Synthesis and biological evaluation of N^6 derivatives of 8-azapurine as novel antiplatelet agents

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Supporting Information

Contents

1. Preparation of Compounds IIf-IIu[1]

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-benzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIf)

A solution of **4b** (346mg, 1mmol) in tetrahydrofuran was added dropwise to a mixture solution of hydrazine hydrate (250mg, 5mmol) and *N,N*-diisopropylethylamine (258mg, 2mmol) in tetrahydrofuran at 0℃, and then the mixture was stirred at 25℃ until the starting material had been consumed. After the completion, **5b** was obtained by filtration and used for the next step without further purification. Benzaldehyde (212mg, 2mmol) and **5b** were dissolved in ethanol, and then the reaction mixture was refluxed for 1-2h. The organic solvent was removed under reduced pressure and residue was purified by silica gel column chromatography to afford the white solid **IIf** (347mg, 81% yield). Mp 163.5 – 164.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.94-1.99 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.10-3.20 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.69-4.75 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH) 7.41-7.54 (3H, m, Ph-H), 7.87 (2H, s, Ph-H), 8.29, 8.55 (1H, =CH), 12.40, 12.60 (1H, NH). ^{13}C NMR (100 MH_Z, DMSO-d_6) δ 13.8, 22.9, 32.7, 36.3, 61.5, 73.6, 74.9, 77.3, 122.8, 127.5, 129.3, 130.4, 134.8, 146.5, 151.7, 153.6, 168.7. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{24}N_7O_3S]^+$ 430.1661, found 430.1653.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-2-hydroxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIg)

The title compound **IIg** (369mg) was prepared from **4b** (390mg, 1mmol) and 2-hydroxybenzaldehyde (244mg, 2mmol) using the procedure described for compound **IIf** in 83% yield as a yellow solid. Mp 231.9 – 232.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.77 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.61-2.68 (1H, m, CH_2), 3.10-3.22 (2H, m, CH_2), 3.82 (1H, s, CH), 3.96(1H, s, CH), 4.70-4.76 (1H, m, CH), 4.99 (1H, OH), 4.97-5.04(1H, m, CH), 5.11(1H, OH), 5.14 (1H, OH), 6.90-6.98 (2H, m, Ph-H), 7.29-7.36 (1H, m, Ph-H), 7.42-7.48 (1H, m, Ph-H), 8.42 (1H, s, =CH),11.06 (1H, s, Ph-OH), 12.68 (1H, br, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.8, 32.7, 36.4, 61.6, 73.6, 74.9, 77.2, 117.4, 118.6, 119.8, 122.8, 131.4, 131.8, 148.7, 151.4, 152.8, 157.3, 169.1. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{24}N_7O_4S]^+$ 446.1610, found 446.1602.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-3-hydroxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIh)

The title compound **IIh** (403mg) was prepared from **4b** (390mg, 1mmol) and 3-hydroxybenzaldehyde (244mg, 2mmol) using the procedure described for compound **IIf** in 85% yield as a yellow solid. Mp 227.6 – 229.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.68-4.73 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11(1H, OH), 5.14 (1H, OH), 6.84 (1H, d, Ph-H, J = 7.2 Hz), 7.23-7.32 (3H, m, Ph-H), 8.19 (1H, s, =CH), 9.70 (1H, s, Ph-OH), 12.37 (1H, br, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.9, 32.7, 36.3, 61.5, 73.6, 74.9, 77.2, 113.3, 117.8, 119.2, 122.8, 130.3, 136.0, 146.9, 151.7, 153.6, 158.1, 168.6. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{24}N_7O_4S]^+$ 446.1610, found 446.1602.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-4-hydroxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIi)

The title compound **IIi** (369mg) was prepared from **4b** (390mg, 1mmol) and 4-

hydroxybenzaldehyde (244mg, 2mmol) using the procedure described for compound **IIf** in 83% yield as a yellow solid. Mp 152.1 – 154.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.78 (2H, m, CH_2), 1.95-2.02 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.68-4.74 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 6.86 (2H, d, Ph-H, J = 8.4 Hz), 7.69 (2H, d, Ph-H, J = 8.4 Hz), 8.18 (1H, s, =CH), 9.96 (1H, s, Ph-OH), 12.25 (1H, br, NH). ^{13}C NMR (100 MHZ, DMSO-d_6) δ 13.7, 22.9, 32.7, 36.3, 61.4, 67.4, 73.7, 74.9, 77.3, 116.2, 122.7, 125.8, 129.3, 130.5, 146.9, 151.6, 153.4, 159.8, 168.6. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{24}N_7O_4S]^+$ 446.1610, found 446.1602.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-2,4-dihydroxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIj)

The title compound **IIj** (359mg) was prepared from **4b** (390mg, 1mmol) and 2,4-dihydroxybenzaldehyde (276mg, 2mmol) using the procedure described for compound **IIf** in 78% yield as a yellow solid. Mp 261.6 – 263.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.61-2.69 (1H, m, CH_2), 3.12-3.18 (2H, m, CH_2), 3.82 (1H, s, CH), 3.96(1H, s, CH), 4.69-4.74 (1H, m, CH), 4.99 (1H, OH), 4.98-5.05 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 7.21-7.41 (2H, m, Ph-H), 8.31 (1H, s, Ph-H), 11.17 (1H, s, Ph-OH), 11.44 (1H, s, Ph-OH), 12.45 (1H, br, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.8, 32.7, 36.3, 61.6, 73.7, 75.0, 77.3, 103.5, 108.6, 110.8, 122.8, 132.9, 133.4, 149.2, 151.4, 152.5, 159.4, 169.0. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{24}N_7O_5S]^+$ 462.1559, found 462.1553.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-2-methoxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIk)

The title compound **IIk** (372mg) was prepared from **4b** (390mg, 1mmol) and 2-methoxybenzaldehyde (272mg, 2mmol) using the procedure described for compound **IIf** in 81% yield as a yellow solid. Mp 129.1 – 130.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.87 (3H, s, OCH_3), 3.97 (1H, s, CH), 4.69-4.76 (1H, m, CH), 4.93 (1H, OH), 5.00-5.06 (1H, m, CH), 5.11(1H,OH), 5.14 (1H, OH), 7.07-7.16 (2H, m, Ph-H), 7.38-7.43 (1H, m, Ph-H), 8.16 (1H, d, Ph-H, J = 5.6 Hz), 8.63 (1H, s, =CH), 12.39 (1H, s, NH). ^{13}C NMR (100 MHZ, DMSO-d_6) δ 13.7, 22.9, 32.7, 36.3, 56.1, 61.5, 73.7, 74.9, 77.3, 112.2, 121.1, 122.8, 126.3, 131.9, 142.0, 144.0, 151.7, 153.5, 158.0, 168.7. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{20}H_{26}N_7O_4S]^+$ 460.1767, found 460.1759.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-4-methoxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIl)

The title compound **IIl** (367mg) was prepared from **4b** (390mg, 1mmol) and 4-methoxybenzaldehyde (272mg, 2mmol) using the procedure described for compound **IIf** in 80% yield as a yellow solid. Mp 148.6 – 150.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (4H, s, CH and OCH_3), 3.96 (1H, s, CH), 4.68-4.74 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11(1H, OH), 5.14 (1H, OH), 7.05 (2H, d, Ph-H, J = 8.4 Hz), 7.81 (2H, d, Ph-H, J = 8.4 Hz), 8.16 (1H, d, Ph-H, J = 5.6 Hz), 8.22 (1H, s, =CH), 12.33 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 22.9, 32.7, 36.3, 55.8, 61.5, 73.6, 74.8, 77.3, 114.8, 122.8, 127.4, 129.2, 146.4, 151.6, 153.5, 161.2, 168.5. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{20}H_{26}N_7O_4S]^+$ 460.1767, found 460.1759.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-3,4-dimethoxybenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIm)

The title compound **IIm** (377mg) was prepared from **4b** (390mg, 1mmol) and 3,4-dimethoxybenzaldehyde (332mg, 2mmol) using the procedure described for compound **IIf** in 77% yield as a yellow solid. Mp 133.5 – 135.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.78 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.96 (1H, s, CH), 4.68-4.75 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 7.04-7.62 (3H, m, Ph-H), 8.20 (1H, s, =CH), 12.35 (1H, br, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.9, 32.7, 36.3, 55.8, 55.9, 61.5, 73.4, 74.9, 77.3, 111.8, 122.8, 123.9, 127.7, 146.4, 149.4, 151.0, 151.6, 153.5, 161.2, 168.6. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{21}H_{28}N_7O_5S]^+$ 490.1875, found 490.1865.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-3,4-difluorobenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIn)

The title compound **IIn** (363mg) was prepared from **4b** (390mg, 1mmol) and 3,4-difluorobenzaldehyde (284mg, 2mmol) using the procedure described for compound **IIf** in 78% yield as a white solid. Mp 153.6 – 155.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.18 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.68-4.74 (1H, m, CH), 4.93 (1H, OH), 5.00-5.06 (1H, m, CH), 5.11(1H, OH), 5.14 (1H, OH), 7.52-7.59 (1H, m, Ph-H), 7.71 (1H, s, Ph-H), 7.94 (1H, s, Ph-H), 8.23 (1H, s, =CH), 12.37 (1H, br, NH). ^{13}C NMR (100 MHZ, DMSO-d_6) δ 13.7, 22.8, 32.7, 36.3, 61.5, 73.6, 74.9, 77.2, 115.4, 115.6, 118.5, 118.6, 122.8, 124.9, 132.8, 143.8, 148.9, 149.1, 149.6, 151.4, 151.5, 151.9, 153.7, 168.7. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{22}F_2N_7O_3S]^+$ 466.1473, found 466.1465.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-2-chlorobenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIo)

The title compound **IIo** (366mg) was prepared from **4b** (390mg, 1mmol) and 2-chlorobenzaldehyde (280mg, 2mmol) using the procedure described for compound **IIf** in 79% yield as a yellow solid. Mp 127.3 – 129.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.61-2.68 (1H, m, CH_2), 3.11-3.17 (2H, m, CH_2), 3.82 (1H, s, CH), 3.96(1H, s, CH), 4.69-4.75 (1H, m, CH), 4.99 (1H, OH), 4.98-5.07 (1H, m, CH), 5.11(1H, OH), 5.14 (1H, OH), 7.45-7.55 (3H, m, Ph-H), 8.30-8.36 (1H, m, Ph-H), 8.67 (1H, s, =CH), 12.62 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.9, 32.8, 36.4, 61.5, 73.6, 74.9, 77.3, 122.8, 127.5, 128.0, 130.3, 131.7, 132.0, 133.3, 142.2, 151.7, 153.6, 168.8. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{23}ClN_7O_3S]^+$ 464.1271, found 464.1265.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-4-chlorobenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIp)

The title compound **IIp** (399mg) was prepared from **4b** (390mg, 1mmol) and 4-chlorobenzaldehyde (280mg, 2mmol) using the procedure described for compound **IIf** in 86% yield as a yellow solid. Mp 142.2 – 144.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.61-2.68 (1H, m, CH_2), 3.10-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.96(1H, s, CH), 4.70-4.77 (1H, m, CH), 4.99 (1H, OH), 4.97-5.03 (1H, m, CH), 5.11(1H, OH), 5.14 (1H, OH), 7.52-7.87 (4H, m, Ph-H), 8.26 (1H, s, =CH), 12.67 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.8, 32.7, 36.4, 61.5, 73.7, 74.9, 77.3, 122.8, 129.1, 129.3,

133.8, 134.8, 145.1, 151.7, 153.6, 168.7. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{23}ClN_7O_3S]^+$ 464.1271, found 464.1265.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-2,4-dichlorobenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIq)

The title compound **IIq** (414mg) was prepared from **4b** (390mg, 1mmol) and 2,4-dichlorobenzaldehyde (350mg, 2mmol) using the procedure described for compound **IIf** in 82% yield as a yellow solid. Mp 203.4 – 204.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.61-2.68 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.96(1H, s, CH), 4.69-4.75 (1H, m, CH), 4.99 (1H, OH), 5.00-5.06 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 7.59-7.73 (2H, m, Ph-H), 8.30-8.35 (1H, m, Ph-H), 8.61 (1H, s, =CH), 12.66 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 22.8, 32.8, 36.4, 61.5, 73.6, 75.0, 77.3, 122.8, 128.4, 128.6, 129.7, 131.2, 133.9, 135.3, 141.0, 151.7, 153.5, 168.8. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{22}Cl_2N_7O_3S]^+$ 498.0882, found 498.0883.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-3-nitrobenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIr)

The title compound **IIr** (379mg) was prepared from **4b** (390mg, 1mmol) and 3-nitrobenzaldehyde (302mg, 2mmol) using the procedure described for compound **IIf** in 80% yield as a yellow solid. Mp 154.8 – 155.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.18 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.69-4.75 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 7.42-8.37 (4H, m, Ph-H), 8.72 (1H, s, =CH), 12.67 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.8, 32.7, 36.4, 61.5, 73.7, 75.0, 77.3, 121.4, 122.8, 124.3, 130.6, 133.5, 136.7, 143.8, 148.5, 151.6, 153.6, 168.8. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{23}N_8O_5S]^+$ 475.1512, found 475.1505.

(1*S*,2*R*,3*S*,4*R*)-4-(7-(2-((*E*)-4-nitrobenzylidene)hydrazinyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIs)

The title compound **IIs** (393mg) was prepared from **4b** (390mg, 1mmol) and 4-nitrobenzaldehyde (302mg, 2mmol) using the procedure described for compound **IIf** in 83% yield as a yellow solid. Mp 156.5 – 157.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.61-2.68 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.96 (1H, s, CH), 4.68-4.75 (1H, m, CH), 4.99 (1H, OH), 5.00-5.05 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 8.11-8.34 (4H, m, Ph-H), 8.49 (1H, s, =CH), 12.75 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.8, 32.8, 36.4, 61.6, 73.6, 75.0, 77.3, 122.9, 124.5, 128.3, 130.0, 141.1, 143.9, 151.7, 153.7, 168.8. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{19}H_{23}N_8O_5S]^+$ 475.1512, found 475.1505.

(1*S*,2*R*,3*S*,4*R*)-4-(5-(propylthio)-7-(2-((*E*)-pyridin-2-ylmethylene)hydrazinyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIt)

The title compound **IIt** (340mg) was prepared from **4b** (390mg, 1mmol) and 2-pyridinecarboxaldehyde (214mg, 2mmol) using the procedure described for compound **IIf** in 79% yield as a yellow solid. Mp 207.7 – 209.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.18 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.68-4.75 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 7.42-8.37 (4H, m, Pyr-H), 8.72 (1H, s, =CH), 12.67 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 22.8, 32.7, 36.4, 61.5, 73.7, 75.0, 77.3, 121.4, 122.8,

124.3, 130.6, 133.5, 143.8, 148.5, 151.6, 153.6, 168.8. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{18}H_{23}N_8O_3S]^+$ 431.1614, found 431.1607.

(1*S*,2*R*,3*S*,4*R*)-4-(5-(propylthio)-7-(2-((*E*)-thiophen-2-ylmethylene)hydrazinyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentane-1,2,3-triol (IIu)

The title compound **IIu** (331mg) was prepared from **4b** (390mg, 1mmol) and 2-thenaldehyde (224mg, 2mmol) using the procedure described for compound **IIf** in 76% yield as a yellow solid. Mp 163.3 – 165.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, CH_3, J = 7.2 Hz), 1.68-1.79 (2H, m, CH_2), 1.95-2.01 (1H, m, CH_2), 2.60-2.67 (1H, m, CH_2), 3.11-3.19 (2H, m, CH_2), 3.82 (1H, s, CH), 3.97 (1H, s, CH), 4.68-4.75 (1H, m, CH), 4.93 (1H, OH), 5.00-5.07 (1H, m, CH), 5.11 (1H, OH), 5.14 (1H, OH), 7.15-7.70 (3H, m, Thio-H), 8.69 (1H, s, =CH), 12.38 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 22.9, 32.7, 36.4, 61.6, 73.7, 74.9, 77.3, 122.6, 128.3, 129.6, 130.9, 139.4, 142.0, 149.8, 153.2, 168.6. HRMS-ESI (m/z) $[M+H]^+$ calcd for $[C_{17}H_{22}N_7O_3S_2]^+$ 436.1225, found 436.1218.

2. Verification of P2Y$_{12}$ Crystal Structure and Docking Method

As shown in Figure S1-S2, the conformation and coordinate position of the re-docked 2MesADP are basically consistent with the original ligand. The adenine skeleton is almost completely coincided, and forming a hydrogen bonds with Asn191; the ribose moiety also has the same orientation and forming two hydrogen bonds with Cys97 and His187; the phosphate groups are located at the top of the pocket and forming three bonds with Cys175, Tyr259 and Gln263. Other interactions, such as π-sigma, π-π, π-alkyl and van der Waals, are also basically the same, which indicates that the P2Y$_{12}$ crystal structure and docking method that we selected are reasonable.

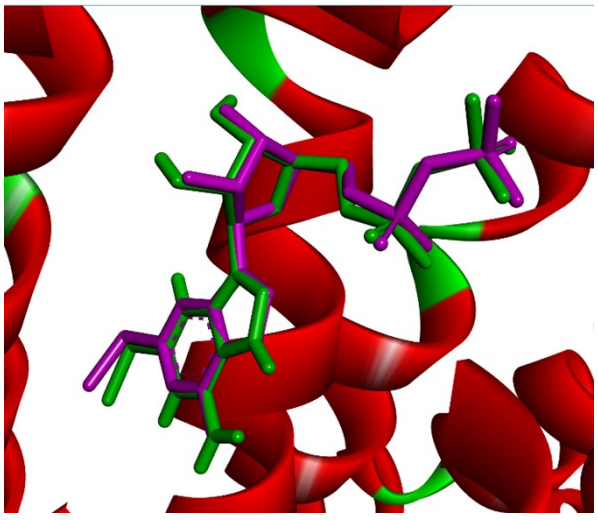


Figure S1. Stacking map of re-docked 2MesADP (green) and the original ligand (purple) with P2Y$_{12}$ (PDB: 4PXZ)

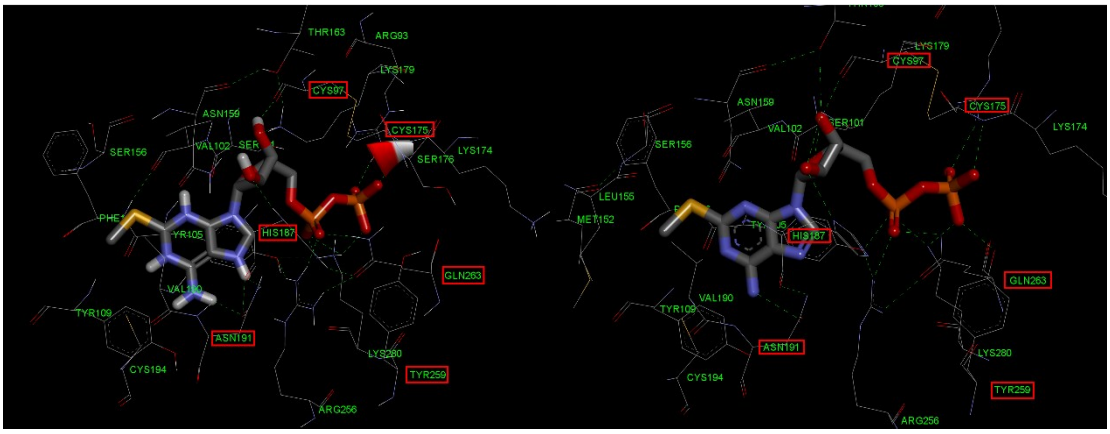


Figure S2. Left: the binding mode of re-docked 2MesADP (left) with $P2Y_{12}$ (PDB: 4PXZ); Right: the binding mode of original ligand with $P2Y_{12}$ (PDB: 4PXZ)

3. X-ray crystal of compound 4b[1]

To unambiguously assign the stereochemical structure of compound **4b**, a single crystal X-ray diffraction study was performed. After many attempts, X-ray quality compound **4b** crystals were obtained by slow evaporation of the mixture of methanol/water at room temperature. The X-ray crystal structure of compound **4b** confirmed the stereochemical assignment. The details of X-ray data collection, structure solution and structure refinement were given in **Table 1**. And the crystallographic data for **4b** has been deposited with Cambridge Crystallographic Data Centre as supplementary number CCDC 1054273. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or email: deposit@ccdc.cam.ac.uk].

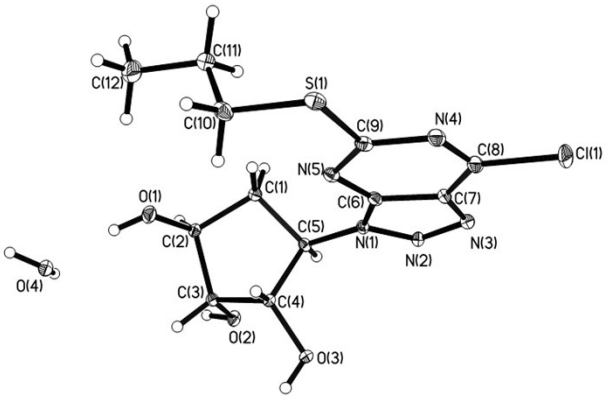


Figure S3. Single crystal structure of **4b**

Table 1 Crystal data and structure refinement for compound **4b** monohydrate

Crystal data	
Empirical formula	$C_{12}H_{18}ClN_5O_4S$
Formula weight	363.82
Temperature	113(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)

a (Å)	4.9617(10)
b (Å)	10.450(2)
c (Å)	31.053(6)
α (°)	90
β (°)	90
γ (°)	90
Volume	1610.1(6) $Å^3$
Z, Calculated density	4, 1.501 Mg/m^3
Absorption coefficient	0.394 mm^{-1}
F(000)	760
Crystal size	0.50 x 0.04 x 0.04 mm
Theta range for data collection	2.06 to 27.92
Limiting indices	-6<=h<=6, -13<=k<=13, -40<=l<=40
Reflections collected / unique	19506 / 3844 [R(int) = 0.0364]
Completeness to theta	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9844 and 0.8272
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3844 / 3 / 221
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R_1 = 0.0331, wR_2 = 0.0909
R indices (all data)	R_1 = 0.0359, wR_2 = 0.1017
Extinction coefficient	0.04(6)
Largest diff. peak and hole	0.467 and -0.461 e. $Å^{-3}$

4. spectra of new compounds

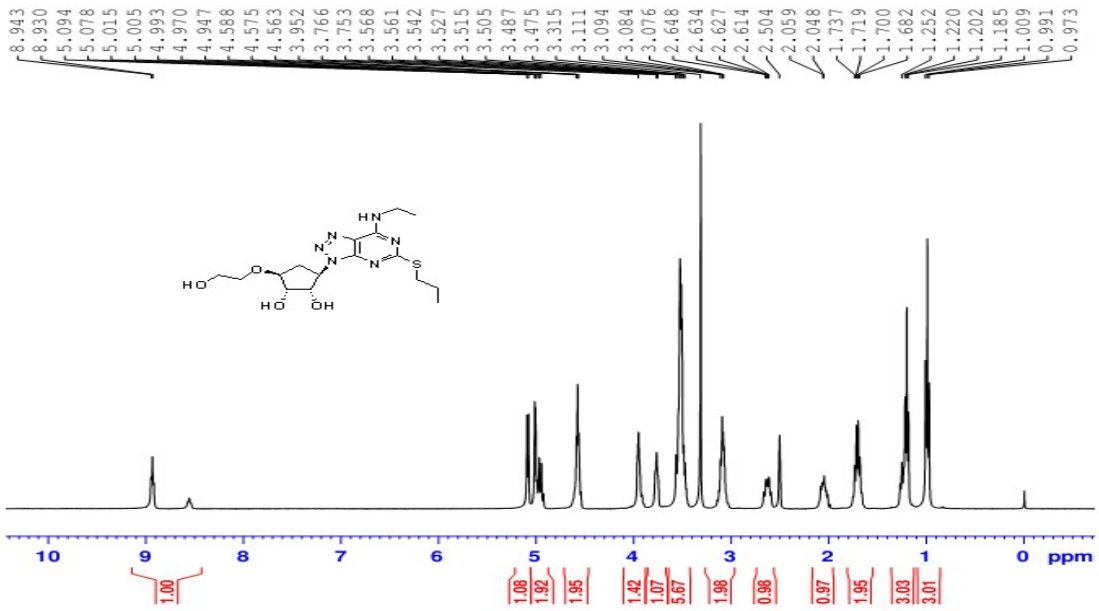


Figure S.4-1 ^{1}H NMR spectra of **Ia**.

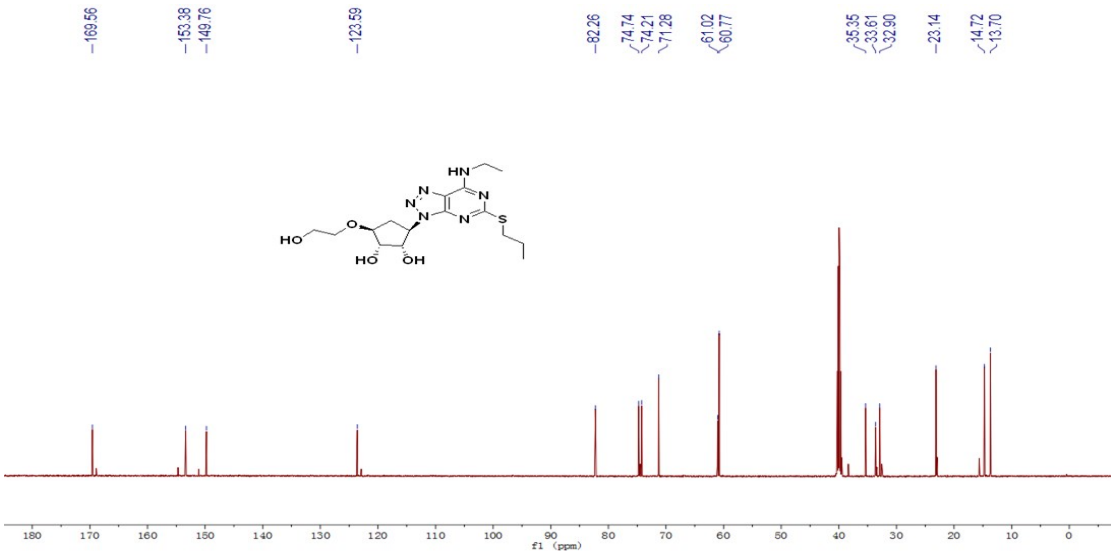


Figure S.4-2 ^{13}C NMR spectra of **Ia**.

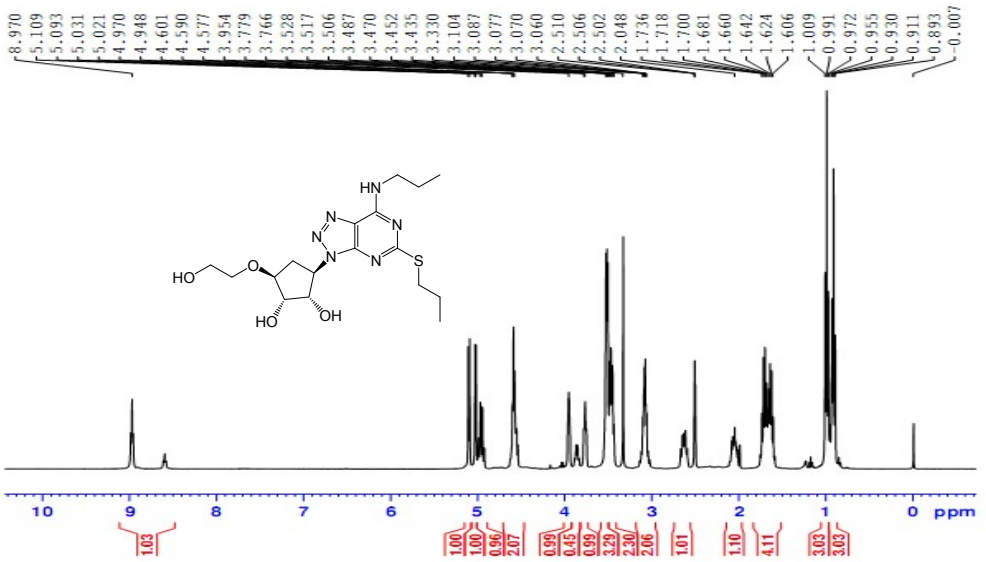


Figure S.4-3 ^{1}H NMR spectra of **Ib**.

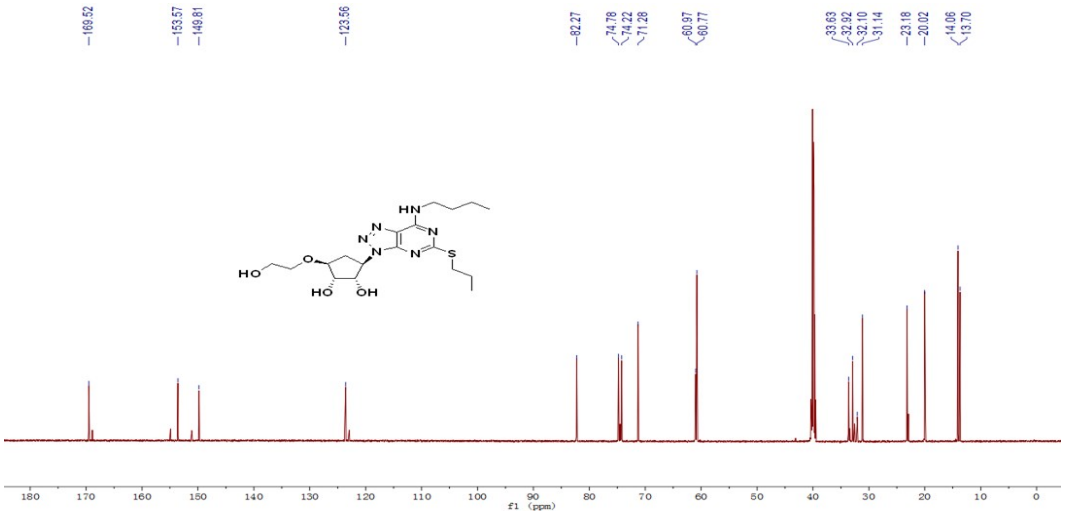


Figure S.4-4 ^{13}C NMR spectra of **Ic**.

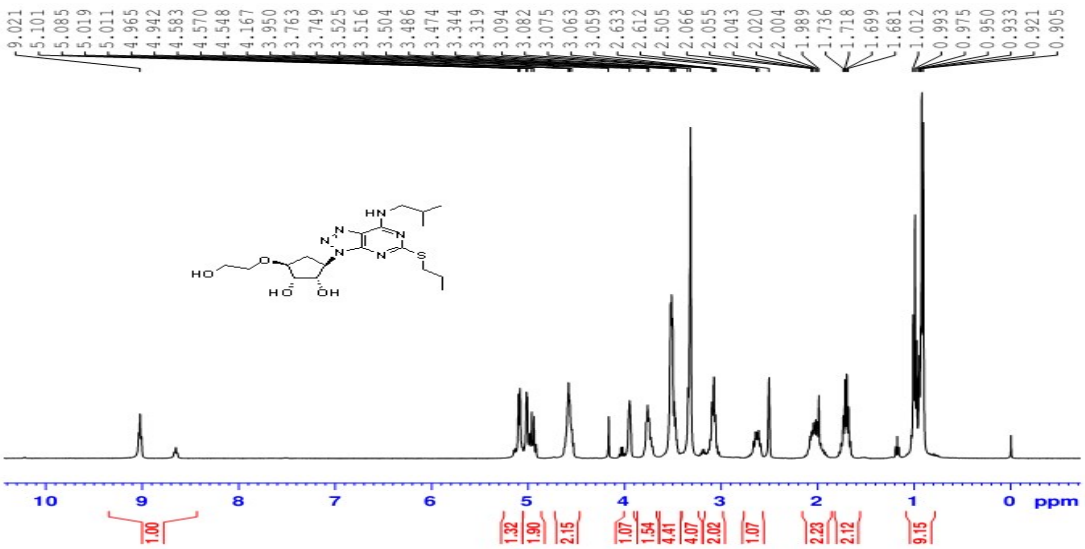


Figure S.4-5 ^{1}H NMR spectra of **Id**.

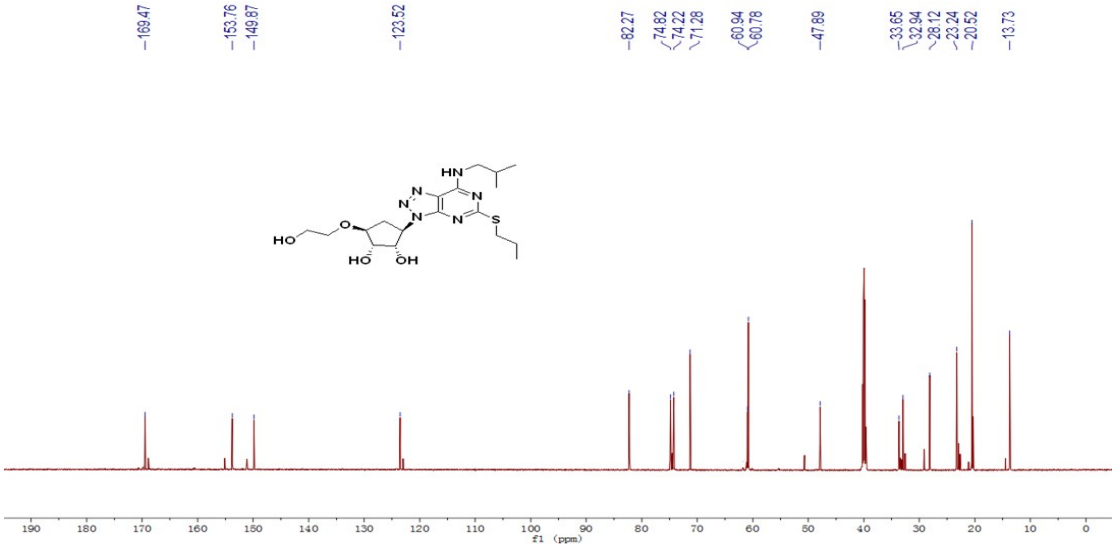


Figure S.4-6 ^{13}C NMR spectra of **Id**.

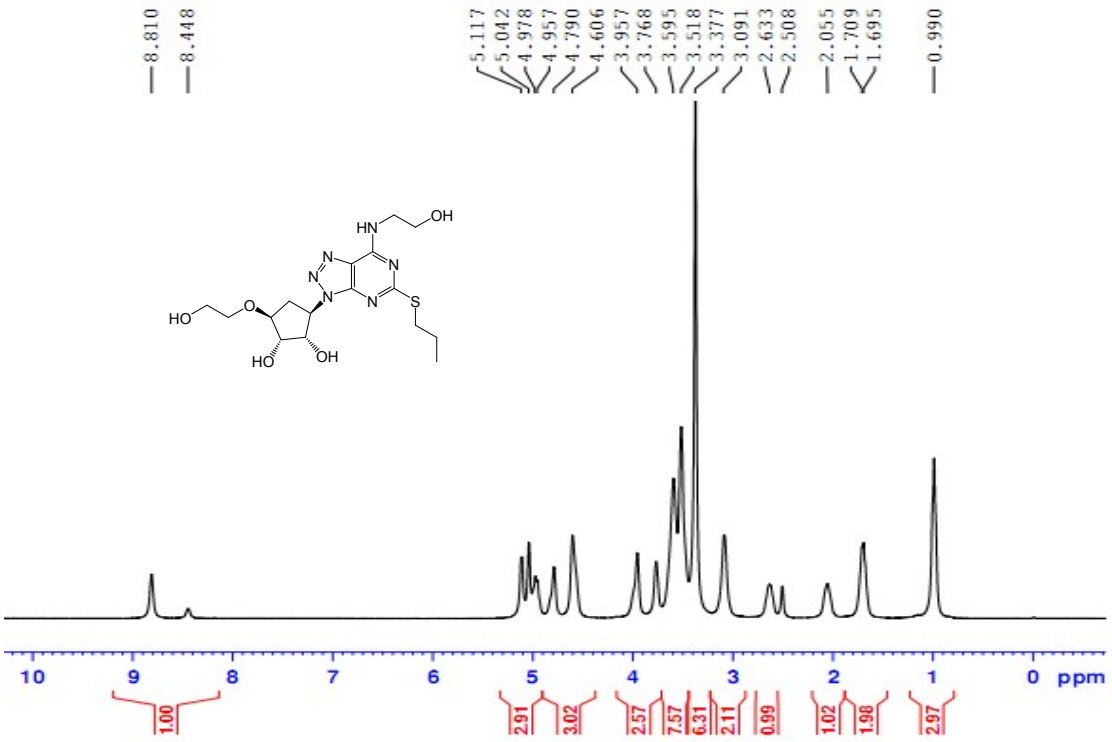


Figure S.4-7 ^{1}H NMR spectra of **Ie**.

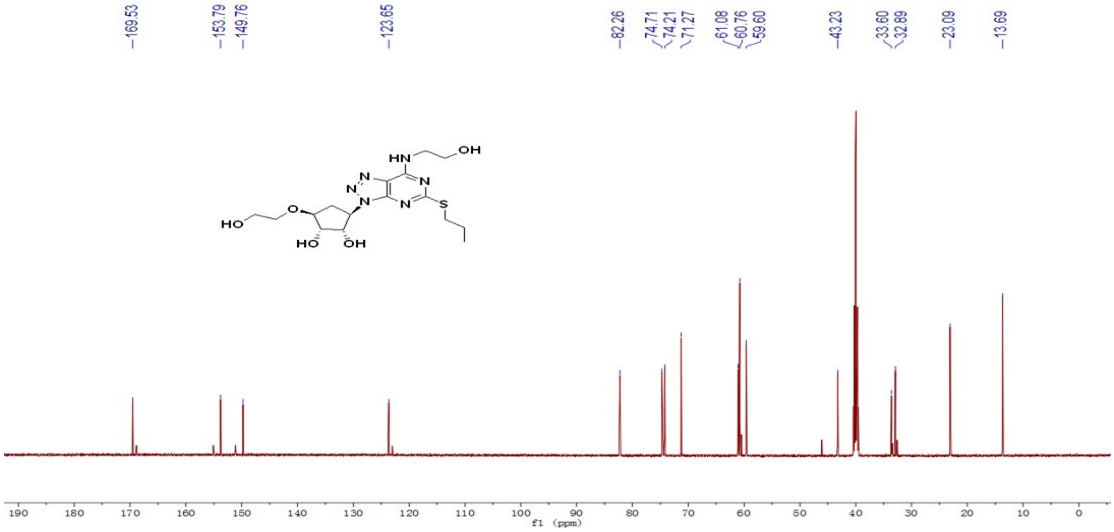


Figure S.4-8 ^{13}C NMR spectra of **Ie**.

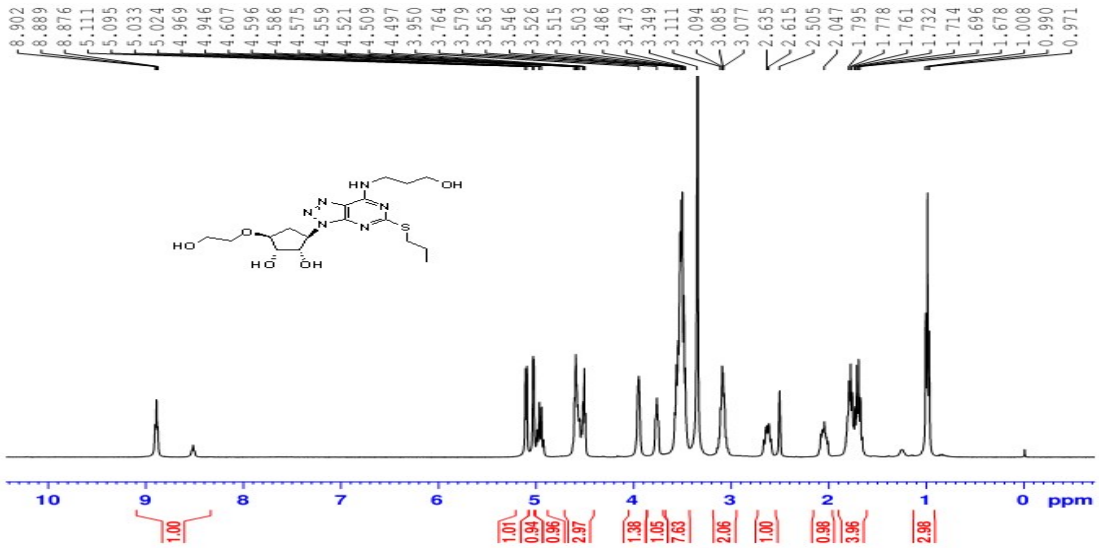


Figure S.4-9 ^{1}H NMR spectra of **If**.

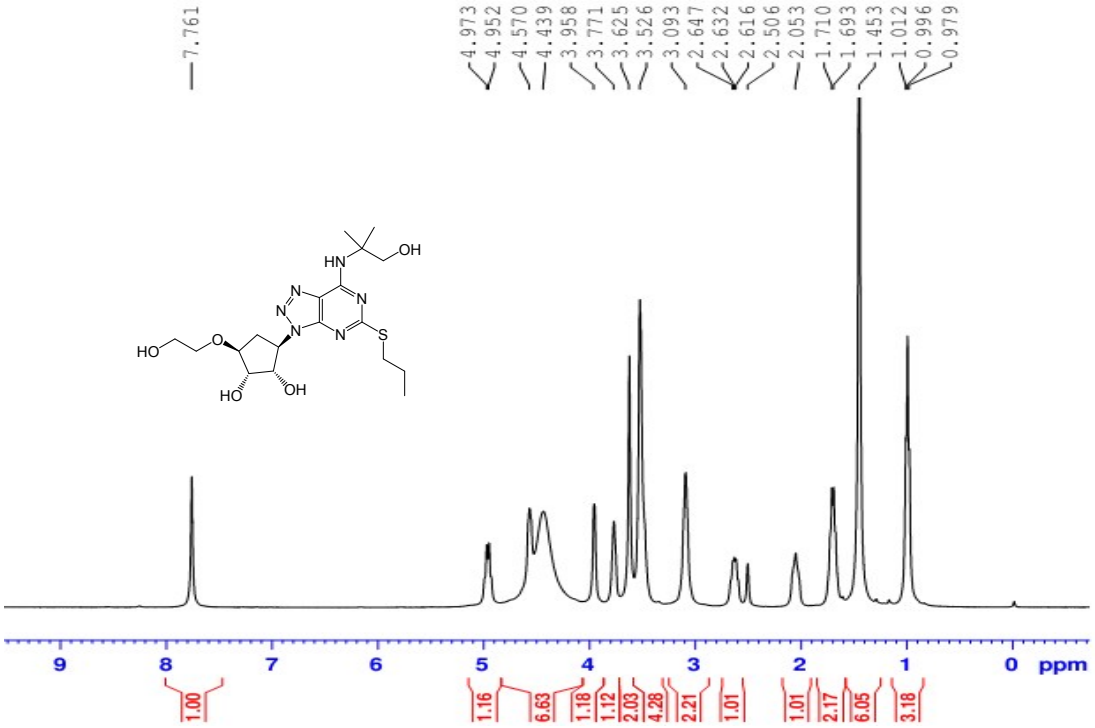


Figure S.4-10 ^{1}H NMR spectra of **Ig**.

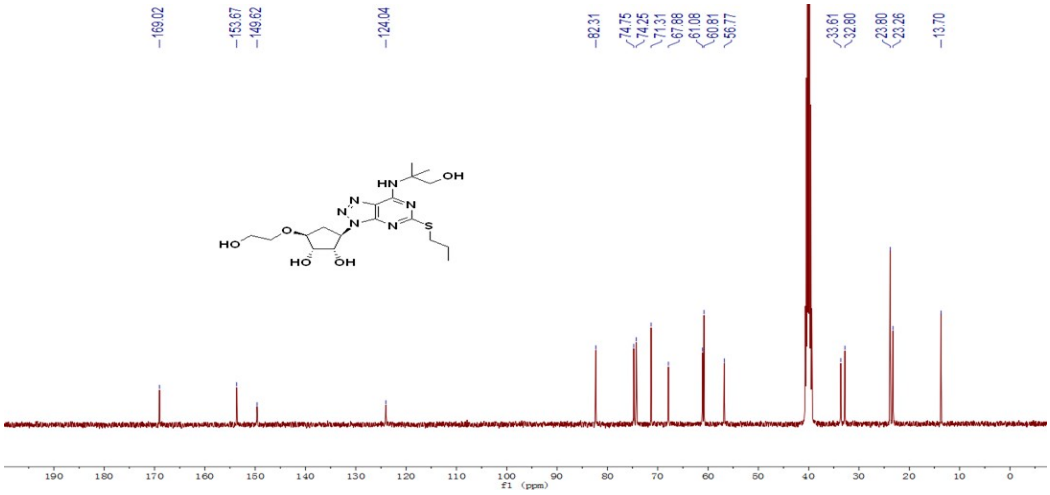


Figure S.4-11 ^{13}C NMR spectra of **Ig**.

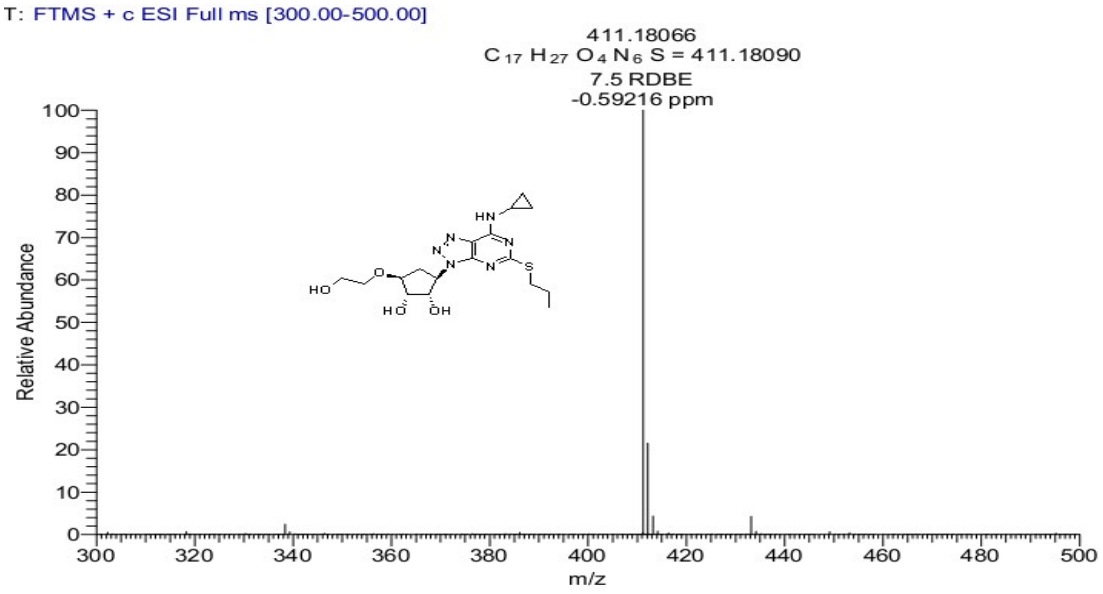


Figure S.4-12 HRMS spectra of **Ih**.

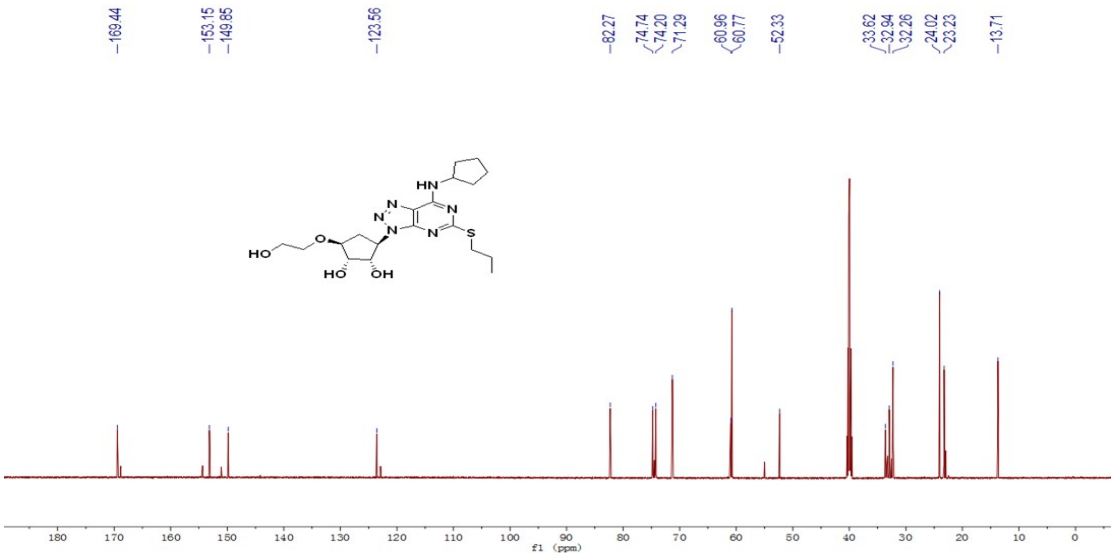


Figure S.4-13 ^{13}C NMR spectra of **Ii**.

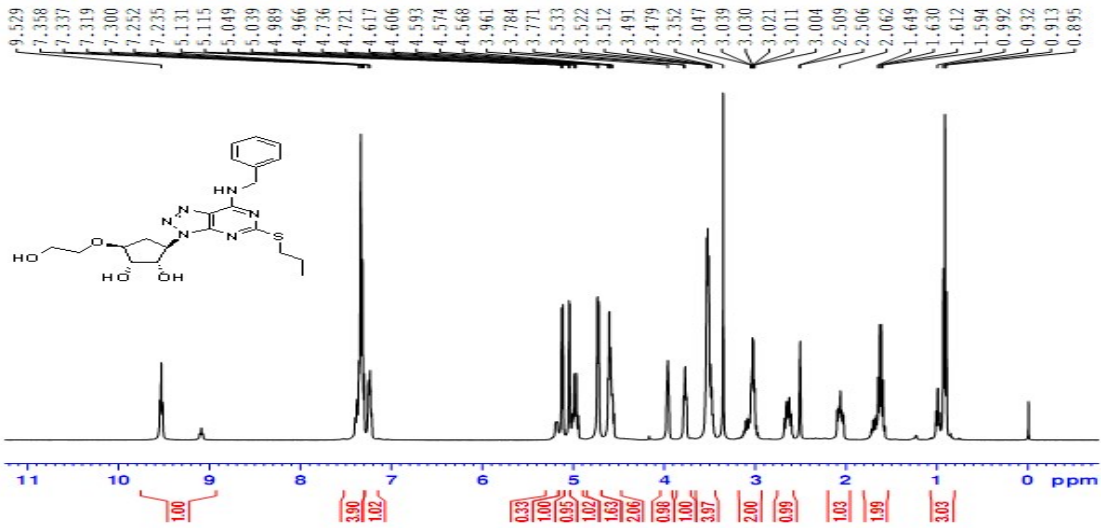


Figure S.4-14 ^{1}H NMR spectra of **Ij**.

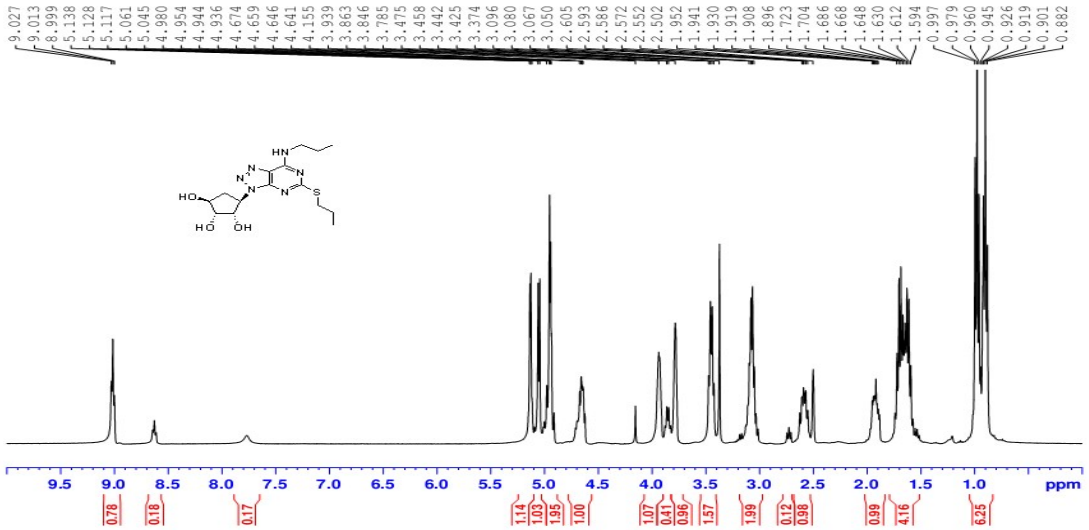


Figure S.4-15 ^{1}H NMR spectra of **Ik**.

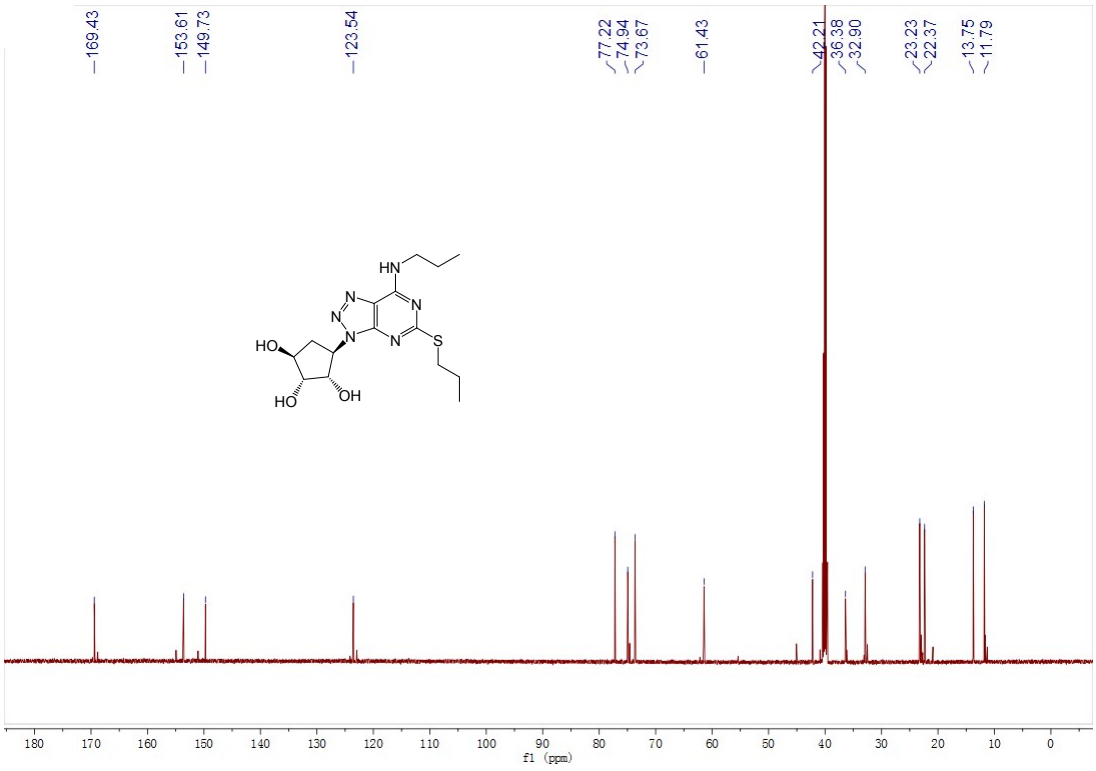


Figure S.4-16 ^{13}C NMR spectra of **Ik**.

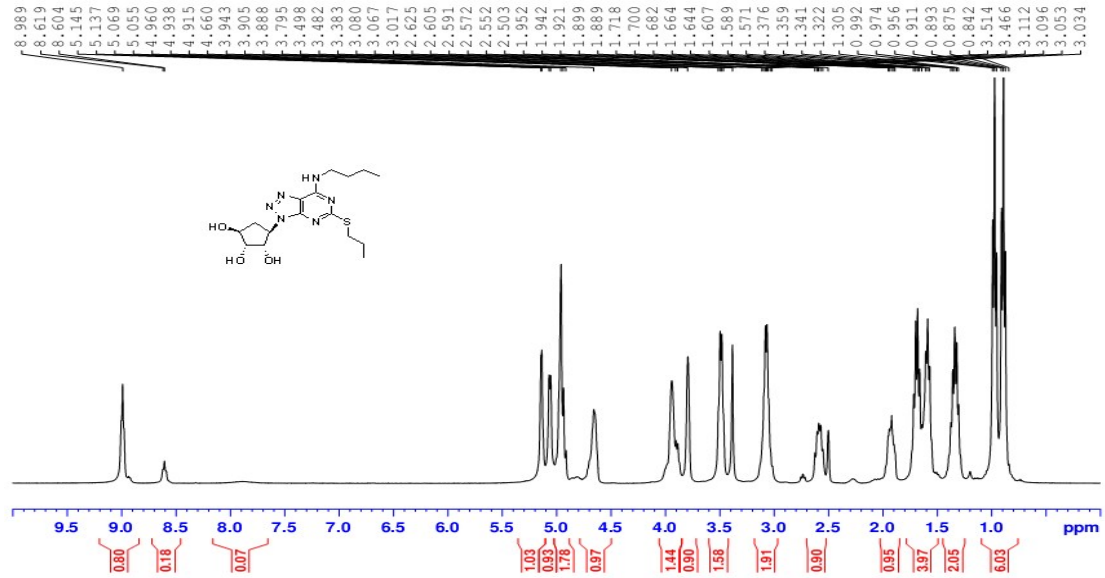


Figure S.4-17 ^{1}H NMR spectra of **Il**.

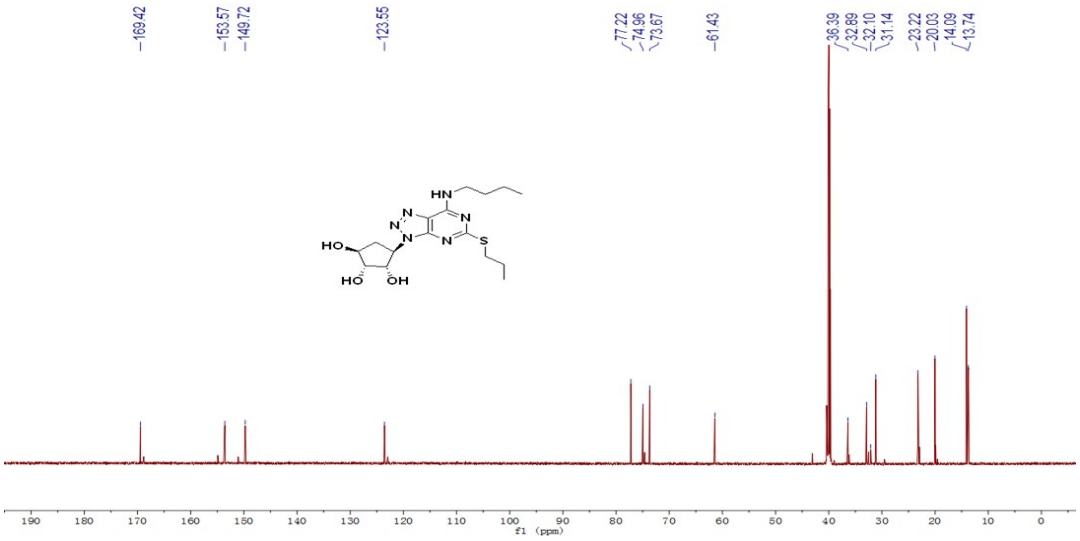


Figure S.4-18 ^{13}C NMR spectra of **II**.

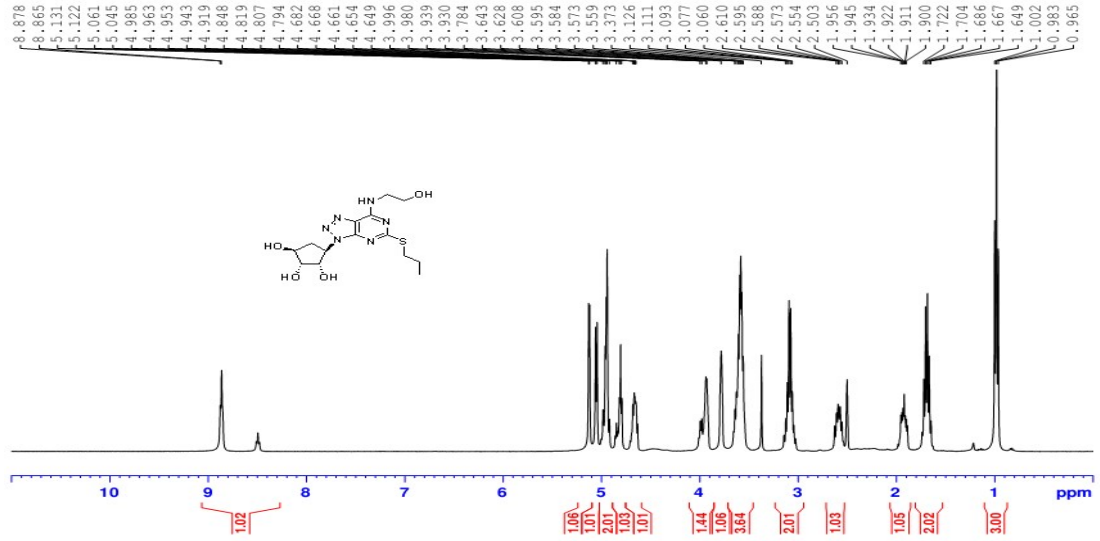


Figure S.4-19 ^{1}H NMR spectra of **Im**.

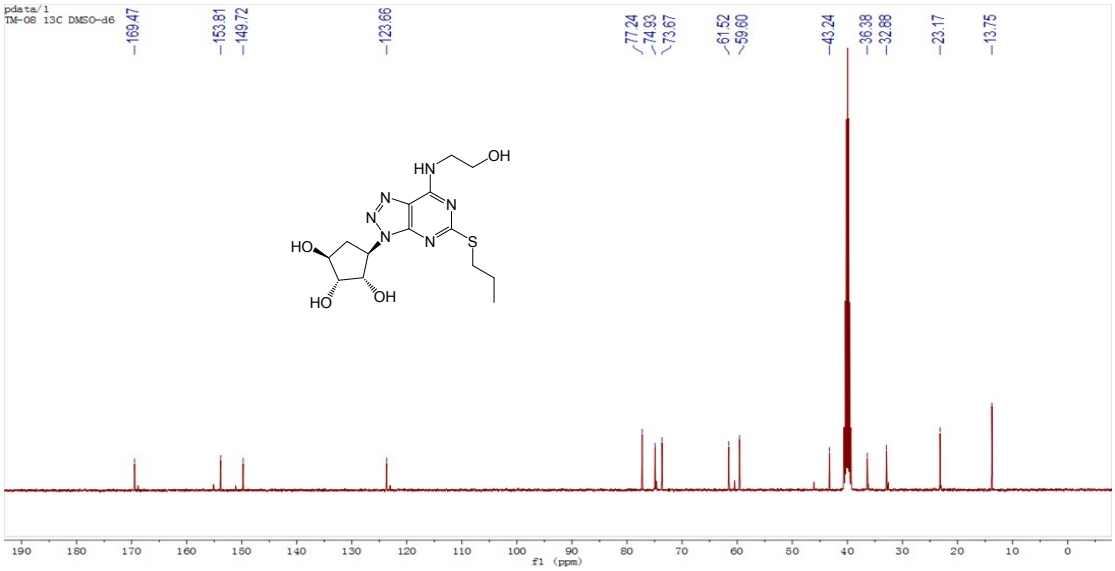


Figure S.4-20 ^{13}C NMR spectra of **Im**.

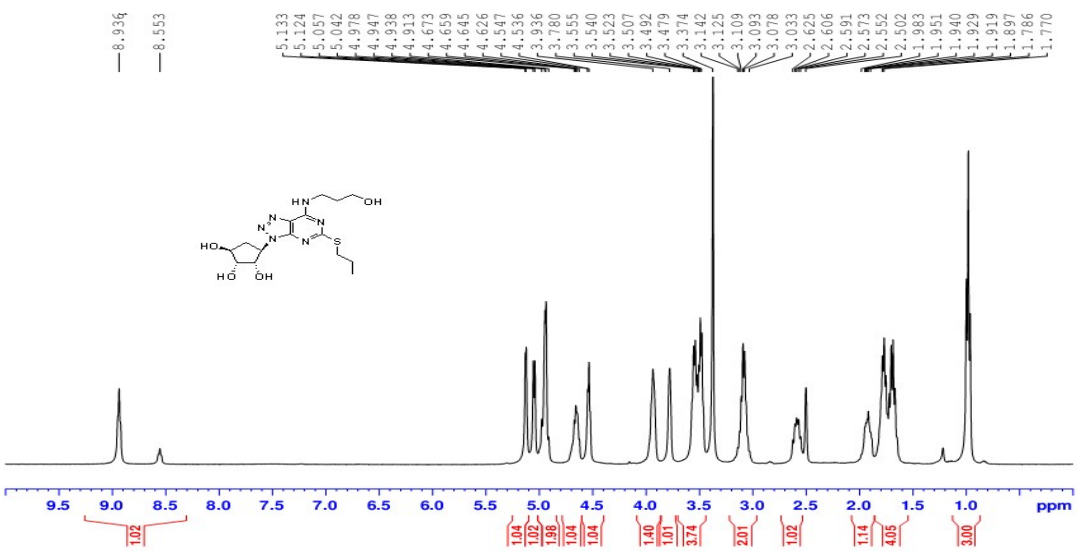


Figure S.4-21 ^{1}H NMR spectra of **In**.

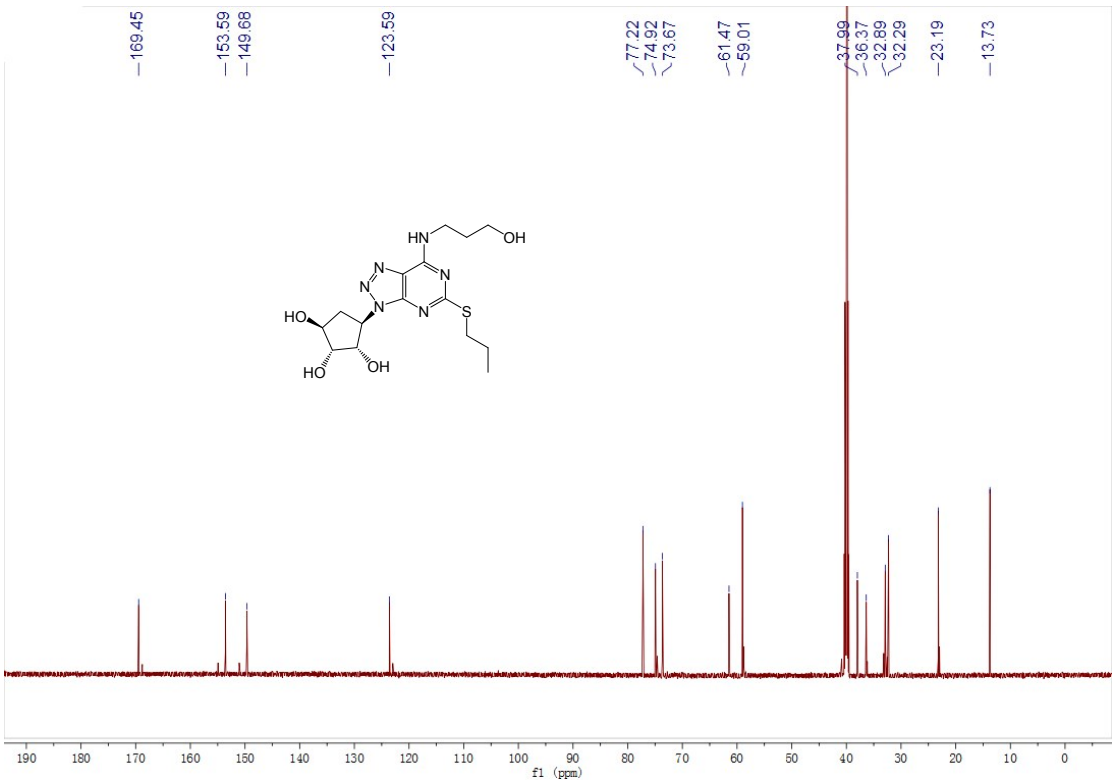


Figure S.4-22 ^{13}C NMR spectra of **In**.

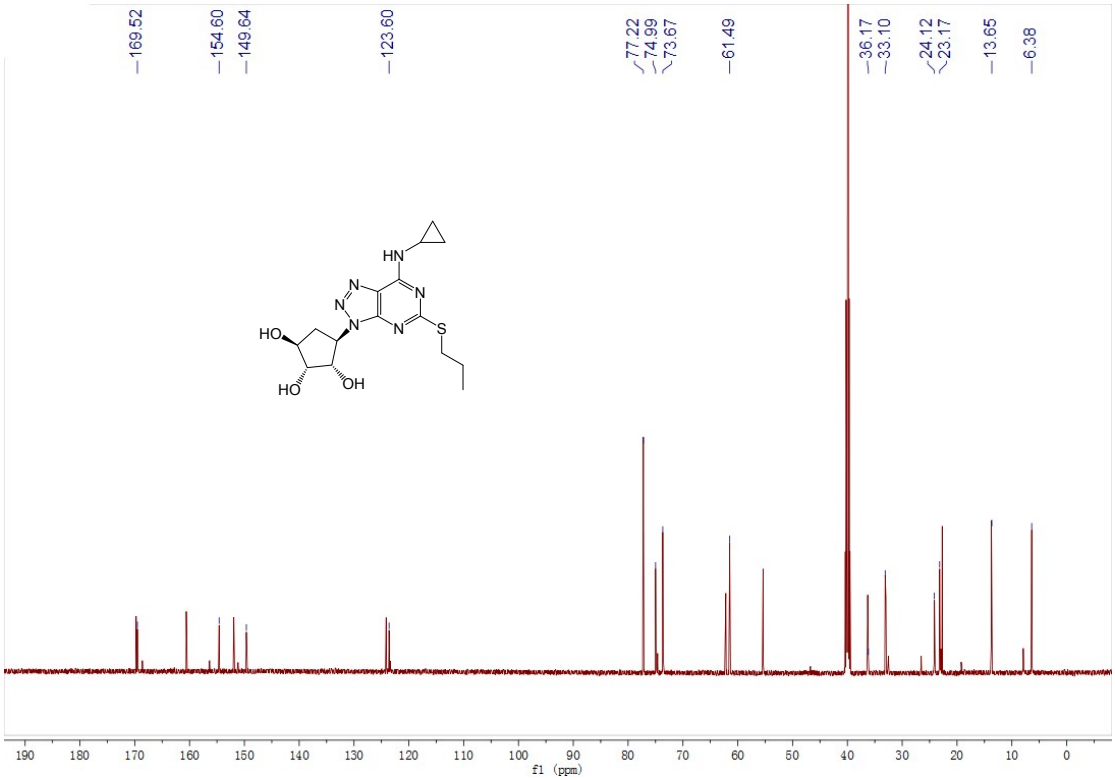


Figure S.4-23 ^{13}C NMR spectra of **Io**.

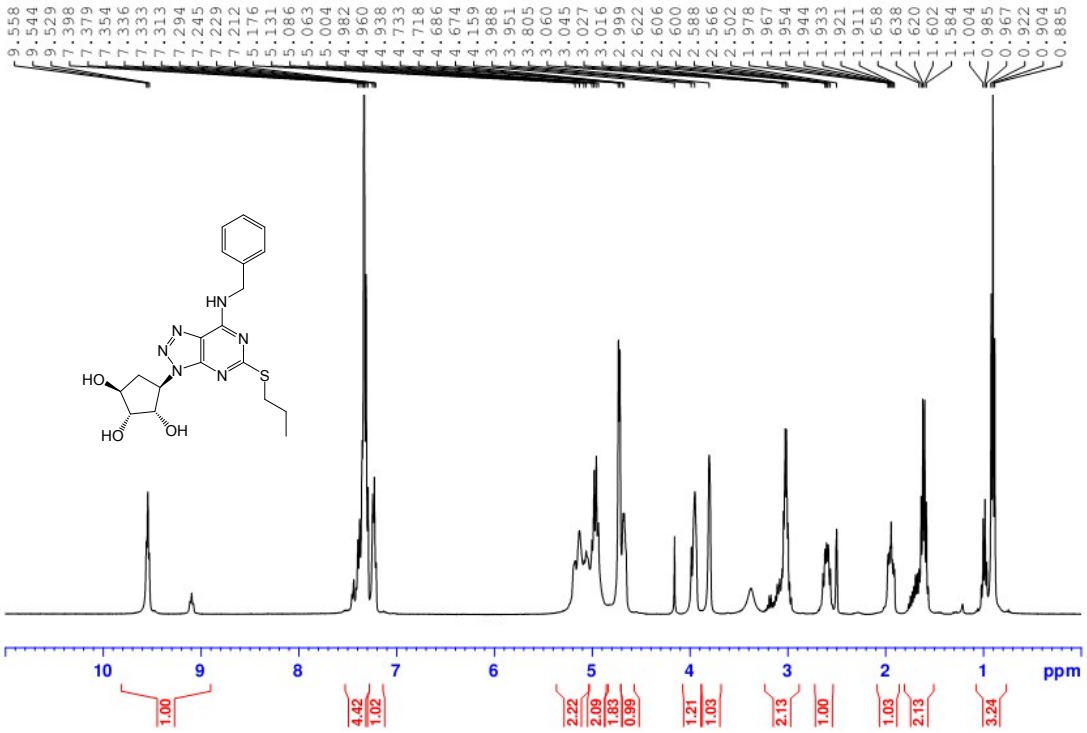


Figure S.4-24 ^{1}H NMR spectra of **Ip**.

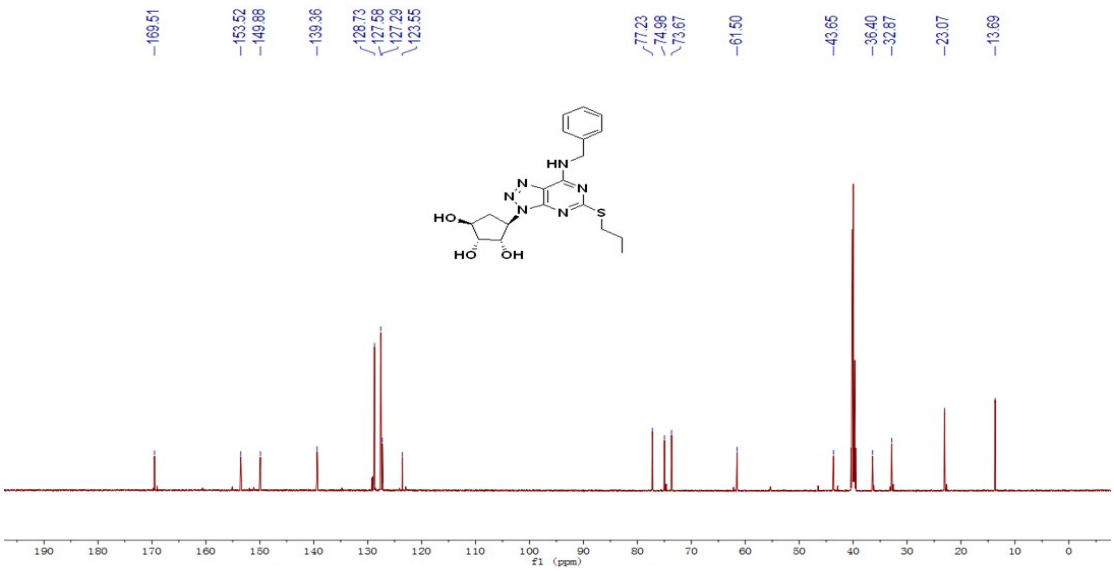


Figure S.4-25 ^{13}C NMR spectra of **Ip**.

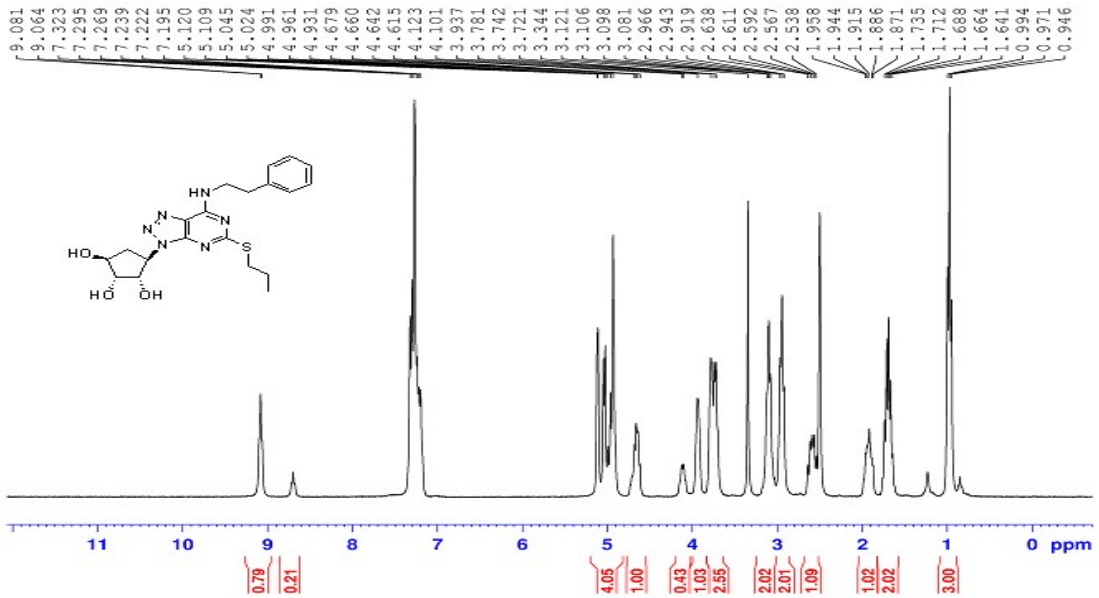


Figure S.4-26 ^{1}H NMR spectra of **Iq**.

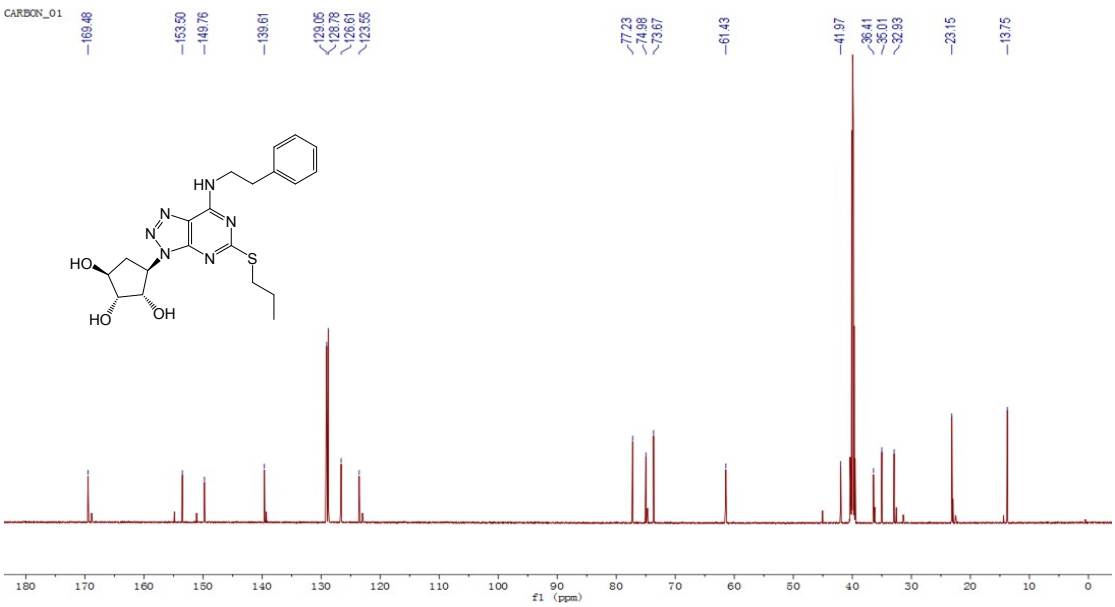


Figure S.4-27 ^{13}C NMR spectra of **Iq**.

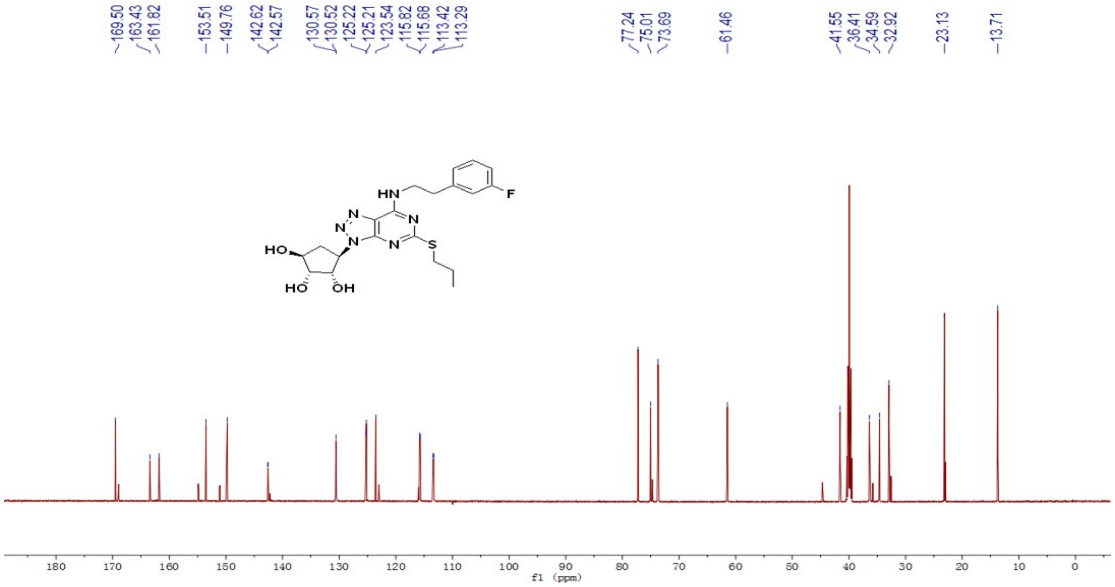


Figure S.4-28 ^{13}C NMR spectra of **Ir**.

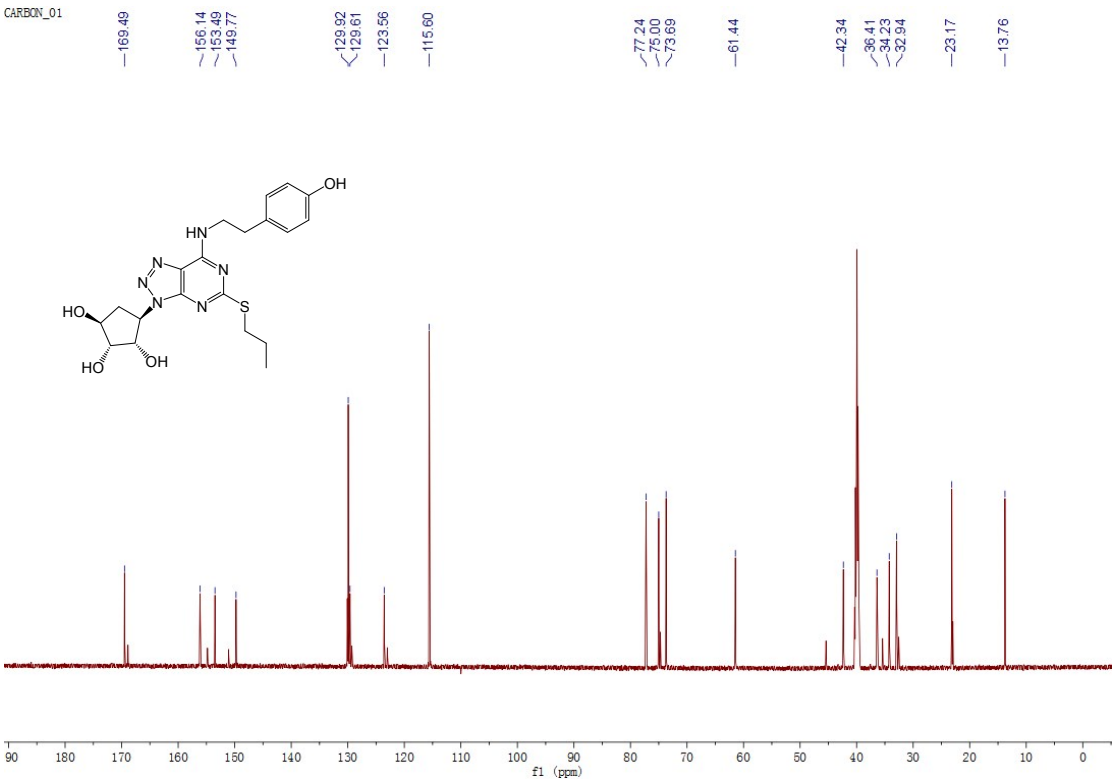


Figure S.4-29 ^{13}C NMR spectra of **Is**.

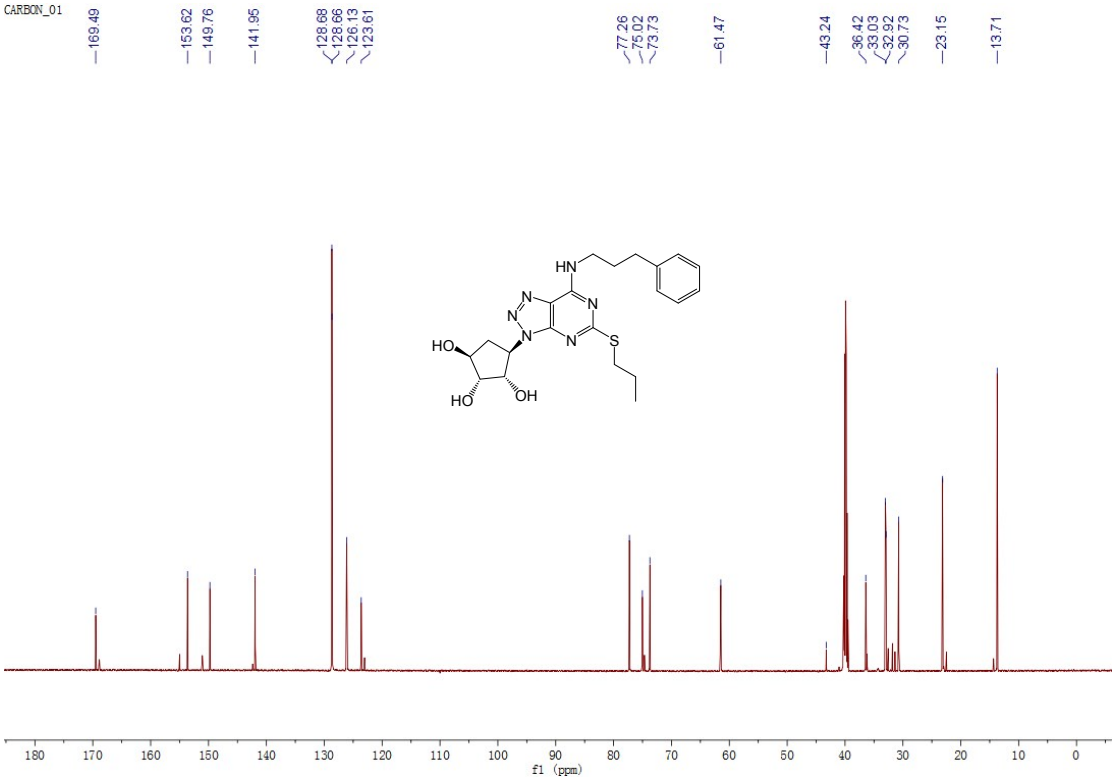


Figure S.4-30 ^{13}C NMR spectra of **It**.

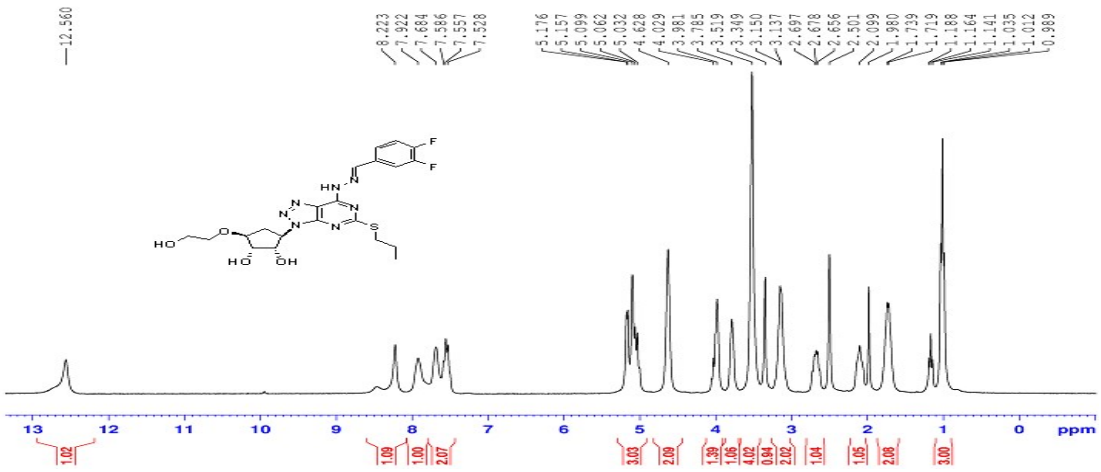


Figure S.4-31 ^{1}H NMR spectra of **IIa**.

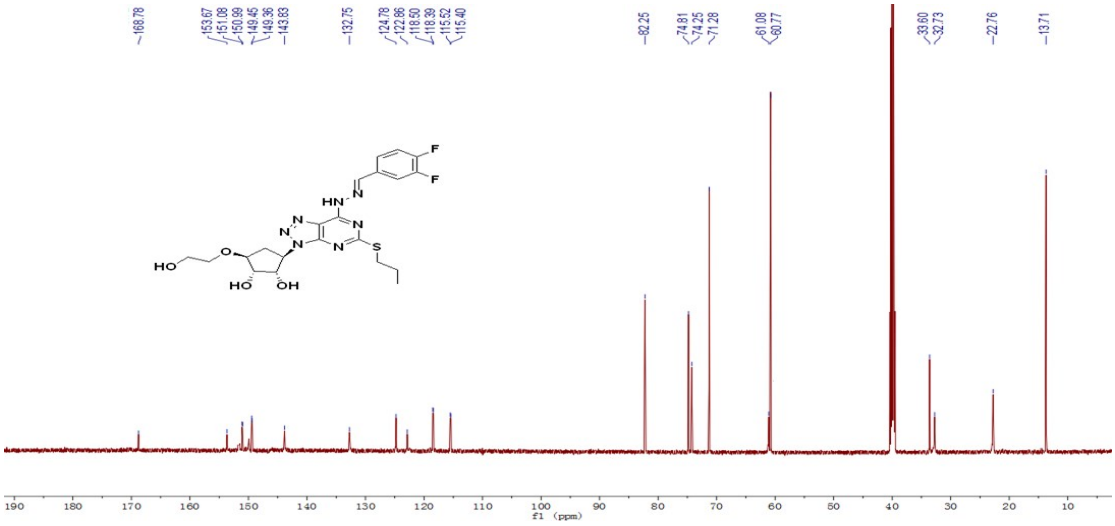


Figure S.4-32 ^{13}C NMR spectra of **IIa**.

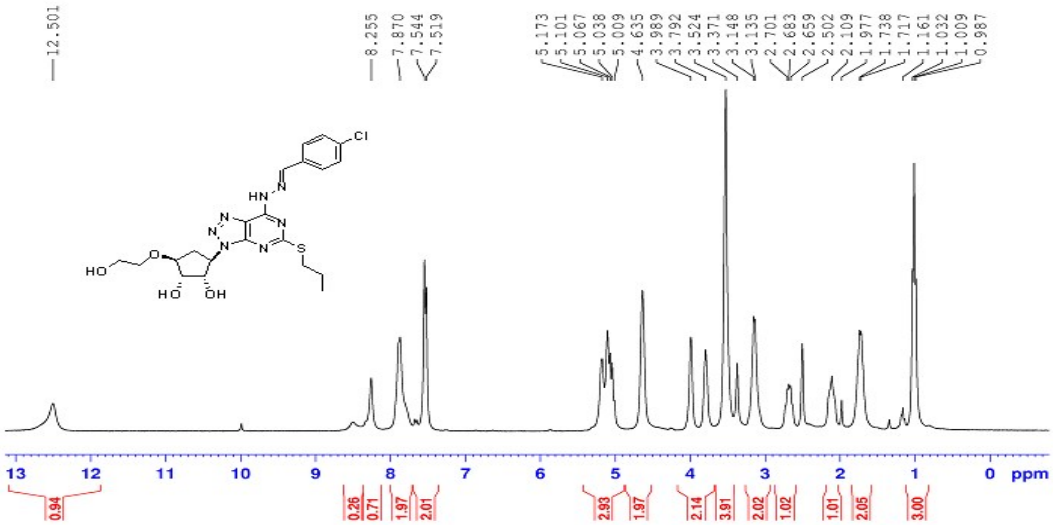


Figure S.4-33 ^{1}H NMR spectra of **IIb**.

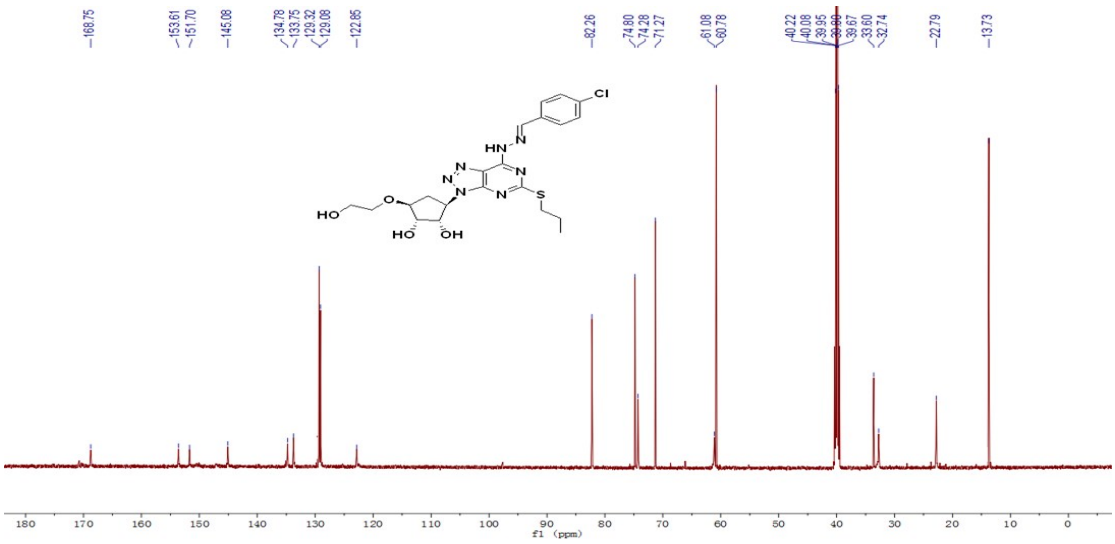


Figure S.4-34 ^{13}C NMR spectra of **IIb**.

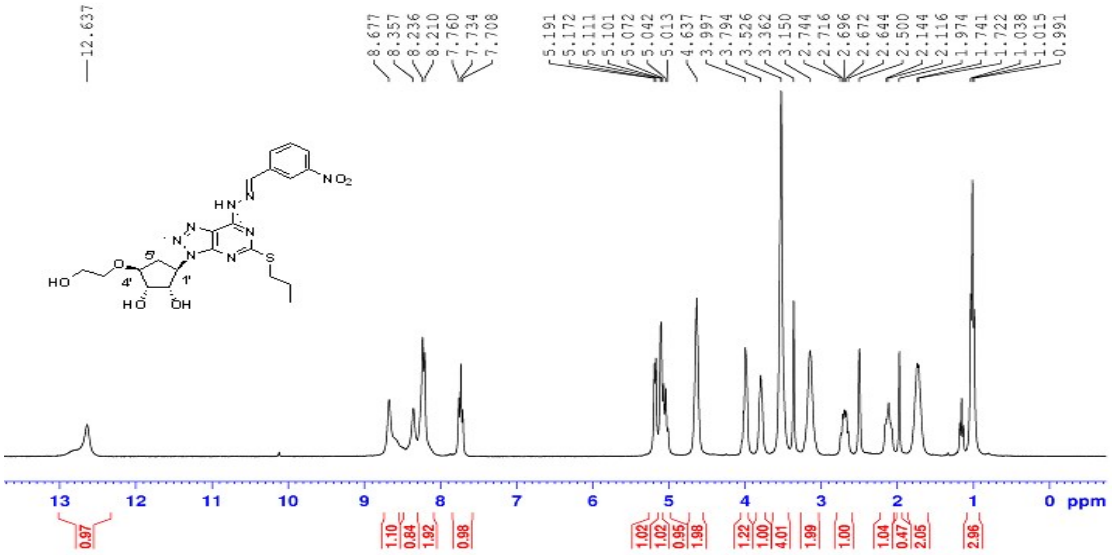


Figure S.4-35 ^{1}H NMR spectra of **IIc**.

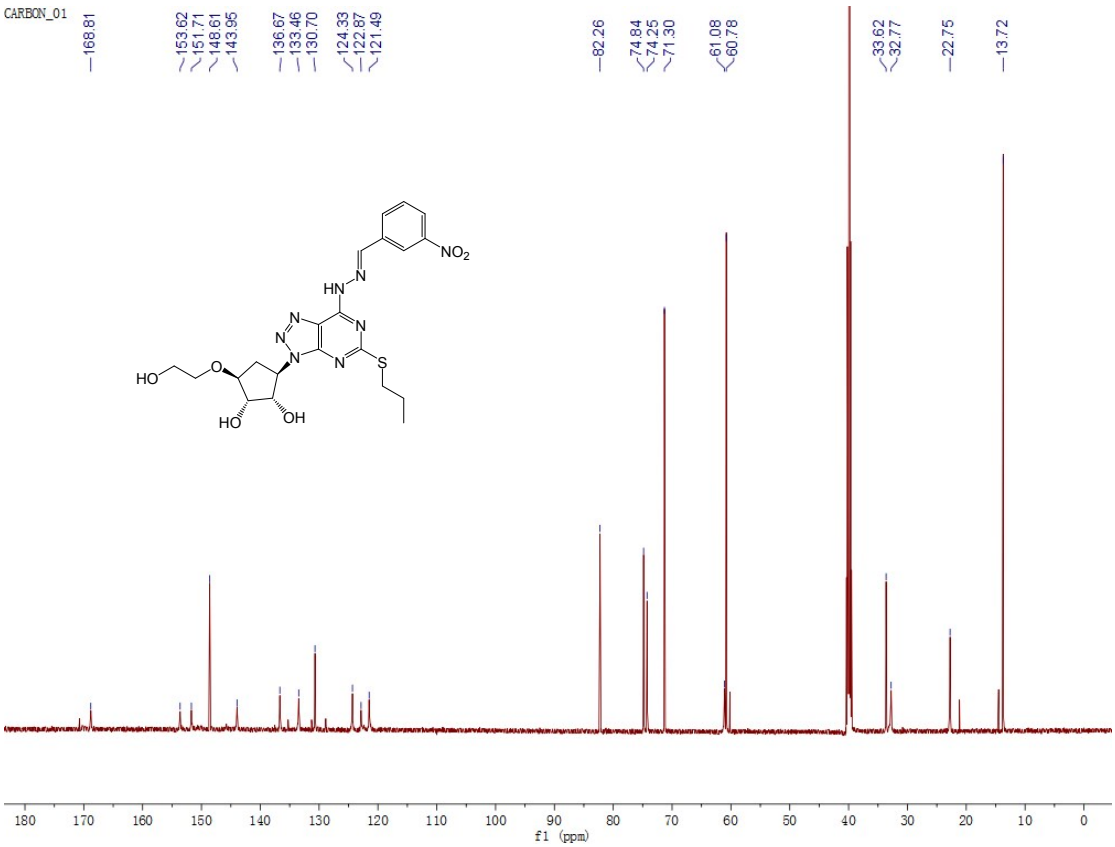


Figure S.4-36 ^{13}C NMR spectra of **IIc**.

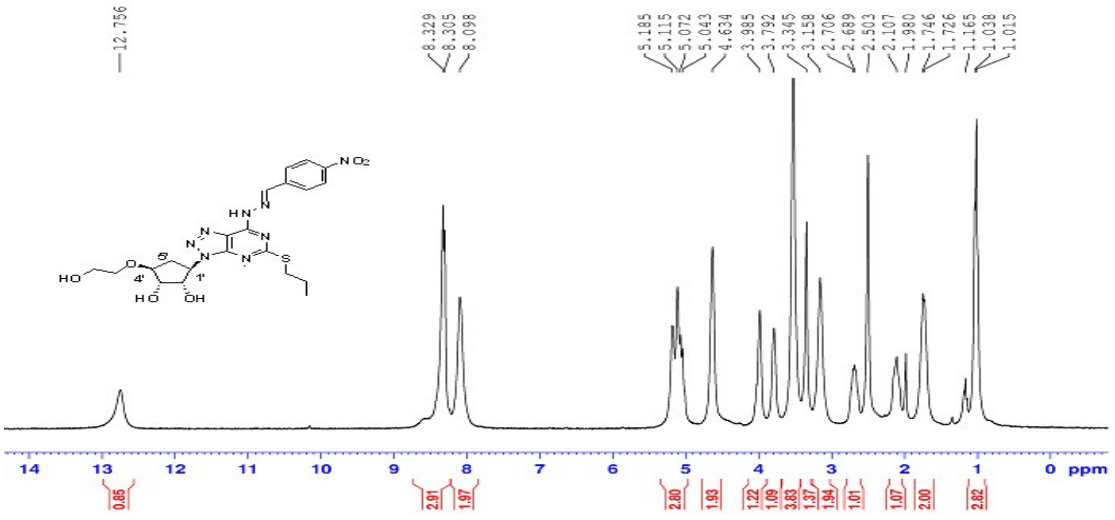


Figure S.4-37 ^{1}H NMR spectra of **IId**.

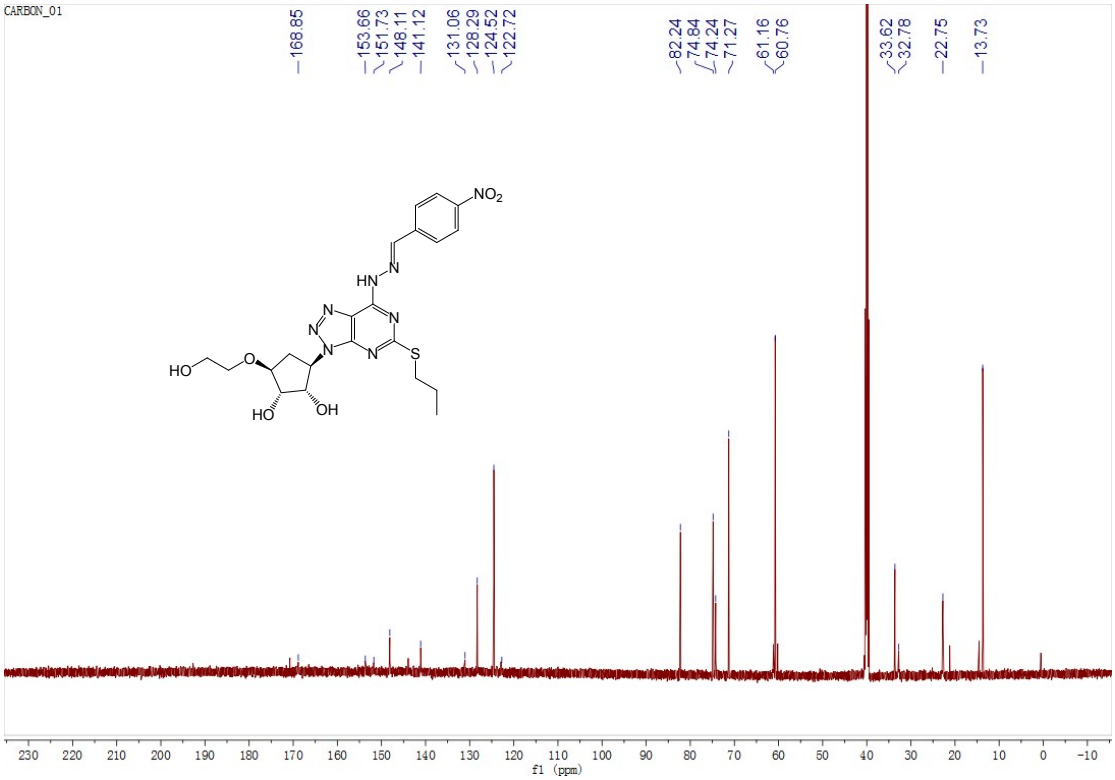


Figure S.4-38 ^{13}C NMR spectra of **IId**.

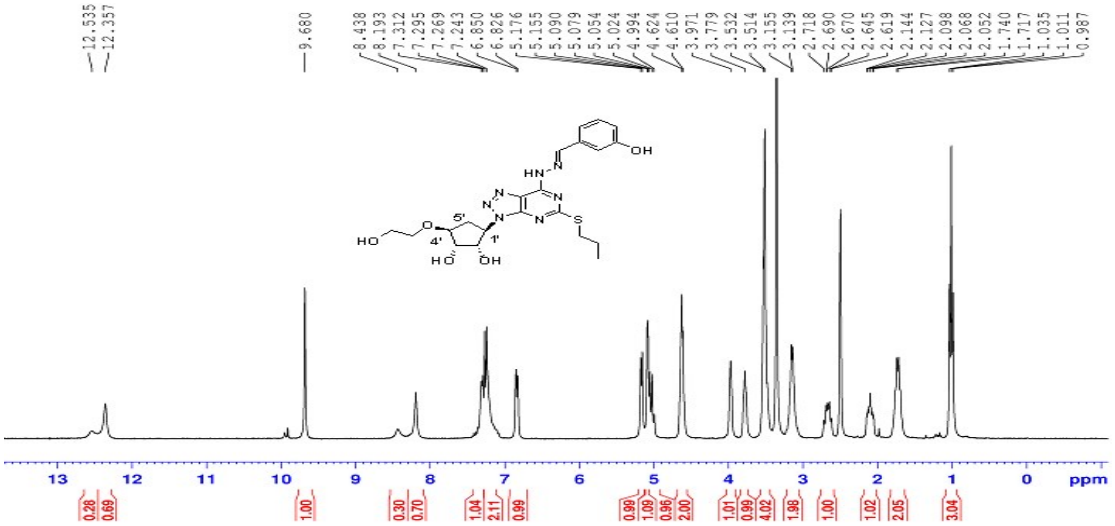


Figure S.4-39 ^{1}H NMR spectra of **IIe**.

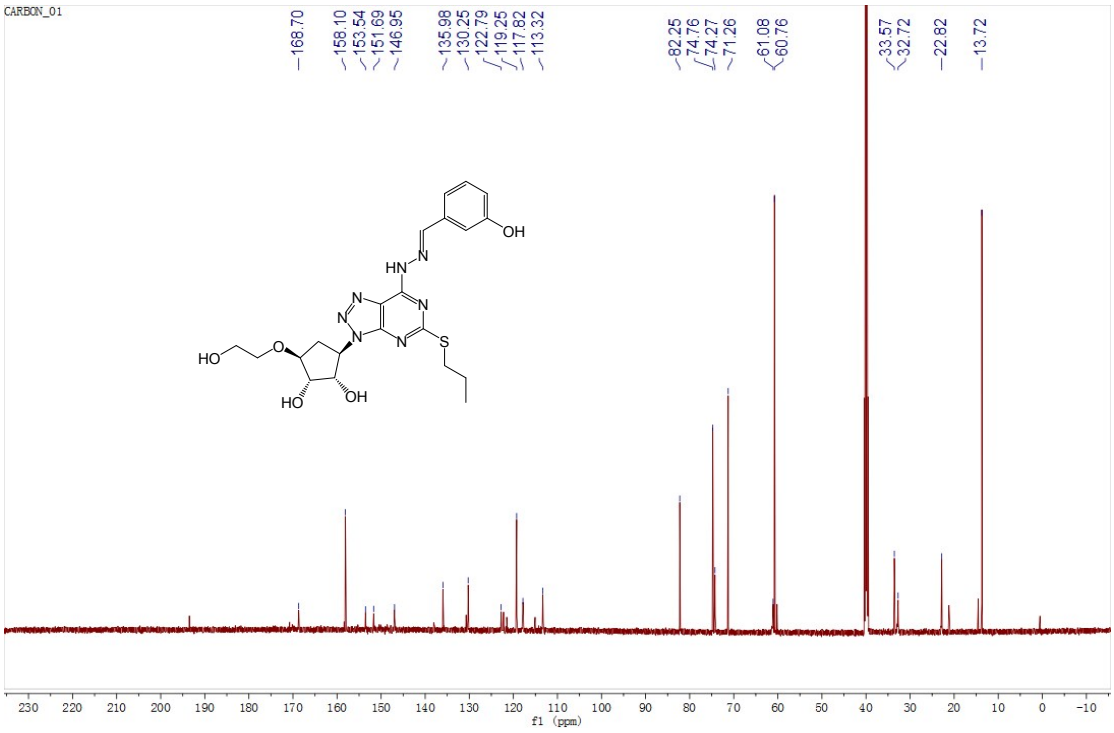


Figure S.4-40 ^{13}C NMR spectra of **IIe**.

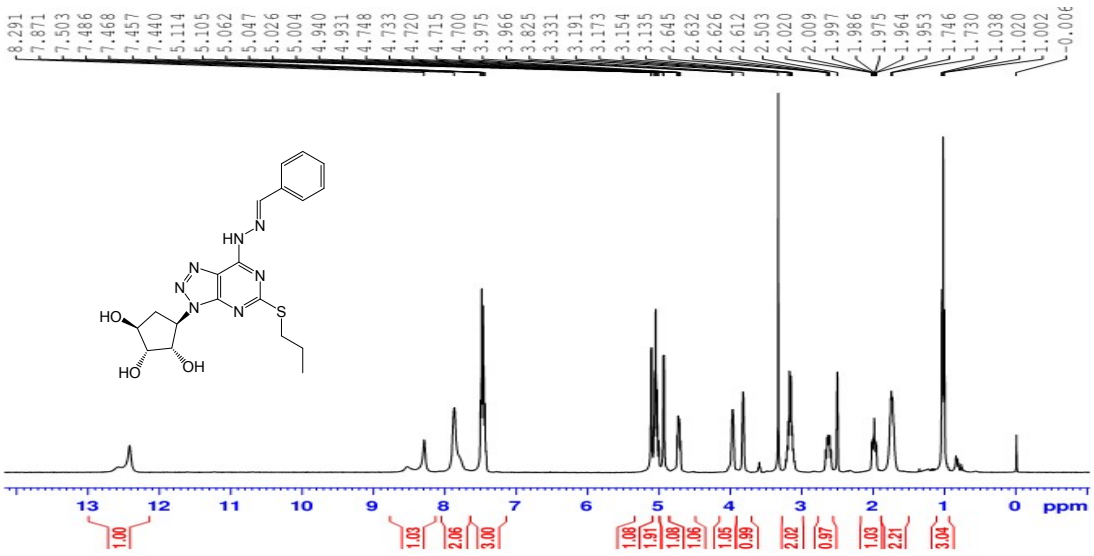


Figure S.4-41 ^{1}H NMR spectra of **IIf**.

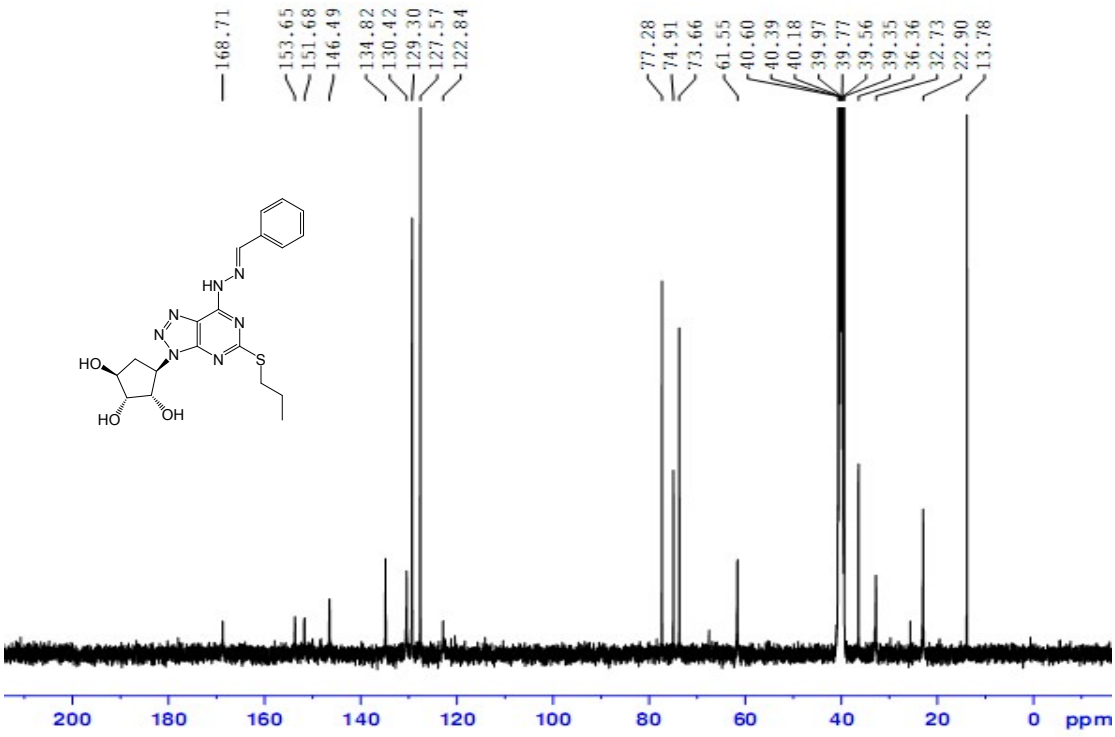


Figure S.4-42 ^{13}C NMR spectra of **IIf**.

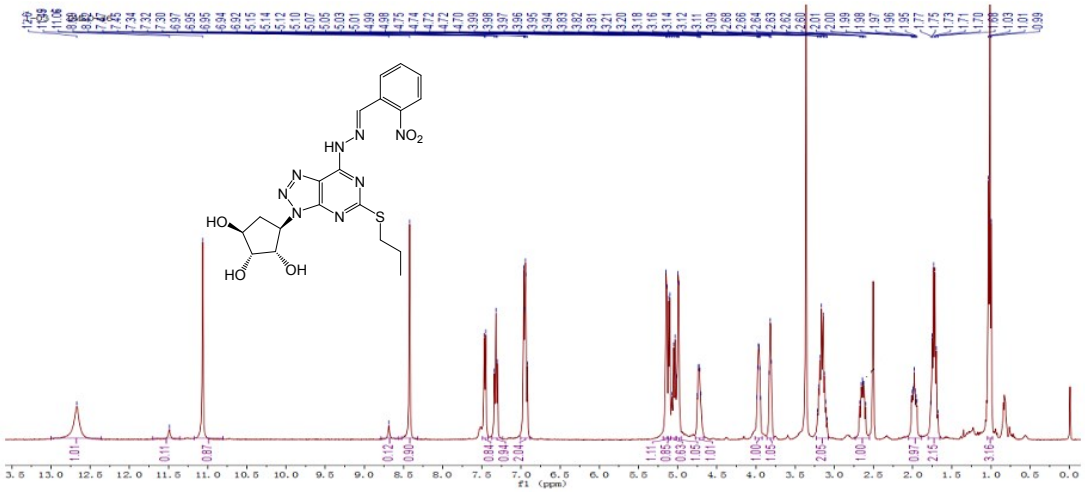


Figure S.4-43 ^{1}H NMR spectra of **IIg**.

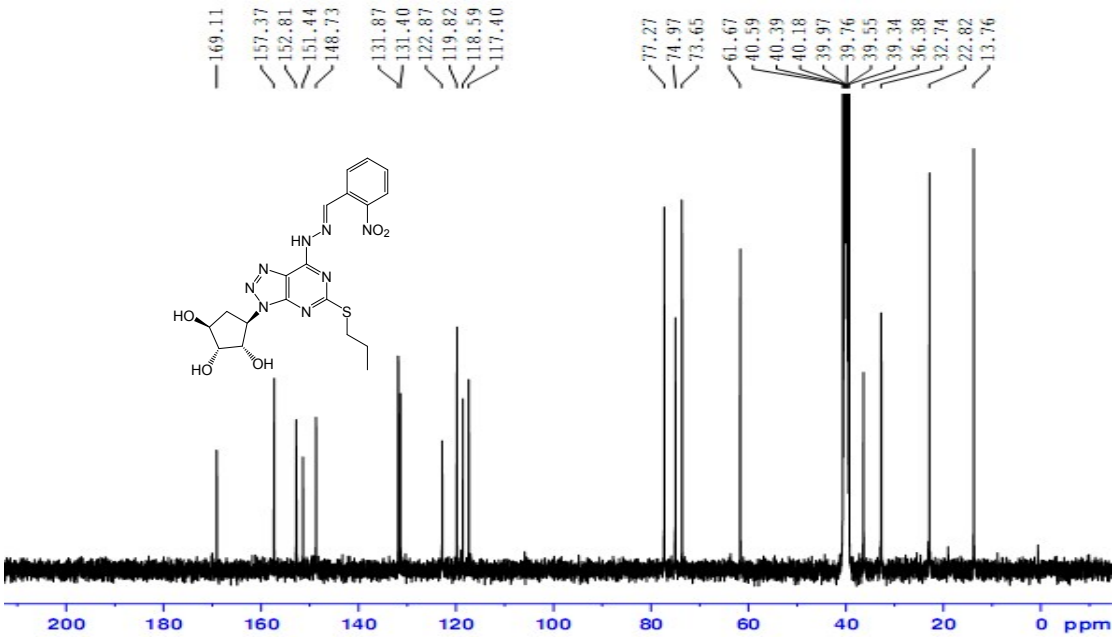


Figure S.4-44 ^{13}C NMR spectra of **IIg**.

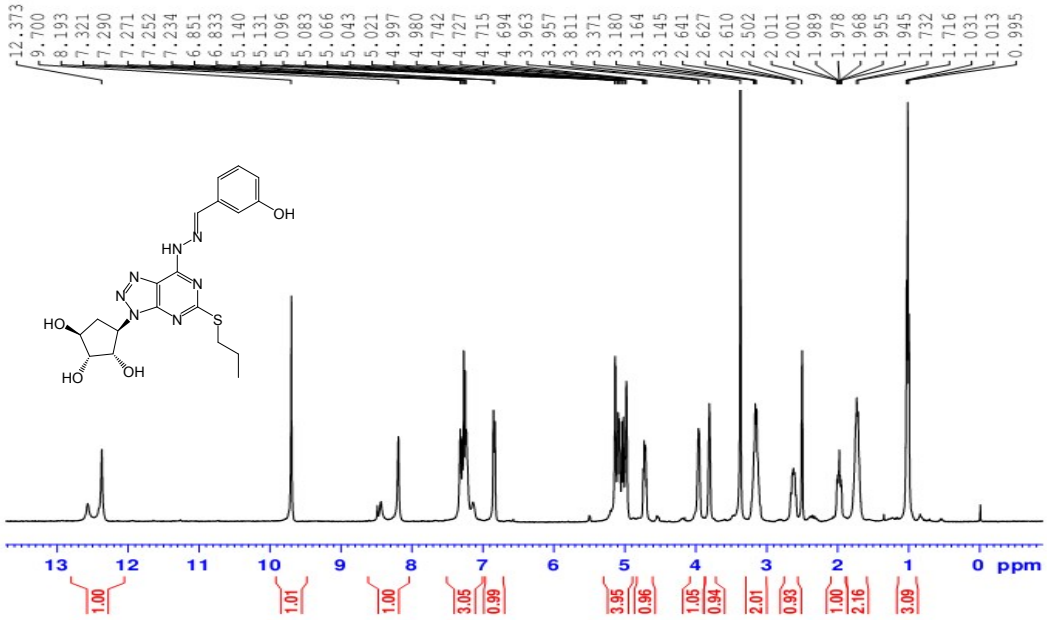


Figure S.4-45 ^{1}H NMR spectra of **IIh**.

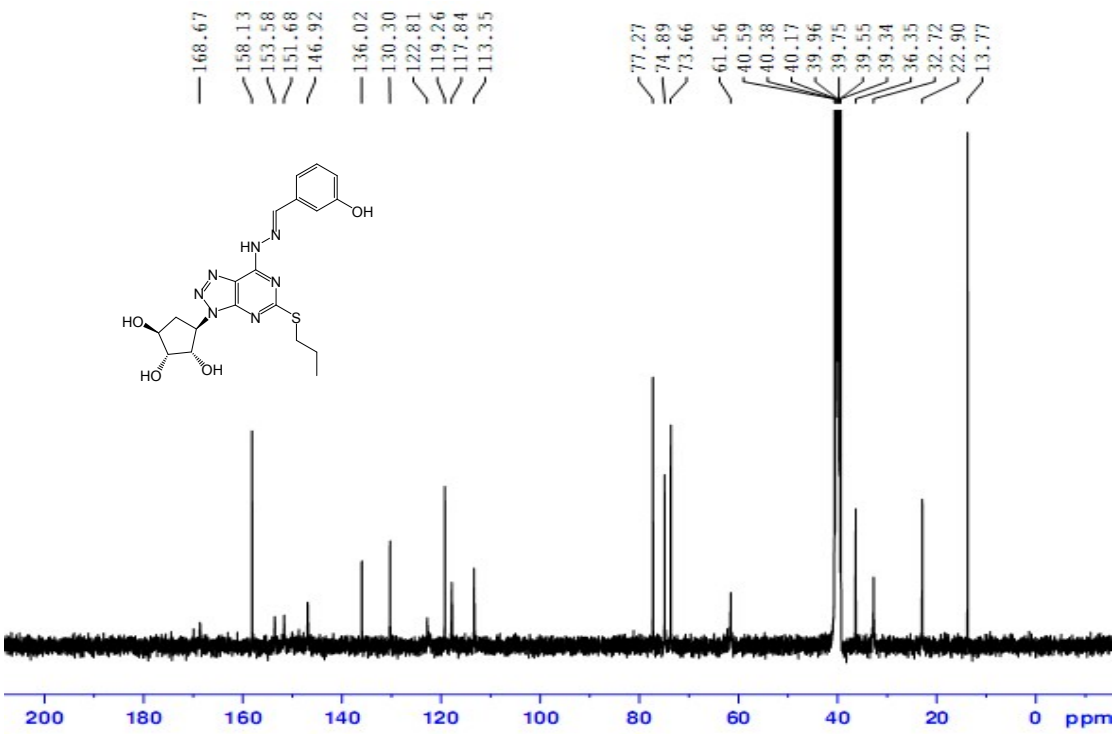


Figure S.4-46 ^{13}C NMR spectra of **IIh**.

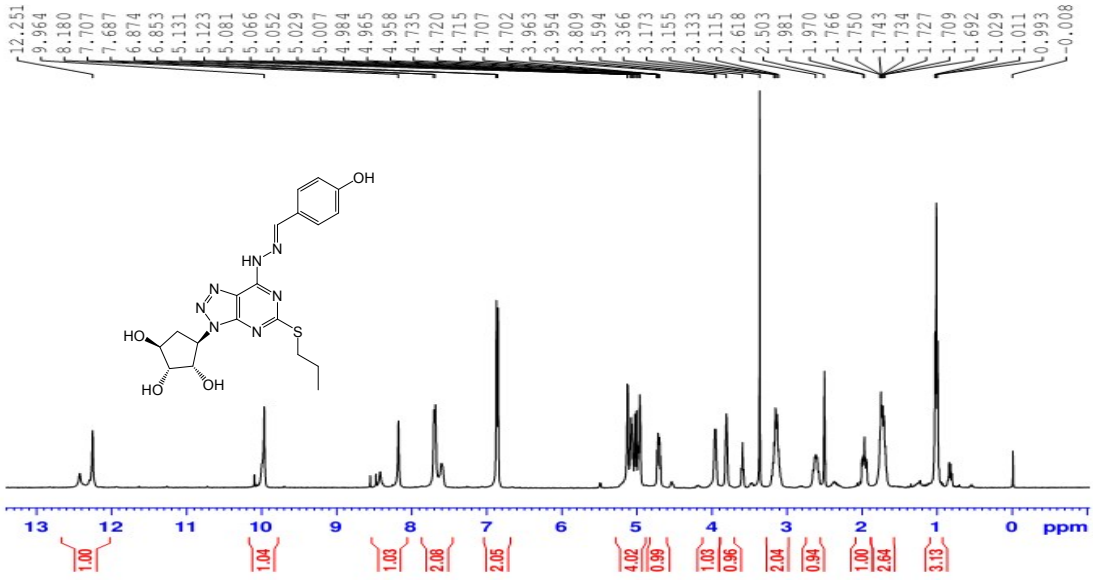


Figure S.4-47 ^{1}H NMR spectra of **IIi**.

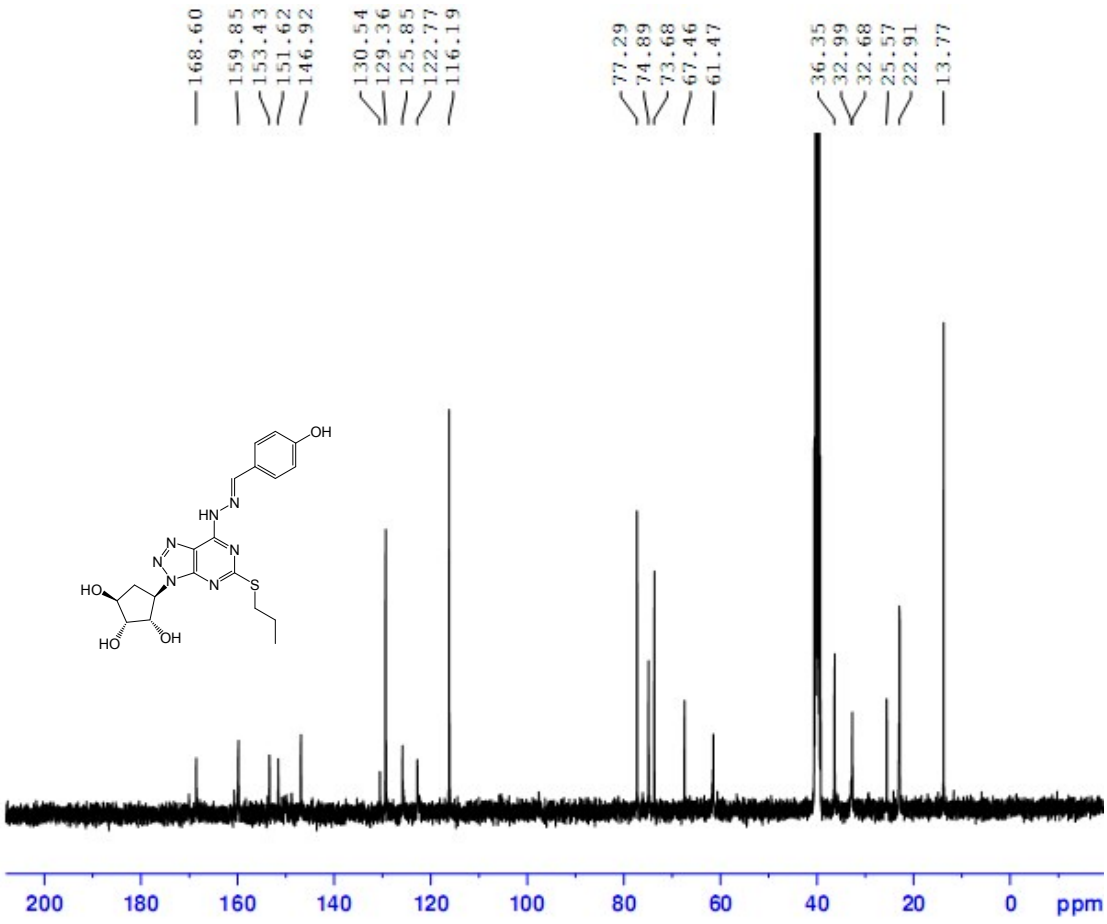


Figure S.4-48 ^{13}C NMR spectra of **IIi**.

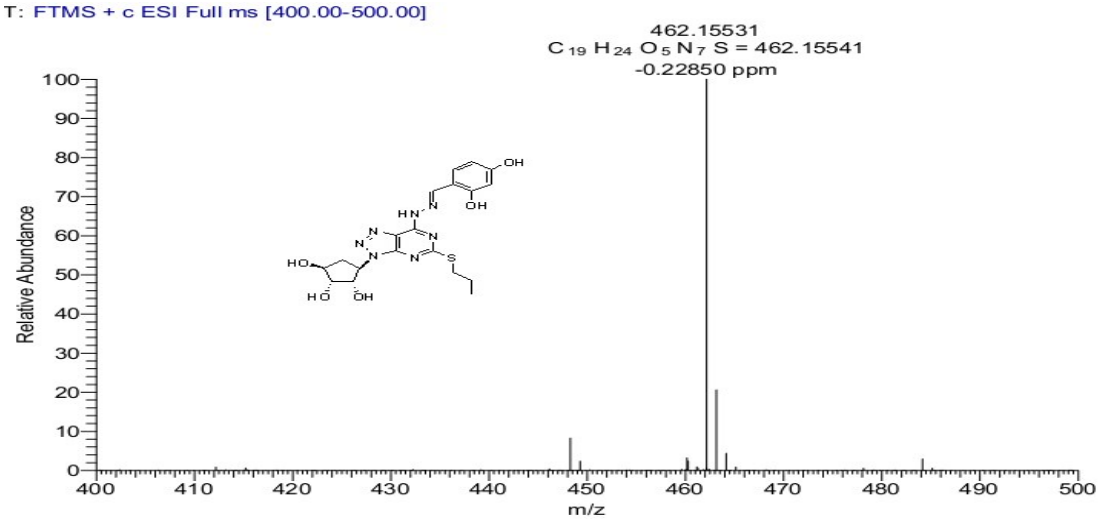


Figure S.4-49 HRMS spectra of **IIj**.

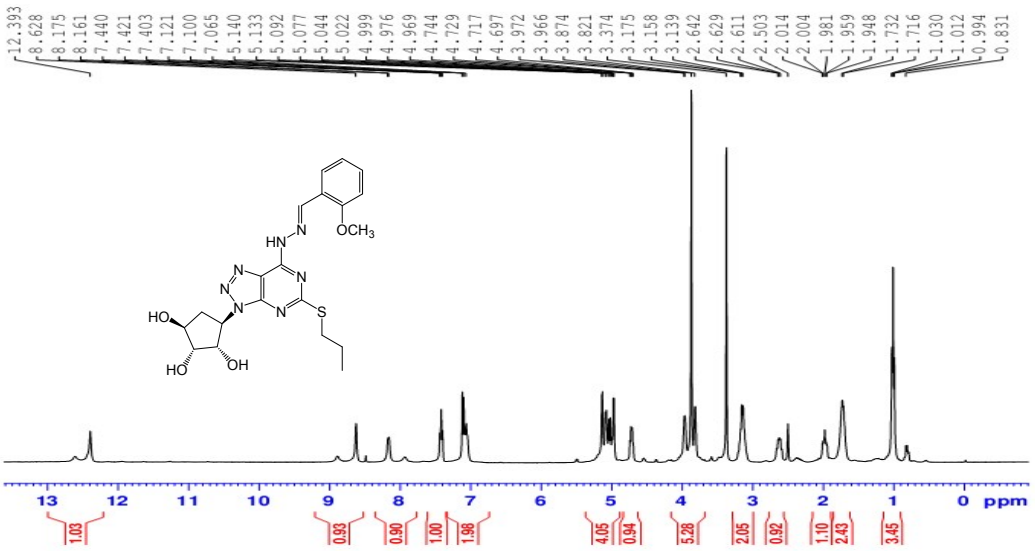


Figure S.4-50 ^{1}H NMR spectra of **IIk**.

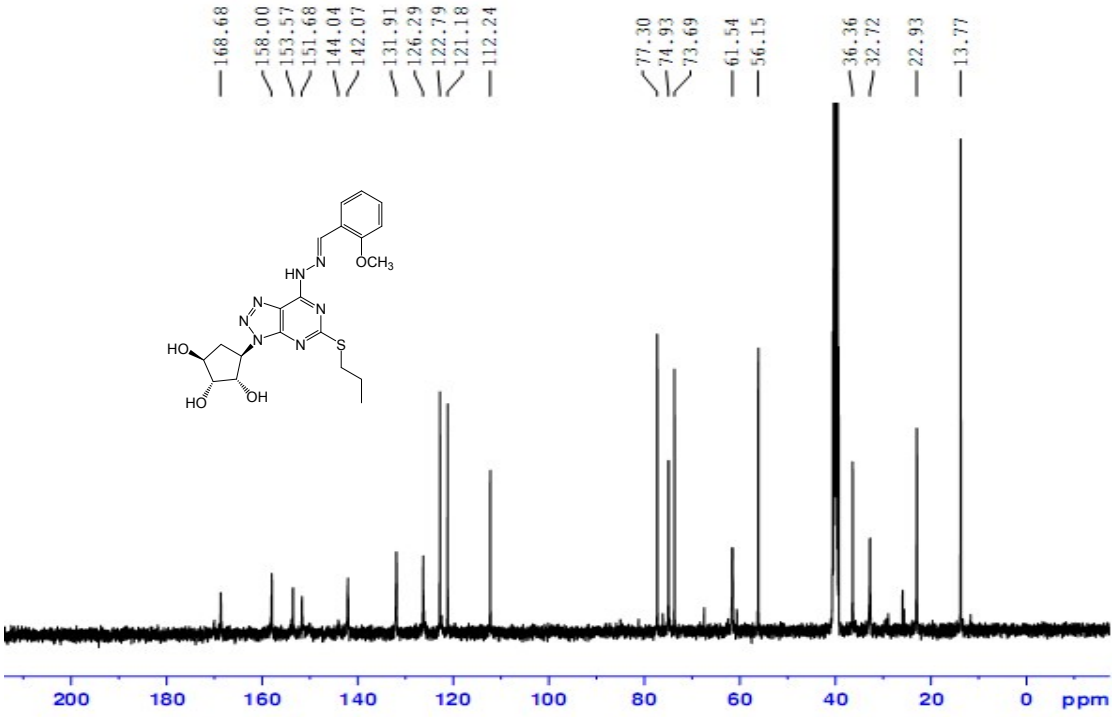


Figure S.4-51 ^{13}C NMR spectra of **IIk**.

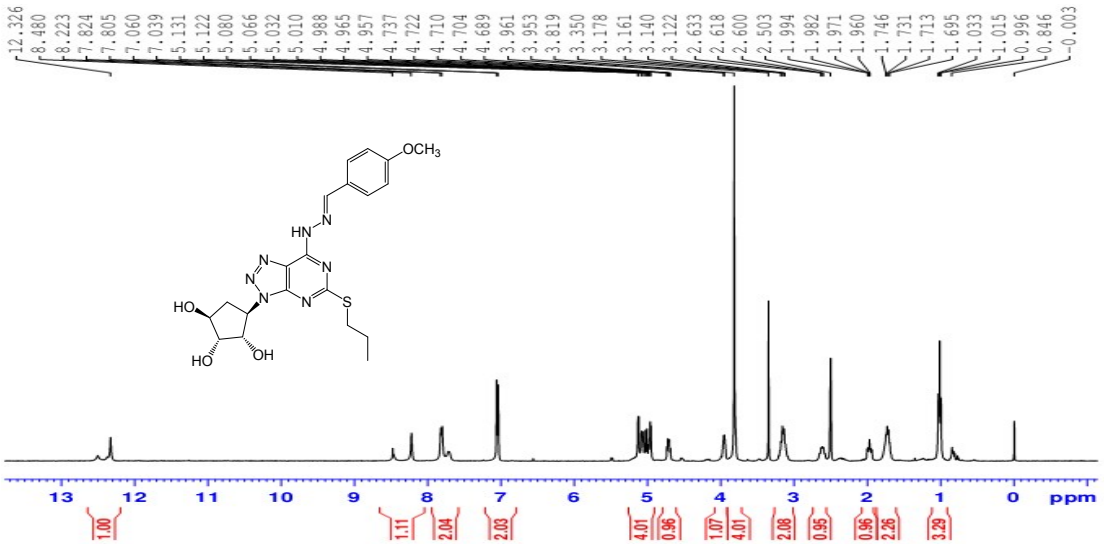


Figure S.4-52 ^{1}H NMR spectra of **III**.

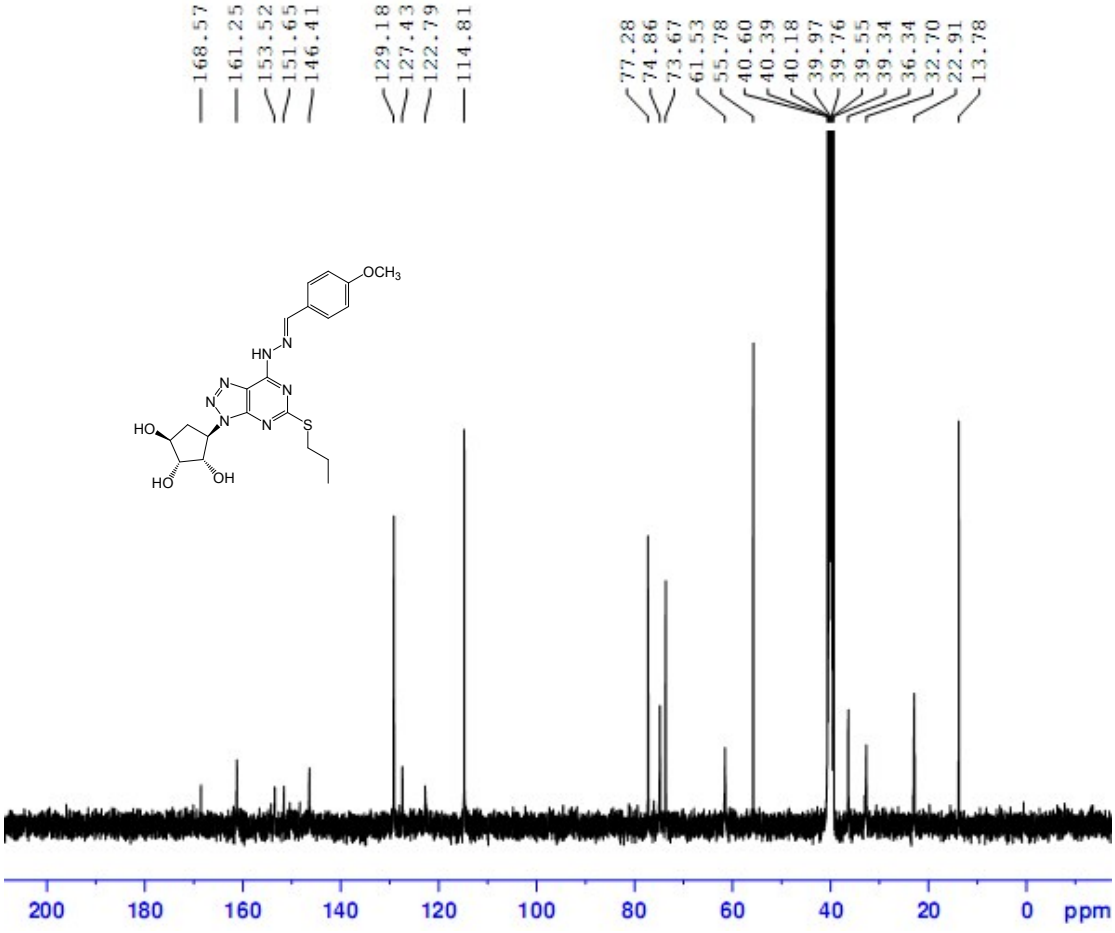


Figure S.4-53 ^{13}C NMR spectra of **III**.

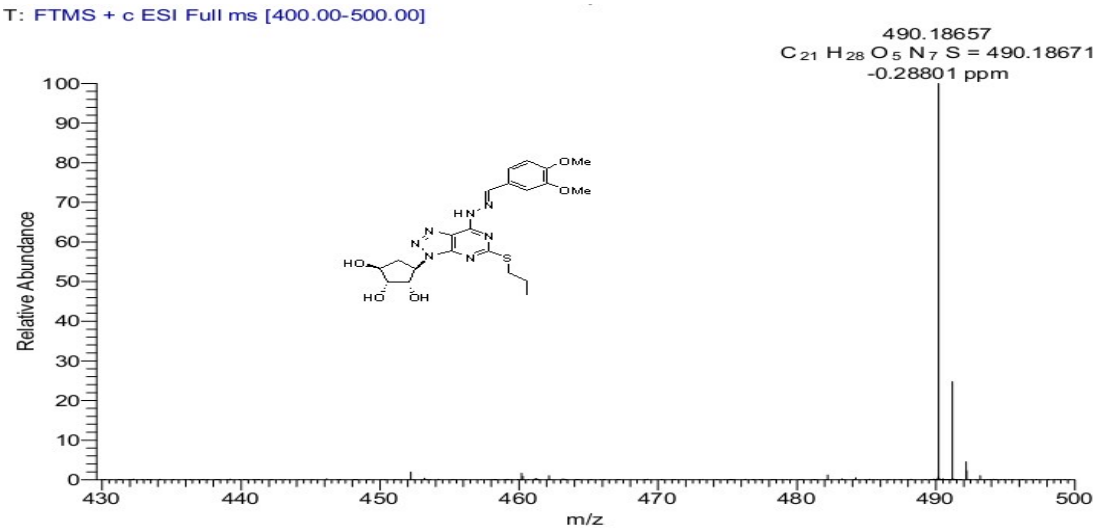


Figure S.4-54 HRMS spectra of **IIm**.

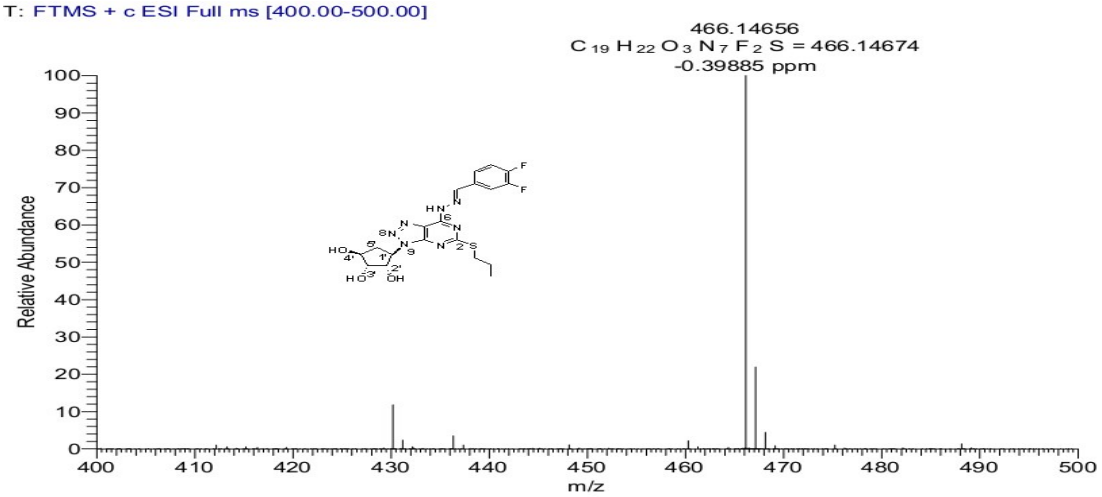


Figure S.4-55 HRMS spectra of **IIn**.

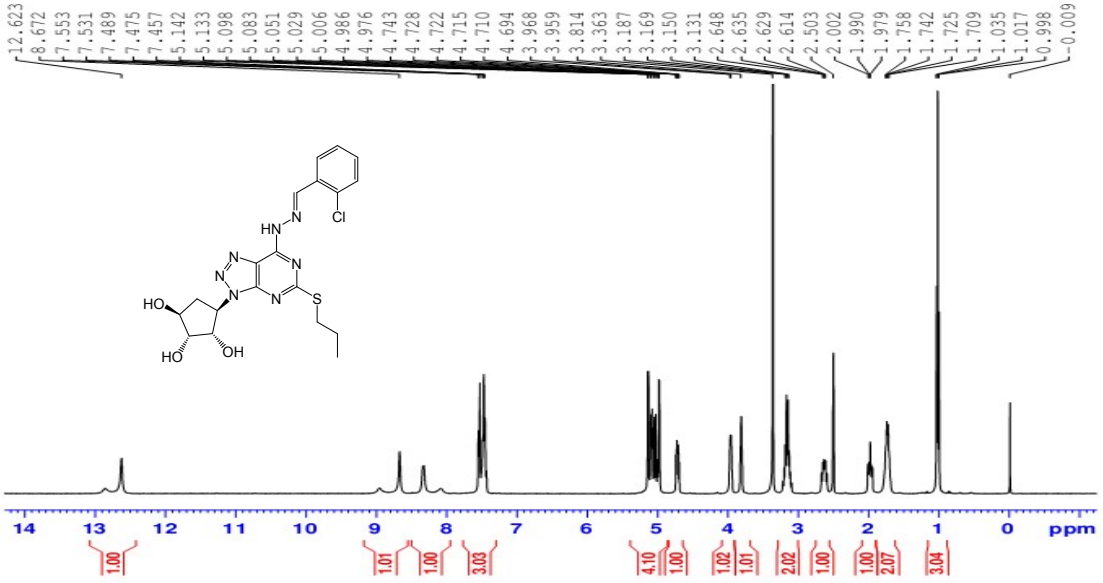


Figure S.4-56 ^{1}H NMR spectra of **IIo**.

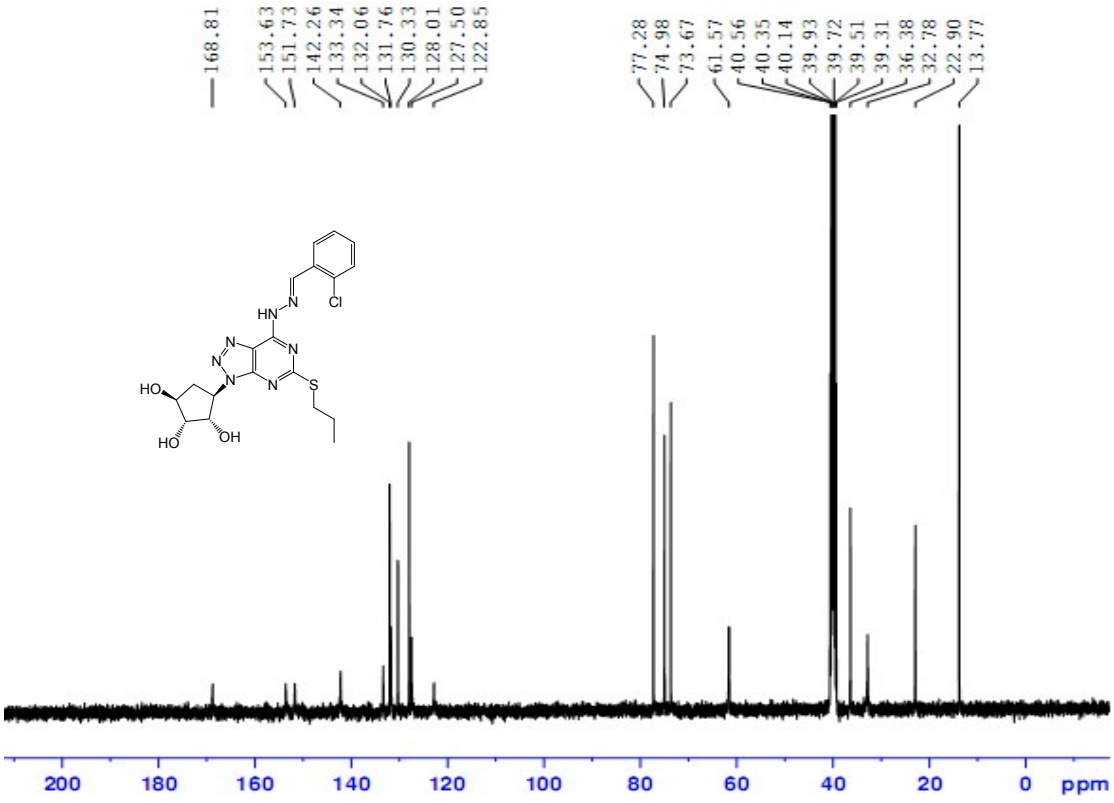


Figure S.4-57 ^{13}C NMR spectra of **IIo**.

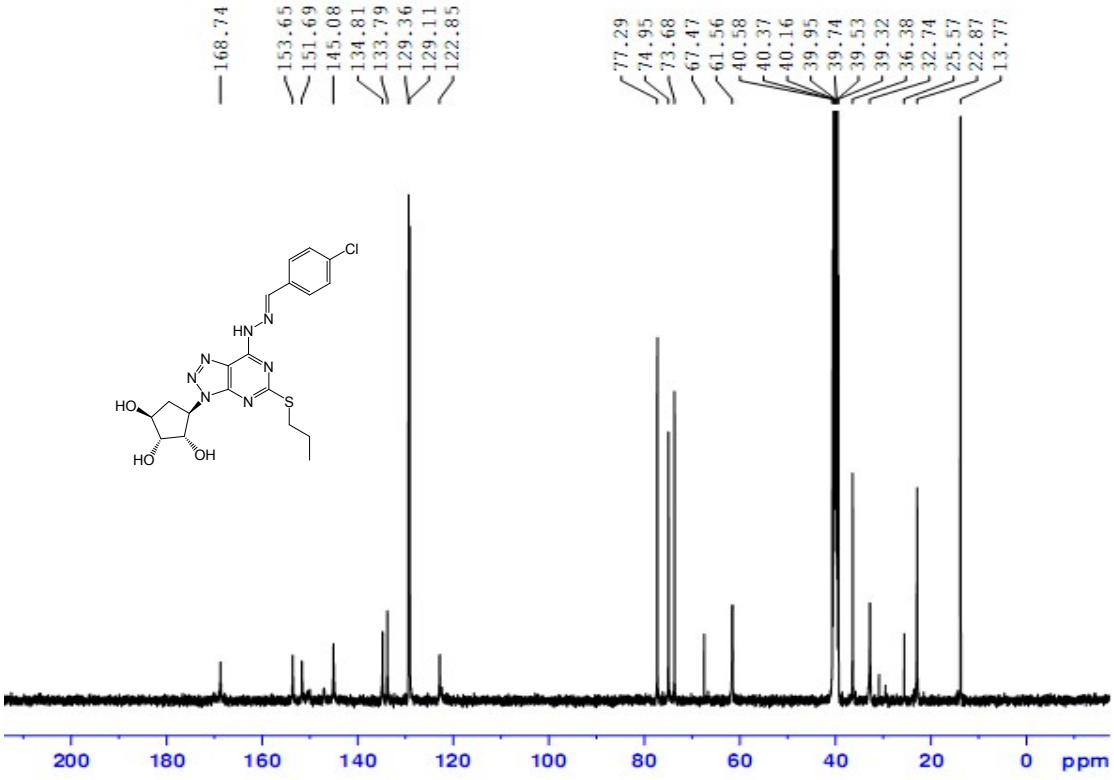


Figure S.4-58 ^{13}C NMR spectra of **IIp**.

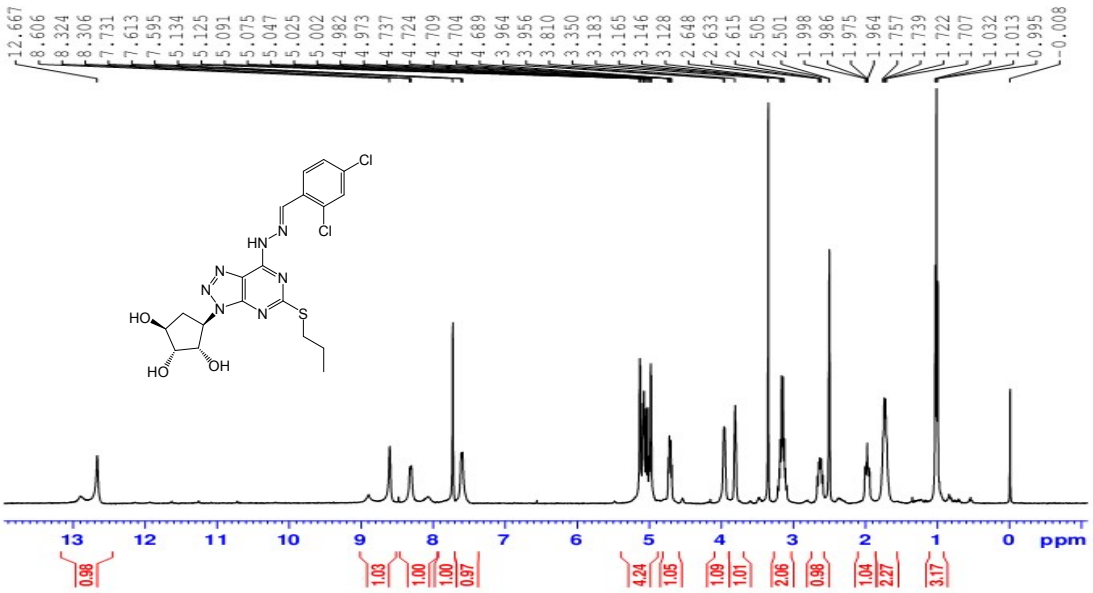


Figure S.4-59 ^{1}H NMR spectra of **IIq**.

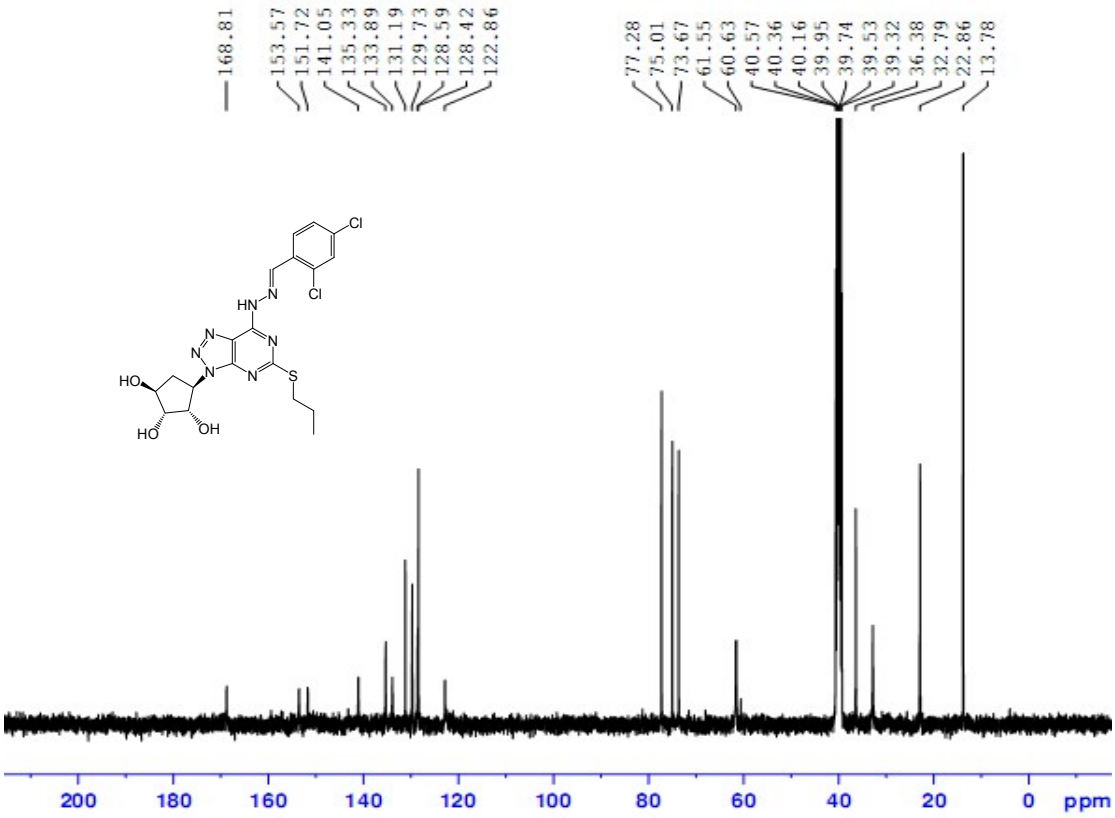


Figure S.4-60 ^{13}C NMR spectra of **IIq**.

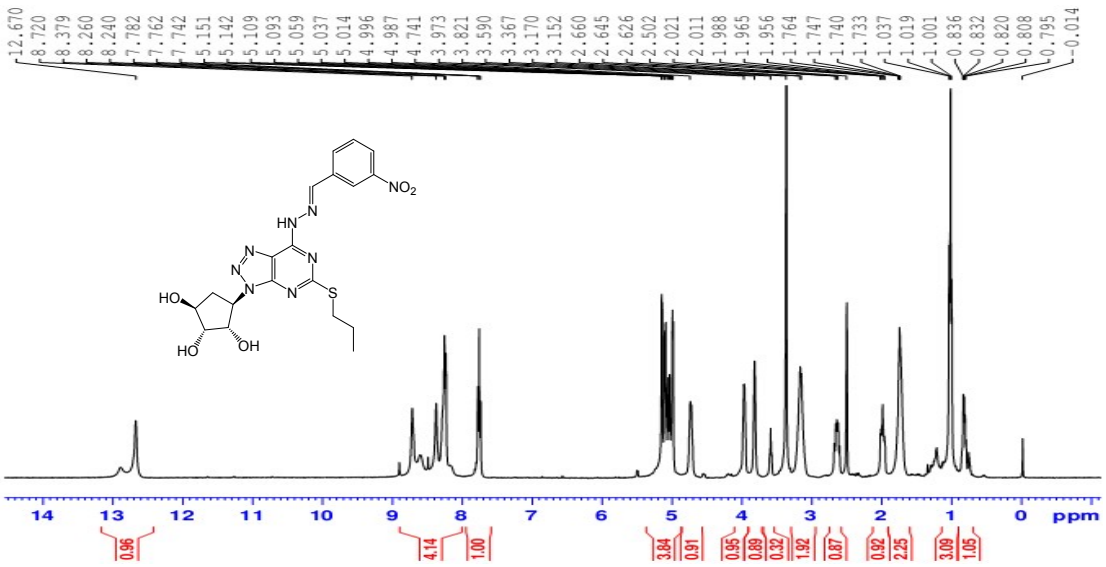


Figure S.4-61 ^{1}H NMR spectra of **IIr**.

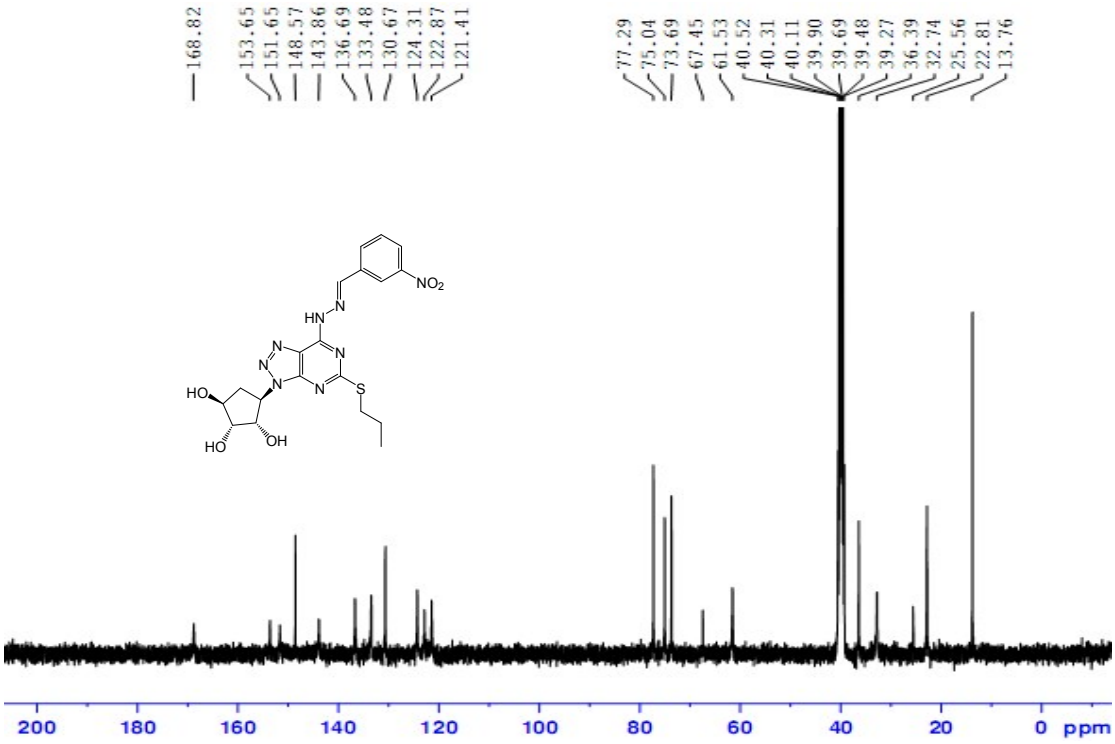


Figure S.4-62 ^{13}C NMR spectra of **IIr**.

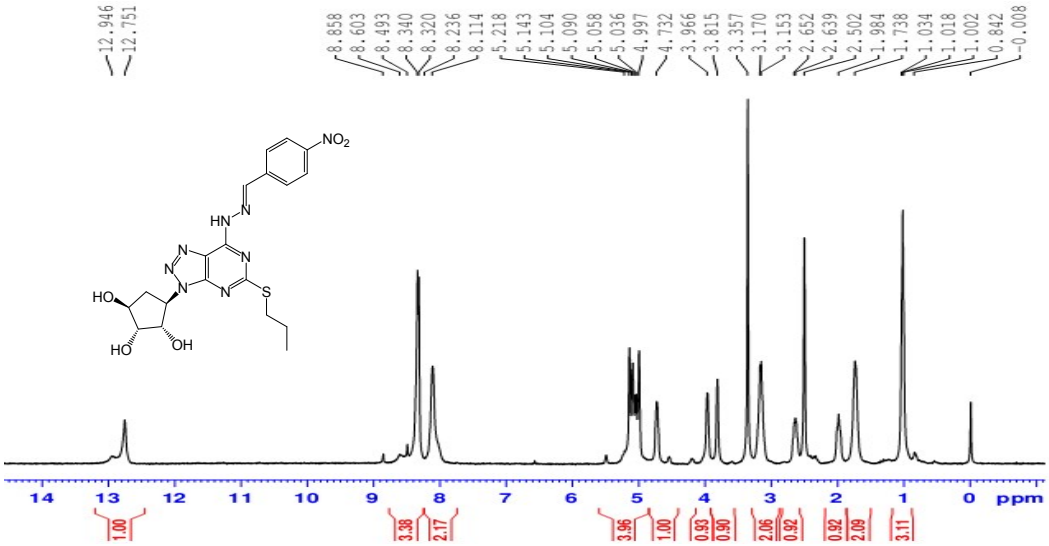


Figure S.4-63 ^{1}H NMR spectra of **IIs**.

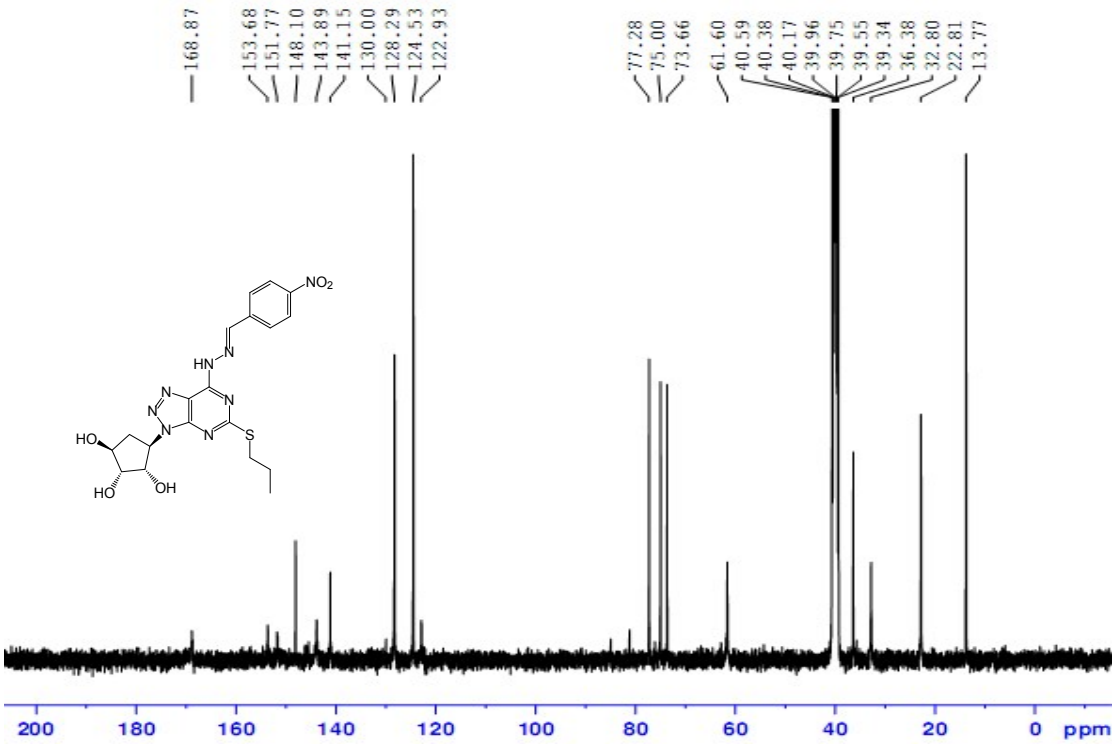


Figure S.4-64 ^{13}C NMR spectra of **IIs**.

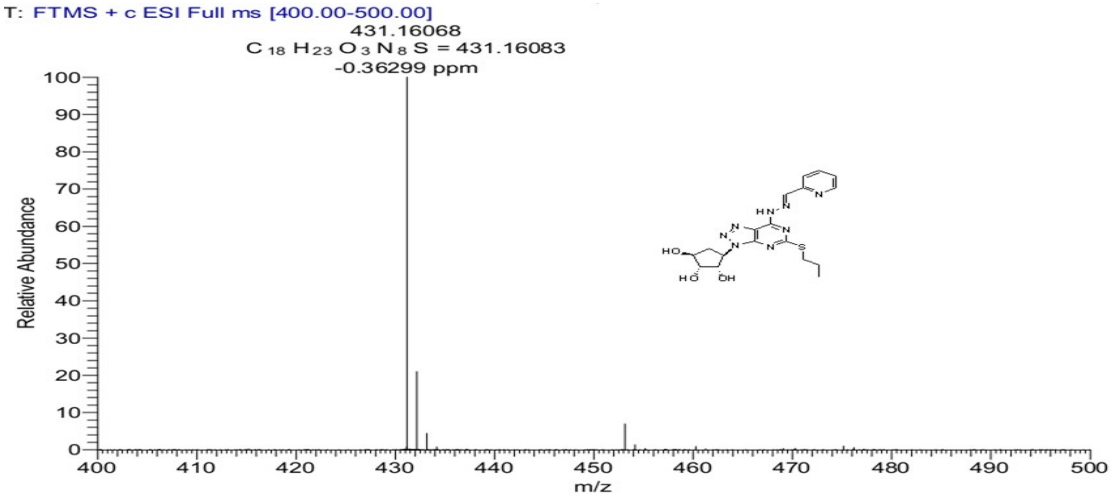


Figure S.4-65 HRMS spectra of **IIt**.

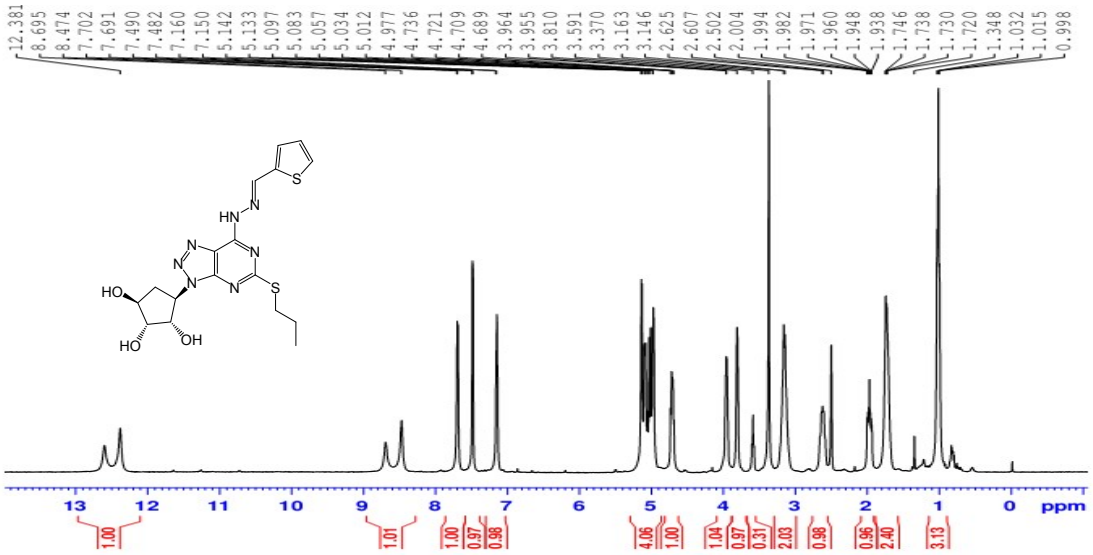
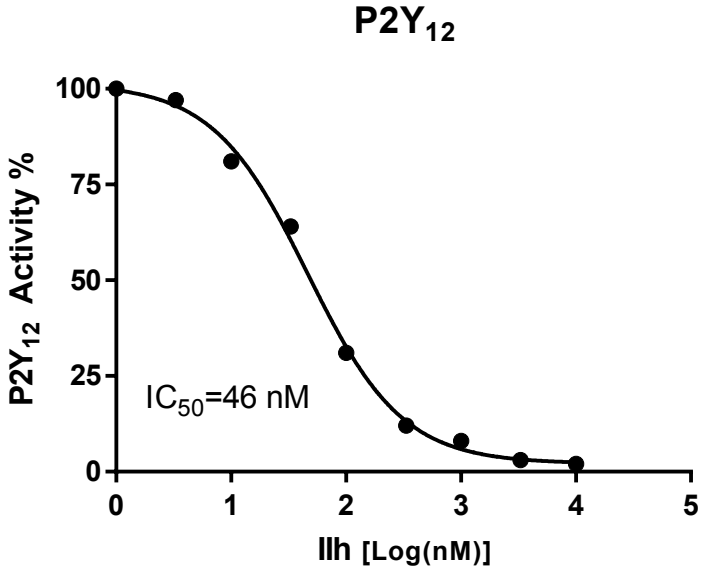
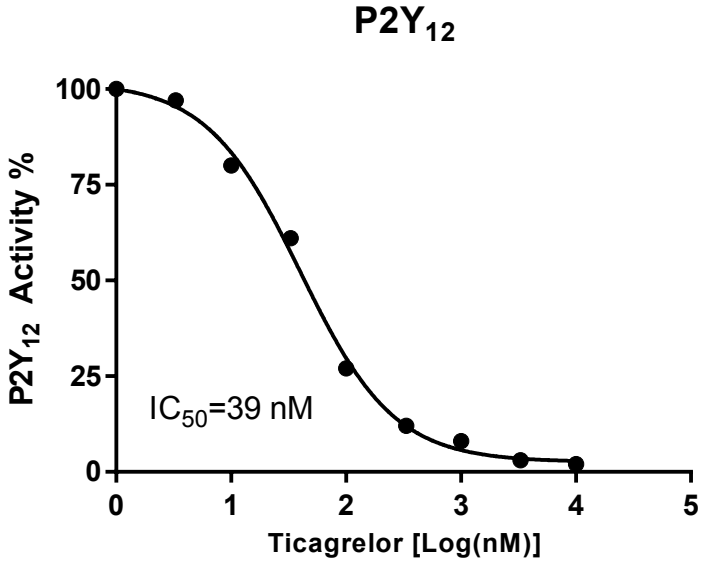


Figure S.4-66 ^{1}H NMR spectra of **IIu**.

5. The data graphs of the inhibitory activity on $P2Y_{12}$ receptor





References

1. Y. Wang, H. Yan, C. Ma and D. Lu, *Bioorganic & medicinal chemistry letters*, 2015, **25**, 4461-4463.