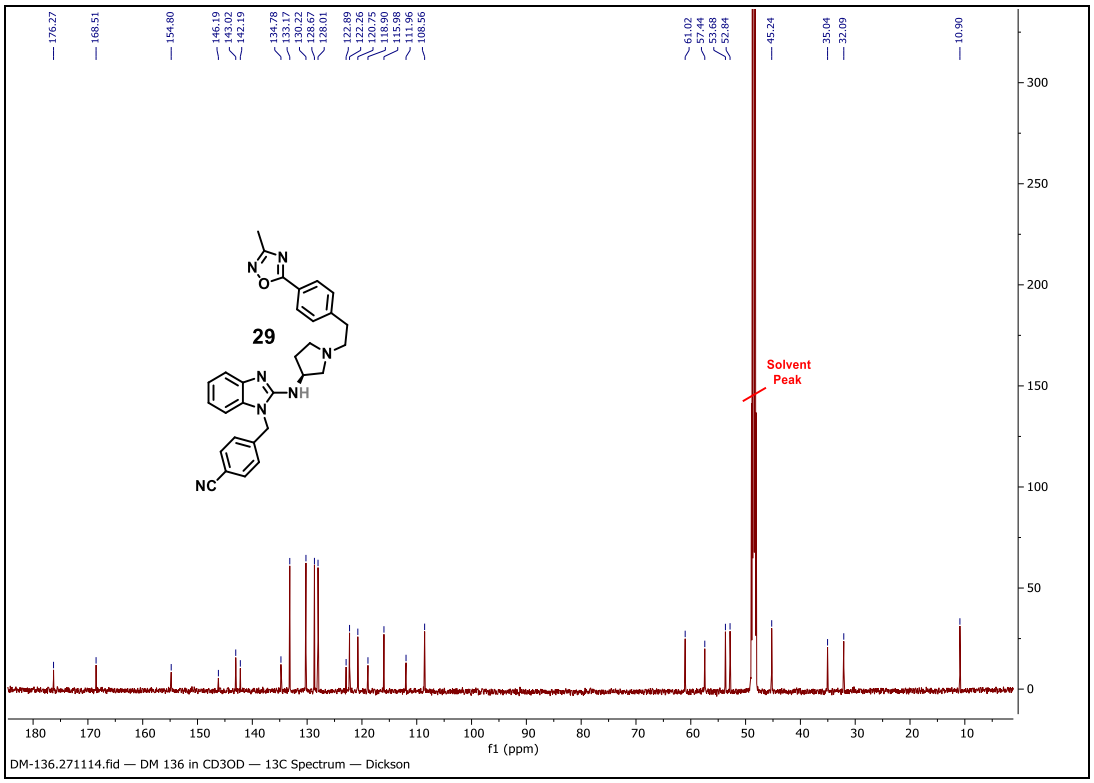

Figure S24: ^{13}C-NMR Spectrum of Compound **29** in Methanol-d_4 at 151 MHz

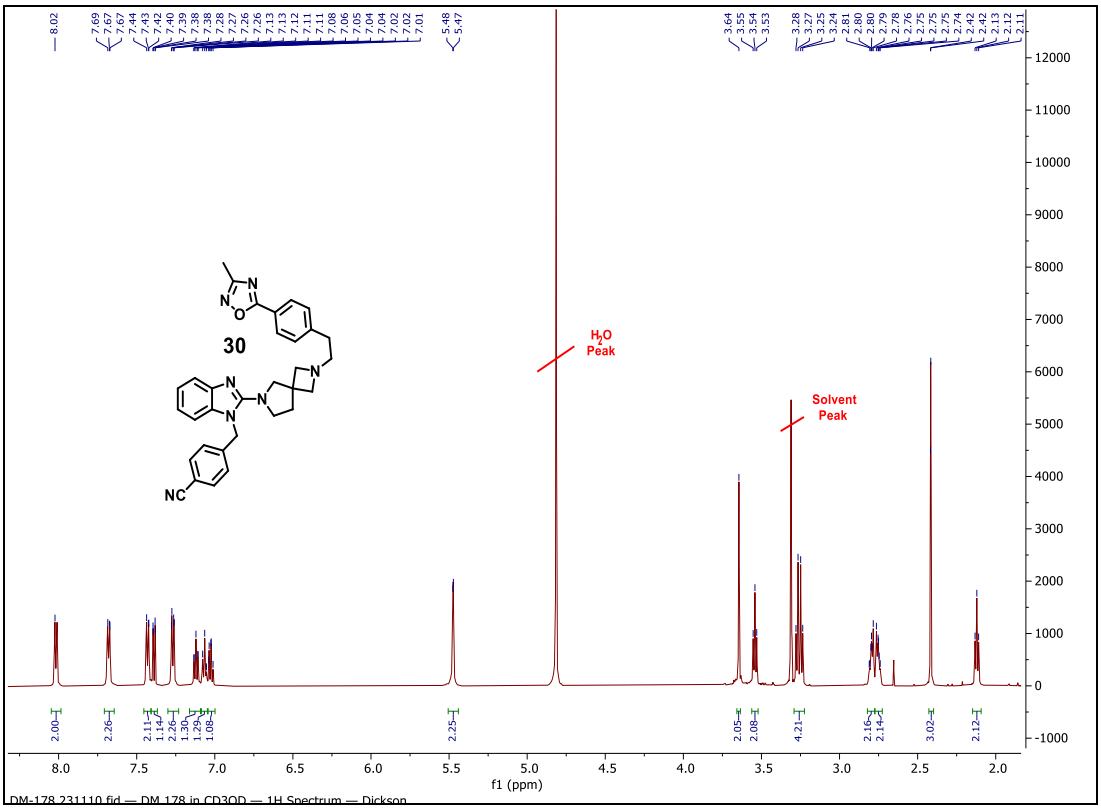

Figure S25: ^{1}H-NMR Spectrum of Compound **30** in Methanol-d_4 at 600 MHz

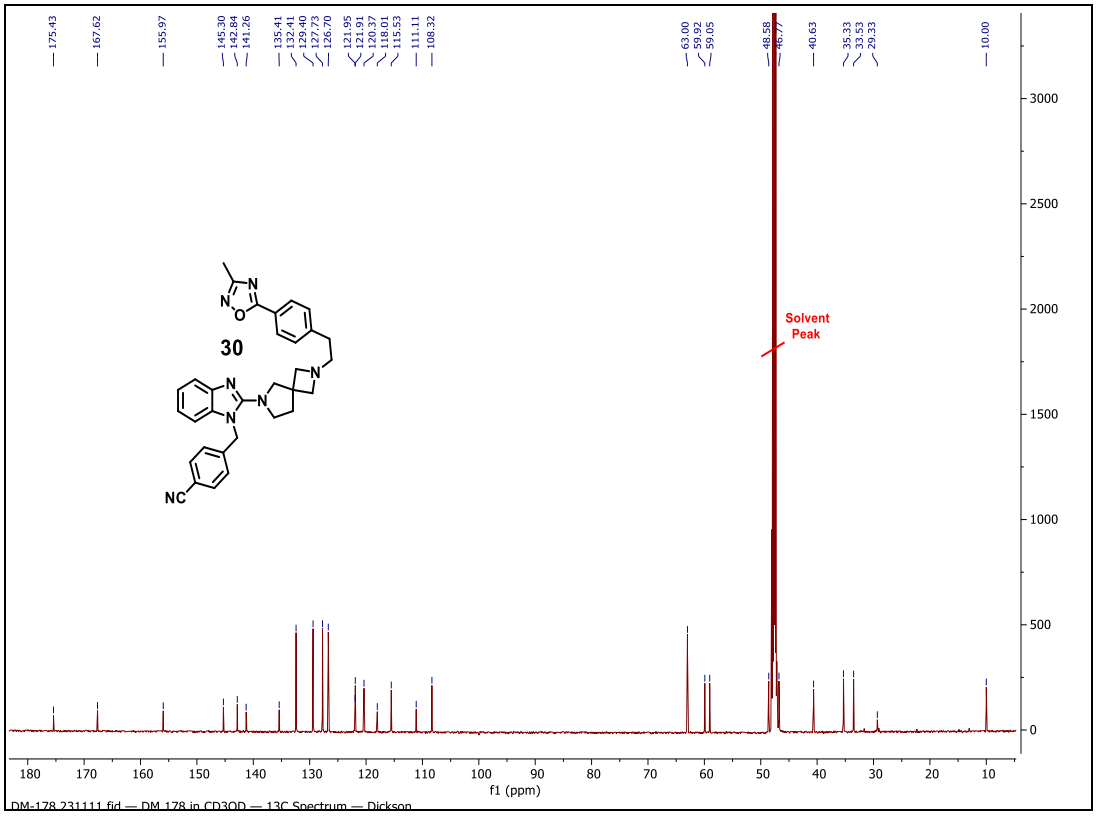

Figure S26: ^{13}C-NMR Spectrum of Compound **30** in Methanol-d_4 at 151 MHz

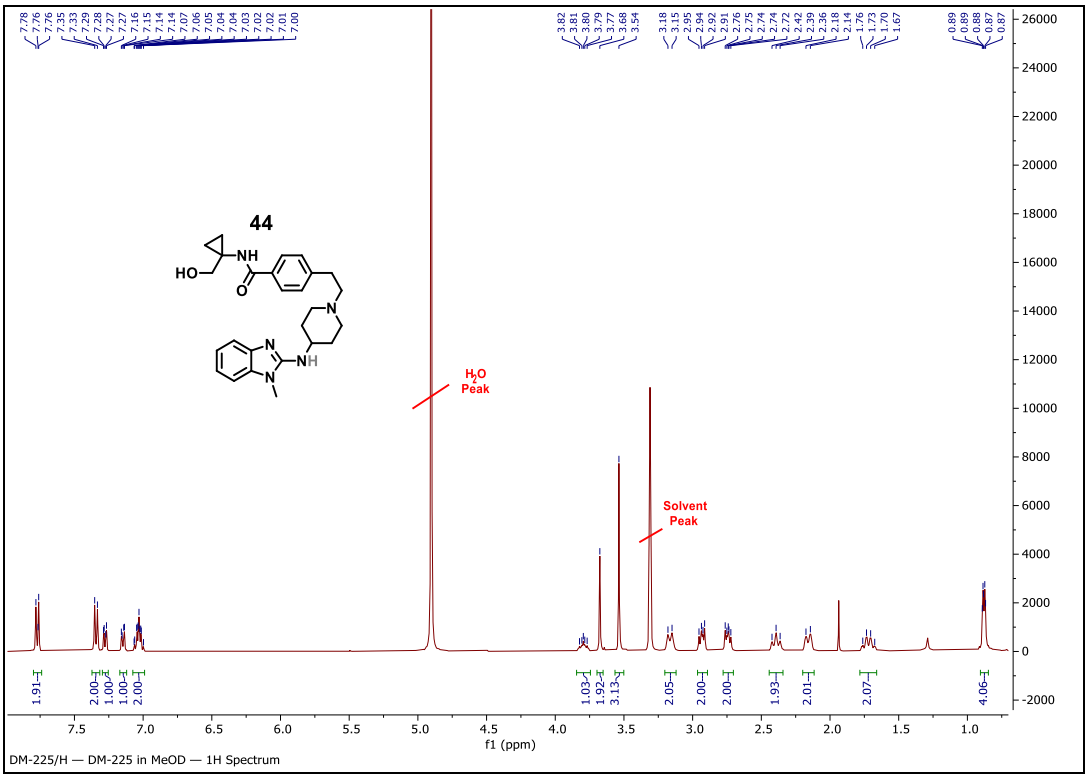

Figure S27: ^{1}H-NMR Spectrum of Compound **44** in Methanol-d_4 at 400 MHz

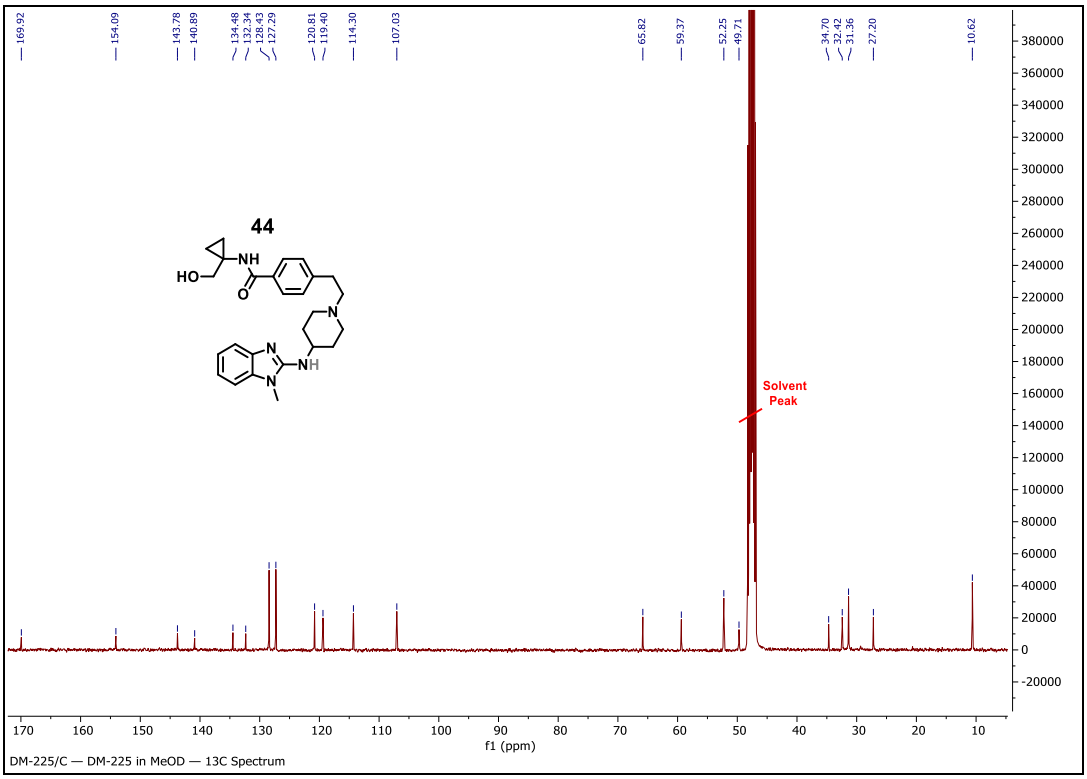

Figure S28: ^{13}C-NMR Spectrum of Compound **44** in Methanol-d_4 at 151 MHz

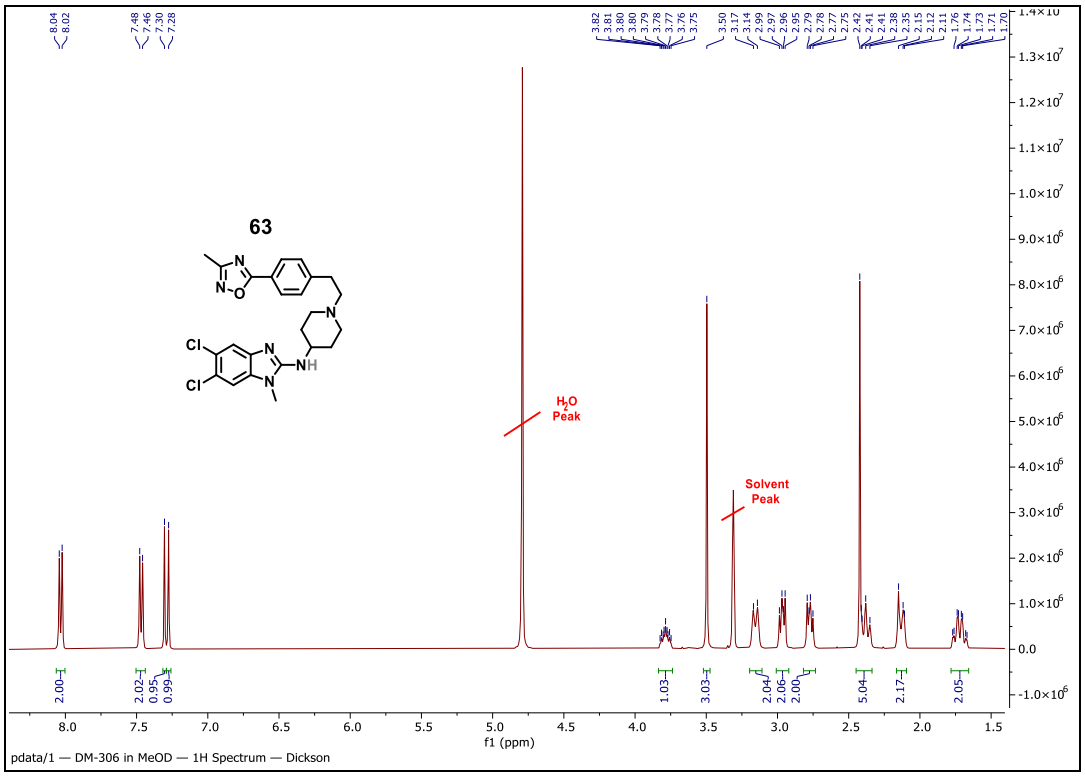

Figure S29: ^{1}H-NMR Spectrum of Compound **63** in Methanol-d_4 at 400 MHz

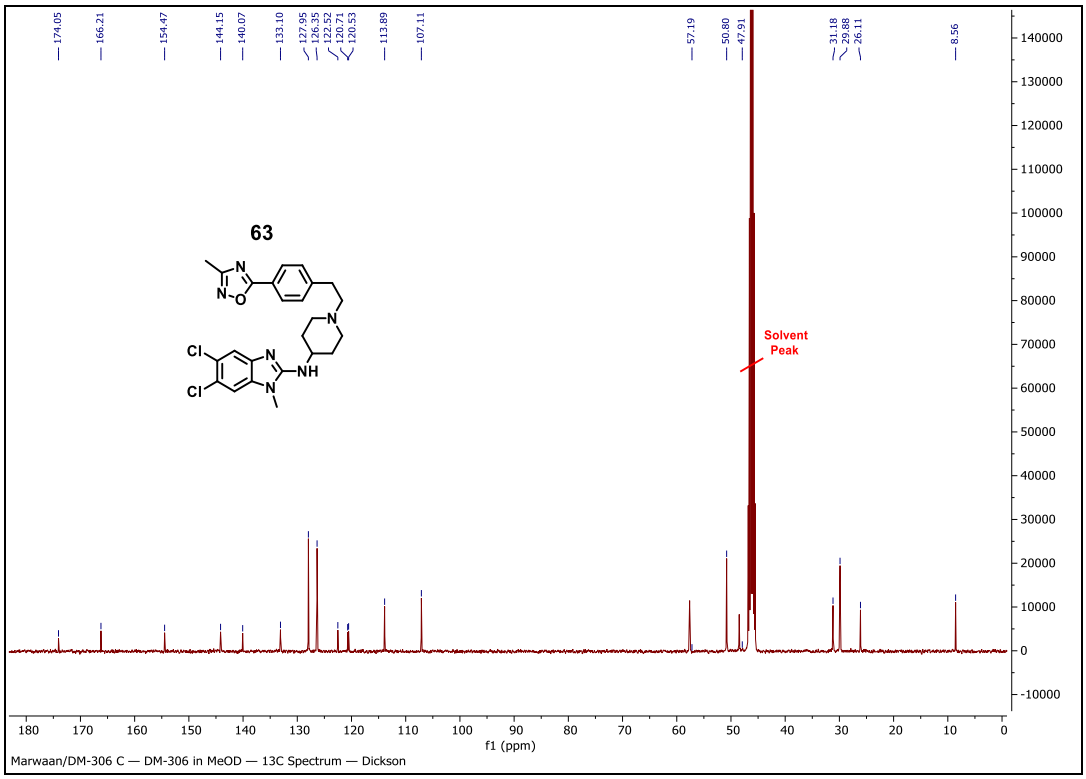

Figure S30: ^{13}C-NMR Spectrum of Compound **63** in Methanol-d_4 at 151 MHz

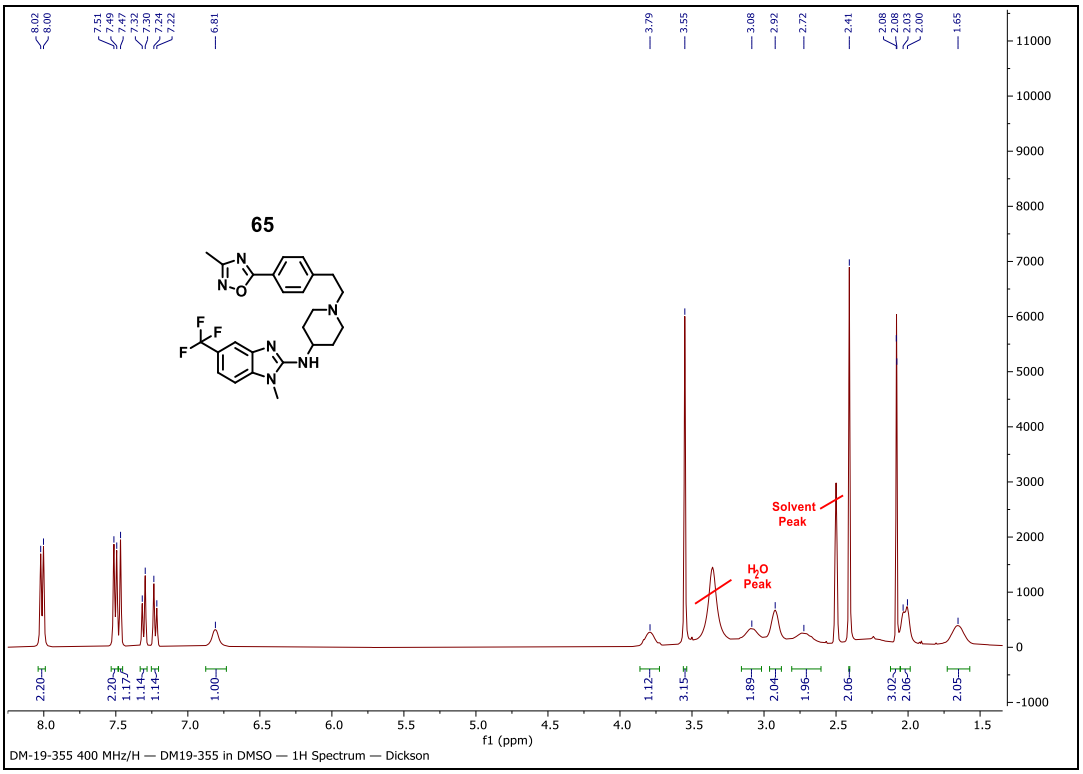

Figure S31: ^{1}H-NMR Spectrum of Compound **65** in DMSO-d_6 at 400 MHz

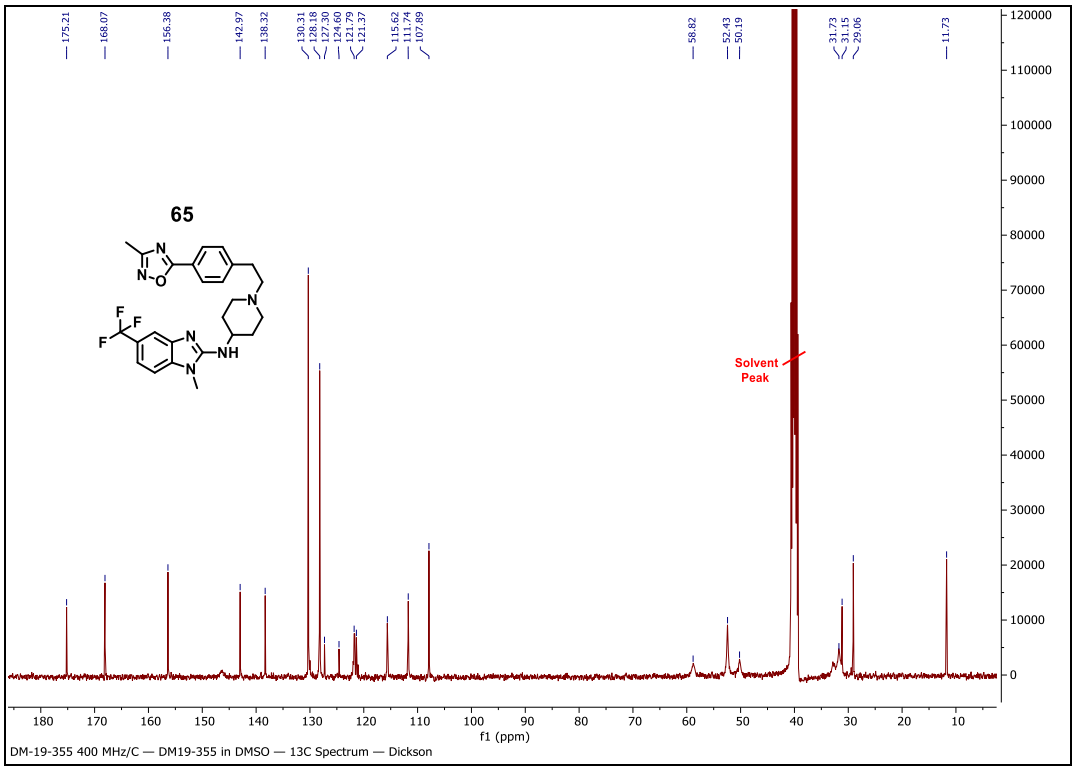

Figure S32: ^{13}C-NMR Spectrum of Compound **65** in DMSO-d_6 at 151 MHz

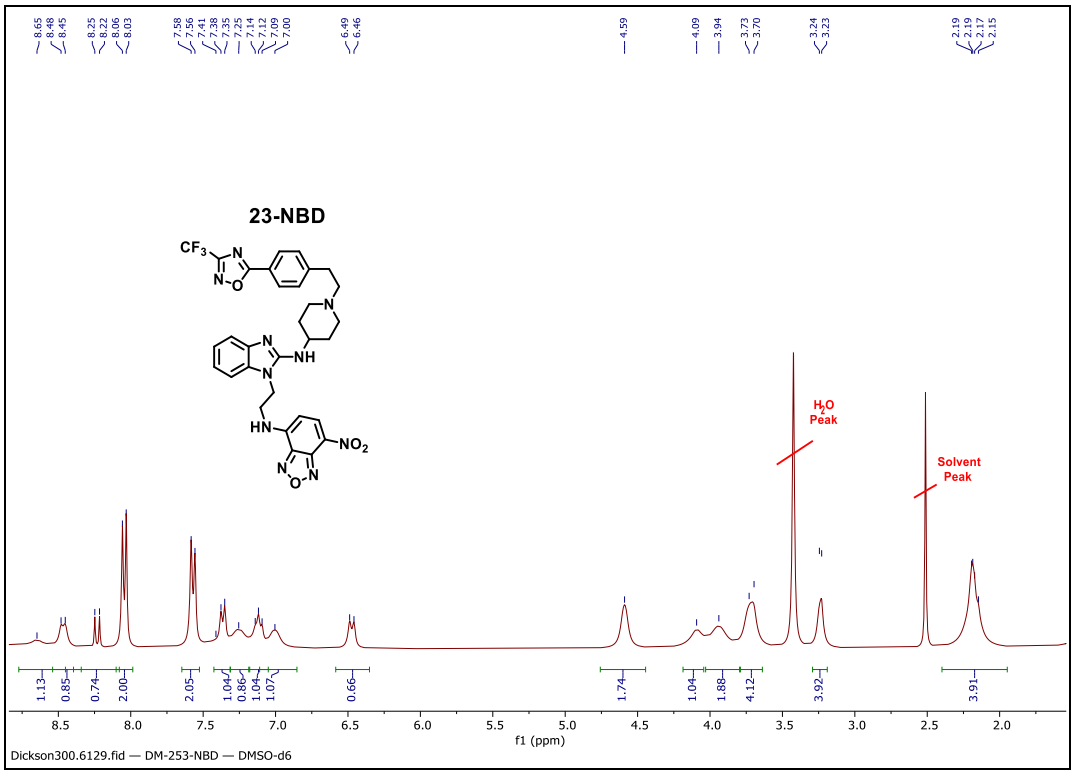

Figure S33: ^{1}H-NMR Spectrum of Compound **23-NBD** in DMSO-d_6 at 300 MHz

HPLC-MS (Low Resolution) spectra of key target compounds

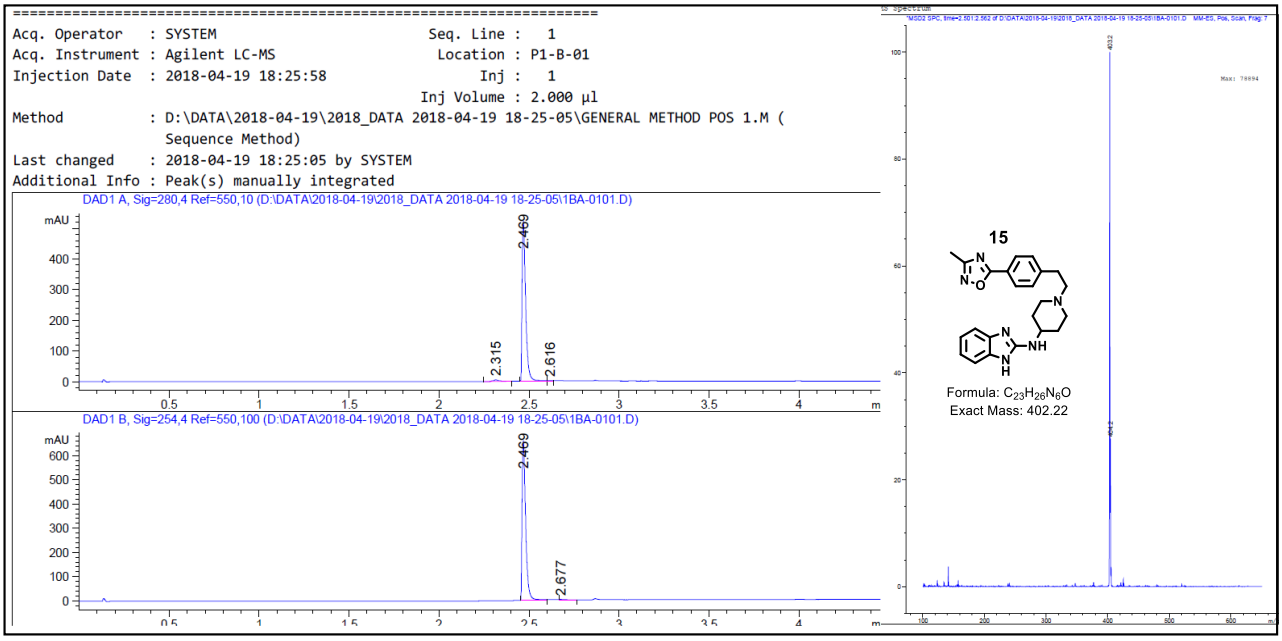

Figure S34: HPLC Chromatogram and Low-Resolution Mass Spectra of Compound **15**

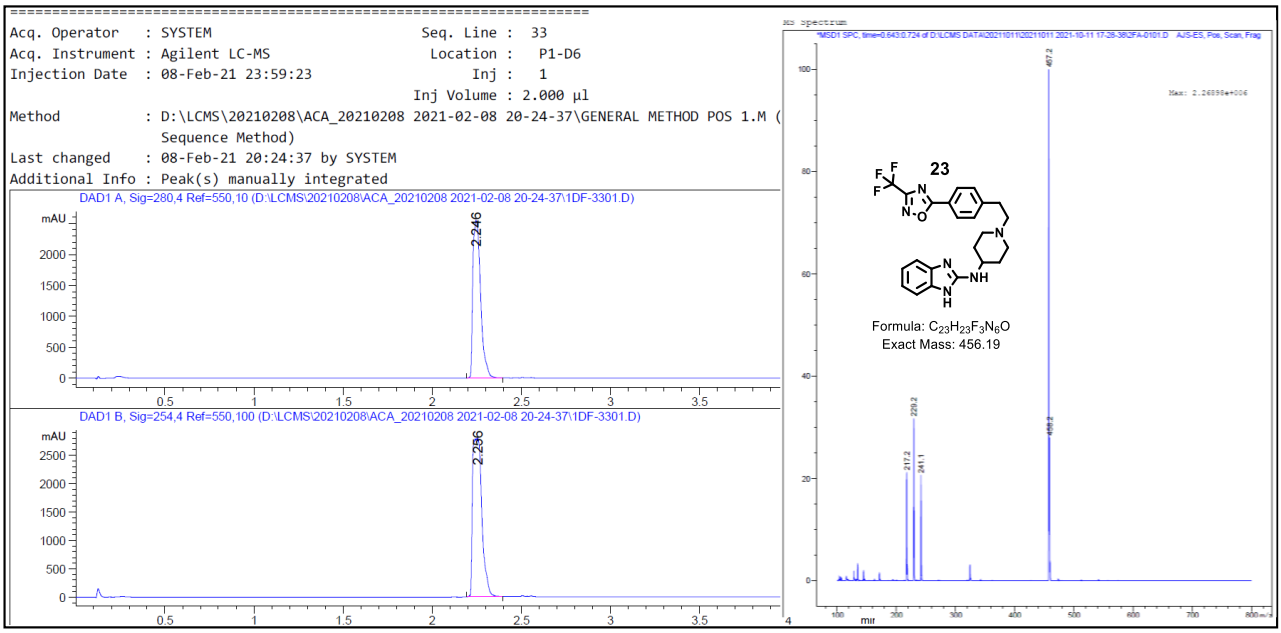

Figure S35: HPLC Chromatogram and Low-Resolution Mass Spectra of Compound **23**

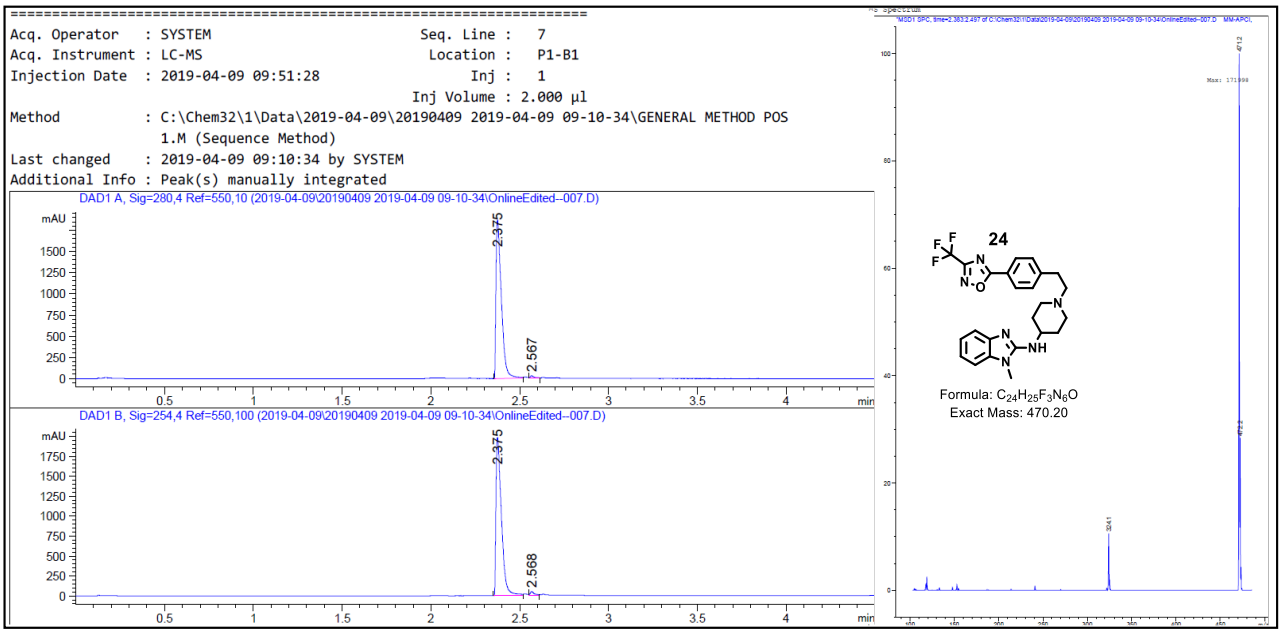

Figure S36: HPLC Chromatogram and Low-Resolution Mass Spectra of Compound **24**

References

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(2) Reader, J.; Botha, M.; Theron, A.; Lauterbach, S. B.; Rossouw, C.; Engelbrecht, D.; Wepener, M.; Smit, A.; Leroy, D.; Mancama, D.; et al. Nowhere to Hide: Interrogating Different Metabolic Parameters of Plasmodium Falciparum Gametocytes in a Transmission Blocking Drug Discovery Pipeline towards Malaria Elimination. *Malar. J.* **2015**, *14* (1), 213. https://doi.org/10.1186/s12936-015-0718-z.

(3) Combrinck, J. M.; Fong, K. Y.; Gibhard, L.; Smith, P. J.; Wright, D. W.; Egan, T. J. Optimization of a Multi-Well Colorimetric Assay to Determine Haem Species in Plasmodium Falciparum in the Presence of Anti-Malarials. *Malar. J.* **2015**, *14* (1), 253. https://doi.org/10.1186/s12936-015-0729-9.