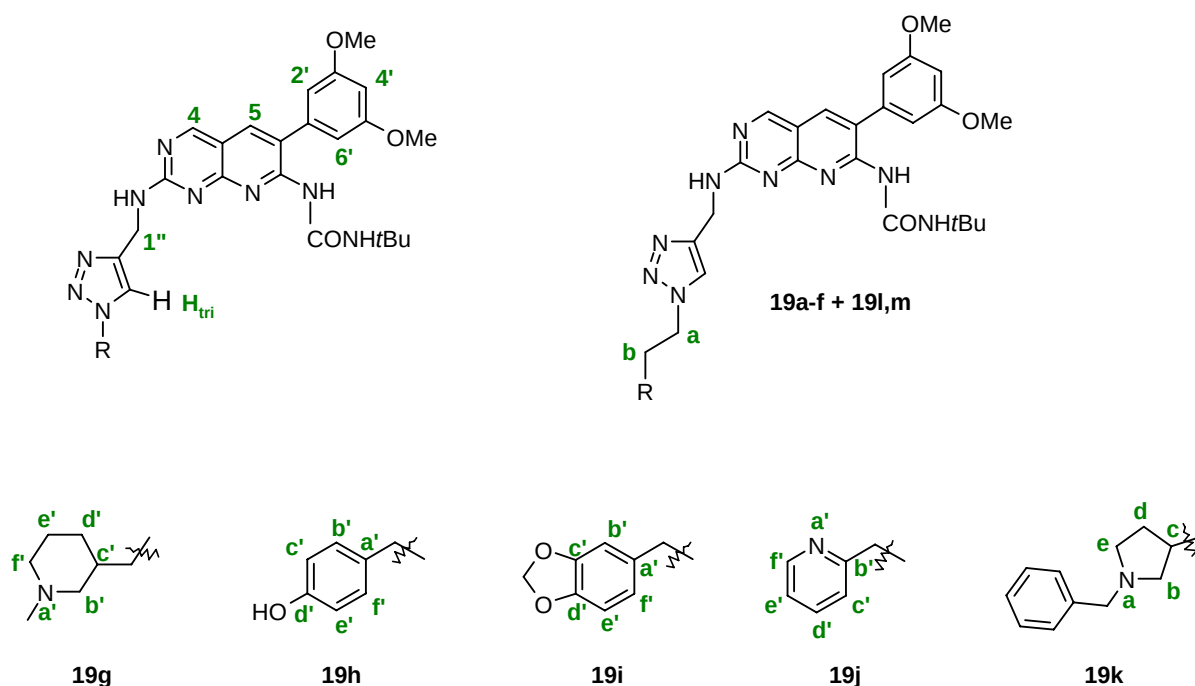


Electronic Supplementary Information for :

Synthesis and biological evaluation of a triazole-based library of pyrido[2,3-d]pyrimidines as FGFR3 tyrosine kinase inhibitors

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1. Numbering system



2. Comprehensive Experimental section

3-(Azidomethyl)-1-methylpiperidine (11b)

To a solution of *N*-methyl-3-piperidinemethanol (1.28 mL, 10 mmol) and NEt_3 (1.97 mL, 14 mmol) in dichloromethane (60 mL) was added dropwise methane sulfonyl chloride (1.08 mL, 14 mmol) at 0 °C. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature for 2 h. Then, the mixture was quenched with saturated aqueous NaHCO_3 (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with water (50 mL), dried over MgSO_4 and concentrated in vacuo. Then, to the crude mesylate (1.91 g, 10 mmol) were added sodium azide (975 mg, 15 mmol) and DMF (50 mL). The mixture was heated at 90 °C for 16 h then cooled to room temperature and concentrated in vacuo. To the residue was added water (50 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with water (3 x 30 mL), dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5) to give compound **11b** (285 mg, 93%) as an orange liquid. R_f 0.23 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90:10); ^1H NMR: δ 3.26-3.11 (m, 2H, CH_2N_3), 2.80-2.68 (m, 2H, H-2, H-6), 2.24 (s, 3H, CH_3), 1.96-1.48 (m, 6H, H-6, H-5, H-4, H-3, H-2), 1.10-0.91 (m, 1H, H-4); ^{13}C NMR: δ 58.1 (C-2), 55.4 (C-6), 54.8 (CH_2N_3), 45.2 (CH_3), 35.0, (C-3), 26.5 (C-4), 23.2 (C-5).

3-Azido-1-benzylpyrrolidine (11c)

Mesylation was performed according to the above procedure from *N*-benzylpyrrolidin-3-ol (1.62 mL, 10 mmol), NEt_3 (1.97 mL, 14 mmol) and methane sulfonyl chloride (1.08 mL, 14 mmol) in dichloromethane (50 mL). To the pure mesylate (2.50 g, 10 mmol) were added DMF (70 mL) and sodium azide (975 mg, 15 mmol) according to the above procedure to give compound **11c** (1.72 g, 83%) as an orange liquid. R_f 0.36 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2); ^1H NMR: δ 7.33-7.25 (m, 5H, H_{Ph}), 3.98-3.90 (m, 1H, H-3), 3.63 (AB, J = 12, 2H, CH_2Ph), 2.95-2.43 (m, 4H, H-2, H-5), 2.29-2.14 and 1.92-1.89 (m, 2H, H-4); ^{13}C NMR: δ 138.5 (C_{Ph}), 128.3, 128.0 and 126.8 (CH_{Ph}), 59.5 (C-3), 59.4 and 59.2 (CH_2Ph , C-2), 52.2 (C-5), 30.8 (C-4).

2-Azido-*N,N*-diethylethanamine (14a)

A mixture of 2-azidoethyl methane sulfonate **13** (1.33 g, 8.06 mmol) and *N,N*-diethylamine (3 mL, 29.0 mmol) was heated at 60 °C for 24 h, then concentrated in vacuo and purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90:10) to give compound **14a** (1.01 g, 89%) as a yellow oil. R_f 0.28 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NEt}_3$ 90:10:0.5); ^1H NMR: δ 3.26 (t, J = 6.3, 2H, H-2), 2.63 (t, J = 6.3, 2H, H-1), 2.55 (q, J = 5.2, 4H, CH_2N), 1.02 (t, J = 7.1, 6H, CH_3); ^{13}C NMR: δ 52.3 (C-1), 49.6 (C-2), 47.4 (2C, CH_2N), 11.9 (2C, CH_3); MS (ESI): m/z = 143 [$\text{M}+\text{H}$] $^+$ 100%.

1-(2-Azidoethyl)piperidine (14b)

To a solution of 2-azidoethyl methane sulfonate **13** (500 mg, 3.03 mmol) in CH_3CN (8 mL) were added piperidine (0.35 mL, 3.63 mmol) and triethylamine (0.83 mL, 5.96 mmol). The mixture was refluxed for 6 h, then concentrated in vacuo and purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NEt}_3$ 97:3:0.5) to give compound **14b** (370 mg, 79%) as a colorless oil. R_f 0.15 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NEt}_3$ 97:3:0.5); ^1H NMR: δ 3.35 (t, J = 6.3, 2H, H-2'), 2.54 (t, J = 6.3, 2H, H-1'), 2.42 (br t, J = 5.2, 4H, H-2), 1.66-1.36 (m, 6H, H-3, H-4); ^{13}C NMR: δ 57.8 (C-1'), 54.6 (C-2), 48.3 (C-2'), 25.9 (C-3), 24.2 (C-4); MS (ESI): m/z = 155 [$\text{M}+\text{H}$] $^+$ 100%.

1-(2-Azidoethyl)-4-methylpiperazine (14c)

To a solution of 2-azidoethyl methane sulfonate **13** (300 mg, 1.82 mmol) in dry CH_3CN (5 mL) were added *N*-methylpiperazine (0.24 mL, 2.18 mmol) and NEt_3 (0.5 mL, 3.59 mmol). The mixture was refluxed for 16 h, concentrated in vacuo and purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NEt}_3$ 90:10:0.5) to give compound **14c** (285 mg, 93%) as a colorless oil. R_f 0.15 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NEt}_3$ 90:10:0.5); ^1H NMR: δ 3.36 (t, J = 6.0, 2H, H-2'), 2.50-2.21 (m, 10H, H-1', H-2, H-3), 2.12 (s, 3H, NCH_3); ^{13}C NMR: δ 56.9 (C-1'), 54.8 (C-2), 52.9 (C-3), 48.0 (C-2'), 45.8 (NCH_3); MS (ESI): m/z = 170 [$\text{M}+\text{H}$] $^+$ 100%.

1-(2-Azidoethyl)-4-(5-(trifluoromethyl)pyridin-2-yl)piperazine (14d)

A mixture of 2-azidoethyl methane sulfonate **13** (214 mg, 1.30 mmol), 1-(5-trifluoromethyl)-2-pyridinyl)-piperazine (300 mg, 1.30 mmol) and triethylamine (0.3 mL, 2.15 mmol) in CH_3CN (3 mL) was heated at 90 °C for 16 h, then concentrated in vacuo. Purification by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) gave compound **14d** (287 mg, 74%) as a yellow oil. R_f 0.65

(CH₂Cl₂/MeOH 98:2); ¹H NMR: δ 8.37 (s, 1H, H_{pyr}), 7.60 (dd, *J* = 9.0, 2.5, 1H, H_{pyr}), 6.61 (d, *J* = 9.0, 1H, H_{pyr}), 3.76-3.56 (m, 4H, H-3), 3.48-3.28 (m, 2H, H-2'), 2.80-2.46 (m, 6H, H-1', H-2); ¹³C NMR: δ 160.5 (C-2''), 145.8 (C-6''), 134.5 (C-4''), 124.7 (q, *J* = 270, CF₃), 115.2 (q, *J* = 33, C-5''), 105.6 (C-3''), 57.2 (C-1'), 52.9 (C-2), 48.2 (C-2'), 44.7 (C-3); MS (ESI): *m/z* = 301 [M+H]⁺ 100.

1-(2-Azidoethyl)-4-(2-(2,5-dimethyl-1H-pyrrol-1-yl)ethyl)piperazine (14e)

A mixture of 2-azidoethyl methane sulfonate **13** (198 mg, 1.20 mmol), 1-[2-(2,5-dimethyl-1H-pyrrol-1-yl)ethyl]piperazine (250 mg, 1.21 mmol) and triethylamine (0.29 mL, 2.08 mmol) in CH₃CN (2.5 mL) was heated at 90 °C for 16 h, then concentrated in vacuo. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5) gave compound **14e** (185 mg, 56%) as a yellow oil. *R_f* 0.42 (CH₂Cl₂/MeOH 90:10); ¹H NMR: δ 5.74 (s, 2H, H_{pyr}), 3.88 (t, *J* = 7.8, 2H, H-2''), 3.34 (t, *J* = 7.8, 2H, H-2'), 2.68-2.42 (m, 12H, H-1', H-1'', H-2, H-3), 2.12 (s, 6H, CH₃); ¹³C NMR: δ 127.2 (C_{pyr}), 105.2 (CH_{pyr}), 58.3 (C-1''), 57.0 (C-1'), 53.4 and 53.0 (C-2, C-3), 48.0 (C-2'), 41.3 (C-2''), 12.4 (CH₃); MS (ESI): *m/z* = 277 [M+H]⁺ 100%.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(prop-2-ynylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (18)

A mixture of **17** (3.81 g, 8.29 mmol) and propargylamine (1.42 mL, 20.73 mmol) in dry dioxane (65 mL) was heated at 50 °C for 20 h. The solvent was then concentrated in vacuo and the crude residue was purified by flash column chromatography (CH₂Cl₂/MeOH 98:2) to give alkyne **18** (3.1 g, 86%) as a white solid. *R_f* 0.26 (CH₂Cl₂/MeOH 98:2); ¹H NMR: δ 10.23 (br s, 1H, NHCO), 8.78 (s, 1H, H-4), 7.71 (s, 1H, H-5), 7.15 (br s, 1H, NHtBu), 6.56-6.44 (m, 3H, H-2', H-4', H-6'), 5.56 (br t, *J* = 5.6, 1H, NHCH₂), 4.39 (dd, *J* = 5.6, 2.5, 2H, H-1''), 3.83 (s, 6H, OCH₃), 2.27 (t, *J* = 2.5, 1H, H-3''), 1.53 (s, 9H, CMe₃); ¹³C NMR: δ 162.1 (C-2), 161.9 (C-3', C-5'), 161.1 (C-4), 158.6 (C-8a), 155.9 (C-7), 152.8 (CONH), 137.2 (C-5), 136.7 (C-1'), 123.3 (C-6), 110.3 (C-4a), 107.4 (C-2', C-6'), 101.0 (C-4'), 80.5 (C-3''), 71.3 (C-2''), 55.7 (OCH₃), 51.1 (CMe₃), 31.5 (C-1''), 29.1 (CMe₃); HRMS (ESI): Calc. for C₂₃H₂₆N₆O₃Na [M+Na]⁺ 457.1964, found 457.1945.

General procedure for the cycloaddition reactions

A mixture of alkyne (1 eq.), azide (1 eq.), sodium ascorbate (0.2 eq.), CuSO₄·5H₂O (0.1 eq.) in 2:1 *t*BuOH/H₂O (26 mL/1 mmol) was vigorously stirred at room temperature for several h (TLC control). Typical reaction times are from 20 h to 3 d. After disappearance of alkyne, the mixture was diluted with CH₂Cl₂ and washed with water, dried (MgSO₄) then concentrated in vacuo. Purification of the crude residue afforded the corresponding triazoles.

1-tert-Butyl-3-(2-((1-(2-(diethylamino)ethyl)-1H-1,2,3-triazol-4-yl)methylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-7-yl)urea (19a)

From alkyne **18** (100 mg, 0.23 mmol), azide **14a** (34 mg, 0.24 mmol), sodium ascorbate (10 mg, 0.05 mmol), CuSO₄·5H₂O (6 mg, 0.024 mmol) in 2:1 *t*BuOH/H₂O (6 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5) gave triazole **19a** (98 mg, 74%) as a white solid. *R_f* 0.24 (CH₂Cl₂/MeOH 93:7); ¹H NMR: δ 10.33 (br s, 1H, NHCO), 8.75 (s, 1H, H-4), 7.72 (br s, 1H, H_{tri}), 7.68 (s, 1H, H-5), 7.15 (br s, 1H, NHtBu), 6.56-6.44 (m, 3H, H-2', H-4', H-6'), 5.94 (t, *J* = 5.9, 1H, NHCH₂), 4.86 (d, *J* = 5.9, 2H, H-1''), 4.37 (t, *J* = 6.4, 2H, H-a), 3.89 (s, 6H, OCH₃), 2.85 (t, *J* = 6.4, 2H, H-b), 2.51 (q, *J* = 7.1, 4H, CH₂CH₃), 1.49 (s, 9H, CMe₃); 1.01 (t, *J* = 7.1, 6H, CH₂CH₃); ¹³C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.1 (C-4), 158.5 (C-8a), 155.7 (C-7), 152.8 (CONH), 145.1 (C_{tri}), 137.2 (C-5), 136.7 (C-1'), 123.1 (CH_{tri}), 122.8 (C-6), 110.0 (C-4a), 107.3 (C-2', C-6'), 100.8 (C-4'), 55.7 and 55.6 (OCH₃), 53.1 (C-b), 51.0 (CMe₃), 49.2 (C-a), 47.4 (CH₂CH₃), 37.2 (C-1''), 29.1 (CMe₃), 12.0 (CH₂CH₃); Anal. Calc. for C₂₉H₄₀N₁₀O₃: C, 60.40; H, 6.99; N, 24.29; found: C, 59.98; H, 7.13; N, 24.16; HRMS (ESI): Calc. for C₂₉H₄₀N₁₀O₃Na [M+Na]⁺ 599.3183, found 599.3144.

3-(4-((7-(3-tert-Butylureido)-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-2-ylamino)methyl)-1H-1,2,3-triazol-1-yl)propanoic acid (19b)

From alkyne **18** (70 mg, 0.161 mmol), azide **2** (20 mg, 0.177 mmol), sodium ascorbate (7 mg, 0.035 mmol), CuSO₄·5H₂O (4 mg, 0.016 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 90:10 to 80:20) gave triazole **19b** (69 mg, 78%) as a yellow solid. *R_f* 0.17 (CH₂Cl₂/MeOH 90:10); ¹H NMR: δ 10.18 (br s, 1H, NHCO), 8.84 (br s, 1H, H-4), 7.95 (br s, 1H, H_{tri}), 7.69 (br s, 1H, H-5), 6.55-6.38 (m, 3H, H-2', H-4', H-6'), 4.93 (br s, 2H, H-1''), 4.69 (t, *J* = 5.0, 2H, H-a), 3.80 (s, 6H, OCH₃), 2.85 (m,

2H, H-b), 1.45 (s, 9H, CMe_3); ^{13}C NMR: δ 175.3 (CO_2H), 162.5 (C-2), 161.9 (C-3', C-5'), 161.7 (C-4), 156.2 (C-7, C-8a), 152.6 (CONH), 145.2 (C_{tri}), 137.3 (C-5), 136.4 (C-1'), 123.6 (C-6), 123.2 (CH_{tri}), 109.7 (C-4a), 107.4 (C-2', C-6'), 101.0 (C-4'), 55.7 and 55.6 (OCH_3), 51.5 (CMe_3), 45.9 (C-a), 37.9 (C-1''), 35.1 (C-b), 29.2 (CMe_3); MS (ESI): m/z = 550 [$M+H$] $^+$ 100%; HRMS (ESI): Calc. for $C_{26}H_{31}N_9O_5Na$ [$M+Na$] $^+$ 572.2346, found 572.2358.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(2-(*N,N'*-bis(*tert*-butoxycarbonyl)guanidino)ethyl)-1*H*-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea hydrochloride (19c)

From alkyne **18** (70 mg, 0.161 mmol), azide **9** (53 mg, 0.170 mmol), sodium ascorbate (7 mg, 0.035 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 *t*BuOH/ H_2O (4 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 96:4) afforded triazole **19c** (111 mg, 90%) as a yellow solid. R_f 0.23 ($CH_2Cl_2/MeOH$ 96:4); 1H NMR: δ 11.42 (s, 1H, $NHBoc$), 10.31 (br s, 1H, $NHCO$), 8.76 (s, 1H, H-4), 8.53 (t, J = 5.3, NH_{gua}), 7.71 (s, 1H, H_{tri}), 7.69 (s, 1H, H-5), 7.18 (s, 1H, $NHtBu$), 6.60-6.40 (m, 3H, H-2', H-4', H-6'), 5.99 (br s, 1H, $NHCH_2$), 4.89 (d, J = 5.5, 2H, H-1''), 4.55 (t, J = 5.3, 2H, H-a), 3.91 (m, 2H, H-b), 3.82 (s, 6H, OCH_3), 1.49 and 1.47 (s, 27H, CMe_3); ^{13}C NMR: δ 163.3 (CO_{gua}), 162.3 (C-2), 161.7 (C-3', C-5'), 161.1 (C-4), 158.4 (C-8a), 156.4 (CO_{gua}), 155.7 (C-7), 153.0 (CN_{gua}), 152.7 (CONH), 145.6 (C_{tri}), 137.2 (C-5), 136.6 (C-1'), 122.8 (C-6, CH_{tri}), 110.0 (C-4a), 107.3 (C-2', C-6'), 100.8 (C-4'), 83.5 and 79.6 (Boc), 55.6 (OCH_3), 51.0 (CMe_3), 49.3 (C-a), 40.6 (C-b), 37.1 (C-1''), 29.1, 28.3 and 28.1 (CMe_3); MS (ESI): m/z = 785 [$M+Na$] $^+$ 100%.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(2-guanidinoethyl)-1*H*-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea hydrochloride (19d)

To a solution of triazole **19c** (30 mg, 0.039 mmol) in dioxane (3 mL) was added 3N HCl (1.3 mL) and the mixture was stirred at room temperature for 3h30 then concentrated in vacuo. The residue was triturated with Et_2O and the solid was filtered then dried under vacuum to afford guanidine **19d** (22 mg, 93%) as a yellow solid. 1H NMR (CD_3OD): δ 9.09 (s, 1H, H-4), 8.41 (s, 1H, H_{tri}), 8.13 (s, 1H, H-5), 6.80-6.60 (m, 3H, H-2', H-4', H-6'), 4.90-4.60 (m, 4H, H-a, H-1''), 3.95-3.75 (m, 8H, OCH_3 , H-b), 1.42 (s, 9H, CMe_3); MS (ESI): m/z = 563 [$M-HCl+H$] $^+$ 100%.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(2-(piperidin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (19e)

From alkyne **18** (100 mg, 0.23 mmol), azide **14b** (36 mg, 0.23 mmol), sodium ascorbate (10 mg, 0.05 mmol), $CuSO_4 \cdot 5H_2O$ (6 mg, 0.024 mmol) in 2:1 *t*BuOH/ H_2O (6 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH/NEt_3$ 93:7:0.5) gave triazole **19e** (58 mg, 84%) as a white solid. R_f 0.37 ($CH_2Cl_2/MeOH/NEt_3$ 90:10:0.5); 1H NMR: δ 10.31 (br s, 1H, $NHCO$), 8.73 (br s, 1H, H-4), 7.75 (br s, 1H, H_{tri}), 7.68 (s, 1H, H-5), 7.13 (br s, 1H, $NHtBu$), 6.55-6.40 (m, 3H, H-2', H-4', H-6'), 5.96 (br t, J = 6.0, 1H, $NHCH_2$), 4.84 (d, J = 6.0, 2H, H-1''), 4.42 (t, J = 6.3, 2H, H-a), 3.80 (s, 6H, OCH_3), 2.73 (t, J = 6.3, 2H, H-b), 2.45-2.30 (m, 4H, H_{pip}), 1.53-1.28 (m, 15H, CMe_3 , H_{pip}); ^{13}C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.1 (C-4), 158.6 (C-8a), 155.7 (C-7), 152.8 (CONH), 145.3 (C_{tri}), 137.3 (C-5), 136.7 (C-1'), 123.1 (CH_{tri}), 122.8 (C-6), 110.0 (C-4a), 107.4 (C-2', C-6'), 100.9 (C-4'), 58.3 (C-b), 55.7 and 55.6 (OCH_3), 54.6 (CH_{pip}), 51.0 (CMe_3), 47.9 (C-a), 37.2 (C-1''), 29.1 (CMe_3), 25.9 and 24.2 (CH_{pip}); Anal. Calc. for $C_{23}H_{26}N_6O_3 \cdot 0.7H_2O$: C, 59.92; H, 6.94; N, 23.29; found: C, 59.90; H, 6.89; N, 23.24; HRMS (ESI): Calc. for $C_{30}H_{40}N_{10}O_3Na$ [$M+Na$] $^+$ 611.3183, found 611.3181.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(2-(4-methylpiperazin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (19f)

From alkyne **18** (50 mg, 0.12 mmol), azide **14c** (20 mg, 0.12 mmol), sodium ascorbate (5 mg, 0.025 mmol), $CuSO_4 \cdot 5H_2O$ (3 mg, 0.012 mmol) in 2:1 *t*BuOH/ H_2O (3 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 95:5) gave triazole **19f** (58 mg, 84%) as a grey solid. R_f 0.12 ($CH_2Cl_2/MeOH/NEt_3$ 90:10:0.3); 1H NMR: δ 10.31 (br s, 1H, $NHCO$), 8.79 (s, 1H, H-4), 7.78 (s, 1H, H_{tri}), 7.73 (s, 1H, H-5), 7.19 (s, 1H, $NHtBu$), 6.60-6.45 (m, 3H, H-2', H-4', H-6'), 6.00 (br t, J = 5.5, 1H, $NHCH_2$), 4.86 (d, J = 5.5, 2H, H-1''), 4.47 (t, J = 6.5, 2H, H-a), 3.86 (s, 6H, OCH_3), 2.84 (t, J = 6.5, 2H, H-b), 2.65-2.30 (m, 8H, H_{pip}), 2.24 (s, 3H, NCH_3), 1.53 (s, 9H, CMe_3); ^{13}C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.2 (C-4), 158.6 (C-8a), 155.7 (C-7), 152.8 (CONH), 145.4 (C_{tri}), 137.3 (C-5), 136.7 (C-1'), 123.1 (CH_{tri}), 122.8 (C-6, C-5''), 110.1 (C-4a), 107.3 (C-2', C-6'), 100.8 (C-4'), 57.6 (C-b), 55.7 and 55.6 (OCH_3), 55.0 and 53.1 (CH_{pip}), 51.0 (CMe_3), 47.9 (C-a), 46.0 (NCH_3), 37.2 (C-1''), 29.2 (CMe_3);

HRMS (ESI): Calc. for $C_{30}H_{41}N_{11}O_3Na$ $[M+Na]^+$ 626.3292, found 626.3284.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-((1-methylpiperidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (19g)

From alkyne **18** (70 mg, 0.161 mmol), azide **11b** (25 mg, 0.161 mmol), sodium ascorbate (8 mg, 0.025 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 $tBuOH/H_2O$ (4 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 90:10) gave triazole **19g** (84 mg, 89%) as a yellow-green solid. R_f 0.17 ($CH_2Cl_2/MeOH$ 90:10); 1H NMR: δ 10.30 (br s, 1H, NHCO), 8.75 (br s, 1H, H-4), 7.69 (br s, 1H, H-5), 7.61 (br s, 1H, H_{tri}), 7.16 (br s, 1H, NHtBu), 6.51-6.47 (m, 3H, H-2', H-4', H-6'), 6.25 (br s, 1H, $NHCH_2$), 4.85 (d, $J = 5.7$, 2H, H-1''), 4.24 (d, $J = 7.1$, 2H, H-a), 3.81 (s, 6H, OCH_3), 2.19 (s, 3H, NCH_3), 1.48 (s, 9H, CMe_3), 2.68-1.00 (m, 8H, H_{pip}); ^{13}C NMR: δ 162.6 (C-2), 162.1 (C-3', C-5'), 161.4 (C-4), 158.8 (C-8a), 156.0 (C-7), 153.0 (CONH), 145.8 (C_{tri}), 137.4 (C-5), 136.9 (C-1'), 123.2 (C-6), 122.9 (CH_{tri}), 110.4 (C-4a), 107.7 (C-2', C-6'), 101.2 (C-4'), 59.3 (C-b'), 56.2 (C-f'), 56.1 and 55.9 (OCH_3), 54.0 (C-a), 51.2 (CMe_3), 46.7 (NCH_3), 37.5 (C-1''), 37.4 (C-c'), 29.4 (CMe_3); 27.8 (C-d'); 24.5 (C-e'); HRMS (ESI): Calc. for $C_{30}H_{40}N_{10}O_3Na$ $[M+Na]^+$ 611.3183, found 611.3165.

1-(2-((1-(4-Hydroxybenzyl)-1H-1,2,3-triazol-4-yl)methylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-7-yl)-3-tert-butylurea (19h)

From alkyne **18** (70 mg, 0.161 mmol), azide **6** (24 mg, 0.161 mmol), sodium ascorbate (8 mg, 0.025 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 $tBuOH/H_2O$ (4 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 90:10) gave triazole **19h** (70 mg, 74%) as a yellow solid. R_f 0.17 ($CH_2Cl_2/MeOH$ 95:5); 1H NMR (500 MHz, $CDCl_3+CD_3OD$): δ 8.97 (br s, 1H, H-4), 7.66 (s, 1H, H-5), 7.50 (s, 1H, H_{tri}), 7.01 (d, $J = 7.0$, 2H, H-b', H-f'), 6.69 (d, $J = 7.0$, 2H, H-c', H-e'), 6.55-6.35 (m, 3H, H-2', H-4', H-6'), 5.31 (s, 2H, H-a), 4.70 (br s, 2H, H-1''), 3.77 (s, 6H, OCH_3), 1.37 (s, 9H, CMe_3); ^{13}C NMR (125 MHz, $CDCl_3+CD_3OD$): δ 161.9 (C-2), 161.8 (C-3', C-5'), 161.4 (C-4), 157.5 (C-8a, C-d'), 155.5 (C-7), 153.1 (CONH), 145.0 (C_{tri}), 137.4 (C-5), 136.3 (C-1'), 129.7 (C-b', C-f'), 125.2 (C-a'), 123.1 (C-6), 122.4 (CH_{tri}), 115.9 (C-c', C-e'), 109.9 (C-4a), 107.3 (C-2', C-6'), 101.0 (C-4'), 55.5 (OCH_3), 53.9 (C-a), 51.1 (CMe_3), 36.8 (C-1''), 28.8 (CMe_3); MS (ESI): $m/z = 583$ $[M]^+$ 100%.

1-(2-((1-(Benzo[d][1,3]dioxol-5-yl)methyl)-1H-1,2,3-triazol-4-yl)methylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-7-yl)-3-tert-butylurea (19i)

From alkyne **18** (50 mg, 0.12 mmol), (1,3-benzodioxol-5-yl)methyl azide **11a** (21 mg, 0.12 mmol), sodium ascorbate (5 mg, 0.025 mmol) and $CuSO_4 \cdot 5H_2O$ (3 mg, 0.012 mmol) in 2:1 $tBuOH/H_2O$ (3 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 95:5) gave triazole **19i** (67 mg, 96%) as a white solid. R_f 0.21 ($CH_2Cl_2/MeOH$ 95:5); 1H NMR (DMF): δ 10.41 (br s, 1H, NHCO), 9.02 (br s, 1H, NHtBu), 8.13 (br s, 1H, C-5'), 8.08 (s, 1H, H-5), 8.02 (s, 1H, H-4), 7.29 (br s, 1H, $NHCH_2$), 6.98-6.82 (m, 3H, H-b', H-e', H-f'), 6.78-6.64 (m, 3H, H-2', H-4', H-6'), 6.05 (s, 2H, OCH_2O), 5.57 (s, 2H, H-a), 4.81 (m, 2H, H-1''), 3.89 (s, 6H, OCH_3), 1.43 (s, 9H, CMe_3); ^{13}C NMR (DMF): δ 163.6-162.9 (C-2, C-4, C-3', C-5'), 159.2 (C-8a), 156.2 (C-7), 153.4 (CONH), 149.0 and 148.6 (C-c', C-d'), 147.8 (C_{tri}), 139.2 (C-5), 138.5 (C-1'), 131.2 (C-a'), 123.8 (CH_{tri}), 122.9 (C-f'), 122.7 (C-6), 111.1 (C-4a), 109.5 and 109.3 (C-b', C-e'), 108.3 (C-2', C-6'), 102.6 (OCH_2O), 101.3 (C-4'), 56.4 and 56.3 (OCH_3), 53.9 (C-a), 51.3 (CMe_3), 37.9 (C-1''), 29.5 (CMe_3); HRMS (ESI): Calc. for $C_{31}H_{33}N_9O_5Na$ $[M+Na]^+$ 634.2502, found 634.2488.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(pyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (19j)

From alkyne **18** (70 mg, 0.161 mmol), azide **4** (19 mg, 0.177 mmol), sodium ascorbate (7 mg, 0.035 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 $tBuOH/H_2O$ (4 mL) according to the above procedure. The crude residue was washed with cyclohexane to afford triazole **19j** (88 mg, 96%) as a yellow solid. 1H NMR: δ 10.26 (br s, 1H, NHCO), 8.72 (s, 1H, H-4), 8.56 (d, $J = 4.9$, 1H, H-f'), 7.76 (br s, 1H, H_{tri}), 7.67 (s, 1H, H-5), 7.65 (td, $J = 7.8$, 1.7, 1H, H-d'), 7.28-7.10 (m, 3H, H-e', H-c', NHtBu), 6.53-6.43 (m, 3H, H-2', H-4', H-6'), 5.93 (t, $J = 5.8$, 1H, $NHCH_2$), 5.61 (s, 2H, H-a), 4.85 (d, $J = 5.8$, 2H, H-1''), 3.80 (s, 6H, OCH_3), 1.43 (s, 9H, CMe_3); ^{13}C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.2 (C-4), 158.6 (C-8a), 155.7 (C-7), 154.6 (CONH), 152.8 (C-b'), 149.9 (C-f'), 146.0 (C_{tri}), 137.4 (C-5), 137.3 (C-d'), 136.7 (C-1'), 123.5 (C-c'), 123.1 (CH_{tri}), 122.9 (C-6), 122.4 (C-e'), 110.1 (C-4a), 107.5 (C-2', C-6'), 100.9 (C-4'), 55.8 (C-a), 55.7 and 55.6 (OCH_3), 51.0 (CMe_3), 37.3 (C-1''), 29.1 (CMe_3); MS (ESI): $m/z = 591$ $[M+Na]^+$ 100%; HRMS (ESI): Calc.

for $C_{29}H_{32}N_{10}O_3Na$ $[M+Na]^+$ 591.2557, found 591.2554.

1-(2-((1-(1-Benzylpyrrolidin-3-yl)-1H-1,2,3-triazol-4-yl)methylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-7-yl)-3-tert-butylurea (19k)

From alkyne **18** (70 mg, 0.161 mmol), azide **11c** (32 mg, 0.161 mmol), sodium ascorbate (8 mg, 0.025 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 $tBuOH/H_2O$ (4 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH/NEt_3$ 90:10:0.5) gave triazole **19k** (88 mg, 86%) as a yellow-green solid. R_f 0.70 ($CH_2Cl_2/MeOH/NEt_3$ 90:10:0.5); 1H NMR: δ 10.35 (br s, 1H, NHCO), 8.77 (br s, 1H, H-4), 7.87 (br s, 1H, H_{tri}), 7.70 (br s, 1H, H-5), 7.26-7.22 (m, 5H, H_{Ph}), 7.16 (br s, 1H, NHtBu), 6.53-6.46 (m, 3H, H-2', H-4', H-6'), 6.13 (br s, 1H, $NHCH_2$), 5.23-5.21 (m, 1H, H-c), 4.87 (d, $J = 5.2$, 2H, H-1''), 3.82 (s, 6 H, OCH_3), 3.70 (AB, $J = 11.9$, 2H, CH_2Ph), 3.11-2.10 (m, 6H, H-b, H-d, H-e), 1.49 (s, 9H, CMe_3); ^{13}C NMR: δ 162.7 (C-2), 162.1 (C-3', C-5'), 161.4 (C-4), 158.8 (C-8a), 156.0 (C-7), 153.0 (CONH), 146.0 (C_{tri}), 138.5 (C_{Ph}), 137.4 (C-5), 136.9 (C-1'), 128.9, 128.7 and 127.7 (CH_{Ph}), 123.2 (C-6), 120.8 (CH_{tri}), 110.4 (C-4a), 107.6 (C-2', C-6'), 101.2 (C-4'), 60.3 and 59.9 (C-b, CH_2Ph), 59.7 (C-c), 55.9 and 55.8 (OCH_3), 53.0 (C-e), 51.2 (CMe_3), 37.6 (C-1''), 33.0 (C-d), 29.3 (CMe_3); MS (ESI): $m/z = 637$ $[M+H]^+$ 100%; HRMS (ESI): Calc. for $C_{34}H_{40}N_{10}O_3Na$ $[M+Na]^+$ 659.3183, found 659.3192.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (19l)

From alkyne **18** (70 mg, 0.161 mmol), azide **14d** (51 mg, 0.170 mmol), sodium ascorbate (7 mg, 0.035 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 $tBuOH/H_2O$ (4 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 97:3) afforded triazole **19l** (103 mg, 87%) as a yellow solid. R_f 0.21 ($CH_2Cl_2/MeOH$ 95:5); 1H NMR: δ 10.31 (br s, 1 H, NHCO), 8.71 (s, 1H, H-4), 8.33 (s, 1H, H_{pyr}), 7.78 (br s, 1H, H_{tri}), 7.63 (s, 1H, H-5), 7.56 (d, $J = 8.9$, 1H, H_{pyr}), 7.17 (s, 1H, NHtBu), 6.64 (br s, 1H, $NHCH_2$), 6.54 (d, $J = 8.9$, 1H, H_{pyr}), 6.50-6.39 (m, 3H, H-2', H-4', H-6'), 4.84 (d, $J = 5.5$, 2H, H-1''), 4.45 (t, $J = 5.8$, 2H, H-a), 3.80 (s, 6H, OCH_3), 3.49 (m, 4H, H_{pip}), 2.83 (t, $J = 5.8$, 2H, H-b), 2.51 (m, 4H, H_{pip}), 1.46 (s, 9H, CMe_3); ^{13}C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.2 (C-4), 160.2 (C_{pyr}), 158.5 (C-7), 155.7 (CONH), 152.8 (C-8a), 145.9 (CH_{pyr}), 145.5 (C_{tri}), 137.3 (C-5), 134.6 (CH_{pyr}), 136.6 (C-1'), 134.6 (CH_{pyr}), 123.0 (CH_{tri}), 122.5 (C-6), 115.4 (q, $J = 130$, C_{pyr}), 110.1 (C-4a), 110.5 (C-2', C-6'), 105.6 (CH_{pyr}), 100.7 (C-4'), 57.6 (C-b), 55.7 and 55.6 (OCH_3), 52.8 (CH_{pip}), 51.0 (CMe_3), 47.8 (C-a), 44.6 (CH_{pip}), 37.2 (C-1''), 29.2 (CMe_3); MS (ESI): $m/z = 736$ $[M+H]^+$ 100%; HRMS (ESI): Calc. for $C_{35}H_{41}N_{12}O_3F_3Na$ $[M+Na]^+$ 757.3274, found 757.3278.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-((1-(2-(4-(2-(2,5-dimethyl-1H-pyrrol-1-yl)ethyl)piperazin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (19m)

From alkyne **18** (70 mg, 0.161 mmol), azide **14e** (47 mg, 0.170 mmol), sodium ascorbate (7 mg, 0.035 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.016 mmol) in 2:1 $tBuOH/H_2O$ (4 mL) according to the above procedure. Purification by flash column chromatography ($CH_2Cl_2/MeOH$ 97:3) afforded triazole **19m** (65 mg, 57%) as a yellow solid. R_f 0.42 ($CH_2Cl_2/MeOH$ 90:10); 1H NMR: δ 10.29 (br s, 1H, NHCO), 8.75 (s, 1H, H-4), 7.70 (s, 1H, H_{tri}), 7.69 (s, 1H, H-5), 7.17 (s, 1H, NHtBu), 6.58-6.42 (m, 3H, H-2', H-4', H-6'), 6.00 (t, $J = 5.8$, 1H, $NHCH_2$), 5.74 (s, 2H, H_{pyr}), 4.86 (d, $J = 5.8$, 2H, H-1''), 4.45 (t, $J = 6.0$, 2H, H-a), 3.89 (m, 2H, CH_2 -pyrrole), 3.82 (s, 6 H, OCH_3), 2.86 (t, $J = 6.0$, 2H, H-b), 2.63-2.40 (m, 10H, H_{pip} , CH_2 -piperazine), 2.17 (s, 6H, CH_3 -pyrrole), 1.49 (s, 9H, CMe_3); ^{13}C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.2 (C-4), 158.6 (C-8a), 155.7 (C-7), 152.8 (CONH), 145.3 (C_{tri}), 137.2 (C-5), 136.6 (C-1'), 127.4 (C_{pyr}), 122.9 (C-6), 122.7 (CH_{tri}), 110.1 (C-4a), 107.4 (C-2', C-6'), 105.4 (CH_{pyr}), 100.8 (C-4'), 58.4 and 57.6 (CH_2 -piperazine, C-b), 55.7 and 55.6 (OCH_3), 53.6, 53.1 (CH_{pip}), 51.0 (CMe_3), 47.8 (C-a), 41.5 (CH_2 -pyrrole), 37.3 (C-1''), 29.1 (CMe_3), 12.6 (CH_3); MS (ESI): $m/z = 712$ $[M+H]^+$ 100%; HRMS (ESI): Calc. for $C_{37}H_{50}N_{12}O_3Na$ $[M+Na]^+$ 733.4034, found 733.4027.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(but-3-ynylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (22a)

To a solution of **17** (414 mg, 0.90 mmol) in dry dioxane (10 mL) was added 3-butyne-1-amine hydrochloride **21a** (95 mg, 0.90 mmol) and DIPEA (0.31 mL, 1.81 mmol). The mixture was heated at 70 °C for 20 h, and then concentrated in vacuo. The crude residue was diluted with CH_2Cl_2 , washed with a saturated solution of $NaHCO_3$ (20 mL) and water (20 mL), dried ($MgSO_4$)

then concentrated in vacuo. Purification by column chromatography (CH₂Cl₂/MeOH 98:2) gave alkyne **22a** (251 mg, 60%) as a yellow solid. *R*_f 0.40 (CH₂Cl₂/MeOH 95:5); ¹H NMR: δ 10.32 (br s, 1H, NHCO), 8.74 (s, 1H, H-4), 7.68 (s, 1H, H-5), 7.16 (br s, 1H, NHtBu), 6.52-6.44 (m, 3H, H-2', H-4', H-6'), 5.96 (br s, 1H, NHCH₂), 3.77 (s, 6H, OCH₃), 3.73 (q, *J* = 6.8, 2H, H-1''), 2.70-2.50 (m, 2H, H-2''), 1.99 (t, *J* = 2.6, H-4''), 1.48 (s, 9H, CMe₃); ¹³C NMR: δ 162.4 (C-2), 161.8 (C-3', C-5'), 161.2 (C-4), 158.5 (C-8a), 155.8 (C-7), 152.8 (CONH), 137.1 (C-5), 136.6 (C-1'), 122.9 (C-6), 110.0 (C-4a), 107.4 (C-2', C-6'), 100.9 (C-4'), 81.8 (C-4''), 70.1 (C-3''), 55.7 and 55.6 (OCH₃), 51.1 (CMe₃), 40.5 (C-1''), 29.0 (CMe₃), 19.2 (C-2''); MS (ESI): *m/z* = 449 [M+H]⁺ 100%.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(pent-4-ynylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (22b)

This compound was prepared according the procedure outlined for compound **22a** starting from **17** (574 mg, 1.25 mmol), 4-pentyn-1-amine hydrochloride **21b** (299 mg, 2.50 mmol) and DIPEA (0.86 mL, 5 mmol) in dry dioxane (12 mL) at 50 °C for 20 h. Purification by flash column chromatography (CH₂Cl₂/MeOH 98:2) furnish alkyne **22b** (411 mg, 35%) as a yellow solid. *R*_f 0.27 (CH₂Cl₂/MeOH 95:5); ¹H NMR: δ 10.34 (br s, 1H, NHCO), 8.71 (s, 1H, H-4), 7.66 (s, 1H, H-5), 7.14 (br s, 1H, NHtBu), 6.50-6.46 (m, 3H, H-2', H-4', H-6'), 5.73 (m, 1H, NHCH₂), 3.81 (s, 6H, OCH₃), 3.70 (q, *J* = 6.7, 2H, H-1''), 2.34 (td, *J* = 6.7, 2.7, 2H, H-3''), 1.99 (t, *J* = 2.7, 1H, H-5''), 1.94 (qt, *J* = 6.7, 6.7, 2H, H-2''), 1.49 (s, 9H, CMe₃); ¹³C NMR: δ 163.1 (C-2), 162.0 (C-3', C-5'), 161.2 (C-4), 158.6 (C-8a), 155.9 (C-7), 153.0 (CONH), 137.4 (C-5), 137.0 (C-1'), 122.7 (C-6), 110.1 (C-4a), 107.6 (C-2', C-6'), 101.1 (C-4'), 83.9 (C-5''), 69.3 (C-4''), 55.9 and 55.8 (OCH₃), 51.2 (CMe₃), 41.0 (C-1''), 29.2 (CMe₃), 28.2 (C-2''), 16.4 (C-3''); MS (ESI): *m/z* = 485 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₂₅H₃₀N₆O₃Na [M+Na]⁺ 485.2277, found 485.2255.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(hex-5-ynylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (22c)

This compound was prepared according the procedure outlined for compound **22b** starting from **17** (344 mg, 0.75 mmol), 5-hexyn-1-amine hydrochloride **21c** (200 mg, 1.50 mmol) and DIPEA (0.50 mL, 2.9 mmol) in dry dioxane (12 mL) at 70 °C for 17 h. Purification by flash chromatography (CH₂Cl₂/MeOH 98:2) furnish alkyne **22c** (109 mg, 31%) as a yellow solid. *R*_f 0.28 (CH₂Cl₂/MeOH 99:1); ¹H NMR (500 MHz): δ 10.35 (br s, 1H, NHCO), 8.75 (br s, 1H, H-4), 7.69 (br s, 1H, H-5), 7.14 (br s, 1H, NHtBu), 6.58-6.48 (m, 3H, H-2', H-4', H-6'), 5.49 (br s, 1H, NHCH₂), 3.83 (s, 6H, OCH₃), 3.63 (m, 2H, H-1''), 2.28 (td, *J* = 7.0, 2.5, 2H, H-4''), 1.96 (t, *J* = 2.5, 1H, H-6''), 1.84 (qt, *J* = 7.0, 2H, H-2''), 1.67 (qt, *J* = 7.0, 2H, H-3''), 1.46 (s, 9H, CMe₃); ¹³C NMR (125 MHz): δ 162.7 (C-2), 161.7 (C-3', C-5'), 161.0 (C-4), 157.0 (C-8a), 155.6 (C-7), 152.8 (CONH), 137.1 (C-5), 136.7 (C-1'), 122.4 (C-6), 109.7 (C-4a), 107.4 (C-2', C-6'), 100.8 (C-4'), 83.9 (C-6''), 68.7 (C-5''), 55.6 (OCH₃), 51.0 (CMe₃), 40.9 (C-1''), 29.0 (CMe₃), 28.6 (C-2''), 25.9 (C-3''), 18.2 (C-4''); MS (ESI): *m/z* = 477 [M+H]⁺ 100%.

1-(2-(2-(1-(1-Benzylpyrrolidin-3-yl)-1H-1,2,3-triazol-4-yl)ethylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl)-3-tert-butylurea (23a)

From alkyne **22a** (75 mg, 0.167 mmol), azide **11c** (34 mg, 0.161 mmol), sodium ascorbate (16 mg, 0.050 mmol), CuSO₄·5H₂O (8 mg, 0.032 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5 to 90:10) gave triazole **23a** (56 mg, 51%) as an orange solid. *R*_f 0.43 (CH₂Cl₂/MeOH 90:10); ¹H NMR: δ 10.35 (br s, 1H, NHCO), 8.70 (br s, 1H, H-4), 7.65 (br s, 1H, H-5), 7.63 (br s, 1H, H_{tri}), 7.40-7.19 (m, 5H, H_{Ph}), 7.15 (br s, 1H, NHtBu), 6.50-6.45 (m, 3 H, H-2', H-4', H-6'), 6.08 (t, *J* = 5.5, 1H, NHCH₂), 5.22-5.16 (m, 1H, H-c), 4.05-3.82 (m, 2H, H-1''), 3.80 (s, 6H, OCH₃), 3.65 (s, 2H, CH₂Ph), 3.25-2.75 (m, 5H, H-2'', H-b, H-e), 2.65-2.35 (m, 2H, H-d, H-e), 2.15-1.95 (m, 1H, H-d), 1.48 (s, 9H, CMe₃); ¹³C NMR: δ 163.0 (C-2), 162.0 (C-3', C-5'), 161.2 (C-4), 158.9 (C-8a), 155.9 (C-7), 153.0 (CONH), 146.0 (C_{tri}), 138.5 (C_{Ph}), 137.4 (C-5), 136.9 (C-1'), 128.9, 128.7 and 127.6 (CH_{Ph}), 122.8 (C-6), 120.0 (CH_{tri}), 110.1 (C-4a), 107.6 (C-2', C-6'), 101.1 (C-4'), 60.4 (C-b), 59.9 (CH₂Ph), 59.6 (C-c), 55.9 and 55.8 (OCH₃), 52.9 (C-e), 51.2 (CMe₃), 41.2 (C-1''), 33.0 (C-d), 29.3 (CMe₃), 25.9 (C-2''); MS (ESI): *m/z* = 673 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₃₅H₄₂N₁₀O₃Na [M+Na]⁺ 673.3339, found 673.3329.

1-(2-(3-(1-(1-Benzylpyrrolidin-3-yl)-1H-1,2,3-triazol-4-yl)propylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl)-3-tert-butylurea (23b)

From alkyne **22b** (77 mg, 0.167 mmol), azide **11c** (34 mg, 0.161 mmol), sodium ascorbate (16

mg, 0.050 mmol), CuSO₄·5H₂O (8 mg, 0.032 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5) gave triazole **23b** (90 mg, 81%) as a yellow solid. *R*_f 0.29 (CH₂Cl₂/MeOH 95:5); ¹H NMR: δ 10.33 (br s, 1H, NHCO), 8.68 (br s, 1H, H-4), 7.62 (br s, 1H, H-5), 7.55 (br s, 1H, H_{tri}), 7.40-7.26 (m, 5H, H_{ph}), 7.14 (br s, 1H, NH*t*Bu), 6.47-6.44 (m, 3H, H-2', H-4', H-6'), 5.99 (t, *J* = 5.2, 1H, NHCH₂), 5.19-5.12 (m, 1H, H-c), 3.78 (s, 6H, OCH₃), 3.63-3.58 (m, 4H, H-1'', CH₂Ph), 3.10-2.70 (m, 5H, H-3'', H-b, H-e), 2.65-2.35 (m, 2H, H-d, H-e), 2.20-1.95 (m, 3H, H-2'', H-d), 1.45 (s, 9H, CMe₃); ¹³C NMR: δ 163.0 (C-2), 162.0 (C-3', C-5'), 161.2 (C-4), 158.9 (C-8a), 155.8 (C-7), 153.0 (CONH), 147.9 (C_{tri}), 138.6 (C_{ph}), 137.4 (C-5), 137.0 (C-1'), 128.8, 128.7 and 127.5 (CH_{ph}), 122.7 (C-6), 119.3 (CH_{tri}), 110.0 (C-4a), 107.6 (C-2', C-6'), 101.0 (C-4'), 60.5 and 59.9 (C-e, CH₂Ph), 59.5 (C-c), 55.8 and 55.7 (OCH₃), 52.9 (C-b), 51.2 (CMe₃), 41.3 (C-1''), 33.0 (C-d), 29.2 (CMe₃), 27.2 (C-2''), 23.5 (C-3''); MS (ESI): *m/z* = 687 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₃₆H₄₄N₁₀O₃Na [M+Na]⁺ 687.3496, found 687.3472.

1-*tert*-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(3-(1-(pyridin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)propylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (23c)

From alkyne **22b** (61 mg, 0.149 mmol), 2-(azidomethyl)pyridine **4** (18 mg, 0.149 mmol), sodium ascorbate (16 mg, 0.050 mmol), CuSO₄·5H₂O (8 mg, 0.032 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 98:2) gave triazole **23c** (59 mg, 81%) as a white solid. *R*_f 0.28 (CH₂Cl₂/MeOH 95:5); ¹H NMR: δ 10.35 (br s, 1H, NHCO), 8.71 (br s, 1H, H-4), 8.64-8.55 (m, 1H, H-f'), 7.71-7.65 (m, 2H, H-5, H-d'), 7.48 (br s, 1H, H_{tri}), 7.25-7.09 (m, 3H, NH*t*Bu, H-c', H-e'), 6.52-6.47 (m, 3H, H-2', H-4', H-6'), 5.86 (t, 1H, *J* = 7.0, NHCH₂), 5.62 (s, 2H, CH₂Pyr), 3.82 (s, 6H, OCH₃), 3.64 (dd, 2H, *J* = 7.0, 7.0, H-1''), 2.86 (t, 2H, *J* = 7.0, H-3''), 2.17-2.07 (m, 2H, H-2''), 1.48 (s, 9H, CMe₃); ¹³C NMR: δ 163.1 (C-2), 162.0 (C-3', C-5'), 161.2 (C-4), 158.9 (C-7), 155.9 (C-8a), 155.0 (C-b'), 153.1 (CONH), 150.0 (C-f'), 148.1 (C-4''), 137.6 (C-d'), 137.4 (C-5), 137.0 (C-1'), 123.7 (C-c'), 122.7 (C-e', C-6), 121.7 (C-5''), 110.0 (C-4a), 107.6 (C-2', C-6'), 101.0 (C-4'), 55.9 and 55.8 (OCH₃), 51.2 (CMe₃), 41.3 (C-1''), 29.2 (CMe₃, C-2''), 23.4 (C-3''); MS (ESI): *m/z* = 597 [M+H]⁺ 100%; HRMS (ESI): Calc. for C₃₁H₃₆N₁₀O₃Na [M+Na]⁺ 619.2870, found 619.2881.

1-*tert*-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(4-(1-((pyridine-2-yl-methyl)methyl)-1*H*-1,2,3-triazol-4-yl)butylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (23d)

From alkyne **22c** (60 mg, 0.16 mmol), 2-(azidomethyl)pyridine **4** (42.9 mg, 0.32 mmol), sodium ascorbate (13.3 mg, 0.067 mmol), CuSO₄·5H₂O (8.0 mg, 0.032 mmol) in 2:1 *t*BuOH/H₂O (4.7 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 98:2) gave triazole **23d** (48 mg, 49%) as a yellow solid. *R*_f 0.27 (CH₂Cl₂/MeOH 95:5); ¹H NMR (500 MHz): δ 10.34 (br s, 1H, NHCO), 8.79 (s, 1H, H-4), 8.56 (d, *J* = 4.8, H-f'), 7.81-7.61 (m, 2H, H-5, H-d), 7.52 (s, 1H, H_{tri}), 7.35-7.10 (m, 3H, H-c', H-e', NH*t*Bu), 6.60-6.40 (m, 3H, H-2', H-4', H-6'); 5.83 (br s, 1H, NHCH₂), 5.64 (s, 2H, CH₂pyr), 3.80 (s, 6H, OCH₃), 3.66 (br s, 2H, H-1''), 2.83 (t, 3H, *J* = 6.8, H-4''), 1.95-1.75 (m, 4H, H-2'', H-3''), 1.51 (s, 9H, CMe₃); ¹³C NMR (125 MHz): δ 162.7 (C-2), 161.8 (C-3', C-5'), 161.0 (C-4), 158.6 (C-8a), 155.6 (C-7), 154.9 (C-b'), 152.8 (CONH), 149.8 (C-f'), 148.4 (C_{tri}), 137.3 (C-d'), 137.2 (C-5), 136.8 (C-1'), 123.4 (CH_{tri}), 122.4 (C-6, C-c'), 121.5 (C-e'), 109.7 (C-4a), 107.4 (C-2', C-6'), 100.8 (C-4'), 55.6 (CH₂pyr, OCH₃), 51.0 (CMe₃), 41.2 (C-1''), 29.0 (CMe₃, C-2''), 26.8 (C-3''), 25.4 (C-4''); MS (ESI): *m/z* = 633 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₃₂H₃₈N₁₀O₃Na [M+Na]⁺ 633.3026, found 633.3017.

1-*tert*-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(3-(1-((1-methylpiperidin-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)propylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (23e)

From alkyne **22b** (51 mg, 0.11 mmol), azide **11b** (17.8 mg, 0.115 mmol), sodium ascorbate (4.7 mg, 0.027 mmol), CuSO₄·5H₂O (2.7 mg, 0.011 mmol) in 2:1 *t*BuOH/H₂O (2.4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 90:10) gave triazole **23e** (31mg, 45%) as a yellow solid. *R*_f 0.11 (CH₂Cl₂/MeOH 90:10); ¹H NMR (500 MHz): δ 10.35 (br s, 1H, NHCO), 8.72 (br s, 1H, H-4), 7.66 (s, 1H, H-5), 7.32 (s, 1H, H_{tri}), 7.13 (s, 1H, NH*t*Bu), 6.51-6.46 (m, 3H, H-2', H-4', H-6'), 5.77 (br s, 1H, NHCH₂), 4.35-4.18 (m, 2H, H-a), 3.81 (s, 6H, OCH₃), 3.71-3.56 (m, 2H, H-1''), 2.85-2.68 (m, 4H, H-b', H-f', H-3''), 2.29-2.20 (m, NCH₃, H-c'), 2.19-2.01 (m, 2H, H-f', H-2''), 1.99-1.84 (m, 1H, H-b'), 1.81-1.60 (m, 3H, H-d', H-e'), 1.48 (s, 9H, CMe₃), 1.15-0.98 (m, 1H, H-d''); ¹³C NMR (125 MHz): δ 162.9 (C-2), 161.8 (C-3', C-5'), 161.0 (C-4), 158.7 (C-8a), 155.7 (C-7), 152.9 (CONH), 147.6 (C_{tri}), 137.3 (C-1'), 136.8 (C-5), 122.6 (C-6), 121.2 (CH_{tri}), 109.8 (C-4a), 107.5 (C-2', C-6'), 100.9 (C-4'), 58.9 (C-b'), 55.8

(C-f'), 55.6 (OCH₃), 53.4 (C-a), 51.0 (CMe₃), 46.3 (NCH₃), 41.1 (C-1''), 36.9 (C-c'), 29.1, 29.0 (CMe₃, C-2''), 27.3 (C-d'), 24.0 (C-e'), 23.2 (C-3''); MS (ESI): *m/z* = 639 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₃₂H₄₄N₁₀O₃Na [M+Na]⁺ 639.3496, found 639.3502.

1-*tert*-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(4-(1-((1-methylpiperidin-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)butylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (23f)

From alkyne **22c** (60 mg, 0.126 mmol), azide **11b** (20.4 mg, 0.132 mmol), sodium ascorbate (5.5 mg, 0.028 mmol), CuSO₄·5H₂O (3.1 mg, 0.012 mmol) in 2:1 *t*BuOH/H₂O (2.9 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH/NEt₃ 90:10:1) gave triazole **23f** (18 mg, 22%) as a yellow solid. *R*_f 0.13 (CH₂Cl₂/MeOH 90:10); ¹H NMR (500 MHz): δ 10.34 (br s, 1H, NHCO), 8.72 (br s, 1H, H-4), 7.68 (s, 1H, H-5), 7.39 (s, 1H, H_{tri}), 7.51 (s, 1H, NH*t*Bu), 6.70-6.35 (m, 3H, H-2', H-4', H-6'), 5.72 (br s, 1H, NHCH₂), 4.45-4.15 (m, 2H, H-a), 3.83 (s, 6H, OCH₃), 3.70-3.55 (m, 2H, H-1''), 3.05-2.70 (m, 4H, H-b', H-f', H-4''), 2.45-2.30 (m, 4H, NCH₃, H-c'), 2.28-2.12 (m, 1H, H-f'), 2.10-1.99 (m, 1H, H-b'), 1.97-1.64 (m, 7H, H-2'', H-3'', H-d', H-e'), 1.49 (s, 9H, CMe₃), 1.20-1.02 (m, 1H, H-d'); ¹³C NMR (125 MHz): δ 162.9 (C-2), 161.8 (C-3', C-5'), 161.0 (C-4), 158.7 (C-8a), 155.7 (C-7), 152.9 (CONH), 148.1 (C_{tri}), 137.3 (C-1'), 136.8 (C-5), 122.6 (C-6), 121.4 (CH_{tri}), 109.8 (C-4a), 107.6 (C-2', C-6'), 100.9 (C-4'), 58.9 (C-b'), 55.8 and 55.6 (OCH₃), 55.2 (C-f'), 53.4 (C-a), 51.0 (CMe₃), 46.2 (NCH₃), 41.3 (C-1''), 36.7 (C-c'), 29.1, 29.0 (CMe₃, C-2''), 27.2 (C-d'), 26.9 (C-3''), 25.4 (C-4''), 24.0 (C-e'); MS (ESI): *m/z* = 631 [M+H]⁺ 100%; HRMS (ESI): Calc. for C₃₃H₄₆N₁₀O₃Na [M+Na]⁺ 653.3652, found 653.3647.

1-(2-(2-Azidoethylamino)-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl)-3-*tert*-butylurea (24)

A mixture of **17** (1.23 g, 2.68 mmol), 2-azidoethylamine salt **8** (1.02 g, 5.08 mmol) and DIPEA (0.92 mL, 5.35 mmol) in dry dioxane (30 mL) was warmed at 50 °C for 24 h; the solvent was removed in vacuo and the crude residue was purified by flash column chromatography (CH₂Cl₂/MeOH 99:1 to 98:2) to give **24** (987 mg, 80%) as a yellow solid. *R*_f 0.26 (CH₂Cl₂/MeOH 97:3); ¹H NMR: δ 10.26 (br s, 1H, NHCO), δ 8.75 (br s, 1H, H-4), 7.69 (br s, 1H, H-5), 7.16 (br s, 1H, NH*t*Bu), 6.55-6.41 (m, 3H, H-2', H-4', H-6'), 5.71 (br s, 1H, NHCH₂), 3.86-3.71 (m, 8H, OCH₃, H-1''), 3.67-3.57 (t, *J* = 5.3, 2H, H-2''), 1.48 (s, 9H, CMe₃); ¹³C NMR: δ 162.6 (C-2), 161.9 (C-3', C-5'), 161.3 (C-4), 158.7 (C-8a), 155.9 (C-7), 152.9 (CONH), 137.3 (C-5), 136.7 (C-1'), 123.2 (C-6), 110.3 (C-4a), 107.5 (C-2', C-6'), 101.0 (C-4'), 55.8 and 55.7 (OCH₃), 51.2 (CMe₃), 50.6 (C-2''), 41.2 (C-1''), 29.1 (CMe₃); MS (ESI): *m/z* = 488 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₂₂H₂₇N₉O₃Na [M+Na]⁺ 488.2135, found 488.2139.

3-(1-(2-(7-(3-*tert*-Butylureido)-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-2-ylamino)ethyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid (26a)

From azide **24** (70 mg, 0.15 mmol), pent-4-ynoic acid **25a** (15 mg, 0.15 mmol), sodium ascorbate (7 mg, 0.035 mmol), CuSO₄·5H₂O (4 mg, 0.016 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. The reaction mixture was then concentrated in vacuo and the residue was diluted with CH₂Cl₂ (40 mL), washed with 10% citric acid (15 mL), water (15 mL) and dried over MgSO₄. After concentration in vacuo, the solid was triturated with Et₂O to afford triazole **26a** (70 mg, 83%) as a yellow solid. *R*_f 0.14 (CH₂Cl₂/MeOH 9:1); ¹H NMR (DMF): δ 12.43 (br s, 1H, CO₂H), 10.47 (br s, 1H, NHCO), 8.99 (s, 1H, H-4), 8.09 (s, 1H, H-5), 7.92 (br s, 1H, H_{tri}), 7.84 (br s, 1H, NH*t*Bu), 6.80-6.60 (m, 3H, H-2', H-4', H-6'), 4.83-4.70 (m, 2H, H-2''), 4.08-3.95 (m, 2H, H-1''), 3.88 (s, 6H, OCH₃), 3.00-2.85 (m, 2H, H-a), 2.70-2.55 (m, 2H, H-b), 1.48 (s, 9H, CMe₃); ¹³C NMR (DMF): δ 174.3 (CO₂H), 164.0 (C-2), 163.3 (C-3', C-5'), 162.9 (C-4), 159.1 (C-8a), 156.2 (C-7), 153.4 (CONH), 147.1 (C_{tri}), 139.3 (C-5), 138.5 (C-1'), 123.3 (CH_{tri}), 122.9 (C-6), 111.1 (C-4a), 108.3 (C-2', C-6'), 101.3 (C-4'), 56.4 and 56.3 (OCH₃), 51.4 (CMe₃), 49.4 (C-2''), 42.8 (C-1''), 34.3 (C-b), 29.1 (CMe₃), 22.1 (C-a); MS (ESI): *m/z* = 564 [M+H]⁺ 100%; HRMS (ESI): Calc. for C₂₇H₃₃N₉O₃Na [M+Na]⁺ 586.2502, found 586.2509.

1-*tert*-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(2-(4-((dimethylamino)methyl)-1*H*-1,2,3-triazol-1-yl)ethylamino)pyrido[2,3-*d*]pyrimidin-7-yl)urea (26b)

From azide **24** (70 mg, 0.16 mmol), alkyne **25b** (26 mg, 0.31 mmol), sodium ascorbate (14 mg, 0.070 mmol), CuSO₄·5H₂O (8 mg, 0.032 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 90:10) gave triazole **26b** (72 mg, 88%) as a white solid. *R*_f 0.30 (CH₂Cl₂/MeOH 80:20); ¹H NMR: δ 10.28 (br s, 1H, NHCO), 8.74 (s, 1H, H-4), 7.93 (br s, 1H, H-5''), 7.70 (s, 1H, H-5), 7.15 (br s, 1H, NH*t*Bu), 6.56-

6.44 (m, 3H, H-2', H-4', H-6'), 5.83 (br s, 1H, NHCH₂), 4.75 (t, *J* = 5.9, 2H, H-2''), 4.15-4.01 (m, 2H, H-1''), 3.94 (br s, 2H, CH₂NMe₂), 3.81 (s, 6H, OCH₃), 2.53 (s, 6H, CH₃), 1.50 (s, 9H, CMe₃); ¹³C NMR: δ 162.5 (C-2), 161.9 (C-3', C-5'), 161.2 (C-4), 158.5 (C-8a), 155.9 (C-7), 152.8 (CONH), 146.1 (C_{tri}), 137.2 (C-5), 136.6 (C-1'), 123.8 (C-5''), 123.3 (C-6), 110.3 (C-4a), 107.5 (C-2', C-6'), 100.9 (C-4'), 55.8 and 55.7 (OCH₃), 54.3 (CH₂NMe₂), 51.1 (CMe₃), 49.2 (C-2''), 45.0 (NMe₂), 42.0 (C-1''), 29.1 (CMe₃); MS (ESI): *m/z* = 549 [M+H]⁺ 100%; HRMS (ESI): Calc. for C₂₇H₃₆N₁₀O₃Na [M+Na]⁺ 571.2870, found 571.2875.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (26c)

From azide **24** (75 mg, 0.161 mmol), alkyne **25c** (9 mg, 0.161 mmol), sodium ascorbate (8 mg, 0.025 mmol), CuSO₄·5H₂O (4 mg, 0.016 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 80:20) gave triazole **26c** (58 mg, 69%) as an orange solid. *R*_f 0.42 (CH₂Cl₂/MeOH 80:20); ¹H NMR (500 MHz, 330 K): δ 9.88 (br s, 1H, NHCO), 8.77 (s, 1H, H-4), 7.72 (br s, 1H, H-5), 7.59 (s, 1H, H-5''), 6.57-6.46 (m, 3H, H-2', H-4', H-6'), 4.77 (s, 2H, CH₂OH), 4.72 (t, *J* = 5.2, 2H, H-2''), 4.17-4.08 (m, 2H, H-1''), 3.84 (s, 6H, OCH₃), 1.52 (s, 9H, CMe₃); ¹³C NMR: δ 162.2 (C-2), 161.9 (C-3', C-5'), 161.3 (C-4), 158.5 (C-8a), 156.0 (C-7), 152.7 (CONH), 137.3 (C-5), 136.4 (C-1'), 123.3 (C-6), 121.9 (CH_{tri}), 110.0 (C-4a), 107.4 (C-2', C-6'), 100.9 (C-4'), 55.9 and 55.6 (OCH₃, CH₂OH), 51.1 (CMe₃), 48.9 (C-2''), 42.1 (C-1''), 29.0 (CMe₃); MS (ESI): *m/z* = 522 [M+H]⁺ 100%; HRMS (ESI): Calc. for C₂₅H₃₁N₉O₄Na [M+Na]⁺ 544.2397, found 544.2391.

1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(2-(4-(2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)ethylamino)pyrido[2,3-d]pyrimidin-7-yl)urea (26d)

From azide **24** (75 mg, 0.161 mmol), alkyne **25d** (22 mg, 0.322 mmol), sodium ascorbate (14 mg, 0.070 mmol), CuSO₄·5H₂O (8 mg, 0.032 mmol) in 2:1 *t*BuOH/H₂O (4 mL), according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 95:5) gave triazole **26d** (73 mg, 85%) as a white solid. *R*_f 0.18 (CH₂Cl₂/MeOH 95:5); ¹H NMR: δ 10.29 (br s, 1H, NHCO), 8.70 (s, 1H, H-4), 7.70 (br s, 1H, H-5), 7.41 (s, 1H, H_{tri}), 7.20 (br s, 1H, NH_tBu), 6.51-6.46 (m, 4H, NHCH₂, H-2', H-4', H-6'), 4.78-4.62 (m, 2H, H-2''), 4.05 (dd, *J* = 5.6, 5.6, 2H, H-1''), 3.88 (t, *J* = 5.8, 2H, H-b), 3.81 (s, 6H, OCH₃), 2.88 (t, *J* = 5.8, 2H, H-a), 1.48 (s, 9H, CMe₃); ¹³C NMR: δ 162.3 (C-2), 161.8 (C-3', C-5'), 161.3 (C-4), 158.4 (C-8a), 155.9 (C-7), 152.7 (CONH), 145.6 (C_{tri}), 137.2 (C-5), 136.5 (C-1'), 123.3 (C-6), 122.7 (CH_{tri}), 110.2 (C-4a), 107.4 (C-2', C-6'), 100.9 (C-4'), 61.5 (C-b), 55.9 and 55.6 (OCH₃), 51.1 (CMe₃), 49.3 (C-2''), 42.1 (C-1''), 29.1 (CMe₃), 28.8 (C-a); MS (ESI): *m/z* = 558 [M+Na]⁺ 100%; HRMS (ESI): Calc. for C₂₆H₃₃N₉O₄Na [M+Na]⁺ 558.2553, found 558.2534.

tert-Butyl(tert-butoxycarbonylamino)((1-(2-(7-(3-tert-butylureido)-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-2-ylamino)ethyl)-1H-1,2,3-triazol-4-yl)methylamino)methylenecarbamate (26e)

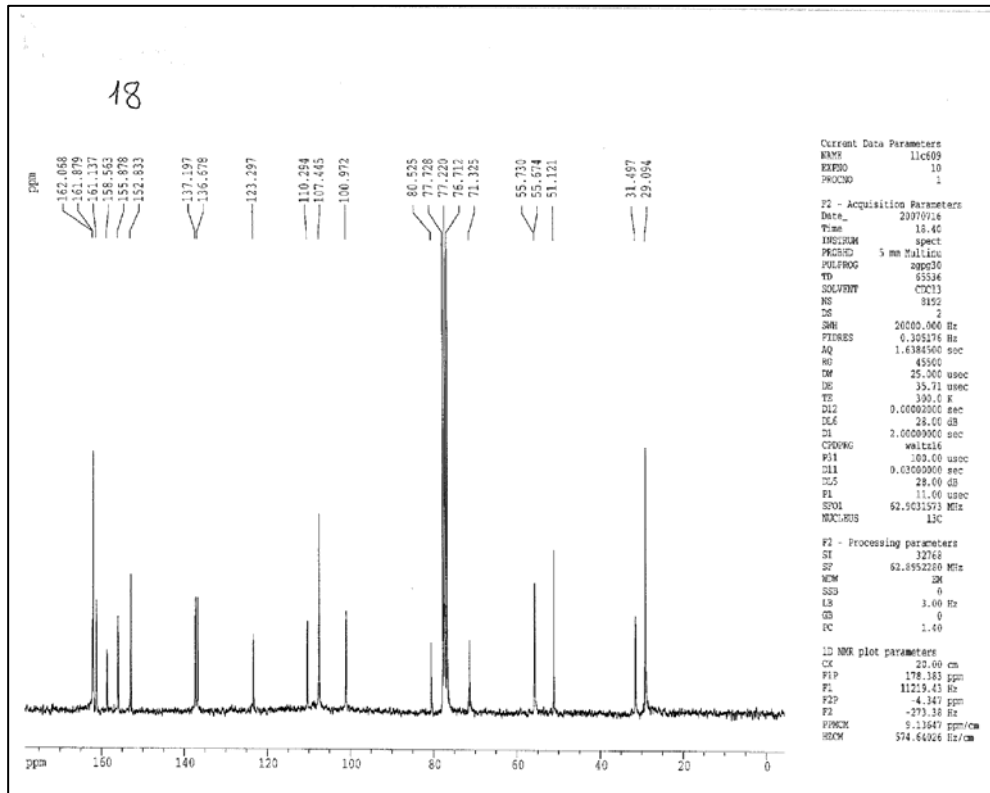
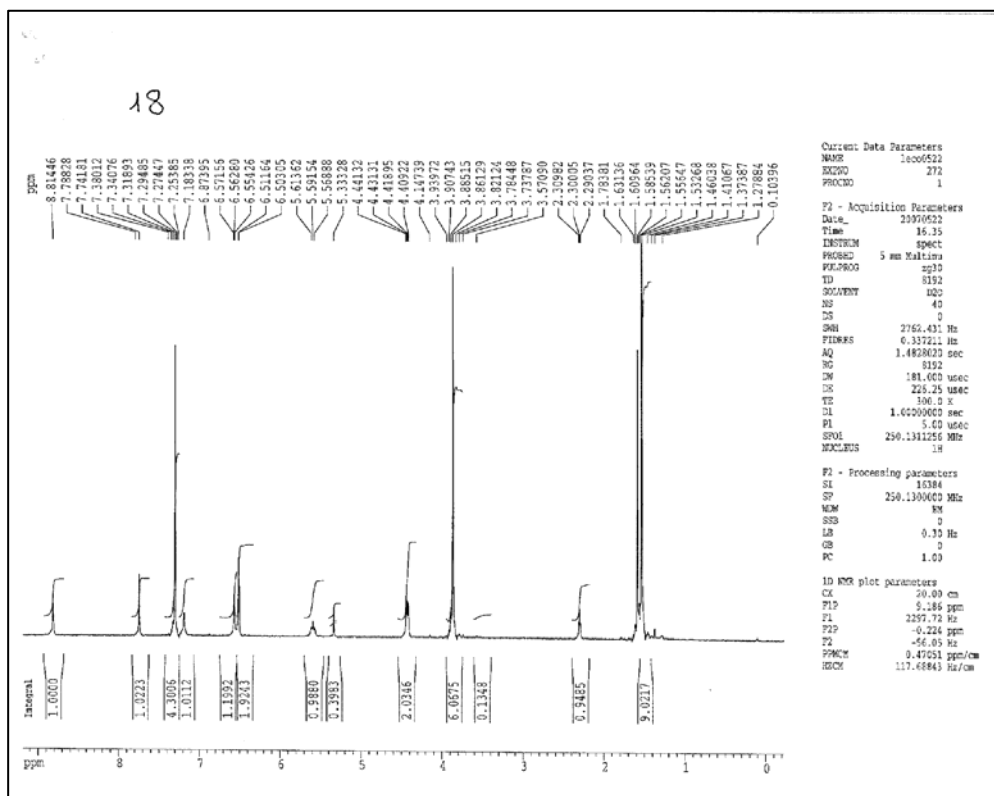
From azide **24** (70 mg, 0.15 mmol), alkyne **25e** (44.6 mg, 0.15 mmol), sodium ascorbate (7 mg, 0.035 mmol), CuSO₄·5H₂O (4 mg, 0.016 mmol) in 2:1 *t*BuOH/H₂O (4 mL) according to the above procedure. Purification by flash column chromatography (CH₂Cl₂/MeOH 96:4) gave triazole **26e** (47 mg, 41%) as an orange solid. *R*_f 0.19 (CH₂Cl₂/MeOH 96:4); ¹H NMR (500 MHz, 330 K): δ 11.40 (s, 1H, NHBoc), 10.33 (br s, 1H, NHCO), 8.73 (br s, 2H, H-4, NH_{gua}), 7.70 (s, 1H, H-5), 7.55 (s, 1H, H_{tri}), 7.19 (s, 1H, NH_tBu), 6.60-6.40 (m, 3H, H-2', H-4', H-6'), 6.32 (br s, 1H, NHCH₂), 4.80-4.55 (m, 4H, H-2'', CH₂-guanidine), 4.05 (br s, 2H, H-1''), 3.79 (s, 6H, OCH₃), 1.46, 1.45 and 1.44 (s, 27 H, CMe₃); ¹⁵C NMR (125 MHz): δ 163.4 (CO_{gua}), 162.4 (C-2), 161.8 (C-3', C-5'), 161.1 (C-4), 158.4 (C-8a), 156.0 (CO_{gua}), 155.8 (C-7), 153.0 (CN_{gua}), 152.7 (CONH), 144.0 (C_{tri}), 137.2 (C-5), 136.5 (C-1'), 123.2 (C-6, CH_{tri}), 110.3 (C-4a), 107.4 (C-2', C-6'), 100.9 (C-4'), 83.3 and 79.4 (Boc), 55.6 (OCH₃), 51.0 (CMe₃), 49.0 (C-2''), 41.8 (C-1''), 36.5 (CH₂-guanidine), 29.0, 28.4 and 28.1 (CMe₃); MS (ESI): *m/z* = 763 [M+H]⁺ 100%; HRMS (ESI): Calc. for C₃₆H₅₀N₁₂O₇Na [M+Na]⁺ 785.3823, found 785.3836.

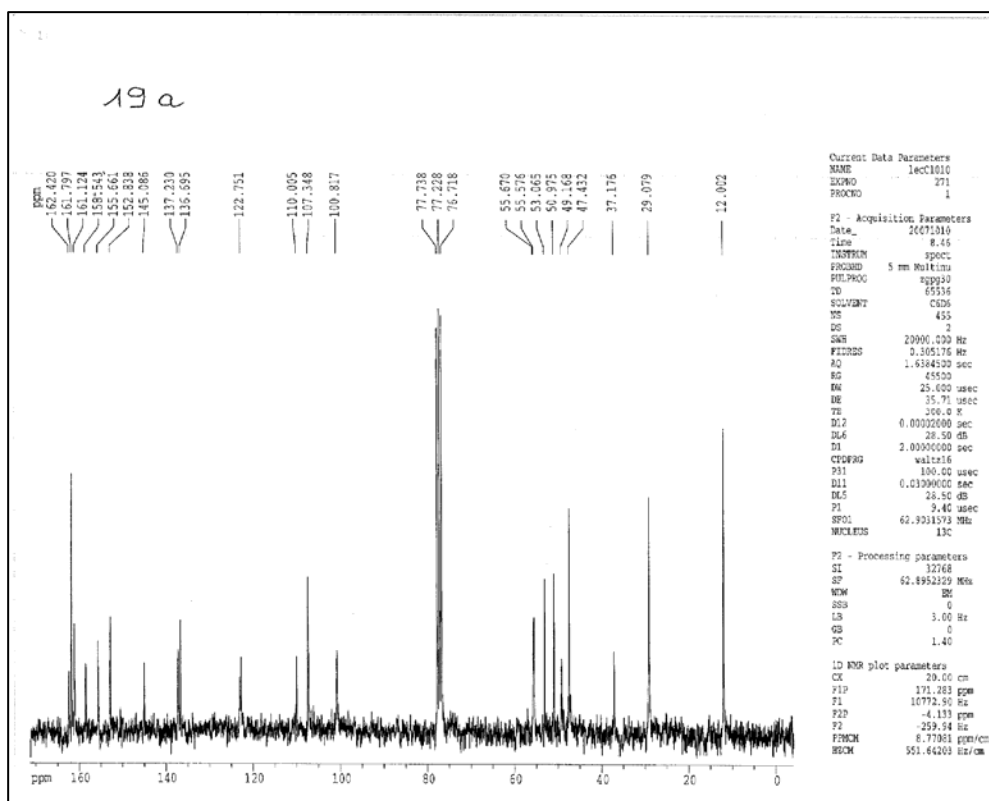
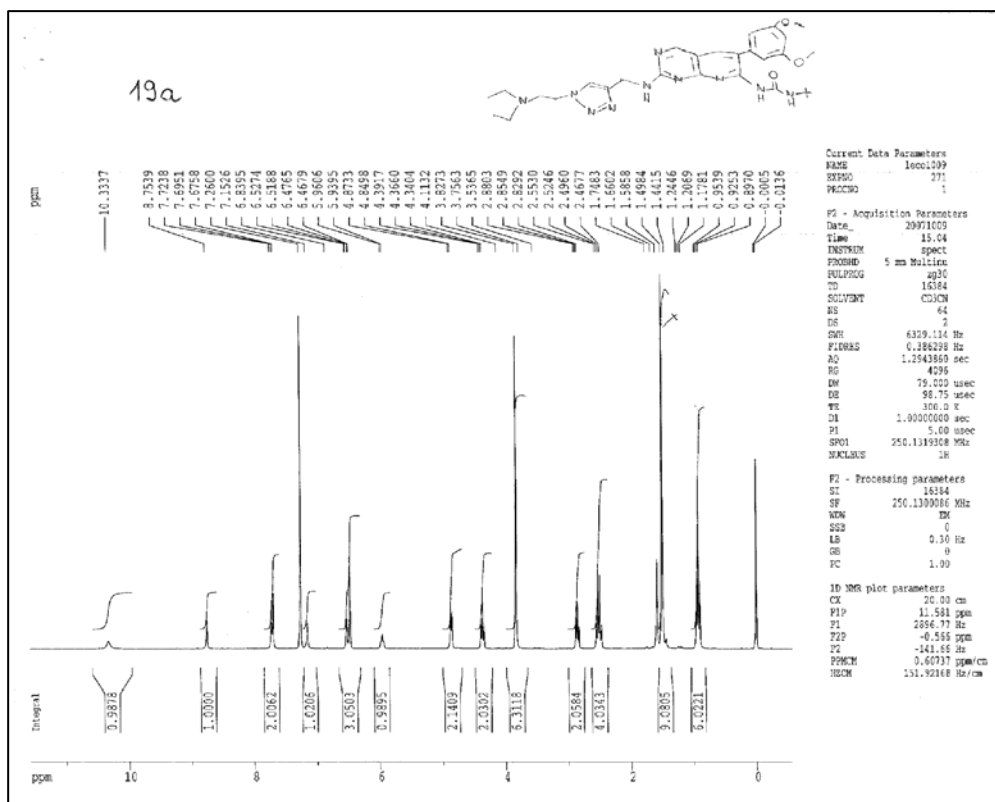
1-tert-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(2-(4-(guanidinomethyl)-1H-1,2,3-triazol-1-yl)ethylamino)pyrido[2,3-d]pyrimidin-7-yl)urea hydrochloride (26f)

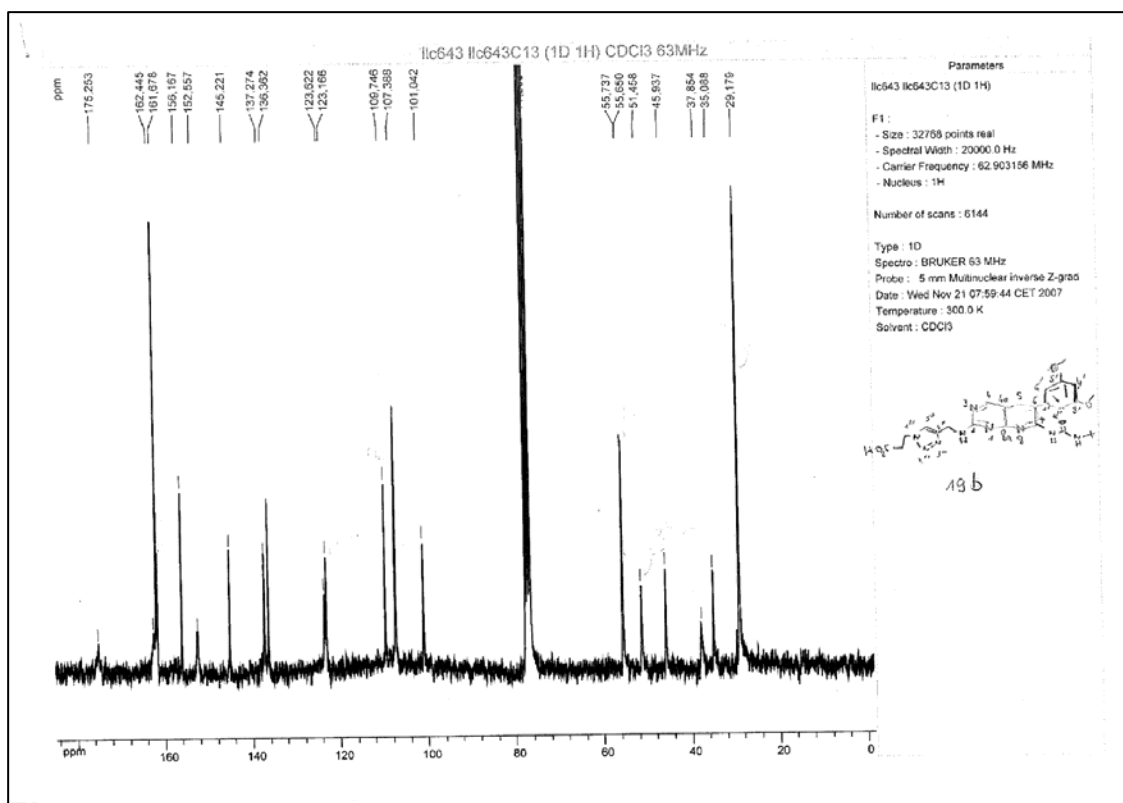
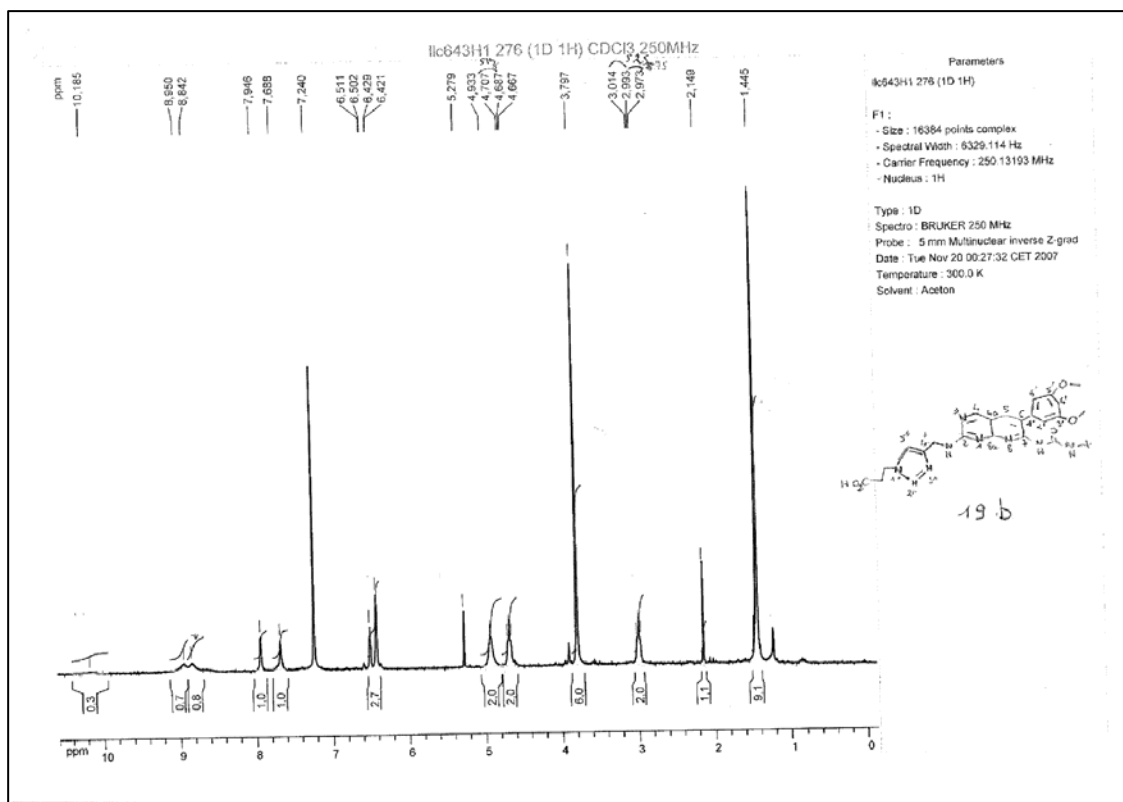
To a solution of triazole **26e** (40 mg, 0.052 mmol) in dioxane (4 mL) was added 3N HCl (1.7 mL) at 0 °C. The ice bath was removed and the mixture was stirred at room temperature for 3h30 then concentrated in vacuo. The residue was washed with Et₂O and dried under vacuum to afford guanidine **26f** (29 mg, 93%) as a yellow solid. ¹H NMR (CD₃OD): δ 8.90 (s, 1H, H-4), 8.04 (s,

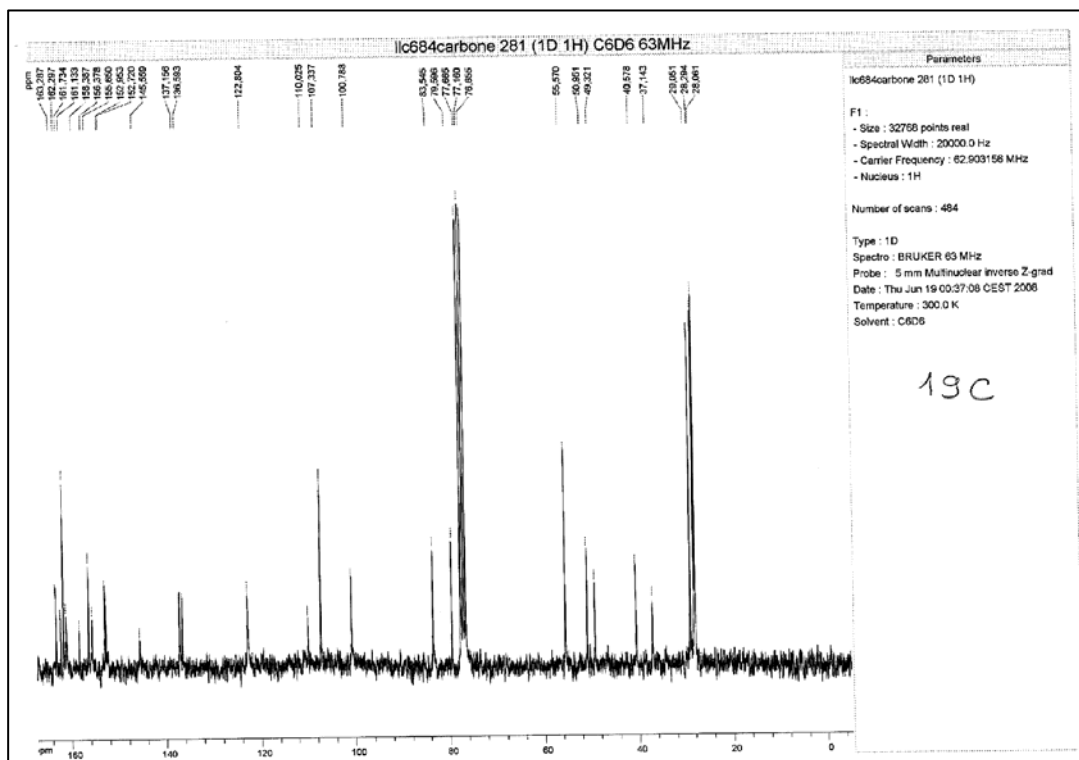
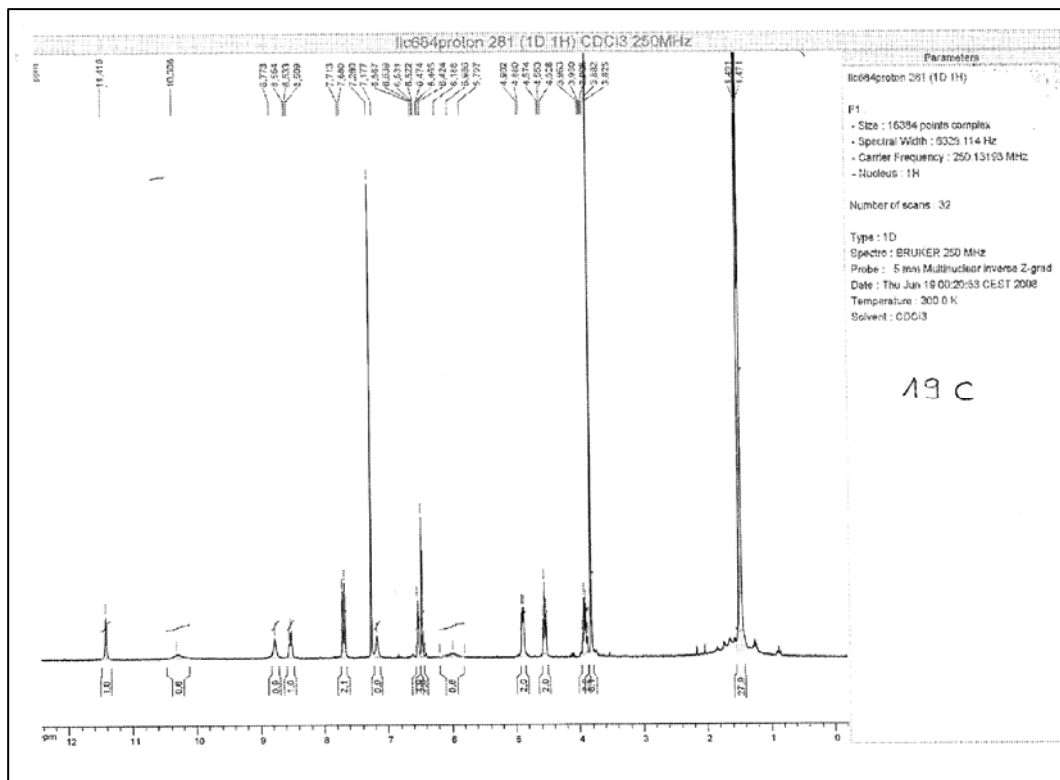
1H, H_{tri}), 7.86 (s, 1H, H-5), 6.65-6.50 (m, 3H, H-2', H-4', H-6'), 4.90-4.70 (m, 2H, H-2''), 4.46 (s, 2H, CH₂-guanidine), 4.05-3.95 (m, 2H, H-1''), 3.84 (s, 6H, OCH₃), 1.42 (s, 9H, CMe₃); MS (ESI): m/z = 563 [M-HCl + H]⁺ 100%; HRMS (ESI): Calc. for C₂₆H₃₅N₁₂O₃ [M-HCl+H]⁺ 563.2955 found 563.2953.

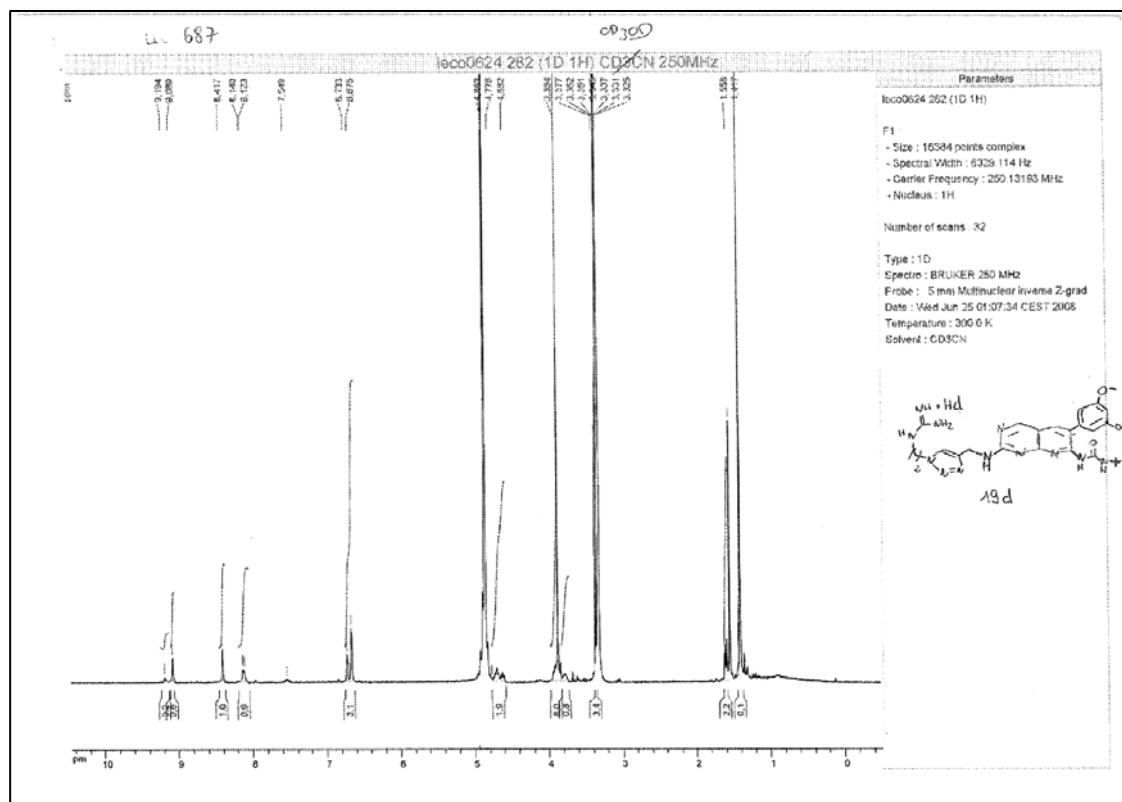
3. ^1H and ^{13}C NMR spectra

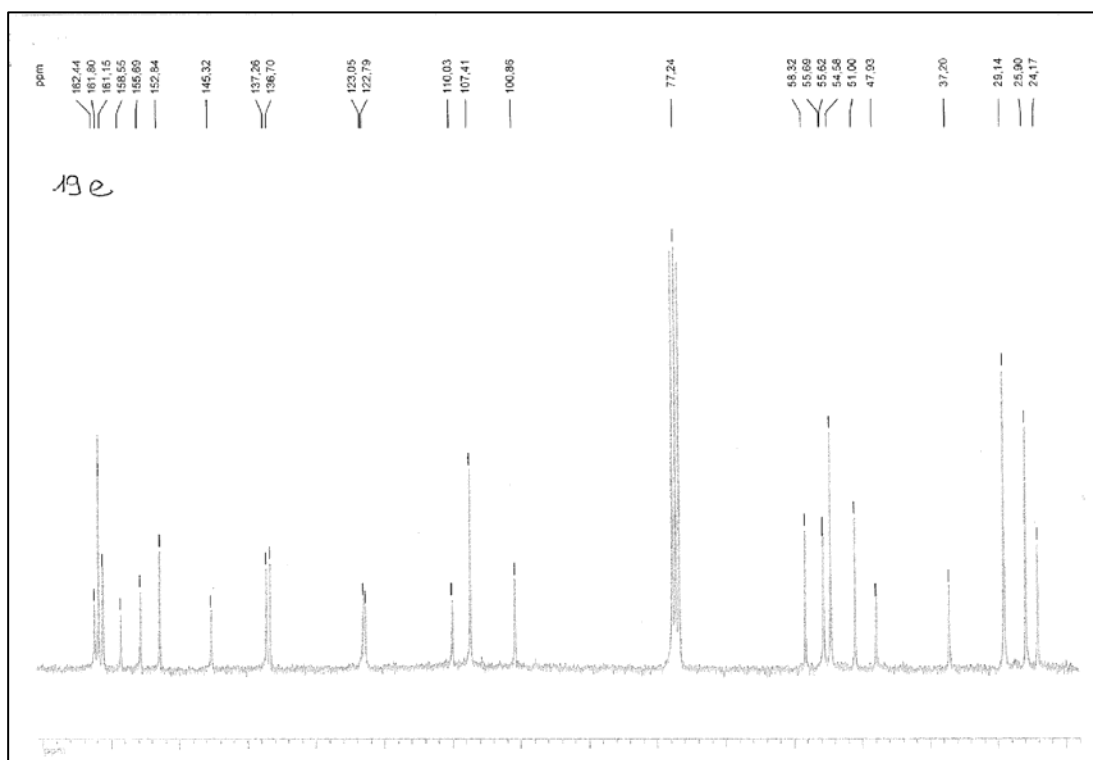


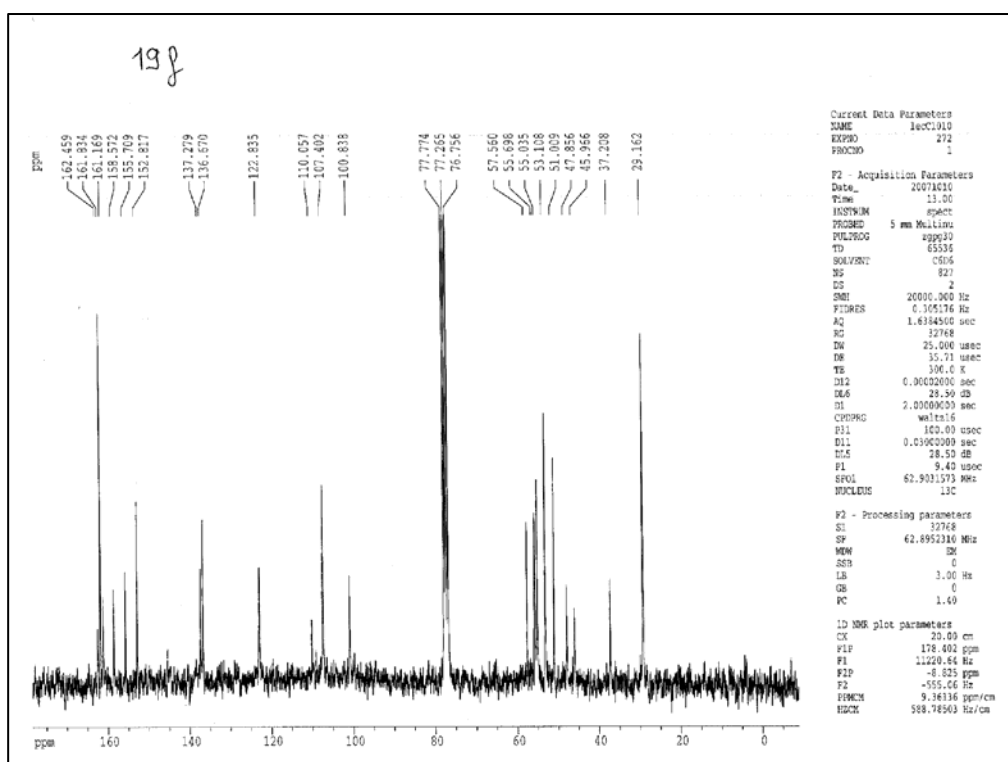


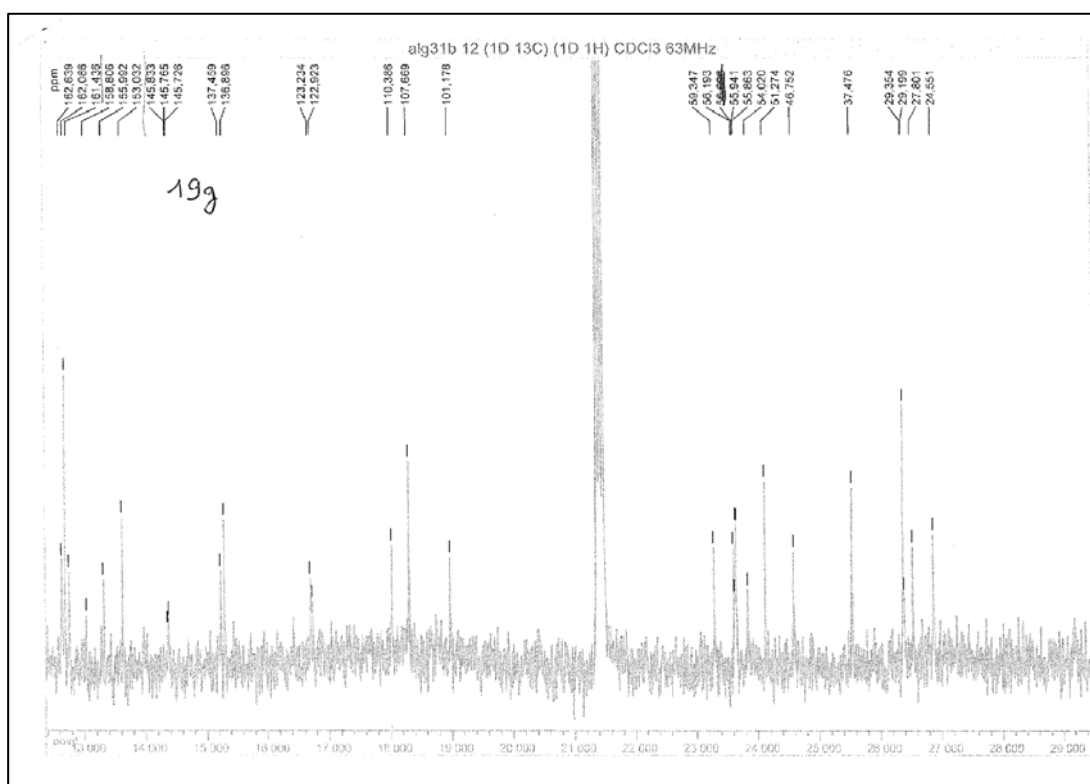
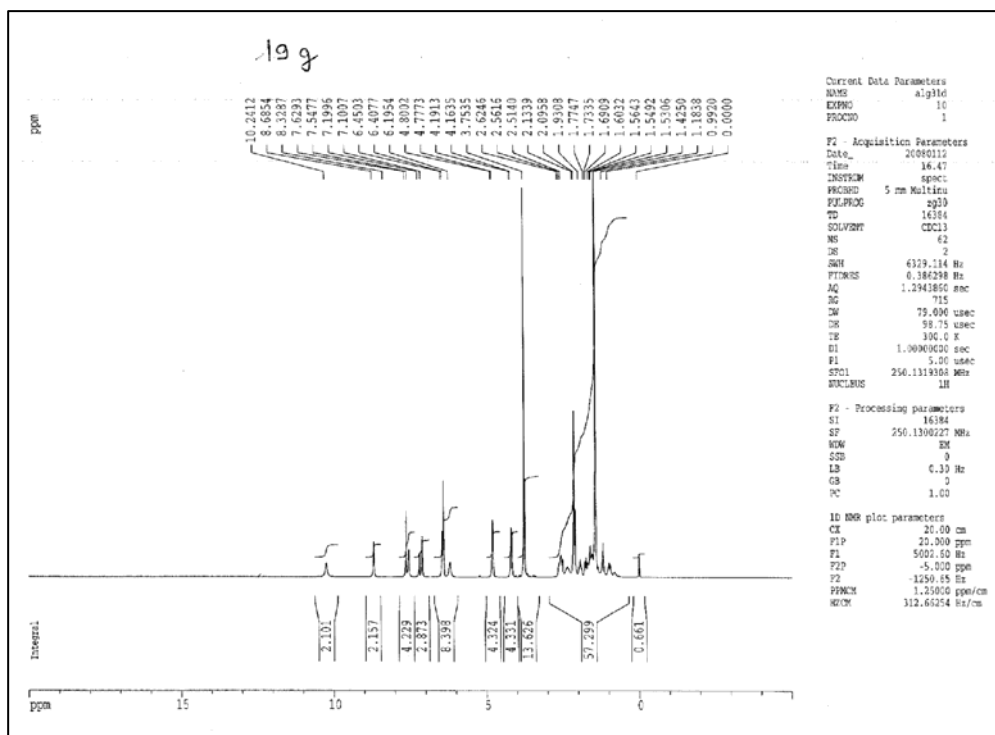


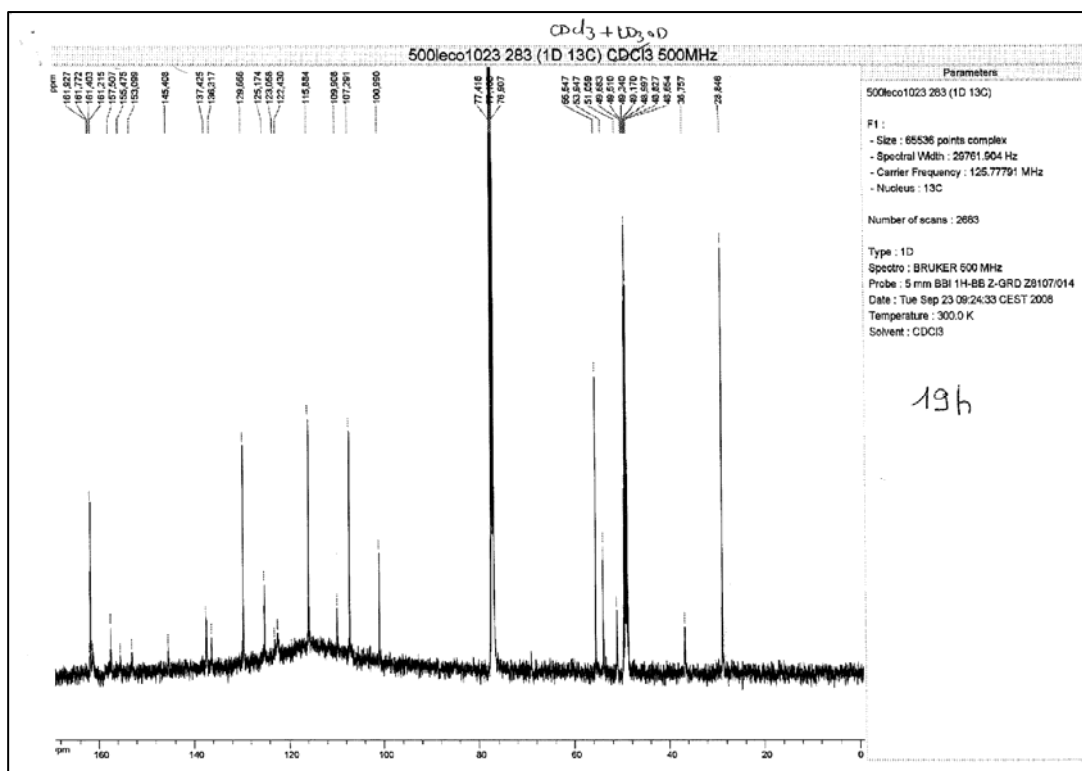
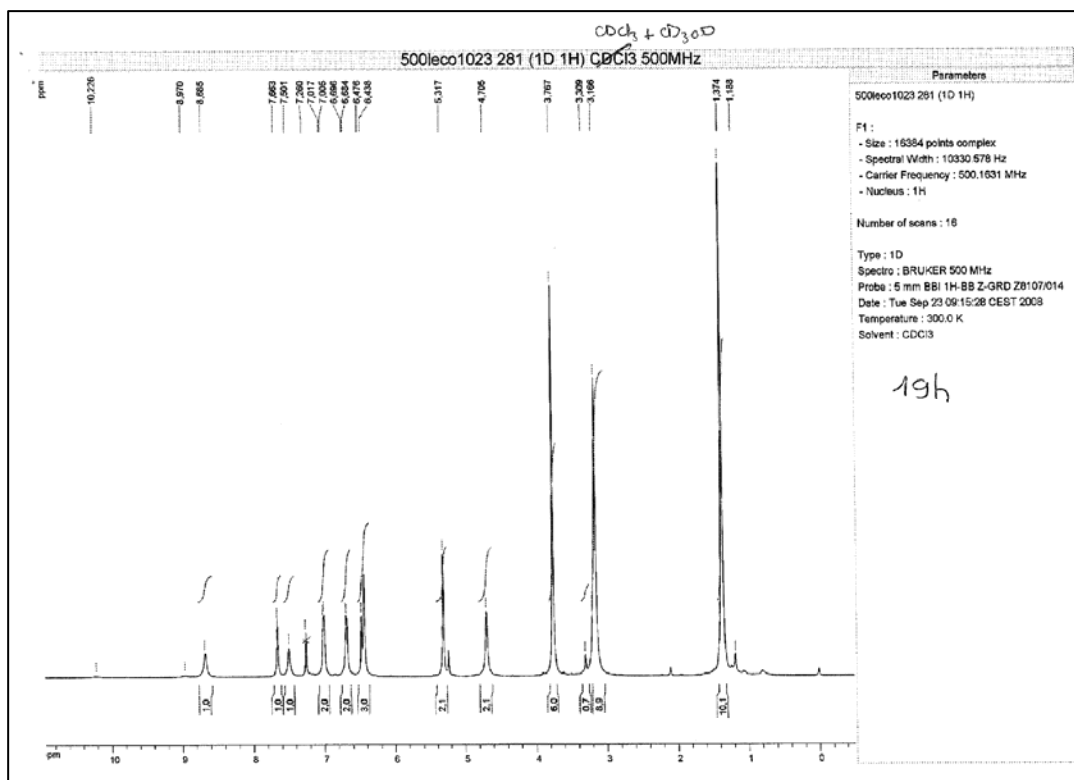


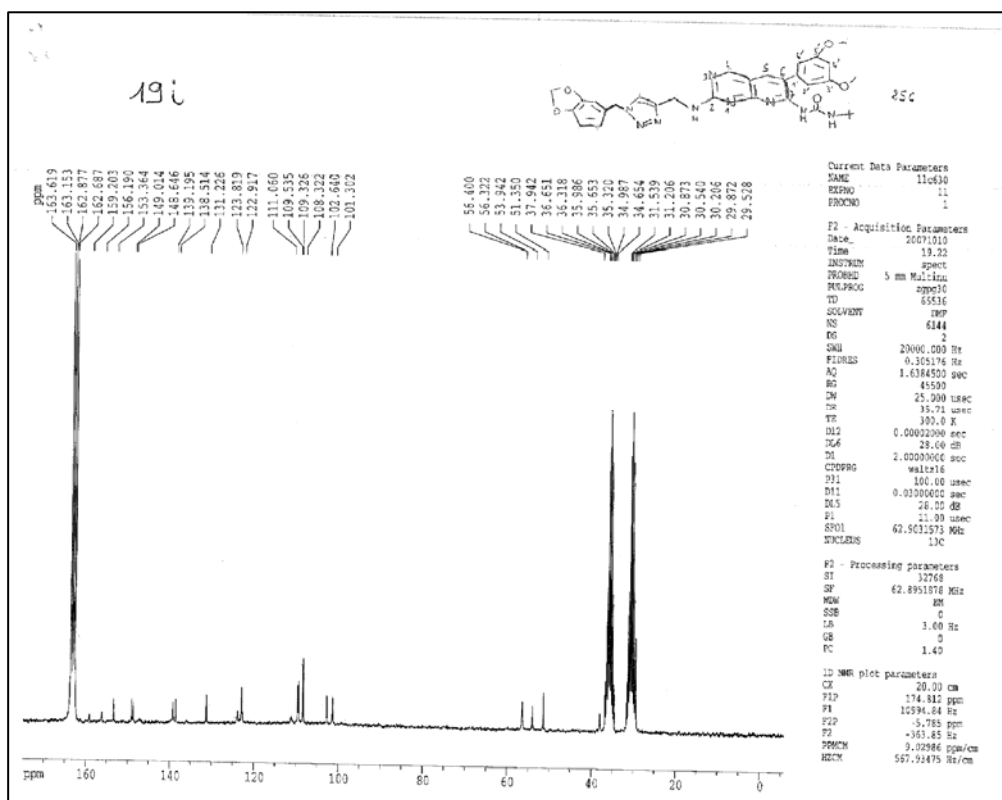
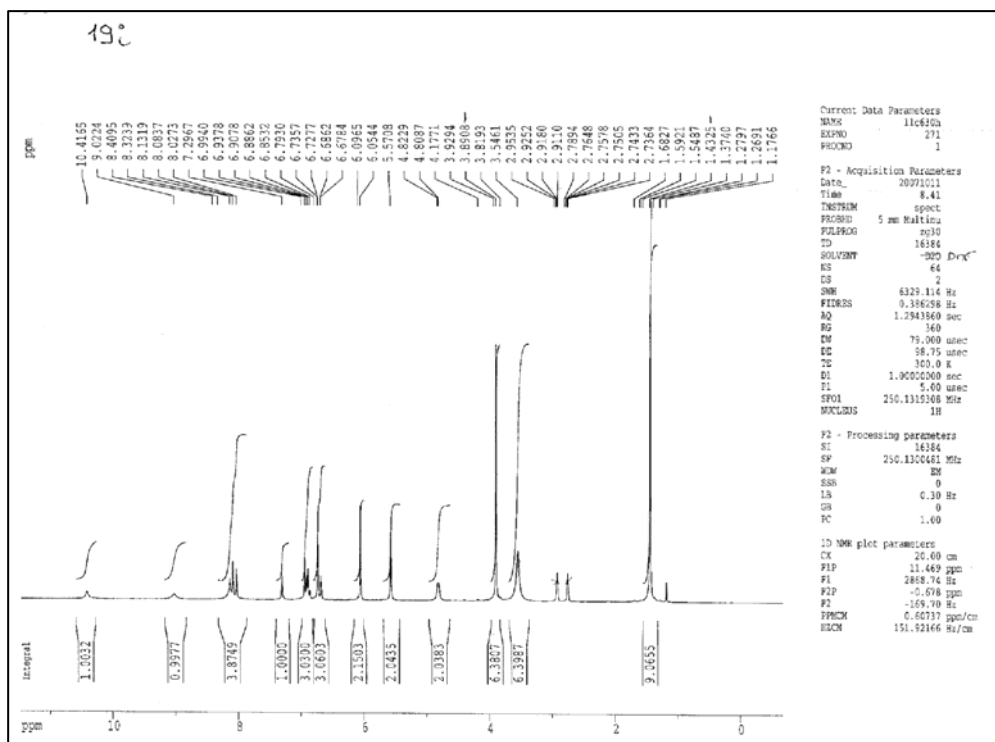


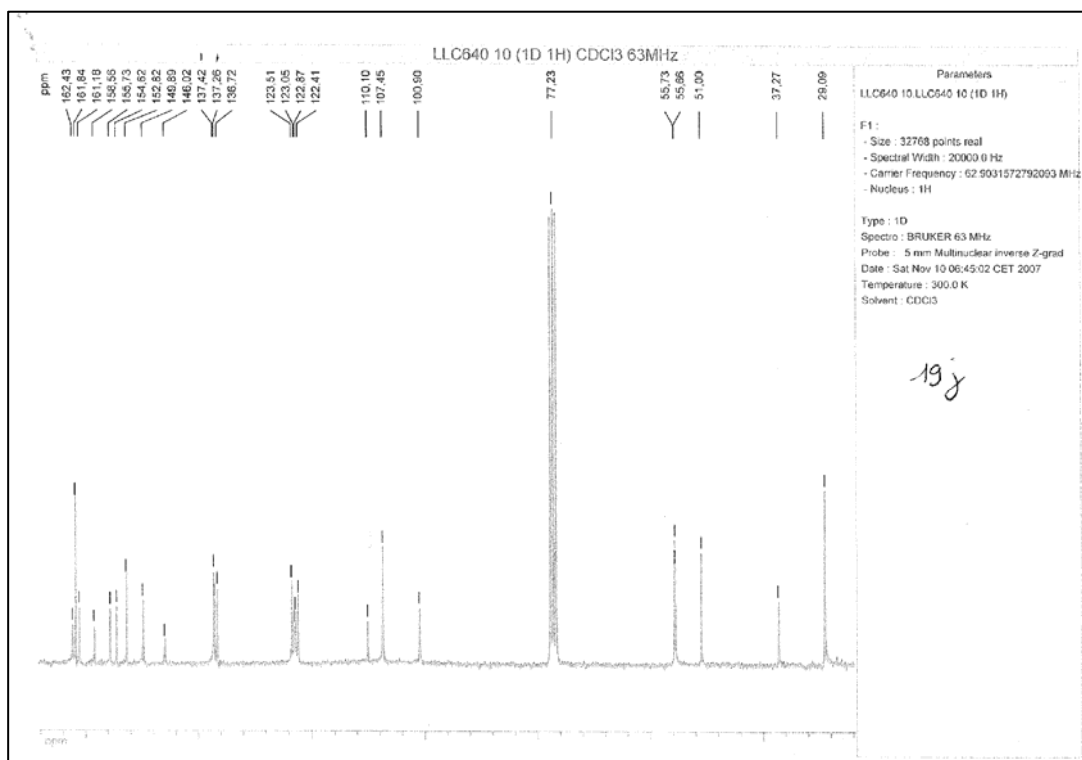
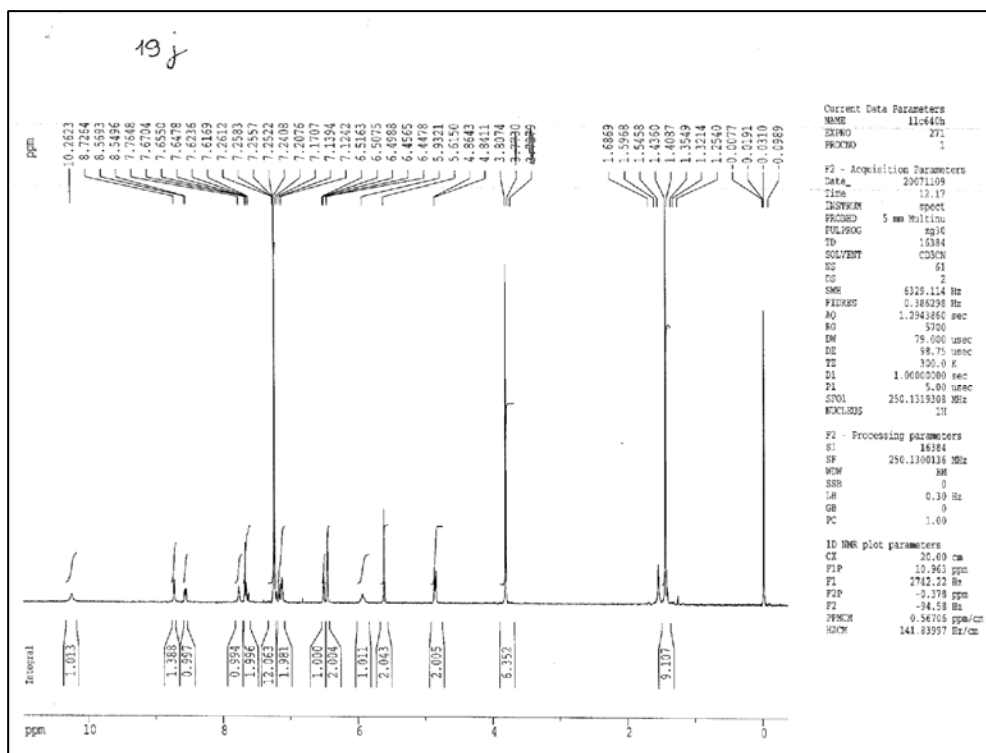


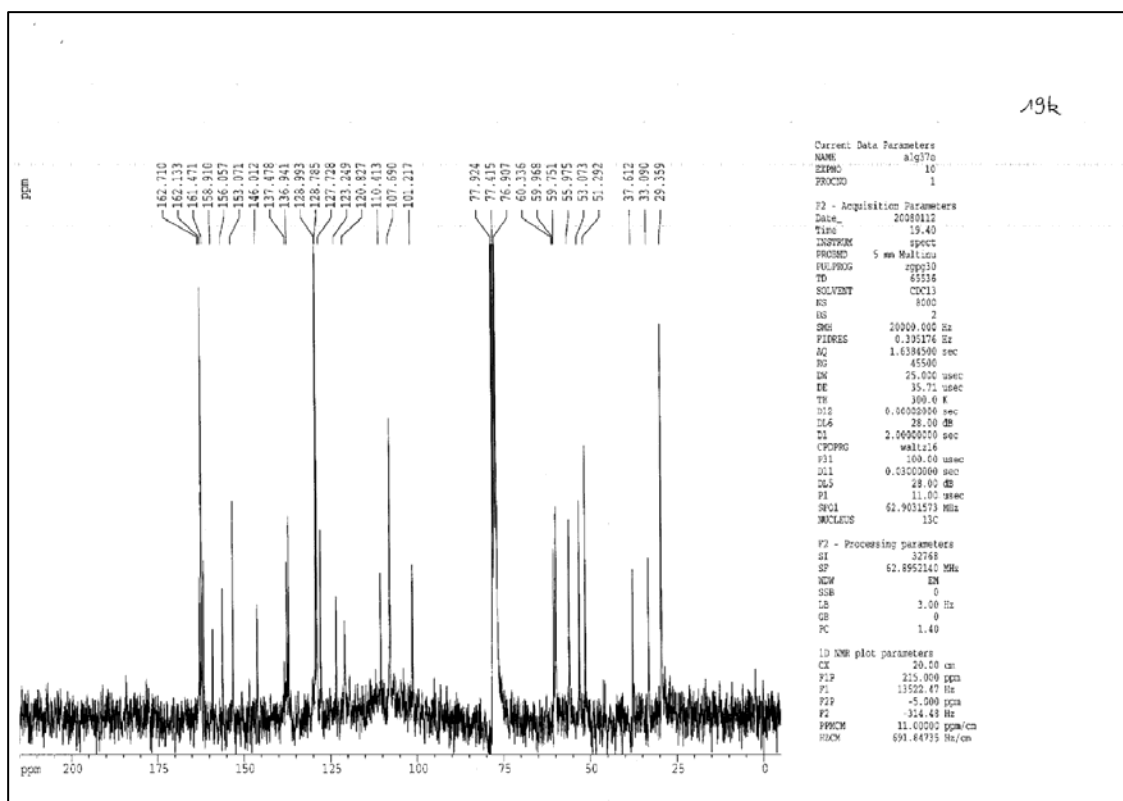


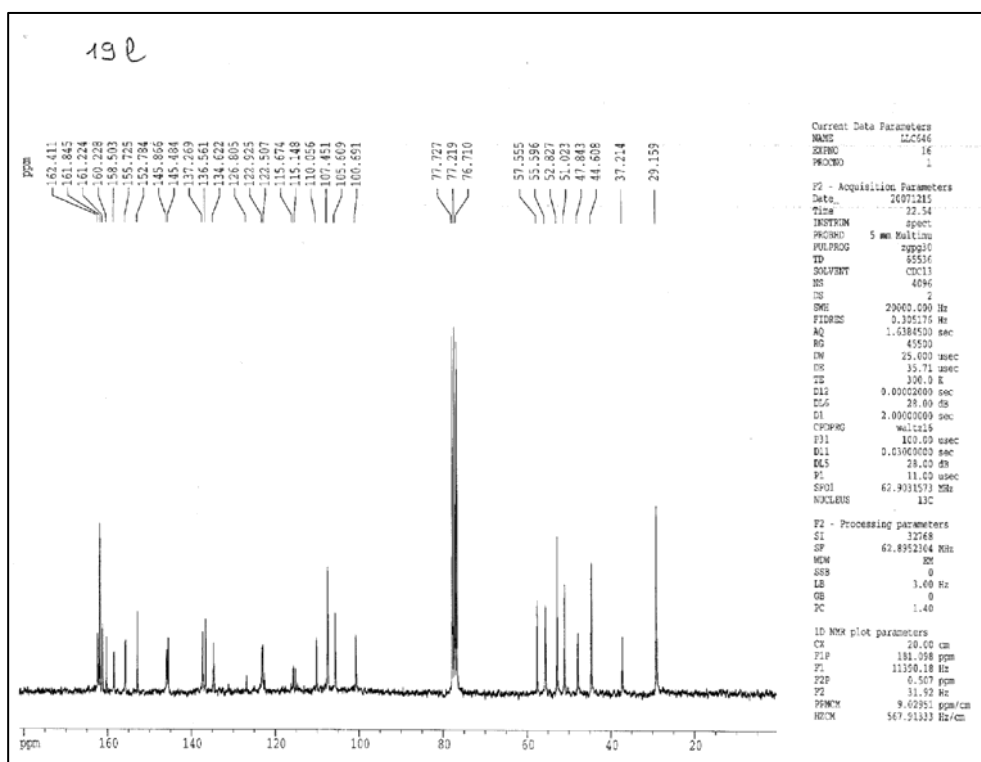
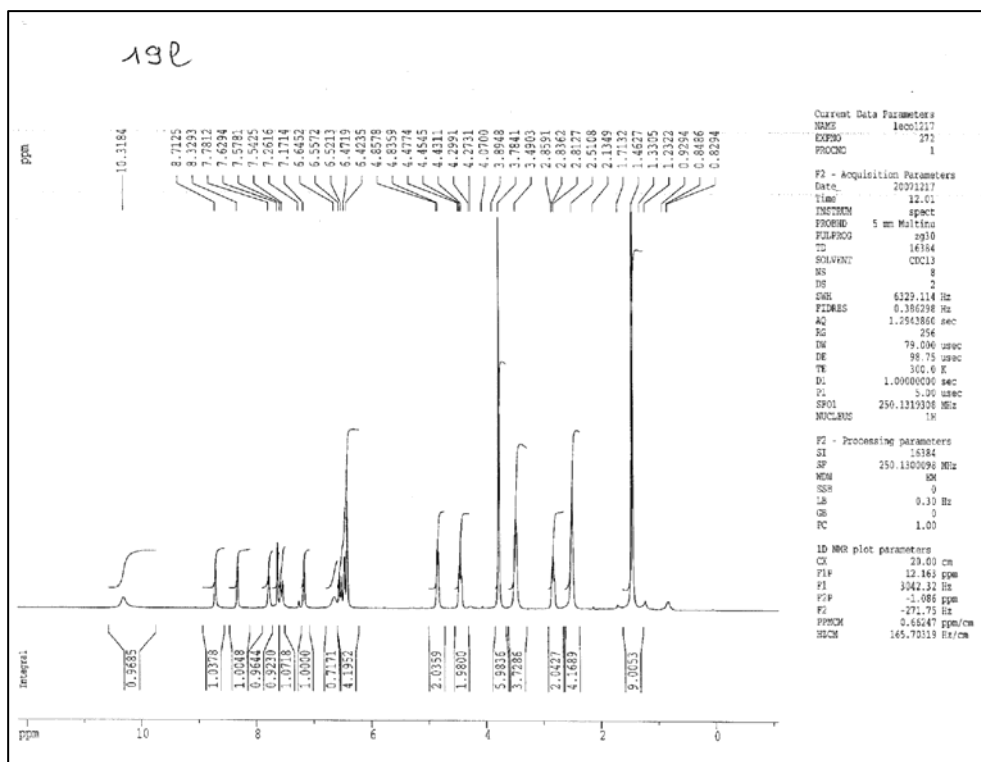


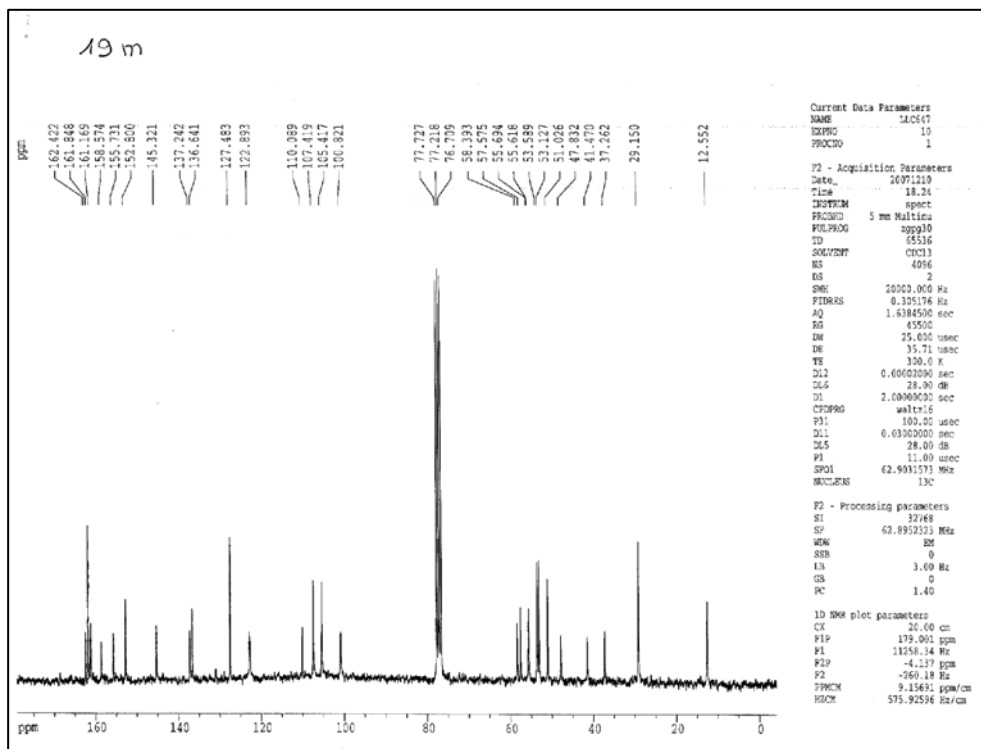
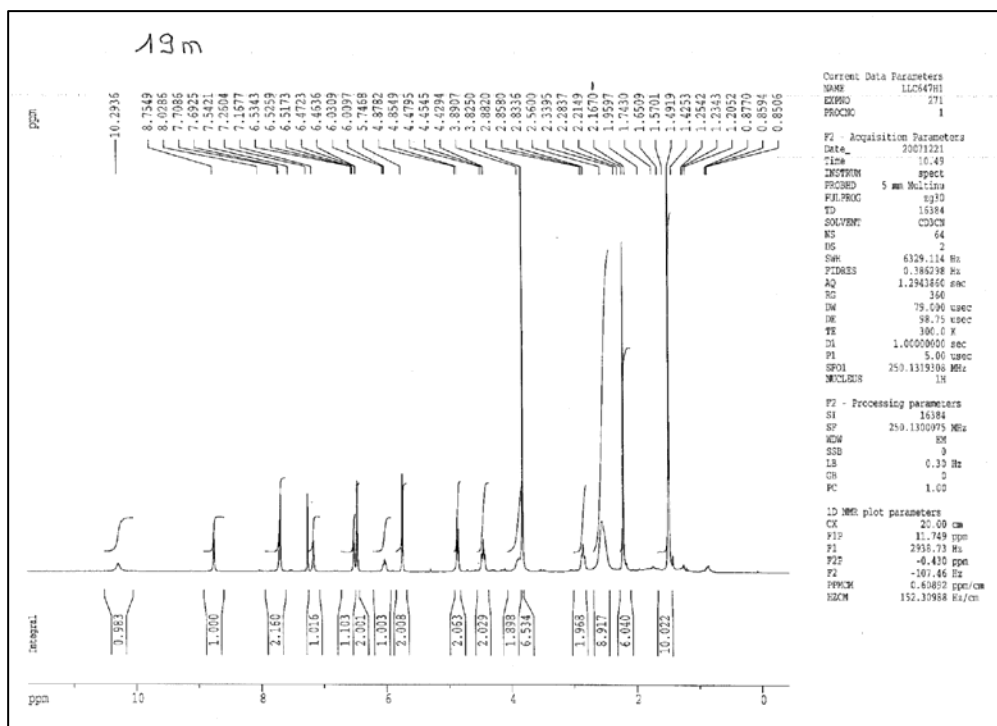


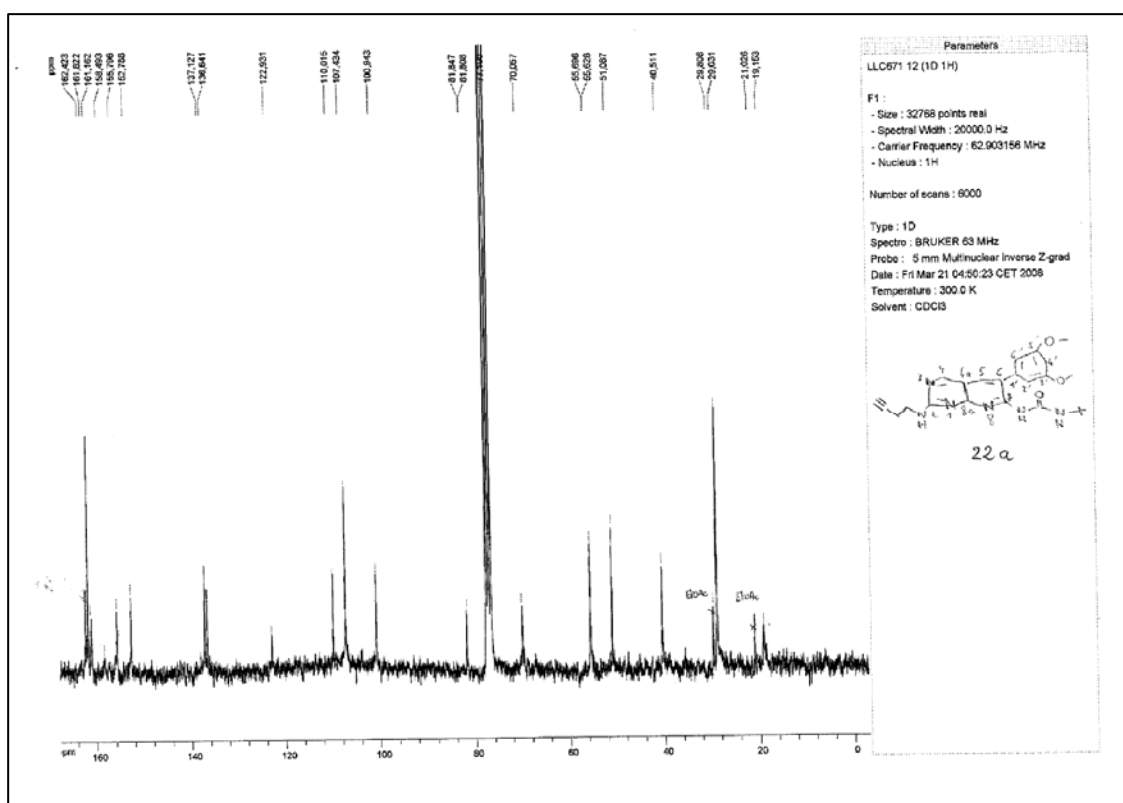


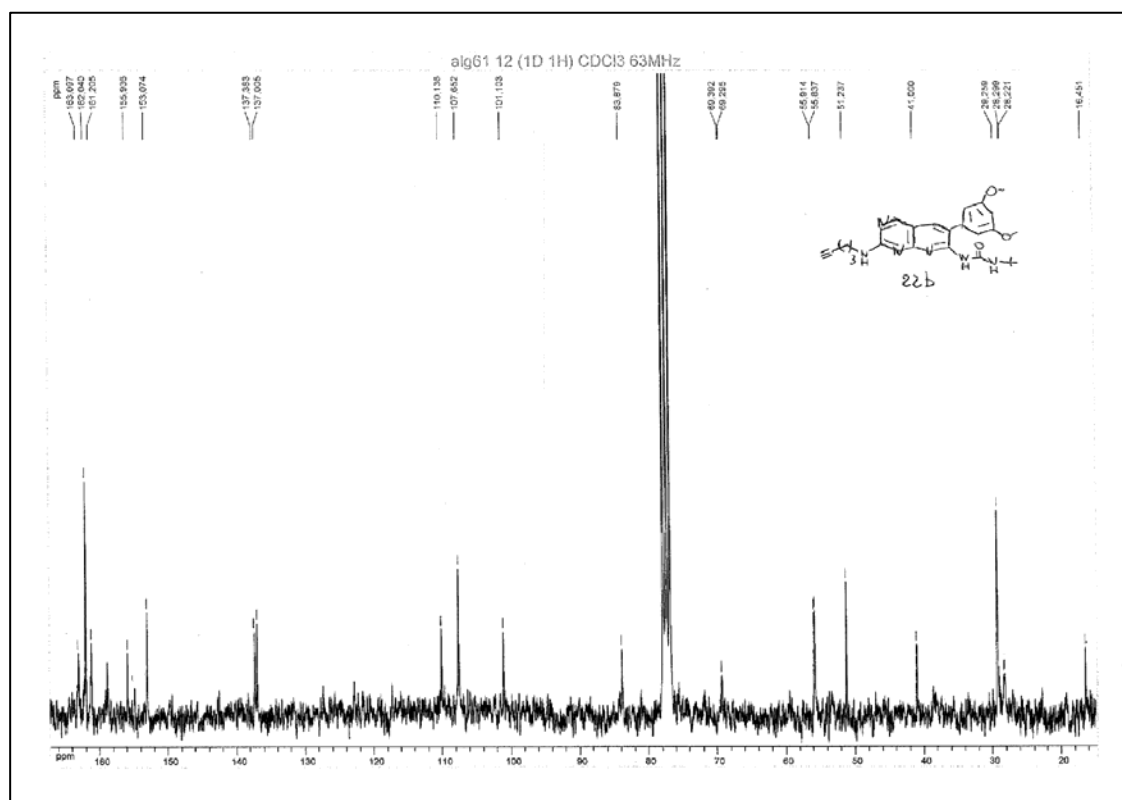
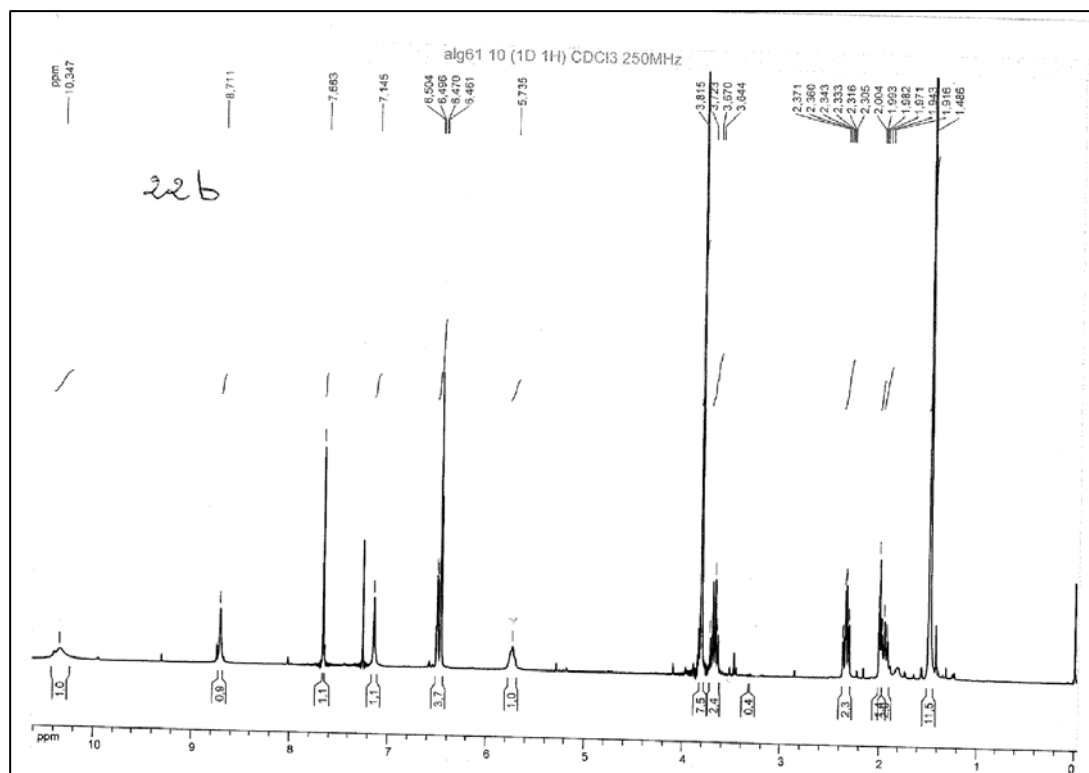


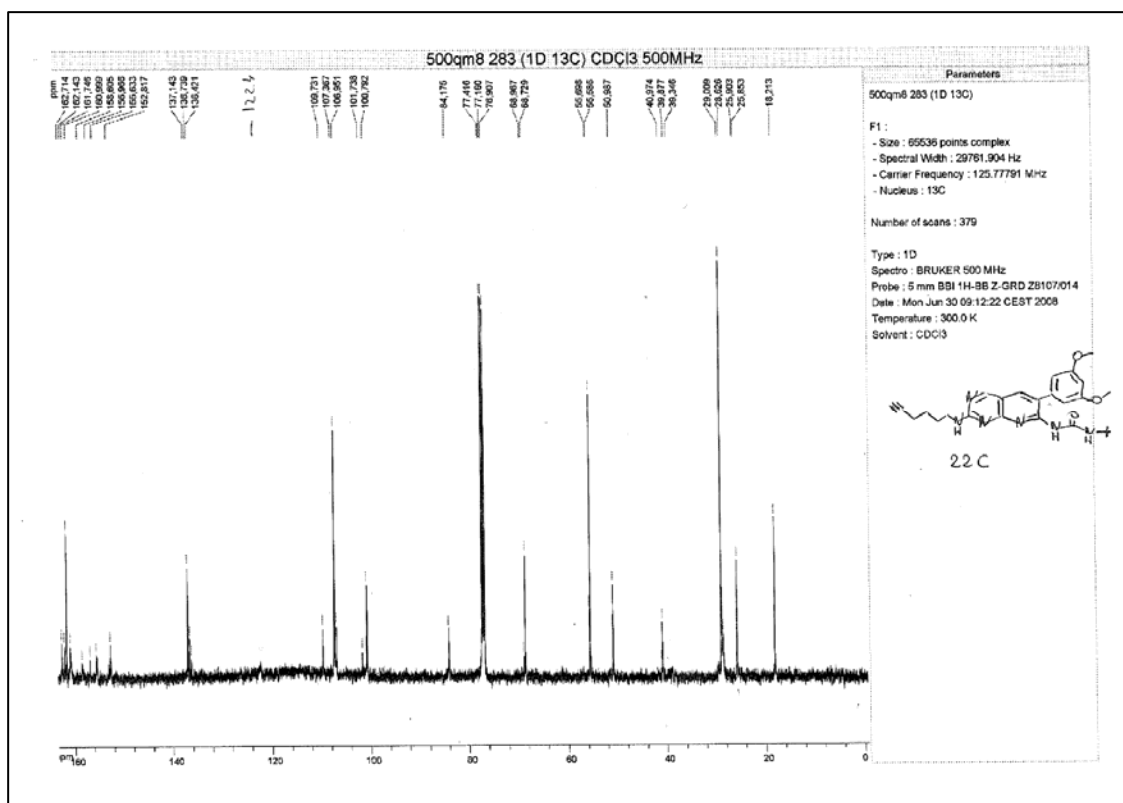
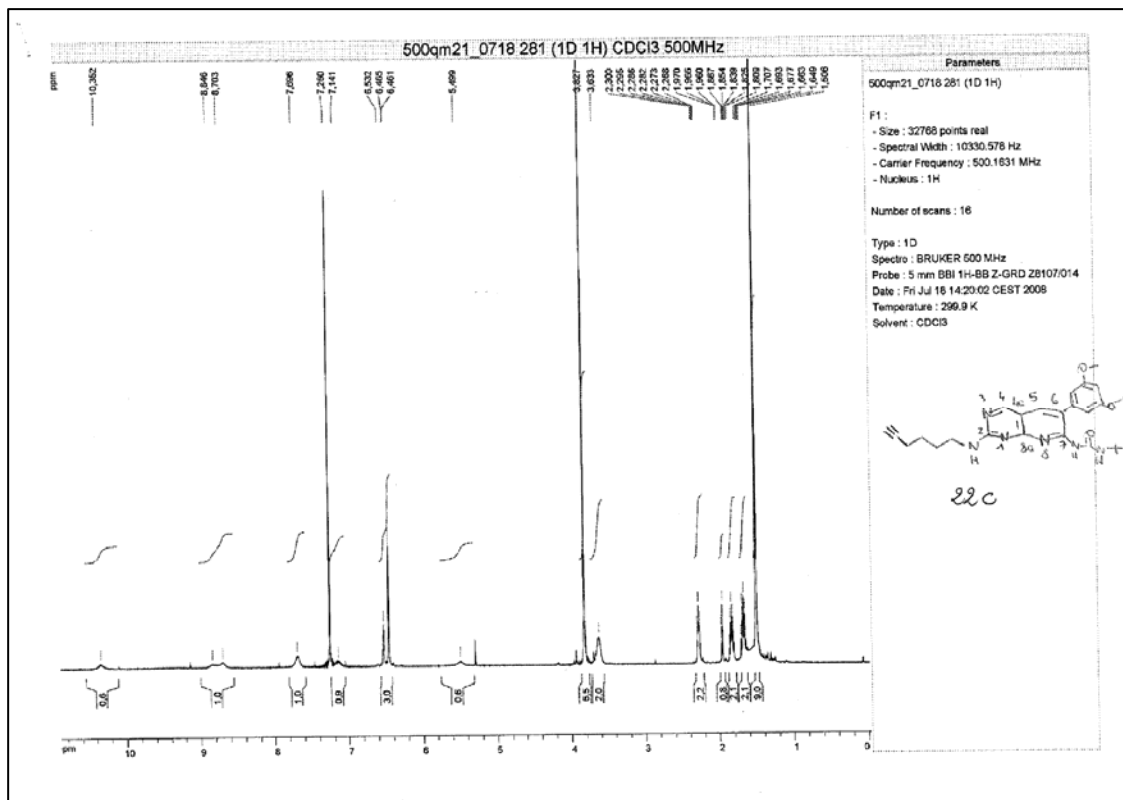


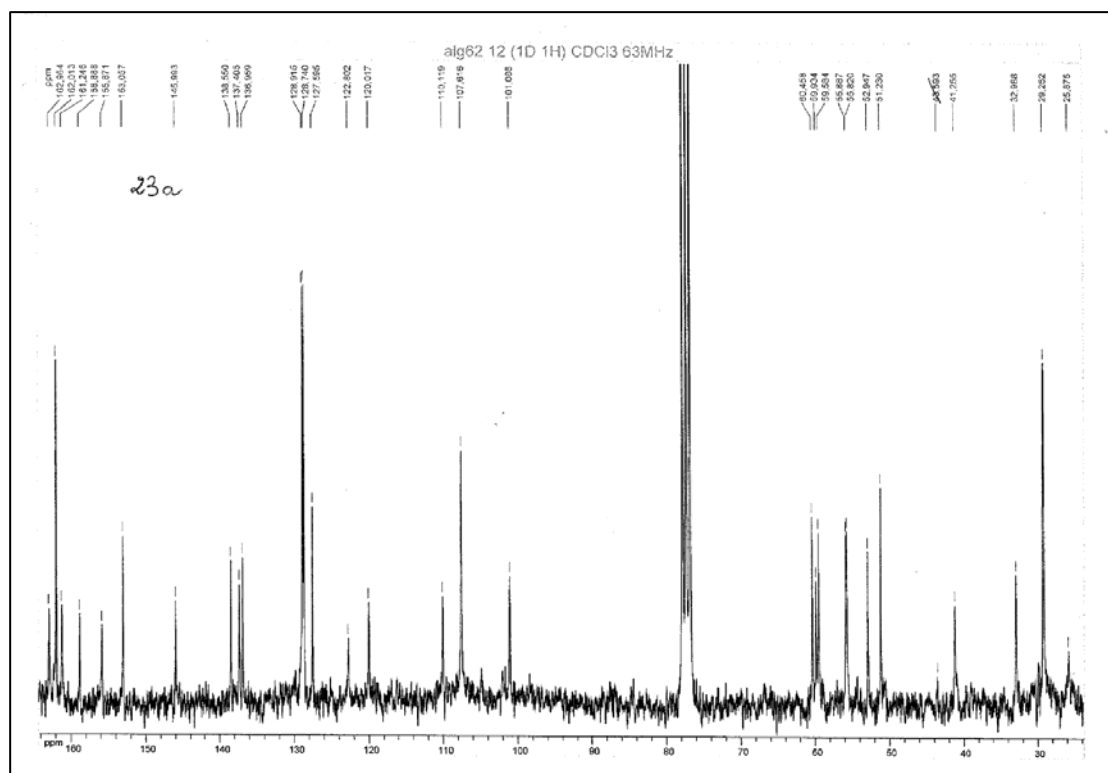
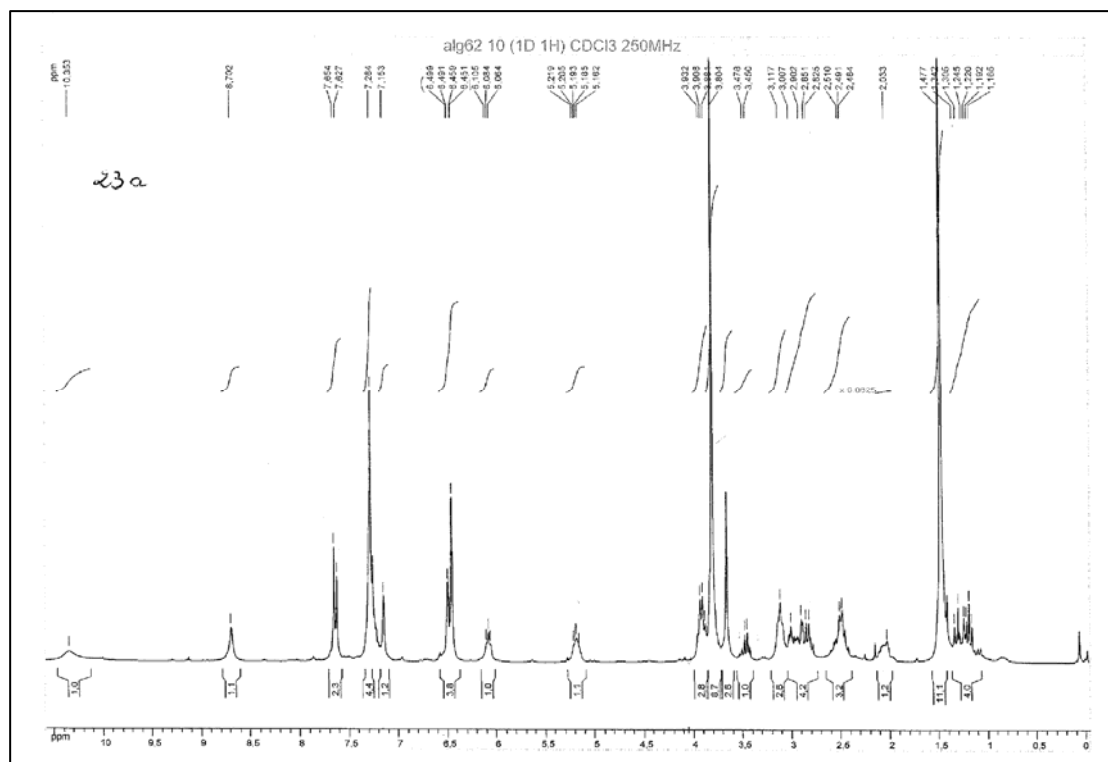


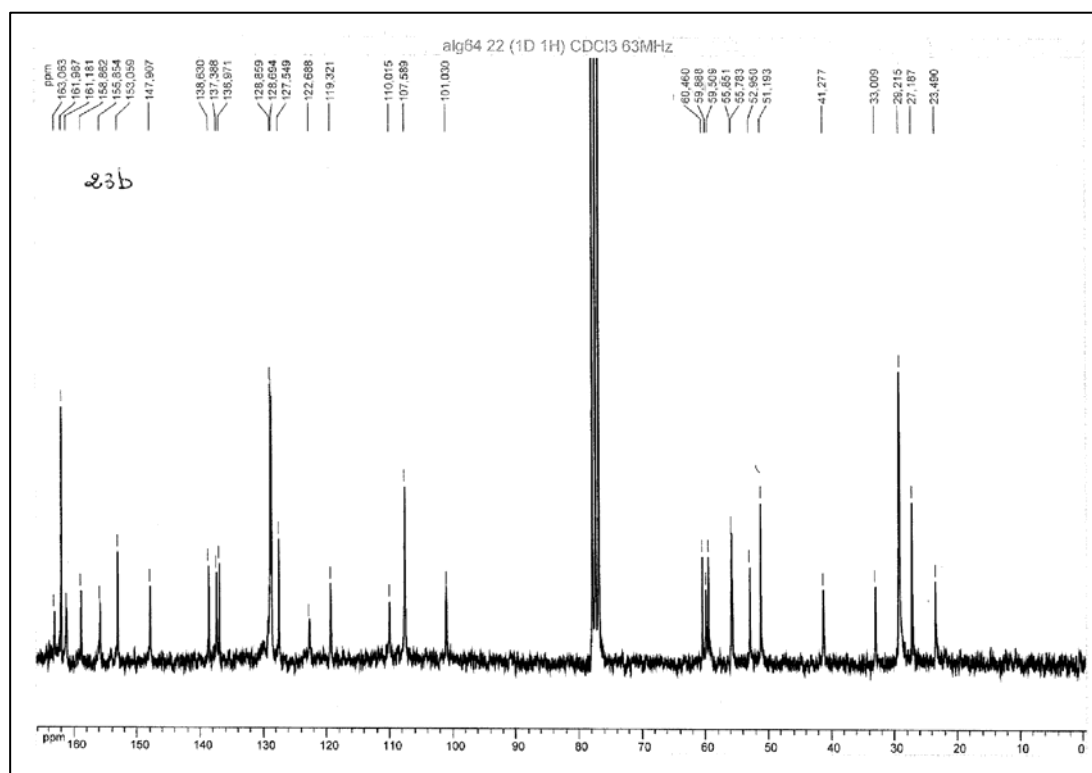
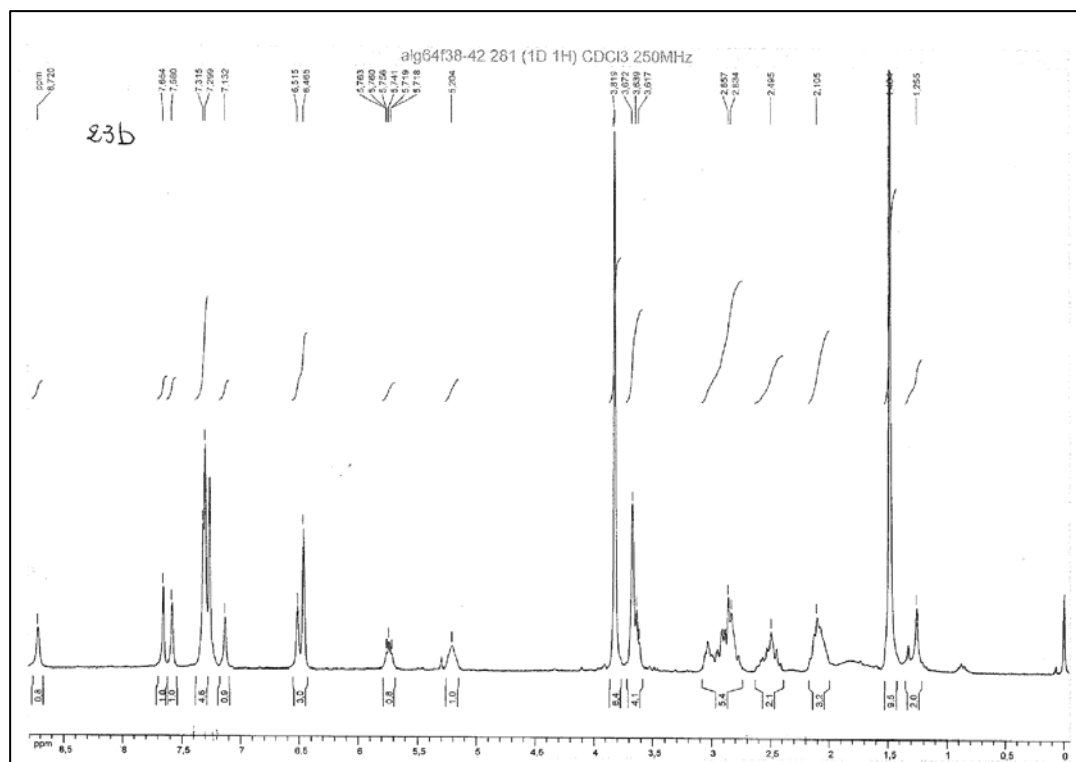


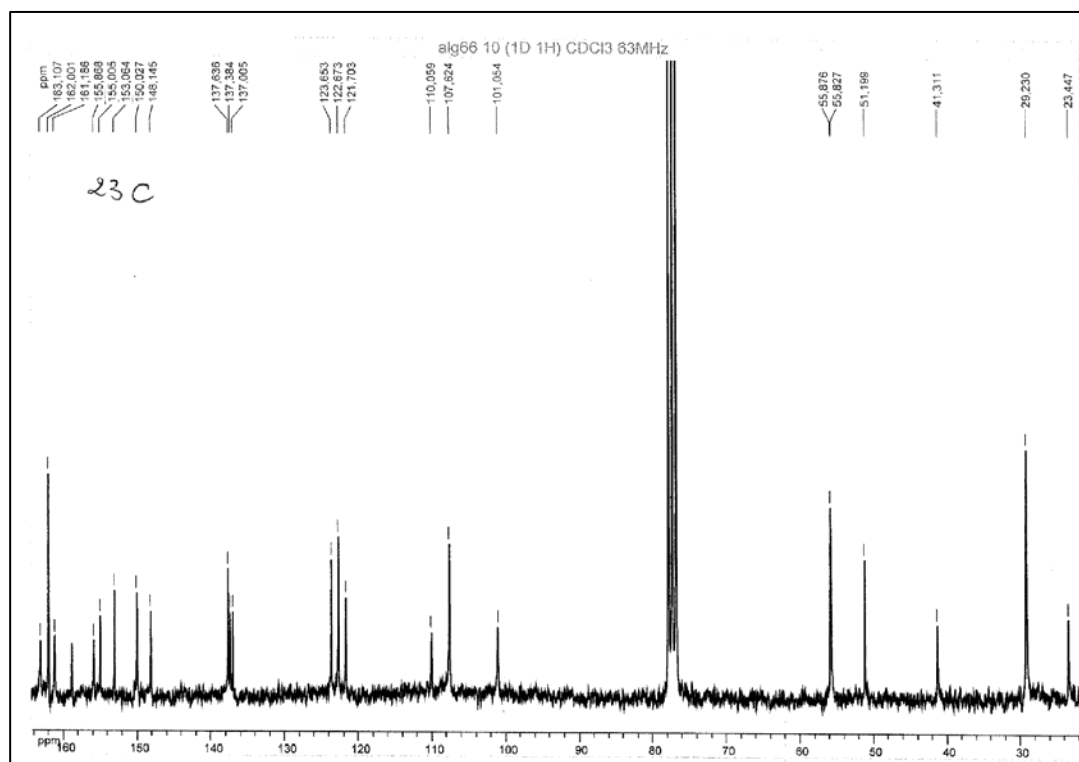
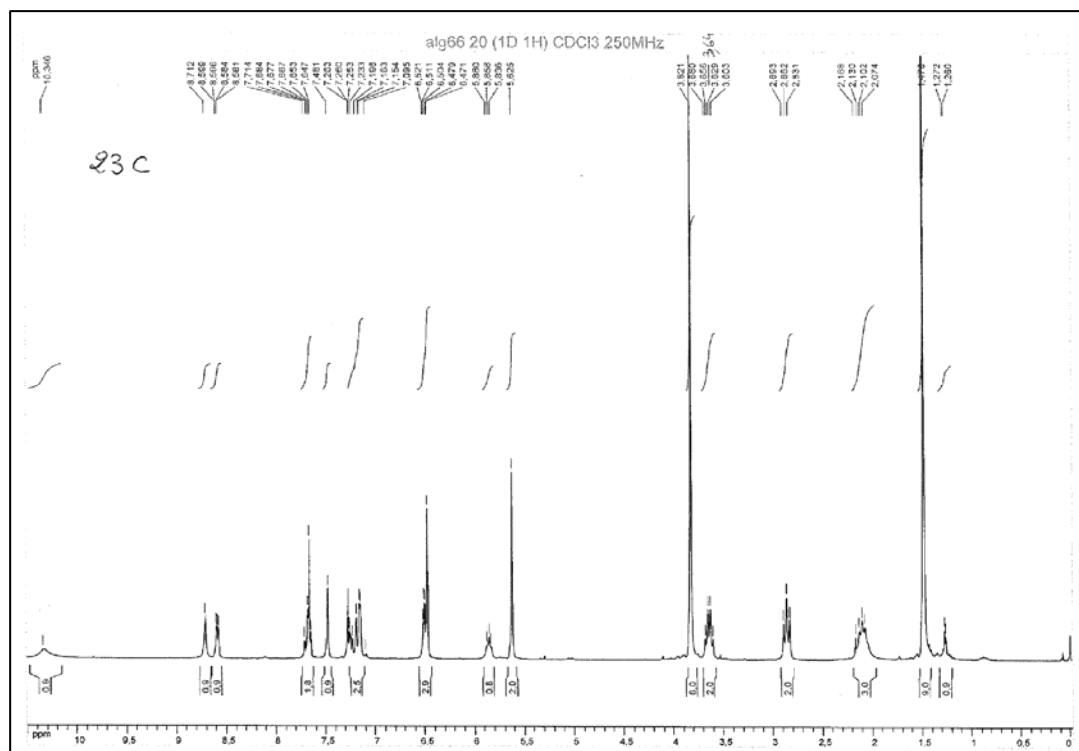


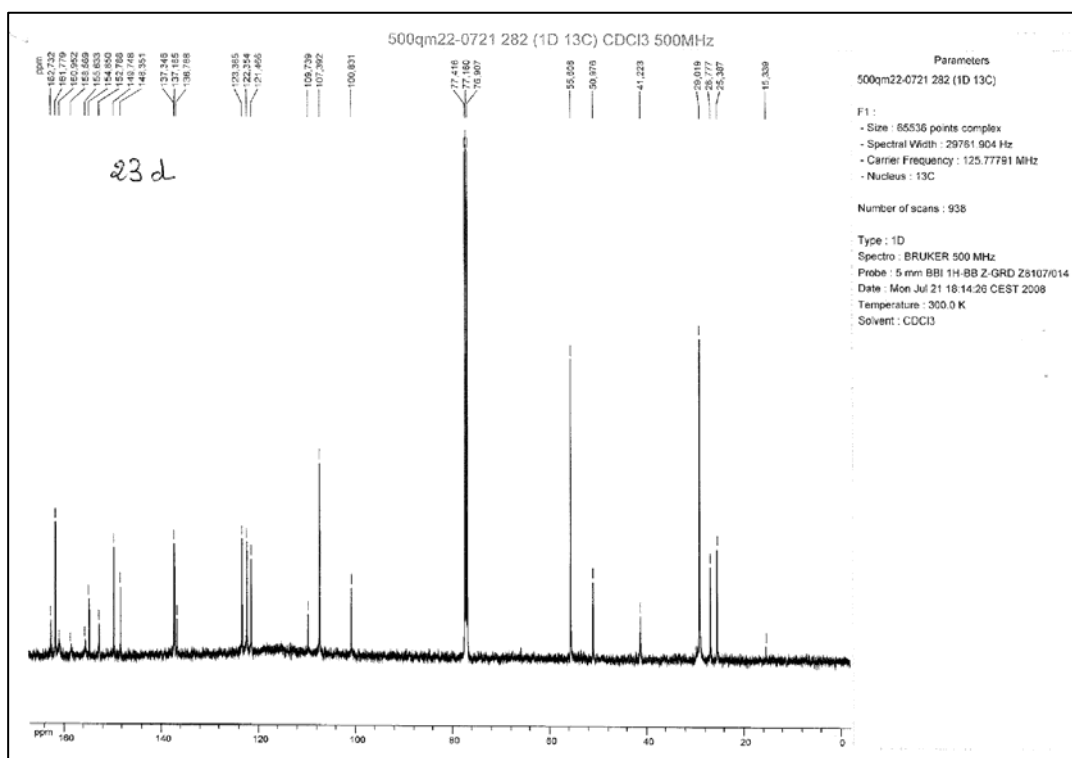




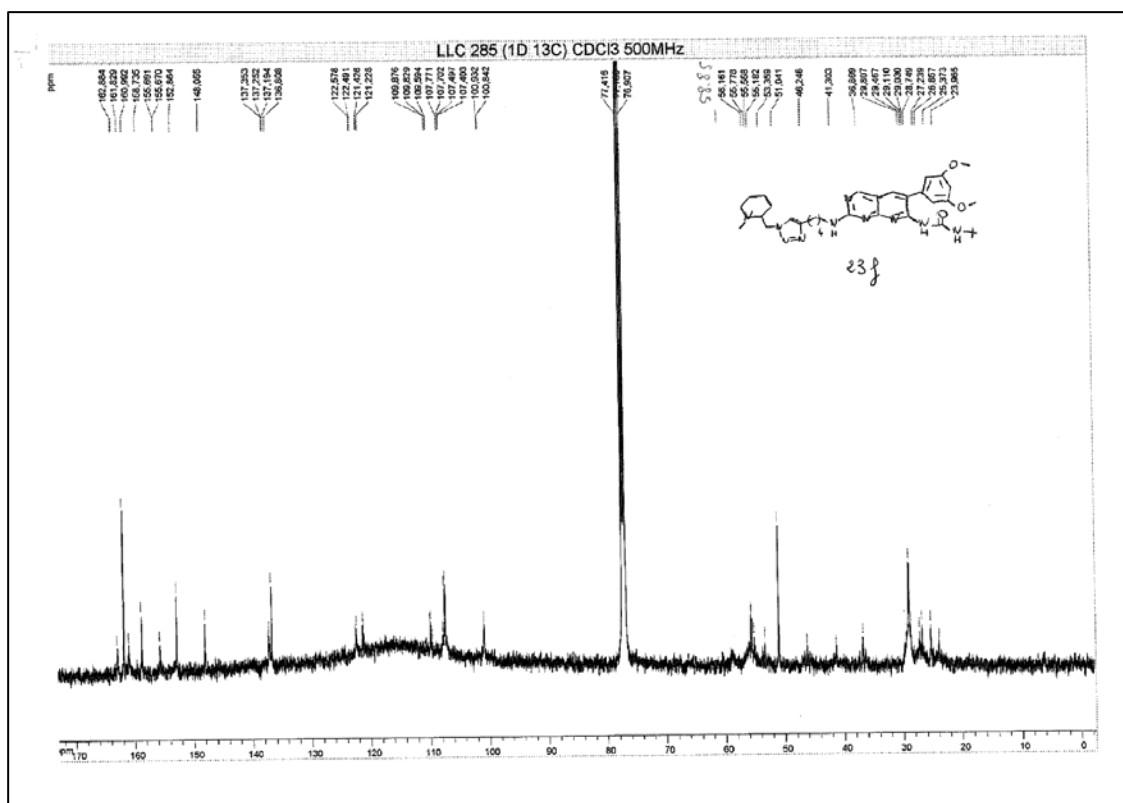
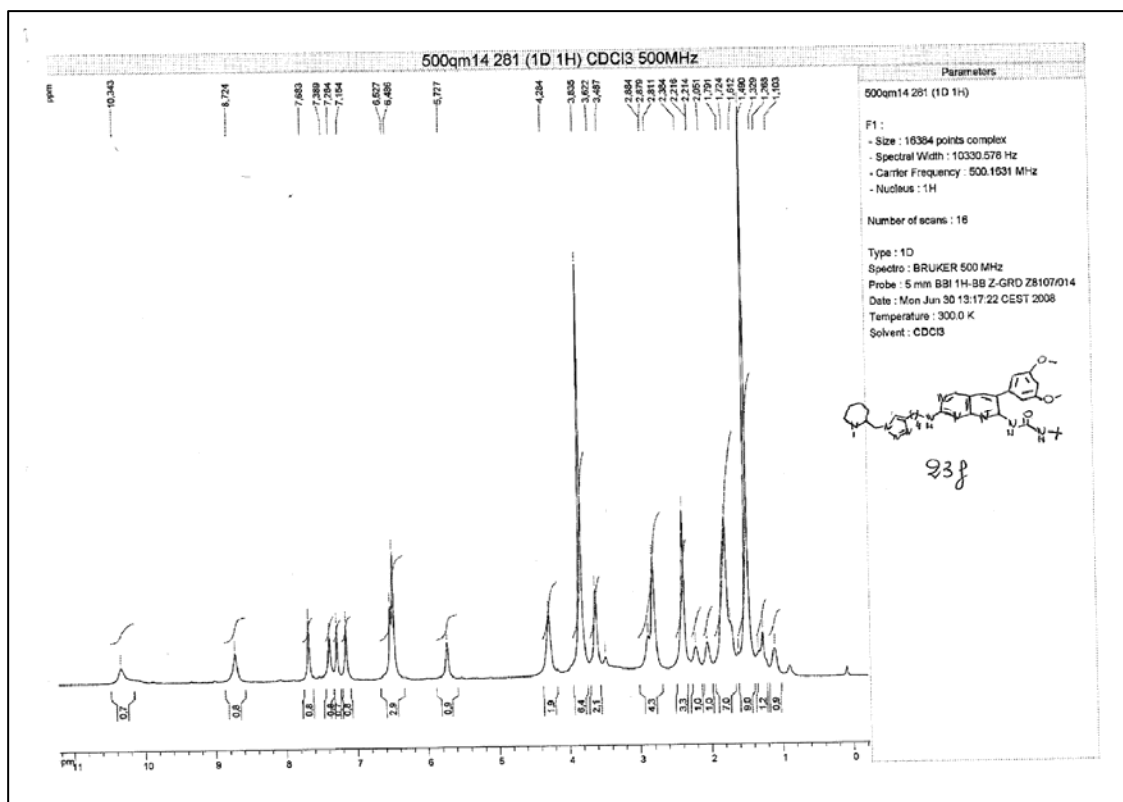


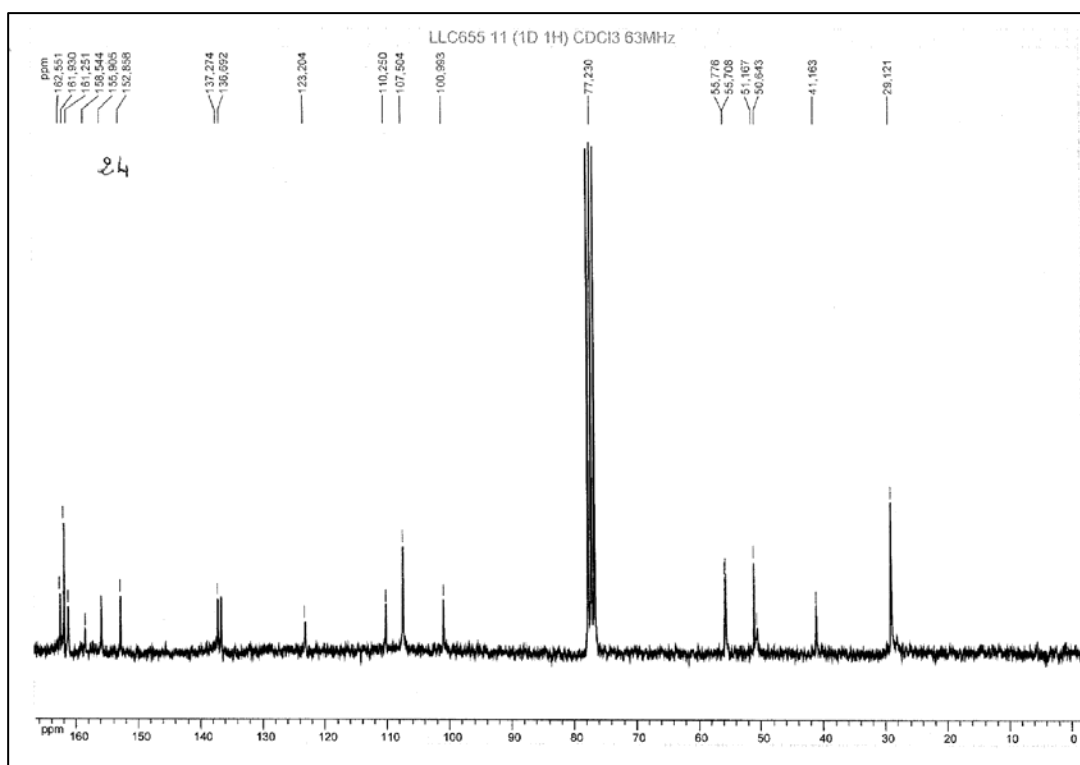
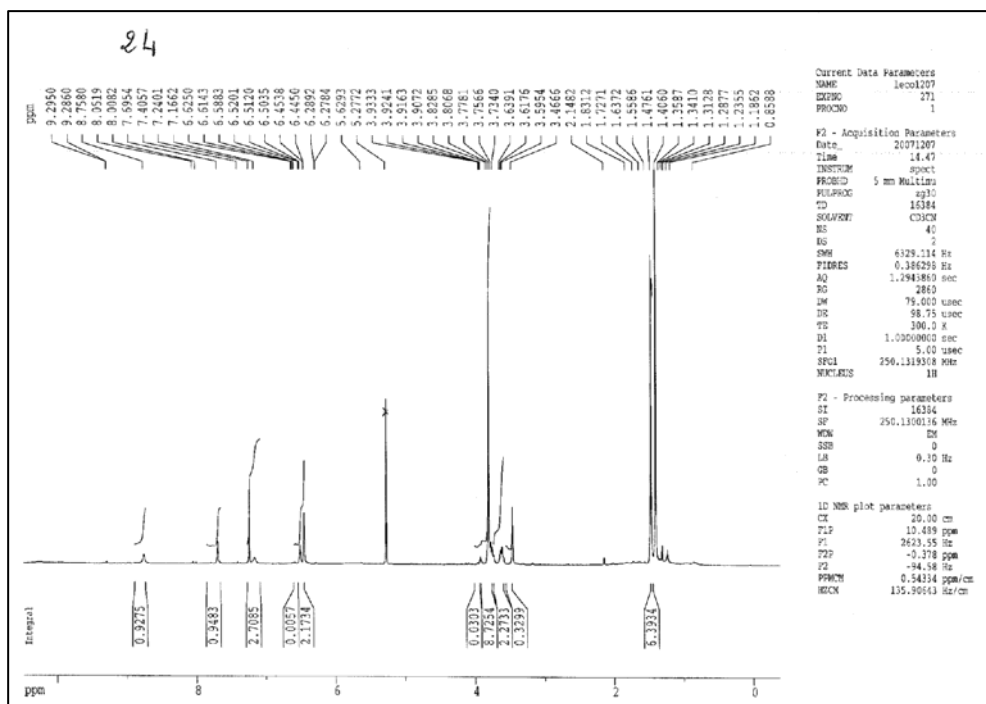


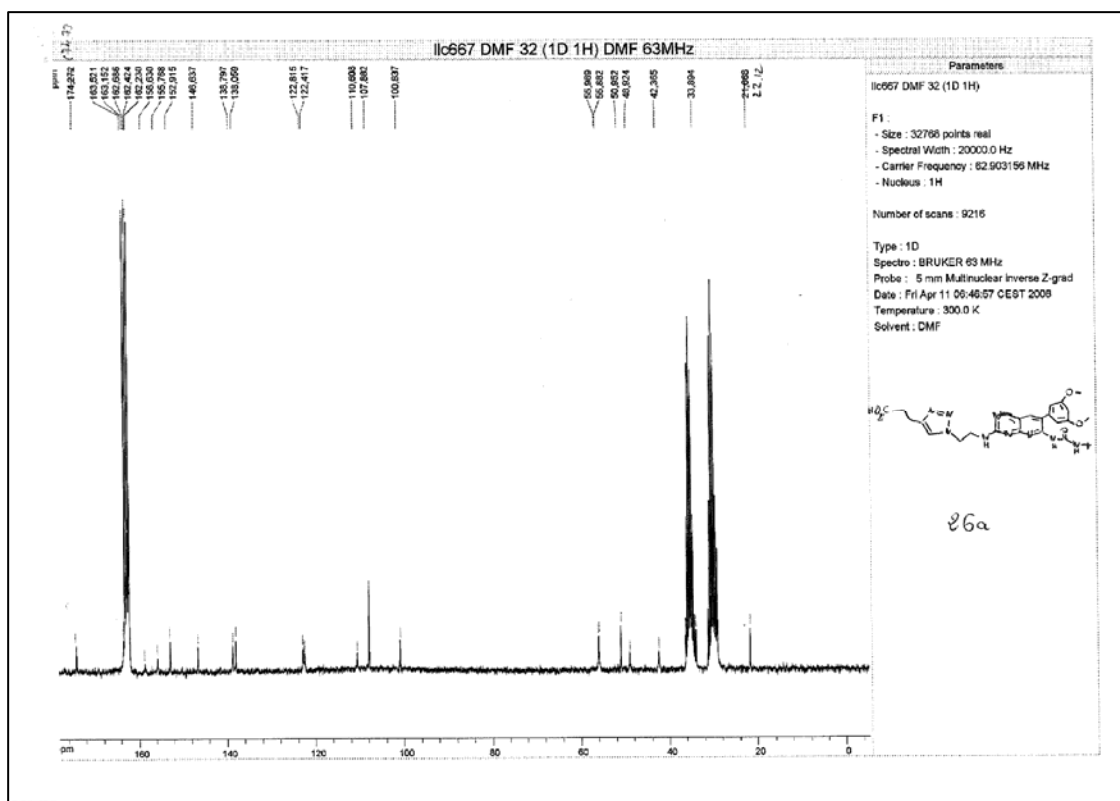
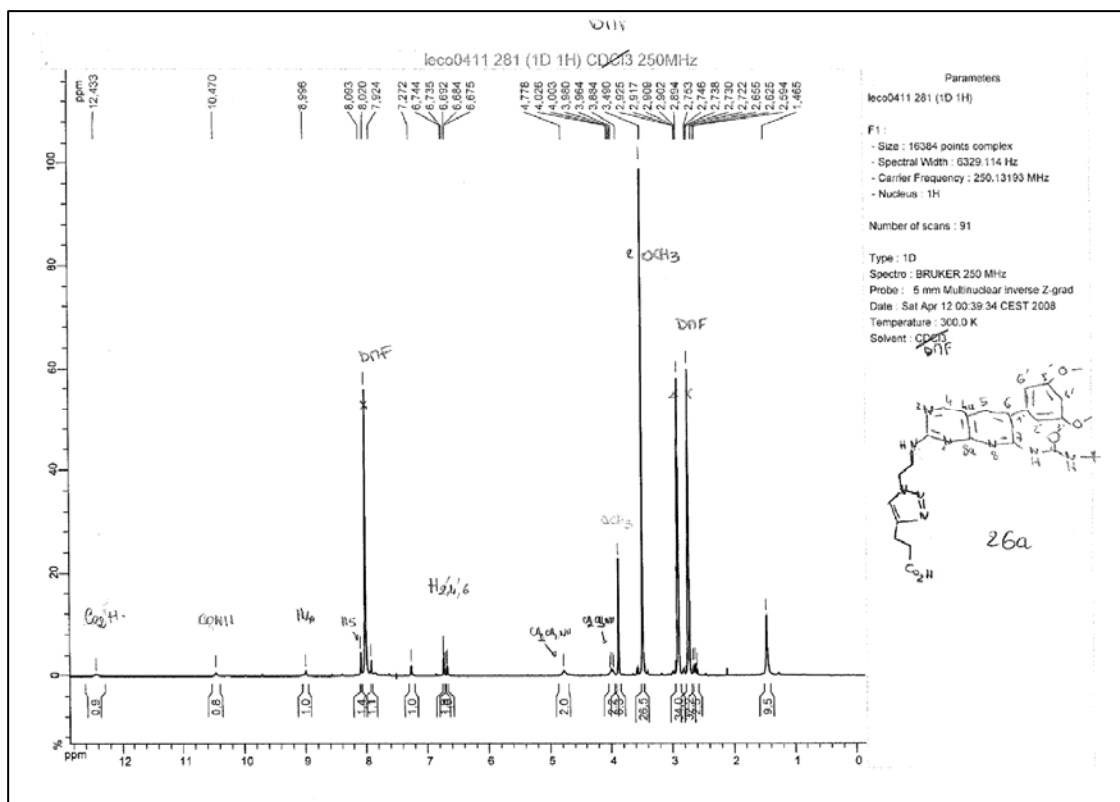


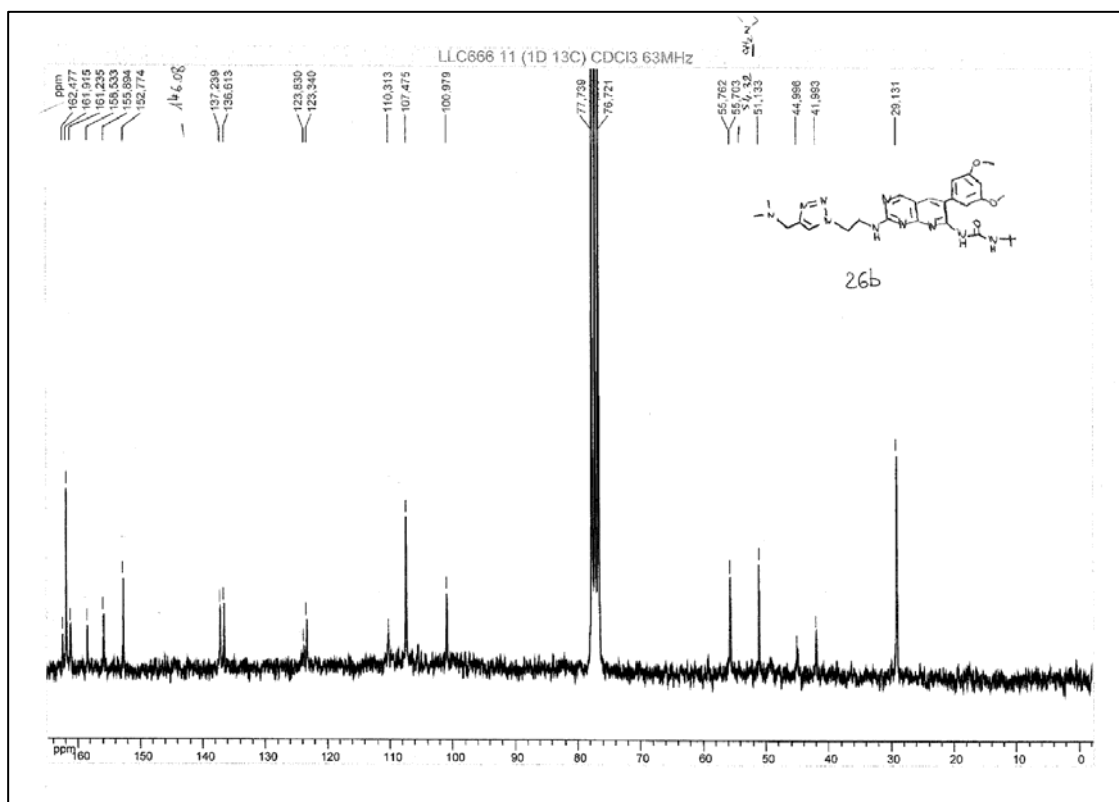
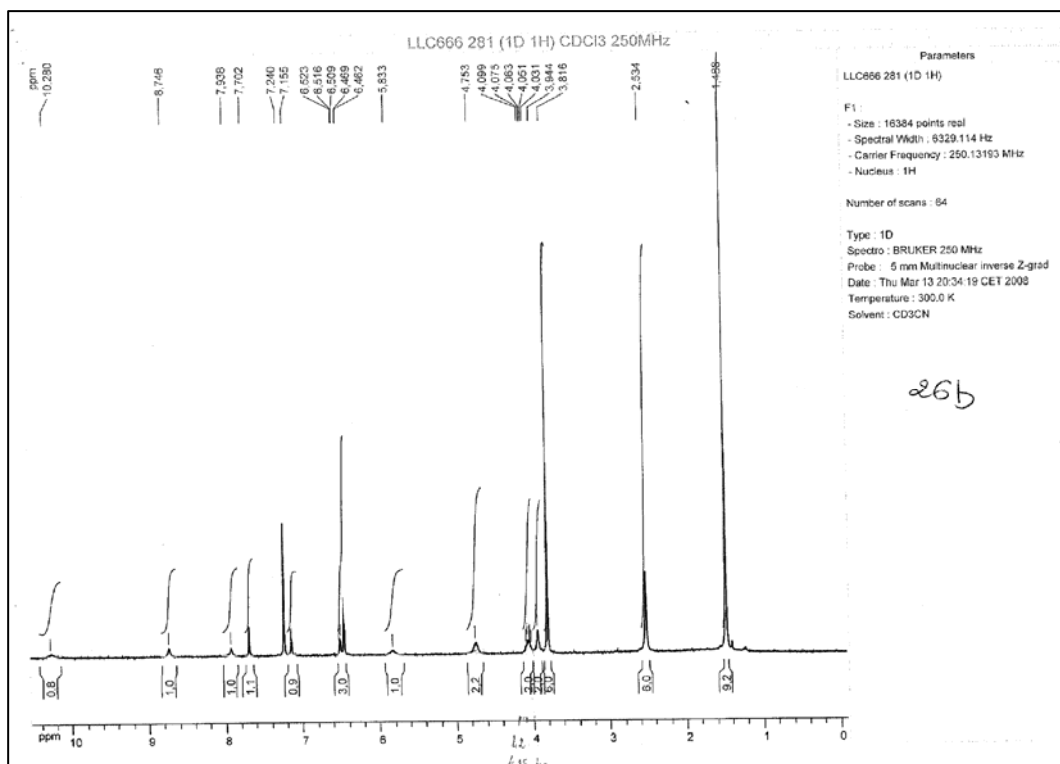


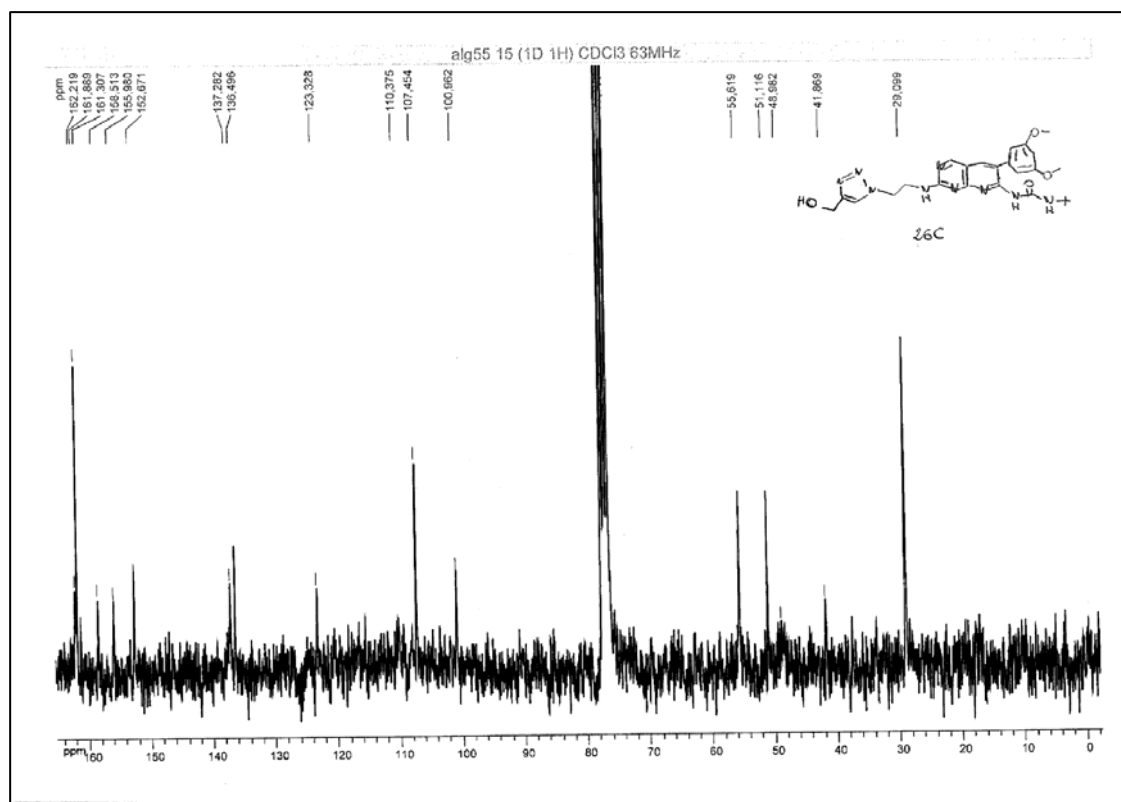
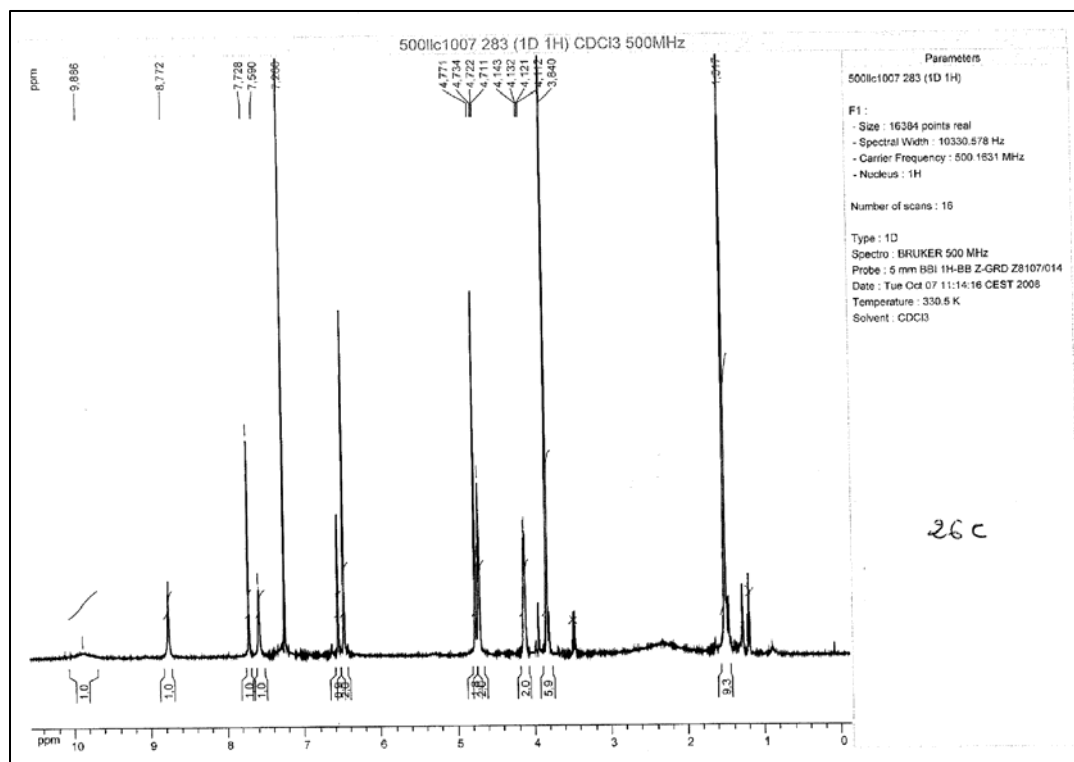


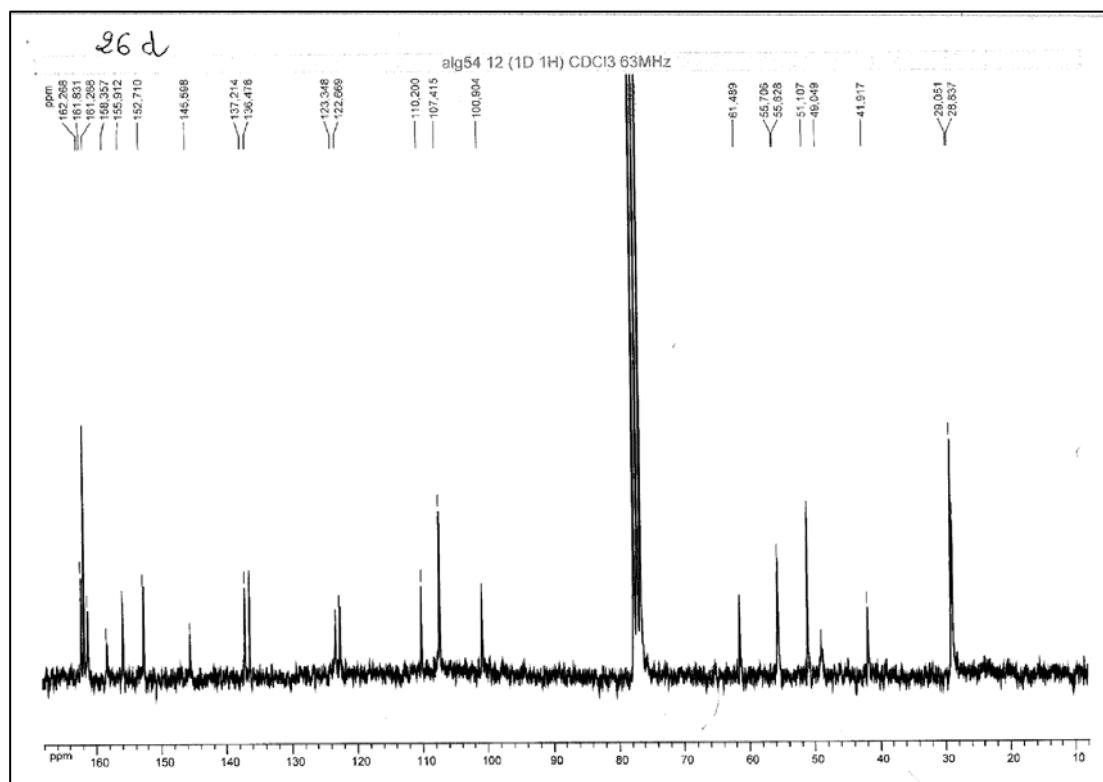
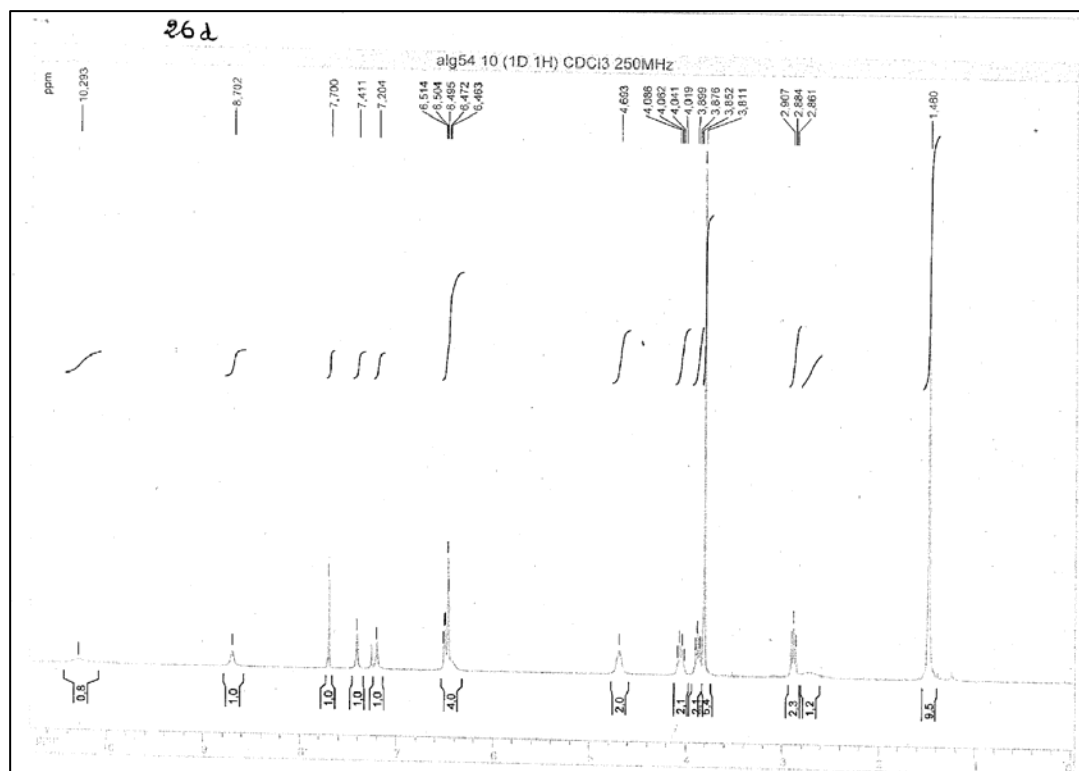


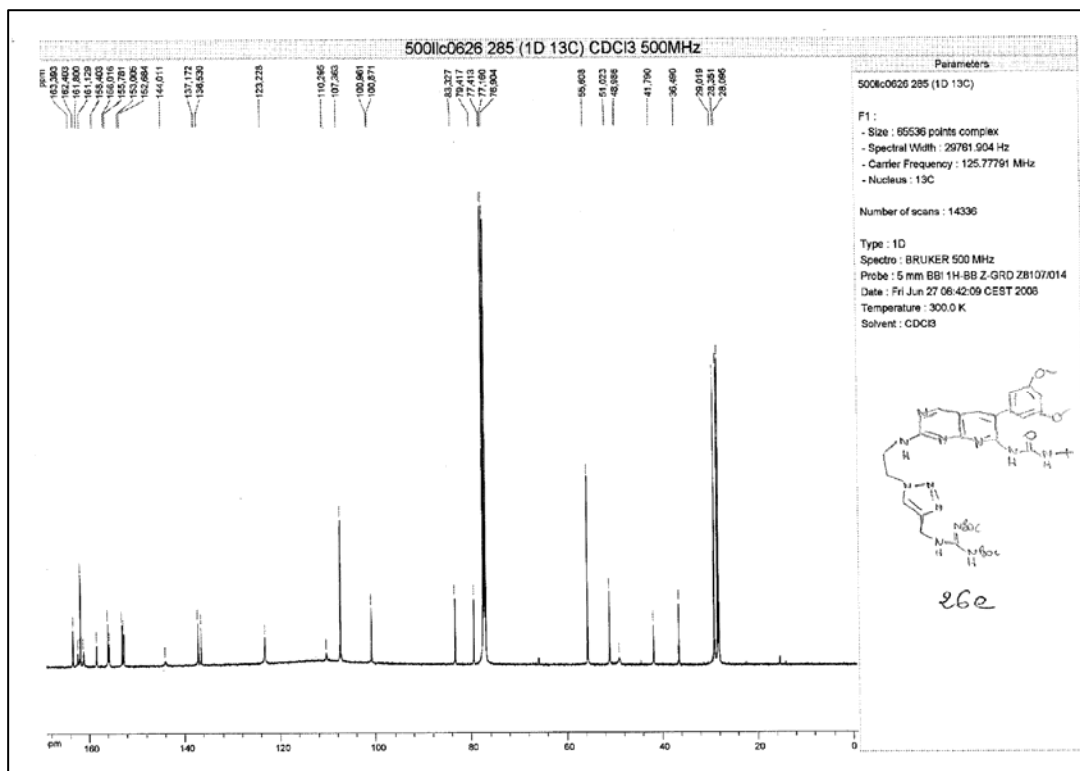
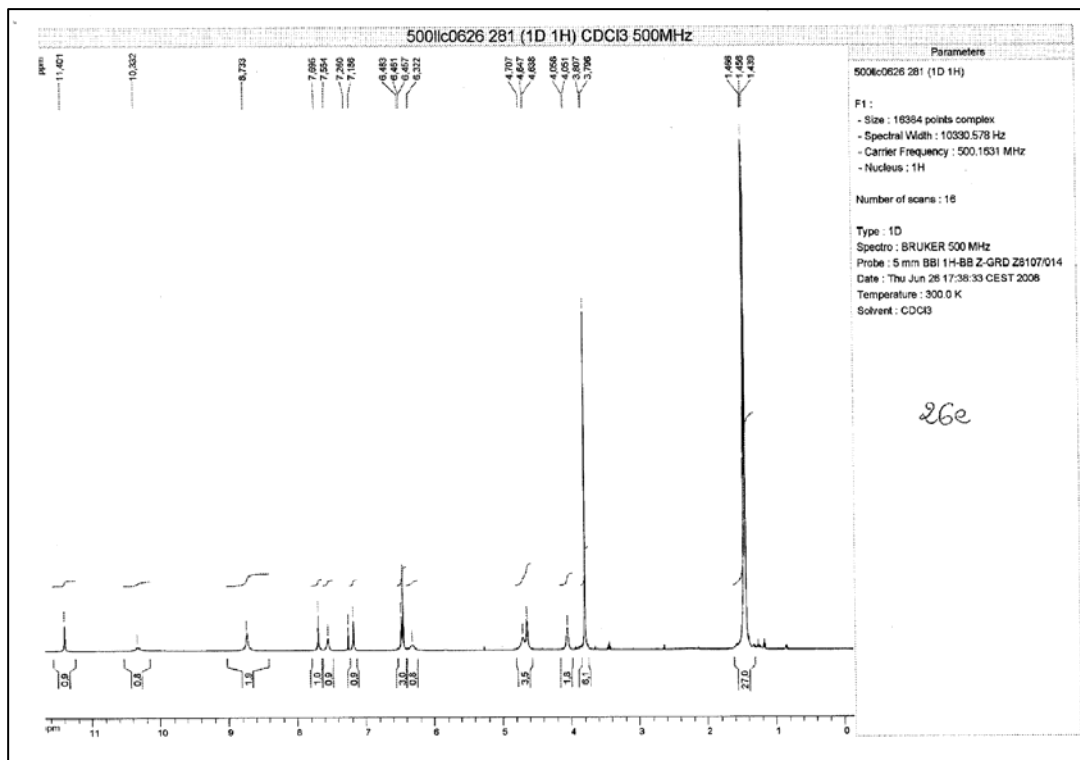


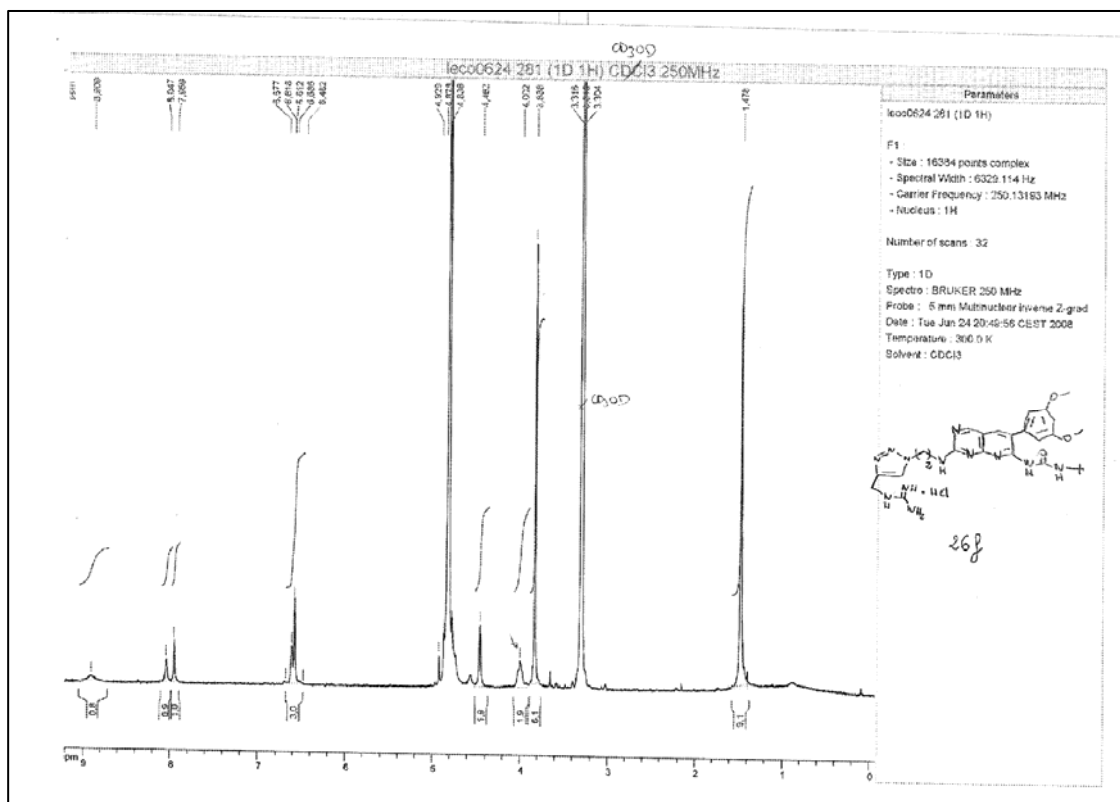












4. Biological data

