SUPPORTING INFORMATION for

Analogues of the Marine Alkaloids Oroidin, Clathrodin, and Hymenidin Induce Apoptosis in Human HepG2 and THP-1 Cancer Cells

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1. Chemistry

All reagents were used as received from commercial sources without further purification unless otherwise indicated. Analytical TLC was performed on Merck silica gel (60 F 254) plates (0.25 mm) and components visualized with staining reagents or ultraviolet light. Column chromatography was carried out on silica gel 60 (particle size 240-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz, respectively, on a Bruker AVANCE III spectrometer in DMSO-d_6, CD_3OD, acetone-d_6 or $CDCl_3$ solution with TMS as an internal standard at 25 °C. Spectra were assigned using gradient COSY, HSQC and DEPT experiments. Mass spectra were obtained using a VGAnalytical Autospec Q mass spectrometer.

For details on the synthesis of **clathrodin**, **oroidin** and compounds **3** and **4** please refer to N. Zidar, S. Montalvão, Ž. Hodnik, D. A. Nawrot, A. Žula, J. Ilaš, D. Kikelj, P. Tammela, L. Peterlin Mašič, *Mar. Drugs*, 2014, **12**, 940.

(*E*)-*N*-(3-(2-Amino-1*H*-imidazol-4-yl)allyl)-1*H*-pyrrole-2-carboxamide (**clathrodin**). ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.05 (dd, 2H, *J* = 6.0 Hz, *J* = 1.2 Hz, -CH=CH-$\underline{CH_2}$-), 5.94 (dt,1H, *J* = 15.8 Hz, *J* = 6.0 Hz, -CH=$\underline{CH}$-CH_2-), 6.18 (dd, 1H, *J* = 3.7 Hz, *J* = 2.6 Hz, Ar-H^4), 6.32 (td, 1H, *J* = 15.8 Hz, *J* = 1.2 Hz, -$\underline{CH}$=CH-CH_2-), 6.51 (s, 1H, imidazole-H), 6.82 (dd, 1H, *J* = 3.7 Hz, *J* = 1.4 Hz, Ar-H^3), 6.93 (dd, 1H, *J* = 2.5 Hz, *J* = 1.4 Hz, Ar-H^5); ^{13}C NMR (100 MHz, MeOH-d_4) δ 42.06, 110.22, 111.78, 117.01, 121.87, 122.66, 122.89, 126.87, 130.82, 151.66, 163.61; HRMS for $C_{11}H_{13}N_5O$: calculated, 231.1120; found, 231.1189.

(*E*)-*N*-(3-(2-Amino-1*H*-imidazol-4-yl)allyl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (**oroidin**). ^{1}H NMR (400MHz, MeOH-d_4) δ 4.03 (d, 2H, *J* = 6.0 Hz, -CH=CH-$\underline{CH_2}$-), 5.91 (dt, 1H, *J* = 15.8 Hz, *J* = 6.0 Hz, -CH=$\underline{CH}$-CH_2-), 6.31 (d, 1H, *J* = 15.8 Hz, -$\underline{CH}$=CH-CH_2-), 6.51 (s, 1H, imidazole-H), 6.85 (s, 1H, Ar-H^3); ^{13}C NMR (100 MHz, MeOH-d_4) δ 42.18, 99.96, 106.09, 114.29, 117.00, 122.12, 122.28, 128.88, 130.94, 151.72, 161.53; HRMS for $C_{11}H_{11}Br_2N_5O$: calculated, 386.9330; found, 386.9408.

***N*-(3-(2-Amino-1*H*-imidazol-4-yl)propyl)-1*H*-pyrrole-2-carboxamide** (**1**). ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.83-1.92 (m, 2H, -$CH_2\underline{CH_2}CH_2$-), 2.53 (t, 2H, *J* = 6.7 Hz, -$\underline{CH_2}CH_2CH_2$-), 3.37 (t, 2H, J = 6.6 Hz, - $CH_2CH_2\underline{CH_2}$-), 6.15-6.21 (m, 1H, pyrrole-$\underline{H}$), 6.39 (s, 1H, imidazole-$\underline{H}$), 6.76-6.81 (m, 1H, pyrrole-$\underline{H}$), 6.90-6.94 (m, 1H, pyrrole-H) ppm. ^{13}C NMR

(100 MHz, MeOH-d_4) δ 163.94, 149.81, 131.88, 126.88, 122.81, 111.57, 111.21, 110.19, 39.59, 30.20, 24.35 ppm.

(*E*)-*N*-(3-(2-amino-1*H*-imidazol-4-yl)allyl)benzamide (**2**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.98 (t, 2H, *J* = 5.3 Hz, -CH=CH-<u>CH$_2$</u>-), 5.99 (td, 1H, *J* = 5.7 Hz, *J* = 15.8 Hz, -CH=<u>CH</u>-CH$_2$), 6.22 (d, 1H, *J* = 16.0 Hz, -<u>CH</u>=CH-CH$_2$-), 6.29 (bs, 2H, imidazole-<u>NH$_2$</u>), 6.65 (s, 1H, imidazole-<u>H</u>), 7.45-7.49 (m, 3H, Ar-<u>H</u>), 7.87-7.90 (m, 2H, Ar-<u>H</u>), 8.75 (t, 1H, *J* = 5.6 Hz, -CO<u>NH</u>-) ppm; ^{13}C NMR (100 MHz, MeOH-d_4,) δ 165.84, 150.23, 134.47, 131.05, 128.23, 127.15, 121.16, 121.00, 120.50, 120.47, 41.05 ppm.

(*E*)-*N*-(3-(2-amino-1*H*-imidazol-4-yl)allyl)-1*H*-indole-2-carboxamide (**3**). ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.12 (dd, 2H, *J* = 6.2 Hz, *J* = 1.3 Hz, -CH=CH-<u>CH$_2$</u>-), 5.96 (ddd, 1H, *J* = 15.8 Hz, *J* = 6.2 Hz, *J* = 5.8 Hz, -CH=<u>CH</u>-CH$_2$-), 6.36 (td, 1H, *J* = 15.8 Hz, *J* = 1.3 Hz, -<u>CH</u>=CH-CH$_2$-), 6.50 (s, 1H, imidazole-H), 7.07 (ddd, 1H, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0, Ar-H^6), 7.11 (d, 1H, *J* = 0.9 Hz, Ar-H^3), 7.22 (ddd, 1H, *J* = 8.3 Hz, *J* = 7.0 Hz, *J* = 1.1, Ar-H^5), 7.45 (ddd, 1H, *J* = 8.3 Hz, *J* = 1.8 Hz, *J* = 0.9, Ar-H^4), 7.61 (td, 1H, *J* = 8.1 Hz, *J* = 1.0 Hz, Ar-H^7); ^{13}C NMR (100 MHz, MeOH-d_4) δ 41.01, 102.99, 111.64, 116.17, 119.74, 120.24, 121.27, 121.34, 123.61, 127.62, 129.83, 130.82, 136.90, 150.54, 162.56; HRMS for $C_{15}H_{15}N_5O$: calculated, 281.1277; found, 281.1344.

(*E*)-*N*-(3-(2-amino-1*H*-imidazol-4-yl)allyl)-5-fluoro-1*H*-indole-2-carboxamide (**4**). ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.11 (dd, 2H, *J* = 6.2 Hz, *J* = 1.3 Hz, -CH=CH-<u>CH$_2$</u>-), 5.95 (td, 1H, *J* = 15.8 Hz, *J* = 6.2 Hz, -CH=<u>CH</u>-CH$_2$-), 6.36 (td, 1H, *J* = 15.8 Hz, *J* = 1.3 Hz, -<u>CH</u>=CH-CH$_2$-), 6.50 (s, 1H, imidazole-H), 7.02 (ddd, 1H, *J* = 8.0 Hz, *J* = 6.9 Hz, *J* = 0.9, Ar-H^6), 7.08 (d, 1H, *J* = 0.9 Hz, Ar-H^3), 7.28 (ddd, 1H, *J* = 9.6 Hz, *J* = 2.1 Hz, *J* = 0.4, Ar-H^4), 7.43 (tdd, 1H, *J* = 9.0 Hz, *J* = 4.5 Hz, *J* = 0.7 Hz, Ar-H^7); ^{13}C NMR (100 MHz, MeOH-d_4) δ 40.96, 102.82 (d, $^4J_{C-F}$ = 5.2 Hz, C-4), 105.28 (d, $^2J_{C-F}$ = 23.2 Hz, C-8), 112.26 (d, $^2J_{C-F}$ = 27.0 Hz, C-2), 112.76 (d, $^3J_{C-F}$ = 9.6 Hz, C-7), 115.93, 120.71, 120.96, 127.73 (d, $^3J_{C-F}$ = 10.3 Hz, C-3), 129.32, 132.58, 133.51, 150.19, 157.96 (d, $^1J_{C-F}$ =234.0 Hz, C-1), 162.19; HRMS for $C_{15}H_{14}FN_5O$: calculated, 299.1182; found, 299.1194.

For details on the synthesis of compounds **1a-14a** please refer to Ž. Hodnik, T. Tomašić, L. Peterlin Mašič, F. Chan, R. W. Kirby, D. J. Madge, D. Kikelj, *Eur. J. Med. Chem.*, 2013, **70**, 154.

***N*-((2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)methyl)-1*H*-pyrrole-2-carboxamide (1a).** ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.36-1.47 (m, 1H, H$_A$-7), 1.82-1.90 (m, 1H, H$_B$-7), 1.93-2.05 (m, 1H, H-6), 2.10-2.25 (m, 1H, H_A-5), 2.31-2.41 (m, 1H, H_A-4), 2.42-2.49 (m, 1H, H_B-4), 2.58 (dd, 1H, J = 5.2, 15.7 Hz, H_B-5), 3.23 (t, 2H, J = 6.5 Hz, $C\underline{H}_2$-NH), 6.06-6.08 (m, 1H, Ar-H-4), 6.62 (s, 2H, 2-NH_2), 6.77-6.79 (m, 1H, Ar-H-3), 6.83-6.85 (m, 1H, Ar-H-5), 8.03 (t, 1H, J = 5.9 Hz, NH-C=O), 11.41 (br s, 1H, Ar-NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.39 (C-4), 26.56 (C-7), 26.70 (C-5), 35.14 (C-6), 43.18 ($\underline{C}H_2$-NH), 108.43 (Ar-C-4), 109.70 (Ar-C-3), 113.63 (C-7a), 121.11 (Ar-C-5), 126.28 (Ar-C-2), 144.62 (C-3a), 160.71 (C=O), 165.63 (C-2). HRMS m/z for $C_{13}H_{16}N_4OS$ ($[M+H^+]^+$): calcd 277.1123; found 277.1124.

***N*-((2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)methyl)-4,5-dibromo-*1H*-pyrrole-2-carboxamide (2a).** ^1H NMR (400 MHz, DMSO-d_6) δ 1.36-1.48 (m, 1H, H_A-7), 1.81-1.89 (m, 1H, H_B-7), 1.93-2.03 (m, 1H, H-6), 2.16-2.26 (m, 1H, H_A-5), 2.31-2.41 (m, 1H, H_A-4), 2.42-2.50 (m, 1H, H_B-4), 2.58 (dd, 1H, J = 5.1, 15.8 Hz, H_B-5), 3.22 (t, 2H, J = 6.7 Hz, $C\underline{H}_2$-NH), 6.62 (s, 2H, 2-NH_2), 6.96 (s, 1H, Ar-H-3), 8.16 (t, 1H, J = 5.8 Hz, NH-C=O), 12.68 (br s, 1H, Ar-NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.34 (C-4), 26.48 (C-7), 26.62 (C-5), 34.96 (C-6), 43.27 ($\underline{C}H_2$-NH), 97.73 (Ar-C-4), 104.40 (Ar-C-5), 112.49 (Ar-C-3), 113.53 (C-7a), 128.15 (Ar-C-2), 144.58 (C-3a), 158.94 (C=O), 165.65 (C-2). HRMS m/z for $C_{13}H_{14}Br_2N_4OS$ ($[M+H^+]^+$): calcd 432.9333; found 432.9342.

***N*-((2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)methyl)-4-bromo-*1H*-pyrrole-2-carboxamide (3a).** ^1H NMR (400 MHz, DMSO-d_6) δ 1.36-1.47 (m, 1H, H_A-7), 1.81-1.89 (m, 1H, H_B-7), 1.92-2.04 (m, 1H, H-6), 2.16-2.26 (m, 1H, H_A-5), 2.31-2.41 (m, 1H, H_A-4), 2.42-2.50 (m, 1H, H_B-4), 2.58 (dd, 1H, J = 5.1, 15.9 Hz, H_B-5), 3.23 (t, 2H, J = 6.1 Hz, $C\underline{H}_2$-NH), 6.62 (s, 2H, 2-NH_2), 6.87-6.90 (m, 1H, Ar-H-5), 6.96-6.99 (m, 1H, Ar-H-3), 8.14 (t, 1H, J = 5.8 Hz, NH-C=O), 11.82 (br s, 1H, Ar-NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.37 (C-4), 26.51 (C-7), 26.65 (C-5), 35.01 (C-6), 43.25 ($\underline{C}H_2$-NH), 94.84 (Ar-C-4), 111.33 (Ar-C-3), 113.56 (C-7a), 121.04 (Ar-C-5), 126.89 (Ar-C-2), 144.63 (C-3a), 159.65 (C=O), 165.64 (C-2). HRMS m/z for $C_{13}H_{15}BrN_4OS$ ($[M+H^+]^+$): calcd 355.0228; found 355.0241.

(2*S*)-*tert*-Butyl-2-(((2-amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)methyl)carbamoyl) pyrrolidine-1-carboxylate (4a). ^1H NMR (400 MHz, CD_3OD) δ 1.36-1.58 (m, 10H, H_A-7, $C(C\underline{H}_3)_3$), 1.82-2.12 (m, 5H, H-6, H_B-7, Pro-H_A-3, Pro-H-4), 2.15-2.35 (m, 2H, H_A-5, Pro-H_B-3), 2.40-2.74 (m, 3H, H-4, H_B-5), 3.13-3.32 (m, 2H, $C\underline{H}_2$-NH), 3.39-3.60 (m, 2H, Pro-H-5), 4.19 (d, 1H, J = 7.5 Hz, Pro-H-2); ^{13}C NMR (101 MHz, CD_3OD) δ 24.65 (25.48) (Pro-C-4), 26.37 (C-4), 27.94 (27.75, 27.79, 27.81, 28.01) (C-5,7), 28.72 ($C(\underline{C}H_3)_3$), 32.71 (31.57) (Pro-C-3), 36.85 (36.69, 36.72, 36.89) (C-6), 45.11 (45.06) ($\underline{C}H_2$-NH), 47.97 (47.90) (Pro-C-5), 62.06 (61.84, 62.02) (Pro-C-2), 81.52 (81.31) ($\underline{C}(CH_3)_3$), 116.15 (116.44) (C-7a), 144.87

(144.73) (C-3a), 156.15 (156.44) (N-C̲OO), 169.54 (C-2), 176.01 (175.68) (NH-C̲=O). HRMS m/z for $C_{18}H_{28}N_4O_3S$ ($[M+H^+]^+$): calcd 381.1960; found 381.1953.

2-Amino-6-(((*S*)-pyrrolidin-1-ium-2-carboxamido)methyl)-4,5,6,7-tetrahydrobenzo[*d*] thiazol-3-ium chloride (5a). ^1H NMR (400 MHz, DMSO-d_6) δ 1.38-1.51 (m, 1H, H_A-7), 1.76-2.03 (m, 5H, H-6, H_B-7, Pro-H_A-3, Pro-H-4), 2.13-2.24 (m, 1H, H_A-5), 2.26-2.69 (m, 4H, H-4, H_B-5, Pro-H_B-3), 3.09-3.27 (m, 4H, C$\underline{H}_2$-NH, Pro-H-5), 4.14-4.24 (m, 1H, Pro-H-2), 8.52 (br s, 1H, $NH_2^+Cl^-$), 8.93 (t, 1H, *J* = 4.7 Hz, NH-C=O), 9.38 (br s, 2H, 2-NH_2), 10.19 (br s, 1H, $NH_2^+Cl^-$), 13.42 (br s, 1H, NH^+Cl^-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.79 (C-4), 23.58 (Pro-C-4), 24.64 (C-7), 25.76 (C-5), 29.71 (Pro-C-3), 33.83 (C-6), 42.92 ($\underline{C}H_2$-NH), 45.37 (Pro-C-5), 58.80 (Pro-C-2), 113.44 (C-7a), 133.02 (C-3a), 168.20 (C=O), 168.35 (C-2). HRMS m/z for $C_{13}H_{20}N_4OS$ ($[M+H^+]^+$): calcd 281.1436; found 281.1437.

***N*-((2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)methyl)-1*H*-indole-2-carboxamide (6a).** ^1H NMR (400 MHz, DMSO-d_6) δ 1.40-1.52 (m, 1H, H_A-7), 1.86-1.94 (m, 1H, H_B-7), 2.00-2.12 (m, 1H, H-6), 2.21-2.31 (m, 1H, H_A-5), 2.32-2.44 (m, 1H, H_A-4), 2.45-2.50 (m, 1H, H_B-4), 2.62 (dd, 1H, *J* = 4.9, 15.8 Hz, H_B-5), 3.32 (t, 2H, *J* = 6.7 Hz, C$\underline{H}_2$-NH), 6.68 (s, 2H, 2-NH_2), 7.01-7.06 (m, 1H, Ar-H), 7.14-7.20 (m, 2H, Ar-H), 7.43 (dd, 1H, *J* = 0.9, 8.2 Hz, Ar-H), 7.61 (dd, 1H, *J* = 0.6, 7.8 Hz, Ar-H), 8.54 (t, 1H, *J* = 5.7 Hz, NH-C=O), 11.57 (br s, 1H, Ar-NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.24 (C-4), 26.49 (C-7), 26.67 (C-5), 34.97 (C-6), 43.47 ($\underline{C}H_2$-NH), 102.38 (Ar-C), 112.24 (Ar-C), 113.61 (C-7a), 119.63 (Ar-C), 121.39 (Ar-C), 123.16 (Ar-C), 127.05 (Ar-C), 131.75 (Ar-C), 136.35 (Ar-C), 144.20 (C-3a), 161.92 (C=O), 165.77 (C-2). HRMS m/z for $C_{17}H_{18}N_4OS$ ($[M+H^+]^+$): calcd 327.1280; found 327.1274.

(*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)-1*H*-pyrrole-2-carboxamide (7a). ^1H NMR (400 MHz, DMSO-d_6) δ 1.73-1.83 (m, 1H, H_A-7), 1.90-1.95 (m, 1H, H_B-7), 2.46-2.55 (m, 3H, signal overlapped with DMSO-d_5, H_A-4, H-5), 2.77 (dd, 1H, *J* = 5.1, 15.2 Hz, H_B-4), 4.10-4.19 (m, 1H, C$\underline{H}$NH), 6.08 (td, 1H, *J* = 2.5, 3.7 Hz, Ar-H-4), 6.71 (s, 2H, 2-NH_2), 6.81 (ddd, 1H, *J* = 1.5, 2.5, 3.7 Hz, Ar-H-3), 6.85 (dt, 1H, *J* = 1.5, 2.5 Hz, Ar-H-5), 7.95 (d, 1H, *J* = 8.0 Hz, NH-C=O), 11.47 (s, 1H, Ar-NH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.1 (C-5), 28.9 (C-4/7), 29.0 (C-4/7), 45.3 (C-6), 108.4 (Ar-C-4), 110.0 (Ar-C-3), 112.5 (C-7a), 121.2 (Ar-C-5), 126.2 (Ar-C-2), 144.2 (C-3a), 160.0 (C=O), 166.1 (C-2) ppm. HRMS m/z for $C_{12}H_{15}N_4OS$ ($[M+H^+]^+$): calcd 263.0967; found 263.0963.

(*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (8a). ^1H NMR (400 MHz, DMSO-d_6) δ 1.73-1.83 (m, 1H, H_A-7), 1.89-1.96 (m, 1H, H_B-7), 2.43-2.54 (m, 3H, signal overlapped with DMSO-d_5, H-5, H_A-4), 2.79 (dd, 1H, *J* =

5.5, 14.7 Hz, H_B-4), 4.08-4.17 (m, 1H, C<u>H</u>NH), 6.69 (s, 2H, 2-NH_2), 7.00 (s, 1H, Ar-H-3), 8.07 (d, 1H, *J* = 7.8 Hz, NH-C=O), 12.69 (s, 1H, Ar-NH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 24.9 (C-5), 28.7 (C-4/7), 28.8 (C-4/7), 45.5 (C-6), 97.8 (Ar-C-4), 104.5 (Ar-C-5), 112.3 (C-7a), 112.9 (Ar-C-3), 128.1 (Ar-C-2), 144.2 (C-3a), 158.3 (C=O), 166.2 (C-2) ppm. HRMS m/z for $C_{12}H_{13}Br_2N_4OS$ ($[M+H^+]^+$): calcd 418.9177; found 418.9178.

(*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)-4-bromo-1*H*-pyrrole-2-carboxamide (9a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.72-1.83 (m, 1H, H_A-7), 1.88-1.96 (m, 1H, H_B-7), 2.44-2.55 (m, 3H, signal overlapped with DMSO-d_5, H-5, H_A-4), 2.78 (dd, 1H, *J* = 5.0, 15.0 Hz, H_B-4), 4.08-4.18 (m, 1H, C<u>H</u>NH), 6.68 (s, 2H, 2-NH_2), 6.92 (dd, 1H, *J* = 1.6, 2.8 Hz, Ar-H-3), 6.98 (dd, 1H, *J* = 1.6, 2.8 Hz, Ar-H-5), 8.03 (d, 1H, *J* = 7.9 Hz, NH-C=O), 11.84 (s, 1H, Ar-NH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.0 (C-5), 28.8 (C-4,7), 45.5 (C-6), 94.8 (Ar-C-4), 111.7 (Ar-C-3), 112.3 (C-7a), 121.1 (Ar-C-5), 126.8 (Ar-C-2), 144.2 (C-3a), 159.0 (C=O), 166.2 (C-2) ppm. HRMS m/z for $C_{12}H_{14}BrN_4OS$ ($[M+H^+]^+$): calcd 341.0072; found 341.0068.

(*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)-1-methyl-1*H*-pyrrole-2-carboxamide (10a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70-1.83 (m, 1H, H_A-7), 1.86-1.97 (m, 1H, H_B-7), 2.46-2.54 (m, 3H, signal overlapped with DMSO-d_5, H-5, H_A-4), 2.75 (dd, 1H, *J* = 5.4, 14.1 Hz, H_B-4), 3.83 (s, 3H, NCH_3), 4.04-4.16 (m, 1H, C<u>H</u>NH), 5.99 (dd, 1H, *J* = 2.4, 3.8 Hz, Ar-H-4), 6.63 (d, 2H, *J* = 4.0 Hz, 2-NH_2), 6.79 (dd, 1H, *J* = 1.7, 3.8 Hz, Ar-H-3), 6.88 (t, 1H, *J* = 2.4 Hz, Ar-H-5), 7.87 (d, 1H, *J* = 7.9 Hz, NH-C=O) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.3 (C-5), 28.8 (C-4/7), 29.0 (C-4/7), 36.2 (NCH_3), 45.3 (C-6), 106.4 (Ar-C-4), 112.3 (Ar-C-3), 112.6 (C-7a), 125.5 (Ar-C-2), 127.6 (Ar-C-5), 144.1 (C-3a), 160.8 (C=O), 166.1 (C-2) ppm. HRMS m/z for $C_{13}H_{17}N_4OS$ ($[M+H^+]^+$): calcd 277.1123; found 277.1120.

(*S*)-2-Amino-6-((*S*)-pyrrolidin-1-ium-2-carboxamido)-4,5,6,7-tetrahydrobenzo[*d*]thiazol-3-ium chloride (11a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74-1.92 (m, 5H, H-7, Pro-H-4, H_A-5), 2.28 (ddd, 1H, *J* = 6.5, 12.9, 14.4 Hz, H_B-5), 2.42 (dd, 1H, *J* = 6.5, 16.3 Hz, Pro-H_A-3), 2.56-2.68 (m, 2H, H-4), 2.80 (dd, 1H, *J* = 4.9, 16.3 Hz, Pro-H_B-3), 3.15-3.26 (m, 2H, Pro-H-5), 4.06-4.14 (m, 1H, Pro-H-2), 4.15-4.22 (m, 1H, H-6), 8.50-8.58 (m, 1H, $NH_2^+Cl^-$), 8.89 (d, 1H, *J* = 7.4 Hz, NH-C=O), 9.37 (s, 2H, 2-NH_2), 10.07-10.16 (m, 1H, $NH_2^+Cl^-$), 13.48 (br s, 1H, NH^+Cl^-) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.5 (C-4), 23.5 (C-7/Pro-C-4), 26.0 (C-7/Pro-C-4), 27.8 (Pro-C-3), 29.8 (C-5), 44.3 (C-6), 45.5 (Pro-C-5), 58.6 (Pro-C-2), 111.9 (C-7a), 132.7 (C-3a), 167.7 (C-2), 168.6 (NH-C=O) ppm. HRMS m/z for $C_{12}H_{19}N_4OS$ ($[M+H^+]^+$): calcd 267.1280; found 267.1281.

(*S*)-*N*^{6}-((1*H*-Pyrrol-2-yl)methyl)-4,5,6,7-tetrahydrobenzo[*d*]thiazole-2,6-diamine (12a). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.47-1.57 (m, 1H, H$_A$-7), 1.87-1.94 (m, 2H, H$_B$-7, H$_A$-5), 2.20-2.26 (m, 1H, H$_B$-5), 2.29-2.38 (m, 1H, H$_A$-4), 2.73 (dd, 1H, *J* = 4.9, 14.9 Hz, H$_B$-4), 2.78-2.84 (m, 1H, CHNH), 3.69 (s, 2H, CH$_2$NH), 5.85-5.87 (m, 1H, Ar-H-4), 5.88-5.90 (m, 1H, Ar-H-3), 6.59 (s, 2H, 2-NH$_2$), 6.61 (dt, 1H, *J* = 1.6, 2.6 Hz, Ar-H-5), 10.59 (br s, 1H, Ar-NH) ppm, signal for CH$_2$NH group not seen; ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 24.7 (C-5), 28.7 (C-4/7), 29.0 (C-4/7), 43.0 (CH$_2$NH), 52.6 (C-6), 105.8 (Ar-C-3/4), 106.9 (Ar-C-3/4), 112.9 (C-7a), 116.7 (Ar-C-5), 130.2 (Ar-C-2), 144.4 (C-3a), 165.8 (C-2) ppm. HRMS m/z for $C_{12}H_{17}N_4S$ ([M+H$^+$]$^+$): calcd 249.1174; found 249.1169.

(*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)furan-2-carboxamide (13a). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.77-1.85 (m, 1H, H$_A$-7), 1.87-1.93 (m, 1H, H$_B$-7), 2.50-2.53 (m, 2H, signal overlapped with DMSO-d$_5$, H-5), 2.55-2.60 (m, 1H, H$_A$-4), 2.75 (dd, 1H, *J* = 5.1, 15.0 Hz, H$_B$-4), 4.09-4.18 (m, 1H, CHNH), 6.63 (dd, 1H, *J* = 1.8, 3.4 Hz, Ar-H-4), 6.68 (s, 2H, 2-NH$_2$), 7.12 (dd, 1H, *J* = 0.8, 3.4 Hz, Ar-H-3), 7.83 (dd, 1H, *J* = 0.8, 1.8 Hz, Ar-H-5), 8.34 (d, 1H, *J* = 8.1 Hz, NH-C=O) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 25.1 (C-5), 28.5 (C-4/7), 28.7 (C-4/7), 45.5 (C-6), 111.8 (Ar-C-4), 112.4 (C-7a), 113.4 (Ar-C-3), 144.2 (Ar-C-2), 144.8 (Ar-C-5), 147.9 (C-3a), 157.2 (C=O), 166.2 (C-2) ppm. HRMS m/z for $C_{12}H_{14}N_3O_2S$ ([M+H$^+$]$^+$): calcd 264.0807; found 264.0796.

(*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzo[*d*]thiazol-6-yl)-1*H*-indole-2-carboxamide (14a). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.78-1.91 (m, 1H, H$_A$-7), 1.94-2.05 (m, 1H, H$_B$-7), 2.51-2.61 (m, 3H, signal overlapped with DMSO-d$_5$, H-5, H$_A$-4), 2.84 (dd, 1H, *J* = 5.5, 15.1 Hz, H$_B$-4), 4.16-4.28 (m, 1H, CHNH), 6.71 (s, 2H, 2-NH$_2$), 7.03 (t, 1H, *J* = 7.9 Hz, Ar-H-5/6), 7.15-7.20 (m, 2H, Ar-H-3, Ar-H-5/6), 7.43 (dd, 1H, *J* = 0.6, 8.2 Hz, Ar-H-4/7), 7.61 (d, 1H, *J* = 7.9 Hz, Ar-H-4/7), 8.39 (d, 1H, *J* = 7.8 Hz, NH-C=O), 11.54 (s, 1H, Ar-NH) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 25.1 (C-5), 28.7 (C-4/7), 28.8 (C-4/7), 45.8 (C-6), 102.8 (Ar-C), 112.2 (Ar-C), 112.4 (C-7a), 119.7 (Ar-C), 121.4 (Ar-C), 123.3 (Ar-C), 127.0 (Ar-C), 131.7 (Ar-C), 136.4 (Ar-C), 144.3 (C-3a), 160.6 (C=O), 166.2 (C-2) ppm. HRMS m/z for $C_{16}H_{17}N_4OS$ ([M+H$^+$]$^+$): calcd 313.1123; found 313.1131.

For details on the synthesis of compounds **1b-10b** please refer to M. Jukič, R. Frlan, F. Chan, R. W. Kirby, D. J. Madge, M. Anderluh, D. Kikelj, *Med. Chem. Res.*, 2014, submitted.

(4-((2-Amino-1*H*-imidazol-4-yl)methyl)piperazin-1-yl)(1*H*-pyrrol-2-yl)methanone (1b).

^{1}H NMR (DMSO-d_6) δ = 3.05-3.10 (m, 2H, -NCH_2), 4.27 (s, 2H, -NCH_2), 4.48-4.52 (m, 2H, -NCH_2), 6.15 (s, 1H, CH_{Ar}), 6.58 (s, 1H, CH_{Ar}), 6.94 (s, 1H, CH_{Ar}), 7.10 (s, 1H, CH_{Ar}), 7.81 (s, 2H, -NH_2), 11.58 (s, 1H, NH), 12.20-12.21 (m, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ = 29.96, 31.69, 41.36, 48.38, 48.45, 50.08, 108.63, 112.57, 115.08, 116.59, 121.90, 123.23, 147.43, 161,47 ppm; HRMS for $C_{13}H_{18}N_6OCl$: calculated 309.1231, found 309.1223.

4-((4-((1*H*-pyrrol-2-yl)methyl)piperazin-1-yl)methyl)-1*H*-imidazol-2-amine (**2b**). ^{1}H NMR (DMSO-d_6) δ = 2.59 (s, 4H, -$N(CH_2)_2$), 3.08 (s, 4H, $N(CH_2)_2$), 3.44 (s, 2H, CH_2), 6.81 (s, 1H, CH_{Ar}), 7.54 (s, 2H, -NH_2), 8.79-8.81 (m, 2H, CH_{Ar}), 12.12 (2, 1H, NH), 12.43-12.46 (m, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ = 8.41, 28.99, 45.31, 47.45, 48.56, 83.71, 114.44, 114.98, 143.22, 147.30, 158.14, 161.59, 188.23 ppm; MS (ESI) m/z (%) = 334 (MH^+).

(*S*)-1-((2-amino-1*H*-imidazol-4-yl)methyl)-4-prolylpiperazine (**3b**). ^{1}H NMR (DMSO-d_6) δ = 1.87-1.92 (m, 3H, CH_2), 2.34-2.35 (m, 1H, CH_2), 3.19-3.21 (m, 6H, -$N(CH_2)_2$), 4.22-4.29 (m, 3H, CH_2), 4.62-4.63 (s, 1H, CH), 7.09-7.11 (s, 1H, CH_{Ar}), 7.75-7.81 (m, 2H, NH_2), 8.51-8.52 (s, 1H, NH), 12.16 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ = 23.63, 28.46, 30.70, 41.64, 45.63, 48.29, 49.35, 49.66 57.19, 115.01, 116.58, 147.41, 166.87 ppm; HRMS for $C_{13}H_{23}N_6OCl_2$: calculated 349.1310, found 349.1320.

(4-((2-Amino-1*H*-imidazol-4-yl)methyl)piperazin-1-yl)(1*H*-indol-2-yl)methanone (**4b**). ^{1}H NMR (DMSO-d_6) δ = 3.06-3.17 (m, 2H, -NCH_2), 4.29 (s, 2H, -NCH_2), 4.57-4.59 (m, 2H, -NCH_2), 6.90 (s, 1H, CH_{Ar}), 7.07 (t, *J*=7.53 Hz, 1H, CHAr), 7.11 (s, 1H, CH_{Ar}), 7.21 (t, *J*=7.54 Hz, 1H, CH_{Ar}), 7.45 (d, *J*=7.85 Hz, 1H, CH_{Ar}), 7.62 (d, *J*=7.74 Hz, 1H, CH_{Ar}) 7.82 (s, 2H, NH_2), 11.69 (s, 1H, NH), 12.21 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d6) δ = 8.39, 30.68, 45.27, 48.46, 50.03, 104.80, 112.16, 115.01, 116.60, 119.88, 121.43, 123.55, 126.68, 128.84, 136.10, 147.45, 162.14 ppm; HRMS for $C_{17}H_{20}N_6OCl$: calculated 359.1387, found 359.1385.

(4-((2-Amino-1*H*-imidazol-4-yl)methyl)piperazin-1-yl)(1*H*-indol-3-yl)methanone (**5b**). ^{1}H NMR (DMSO-d_6) δ = 3.06-3.12 (m, 2H, NCH_2), 4.26-4.28 (m, 2H, -NCH_2), 4.39-4.43 (m, 2H, NCH_2), 7.11-7.18 (m, 3H, CH_{Ar}), 7.47 (d, *J*=7.42 Hz, 1H, CH_{Ar}), 7.72-7-79 (m, 2H, CH_{Ar}), 11.47-11.55 (s, 1H, NH), 11.77 (s, 1H, NH), 12.04-12.05 (m, 1H, NH) ppm; ^{13}C NMR (DMSO-d6) δ = 50.23, 50.32, 67.96, 97.96, 112.05, 120.09, 120.41, 122.05, 125.89, 128.79, 135.75, 147.43, 155.04, 165.73, 178.58 ppm; MS (ESI) m/z (%) = 359 ($M\text{-}HCl^-$).

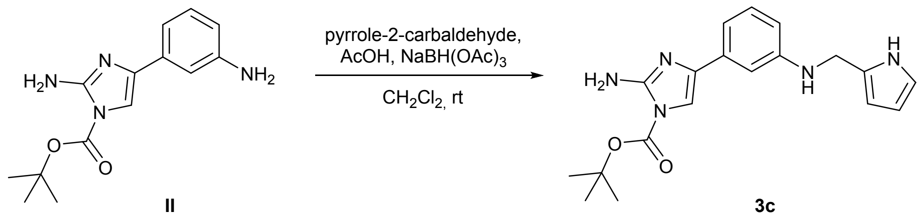
4-((4-Benzylpiperazin-1-yl)methyl)-1*H*-imidazol-2-amine (**6b**). ^{1}H NMR (DMSO-d_6) δ = 2.09 (s, 4H, -$N(CH_2)_2$), 4.06-4.10 (m, 2H, CH_2), 4.37 (s, 2H, CH_2), 7.03 (s, 1H, CH_{Ar}), 7.45-7.73 (m, 5H, CHAr), 12.14-12.24 (m, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d6) δ = 28.97, 30.68, 47.13, 48.16, 58.37, 78.98, 128.73, 128.86, 129.47, 129.56, 131.42, 131.56, 147.31, 206.54 ppm; HRMS for $C_{15}H_{22}N_5Cl_2$: calculated 342.1252, found 342.1254.

(4-((2-Amino-1*H*-imidazol-4-yl)methyl)piperazin-1-yl)(pyridin-3-yl)methanone (7b).
^{1}H NMR (DMSO-d$_6$) δ = 3.12-3.15 (m, 8H, -N(CH$_2$)$_2$), 4.27 (s, 2H, CH$_2$), 7.12 (s, 1H, CH$_{Ar}$), 7.72 (dd, *J*=7.34, 5.11 Hz, 1H, CH$_{Ar}$), 7.81 (s, 1H, CH$_{Ar}$), 8.14 (d, *J*=7.65 Hz, 1H, CH$_{Ar}$), 8.79-8.82 (m, 2H, CH$_{Ar}$, NH), 12.18-12-20 (m, 2H, NH$_2$) ppm; ^{13}C NMR (DMSO-d$_6$) δ = 33.08, 42.24, 43.79, 48.31, 49.49, 114.79, 116.78, 125.19, 132.07, 138.85, 144.79, 147.43, 147.48, 165.62 ppm; HRMS for $C_{14}H_{18}N_6OCl$: calculated 321.1231, found 321.1235.
(4-((1*H*-Imidazol-4-yl)methyl)piperazin-1-yl)(1*H*-pyrrol-2-yl)methanone (8b). ^{1}H NMR (DMSO-d$_6$) δ = 2.37-2.40 (m, 4H, -N(CH$_2$)$_2$-], 3.43 (s, 2H, -CH$_2$-), 3.62-3.69 (m, 4H, -N(CH$_2$)$_2$-), 6.07-6.10 (m, 1H, Ar), 6.43-6.47 (m, 1H, Ar), 6.84-6.91 (m, 2H, Ar, Ar-imi.), 7.52-7.56 (m, 1H, Ar-imi.), 11.40 (s, 1H, Ar-NH), 11.93 (s, 1H, Ar-imi.-NH) ppm; ^{13}C NMR (DMSO-d$_6$) δ = 44.23, 44.33, 44.46, 44.52, 52.47, 108.27, 111.65, 120.99, 124.19, 134.81, 134.85, 134.96, 161.32 ppm; HRMS for $C_{13}H_{18}N_5O$: calculated 260.1511, found 260.1514.
1-(4-(1*H*-Pyrrole-2-carbonyl)piperazin-1-yl)-2-(2-aminothiazol-5-yl)ethan-1-one (9b). ^{1}H NMR (DMSO-d$_6$) δ = 3.50-3.56 (m, 4H, -N(CH$_2$)$_2$-), 3.59-3.63 (m, 2H, -CO-CH$_2$-), 3.64-3.72 (m, 4H, -N(CH$_2$)$_2$-), 6.12 (td, *J* = 3.49, 2.45, 2.45 Hz, 1H, Ar), 6.26 (s, 1H, -S-CH=C-), 6.51 (ddd, *J* = 3.67, 2.50, 1.35 Hz, 1H, Ar), 6.85 (s, 2H, -NH$_2$), 6.89 (dt, *J* = 2.80, 2.70, 1.37 Hz, 1H, Ar), 11.44 (s, 1H, Ar-NH) ppm; ^{13}C NMR (DMSO-d$_6$) δ = 21.04, 36.69, 41.25, 45.57, 102.28, 108.42, 112.02, 121.30, 123.99, 145.56, 161.58, 168.03, 168.14, 172.01 ppm; HRMS for $C_{14}H_{18}N_5O_2S$: calculated 320.1181, found 320.1185.
(4-(1*H*-Pyrrole-2-carbonyl)piperazin-1-yl)(2-aminothiazol-5-yl)methanone (10b). ^{1}H NMR (DMSO-d$_6$) δ = 3.73 (s, 4H, -N(CH$_2$)$_2$), 3.79 (s, 4H, -N(CH$_2$)$_2$), 6.14 (s, 1H, CH$_{Ar}$), 6.51-6.55 (m, 1H, CH$_{Ar}$), 6.92 (s, 1H, CH$_{Ar}$), 7.54 (s, 1H, CH$_{Ar}$), 8.09-8.12 (m, 2H, -NH$_2$). 11.52 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d$_6$) δ = 44.43, 44.45, 108.49, 112.14, 119.59, 121.42, 123.99, 139.05, 158.13, 158.49, 160.72, 161.51, 170.83 ppm; HRMS for $C_{13}H_{16}N_5O_2S$: calculated 306.1025, found 306.1020.

For details on the synthesis of compounds **1c, 2c, 4c-6c, 14c-23c, 31c-34c, 37c-44c** please refer to N. Zidar, Ž. Jakopin, D. J. Madge, F. Chan, J. Tytgat, S. Peigneur, M. Sollner Dolenc, T. Tomašić, J. Ilaš, L. Peterlin Mašič, D. Kikelj, *Eur. J. Med. Chem*., 2014, **74**, 23, and for compounds **7c-13c**, **24c-30c**, **35c**, **36c** refer to N. Zidar, S. Montalvão, Ž. Hodnik, D. A. Nawrot, A. Žula, J. Ilaš, D. Kikelj, P. Tammela, L. Peterlin Mašič, *Mar. Drugs*, 2014, **12**, 940.

***tert*-Butyl 4-(3-(1*H*-pyrrole-2-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (1c).** ^{1}H NMR (DMSO-d_6) δ 1.59 (s, 9H, *t*-Bu), 6.16–6.18 (m, 1H, Pyrr-H), 6.63 (br s, 2H, NH_2), 6.96–6.98 (m, 1H, Pyrr-H), 7.09–7.11 (m, 1H, Pyrr-H), 7.26 (s, 1H, Ar-H-5), 7.29 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.41–7.43 (m, 1H, Ar-H-4'/6'), 7.67–7.69 (m, 1H, Ar-H-4'/6'), 8.07 (t, 1H, ^4J = 2.0 Hz, Ar-H-2'), 9.77 (s, 1H, NH), 11.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C<u>C</u>H$_3$), 84.67 (<u>C</u>CH$_3$), 105.93, 108.89, 111.25, 116.28, 118.54, 119.41, 122.47, 126.06, 128.57, 133.69, 137.03, 139.47, 148.88, 150.39, 159.08; HRMS for $C_{19}H_{22}N_5O_3$: calculated 368.1723; found 368.1724.

***tert*-Butyl 4-(3-(1*H*-pyrrole-3-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (2c).** ^{1}H NMR (DMSO-d_6) δ 1.59 (s, 9H, *t*-Bu), 6.61 (br s, 2H, NH_2), 6.66–6.67 (m, 1H, Pyrr-H), 6.81–6.83 (m, 1H, Pyrr-H), 7.24 (s, 1H, ArH-5), 7.26 (t, 1H, ^3J= 8.0 Hz, Ar-H-5'), 7.38–7.41 (m, 1H, Ar-H-4'/6'), 7.54–7.56 (m, 1H, Pyrr-H), 7.65–7.68 (m, 1H, Ar-H-4'/6'), 8.06 (t, 1H, ^4J = 2.0 Hz, Ar-H-2'), 9.52 (s, 1H, NH), 11.29 (br s, 1H, NH); ^{13}C NMR (MeOH-d_4) δ 26.73 (C<u>C</u>H$_3$), 85.27 (<u>C</u>CH$_3$), 106.21, 107.16, 117.15, 118.69, 119.07, 119.82, 120.28, 121.56, 128.50, 133.40, 137.02, 139.02, 149.26, 151.38, 165.27; HRMS for $C_{19}H_{22}N_5O_3$: calculated 368.1723; found 368.1726.



***tert*-Butyl 4-(3-(((1*H*-pyrrole-2-yl)methyl)amino)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (3c)**. To a solution of *tert*-butyl 2-amino-4-(3-aminophenyl)-1*H*-imidazole-1-carboxylate (**II**) (200 mg, 0.73 mmol) in dichloromethane (20 mL) were successively added pyrrole-2-carbaldehyde (97 mg mg, 1.02 mmol), glacial acetic acid (42 µL, 0.73 mmol), and NaBH(OAc)$_3$ (232 mg, 1.09 mmol) and the mixture was stirred at rt for 10 h. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (30 mL), washed with water (2 × 15 mL), saturated aqueous $NaHCO_3$ solution (2 × 15 mL), and brine (1 × 15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Crude product was purified with flash column chromatography (eluent: ethyl acetate/petroleum ether = 1:1) to give **3c** (197 mg) as a brown solid. Yield, 76%; mp 122–126 °C; IR (ATR) ν = 3359, 2977, 2933, 1734, 1684, 1605, 1481, 1432, 1352, 1257, 1202, 1154, 1118, 1027, 991, 842, 771, 720 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.58 (s, 9H, *t*-Bu), 4.17 (d, 2H, ^3J = 5.2 Hz, CH_2), 5.73–5.76 (m, 1H, N<u>H</u>CH$_2$), 5.92–5.96 (m, 2H, 2 × Ar-H), 6.52–6.56 (m, 3H, Ar-H, NH_2), 6.64–6.66 (m, 1H, Ar-H), 6.92–6.93 (m, 1H, Ar-H), 7.01–7.05 (m, 2H, Ar-H), 7.17 (s, 1H, Ar-H), 10.72 (br s, 1H, NH); MS (ESI) *m/z* (%) = 354.2 (MH^+, 20), 298.1 (100), 254.1 (40). HRMS for $C_{19}H_{24}N_5O_2$: calculated 354.1930; found 354.1935. HPLC: Phenomenex Luna 5 µm C18 column (4.6 mm × 150 mm); mobile phase: 10–90% of MeOH in TFA (0.1%) in 20 min; flow rate 1.0 mL/min; injection volume: 10 µL; retention time: 4.583 min (97.8% at 254 nm).

***tert*-Butyl (*R*)-2-amino-4-(3-(1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (4c).** ^1H NMR (DMSO-d_6) δ 1.28 (s, 5.85H, *t*-Bu-*cis*/*trans*), 1.41 (s, 3.15H, *t*-Bu-*cis*/*trans*), 1.59 (s, 9H, *t*-Bu), 1.75–1.94 (m, 3H, H_A from CHC$\underline{H}_2$, CH_2), 2.13–2.25 (m, 1H, H_B from CHC$\underline{H}_2$), 3.30–3.46 (m, 2H, NCH_2), 4.18–4.21 (m, 0.65H, CH-*cis*/*trans*), 4.25–4.27 (m, 0.35H, CH- *cis*/*trans*), 6.61 (s, 2H, NH_2), 7.22–7.29 (m, 2H, 2 × Ar-H), 7.40–7.50 (m, 2H, 2 × Ar-H), 7.97 (s, 0.65H, Ar-H-2'- *cis*/*trans*), 8.02 (s, 0.35H, Ar-H-2'-*cis*/*trans*), 10.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.36 and 23.93 (CH_2, *cis* and *trans*), 27.50 (C$\underline{C}H_3$), 27.92 and 28.13 (C$\underline{C}H_3$, *cis* and *trans*), 30.18 and 30.96 (CH_2, *cis* and *trans*), 46.52 and 46.71 (CH_2, *cis* and *trans*), 59.98 and 60.37 (CH, *cis* and *trans*), 78.43 and 78.61 ($\underline{C}CH_3$, *cis* and *trans*), 84.69 (C$\underline{C}H_3$), 105.93, 115.56 and 115.63 (Ar-C, *cis* and *trans*), 117.83, 119.62, 128.71, 133.79, 136.92, 139.21, 148.85, 150.39, 153.14 and 153.56 (C=O, *cis* and *trans*), 171.01 and 171.48 (C=O, *cis* and *trans*); HRMS for $C_{24}H_{34}N_5O_5$: calculated 472.2560; found 472.2570.

***tert*-Butyl 4-(3-(1*H*-indole-2-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (5c).** ^1H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 6.64 (br s, 2H, NH_2), 7.08 (t, 1H, ^3J = 7.6 Hz, Ar-H), 7.23 (dt, 1H, ^3J = 7.6 Hz, ^4J = 1.2 Hz, Ar-H), 7.30 (s, 1H, Ar-H-5), 7.34 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.47–7.49 (m, 3H, 3 × Ar-H), 7.69 (d, 1H, ^3J = 7.6 Hz, Ar-H), 7.73–7.75 (m, 1H, Ar-H), 8.15 (s, 1H, Ar-H-2'), 10.24 (s, 1H, NH), 11.72 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 84.70 ($\underline{C}CH_3$), 103.81, 106.08, 112.35, 116.52, 118.77, 119.88, 119.96, 121,74, 123.75, 127.04, 128.71, 131.47, 133.82, 136.77, 136.94, 139.09, 148.88, 150.43, 159.65; HRMS for $C_{23}H_{24}N_5O_3$: calculated 418.1879; found 418.1884.

***tert*-Butyl 4-(3-(1*H*-indole-3-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (6c).** ^1H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 6.59 (br s, 2H, NH_2), 7.13–7.22 (m, 2 H, 2 × Ar-H), 7.26–7.32 (m, 2H, Ar-H-5, ArH-5'), 7.41 (d, 1H, ^3J = 7.8 Hz, Ar-H), 7.46–7.49 (m, 1H, Ar-H), 7.68–7.71 (m, 1H, Ar-H), 8.12 (s, 1H, ArH-2'), 8.20–8.22 (m, 1H, Ar-H), 8.32 (d, 1H, ^4J = 3.0 Hz, Ar-H), 9.71 (s, 1H, NH), 11.71 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.53 (C$\underline{C}H_3$), 84.67 ($\underline{C}CH_3$), 105.89, 110.43, 111.92, 116.10, 118.39, 119.10, 120.66, 121.06, 122.11, 126.43, 128.52, 128.63, 133.65, 136.17, 137.15, 139.95, 148.91, 150.37, 163.27; HRMS for $C_{23}H_{24}N_5O_3$: calculated 418.1879; found 418.1898.

***tert*-Butyl 2-amino-4-(3-(5-methoxy-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (7c)**. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 3.79 (s, 3H, OCH_3), 6.64 (s, 2H, NH_2), 6.89 (dd, 1H, ^3J = 9.2 Hz, ^4J = 2.4 Hz, Ar-H), 7.14 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.29–7.38 (m, 4H, 4 × Ar-H), 7.48 (dd, 1H, ^3J = 7.6 Hz, ^4J = 0.8 Hz, Ar-H), 7.72–7.75 (m, 1H, Ar-H), 8.13 (s, 1H, Ar-H), 10.19 (s, 1H, NH), 11.57 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 55.25 (OCH_3), 84.70 ($\underline{C}CH_3$), 102.04, 103.52, 106.07, 113.19, 115.04, 116.55, 118.81, 119.92, 127.35, 128.69, 131.74, 132.08, 133.80, 136.95, 139.12, 148.88, 150.43, 153.82, 159.61; HRMS for $C_{24}H_{26}N_5O_4$: calculated, 448.1985; found, 448.1983.

***tert*-Butyl 2-amino-4-(3-(5-(benzyloxy)-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (8c)**. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 5.13 (s, 2H, OCH_2), 6.64 (s, 2H, NH_2), 6.97 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.4 Hz, Ar-H), 7.25–7.51 (m, 11H, 11 × Ar-H), 7.72–7.75 (m, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 10.18 (s, 1H, NH), 11.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 69.61 (OCH_2), 84.70 ($\underline{C}CH_3$), 103.54, 103.67, 106.07, 113.21, 115.53, 116.51, 118.77, 119.92, 127.30, 127.68, 128.36, 128.69, 131.84, 132.22, 133.80, 136.95, 137.54, 139.12, 148.88, 150.43, 152.81, 159.59 (signals for two C atoms overlap); HRMS for $C_{30}H_{30}N_5O_4$: calculated, 524.2298; found, 524.2302.

***tert*-Butyl 2-Amino-4-(3-(5-hydroxy-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (9c)**. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 6.64 (br s, 2H, NH_2), 6.78 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.4 Hz, Ar-H), 6.93 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.26–7.35 (m, 4H, 4 × Ar-H), 7.47 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.6 Hz, Ar-H), 7.71–7.73 (m, 1H, Ar-H), 8.13–8.14 (m, 1H, Ar-H), 8.86 (s, 1H, OH), 10.12 (s, 1H, NH), 11.43 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 84.69 ($\underline{C}CH_3$), 102.93, 104.35, 106.04, 112.85, 115.04, 116.45, 118.71, 119.85, 127.73, 128.68, 131.59, 131.60, 133.79, 136.97, 139.18, 148.88, 150.42, 151.19, 159.69; HRMS for $C_{23}H_{24}N_5O_4$: calculated, 434.1828; found, 434.1823.

***tert*-Butyl 2-amino-4-(3-(5-(trifluoromethoxy)-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (10c)**. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 6.64 (s, 2H, NH_2), 7.22 (dd, 1H, ^3J = 9.2 Hz, ^4J = 1.6 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.35 (t, 1H, ^3J = 8.0 Hz, Ar-H), 7.49–7.57 (m, 3H, 3 × Ar-H), 7.74–7.76 (m, 2H, 2 × Ar-H), 8.14 (s, 1H, Ar-H), 10.36 (s, 1H, NH), 12.01 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 84.70 ($\underline{C}CH_3$), 104.09, 106.13, 113.61, 113.96, 116.63, 117.63, 118.88, 120.15, 120.41 (q, 1C, $^1J_{C\text{-}F}$ = 253 Hz, CF_3), 127.02, 128.73, 133.56, 133.85, 135.15, 136.89, 138.90, 142.20, 148.87, 150.43, 159.22; ^{19}F

NMR (DMSO-d_6) δ −59.92 (s, 3F, CF_3); HRMS for $C_{24}H_{23}N_5O_4F_3$: calculated, 502.1702; found, 502.1712.

***tert*-Butyl 2-amino-4-(3-(5-fluoro-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (11c)**. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 6.64 (s, 2H, NH_2), 7.10 (dt, 1H, ^3J = 9.2 Hz, ^4J = 2.4 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.34 (t, 1H, ^3J = 8.0 Hz, Ar-H), 7.45–7.50 (m, 4H, 4 × Ar-H), 7.72–7.75 (m, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 10.29 (s, 1H, NH), 11.84 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 84.70 ($\underline{C}CH_3$), 103.79 (d, 1C, $^4J_{C-F}$ = 5 Hz), 105.88 (d, 1C, $^2J_{C-F}$ = 23 Hz), 106.11, 112.51 (d, 1C, $^2J_{C-F}$ = 27 Hz), 113.57 (d, 1C, $^3J_{C-F}$ = 9 Hz), 116.58, 118.83, 120.08, 127.09 (d, 1C, $^3J_{C-F}$ = 10 Hz), 128.72, 133.17, 133.50, 133.84, 136.91, 138.98, 148.87, 150.43, 157.19 (d, 1C, $^1J_{C-F}$ = 231 Hz), 159.35; ^{19}F NMR (DMSO-d_6) δ −123.68 (s, 1F); MS (ESI) *m/z* (%) = 436.2 (MH^+, 100). HRMS for $C_{23}H_{23}N_5O_3F$: calculated, 436.1785; found, 436.1780.

***tert*-Butyl 2-amino-4-(3-(5-chloro-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (12c)**. ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 6.64 (s, 2H, NH_2), 7.24 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.35 (t, 1H, ^3J = 8.0 Hz, Ar-H), 7.45–7.50 (m, 3H, 3 × Ar-H), 7.72–7.75 (m, 1H, Ar-H), 7.79 (d, 1H, ^4J = 2.0 Hz, Ar-H), 8.14 (t, 1H, ^4J = 1.6 Hz, Ar-H), 10.32 (s, 1H, NH), 11.94 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.51 (C$\underline{C}H_3$), 84.70 ($\underline{C}CH_3$), 103.34, 106.11, 113.96, 116.58, 118.83, 120.11, 120.80, 123.85, 124.36, 128.07, 128.73, 132.97, 133.84, 135.14, 136.90, 138.95, 148.87, 150.44, 159.28; HRMS for $C_{23}H_{23}N_5O_3Cl$: calculated, 452.1489; found, 452.1487.

***tert*-Butyl 4-(3-(4*H*-thieno[3,2-*b*]pyrrole-5-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (13c)**. ^{1}H NMR (acetone-d_6) δ 1.67 (s, 9H, *t*-Bu), 6.44 (s, 2H, NH_2), 7.09 (d, 1H, *J* = 5.2 Hz, Ar-H), 7.29–7.33 (m, 2H, 2 × Ar-H), 7.40–7.43 (m, 2H, 2 × Ar-H), 7.48–7.51 (m, 1H, Ar-H), 7.76–7.79 (m, 1H, Ar-H), 8.16 (s, 1H, Ar-H), 9.44 (s, 1H, NH), 11.07 (s, 1H, NH); ^{13}C NMR (acetone-d_6) δ 28.10 (C$\underline{C}H_3$), 85.61 ($\underline{C}CH_3$), 103.42, 107.05, 112.65, 117.25, 119.36, 120.84, 124.93, 128.62, 129.52, 132.06, 135.32, 138.56, 140.40, 142.30, 150.40, 151.58, 160.34; HRMS for $C_{21}H_{22}N_5O_3S$: calculated, 424.1443; found, 424.1450.

***tert*-Butyl 4-(3-(1*H*-pyrrole-2-carboxamido)phenyl)-2-(methylamino)-4,5-dihydro-1*H*-imidazole-1-carboxylate (14c).** ^{1}H NMR (DMSO-d_6) *δ* 1.45 (s, 9H, *t*-Bu), 2.83 (d, 3H, ^3J = 4.8 Hz, CH_3), 3.39 (dd, 1H, ^2J = 10.0 Hz, ^3J = 6.8 Hz, H_A from CH_2), 4.17 (t, 1H, *J* = 10.0 Hz, H_B from CH_2), 4.85 (dd, 1H, $^3J_1$ = 10.0 Hz, $^3J_2$ = 6.8 Hz, NCH), 6.15–6.17 (m, 1H, Pyrr-H), 6.77 (br s, 1H, NH), 6.95–6.98 (m, 2H, Pyrr-H, Ar-H-4'/6'), 7.07–7.09 (m, 1H, Pyrr-H), 7.27 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.58 (s, 1H, Ar-H-2'), 7.70–7.72 (m, 1H, Ar-H-4'/6'), 9.74 (s, 1H, NH), 11.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) *δ* 27.74 (C$\underline{C}H_3$), 29.08 (NCH_3), 54.48

(CH_2), 62.32 (NCH), 81.52 ($\underline{C}CH_3$), 108.85, 111.24, 117.63, 118.40, 121.05, 122.44, 126.05, 128.39, 139.36, 145.82, 151.58, 153.56, 159.08; HRMS for $C_{20}H_{26}N_5O_3$: calculated 384.2036; found 384.2035.

***tert*-Butyl 4-(3-(furan-2-carboxamido)phenyl)-2-(methylamino)-4,5-dihydro-1*H*-imidazole-1-carboxylate (15c).** ^{1}H NMR (DMSO-d_6) δ 1.45 (s, 9H, *t*-Bu), 2.83 (d, 3H, ^3J = 4.4 Hz, CH_3), 3.39 (dd, 1H, ^2J = 10.0 Hz, ^3J = 6.8 Hz, H_A from CH_2), 4.17 (t, 1H, J = 10.0 Hz, H_B from CH_2), 4.85 (dd, 1H, $^3J_1$ = 10.0 Hz, $^3J_2$ = 6.8 Hz, NCH), 6.70 (dd, 1H, ^3J = 3.6 Hz, ^3J = 1.6 Hz, Fur-H), 6.78 (br s, 1H, NH), 7.02 (d, 1H, ^3J = 8.0, Ar-H-4'/6'), 7.29 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.35 (dd, 1H, ^3J = 3.6 Hz, ^4J = 0.8 Hz, Fur-H), 7.62 (t, 1H, ^4J = 1.6 Hz, Ar-H-2'), 7.68–7.70 (m, 1H, Ar-H-4'/6'), 7.94 (dd, 1H, ^3J = 1.6 Hz, ^4J = 0.8 Hz, Fur-H), 10.17 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.73 ($C\underline{C}H_3$), 29.08 (NCH_3), 54.43 (CH_2), 62.24 (NCH), 81.54 ($\underline{C}CH_3$), 112.07, 114.57, 118.17, 118.84, 121.80, 128.47, 138.54, 145.68, 145.89, 147.48, 151.57, 153.59, 156.15; HRMS for $C_{20}H_{25}N_4O_4$: calculated 385.1876; found 385.1872.

***tert*-Butyl 4-(3-(1*H*-indole-2-carboxamido)phenyl)-2-(methylamino)-4,5-dihydro-1*H*-imidazole-1-carboxylate (16c).** ^{1}H NMR (DMSO-d_6) δ 1.45 (s, 9H, *t*-Bu), 2.85 (d, 3H, ^3J = 4.8 Hz, CH_3), 3.41 (dd, 1H, ^2J = 9.6 Hz, ^3J = 6.8 Hz, H_A from CH_2), 4.19 (t, 1H, J = 9.6 Hz, H_B from CH_2), 4.88 (dd, 1H, $^3J_1$ = 9.6 Hz, $^3J_2$ = 6.8 Hz, NCH), 6.80 (br s, 1H, NH), 7.03 (d, 1H, ^3J = 7.6 Hz, Ar-H), 7.06–7.10 (m, 1H, Ar-H), 7.21–7.25 (m, 1H, Ar-H), 7.32 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.44–7.48 (m, 2H, 2 × Ar-H), 7.67–7.69 (m, 2H, 2 × Ar-H), 7.77–7.80 (m, 1H, Ar-H-4'/6'), 10.22 (s, 1H, NH), 11.74 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.74 ($C\underline{C}H_3$), 29.10 (NCH_3), 54.47 (CH_2), 62.24 (NCH), 81.55 ($\underline{C}CH_3$), 103.80, 112.34, 117.86, 118.61, 119.86, 121.61, 121.72, 123.72, 127.02, 128.54, 131.47, 136.76, 138.99, 145.95, 151.57, 153.62, 159.64; HRMS for $C_{24}H_{28}N_5O_3$: calculated 434.2192; found 434.2183.

***tert*-Butyl 4-(3-(furan-2-carboxamido)phenyl)-2-(methylamino)-1*H*-imidazole-1-carboxylate (17c).** ^{1}H NMR (DMSO-d_6) δ 1.59 (s, 9H, *t*-Bu), 2.96 (d, 3H, ^3J = 4.8 Hz, CH_3), 6.71 (dd, 1H, $^3J_1$ = 3.6 Hz, $^3J_2$ = 1.6 Hz, Fur-H), 6.75 (q, 1H, ^3J = 4.8 Hz, NH), 7.30–7.34 (m, 2H, Ar-H-5, Ar-H-5'), 7.38 (dd, 1H, ^3J = 3.6 Hz, ^4J = 0.8 Hz, Fur-H), 7.50–7.52 (m, 1H, Ar-H-4'/6'), 7.71–7.74 (m, 1H, Ar-H-4'/6'), 7.95 (dd, 1H, ^3J = 1.6 Hz, ^4J = 0.8 Hz, Fur-H), 8.05 (t, 1H, ^4J = 2.0 Hz, Ar-H-2'), 10.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.53 ($C\underline{C}H_3$), 29.41 (NCH_3), 84.58 ($\underline{C}CH_3$), 106.48, 112.08, 114.58, 116.78, 119.10, 120.32, 128.61, 133.79, 137.11, 138.62, 145.73, 147.47, 148.93, 151.38, 156.21; HRMS for $C_{20}H_{23}N_4O_4$: calculated 383.1719; found 383.1713.

***tert*-Butyl 4-(3-(1*H*-indole-2-carboxamido)phenyl)-2-(methylamino)-1*H*-imidazole-1-carboxylate (18c).** ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 9H, *t*-Bu), 2.97 (d, 3H, ^3J = 4.8 Hz, CH_3), 6.77 (q, 1H, ^3J = 4.8 Hz, NH), 7.08 (dt, 1H, ^3J = 8.0 Hz, ^4J = 1.2 Hz, Indol-H), 7.23 (dt, 1H, ^3J = 8.0 Hz, ^4J = 1.2 Hz, Indol-H), 7.33–7.37 (m, 2H, Ar-H-5, Ar-H-5'), 7.46–7.53 (m, 3H, 2 × Indol-H, Ar-H-4'/6'), 7.69 (d, 1H, ^3J = 8.0 Hz, Indol-H), 7.82–7.84 (m, 1H, Ar-H-4'/6'), 8.11 (t, 1H, ^4J = 2.0 Hz, Ar-H-2'), 10.28 (s, 1H, NH), 11.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.53 (C$\underline{C}H_3$), 29.42 (NCH_3), 84.58 ($\underline{C}CH_3$), 103.85, 106.50, 112.34, 116.54, 118.86, 119.86, 120.09, 121.74, 123.73, 127.05, 128.67, 131.48, 133.83, 136.77, 137.16, 139.08, 148.94, 151.41, 159.71; HRMS for $C_{24}H_{26}N_5O_3$: calculated 432.2036; found 432.2022.

4-(3-(1*H*-Pyrrole-2-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (19c). ^{1}H NMR (DMSO-d_6) δ 6.17–6.19 (m, 1H, Pyrr-H), 6.97–6.99 (m, 1H, Pyrr-H), 7.09–7.11 (m, 1H, Pyrr-H), 7.28 (s, 1H, Ar-H-5), 7.34 (d, 1H, ^3J = 8.0 Hz, Ar-H-4'/6'), 7.41 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.48 (s, 2H, NH_2), 7.67 (d, 1H, ^3J = 8.0 Hz, Ar-H-4'/6'), 8.03 (s, 1H, Ar-H-2'), 10.04 (s, 1H, NH), 11.80 (s, 1H, NH), 12.18 (br s, 1H, NH), 12.87 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 108.95, 109.32, 111.86, 116.11, 119.22, 120.00, 122.65, 125.86, 126.48, 128.01, 129.20, 139.83, 147.77, 159.12; HRMS for $C_{14}H_{14}N_5O$: calculated 268.1198; found 268.1193.

4-(3-(1*H*-Pyrrole-3-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (20c). ^{1}H NMR (DMSO-d_6) δ 6.66–6.68 (m, 1H, Pyrr-H), 6.83–6.85 (m, 1H, Pyrr-H), 7.29–7.32 (m, 2H, 2 × Ar-H), 7.38 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.45 (br s, 2H, NH_2), 7.57–7.59 (m, 2H, 2 × Ar-H), 8.09 (t, 1H, ^4J = 2.0 Hz, Ar-H-2'), 9.68 (s, 1H, NH), 11.38 (s, 1H, NH), 12.13 (s, 1H, NH), 12.77 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 107.77, 109.24, 116.03, 118.82, 118.87, 119.31, 119.89, 121.53, 126.55, 127.89, 129.08, 140.24, 147.74, 162.90 (CO); HRMS for $C_{14}H_{14}N_5O$: calculated 268.1198; found 268.1201.

(*R*)-2-Amino-4-(3-(pyrrolidin-1-ium-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (21c). ^{1}H NMR (DMSO-d_6) δ 1.92–2.02 (m, 3H, H_A from CHC$\underline{H_2}$, CH_2), 2.42–2.51 (m, 1H, H_B from CHC$\underline{H_2}$), 3.23–3.32 (m, 2H, NCH_2), 4.43–4.46 (m, 1H, CH), 7.28 (s, 1H, ArH-5), 7.40–7.46 (m, 2H, Ar-H-4'/6', Ar-H-5'), 7.50 (s, 2H, NH_2), 7.57–7.60 (m, 1H, Ar-H-4'/6'), 7.85 (s, 1H, Ar-H-2'), 8.69 (br s, 1H, NH), 10.19 (br s, 1H, NH), 11.15 (s, 1H, NH), 12.25 (br s, 1H, NH), 12.97 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.57 (CH_2), 29.72 (CH_2), 45.62 (CH_2), 59.46 (CH_2), 109.60, 115.46, 119.48, 120.34, 126.08, 128.42, 129.60, 138.68, 147.89, 167.05 (C=O); HRMS for $C_{14}H_{18}N_5O$: calculated 272.1511; found 272.1513.

4-(3-(1*H*-Indole-2-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (22c). ^{1}H NMR (DMSO-d_6) δ 7.08 (dt, 1H, ^3J = 7.2 Hz, ^4J = 0.9 Hz, Ar-H), 7.24 (dt, 1H, ^3J = 8.1 Hz, ^4J = 0.9 Hz, Ar-H), 7.31 (s, 1H, ArH-5), 7.38–7.50 (m, 6H, NH_2, 4 × Ar-H), 7.67–7.72 (m, 2H, Ar-H), 8.09 (s, 1H, Ar-H-2'), 10.43 (s, 1H, NH), 11.81 (s, 1H, NH), 12.13 (br s, 1H, NH), 12.82 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 104.39, 109.47, 112.39, 116.46, 119.81, 119.94, 120.32, 121.77, 123.87, 126.39, 129.95, 128.15, 129.33, 131.27, 136.84, 139.40, 147.81, 159.76; HRMS for $C_{18}H_{16}N_5O$: calculated 318.1355; found 318.1344.

4-(3-(1*H*-Indole-3-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (23c). ^{1}H NMR (DMSO-d_6) δ 7.13–7.23 (m, 2 H, 2 × Ar-H), 7.30–7.50 (m, 6H, NH_2, 4 × Ar-H), 7.60 (d, 1H, ^3J = 8.0 Hz, Ar-H), 8.17 (s, 1H, ArH-2'), 8.21 (d, 1H, ^3J = 7.6 Hz, Ar-H), 8.43 (d, 1H, ^4J = 3.2 Hz, Ar-H), 9.95 (s, 1H, NH), 11.86 (br s, 1H, NH), 12.16 (br s, 1H, NH), 12.79 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 109.35, 110.12, 112.01, 115.87, 118.88, 119.75, 120.72, 120.97, 122.15, 126.40, 126.63, 127.97, 129.02, 129.15, 136.21, 140.33, 147.73, 163.37; HRMS for $C_{18}H_{16}N_5O$: calculated 318.1355; found 318.1357.

2-Amino-4-(3-(5-methoxy-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**24c**). ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H, OCH_3), 6.89 (dd, 1H, ^3J = 9.2 Hz, ^4J = 2.4 Hz, Ar-H), 7.15 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.33 (s, 1H, Ar-H), 7.37–7.49 (m, 6H, 4 × Ar-H, NH_2), 7.69–7.72 (m, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 10.42 (s, 1H, NH), 11.70 (s, 1H, NH), 12.16 (s, 1H, NH), 12.85 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.25 (OCH_3), 102.02, 104.14, 109.43, 113.23, 115.19, 116.46, 119.74, 120.33, 126.39, 127.26, 128.12, 129.30, 131.54, 132.16, 139.45, 147.82, 153.84, 159.72; HRMS for $C_{19}H_{18}N_5O_2$: calculated, 348.1461; found, 348.1459.

2-Amino-4-(3-(5-(benzyloxy)-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**25c**). ^{1}H NMR (DMSO-d_6) δ 5.13 (s, 2H, OCH_2), 6.98 (dd, 1H, ^3J = 9.2 Hz, ^4J = 2.4 Hz, Ar-H), 7.26 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.32–7.51 (m, 12H, 10 × Ar-H, NH_2), 7.67–7.69 (m, 1H, Ar-H), 8.08 (t, 1H, ^4J = 2.0 Hz, Ar-H), 10.37 (s, 1H, NH), 11.69 (s, 1H, NH), 12.12 (s, 1H, NH), 12.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 69.61 (OCH_2), 103.67, 103.92, 109.59, 113.27, 115.69, 116.50, 119.85, 120.33, 126.49, 127.23, 127.68, 128.15, 128.37, 129.34, 131.59, 132.31, 137.52, 139.38, 147.74, 152.85, 159.72 (signals for two C atoms overlap); HRMS for $C_{25}H_{22}N_5O_2$: calculated, 424.1774; found, 424.1771.

2-Amino-4-(3-(5-hydroxy-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**26c**). ^{1}H NMR (DMSO-d_6) δ 6.79 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz, Ar-H), 6.94 (d, 1H, ^4J = 2.0 Hz, Ar-H), 7.26–7.48 (m, 7H, 5 × Ar-H, NH_2), 7.67–7.69 (m, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 8.91 (s, 1H, OH), 10.32 (s, 1H, NH), 11.52 (s, 1H, NH), 12.12 (s, 1H, NH), 12.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 103.40, 104.34, 109.51, 112.89, 115.22, 116.39, 119.73, 120.24, 126.46, 127.65, 128.12, 129.31, 131.35, 131.66, 139.48, 147.77, 151.26, 159.82; HRMS for $C_{18}H_{16}N_5O_2$: calculated, 334.1304; found, 334.1296.

2-Amino-4-(3-(5-(trifluoromethoxy)-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**27c**). ^{1}H NMR (DMSO-d_6) δ 7.22–7.25 (m, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.41–7.58 (m, 6H, 4 × Ar-H, NH_2), 7.68–7.71 (m, 1H, Ar-H), 7.74 (s, 1H, Ar-H), 8.07 (t, 1H, ^{4}J = 1.6 Hz, Ar-H), 10.55 (s, 1H, NH), 12.11 (s, 1H, NH), 12.13 (s, 1H, NH), 12.81 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 104.71, 109.50, 113.67, 113.95, 116.58, 117.75, 120.00, 120.40 (q, 1C, $^{1}J_{C\text{-}F}$ = 253 Hz, CF_3), 120.44, 126.34, 126.92, 128.18, 129.35, 133.36, 135.21, 139.21, 142.21, 147.83, 159.34; ^{19}F NMR (DMSO-d_6) δ −56.93 (s, 3F, CF_3); HRMS for $C_{19}H_{15}N_5O_2F_3$: calculated, 402.1178; found, 402.1171.

2-Amino-4-(3-(5-fluoro-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**28c**). ^{1}H NMR (DMSO-d_6) δ 7.11 (dt, 1H, ^{3}J = 9.2 Hz, ^{4}J = 2.0 Hz, Ar-H), 7.33 (s, 1H, Ar-H), 7.40–7.50 (m, 7H, 5 × Ar-H, NH_2), 7.69–7.71 (m, 1H, Ar-H), 8.08 (t, 1H, ^{4}J = 1.6 Hz, Ar-H), 10.49 (s, 1H, NH), 11.95 (s, 1H, NH), 12.14 (s, 1H, NH), 12.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 104.34 (d, 1C, $^{4}J_{C\text{-}F}$ = 5 Hz), 105.89 (d, 1C, $^{2}J_{C\text{-}F}$ = 23 Hz), 109.51, 112.65 (d, 1C, $^{2}J_{C\text{-}F}$ = 26 Hz), 113.63 (d, 1C, $^{3}J_{C\text{-}F}$ = 9 Hz), 116.52, 119.93, 120.39, 126.37, 127.00 (d, 1C, $^{3}J_{C\text{-}F}$ = 9 Hz), 128.17, 129.35, 132.96, 133.57, 139.28, 147.81, 157.20 (d, 1C, $^{1}J_{C\text{-}F}$ = 231 Hz), 159.47; ^{19}F NMR (DMSO-d_6) δ −123.59 (s, 1F); HRMS for $C_{18}H_{15}N_5OF$: calculated, 336.1261; found, 336.1264.

2-Amino-4-(3-(5-chloro-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**29c**). ^{1}H NMR (DMSO-d_6) δ 7.25 (dd, 1H, ^{3}J = 8.8 Hz, ^{4}J = 2.0 Hz, Ar-H), 7.33 (s, 1H, Ar-H), 7.40–7.51 (m, 6H, 4 × Ar-H, NH_2), 7.69–7.71 (m, 1H, Ar-H), 7.79 (d, 1H, ^{4}J = 2.0 Hz, Ar-H), 8.07 (s, 1H, Ar-H), 10.53 (s, 1H, NH), 12.05 (s, 1H, NH), 12.14 (s, 1H, NH), 12.84 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 103.87, 109.52, 114.01, 116.53, 119.98, 120.40, 120.82, 123.98, 124.42, 126.37, 127.98, 128.18, 129.36, 132.75, 135.21, 139.23, 147.80, 159.41; HRMS for $C_{18}H_{15}N_5OCl$: calculated, 352.0965; found, 352.0959.

4-(3-(4*H*-Thieno[3,2-*b*]pyrrole-5-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (**30c**). ^{1}H NMR (DMSO-d_6) δ 7.03 (dd, 1H, ^{3}J = 5.2 Hz, ^{4}J = 0.8 Hz, Ar-H), 7.31 (s, 1H, Ar-H), 7.36–7.49 (m, 6H, 4 × Ar-H, NH_2), 7.66–7.69 (m, 1H, Ar-H), 8.06 (t, 1H, ^{4}J = 1.6 Hz, Ar-H), 10.24 (s, 1H, NH), 11.99 (s, 1H, NH), 12.14 (s, 1H, NH), 12.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 103.91, 109.43, 111.90, 116.27, 119.48, 120.15, 122.94, 126.45, 128.08, 128.28, 129.26, 130.49, 139.64, 141.32, 147.77, 159.41; HRMS for $C_{16}H_{14}N_5OS$: calculated, 324.0919; found, 324.0911.

4-(3-(1*H*-Pyrrole-2-carboxamido)phenyl)-2-(methylamino)-4,5-dihydro-1*H*-imidazol-3-ium chloride (31c). ^{1}H NMR (DMSO-d_6) *δ* 2.86 (d, 3H, ^{3}J = 4.8 Hz, CH_3), 3.43 (m, 1H, H_A from CH_2, overlaping with the peak for water), 4.07 (br t, 1H, *J* = 9.0 Hz, H_B from CH_2), 5.09

(br t, 1H, ^3J = 9.0 Hz, NCH), 6.16–6.18 (m, 1H, Pyrr-H), 6.97–6.99 (m, 1H, Pyrr-H), 7.05–7.10 (m, 2H, Pyrr-H, Ar-H-4'/6'), 7.37 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.78 (d, 1H, ^3J = 8.0 Hz, Ar-H-4'/6'), 7.85 (s, 1H, Ar-H-2'), 8.01 (br s, ½H, NH), 8.35–8.41 (m, 1H, N$\underline{H}$CH$_3$), 8.61 (br s, ½H, NH), 8.65 (br s, ½H, NH), 9.08 (br s, ½H, NH), 9.98 (s, 1H, NH), 11.77 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.91 (NCH$_3$), 50.96 (CH$_2$), 57.93 (NCH), 108.91, 111.92, 117.32, 119.52, 120.89, 122.54, 125.96, 128.97, 140.01, 141.13, 159.10, 159.52; HRMS for $C_{15}H_{18}N_5O$: calculated 284.1511; found 284.1515.

4-(3-(Furan-2-carboxamido)phenyl)-2-(methylamino)-4,5-dihydro-1*H*-imidazol-3-ium chloride (32c). ^{1}H NMR (DMSO-d_6) δ 2.86 (d, 3H, ^3J = 4.8 Hz, CH$_3$), 3.41 (m, 1H, H$_A$ from CH$_2$, overlaping with the peak for water), 4.07 (br t, 1H, J = 8.4 Hz, H$_B$ from CH$_2$), 5.10 (br t, 1H, ^3J = 8.4 Hz, NCH), 6.72 (dd, 1H, ^3J = 3.6 Hz, ^3J = 1.6 Hz, Fur-H), 7.11 (d, 1H, ^3J = 7.6 Hz, Ar-H-4'/6'), 7.37–7.41 (m, 2H, Ar-H-5', Fur-H), 7.75 (d, 1H, ^3J = 7.6 Hz, Ar-H-4'/6'), 7.86 (s, 1H, Ar-H-2'), 7.95 (dd, 1H, ^3J = 1.6 Hz, ^4J = 0.8 Hz, Fur-H), 8.01 (br s, ½H, NH), 8.36–8.39 (m, 1H, N$\underline{H}$CH$_3$), 8.60 (br s, ½H, NH), 8.66 (br s, ½H, NH), 9.08 (br s, ½H, NH), 10.34 (s, 1H, NH; ^{13}C NMR (DMSO-d_6) δ 28.91 (NCH$_3$), 50.96 (CH$_2$), 57.86 (NCH), 112.12, 114.93, 117.93, 120.05, 121.69, 129.05, 139.11, 141.22, 145.85, 147.29, 156.27, 159.53; HRMS for $C_{15}H_{17}N_4O_2$: calculated 285.1352; found 285.1353.

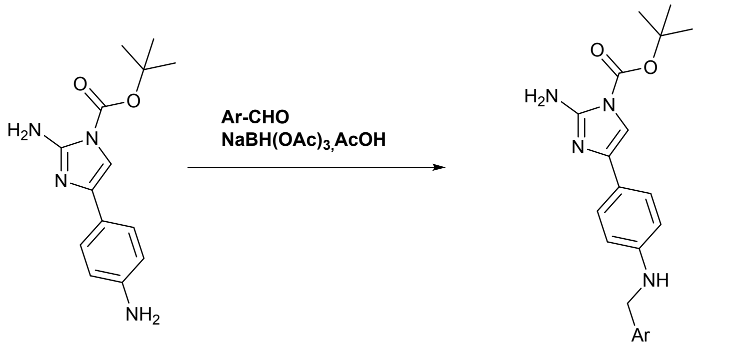
4-(3-(1*H*-Indole-2-carboxamido)phenyl)-2-(methylamino)-4,5-dihydro-1*H*-imidazol-3-ium chloride (33c). ^{1}H NMR (DMSO-d_6) δ 2.87 (d, 3H, ^3J = 5.2 Hz, CH$_3$), 3.41 (m, 1H, H$_A$ from CH$_2$, overlaping with the peak for water), 4.09 (br t, 1H, J = 8.6 Hz, H$_B$ from CH$_2$), 5.12 (br t, 1H, ^3J = 8.6 Hz, NCH), 7.06–7.13 (m, 2H, 2 × Ar-H), 7.22–7.26 (m, 1H, Ar-H), 7.42 (t, 1H, ^3J = 8.0 Hz, Ar-H-5'), 7.47–7.49 (m, 2H, 2 × Ar-H), 7.68 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.85 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.91 (s, 1H, Ar-H), 8.03 (br s, ½H, NH), 8.37–8.41 (m, 1H, N$\underline{H}$CH$_3$), 8.63 (br s, ½H, NH), 8.68 (br s, ½H, NH), 9.11 (br s, ½H, NH), 10.44 (s, 1H, NH), 11.85 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.93 (NCH$_3$), 50.98 (CH$_2$), 57.89 (NCH), 104.42, 112.35, 117.62, 119.80, 119.91, 121.47, 121.74, 123.84, 126.94, 129.11, 131.35, 136.80, 139.59, 141.30, 159.54, 159.72; HRMS for $C_{19}H_{20}N_5O$: calculated 334.1668; found 334.1658.

4-(3-(1*H*-Indole-2-carboxamido)phenyl)-2-(methylamino)-1*H*-imidazol-3-ium chloride (34c). ^{1}H NMR (DMSO-d_6) δ 2.95 (d, 3H, ^3J = 4.8 Hz, CH$_3$), 7.09 (dt, 1H, ^3J = 6.8 Hz, ^4J = 1.2 Hz, Indol-H), 7.24 (dt, 1H, ^3J = 6.8 Hz, ^4J = 1.2 Hz, Indol-H), 7.43–7.50 (m, 5H, 5 × Ar-H), 7.68–7.72 (m, 2H, 2 × Ar-H), 7.84 (q, 1H, ^3J = 4.8 Hz, NH), 8.11 (t, 1H, ^4J = 2.0 Hz, Ar-H-2'), 10.44 (s, 1H, NH), 11.82 (s, 1H, NH), 12.40 (br s, 1H, NH), 12.62 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 30.07 (CH$_3$), 105.00, 110.20, 112.88, 117.28, 120.42, 120.67, 120.87, 122.25, 124.35, 127.43, 127.45, 128.69, 129.72, 131.80, 137.33, 139.87, 149.08, 160.25; HRMS for $C_{19}H_{18}N_5O$: calculated 332.1511; found 332.1499.

***N*-(3-(2-Amino-1-benzyl-1*H*-imidazol-4-yl)phenyl)-1*H*-pyrrole-2-carboxamide** (**35c**). ^{1}H NMR (DMSO-d_6) δ 5.02 (s, 2H, CH_2), 5.69 (s, 2H, NH_2), 6.15–6.18 (m, 1H, Ar-H), 6.95–6.98 (m, 1H, Ar-H), 7.03 (s, 1H, Ar-H), 7.08–7.12 (m, 1H, Ar-H), 7.21 (t, 1H, ^3J = 7.8 Hz, Ar-H), 7.26–7.32 (m, 4H, 4 × Ar-H), 7.35–7.40 (m, 2H, 2 × Ar-H), 7.54–7.58 (m, 1H, Ar-H), 7.94–7.97 (m, 1H, Ar-H), 9.70 (s, 1H, NH) 11.60 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 47.20, 108.84, 110.73, 111.29, 115.37, 117.14, 118.45, 122.30, 126.18, 127.35, 127.44, 128.34, 128.52, 135.40, 135.49, 137.76, 139.34, 149.52, 158.99; HRMS for $C_{21}H_{20}N_5O$: calculated, 358.1668; found, 358.1661.

4-(3-(((1*H*-Pyrrol-2-yl)methyl)amino)phenyl)-1-benzyl-1*H*-imidazol-2-amine (**36c**). ^{1}H NMR (DMSO-d_6) δ 4.14 (d, 2H, ^3J = 5.5 Hz, CH_2) 4.97 (s, 2H, CH_2), 5.56–5.62 (m, 3H, NH, NH_2), 5.91–5.96 (m, 2H, 2 × Ar-H), 6.40–6.44 (m, 1H, Ar-H), 6.62–6.65 (m, 1H, Ar-H), 6.80–6.84 (m, 1H, Ar-H), 6.93–6.98 (m, 3H, 3 × Ar-H), 7.23–7.31 (m, 3H, 3 × Ar-H), 7.33–7.39 (m, 2H, 2 × Ar-H), 10.70 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 40.44, 47.12, 105.71, 107.11, 107.66, 110.20, 110.33, 112.09, 116.70, 127.27, 127.32, 128.47 (2 signals overlapped), 128.68, 135.62, 136.30, 137.90, 148.70, 149.29; HRMS for $C_{21}H_{22}N_5$: calculated, 344.1875; found, 344.1873.

***tert*-Butyl 4-(4-(1*H*-pyrrole-2-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (37c).** ^{1}H NMR (DMSO-d_6) *δ* 1.59 (s, 9H, *t*-Bu), 6.16–6.18 (m, 1H, Pyrr-H), 6.56 (br s, 2H, NH_2), 6.59–6.60 (m, 1H, Pyrr-H), 7.07 (s, 1H, Pyrr-H), 7.28 (s, 1H, Ar-H-5), 7.67 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 7.72 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 9.76 (s, 1H, NH), 11.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) *δ* 27.53 (C<u>C</u>H$_3$), 84.51 (<u>C</u>CH$_3$), 105.29, 108.87, 111.25, 119.70, 122.51, 124.89, 126.04, 128.19, 136.85, 138.18, 148.93, 150.34, 158.99; HRMS for $C_{19}H_{22}N_5O_3$: calculated 368.1723; found 368.1734.



38c (Ar = pyrrol-2-yl)
39c (Ar = imidazol-4-yl)

To a suspension of *tert*-butyl 2-amino-4-(4-aminophenyl)-1*H*-imidazole-1-carboxylate (**I**) (190 mg, 0.69 mmol) in dichloromethane (30 mL) were added pyrrole-2-carboxaldehyde (208 mg, 1.04 mmol) and glacial acetic acid (40 µL, 0.69 mmol). The mixture became clear, whereupon $NaBH(OAc)_3$ (208 mg, 1.04 mmol) was added and the mixture was stirred at room temperature for 13 h. The solution was diluted with dichloromethane (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 30 mL) and brine (1 × 30 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Crude product was purified with column chromatography (eluent: dichloromethane/MeOH = 9:1 + NH_3) to give **38c** (114 mg; 47% yield) as an orange solid.

***tert*-Butyl 4-(4-(((1*H*-pyrrol-2-yl)methyl)amino)phenyl)-2-amino-1*H*-imidazole-1-carboxylate** (**38c**). Yield, 47%; orange solid; mp 160–163 °C; IR (KBr) ν = 3396, 3282, 3126, 2974, 1740, 1639, 1616, 1593, 1512, 1458, 1394, 1373, 1359, 1320, 1296, 1270, 1212, 1180, 1160, 1125, 1094, 1074, 1025, 937, 885, 849, 834, 770, 737, 719, 696, 599, 558, 514 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.57 (s, 9H, *t*-Bu), 4.14 (d, 2H, ^3J = 5.2 Hz, CH_2), 5.86–5.88 (m, 1H, NH), 5.92–5.97 (m, 2H, 2×Ar-H), 6.52 (s, 2H, NH_2), 6.61–6.66 (m, 3H, 3×Ar-H), 7.03 (s, 1H, Ar-H), 7.43 (d, 2H, ^3J = 8.8 Hz, Ar-H), 10.72 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.54, 83.79, 102.96, 105.86, 107.15, 112.11, 125.49, 129.42, 129.89, 136.26, 140.22, 140.76, 150.01, 159.91, 161.88; MS (ESI) *m*/*z* (%) = 354.2 (MH^+, 100). HRMS for $C_{19}H_{24}N_5O_2$: calculated 354.1930; found 354.1921. HPLC: Phenomenex Luna 5 µm C18 column (4.6 mm × 150 mm); mobile phase: 10–90% of MeOH in TFA (0.1%) in 20 min; flow rate 1.0 mL/min; injection volume: 10 µL; retention time: 14.879 min (95.4% at 254 nm).

***tert*-Butyl 4-(4-(((1*H*-imidazol-4-yl)methyl)amino)phenyl)-2-amino-1*H*-imidazole-1-carboxylate** (**39c**). Yield, 22%; orange solid; mp 170–172 °C; IR (KBr) ν = 3380, 2978, 1735, 1615, 1516, 1356, 1292, 1257, 1158, 1118, 1011, 936, 828, 772, 738, 698, 659, 621 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.57 (s, 9H, *t*-Bu), 4.14 (d, 2H, ^3J = 5.2 Hz, CH_2), 5.88–5.91 (m, 1H, NH), 6.52 (s, 2H, NH_2), 6.61 (d, 2H, ^3J = 8.8 Hz, 2×Ar-H), 6.93 (s, 1H, Ar-H), 7.03 (s, 1H, Ar-H), 7.43 (d, 2H, ^3J = 8.8 Hz, Ar-H), 7.57 (s, 1H, Ar-H), 11.90 (br s, 1H, NH); MS (ESI) *m*/*z* (%) = 355.2 (MH^+, 100). HRMS for $C_{18}H_{23}N_6O_2$: calculated 355.1882; found 355.1890. HPLC: Phenomenex Luna 5 µm C18 column (4.6 mm × 150 mm); mobile phase: 10–90% of MeOH in TFA (0.1%) in 20 min; flow rate 1.0 mL/min; injection volume: 10 µL; retention time: 19.623 min (97.3% at 254 nm).

***tert*-Butyl (*S*)-2-amino-4-(4-(1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (40c).** ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9H, *t*-Bu), 1.58 (s, 9H, *t*-Bu), 1.74–2.27 (m, 4H, CH_2CH_2), 3.28–3.47 (m, 2H, NCH_2), 4.17–4.27 (m, 1H, COCHN), 6.56 (br s, 2H, NH_2), 7.25 (s, 1H, Ar-H-5), 7.57 (d, 2H, ^3J = 7.7 Hz, Ar-H-2',6'/3',5'), 7.66 (d, 2H, ^3J = 7.7 Hz, Ar-H-2',6'/3',5'), 9.96 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.36 and 23.94 (*cis* and *trans*), 27.51, 27.91 and 28.12 (*cis* and *trans*), 30.18 and 30.97 (*cis* and *trans*), 46.53 and 46.71 (*cis* and *trans*), 59.98 and 60.35 (*cis* and *trans*), 78.44 and 78.63 (*cis* and *trans*), 84.52, 105.36, 119.11, 125.01, 128.46, 136.76, 137.88, 148.93, 150.34, 153.12, 171.37; HRMS for $C_{24}H_{34}N_5O_5$: calculated 472.2560; found 472.2568.

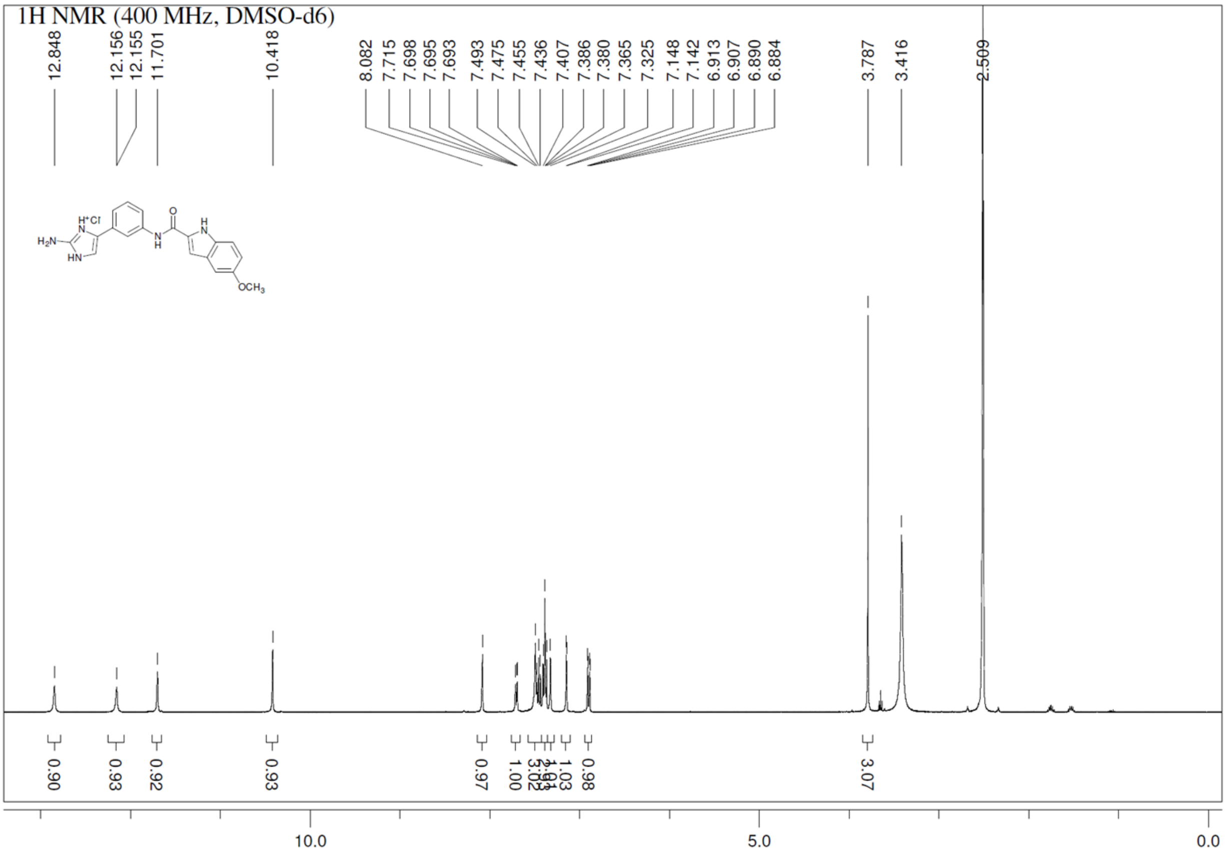
***tert*-Butyl (*R*)-2-amino-4-(4-(1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)phenyl)-1*H*-imidazole-1-carboxylate (41c).** ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9H, *t*-Bu), 1.58 (s, 9H, *t*-Bu), 1.75–1.95 (m, 4H, CH_2CH_2), 3.24–3.46 (m, 2H, NCH_2), 4.19–4.25 (m, 1H, COCHN), 6.55 (br s, 2H, NH_2), 7.25 (s, 1H, Ar-H-5), 7.57 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 7.67 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 9.96 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.36 and 23.94 (*cis* and *trans*), 27.51, 27.91 and 28.12 (*cis* and *trans*), 30.18 and 30.97 (*cis* and *trans*), 46.53 and 46.71 (*cis* and *trans*), 59.98 and 60.35 (*cis* and *trans*), 78.44 and 78.63 (*cis* and *trans*), 84.52, 105.36, 119.11, 125.01, 128.46, 136.76, 137.88, 148.93, 150.34, 153.12, 171.37; HRMS for $C_{24}H_{34}N_5O_5$: calculated 472.2560; found 472.2569.

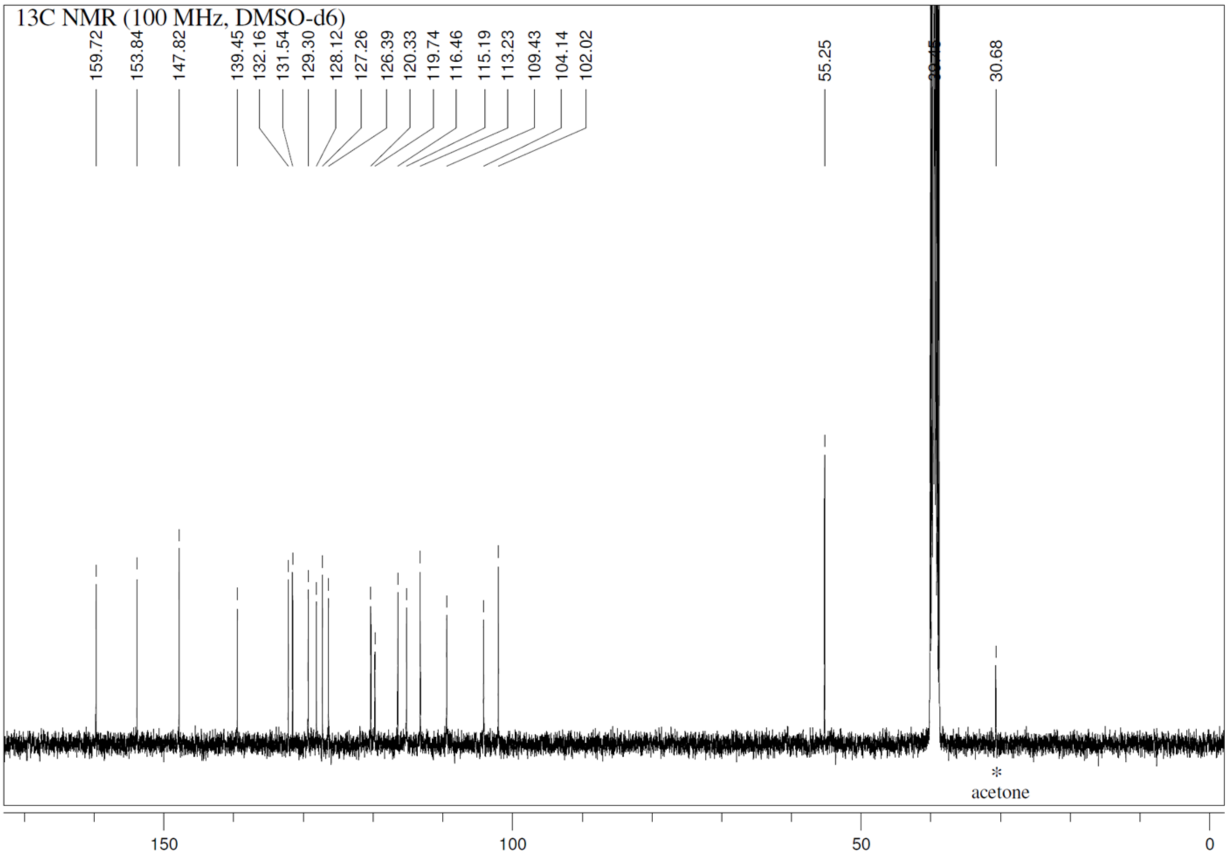
***tert*-Butyl 4-(4-(1*H*-indole-2-carboxamido)phenyl)-2-amino-1*H*-imidazole-1-carboxylate (42c).** ^{1}H NMR (DMSO-d_6) δ 1.59 (s, 9H, *t*-Bu), 6.58 (br s, 2H, NH_2), 7.07 (t, 1H, ^3J = 7.2 Hz, Ar-H), 7.23 (t, 1H, ^3J = 7.5 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.42–4.79 (m, 2H, 2 × Ar-H), 7.68 (d, 1H, ^3J = 7.8 Hz, Ar-H), 7.72 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 7.80 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 10.20 (s, 1H, NH), 11.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.53 ($C\underline{C}H_3$), 84.55 ($\underline{C}CH_3$), 103.79, 105.51, 112.36, 119.90, 119.96, 121.71, 123.74, 124.35, 124.98, 127.00, 128.75, 131.47, 136.78, 137.77, 148.93, 150.38, 159.55; HRMS for $C_{23}H_{24}N_5O_3$: calculated 418.1879; found 418.1875.

4-(4-(1*H*-Pyrrole-2-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (43c). ^{1}H NMR (DMSO-d_6) δ 6.16–6.19 (m, 1H, Pyrr-H), 6.98 (br s, 2H, NH_2), 7.08 (s, 1H, Pyrr-H), 7.29 (s, 1H, Pyrr-H), 7.41 (s, 1H, Ar-H-5), 7.61 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 7.84 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 9.94 (s, 1H, NH), 11.73 (s, 1H, NH), 12.02 (s, 1H, NH), 12.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 108.44, 108.96, 111.73, 119.88, 122.24, 122.73, 124.60, 125.89, 126.45, 139.20, 147.46, 159.08; MS (ESI) m/z = 268 $[M\text{-}Cl]^+$. HRMS for $C_{14}H_{14}N_5O$: calculated 268.1198; found 268.1194.

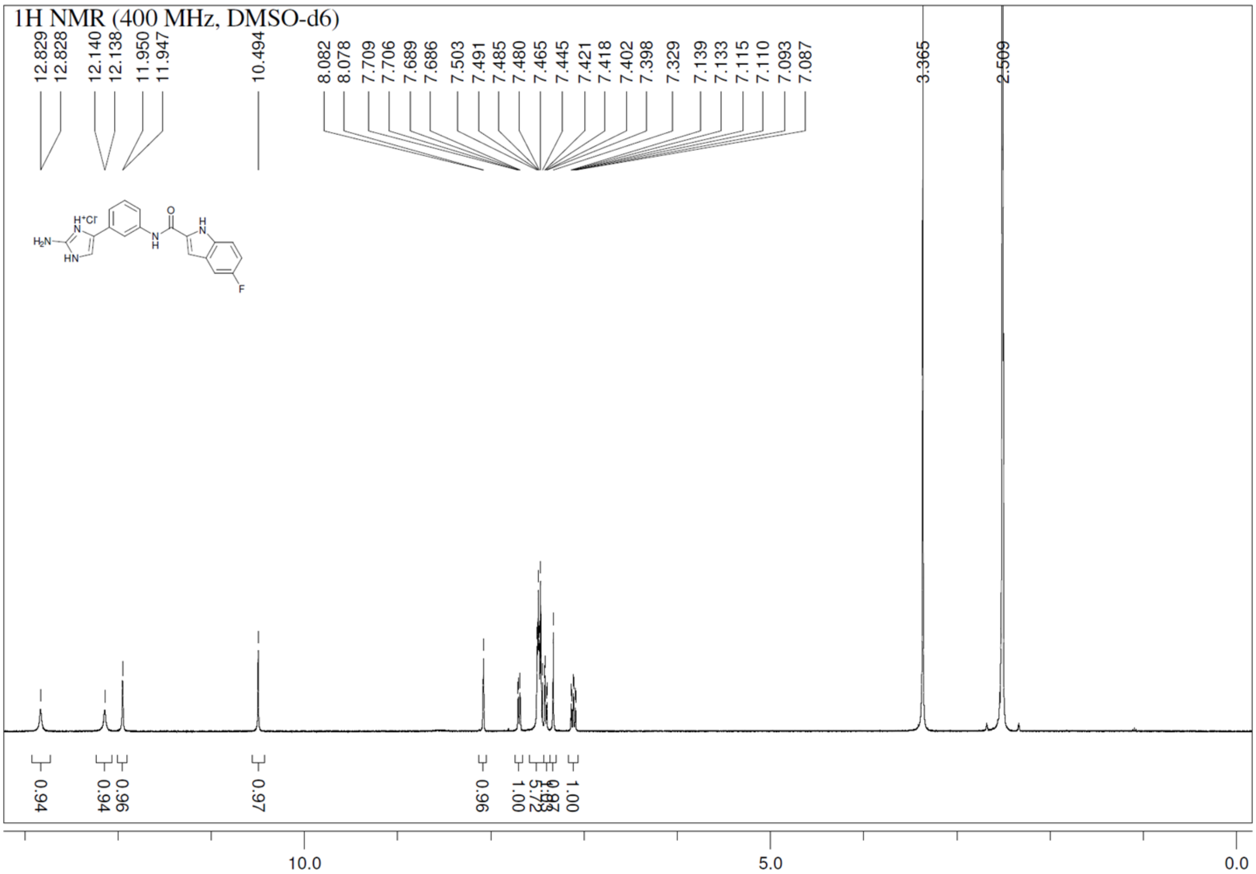
(*S*)-2-Amino-4-(4-(pyrrolidin-1-ium-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (44c). ^{1}H NMR (DMSO-d_6) δ 1.93–2.01 (m, 4H, CH_2CH_2), 3.25–3.31 (m, 2H, NCH_2), 4.36–4.44 (m, 1H, COCHN), 7.34 (br s, 2H, NH_2), 7.43 (s, 1H, Ar-H-5), 7.65 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 7.70 (d, 2H, ^3J = 8.7 Hz, Ar-H-2',6'/3',5'), 8.67 (s, 1H, NH), 9.81 (s, 1H, NH), 10.99 (s, 1H, NH), 12.07 (s, 1H, NH), 12.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.59, 29.65, 45.69, 59.59, 108.92, 119.65, 123.49, 124.83, 126.08, 137.82, 147.58, 166.93; HRMS for $C_{14}H_{19}N_5O$: calculated 272.1511; found 272.1520.

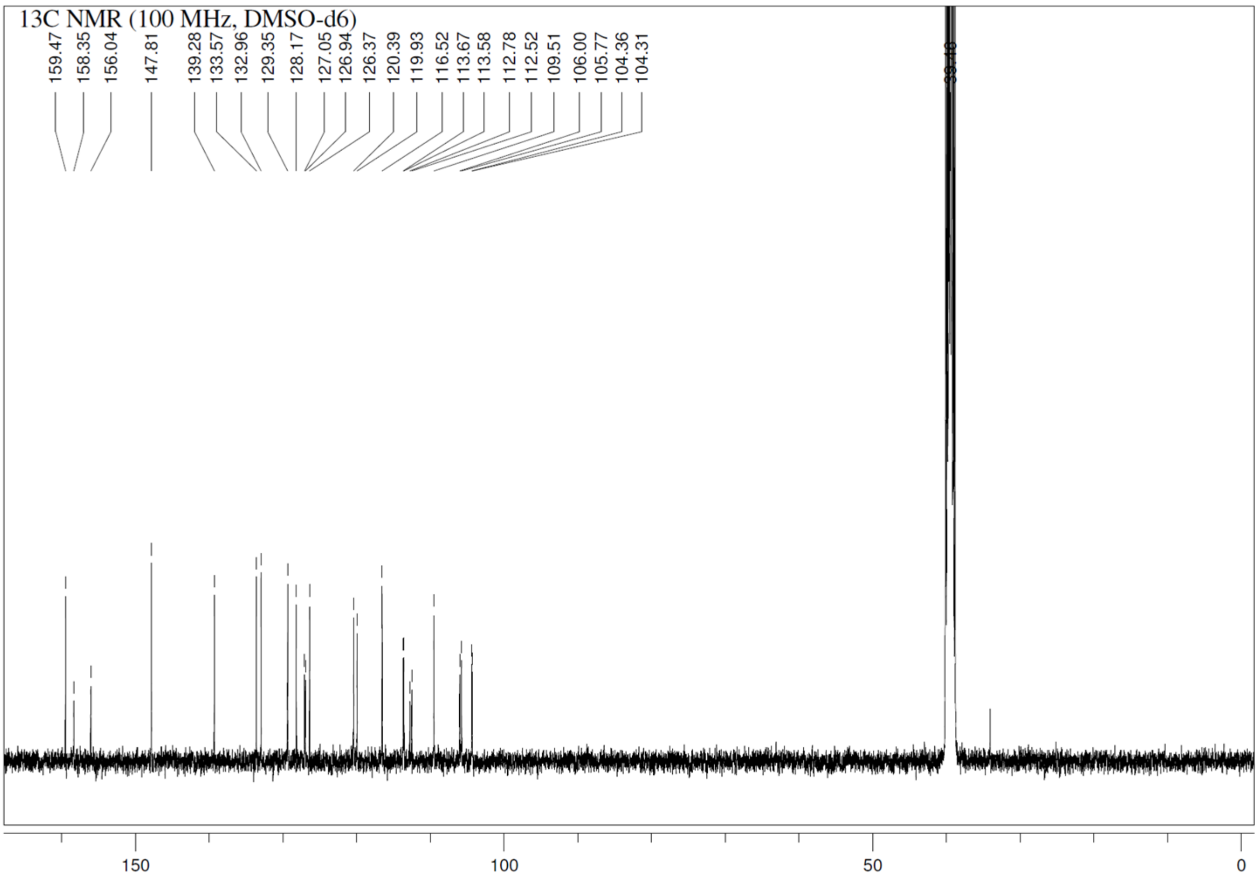
2-Amino-4-(3-(5-methoxy-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**24c**)



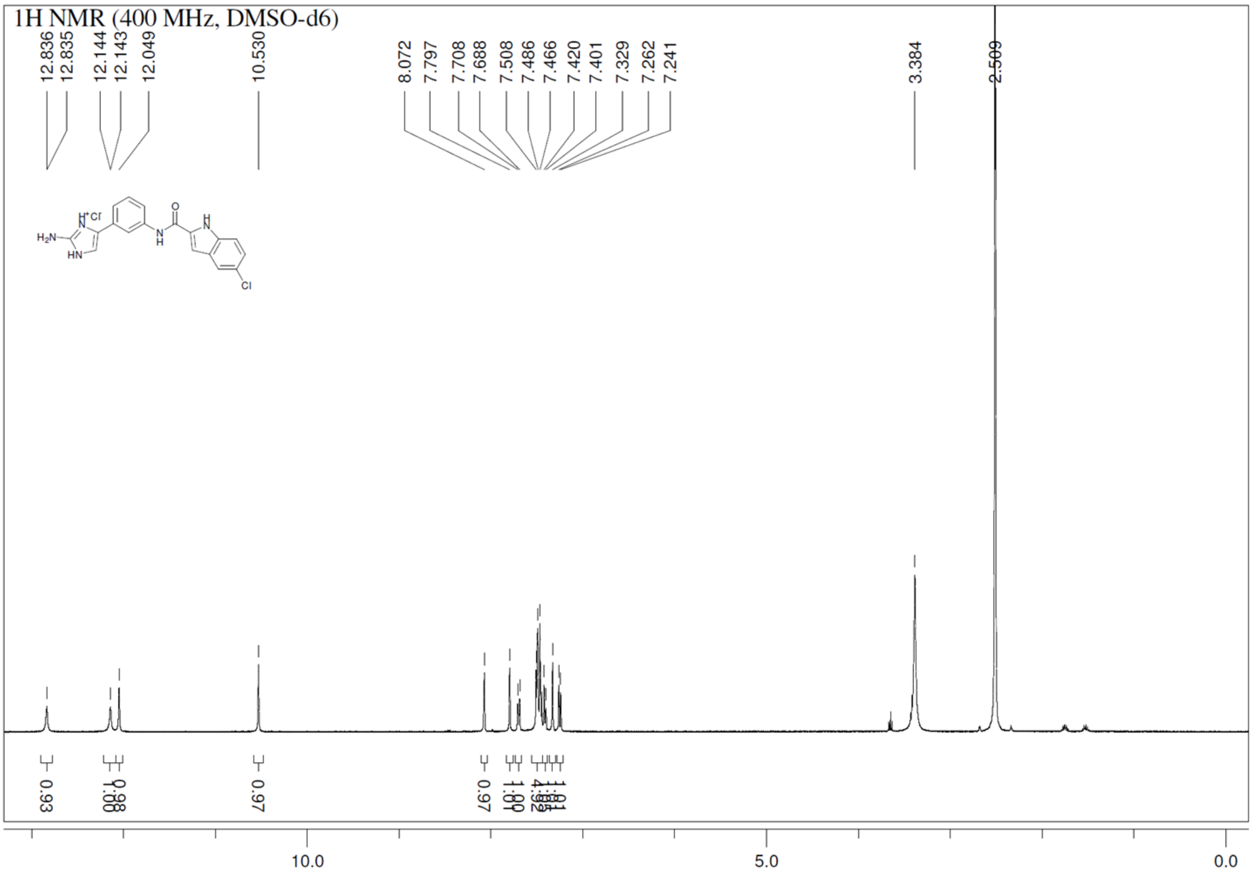


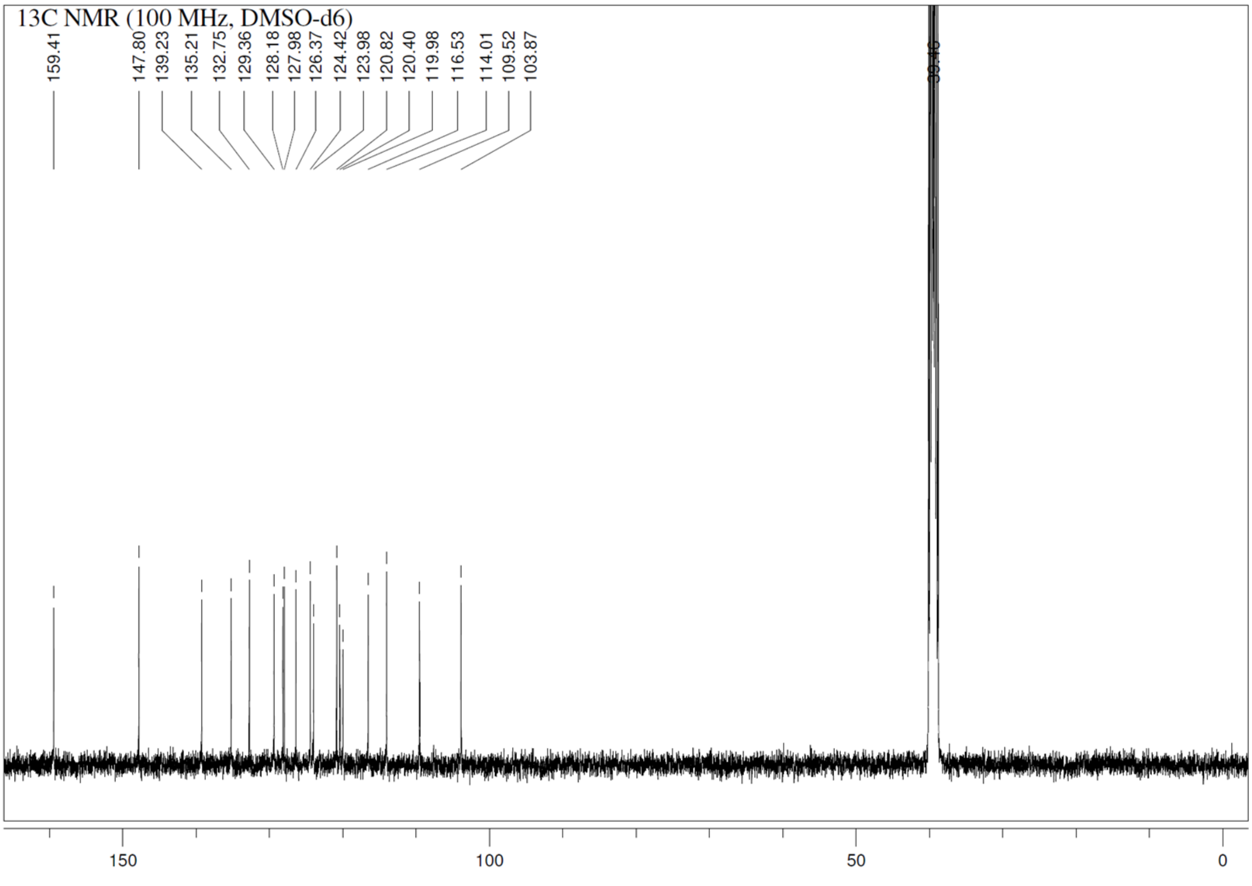
2-Amino-4-(3-(5-fluoro-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**28c**)



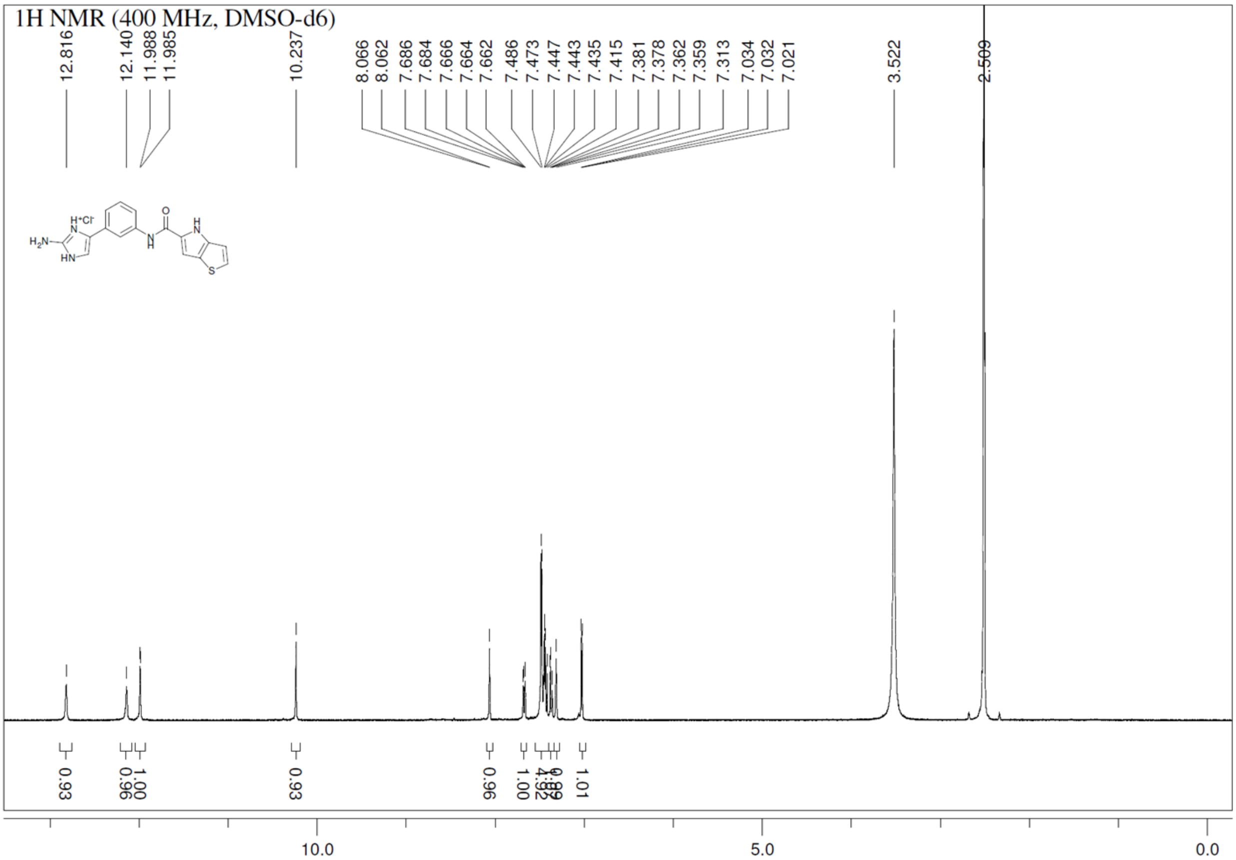


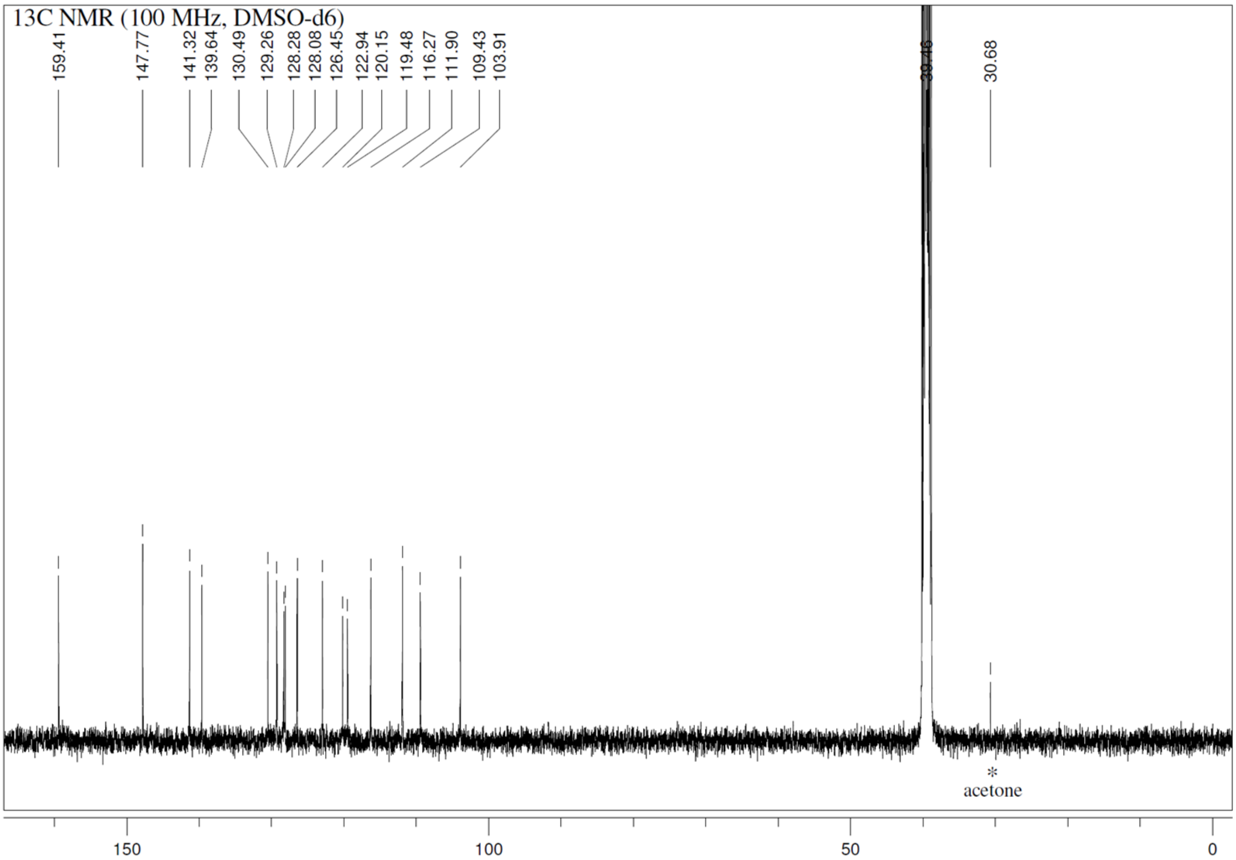
2-Amino-4-(3-(5-chloro-1*H*-indole-2-carboxamido)phenyl)-1*H*-imidazol-3-ium chloride (**29c**)



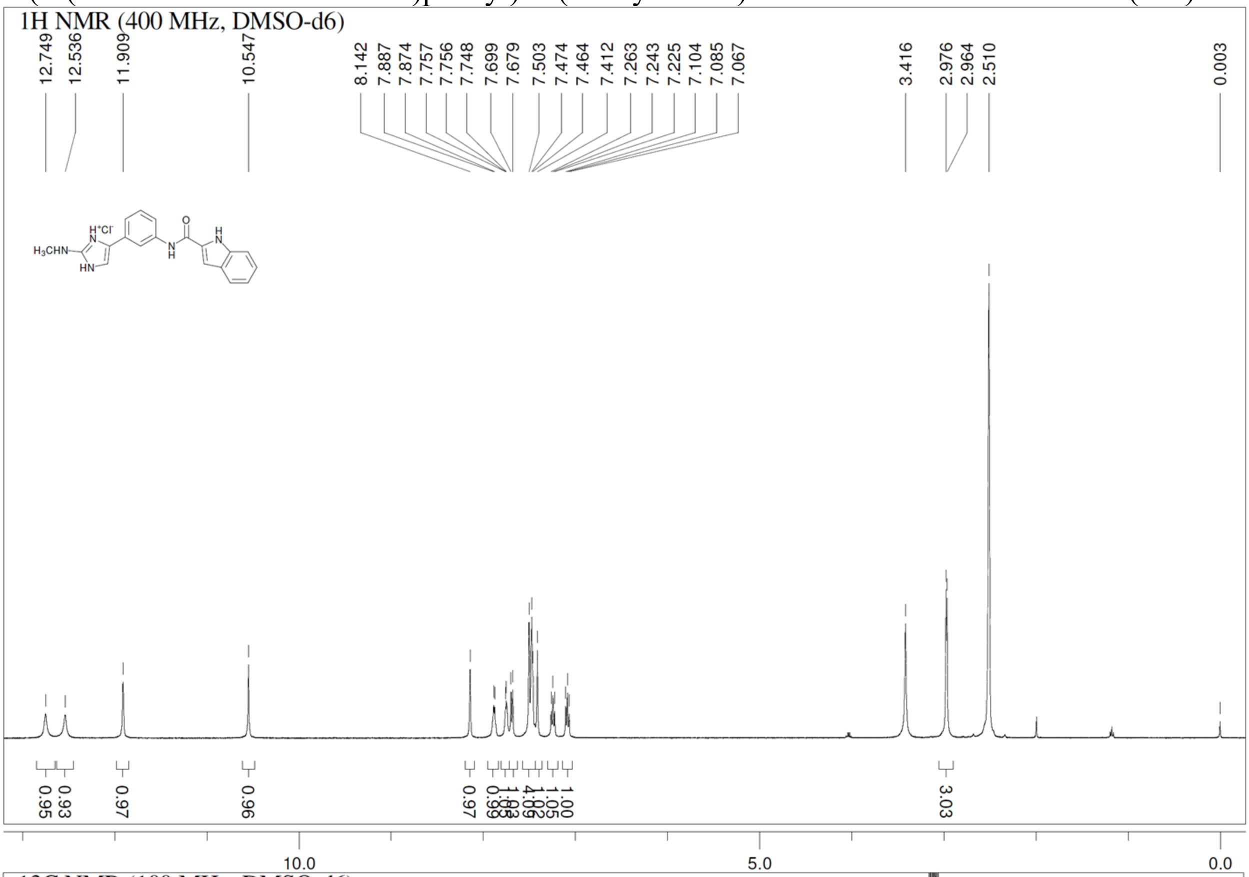


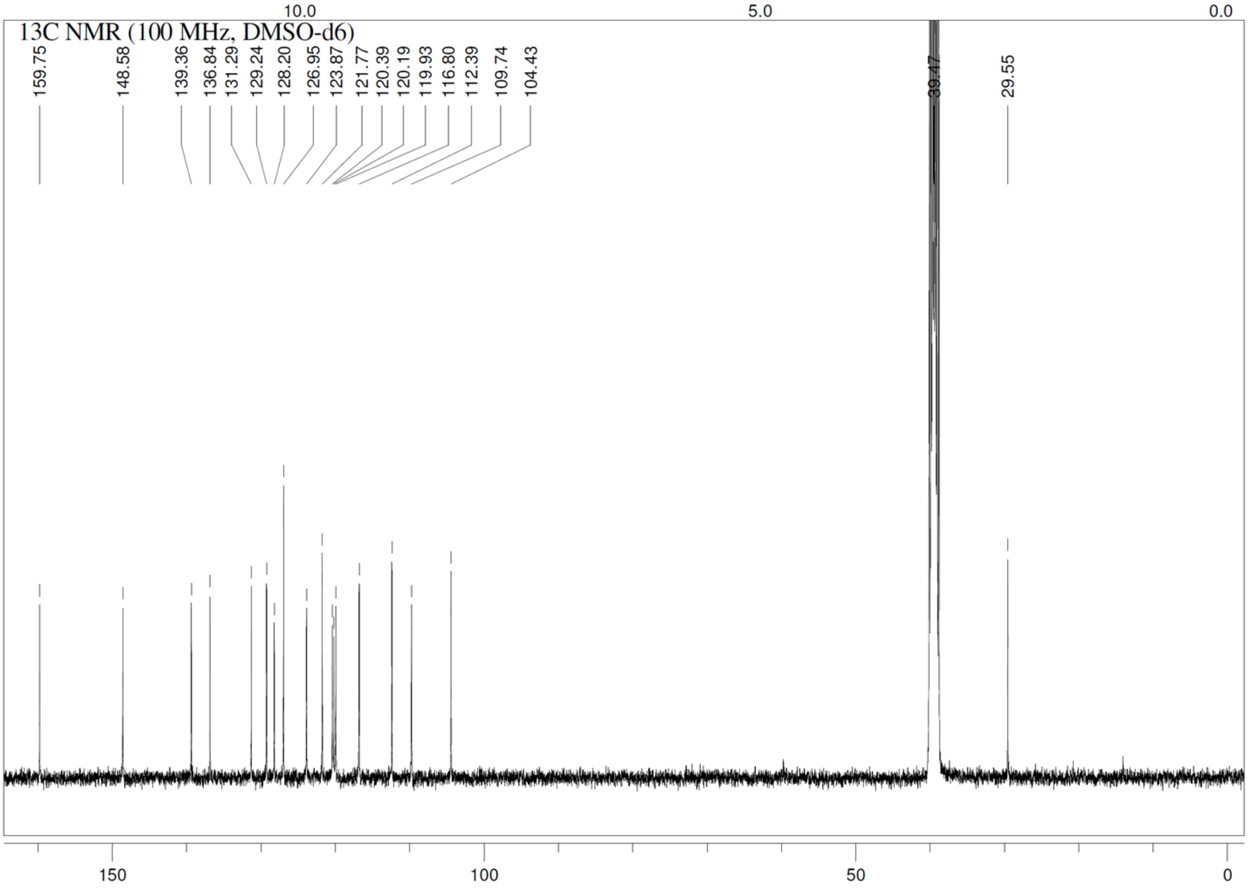
4-(3-(4*H*-Thieno[3,2-*b*]pyrrole-5-carboxamido)phenyl)-2-amino-1*H*-imidazol-3-ium chloride (**30c**)





4-(3-(1*H*-Indole-2-carboxamido)phenyl)-2-(methylamino)-1*H*-imidazol-3-ium chloride (**34c**)





2. Cells, cell cultures, cells incubations and apoptosis monitoring

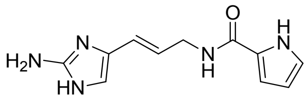
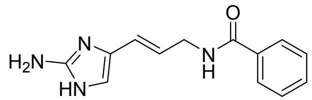
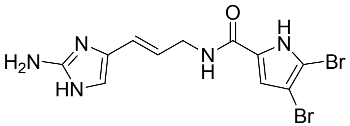
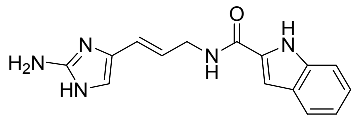
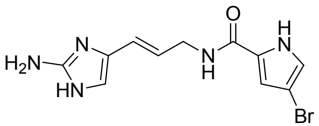
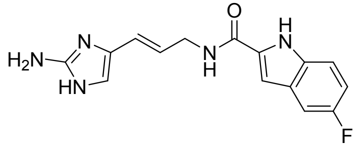
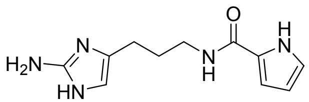
The human hepatocellular carcinoma cell line HepG2 was obtained from the American Type Culture Collection (Maryland, USA) and was maintained in DMEM culture medium supplemented with 10% FBS, Penicillin/Streptomycin (100 unit/mL and 100 μg/mL) and Glutamine (2 mM). Cells were grown at 37 °C in a humidified incubator equilibrated with 5% CO_2. Cells were trypsinized and subcultured twice a week.[2] The human monocytic cell line THP-1 (from American Type Culture Collection, ATCC) was routinely maintained in RPMI 1640 culture medium supplemented with 10% (v/v) FBS and Penicillin/Streptomycin (100 unit/mL and 100 μg/mL). Cells were grown in the same condition as previously described and were subcultured three times per week.[3]

HepG2 and THP-1 cells were incubated in 96-well culture plates for 24 h, at 37 °C in a humidified 5% CO_2/95% air atmosphere in presence of increasing doses of the tested compounds. The final concentration of cells was $1x10^5$/mL in a final volume of 200 μL per well. Final concentration of DMSO applied to cells during incubation with tested compounds was 0.5%. In the tested setup these concentrations had no adverse effects on cell viability nor cell morphology.

Apoptosis assay was performed using Annexin V-FITC (ImmunoTools) and propidium iodide (MiltenyiBiotec) according to manufacturer instructions.[4] Measurements were done by micro-capillary flow cytometry (Guava EasyCyte™, Millipore/Merck, CA, USA) and the cellular fluorescence intensity of Annexin V-FITC at 530/40 nm was computed on the Guava InCyte software (GuavaSoft 2.7, Millipore/Merck, CA, USA) in terms of x-geometric mean arbitrary units (AU). 2,000 events per sample were analysed. To discriminate between negative and positive events in the analysis, a non-stained control sample from each culture condition always accompanied acquisition of the stained cells to define the cut off. Negative control, i.e. sample with cells without compounds but with the same % of DMSO (v/v) as for diluted compounds, was included in each experiment. Celastrol was used as positive control for apoptotic assays. Gates were drawn around the appropriate cell populations using a forward scatter (FSC) versus side scatter (SSC) acquisition dot plot to exclude debris. Cytometers performances are checked weekly using the Guava easyCheck Kit 4500-0025 (Millipore /Merck, CA, USA).

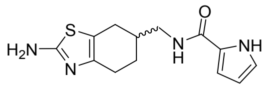
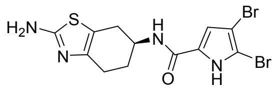
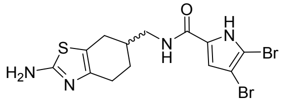
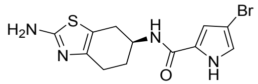
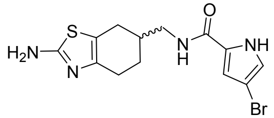
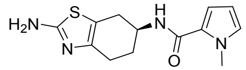
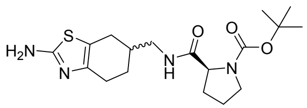
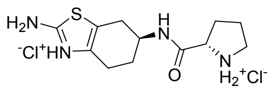
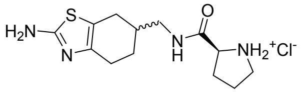
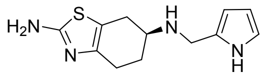
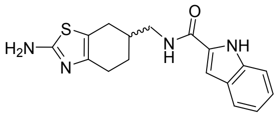
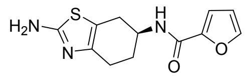
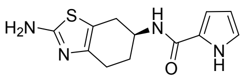
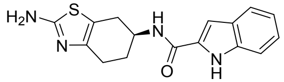
Cell cycle assay was performed as already reported.[5] Briefly, cells were first treated with compounds and after 24 h or 48 h of incubation, approximately 10^6 cells were collected, washed with PBS and centrifuged at 200g, pellet suspended in 0.5 mL of PBS and then fixed in 70% ethanol, on ice. Ethanol-suspended cells were kept at -20 °C during the night. Next day, ethanol was thoroughly removed by centrifugation at 400g. After that, cells were washed with PBS, centrifuged at 400g and stained with propidium iodide (FxCycle™ PI/RNase Staining Solution, Molecular Probes, Life Technologies), according to the manufacturer instructions. Specific DNA staining was achieved by enzymatic removal of RNA by RNAase. Samples were analyzed by a micro-capillary flow cytometer and data was computed on the Guava InCyte software. 5,000 events per sample were analysed. Debris and doublets were excluded by appropriate gating before further cell cycle analysis.

Table S1. Apoptosis-inducing activity of clathrodin, oroidin, hymenidin and their analogues **1-4** in HepG2 cell line.

Compound	**Structure**	**% of apoptosis of HepG2 at 50 μM[a]**	**Compound**	**Structure**	**% of apoptosis of HepG2 at 50 μM[a]**
clathrodin		27±19	**2**		33±10
oroidin		35±10	**3**		36±17
hymenidin		25±9	**4**		38±11
1		25±16			

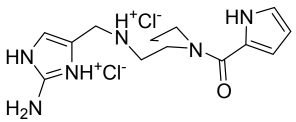
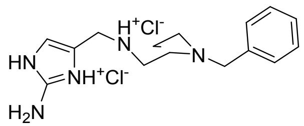
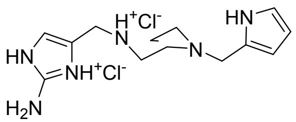
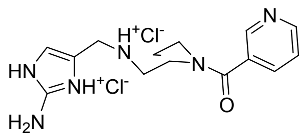
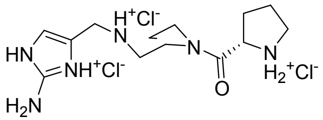
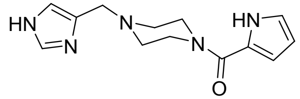
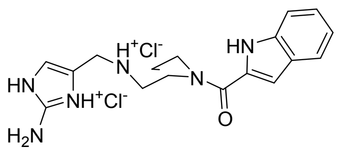
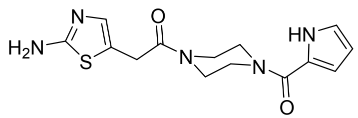
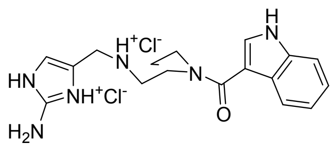
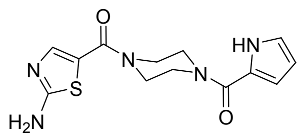
[a]Results are the mean of four independent experiments.

Table S2 Apoptosis-inducing activity of type **A** analogues **1a-14a** in HepG2 cell line.

Compound	Structure	% of apoptosis of HepG2 at 50 μM[a]	Compound	Structure	% of apoptosis of HepG2 at 50 μM[a]
1a		20±9	**8a**		35±8
2a		23±15	**9a**		28±10
3a		38±12	**10a**		20±10
4a		23±8	**11a**		22±10
5a		27±12	**12a**		30±21
6a		32±7	**13a**		29±11
7a		23±6	**14a**		27±7

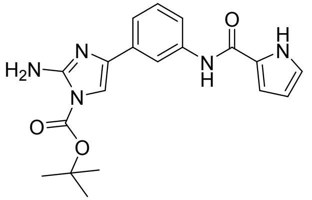
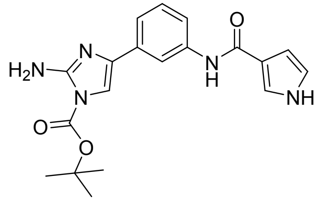
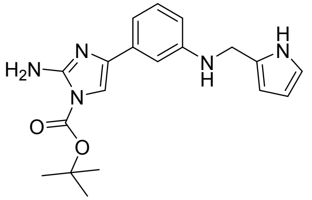
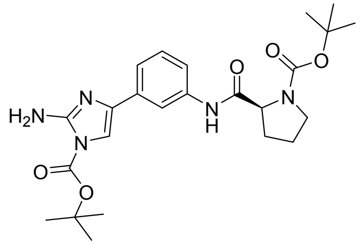
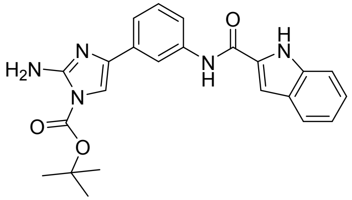
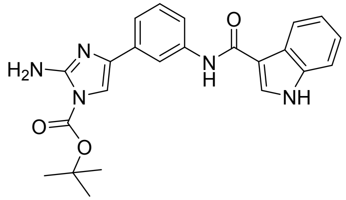
[a]Results are the mean of four independent experiments.

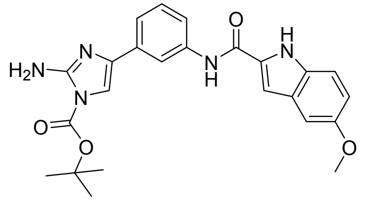
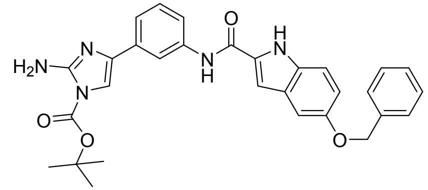
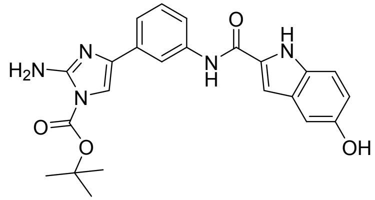
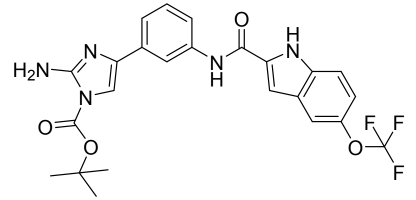
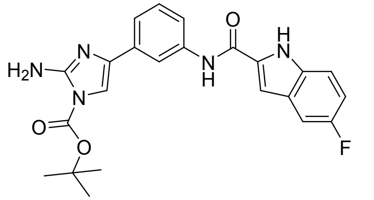
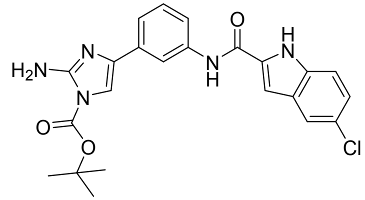
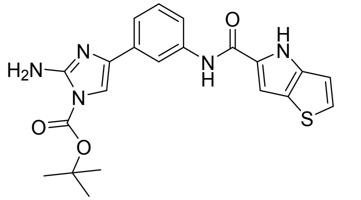
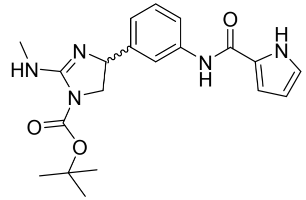
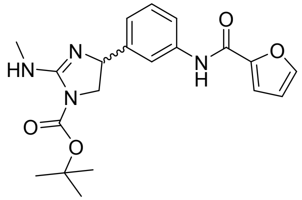
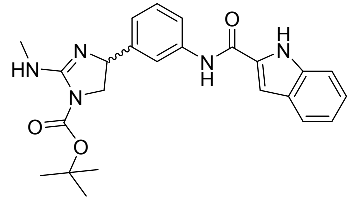
Table S3. Apoptosis-inducing activity of type **B** analogues **1b-10b** in HepG2 cell line.

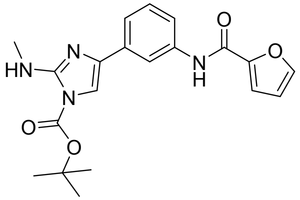
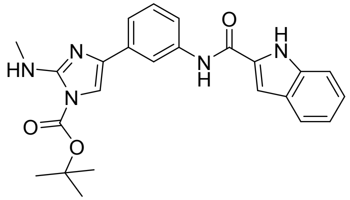
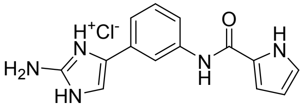
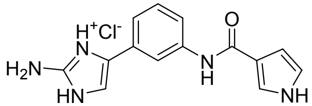
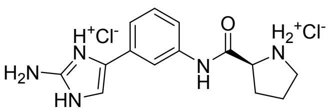
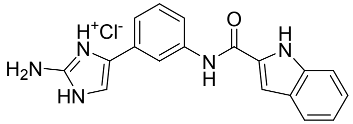
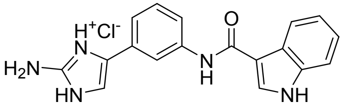
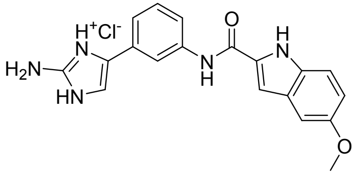
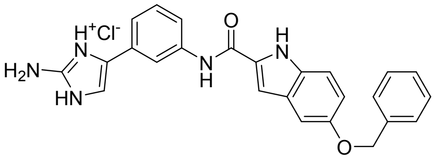
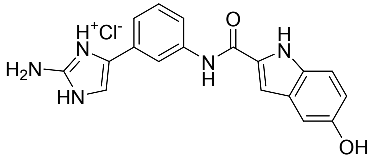
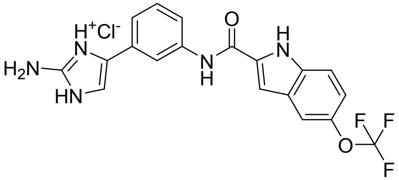
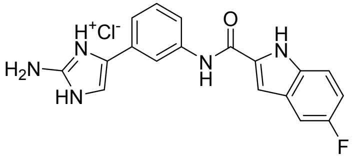
Compound	Structure	% of apoptosis of HepG2 at 50 μM[a]	Compound	Structure	% of apoptosis of HepG2 at 50 μM[a]
1b		27±7	**6b**		32±14
2b		34±13	**7b**		28±9
3b		28±10	**8b**		23±9
4b		32±15	**9b**		23±7
5b		30±19	**10b**		20±7

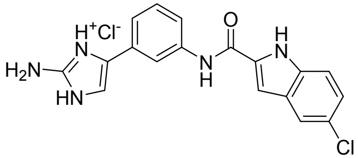
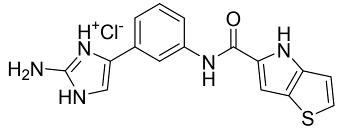
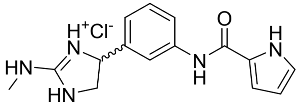
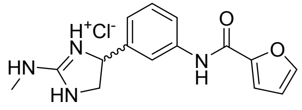
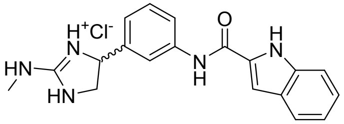
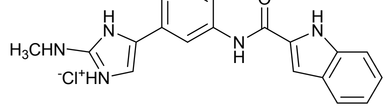
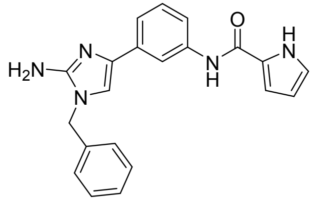
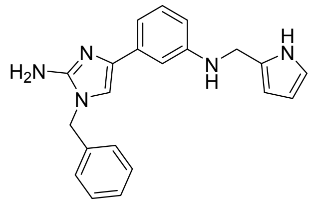
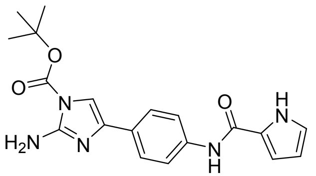
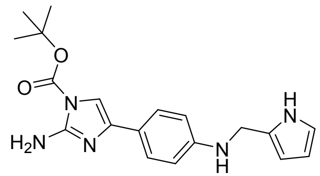
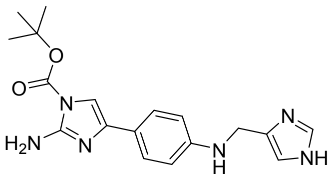
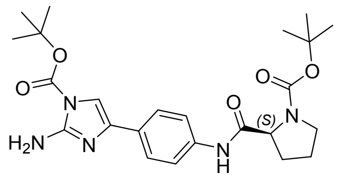
[a]Results are the mean of four independent experiments.

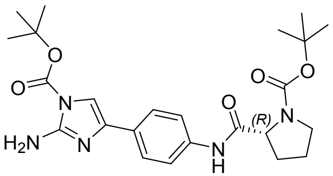
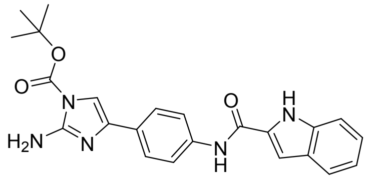
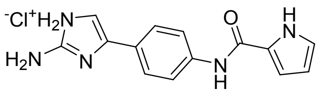
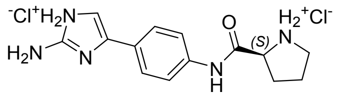
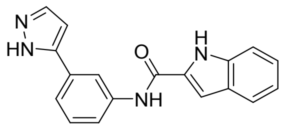
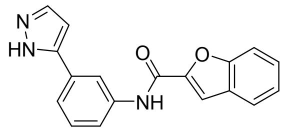
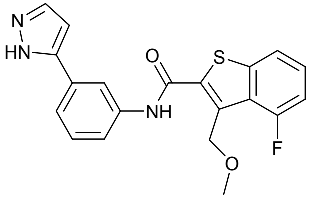
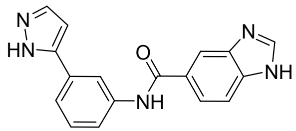
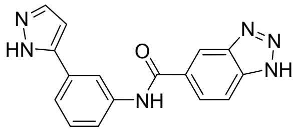
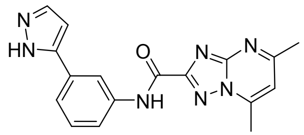
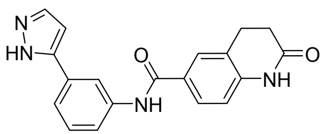
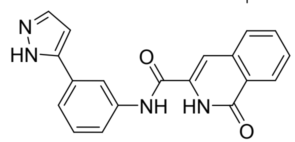
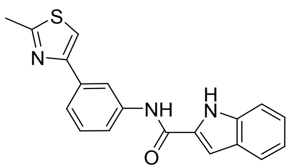
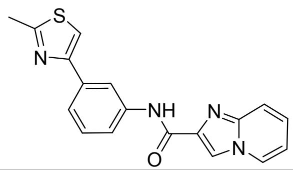
Table S4. Apoptosis-inducing activity of type **C** analogues **1c-65c** in HepG2 cell line.

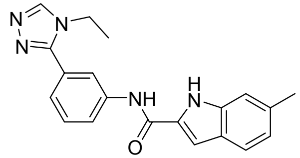
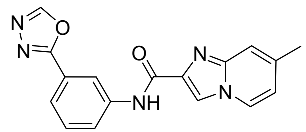
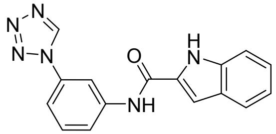
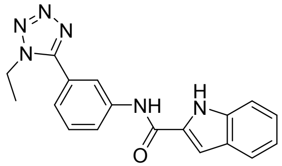
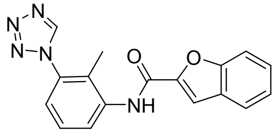
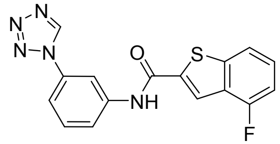
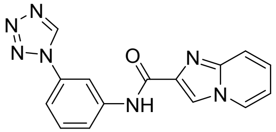
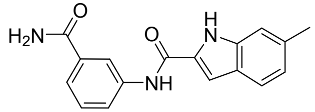
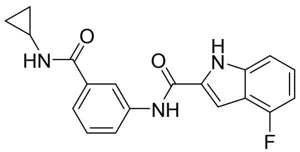
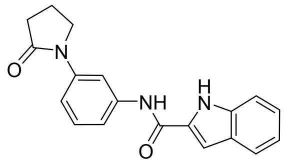
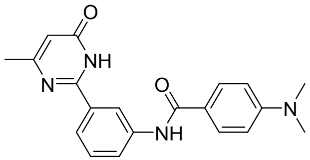
Compound	Structure	% of apoptosis of HepG2 at 50 μM[a]	Compound	Structure	% of apoptosis of HepG2 at 50 μM[a]
1c		21±18	**2c**		19±11
3c		40±21	**4c**		18±9
5c		75±8	**6c**		62±13

7c		87±3	**8c**		81±11
9c		56±22	**10c**		43±16
11c		89±8	**12c**		91±7
13c		86±5	**14c**		31±6
15c		32±7	**16c**		74±14

17c		44±14	**18c**		90±5
19c		13±8	**20c**		16±7
21c		16±9	**22c**		77±8
23c		55±14	**24c**		78±25
25c		50±36	**26c**		19±16
27c		66±20	**28c**		98±4

29c		93±6	**30c**		96±5
31c		28±11	**32c**		28±22
33c		27±8	**34c**		91±9
35c		54±12	**36c**		86±12
37c		24±16	**38c**		34±15
39c		39±21	**40c**		20±12

41c		23±9	**42c**		90±6
43c		20±8	**44c**		22±7
45c		68±18	**46c**		40±12
47c		65±22	**48c**		47±21
49c		20±10	**50c**		31±8
51c		26±17	**52c**		91±6
53c		57±10	**54c**		25±8

55c		55±16	**56c**		6±3
57c		56±17	**58c**		28±7
59c		45±14	**60c**		39±23
61c		27±10	**62c**		66±19
63c		51±22	**64c**		43±21
65c		37±19			

[a]Results are the mean of four independent experiments.

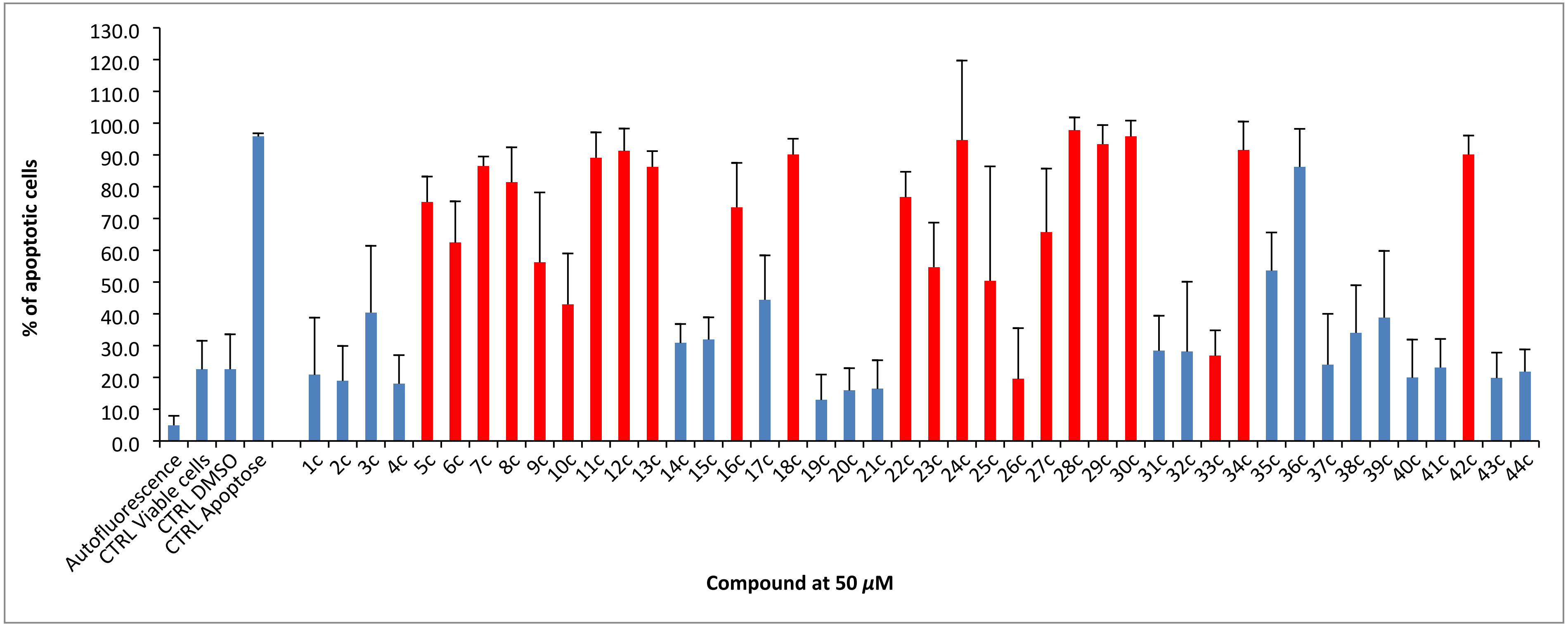


Figure S1. Induction of apoptosis in HepG2 cells by type **C** analogues **1c-44c** at 50 μM. Indole-based compounds are coloured *red* to highlight the importance of the indole moiety for potent apoptosis-inducing activity. Celastrol and DMSO were used as positive and negative controls, respectively.

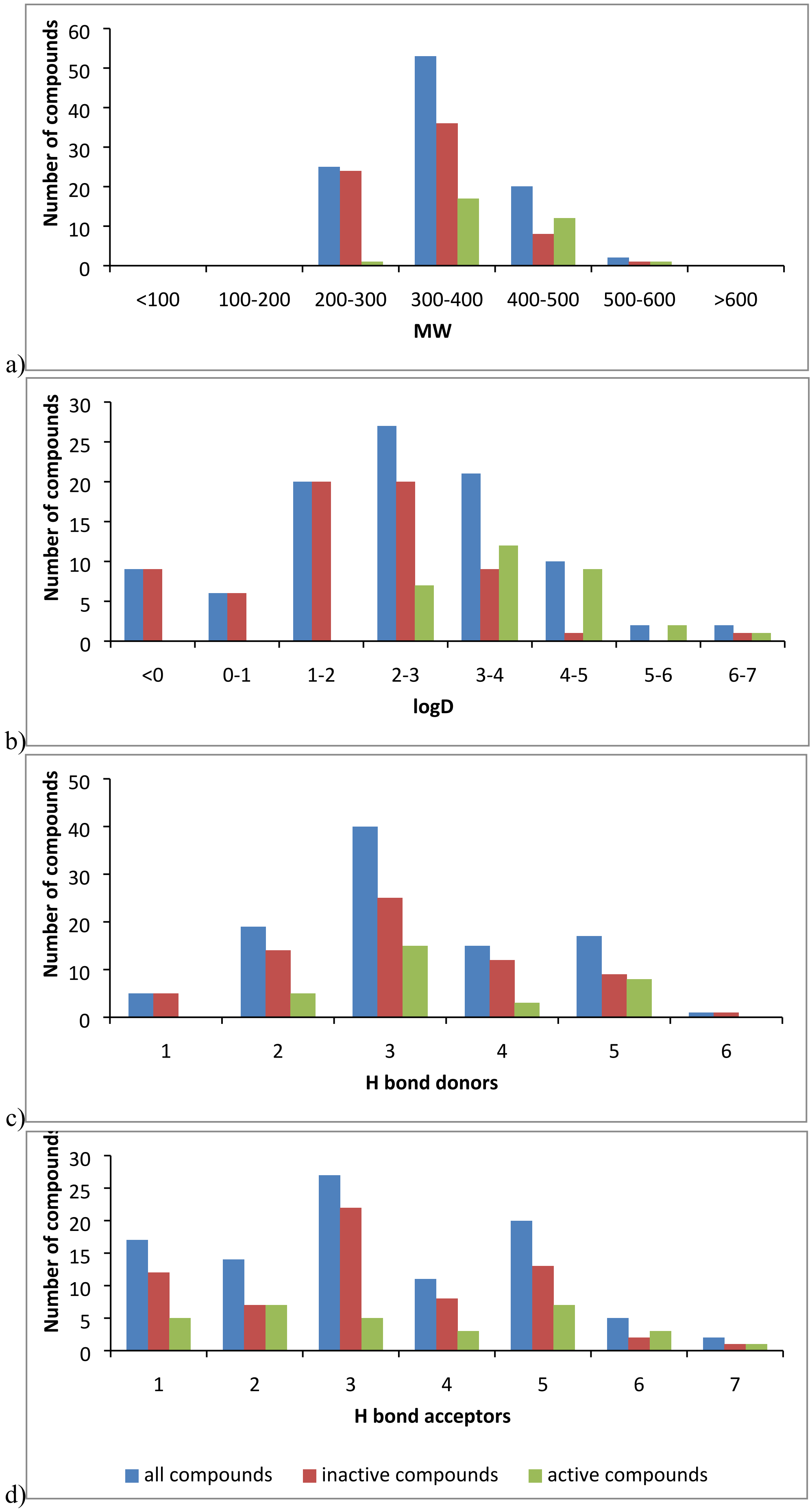

a)
Number of compounds
60
50
40
30
20
10
0
<100
100-200
200-300
300-400
400-500
500-600
>600
MW
b)
Number of compounds
30
25
20
15
10
5
0
<0
0-1
1-2
2-3
3-4
4-5
5-6
6-7
logD
c)
Number of compounds
50
40
30
20
10
0
1
2
3
4
5
6
H bond donors
d)
30
25
20
15
10
5
0
1
2
3
4
5
6
7
H bond acceptors
all compounds
inactive compounds
active compounds

Figure S2. Distribution of a) MW, b) logD, c) number of hydrogen bond donors and d) number of hydrogen bond acceptors in the library of oroidin analogs. Active compounds (>50% apoptotic HepG2 cells at 50 μM) are colored green, inactive compounds (<50% apoptotic HepG2 cells at 50 μM) are colored red and blue color indicates the sum of both.

Calculation of Molecular Descriptors. The three-dimensional models of clathrodin, oroidin, hymenidin and their analogues were built in ChemBio3D Ultra 13.0. The geometries of the molecules were optimized using MMFF94[6] force field and partial atomic charges. The energy was minimized until the gradient value was smaller than 0.001 kcal/(mol Å). The optimized structure was further refined with GAMESS interface in ChemBio3D Ultra 13.0 using semiempirical PM3 method, QA optimization algorithm and Gasteiger Hückel charges for all atoms for 100 steps.[7] Molecular descriptors were calculated using Calculate Molecular Properties protocol as available in Accelrys Discovery Studio 3.0.[8]

Table S5. Percent of sub-G1 population of THP-1 cells after 24 h and 48 h treatment with DMSO (0.25%) as a negative control and compounds **24c**, **28c**, **29c**, and **34c** at 25 μM.

	sub-G1 population [%][a]	
	24 h	48 h
control	2 ± 1	2 ± 1
24c	45 ± 1	60 ± 1
28c	36 ± 2	41 ± 2
29c	26 ± 3	40 ± 1
34c	18 ± 1	49 ± 3

[a]Results are the mean ± SD of three independent experiments.

REFERENCES

1 N. Zidar, S. Montalvão, Ž. Hodnik, D. A. Nawrot, A. Žula, J. Ilaš, D. Kikelj, P. Tammela, L. Peterlin Mašič, *Mar. Drugs*, 2014, **12**, 940.

2 L. Saab, J. Peluso, C. D: Muller, G. Ubeaud-Sequier, *Cytometry A*, 2013, **83**, 403.

3 H. Moreira-Tabaka, J. Peluso, J. L. Vonesch, D. Hentsch, P. Kessler, J. M. Reimund, S. Dumont, C. D. Muller, *PLoS One*, 2012, **7**, e34184.

4 I. Vermes, C. Haanen, H. Steffens-Nakken, C. Reutelingsperger, *J. Immunol. Methods*, 1995, **184**, 39.

5 C. Riccardi, I. Nicoletti, *Nat. Protoc.*, 2006, **1**, 1458.

6 T. A. Halgren, *J. Comput. Chem*., 1996, **17**, 490.

7 GAMESS interface, ChemBio3D Ultra 13.0, ChemBioOffice Ultra 13.0, CambridgeSoft.

8 Accelrys Discovery Studio 3.0. Accelrys, Inc.