Supplementary Information for

Synthesis and inhibitory activity against MurA and MurZ enzymes of 4*H*-pyrano[2,3-*d*]pyrimidine−1*H*-1,2,3-triazole hybrid compounds having piperidine and morpholine rings

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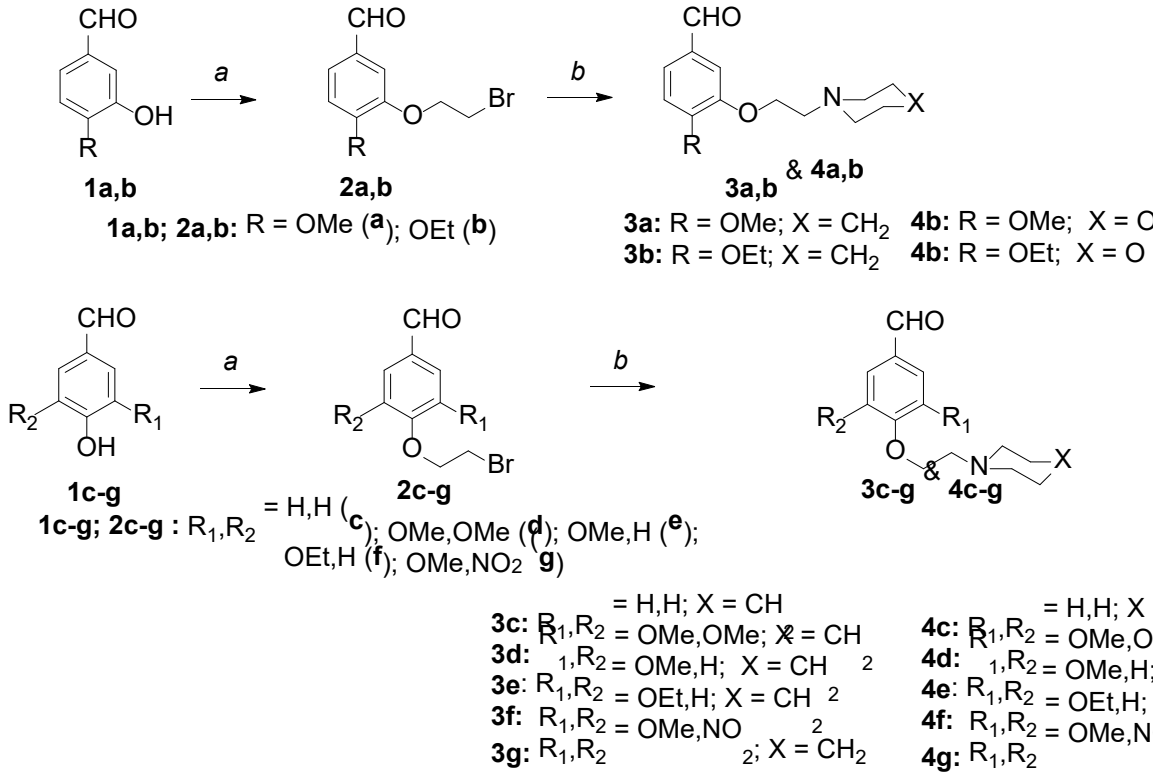
1. General procedure for synthesis of substituted 3-(2-(piperidin-1-yl)ethoxy)/3-(2-morpholinoethoxy)benzaldehydes (3a-g) and 4-(2-(piperidin-1-yl)ethoxy)/4-(2-morpholinoethoxy)benzaldehydes (4a-g)



Scheme 1S. Synthesis of some substituted benzaldehydes having 2-(piperidin-1-yl)ethoxy)- (**3a-g**) and 2-morpholinoethoxy groups (**4a-g**) at positions 3 and 4. Reaction conditions: (*a*) $BrCH_2CH_2Br$, anhydrous K_2CO_3, CTAB, dried DMF, rt, 24 h to 50°C, 8 h. (*b*) Piperidine or morpholine, anhydrous K_2CO_3, CTAB, dried acetone, rt, 24 h, to 50°C, 10 h.

Procedure. Appropriate substituted 3- or 4-hydroxylbenzaldehydes (**1a-g**, 5 mmol) were dissolved in dried DMF (100 mL), then anhydrous K_2CO_3 (7.5 mmol) and CTAB (0.01 mmol) was added. 1.2-Dibromoethane (5.5 mmol) was added dropwise to the stirring reaction mixture for 20 min. The reaction mixture then continued stirring at room temperature for 24 h, and then at 50°C for 8 h. After DMF was removed under reduced pressure, water (200 mL) was added to dissolve inorganic salts. The separated precipitates were crystallized from 96% ethanol to afford corresponding substituted 2-bromoethylenoxybenzaldehydes **2a-g**. These benzaldehydes received were pure enough for the next conversion reaction.

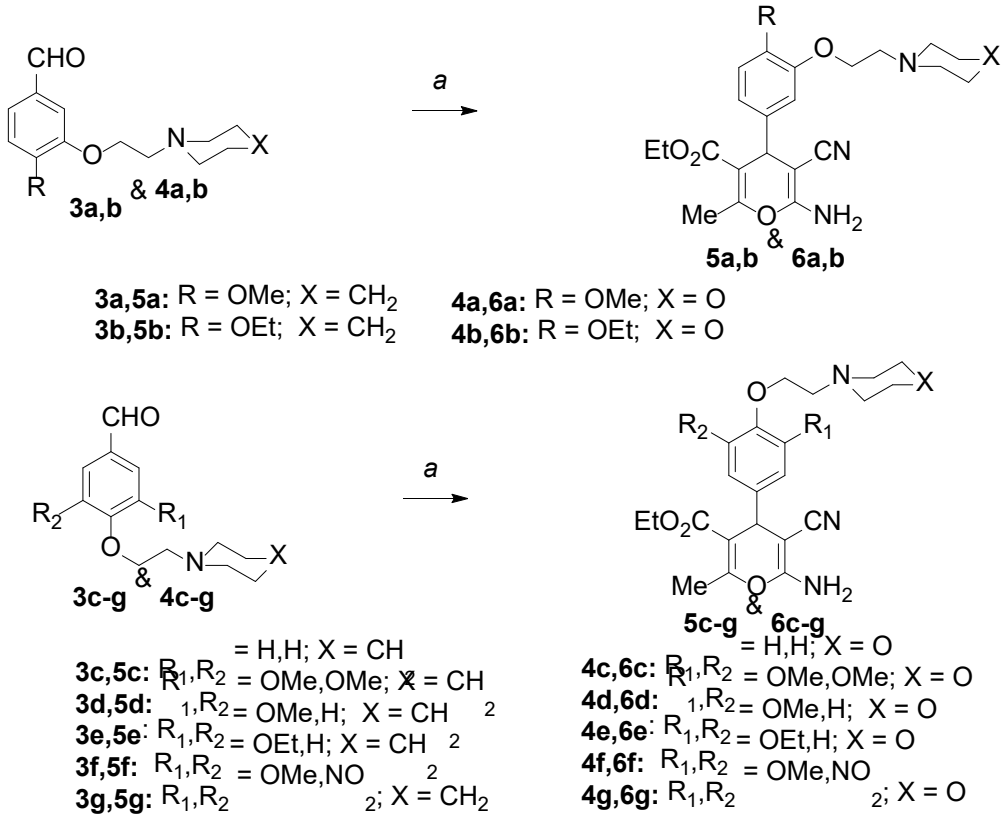
Then, each of these substituted benzaldehydes **2a-g** (1 mmol) were dissolved in dried acetone (20 mL), following anhydrous K_2CO_3 (1.5 mmol) and CTAB (0.005 mmol) were added. Piperidine or morpholine (1.2 mmol) was added to stirring mixture. The obtained mixture continued stirring for 24 h at rt then 50°C for 10 h. Acetone was removed, and water (50 mL) was added to dissolve inorganic salts, filtered and washed with diluted HCl solution, crystallized from 96% ethanol to afford the corresponding compounds, substituted 3-(2-(piperidin-1-yl)ethoxy)-/4-(2-(piperidin-1-yl)ethoxy)benzaldehydes (**3a-g**), and 3-(2-morpholinoethoxy)/4-(2-morpholinoethoxy)benzaldehydes (**4a-g**)**,** respectively (Table 1S) with yields of 62–77%.

Table 1S. Synthesis of (**3a-g**) and (**4a-g**)

Compd.	Substituents	Yield (%)	M.p. (°C)
3a	4-Methoxy-3-(2-(piperidin-1-yl)ethoxy)	62	127−129
3b	4-Ethoxy-3-(2-(piperidin-1-yl)ethoxy)	65	129−131
3c	4-(2-(Piperidin-1-yl)ethoxy)	67	111−113
3d	3,5-Dimethoxy-4-(2-(piperidin-1-yl)ethoxy)	71	132−134
3e	3-Methoxy-4-(2-(piperidin-1-yl)ethoxy)	75	137−139
3f	3-Ethoxy-4-(2-(piperidin-1-yl)ethoxy)	77	110−112
3g	3-Ethoxy-5-nitro-4-(2-(piperidin-1-yl)ethoxy)	71	130−132
4a	4-Methoxy-3-(2-morpholinoethoxy)	73	135−137
4b	4-Ethoxy-3-(2-morpholinoethoxy)	69	127−129
4c	4-(2-Morpholinoethoxy)	72	138−140
4d	3,5-Dimethoxy-4-(2-morpholinoethoxy)	75	132−134

Compd.	Substituents	Yield (%)	M.p. (°C)
4e	3-Methoxy-4-(2-morpholinoethoxy)	73	140−142
4f	3-Ethoxy-4-(2-morpholinoethoxy)	75	143−145
4g	3-Ethoxy-4-(2-morpholinoethoxy)-5-nitro	72	145−147

2. General procedure for synthesis of substituted ethyl 4*H*-pyran-3-carboxylates having piperidine (5a-g) and morpholine rings (6a-g)



Scheme 2S. Synthesis of substituted ethyl 6-amino-5-cyano-4-(4-aryl)-2-methyl-4*H*-pyran-3-carboxylates having piperidine (**5a-g**) or morpholine rings (**6a-g**). Reaction conditions: (*a*) ethyl acetoacetate, malononitrile, THEAA, 96% EtOH, 25 °C, 20 min ultrasonic.

Procedure. Ethyl 6-amino-5-cyano-2-methyl-4-(substituted phenyl)-4*H*-pyran-3-carboxylates (**5a-g** & **6a-g**) were synthesized as follows. To a solution of appropriate substituted benzaldehydes **3a-g** or **4a-g** (5 mmol), ethyl acetoacetate (5 mmol, 0.77g, 0.7 mL), malononitrile (5 mmol, 0.33 g, 0.31 mL) and in 96% ethanol (10 mL) was added THEAA (5 mol%, 1.57 g).[1] The reaction mixture was stirred at 25 °C for 20 min. The separated solid product was filtered, washed by water and recrystallized from 96% ethanol to afford the titled ethyl esters **5a-g** or **6a-g** with yields of 63−75% (Table 2S).

Table 2S. Synthesis of substituted ethyl 4*H*-pyran-3-carboxylates having piperidine (**5a-g**) and morpholine rings (**6a-g**)

Compd.	Substituents	Yield [b]		M.p. (°C)
		In %	In grams	
5a	4-Methoxy-3-(2-(piperidin-1-yl)ethoxy)	63	1.39	58−60
5b	4-Ethoxy-3-(2-(piperidin-1-yl)ethoxy)	75	1.71	59–61
5c	4-(2-(Piperidin-1-yl)ethoxy)	66	1.36	78–80
5d	3,5-Dimethoxy-4-(2-(piperidin-1-yl)ethoxy)	73	1.72	67–69
5e	3-Methoxy-4-(2-(piperidin-1-yl)ethoxy)	66	1.46	62–64
5f	3-Ethoxy-4-(2-(piperidin-1-yl)ethoxy)	73	1.66	65–67
5g	3-Ethoxy-5-nitro-4-(2-(piperidin-1-yl)ethoxy)	76	1.90	81–83
6a	4-Methoxy-3-(2-morpholinoethoxy)	65	1.44	62−64
6b	4-Ethoxy-3-(2-morpholinoethoxy)	75	1,71	65–67
6c	4-(2-Morpholinoethoxy)	68	1.40	79−81
6d	3,5-Dimethoxy-4-(2-morpholinoethoxy)	71	1.68	70–72
6e	3-Methoxy-4-(2-morpholinoethoxy)	72	1.59	64–66
6f	3-Ethoxy-4-(2-morpholinoethoxy)	73	1.67	67–69
6g	3-Ethoxy-4-(2-morpholinoethoxy)-5-nitro	68	1.71	83–85

Some selected compounds were displayed below.

*Ethyl 6-amino-5-cyano-4-(4-methoxy-2-(2-(piperidin-1-yl)ethoxy)phenyl)-2-methyl-4H-pyran-3-carboxylate (**5a**)*

From **3a** (5 mmol, 1.32 g). Yield: 1.39 g (63%) of **5a** as white solid. M.p. 58−60°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 7.24 (d, *J* = 7.5 Hz, 1H, H-6 phenyl), 6.77 (s, 2H, 6-NH_2 pyran), 6.46 (d, *J* = 7.5 Hz, 1H, H-5 phenyl), 6.44 (s, 1H, H-3 phenyl), 4.59 (s, H-4 pyran), 4.17−4.11 (m, 1H, H_a in bridge 4-O**CH_2**CH_2N<), 4.07−3.99 (m, 3H, H_b in bridge 4-O**CH_2**CH_2N< & 3-CO_2**CH_2**CH_3 pyran), 3.82 (s, 3H, 4-OCH_3 phenyl), 3.09−3.04 (m, 1H, H_a in bridge 4-OCH_2**CH_2**N<), 2.91−2.85 (m, 1H, H_b in bridge 4-OCH_2**CH_2**N<), 2.54−2.52 (m, 4H, 2×N**CH_2**CH_2CH_2 piperidine), 2.29 (s, 3H, 2-CH_3 pyran), 1.57−1.51 (m, 4H, 2×NCH_2**CH_2**CH_2 piperidine), 1.45−1.41 (m, 2H, 4H, 2×NCH_2CH_2**CH_2** piperidine), 1.21 (t,

J=6.0 Hz, 3H, 3-$CO_2CH_2\mathbf{CH_3}$ pyran). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 166.8, 160.6, 160.1, 158.1, 154.6, 129.1, 124.5, 119.1, 109.2, 107.7, 100.2, 66.8, 60.8, 56.7, 55.6, 54.8, 54.3, 34.0, 23.7, 23.1, 18.9, 14.4.

*Ethyl 6-amino-5-cyano-2-methyl-4-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-4H-pyran-3-carboxylate (**5c**)*

From **3c** (5 mmol, 1.17 g). Yield: 1.36 g (66%) of **5c** as white solid. M.p. 78–80°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 7.14 (d, *J* = 7.5 Hz, 2H, H-2 & H-6 phenyl), 6.83 (d, *J* = 7.5 Hz, 2H, H-3 & H-5 phenyl), 6.77 (s, 2H, 6-NH_2 pyran), 4.33 (s, H-4 pyran), 4.13−4.04 (m, 2H, H_a in 3-$CO_2\mathbf{CH_2}CH_3$ pyran & H_a in bridge 4-$O\mathbf{CH_2}CH_2N$<), 4.04−3.98 (m, 2H, H_b in 3-$CO_2\mathbf{CH_2}CH_3$ pyran & H_b in bridge 4-$O\mathbf{CH_2}CH_2N$<), 3.07 (dt, *J* = 7.5, 3.5 Hz, 1H, H_a in bridge 4-$OCH_2\mathbf{CH_2}N$<), 2.86 (dt, *J* = 7.5, 3.5 Hz, 1H, H_b in bridge 4-$OCH_2\mathbf{CH_2}N$<), 2.49−2.47 (m, 4H, 2×$N\mathbf{CH_2}CH_2CH_2$ piperidine), 2.28 (s, 3H, 2-CH_3 pyran), 1.55−1.50 (m, 4H, 2×$NCH_2\mathbf{CH_2}CH_2$ piperidine), 1.44−1.40 (m, 2H, 4H, 2×$NCH_2CH_2\mathbf{CH_2}$ piperidine), 1.23 (t, *J*=6.0 Hz, 3H, 3-$CO_2CH_2\mathbf{CH_3}$ pyran). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 166.8, 160.3, 158.4, 155.0, 136.6, 128.5, 119.8, 114.9, 106.1, 66.4, 60.8, 56.6, 54.8, 54.3, 40.7, 23.7, 23.1, 19.1, 14.4.

*Ethyl 6-amino-5-cyano-2-methyl-4-(4-methoxy-2-(2-morpholinoethoxy)phenyl)-4H-pyran-3-carboxylate (**6a**)*

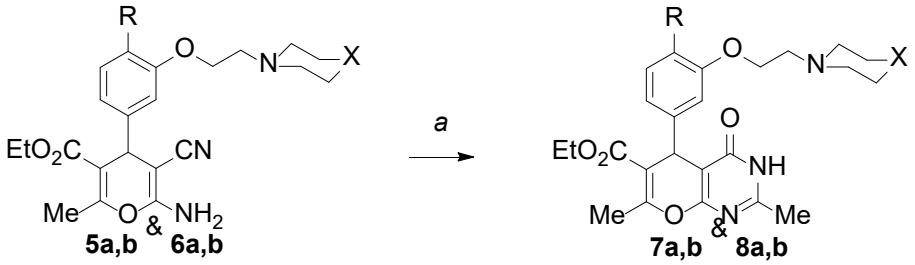
From **4a** (5 mmol, 1.33 g). Yield: 1.44 g (65%) of **6a** as white solid. M.p. 62−64°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 7.19 (d, *J* = 7.5 Hz, 1H, H-6 phenyl), 6.78 (s, 2H, 6-NH_2 pyran), 6.45 (d, *J* = 7.5 Hz, 1H, H-5 phenyl), 6.43 (s, 1H, H-3 phenyl), 4.62 (s, H-4 pyran), 4.14−4.10 (m, 1H, H_a in bridge 4-$O\mathbf{CH_2}CH_2N$<), 4.08−3.99 (m, 3H, H_b in bridge 4-$O\mathbf{CH_2}CH_2N$< & 2H in 3-$CO_2\mathbf{CH_2}CH_3$ pyran), 3.82 (s, 3H, 4-OCH_3 phenyl), 3.72−3.70 (m, 4H, $O\mathbf{CH_2}CH_2N$ morpholine), 2.82 (dt, *J* = 7.5, 4.0 Hz, H_a in bridge 4-$OCH_2\mathbf{CH_2}N$<), 2.67−2.60 (m, 3H, H_b in bridge 4-$OCH_2\mathbf{CH_2}N$< & 2×H_a in $OCH_2\mathbf{CH_2}N$ morpholine), 2.54−2.50 (m, 2H, 2×H_b in $OCH_2\mathbf{CH_2}N$ morpholine), 2.29 (s, 3H, 2-CH_3 pyran), 1.22 (t, *J*=6.0 Hz, 3H, 3-$CO_2CH_2\mathbf{CH_3}$ pyran). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 166.8, 160.6, 160.1, 158.1, 154.6, 129.1, 124.5, 119.1, 109.2, 107.7, 100.3, 66.9, 66.1, 60.7, 56.7, 55.7, 55.6, 53.5, 34.0, 18.9, 14.4.

*Ethyl 6-amino-5-cyano-2-methyl-4-(2-morpholinoethoxy)phenyl)-4H-pyran-3-carboxylate (**6c**)*

From **4c** (5 mmol, 1.18 g). Yield: 1.40 g (68%) of **6c** as white solid. M.p. 79−81°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 7.14 (d, *J* = 7.5 Hz, 2H, H-2 & H-6 phenyl), 6.83 (d, *J* = 7.5 Hz, 2H, H-3 & H-5 phenyl), 6.78 (s, 2H, 6-NH_2 pyran), 4.33 (s, H-4 pyran), 4.13−3.70 (m,

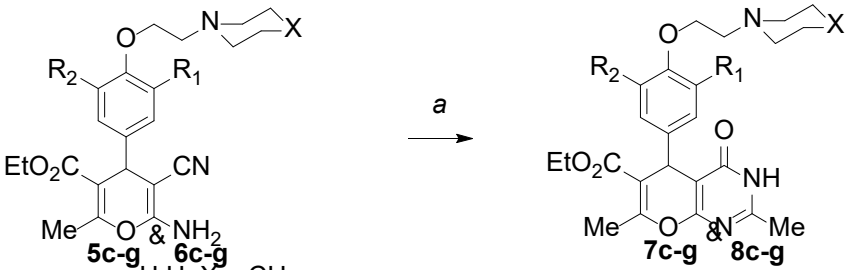
4H, 3-CO_2**C**$\mathbf{H_2}$$CH_3$ pyran & bridge 4-O**C**$\mathbf{H_2}$$CH_2$N<), 3.73−3.70 (m, 4H, O**C**$\mathbf{H_2}$$CH_2$N morpholine), 2.86 (dt, *J* = 7.5, 4.0 Hz, H_a in bridge 4-OCH_2**C**$\mathbf{H_2}$N<), 2.65−2.60 (m, 3H, H_a in bridge 4-OCH_2**C**$\mathbf{H_2}$N< & 2×H_a in OCH_2**C**$\mathbf{H_2}$N morpholine), 2.54−2.50 (m, 2H, 2×H_b in OCH_2**C**$\mathbf{H_2}$N morpholine), 2.28 (s, 3H, 2-CH_3 pyran), 1.23 (t, *J*=6.0 Hz, 3H, 3-CO_2CH_2**C**$\mathbf{H_3}$ pyran). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 166.7, 160.3, 158.4, 155.0, 136.6, 128.5, 119.8, 114.9, 106.1, 66.4, 66.1, 60.7, 56.6, 56.0, 53.4, 40.7, 19.1, 14.4.

3. General procedure for synthesis of substituted ethyl 2,7-dimethyl-5-(substituted phenyl)-4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates (7a-g & 8a-g)



5a,7a: R = OMe; X = CH_2
5b,7b: R = OEt; X = CH_2

6a,8a: R = OMe; X = O
6b,8a: R = OEt; X = O



5c,7c: R_1,R_2 = H,H; X = CH_2
5d,7d: R_1,R_2 = OMe,OMe; X = CH_2
5e,7e: R_1,R_2 = OMe,H; X = CH_2
5f,7f: R_1,R_2 = OEt,H; X = CH_2
5g,7g: R_1,R_2 = OMe,NO_2; X = CH_2

6c,8c: R_1,R_2 = H,H; X = O
6d,8d: R_1,R_2 = OMe,OMe; X = O
6e,8e: R_1,R_2 = OMe,H; X = O
6f,8f: R_1,R_2 = OEt,H; X = O
6g,8g: R_1,R_2 = OMe,NO_2; X = O

Scheme 3S. Synthesis of substituted ethyl 2,7-dimethyl-5-(substituted phenyl)-4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates (**7a-g** & **8a-g**). Reaction conditions: (*a*) Acetic anhydride, TFA, 100°C, 15 min, then rt, 24 h.

Procedure. Reaction mixture of corresponding 4*H*-pyrans **5a-g** or **6a-g** (1 mmol), anhydride acetic (1.25mL), and trifluoroacetic acid (0.025 mL) was heated under reflux at 100 °C for 15 min, then cooled to room temperature and left overnight (24 h).[2] Upon completion, as monitored using TLC plates, the mixture was poured into cold water (10 mL). The crude product of 4*H*-pyrano[2,3-*d*]pyrimidine was filtered, washed by water (3×2.5ml), recrystallized from 96% ethanol to afford corresponding compounds **7a-g** or **8a-g** with yields of 69–78% (Table 3S).

Table 3S. Synthesis of substituted ethyl 2,7-dimethyl-5-(substituted phenyl)-4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates having piperidine (**7a-g**) and morpholine rings (**8a-g**)

Compd.	Substituents	Yield [b]		M.p. (°C)
		In %	In milligrams	
7a	4-Methoxy-3-(2-(piperidin-1-yl)ethoxy)	69	333	134−136
7b	4-Ethoxy-3-(2-(piperidin-1-yl)ethoxy)	72	358	145–147
7c	4-(2-(Piperidin-1-yl)ethoxy)	76	344	141−142
7d	3,5-Dimethoxy-4-(2-(piperidin-1-yl)ethoxy)	75	385	137-139
7e	3-Methoxy-4-(2-(piperidin-1-yl)ethoxy)	76	367	146–148
7f	3-Ethoxy-4-(2-(piperidin-1-yl)ethoxy)	75	373	151–153
7g	3-Ethoxy-5-nitro-4-(2-(piperidin-1-yl)ethoxy)	77	407	165–167
8a	4-Methoxy-3-(2-morpholinoethoxy)	71	344	151−153
8b	4-Ethoxy-3-(2-morpholinoethoxy)	72	359	144–146
8c	4-(2-Morpholinoethoxy)	78	355	145−147
8d	3,5-Dimethoxy-4-(2-morpholinoethoxy)	75	386	153–155
8e	3-Methoxy-4-(2-morpholinoethoxy)	75	364	154–156
8f	3-Ethoxy-4-(2-morpholinoethoxy)	73	364	157–159
8g	3-Ethoxy-4-(2-morpholinoethoxy)-5-nitro	69	366	162–165

Some selected remained compounds were represented below.

*Ethyl 5-(4-methoxy-2-(2-(piperidin-1-yl)ethoxy)phenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidine-6-carboxylate (**7a**)*

From **5a** (1 mmol, 441 mg). Yield: 333 mg (69%) of **7a** as white solid. M.p.: 134−136°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 11.75 (s, 1H, NH pyranopyrimidin-4-one), 7.21 (d, *J* = 7.5 Hz, 1H, H-6 phenyl), 6.42 (d, *J* = 7.5 Hz, 1H, H-5 phenyl), 6.38 (s, 1H, H-3 phenyl), 5.48 (s, H-4 pyranopyrimidin-4-one), 4.16−4.12 (m, 1H, H_a in bridge 4-O**CH_2**CH_2N<), 4.09−3.99 (m, 3H, H_b in bridge 4-O**CH_2**CH_2N< & 6-CO_2**CH_2**CH_3 pyranopyrimidin-4-one), 3.82 (s, 3H, 4-OCH_3 phenyl), 3.06 (dt, *J* = 7.5, 3.5 Hz, 1H, H_a in bridge 4-OCH_2**CH_2**N<), 2.88

(dt, *J* = 7.5, 3.5 Hz, 1H, H_b in bridge 4-OCH_2**CH_2**N<), 2.57−2.54 (m, 4H, 2×N**CH_2**CH_2CH_2 piperidine), 2.38 (s, 3H, 7-CH_3 pyranopyrimidin-4-one), 2.28 (s, 3H, 2-CH_3 pyranopyrimidin-4-one), 1.57−1.51 (m, 4H, 2×NCH_2**CH_2**CH_2 piperidine), 1.46−1.41 (m, 2H, 4H, 2×NCH_2CH_2**CH_2** piperidine), 1.21 (t, *J*=6.0 Hz, 3H, 6-CO_2CH_2**CH_3** pyranopyrimidin-4-one). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 167.0, 162.6, 160.5, 159.6, 157.4, 157.3, 154.3, 129.0, 124.8, 109.2, 109.1, 100.3, 98.3, 66.8, 60.8, 55.6, 54.8, 54.4, 31.6, 23.8, 23.1, 20.7, 18.4, 14.4.

*Ethyl 5-(2-(piperidin-1-yl)ethoxy)phenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidine-6-carboxylate (**7c**)*

From **5c** (1 mmol, 411 mg). Yield: 344 mg (76%) of **7c** as white solid. M.p.: 141−142°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 11.85 (s, 1H, NH pyranopyrimidin-4-one), 7.18 (d, *J* = 7.5 Hz, 2H, H-2 & H-6 phenyl), 6.82 (d, *J* = 7.5 Hz, 2H, H-3 & H-5 phenyl), 5.87 (s, H-4 pyranopyrimidin-4-one), 4.15−4.11 (m, 1H, H_a in bridge 4-O**CH_2**CH_2N<), 4.08−3.99 (m, 3H, H_b in bridge 4-O**CH_2**CH_2N< & 2H in 6-CO_2**CH_2**CH_3 pyranopyrimidin-4-one), 3.05 (dt, *J* = 7.5, 3.5 Hz, 1H, H_a in bridge 4-OCH_2**CH_2**N<), 2.86 (dt, *J* = 7.5, 3.5 Hz, 1H, H_b in bridge 4-OCH_2**CH_2**N<), 2.55−2.53 (m, 4H, 2×N**CH_2**CH_2CH_2 piperidine), 2.38 (s, 3H, 7-CH_3 pyranopyrimidin-4-one), 2.29 (s, 3H, 2-CH_3 pyranopyrimidin-4-one), 1.57−1.51 (m, 4H, 2×NCH_2**CH_2**CH_2 piperidine), 1.45−1.41 (m, 2H, 4H, 2×NCH_2CH_2**CH_2** piperidine), 1.20 (t, *J*=6.0 Hz, 3H, 6-CO_2CH_2**CH_3** pyranopyrimidin-4-one). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 166.9, 162.7, 159.0, 158.5, 157.7, 154.3, 136.7, 128.5, 115.0, 107.9, 100.1, 66.5, 60.8, 54.9, 54.4, 36.2, 23.7, 23.1, 20.6, 18.9, 14.4.

*Ethyl 5-(4-methoxy-2-(2-morpholinoethoxy)phenyl)-2,7-dimethyl-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidine-6-carboxylate (**8a**)*

From **6a** (1 mmol, 443 mg). Yield: 344 mg (71%) of **8a** as white solid. M.p.: 151−153°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 11.75 (s, 1H, NH pyranopyrimidin-4-one), 7.22 (d, *J* = 7.5 Hz, 1H, H-6 phenyl), 6.42 (d, *J* = 7.5 Hz, 1H, H-5 phenyl), 6.38 (s, 1H, H-3 phenyl), 5.48 (s, H-4 pyranopyrimidin-4-one), 4.16−4.11 (m, 1H, H_a in bridge 4-O**CH_2**CH_2N<), 4.09−3.98 (m, 3H, H_b in bridge 4-O**CH_2**CH_2N< & 2H in 6-CO_2**CH_2**CH_3 pyranopyrimidin-4-one), 3.82 (s, 3H, 4-OCH_3 phenyl), 3.72−3.69 (m, 4H, O**CH_2**CH_2N morpholine), 2.82 (dt, *J* = 7.5, 4.0 Hz, H_a in bridge 4-OCH_2**CH_2**N<), 2.64 (dt, *J* = 7.5, 4.0 Hz, H_b in bridge 4-OCH_2**CH_2**N<), 2.58−2.51 (m, 4H, OCH_2**CH_2**N morpholine), 2.38 (s, 3H, 7-CH_3 pyranopyrimidin-4-one), 2.28 (s, 3H, 2-CH_3 pyranopyrimidin-4-one), 1.22 (t, *J*=6.0 Hz, 3H, 6-CO_2CH_2**CH_3** pyranopyrimidin-4-one). ^{13}C NMR (125 MHz, Chloroform-*d*) δ (ppm): 167.0,

162.6, 160.5, 159.6, 157.4, 157.3, 154.3, 129.0, 124.8, 109.2, 109.1, 100.4, 98.3, 66.8, 65.9, 60.8, 55.6, 55.4, 53.5, 31.6, 20.7, 18.4, 14.4.

*Ethyl 2,7-dimethyl-5-(4-(2-morpholinoethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidine-6-carboxylate (**8c**)*

From **6c** (1 mmol, 413 mg). Yield: 355 mg (78%) of **8c** as white solid. M.p.: 145−147°C. ^{1}H NMR (500 MHz, Chloroform-*d*), δ (ppm): 11.85 (s, 1H, NH pyranopyrimidin-4-one), 7.18 (d, *J* = 7.5 Hz, 2H, H-2 & H-6 phenyl), 6.82 (d, *J* = 7.5 Hz, 2H, H-3 & H-5 phenyl), 5.89 (s, H-4 pyranopyrimidin-4-one), 4.13−4.09 (m, 1H, H_a in bridge 4-O**CH_2**CH_2N<), 4.07−3.99 (m, 3H, H_b in bridge 4-O**CH_2**CH_2N< & 2H in 6-CO_2**CH_2**CH_3 pyranopyrimidin-4-one), 3.73−3.71 (m, 4H, O**CH_2**CH_2N morpholine), 2.82 (dt, *J* = 7.5, 4.0 Hz, H_a in bridge 4-OCH_2**CH_2**N<), 2.65−2.60 (m, 3H, H_a in bridge 4-OCH_2**CH_2**N< & 2×H_a in OCH_2**CH_2**N morpholine), 2.55−2.50 (m, 2H, 2×H_b in OCH_2**CH_2**N morpholine), 2.38 (s, 3H, 7-CH_3 pyranopyrimidin-4-one), 2.29 (s, 3H, 2-CH_3 pyranopyrimidin-4-one), 1.20 (t, *J*=6.0 Hz, 3H, 6-CO_2CH_2**CH_3** pyranopyrimidin-4-one). ^{13}C NMR (125 MHz, Chloroform-*d*), δ (ppm): 166.9, 162.7, 159.0, 158.5, 157.7, 154.3, 136.7, 128.5, 115.0, 107.9, 100.1, 66.6, 65.9, 60.8, 55.8, 53.5, 36.2, 20.6, 18.9, 14.4.

4. Molecular simulations

4.1. Induced fit docking results

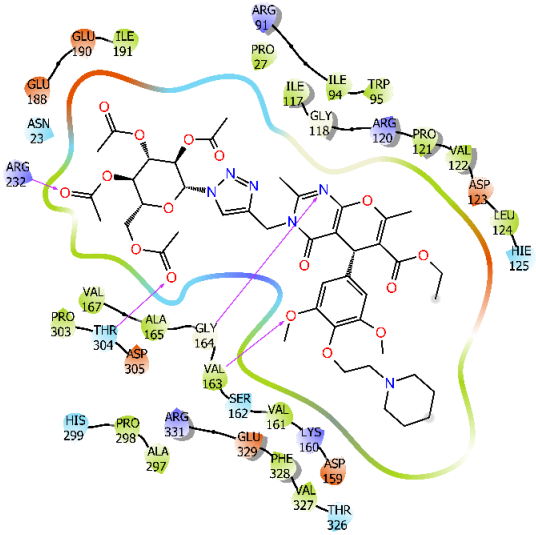
The low-energy conformation thus obtained was used for the modelling studies (Table 4S). Some other obtained docking results for ligands **12d**,**12e**, and **13b** as well as UD1 (Uridine diphosphate *N*-acetylglucosamine) were displayed below.

Table 4S. Docking glide scores of ligands **12d**,**12e**, and **13b**, and UD1 on the receptor of enzyme 1UAE

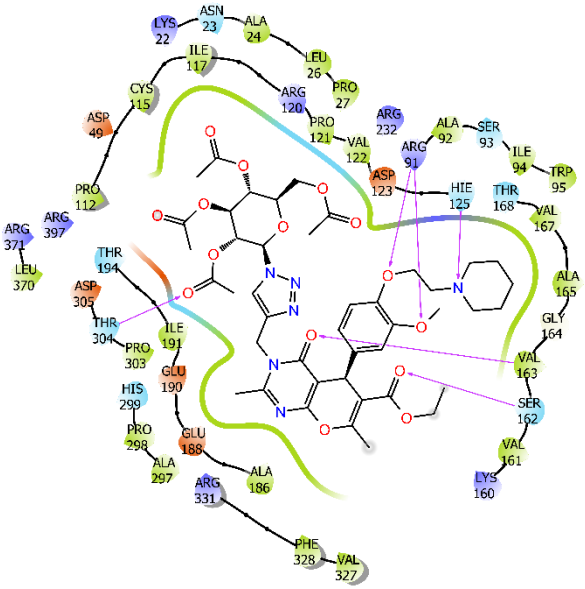
Ligands	IFD Score (kcal/mol)
12d	−912.020
12e	−916.268
13b	−916.071

13d	−901.141
D1	−912.501

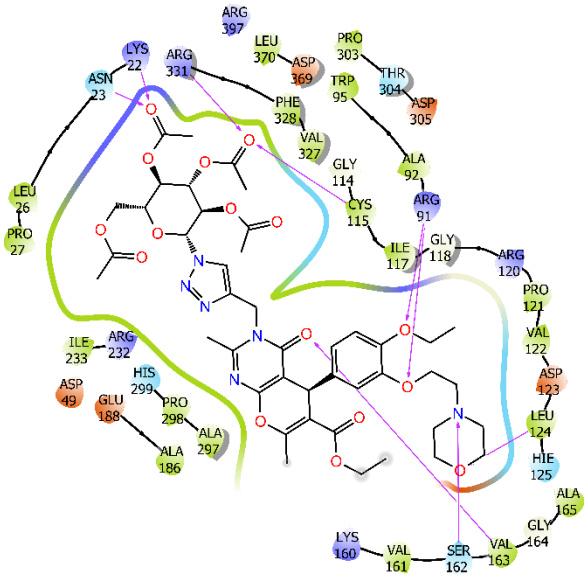
(A) R = 3,5-diOMe-4-(2-(Piperidin-1-yl)-ethoxy) (**12d**)



(B) R = 3-OMe-4-(2-(Piperidin-1-yl)ethoxy) (**12e**)



(C) R = 4-OEt-3-Morpholinoethoxy (**13b**)



(D) UD1

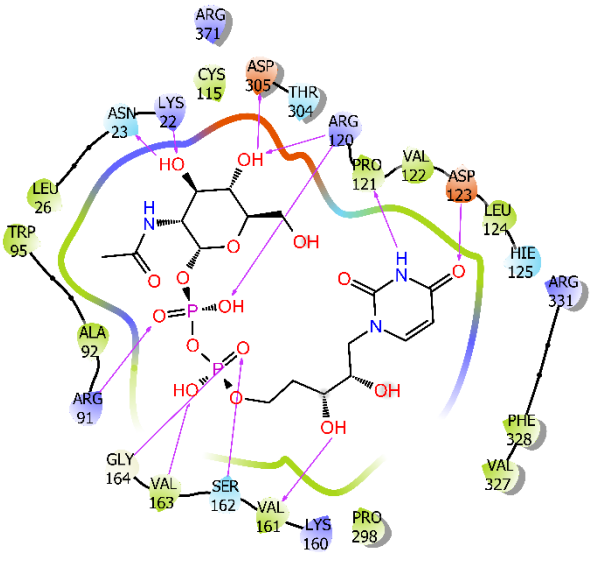


Figure 1S. Two-dimensional diagram in ligand interaction of ligands **12d** (A), **12e** (B), **13b** (C), and UD1 (D) in active site of enzyme 1UAE showed active ligand-protein interactions of the ligand−interactions. The intermolecular hydrogen bond is colored in magenta line.

4.2. Molecular dynamics simulation

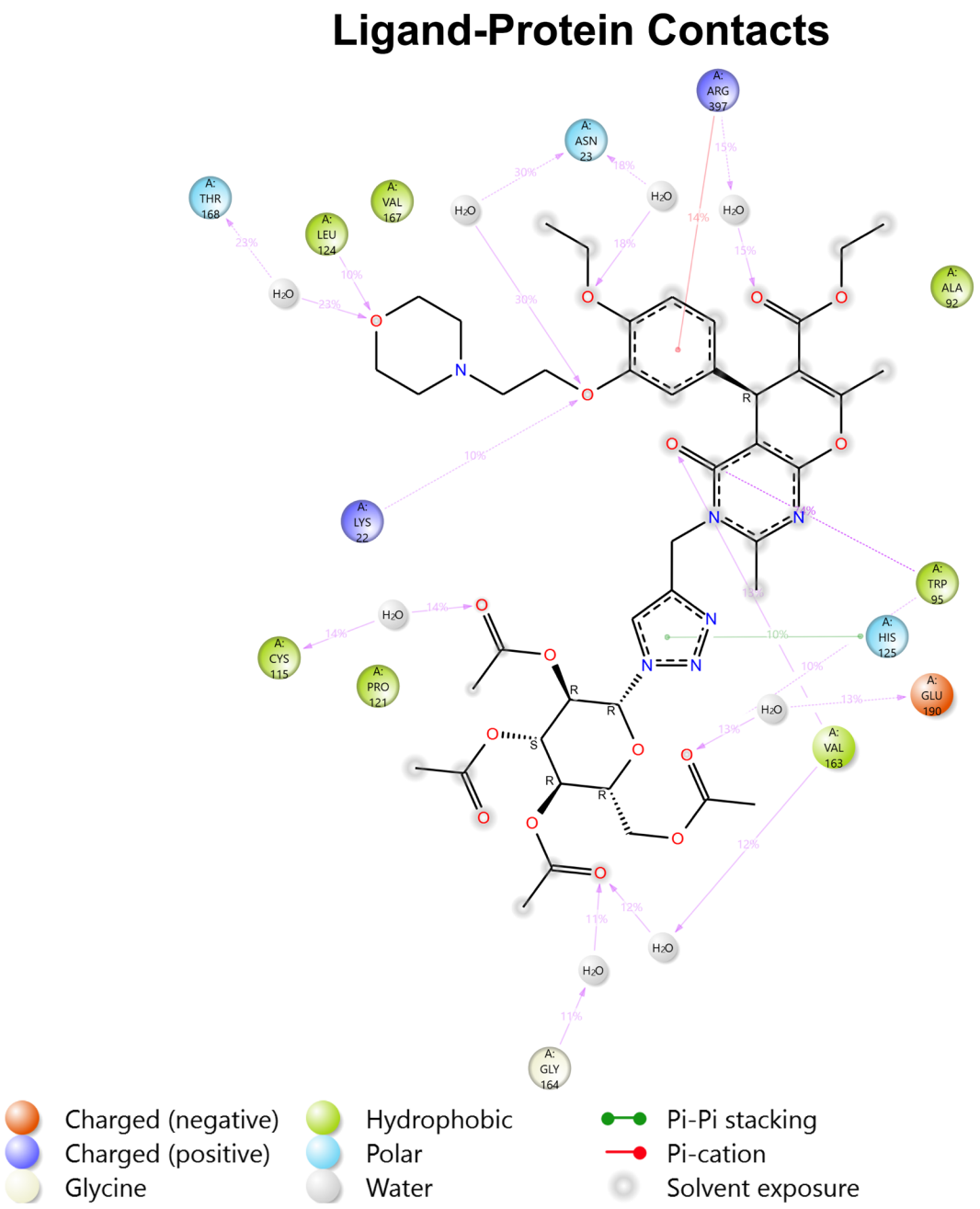


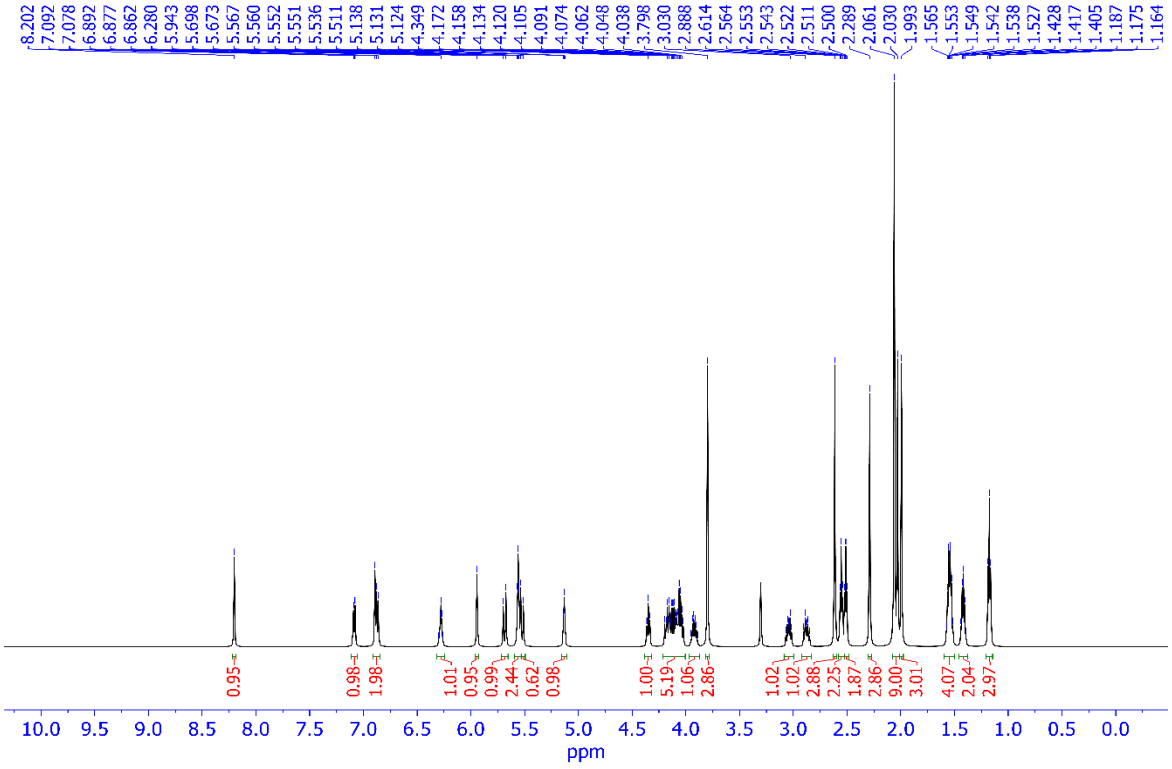
Figure 2S. Plot represent ligand-protein contacts in **13b**/1UAE complex during MD simulation.

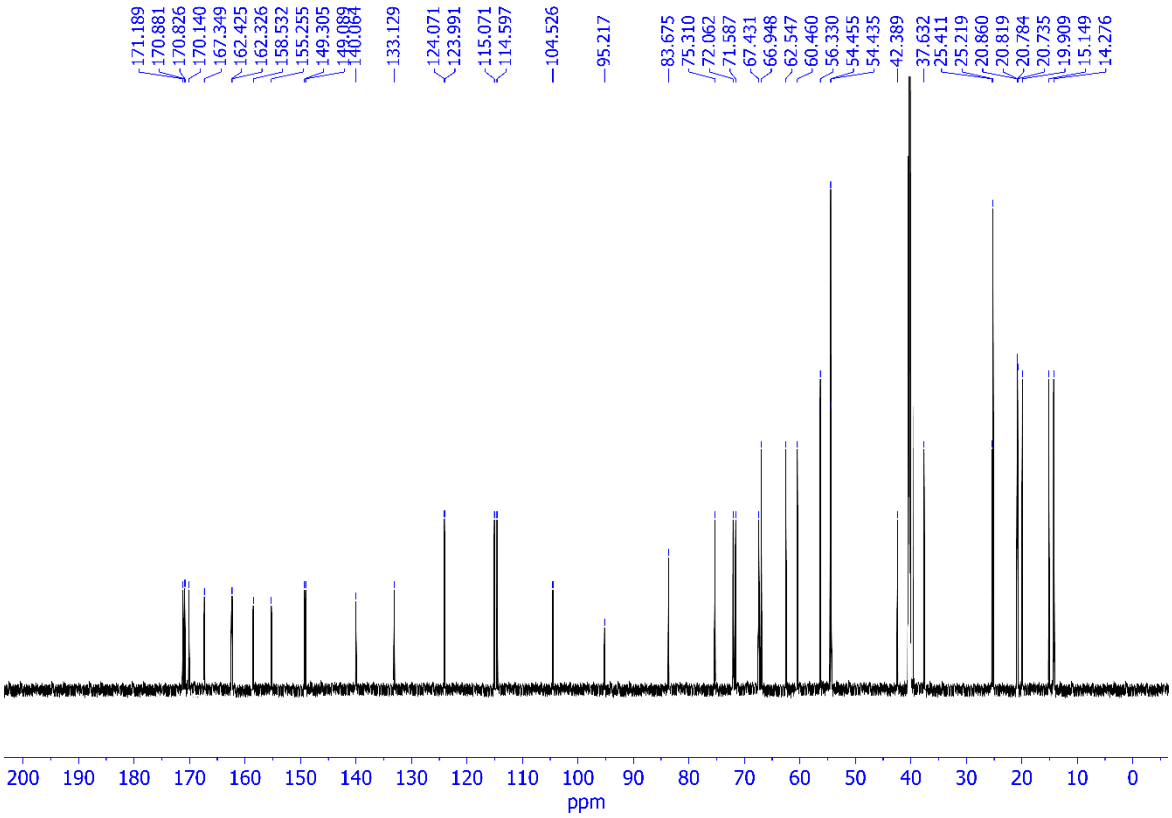
References

1. D. S. Hai, N. T. T. Ha, D. T. Tung, C. T. Le, H. H. Anh, V. N. Toan, H. T. K. Van, D. N. Toan, N. T. K. Giang, N. T. T. Huong and N. D. Thanh, *Chem. Pap.*, 2022, **76**, 5281-5292.
2. N. D. Thanh, D. S. Hai, N. T. T. Ha, D. T. Tung, C. T. Le, H. T. K. Van, V. N. Toan, D. N. Toan and L. H. Dang, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 164-171.

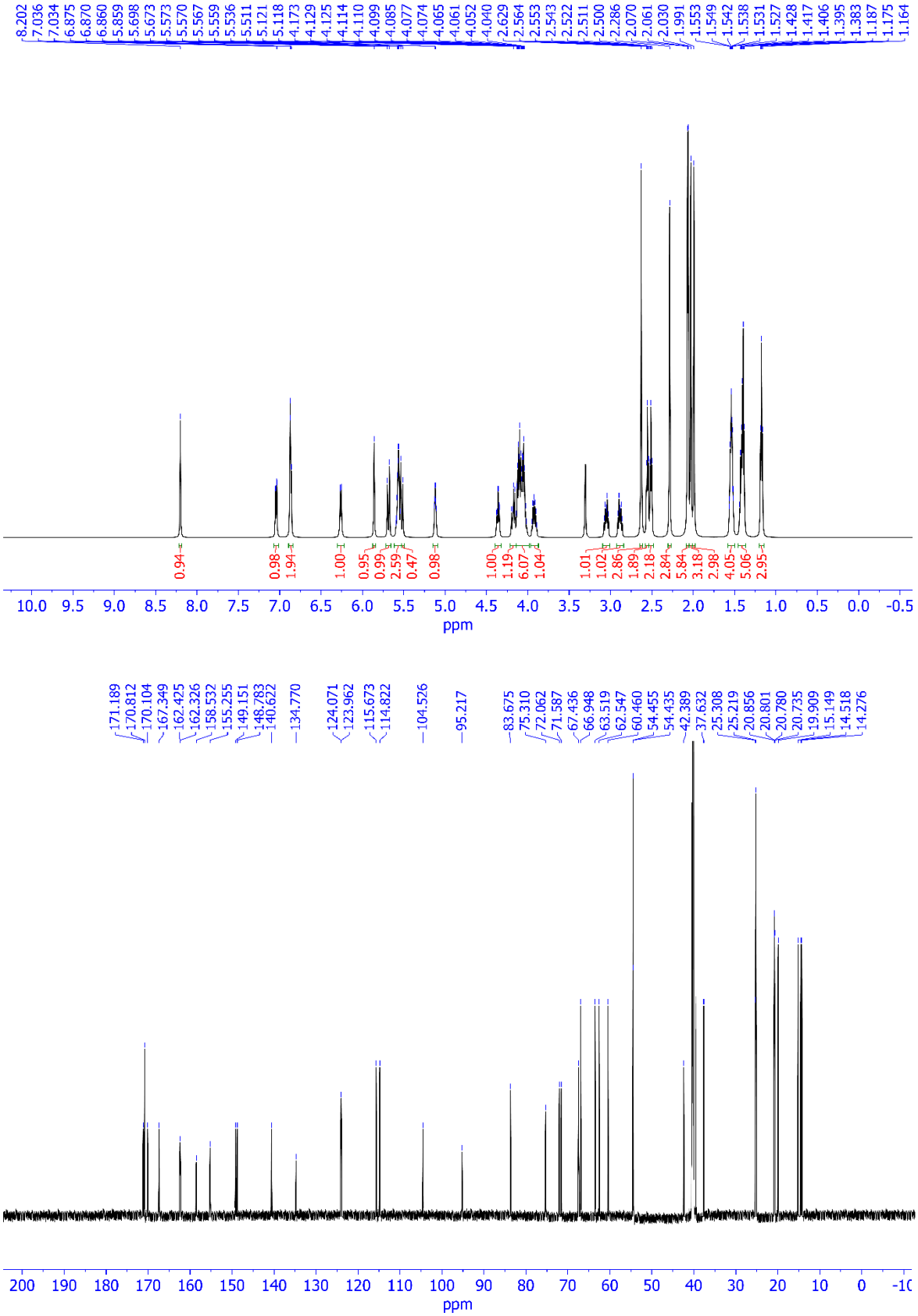
5. Selected NMR and mass spectra of compounds 12a-g & 13a-g

*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(4-methoxy-3-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12a**)*

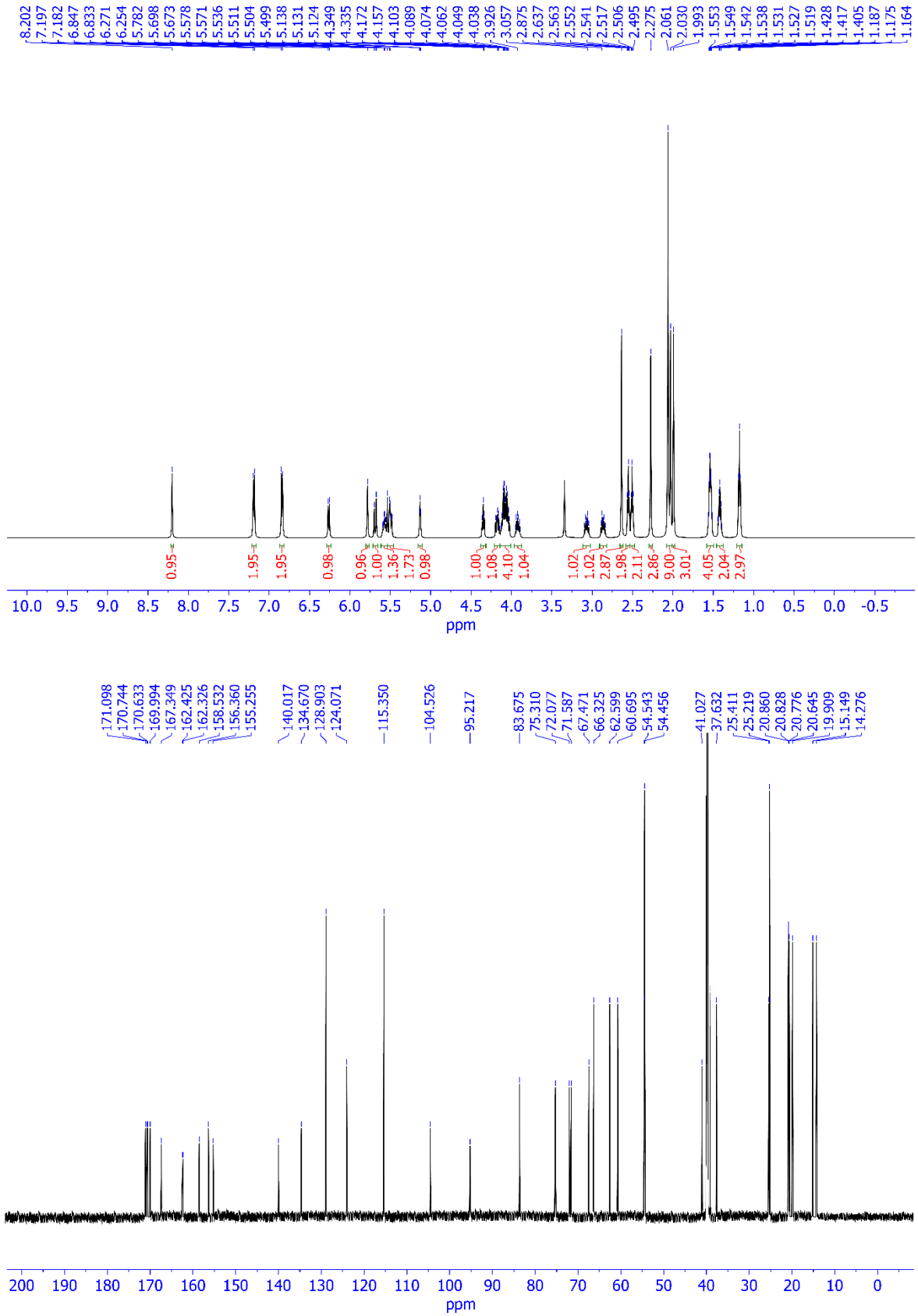




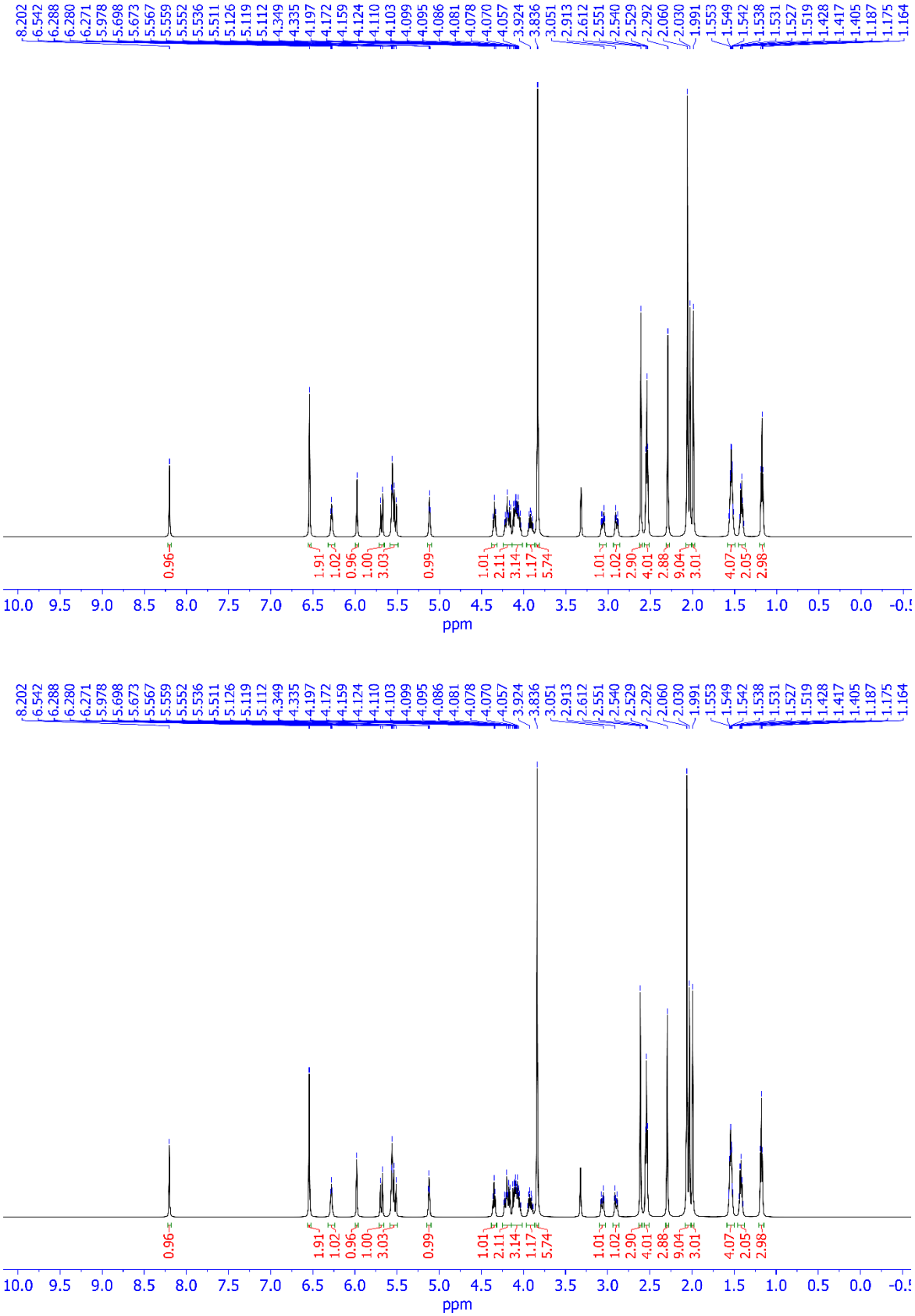
*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(4-ethoxy-3-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12b**)*



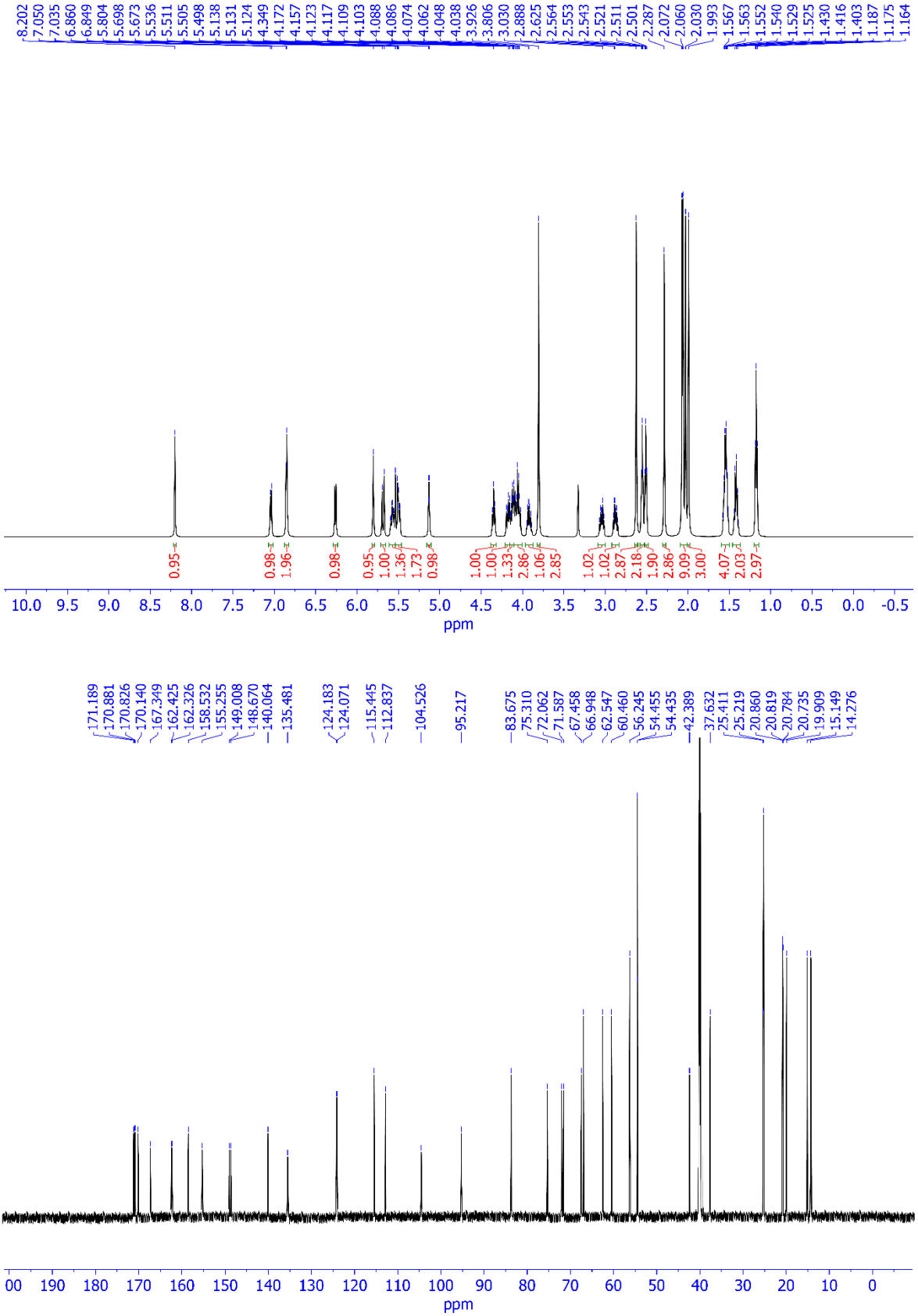
*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12c**)*



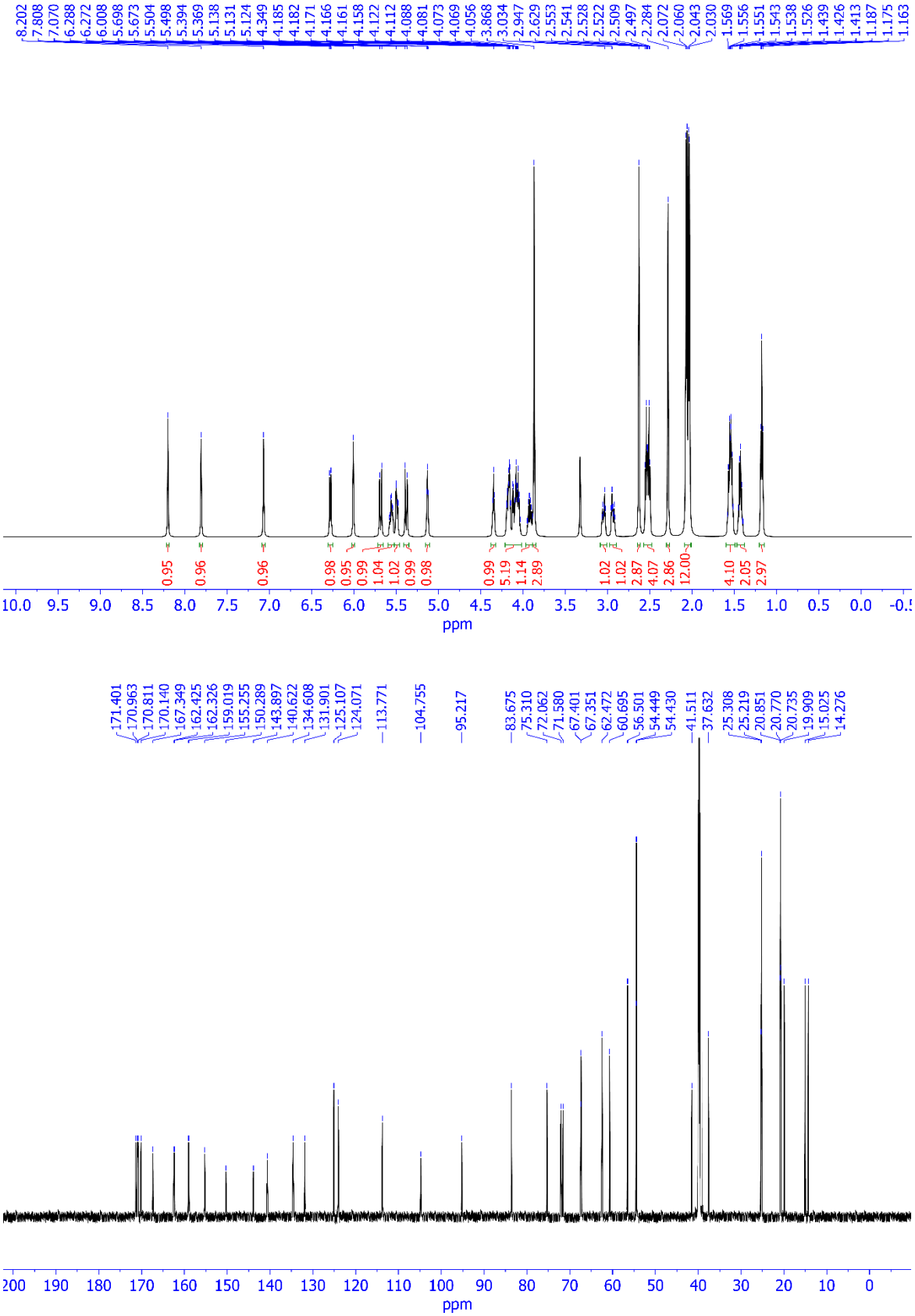
*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3,5-dimethoxy-4-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12d**)*



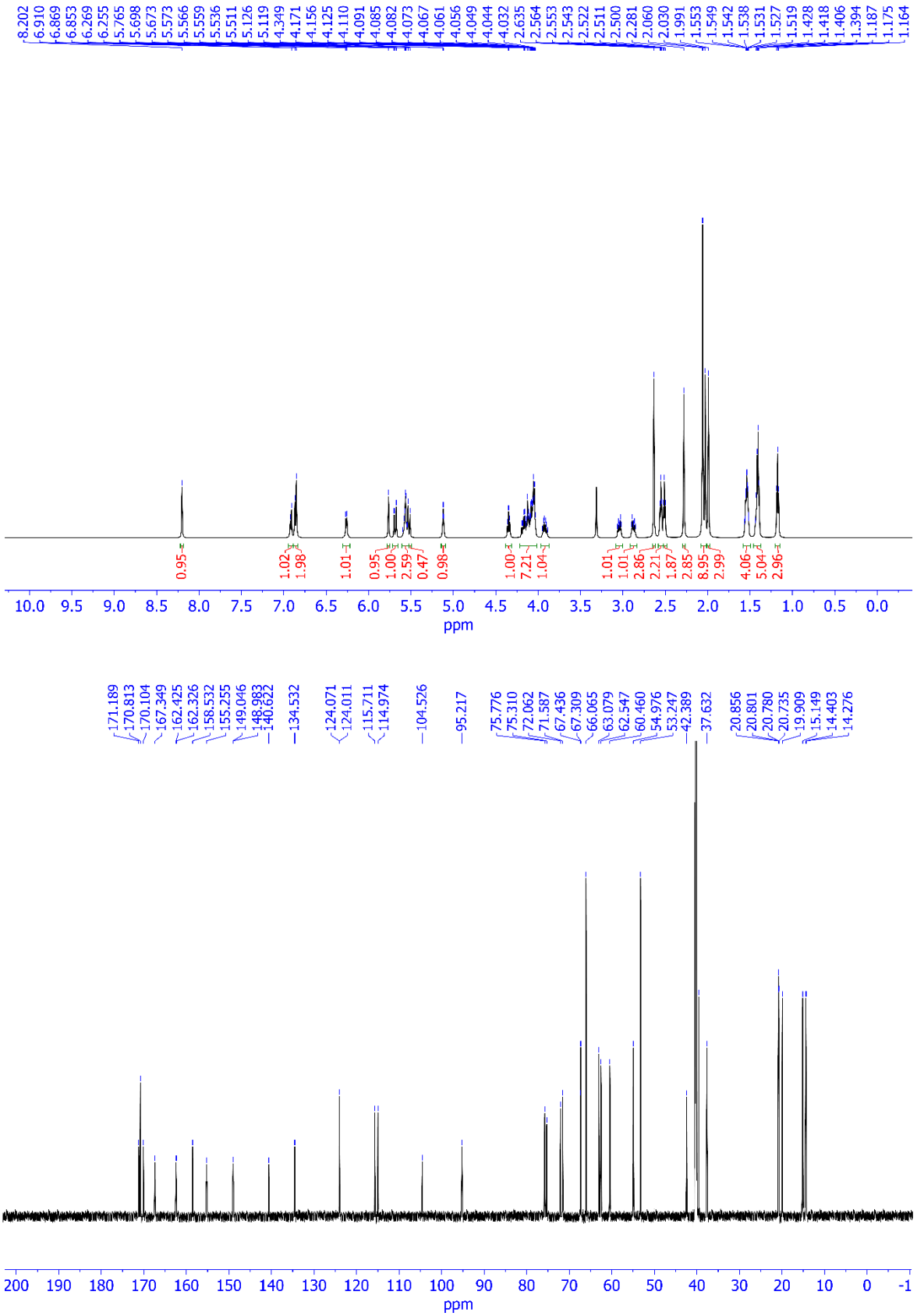
*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12e**)*



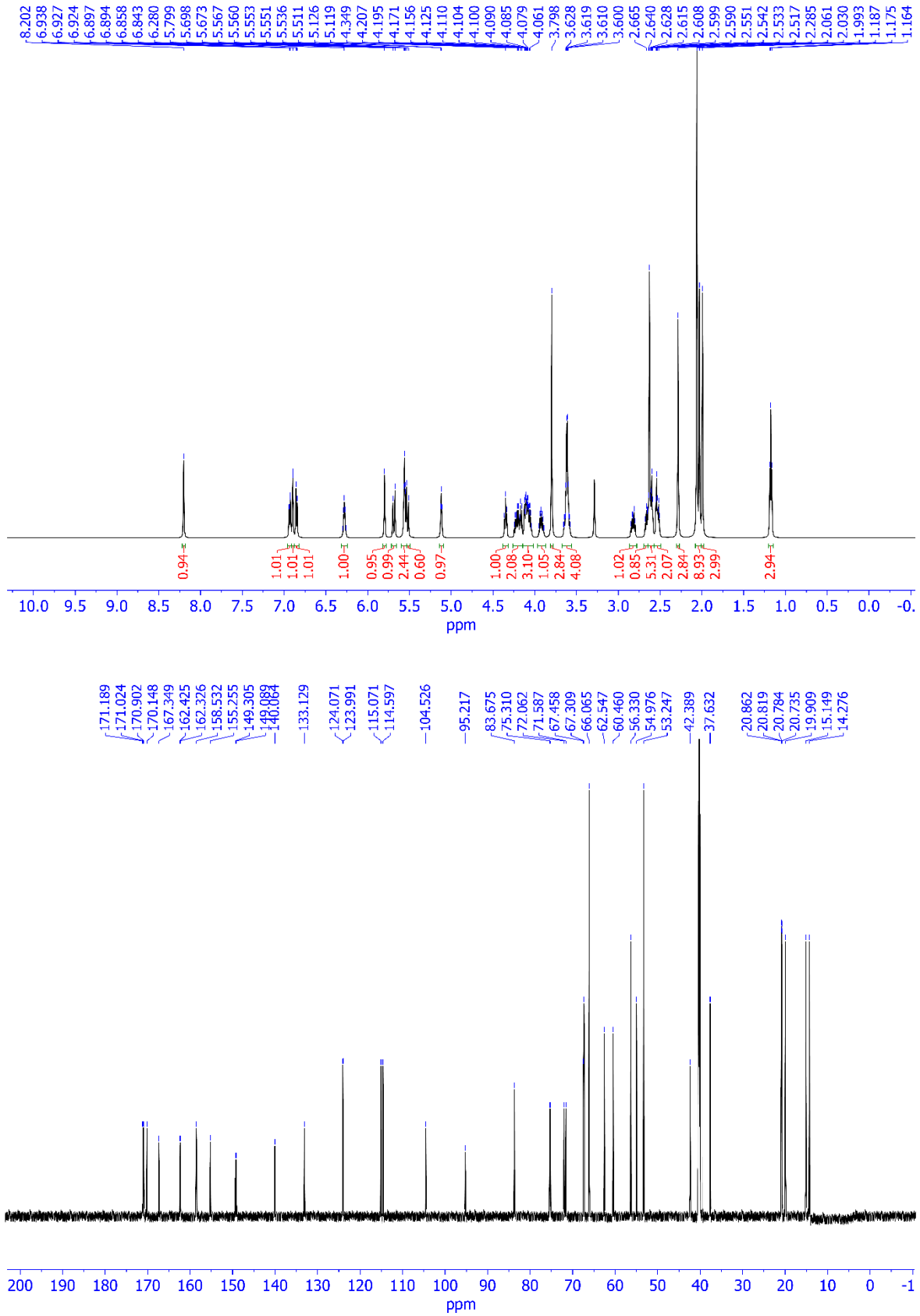
*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3-methoxy-5-nitro-4-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12f**)*



*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3-ethoxy-4-(2-(piperidin-1-yl)ethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**12g**)*



*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(4-methoxy-3-(2-morpholinoethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**13a**)*



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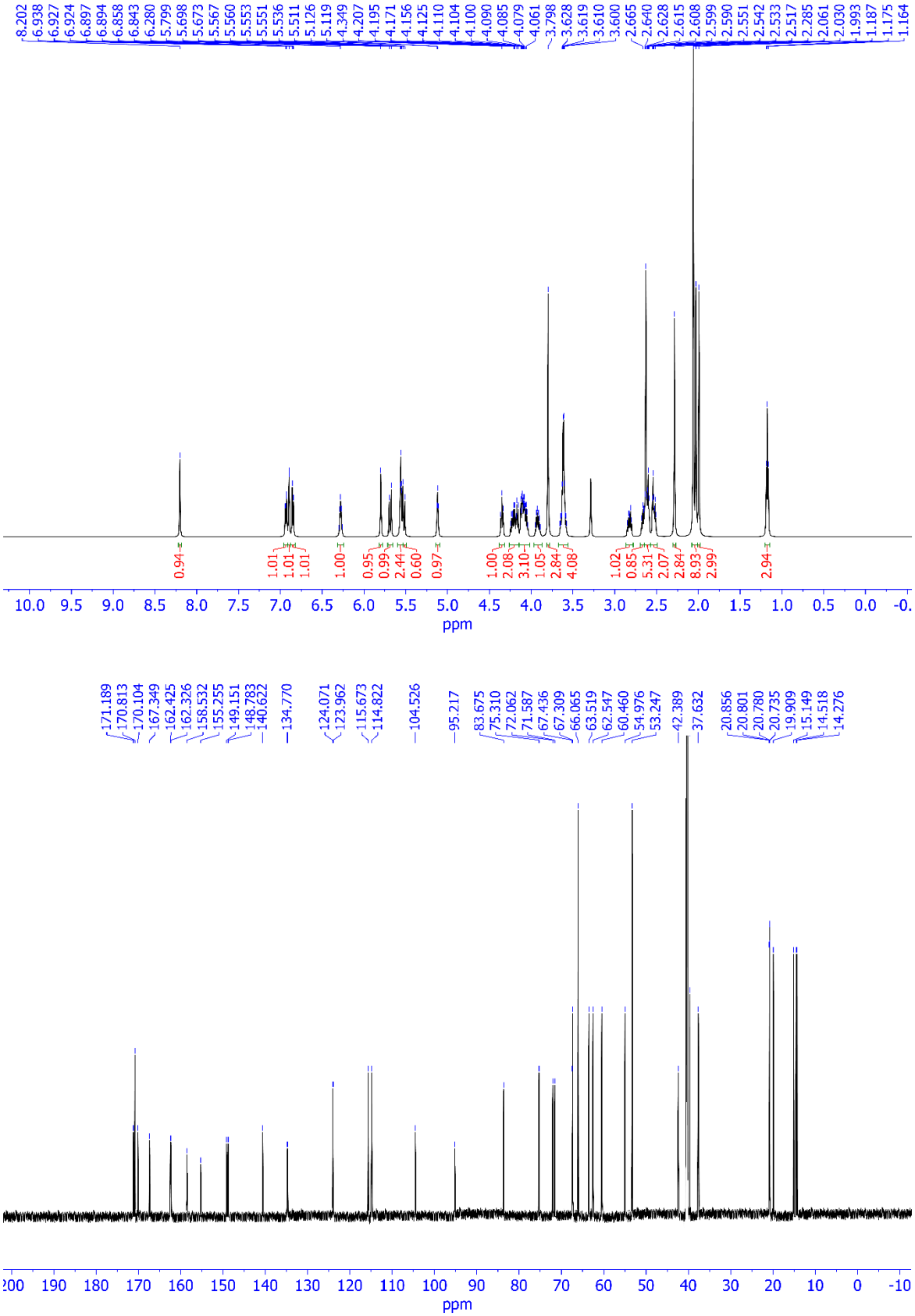
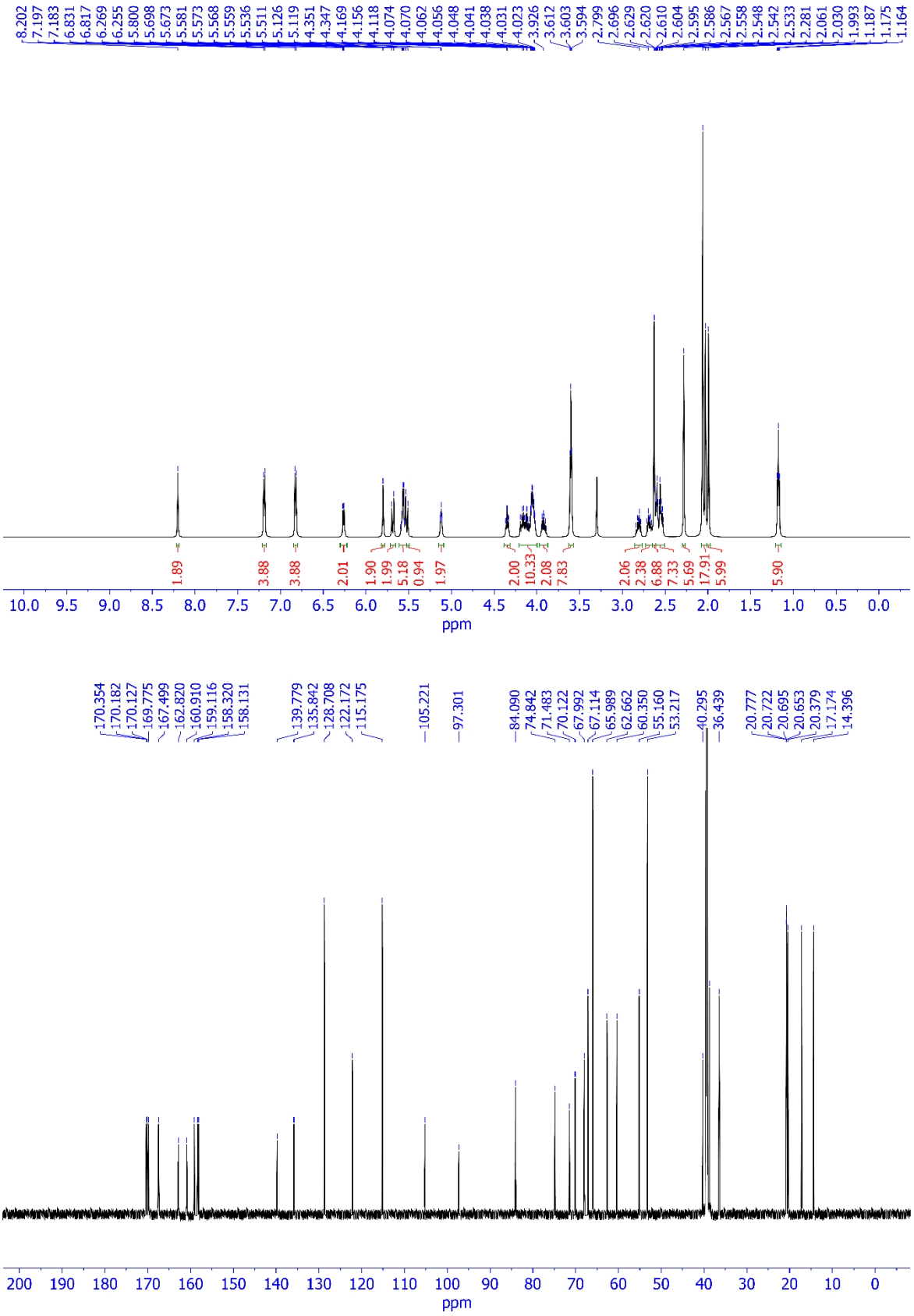


*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(4-(2-morpholinoethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**13c**)*



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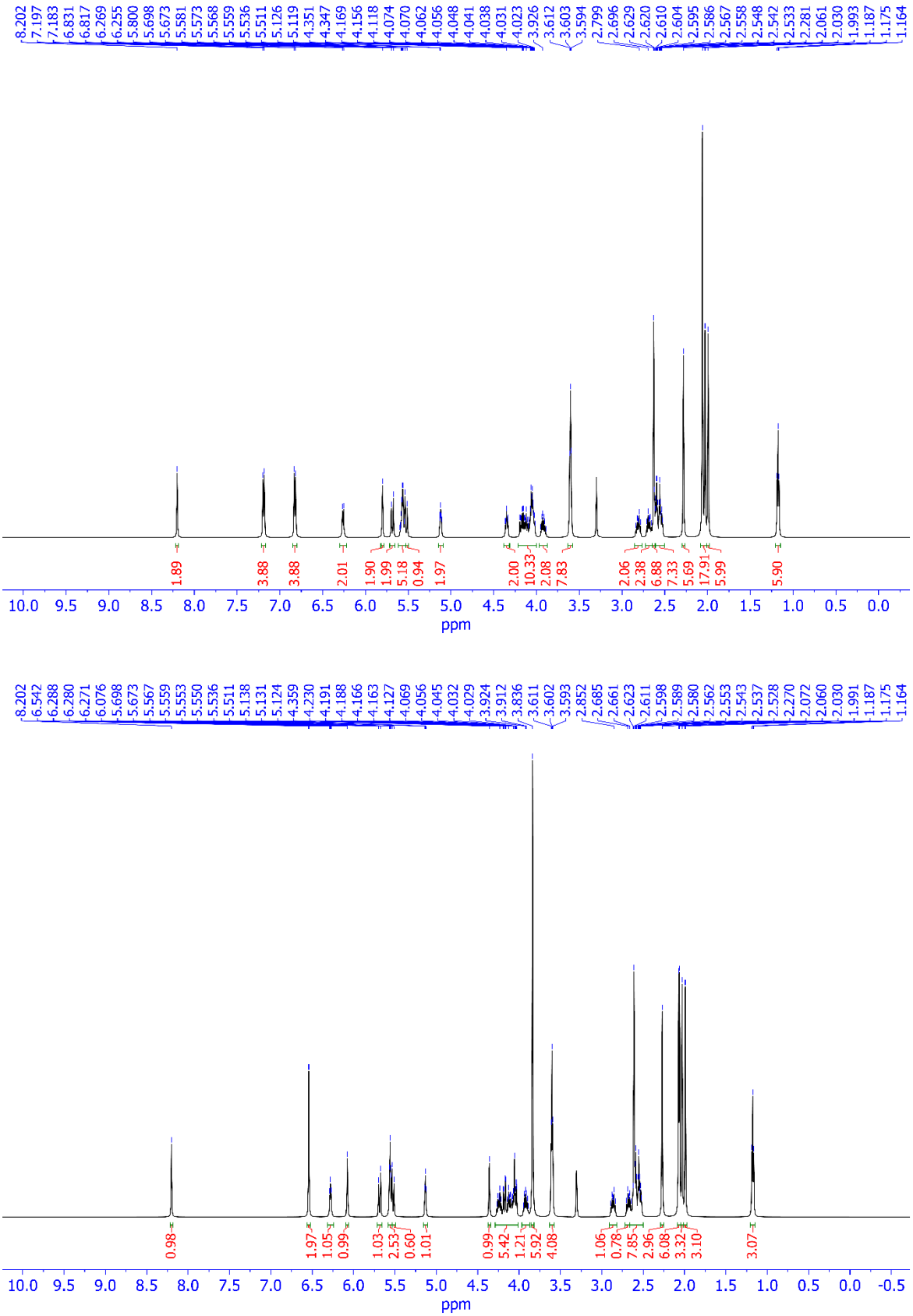
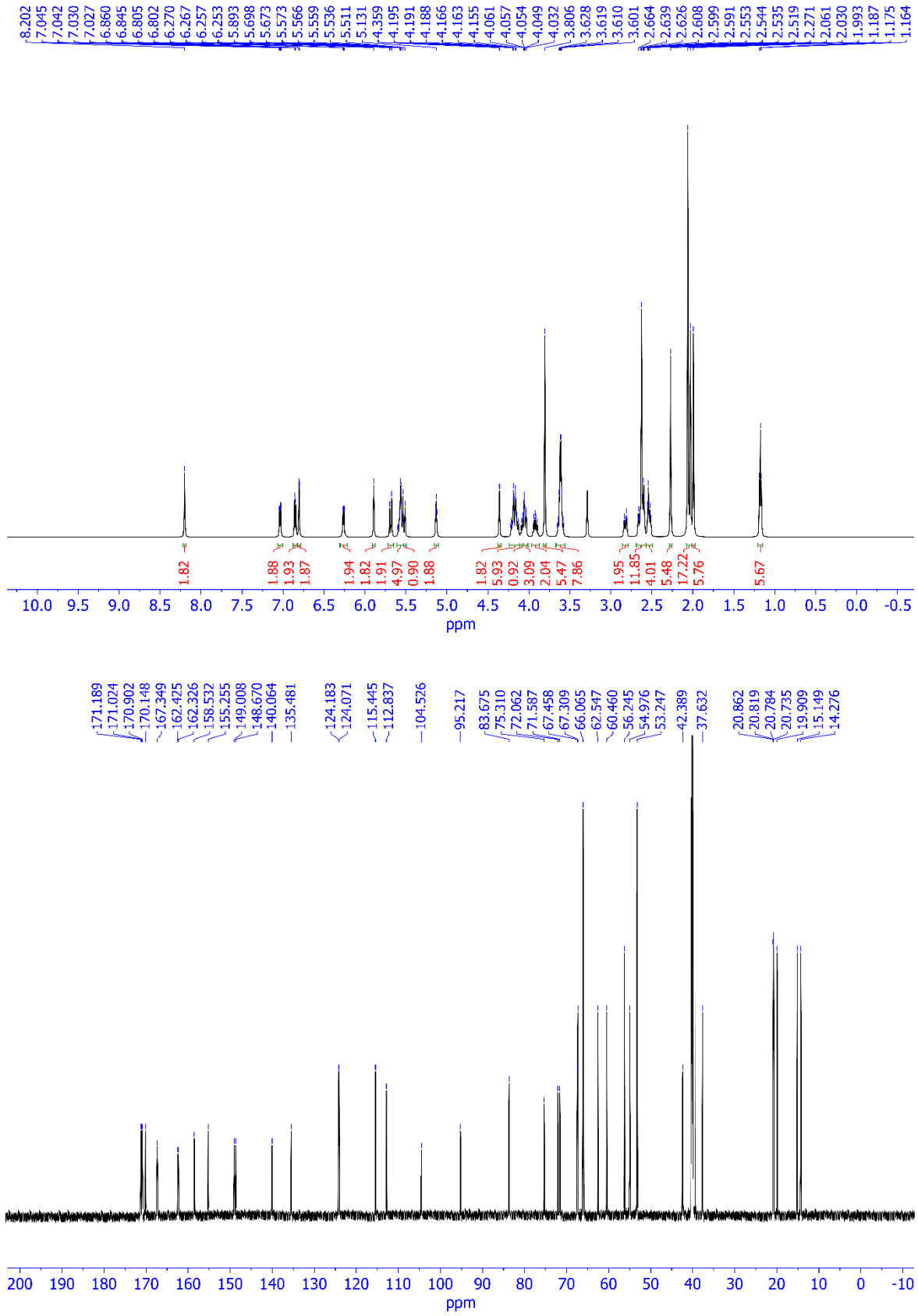
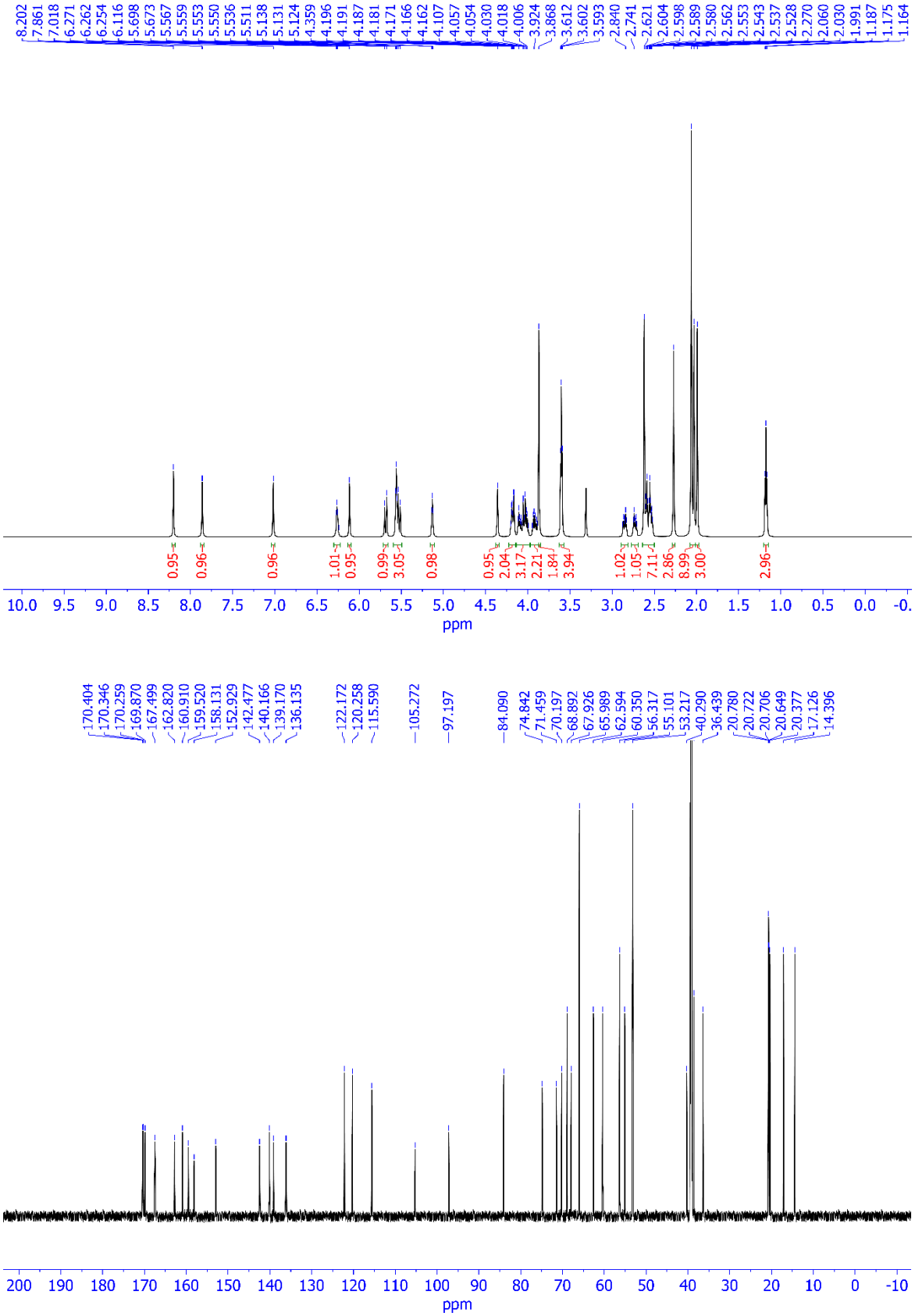


*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**13e**)*



*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3-methoxy-4-(2-morpholinoethoxy)-5-nitrophenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**13f**)*



*Ethyl 3-(1-((2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl))-1H-1,2,3-triazol-4-yl)methyl-2,7-dimethyl-5-(3-ethoxy-4-(2-morpholinoethoxy)phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylate (**13g**)*