Supporting Information for

Design, synthesis and induced fit docking study of D-glucose-conjugated thioureas containing pyrimidine ring and their inhibition activity against α-amylase, α-glucosidase (ddP-4, PTP1B in treatment for Type II diabetes mellitus

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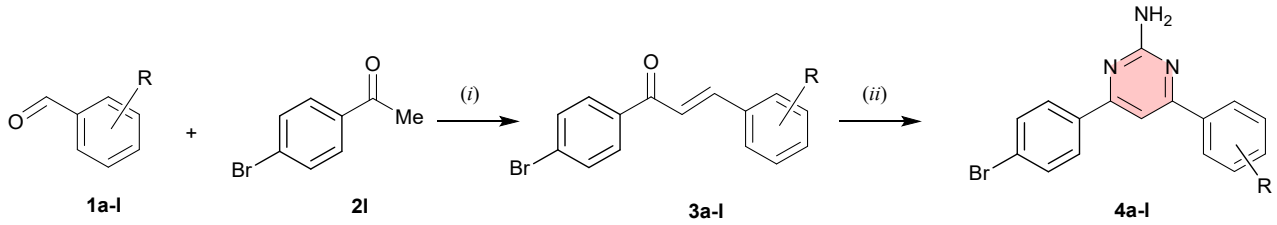
Reaction Scheme



1. General procedure for synthesis of α,β-unsaturated ketones (chalcones) (3a-l)

Appropriate (un)substituted benzaldehydes (**1a-l**, 0.02 mol) was dissolved into 96% ethanol (5 mL), then 4-bromoacetophenone (**2**, 0.02 mol, 3.98 g) was added with stirring. Next, potassium hydroxide solution (that was prepared from 0.84 g KOH in 4 ml of water) was slowly dropped into the stirring reaction mixture while reaction temperature was always kept at about 15-20°C. After that, the reaction mixture was stirred further for 4–5 h at r.t. (controlled by TLC, ethyl acetate/*n*-hexane solvent, ratio of 2: 1 in volume). The solid product was collected by filtration and washed the product thoroughly with cold to neutral reaction. Raw product of yellow or light-yellow colour was obtained. After recrystallization from ethanol or ethanol-toluene mixture (ration of 1:1 in volume) to afford α,β-unsaturated ketone **3a-l** as needle-shaped crystals.[1-4]

1.1. (E)-1-(4-Bromophenyl)-3-phenylprop-2-en-1-one (3a)

From **1** and **2a** (0.02 mol, 3.70 g). Yield: 4.59 g (80%). M.p.: 111−112°C. Ref:[5] No m.p. data, ref. :[6] 96–98°C.

1.2. (E)-1-(4-Bromophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (3b)

From **1** and **2b** (0.02 mol, 2.48 g). Yield: 4.76 g (78%). M.p.: 99–100°C. Ref.:[7] 89–93°C.

1.3. (E)-1-(4-Bromophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (3c)

From **1** and **2c** (0.02 mol, 2.81 g). Yield: 5.10 g (78%). M.p.: 161−162°C. Ref.:[8] No m.p. data.

1.4. (E)-1-(4-Bromophenyl)-3-(3-chlorophenyl)prop-2-en-1-one (3d)

From **1** and **2d** (0.02 mol, 2.81 g). Yield: 4.95 g (77%). M.p.: 90–91°C. Ref.:[8] No m.p. data.

1.5. (E)-1-(4-Bromophenyl)-3-(2-chlorophenyl)prop-2-en-1-one (3e)

From **1** and **2e** (0.02 mol, 2.81 g). Yield: 4.10 g (62%). M.p.: 69–70°C. Ref.:[9] No m.p. data.

1.6. (E)-1,3-bis(4-bromophenyl)prop-2-en-1-one (3f)

From **1** and **2f** (0.02 mol, 3.70 g). Yield: 4.30 g (75%). M.p.: 166−167°C. Ref.:[10] No m.p. data.

1.7. (E)-1-(4-Bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (3g)

From **1** and **2g** (0.02 mol, 2.40 g). Yield: 4.64 g (77%). M.p.: 81−82°C. Ref.:[11] No m.p. data.

1.8. (E)-1-(4-Bromophenyl)-3-(4-isopropylphenyl)prop-2-en-1-one (3h)

From **1** and **2g** (0.02 mol, 2.96 g). Yield: 5.26 g (80%). M.p.: 86−87°C. Ref.:[8] No m.p. data..

1.9. (E)-1-(4-Bromophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3i)

From **1** and **2i** (0.02 mol, 2.72 g). Yield: 4.44 g (70%). M.p.: 120–121°C. Ref.:[12] No m.p. data.

1.10. (E)-1-(4-Bromophenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (3j)

From **1** and **2j** (0.02 mol, 2.72 g). Yield: 3.93 g (62%). M.p.: 69–70°C. Ref.:[13] No m.p. data.

1.11. (E)-1-(4-Bromophenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (3k)

From **1** and **2k** (0.02 mol, 2.72 g). Yield: 4.50 g (71%). M.p.: 89–90°C. Ref.: [13] No m.p. data.

1.12. (E)-1-(4-Bromophenyl)-3-(4-(dimethylamine)phenyl)prop-2-en-1-one (3l)

From **1** and **2l** (0.02 mol, 2.98 g). Yield: 5.08 g (77%). M.p.: 115–116°C. Ref.:[14] No m.p. data.

2. General procedure for synthesis of 2-(4-bromophenyl)-6-aryl-2-aminopyrimidines (4a-l)

These 2-aminopyrimidines were obtained from corresponding chalcone by its reaction with guanidine hydrochloride in 96% ethanol in the presence of NaOH as base (Scheme 1) using three different procedures were studied, including **Procedure A** (using conventional heating method, with solid NaOH in 96% EtOH under reflux conditions for 12−14 h), **Procedure B** (using microwave-assisted heating method under reflux conditions), with solid NaOH in 96% EtOH for 7–9 min), and **Procedure C** (using microwave-assisted heating solvent-free method with solid NaOH for 15–18 min, *see* Table 1S in SI). The yields achieved for each procedure were 61–82%, 74–81%, and 68–88%, respectively. From the data in Table 1S, we see that Proc. B could be considered the

optimal procedure for synthesizing substituted 2-aminopyrimidines **4a-l**.

Table 1S. Synthesis of substituted 2-amino-4-(4bromophenyl)-6-arylpyrimidines (**4a-l**)

Compd.	R	Reaction times[a]			Yields (%)[b]			M.p. (°C)
		Proc. A (h)	Proc. B (min)	Proc. C (min)	Proc. A	Proc. B	Proc. C	
4a	H	12	8	15	70	74	86	171–172
4b	4-F	13	9	17	76	79	76	198–199
4c	4-Cl	13	9	17	82	82	76	219–220
4d	3-Cl	14	9	18	79	81	78	184–185
4e	2-Cl	14	9	15	61	77	56	170–171
4f	4-Br	12	8	16	78	78	68	225–226
4g	4-Me	10	7	15	75	78	77	152–153
4h	4-^{i}Pr	10	7	15	80	81	76	155–156
4i	4-OMe	10	7	15	80	80	77	171–172
4j	3-OMe	10	7	15	77	80	80	182–183
4k	2-OMe	12	8	16	76	77	80	150–151
4l	4-NMe_2	10	7	15	80	80	82	185–186

Notes: **Procedure A** (using conventional heating method): solid NaOH (7.5 mmol), 96% EtOH (20 mL), under reflux for 10–14 h; **Procedure B** (using microwave-assisted heating method): solid NaOH (7.5 mmol), 96% EtOH (5 mL), under reflux for 7–9 min; **Procedure C** (using microwave-assisted heating method under solvent-free conditions): solid NaOH (7.5 mmol), 15–18 min; [b] Isolated yields.

Procedure A: Using conventional heating method under reflux

Appropriate chalcone (**3a-l**, 5 mmol) was dissolved in 96% ethanol (20 mL) then guanidine hydrochloride (7.5 mmol, 0.7 g) and solid NaOH (22.5 mol, 0.9 g) were added to this solution. The reaction mixture was heated under reflux for 10–14 h. The solvent was removed under reduced pressure and water was added. The separated product as a solid was filtered washed with water to a neutral reaction. Recrystallization from ethanol/toluene mixture (1: 1 by volume) to afford the titled 2-(4-bromophenyl)-6-aryl-2-aminepyrrimidines (**-a-l**).[15]

Procedure B: Using microwave-assisted heating method under reflux conditions

A reaction mixture of appropriate substituted benzylideneacetophenones (**3a-l**, 5 mmol), guanidine hydrochloride (7.5 mmol) and sodium hydroxide (22.5 mmol) were mixed carefully in 96% ethanol

(5 mL). Then, the reaction mixture was heated under microwave-assisted for 7–9 min, the reaction mixture had become dark-yellow. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then triturated with water and the formed precipitate was filtered by suction and washed with water until neutral to afford the titled compounds **4a-l**, recrystallized from 1: 1 EtOH-toluene to give ivory-white crystals.

Procedure C: Using microwave-assisted heating method under solvent-free conditions

A reaction mixture of appropriate substituted benzylideneacetophenones (**3a-l**, 5 mmol), guanidine hydrochloride (7.5 mmol) and sodium hydroxide (22.5 mmol) were mixed carefully with a little water so that the gelatinous mass is received. Then, the reaction mixture was heated under microwave-assisted conditions for 15–18 min, the reaction mixture had become dark-yellow. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then triturated with water and the formed precipitate was filtered by suction and washed with water until neutral to afford the titled compounds **4a-l**, recrystallized from 1: 1 EtOH-toluene to give ivory-white crystals.

2.1. 4-(4-Bromophenyl)-6-phenylpyrimidin-2-amine (4a)

From (*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (**3a**, 5 mmol, 1.19 g). M.p.: 171–172°C. Yield: 1.14 g (70%, Proc. A), 1.21 g (74%, Proc. B), 1.40 g (86%, Proc. C), 1.12 g (69%, QTA2-3). ^{13}C NMR (500 MHz, DMSO-d_6), δ (ppm): 8.22–8.21 (m, 2H, H-3′ & H-5′ phenyl), 8.18 (d, J = 8.5 Hz, 2H, H-3″ & H-5″ phenyl), 7.72 (d, J = 8.5 Hz, 2H, H-2″ & H-4″ phenyl), 7.71 (s, 1H, H-5 pyrimidine), 7.53–7.51 (m, 3H, H-2′, H-4′ & H-6′ phenyl), 6.76 (s, 2H, 2-NH_2 amine); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm):(ppm): 162.10, 158.56, 158.54, 136.34, 132.10, 131.46, 129.51, 128.74, 127.79, 127.50, 121.76, 108.35.

2.2. 4-(4-Bromophenyl)-6-(4-fluorophenyl)pyrimidin-2-amine (4b)

From (*E*)-1-(4-bromophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**3b**, 5 mmol, 1.53 g). M.p.: 198-199ºC. Yield: 1.37 g (76%, Proc. A), 1.42 g (79%, Proc. B), 1.37 g (76%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.29 (dd, J = 9.0 Hz, J_{HF} =5.5, 2H, H-2″ phenyl & H-6″ phenyl), 8.20 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 7.74 (s, 1H, H-5 pyrimidine), 7.72 (t, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.35 (t, J = 8.5 Hz, 2H, H-3″ & H-5″ phenyl), 6.79 (s, 2H, 2-NH_2 amine); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 164.65, 162.63, 162.13, 159.11, 158.56, 131.95, 131.50, 129.93, 129.90, 128.13, 128.07, 127.79, 121.84, 115.72, 115.56, 108.38.

2.3. 4-(4-Bromophenyl)-6-(4-chlorophenyl)pyrimidin-2-amine (4c)

From (*E*)-1-(4-bromophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**3c**, 5 mmol, 1.16 g). M.p.: 219–222°C. Yield: 1.48 g (82%, Proc. A), 1.48 g (82%, Proc. B), 1.37 g (76%, Proc. C). ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 8.25 (d, J = 8.5 Hz, 2H, H-2″ & H-6″ phenyl), 8.18 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 7.72 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.59 (s, 1H, H-5 pyrimidine), 7.58 (d, J = 8.5 Hz, 2H, H-3″ & H-5″ phenyl), 6.82 (s, 2H, 2-NH_2 amine); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.13, 158.61, 158.06, 135.90, 131.91, 131.52, 131.43, 128.79, 128.68, 127.80, 121.90, 108.38.

2.4. 4-(4-Bromophenyl)-6-(3-chlorophenyl)pyrimidin-2-amine (4d)

From (*E*)-1-(4-bromophenyl)-3-(3-chlorophenyl)prop-2-en-1-one (**3d,** J = 5 mmol, 1.16 g). M.p.: 184–185°C. Yield: 1.42 g (79%, Proc. A), 1.46 g (81%, Proc. B), 1.40 g (78%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.31–8.30 (m, 1H, H-2″ phenyl), 8.22–8.19 (m, 1H, H-6″ phenyl), 8.21 (d, J = 9.0 Hz, 2H, H-2′ & H-6′ phenyl), 7.81 (s, 1H, H-5 pyrimidine), 7.73 (d, J = 9.0 Hz, 2H, H-3′ & H-5′ phenyl), 7.59–7.54 (m, 2H, H-4″ & H-5″ phenyl), 6.86 (s, 2H, 2-NH_2 amine); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.19, 158.46, 158.07, 134.82, 132.90, 131.91, 131.52, 129.66, 128.98, 127.80, 126.79, 125.27, 121.90, 108.89.

2.5. 4-(4-Bromophenyl)-6-(2-chlorophenyl)pyrimidin-2-amine (4e)

From (*E*)-1-(4-bromophenyl)-3-(3-chlorophenyl)prop-2-en-1-one (**3e**, 5 mmol, 1.16 g). M.p.: 170–171°C. Yield: 1.10 g (61%, Proc. A), 1.39 g (77%, Proc. B), 1.00 g (56%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.07 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 7.71 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.61–7.57 (m, 2H, H-3″ & H-6″ phenyl), 7.49–7.46 (m, 2H, H-4″ & H-5″ phenyl), 7.34 (s, 1H, H-5 pyrimidine), 6.89 (s, 2H, 2-NH_2 amine); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.68, 158.74, 158.65, 133.38, 133.05, 131.78, 131.52, 130.87, 128.93, 128.84, 127.80, 126.81, 121.90, 108.80.

2.6. 4,6-bis(4-Bromophenyl)pyrimidin-2-amine (4f)

From (*E*)-1-bis(4-bromophenyl)prop-2-en-1-one (**3f**, 5 mmol, 1.83 g). M.p.: 225–226°C. Yield: 1.58 g (78%, Proc. A), 1.58 g (78%, Proc. B), 1.38 g (68%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.18 (d, J = 8.5 Hz, 4H, H-2′, H-6′ & H-2″, H-6″ phenyl), 7.76 (s, 1H, H-5 pyrimidine), 7.73 (d, J = 8.5 Hz, 4H, H-3′, H-5′ & H-3″, H-5″ phenyl), 6.83 (s, 2H, 2-NH_2 amine); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.13, 158.95, 132.01, 131.43, 128.00, 121.78, 108.38.

2.7. 4-(4-Bromophenyl)-6-(4-methylphenyl)pyrimidin-2-amine (4g)

From (*E*)-1-(4-bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**3g**, 5 mmol, 1.51 g). M.p.: 152–153°C. Yield: (80%, Proc. A), (80%, Proc. B), (82%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.18 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 8.13 (d, J = 8.0, 2H, H-2″ & H-6″ phenyl), 7.71 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.70 (s, 1H, H-5 pyrimidine), 7.32 (d, J = 8.0 Hz, 2H, H-3″ & H-5″ phenyl), 6.74 (s, 2H, 2-NH_2 amine), 2.37 (s, 2H, 4″-CH_3 phenyl); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.13, 158.56, 158.45, 140.37, 131.95, 131.55, 131.50, 128.96, 128.06, 127.79, 121.59, 108.31, 21.23.

2.8. 4-(4-Bromophenyl)-6-(4-isopropylphenyl)pyrimidin-2-amine (4h)

From (*E*)-1-(4-bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**3h**, 5 mmol, 1.64 g). M.p.: 155–156°C. Yield: 1.47 g (80%, Proc. A), 1.49 g (81%, Proc. B), 1.40 g (76%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.17 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 8.14 (d, J = 8.25 Hz, 2H, H-2″ & H-6″ phenyl), 7.72 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.69 (s, 1H, H-5 pyrimidine), 7.38 (d, J = 8.25 Hz, 2H, H-3″ & H-5″ phenyl), 6.74 (s, 2H, 2-NH_2 amine), 2.96 [septet, J = 7.75 Hz, 1H, 4″-**CH**$(CH_3)_2$ phenyl], 1.24 [d, J = 7.75 Hz, 6H, 4″-CH**$(CH_3)_2$** phenyl]; ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 161.79, 157.31, 157.29, 147.18, 132.32, 132.25, 131.46, 128.46, 127.97, 125.61, 121.73, 108.47, 33.75, 23.93.

2.9. 4-(4-Bromophenyl)-6-(4-methoxyphenyl)pyrimidin-2-amine (4i)

From (*E*)-1-(4-bromophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**3i**, 5 mmol, 1.59 g). M.p.: 171–172°C. Yield: 1.42 g (80%, Proc. A), 1.42 g (80%, Proc. B), 1.37 g (77%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.20 (d, J = 8.5 Hz, 2H, H-2″ & H-6″ phenyl), 8.17 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 7.71 (d, J = 8.5 Hz, 2H, H-3″ & H-5″ phenyl), 7.68 (s, 1H, H-5 pyrimidine), 7.06 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 6.69 (s, 2H, 2-NH_2 amine), 3.84 (s, 3H, 4′- OCH_3 phenyl); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.13, 159.13, 158.44, 158.06, 132.00, 131.46, 128.62, 128.19, 127.80, 121.90, 114.00, 108.80, 55.33.

2.10. 4-(4-Bromophenyl)-6-(3-methoxyphenyl)pyrimidin-2-amine (4j)

From (*E*)-1-(4-bromophenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (**3j**, 5 mmol, 1.59 g). M.p.: 182–183°C. Yield: 1.37 g (77%, Proc. A), 1.42 g (80%, Proc. B), 1.42 g (80%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.19 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 7.80 (d, J = 7.5 Hz, 1H, H-6″ phenyl), 7.76 (d, J = 2.5 Hz, 1H, H-2″ phenyl), 7.73 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.72 (s, 1H, H-5 pyrimidine), 7.43 (t, J = 7.5 Hz, 1H, H-5″ phenyl), 7.09 (dd, J = 2.5, 8.0 Hz, 1H, H-4″ phenyl), 6.78 (s, 2H, 2-NH_2 amine), 3.85 (s, 3H, 3″-OCH_3 phenyl); ^{13}C NMR (125 MHz,

DMSO-d_6), δ (ppm): 162.19, 160.00, 158.69, 158.46, 132.30, 132.00, 131.46, 129.53, 127.80, 121.95, 121.90, 114.43, 111.09, 108.95, 55.31.

2.11. 4-(4-Bromophenyl)-6-(2-methoxyphenyl)pyrimidin-2-amine (4k)

From (*E*)-1-(4-bromophenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**3k**, 5 mmol, 1.59 g). M.p.: 150–151ºC. Yield: 1.35 g (76 %, Proc. A), 1.37 g (77%, Proc. B), 1.42 g (80%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 7.86 (m, 2H, H-2′ & H-6′ phenyl), 7.77 (s, 1H, H-5 pyrimidine), 7.68 (dd, J = 1.5, 7.5 Hz, 1H, H-6″ phenyl), 7.58 (m, 2H, H-3′ & H-5′ phenyl), 7.38 (td, J = 1.5, 7.5 Hz, 1H, H-4″ phenyl), 7.14 (td, J = 1.5, 7.5 Hz, 1H, H-5″ phenyl), 7.10 (d, J = 7.5 Hz, 1H, H_a in NH_2 amine), 6.90 (dd, J = 1.5, 7.5 Hz, 1H, H-3″ phenyl), 6.08 (d, J = 7.5 Hz, 1H, H_a in NH_2 amine), 3.84 (s, 4′- OCH_3 phenyl); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 162.31, 159.43, 158.14, 156.51, 131.78, 131.46, 130.98, 128.81, 127.80, 124.56, 121.90, 120.79, 113.86, 108.60, 55.75.

2.12. 4-(4-Bromophenyl)-6-(4-(dimethylamino)phenyl)pyrimidin-2-amine (4l)

From (*E*)-1-(4-bromophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (**3l**, 5 mmol, 1.65 g). M.p.: 185–186°C. Yield: 1.48 g (80%, Proc. A), 1.48 g (80%, Proc. B), 1.52 g (82%, Proc. C). NMR (500 MHz, DMSO-d_6), δ (ppm): 8.15 (d, J = 8.5 Hz, 2H, H-2′ & H-6′ phenyl), 8.10 (d, J = 8.75 Hz, 2H, H-2″ & H-6″ phenyl), 7.70 (d, J = 8.5 Hz, 2H, H-3′ & H-5′ phenyl), 7.59 (s, 1H, H-5 pyrimidine), 6.78 (d, J = 8.75 Hz, 2H, H-3″ & H-5″ phenyl), 6.55 (s, 2H, 2-NH_2 amine), 3.00 [s, 6H, 4″-$N(CH_3)_2$ phenyl]; ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 161.79, 157.86, 157.31, 151.48, 132.25, 131.46, 128.47, 128.22, 127.97, 121.73, 112.08, 108.47, 40.26.

3. General procedure for synthesis of 4,6-diarylpyrimidine thioureas (8a-l)

Two synthesis procedures were applied (*see* Table 2S) for synthesis of these thioureas. In **Procedure D**, dioxan was used as solvent (10 mL for 1 mmol of each reagent, including 4 and 7) and the reaction was carried out under conventional heating method. The solvent-free microwave-assisted conditions were applied in Procedure E. In the refluxing cases (Proc. D), appropriate 2-aminopyrimidines **4a-l** and peracetylated glucopyranosyl isothiocyanate **7** were dissolved in anhydrous dioxane. Then, the reaction mixture was heated under refluxing for 14–16 h. Thioureas **8a-l** were obtained with yields of 54–76%. In MW irradiation cases (Proc. E), reaction mixture of appropriate 2-aminopyrimidines **4a-l** and peracetylated glucopyranosyl isothiocyanate **7** was grinded to mix together, and any solvent wasn't used. The solid reaction mixture obtained then was irradiated under microwave-assisted conditions. After first several minutes (usually, 2–3 min) of microwave irradiation (MWI), the reaction mixture became pasty and this reaction was complete for 3–10 min (Table 1). Thioureas were obtained yields of 67–82%. It showed that the essential

disadvantages of Procedure E were that the reaction time was prolonged (14 h) and the solvent was used in large amount (20 mL for 4 mmol of reactants). Meanwhile, the advantage of Procedure F was higher product yields with shorter reaction time, in addition, the green chemistry aspect of this reaction procedure that it carried out without any solvent (i.e., under solvent-free conditions).

Table 2 Synthesis of *N*-(per-*O*-acetyl-β-D-glucopyranosyl)-*N*'-(4,6-diarylpyrimidine-2-yl)thioureas (**8a-l**)

Compd.	R	Reaction times[a]		Yields (%)[b]		M.p. (°C)
		Procedure D (h)	Procedure E (min)	Procedure D	Procedure E	
8a	H	15	5	66	76	223–224
8b	4-F	14	5	76	79	201–202
8c	4-Cl	16	10	76	67	221–222
8d	3-Cl	14	5	76	76	132–133
8e	2-Cl	15	8	59	67	220–221
8f	4-Br	14	3	76	79	232–233
8g	4-Me	15	5	67	80	225–226
8h	4-^{i}Pr	14	3	71	82	218–219
8i	4-OMe	14	3	72	72	195–196
8j	3-OMe	14	3	69	75	226–227
8k	2-OMe	15	3	54	73	253–254
8l	4-NMe_2	15	9	69	80	199–200

[a] **Procedure D**: Dioxan as solvent (10 mL for 1 mmol of each reagent) under conventional heating method; **Procedure E**: under solvent-free microwave-assisted conditions; [b] Isolated yields.

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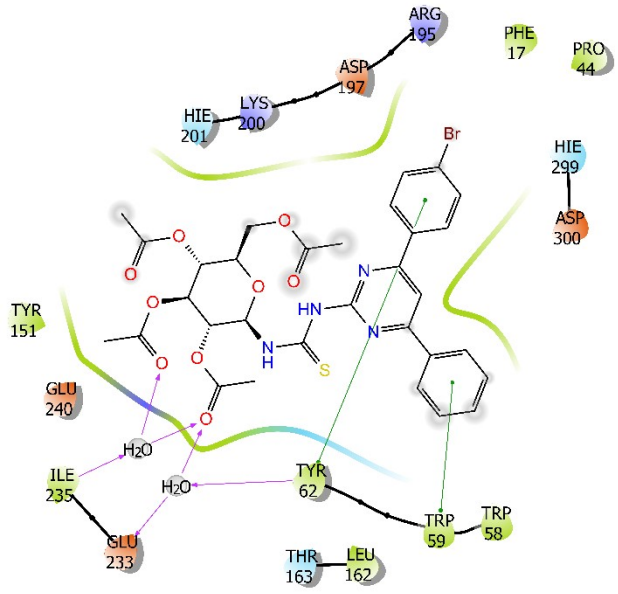
3. Molecular docking study

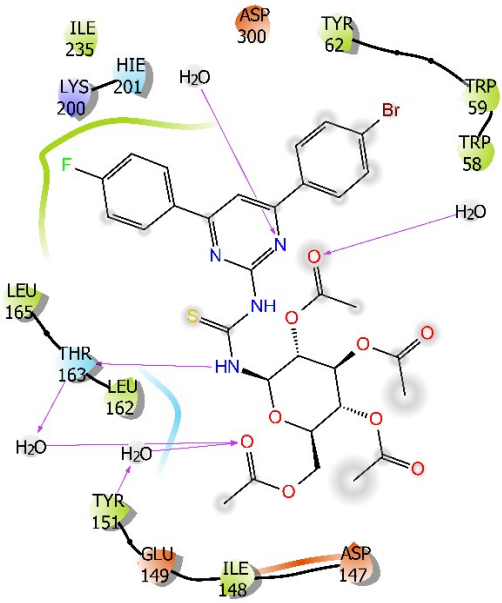
3. Induced fit docking study

3.1. For α-amylase on enzyme 4W93

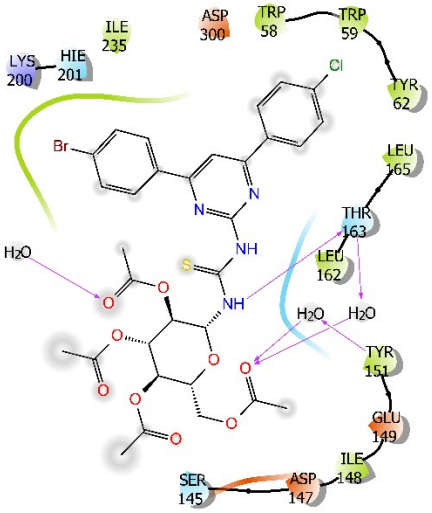
H (**8a**), G_{score} = –8.257 kcal/mol, IC_{50} = 64.32 ± 1.15 µM



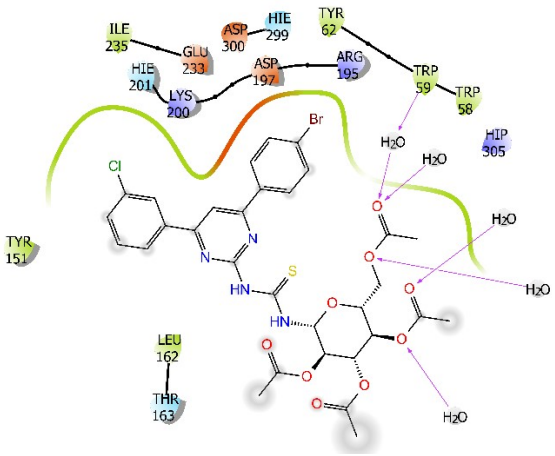
4-F (**8b**), G_{score} = –9.176 kcal/mol, IC_{50} = 18.12 ± 1.12 µM



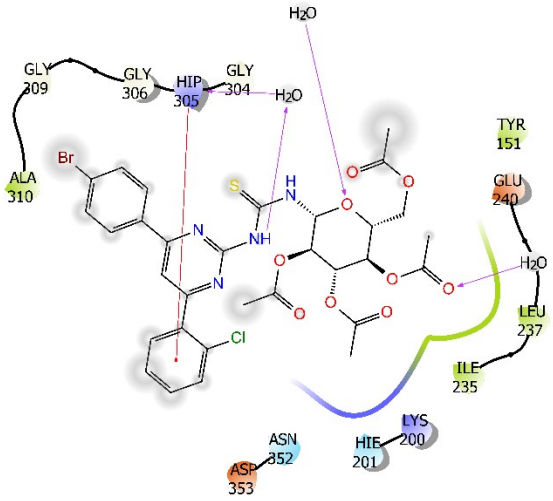
4-Cl (**8c**), G_{score} = –8.984 kcal/mol, IC_{50} = 25.22 ± 1.12 μM



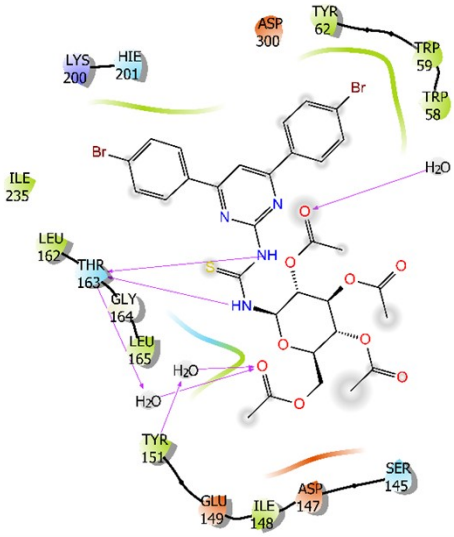
3-Cl (**8d**), G_{score} = –7.853 kcal/mol, IC_{50} = 74.51 ± 1.13 μM



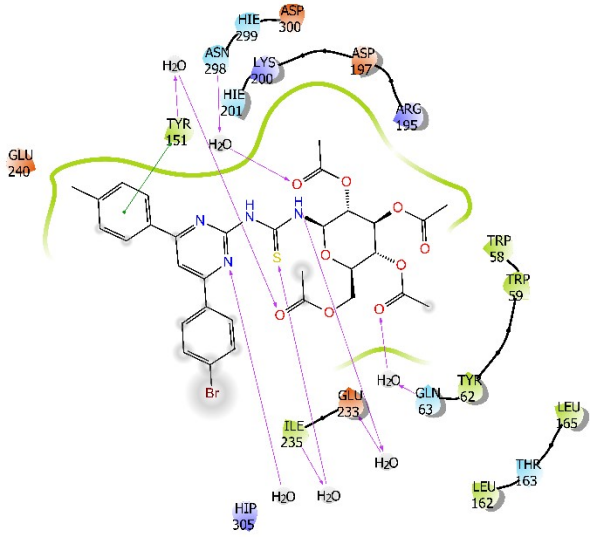
2-Cl (**8e**), G_{score} = –6.913 kcal/mol, IC_{50} = 93.12 ± 1.12 μM



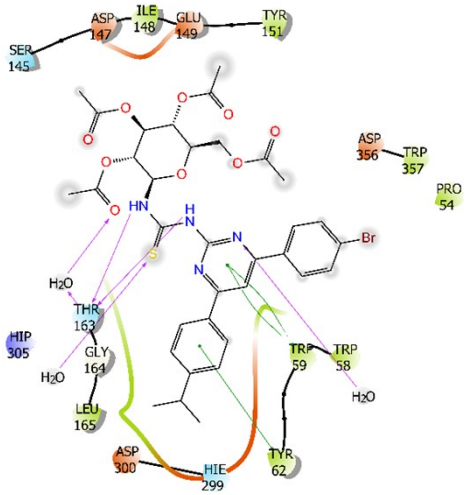
4-Br (**8f**), G_{score} = –9.542 kcal/mol, IC_{50} = 12.15 ± 0.33 μM



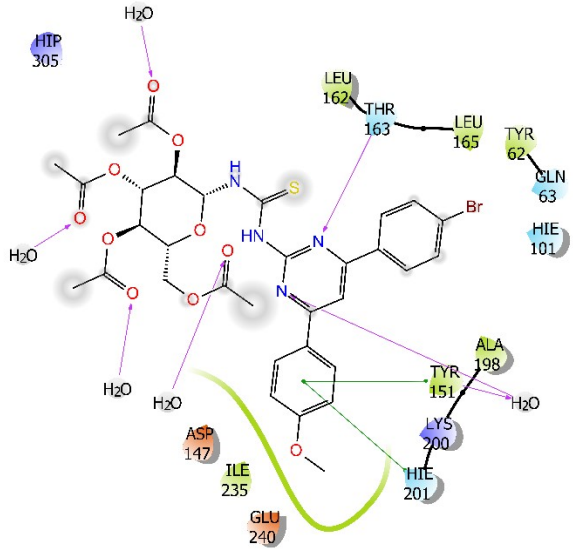
4-Me (**8g**), G_{score} = –8.756 kcal/mol, IC_{50} = 35.12 ± 1.15 μM



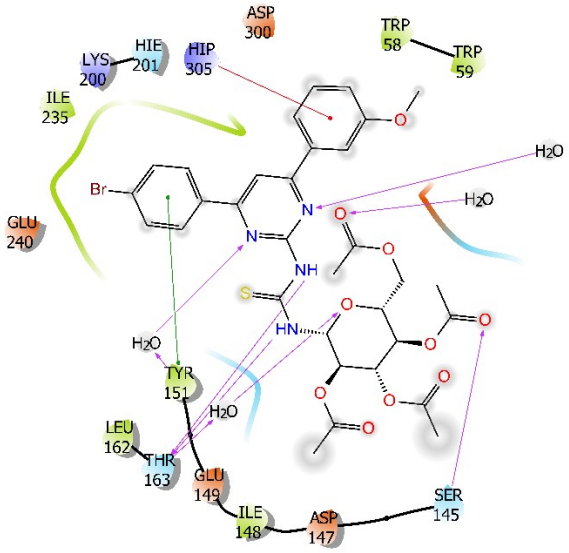
4-^{i}Pr (**8h**), G_{score} = –8.995 kcal/mol, IC_{50} = 24.27 ± 1.12 μM



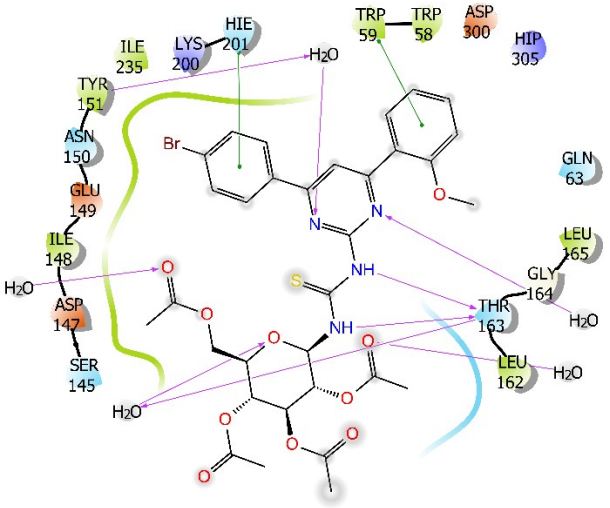
4-OMe (**8i**), G_{score} = –8.916 kcal/mol, IC_{50} = 27.71 ± 1.13 µM



3-OMe (**8j**), G_{score} = –8.437 kcal/mol, IC_{50} = 54.61 ± 1.12 µM



2-OMe (**8k**), G_{score} = –9.815 kcal/mol, IC_{50} = 9.72 ± 0.34 µM



4-NMe_2 (**8l**), G_{score} = –8.979 kcal/mol, IC_{50} = 25.74 ± 1.12 µM

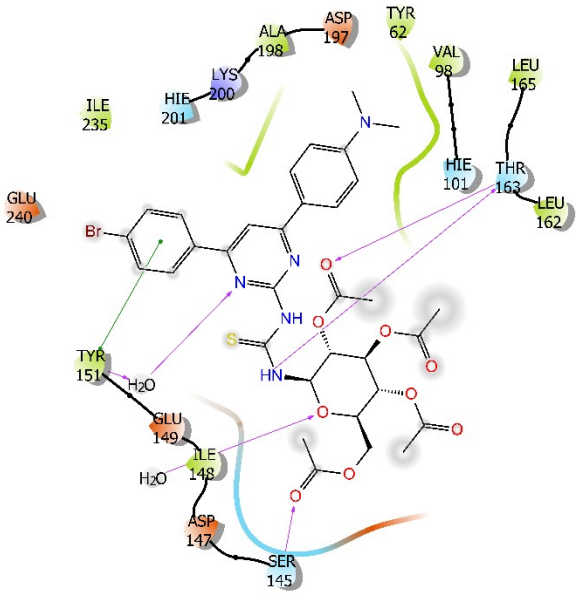


Fig. 1S The mode of interaction in the 2D-presentation of ligand **8a-l** in the active pocket of enzyme 4W93 indicated the H bond, stacking π-π and lipophilic interactions of each ligand corresponding to the residues.

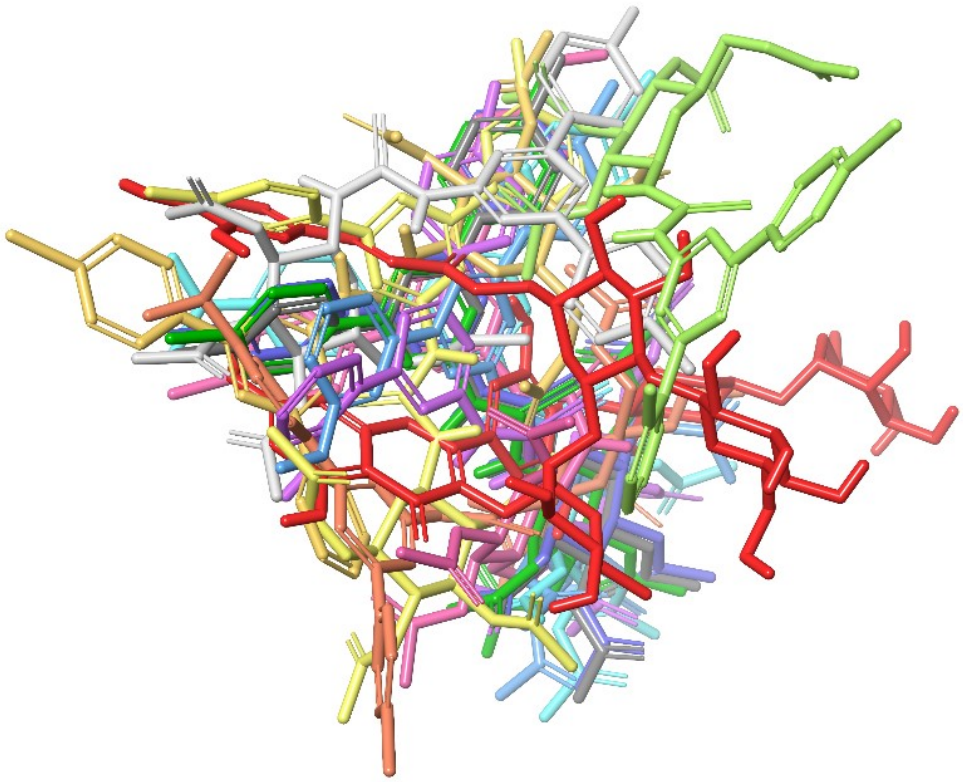
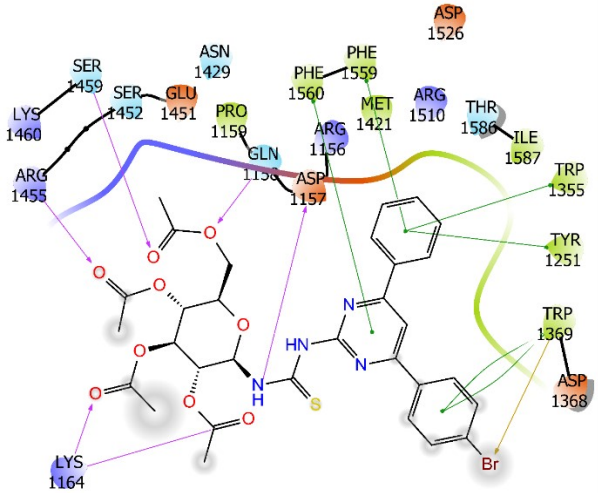


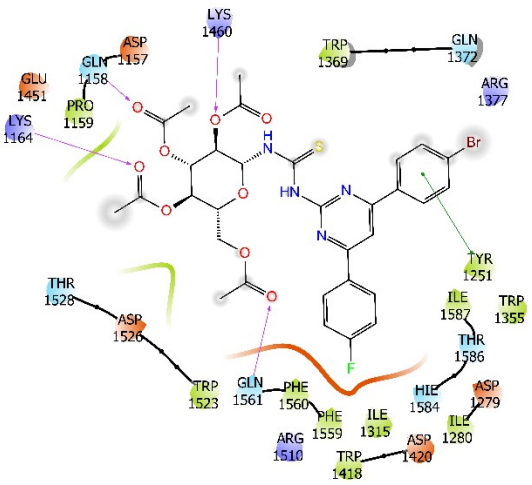
Fig. 2S Superimposing of ligands **8a-l** in active pocket of enzyme 4W93, where, compound **8a** (R=H, faded orange colour), **8b** (R=4-F, blue colour), **8c** (R=4-Cl, dark grey colour), **8d** (R=3-Cl, yellow colour), **8e** (R=2-Cl, faded yellow-green colour), **8f** (R=4-Br, green colour), **8g** (R=4-Me, grey colour), **8h** (R=4-^{i}Pr, faded red-orange colour), **8i** (R=4-OMe, magenta colour), **8j** (R=3-OMe, faded azure colour), **8k** (R=2-OMe, violet colour), **8l** (R=4-NMe_2, cyan colour). Co-crystal, montbretin A, was in red colour.

3.2. For α-glucosidase on enzyme 3TOP

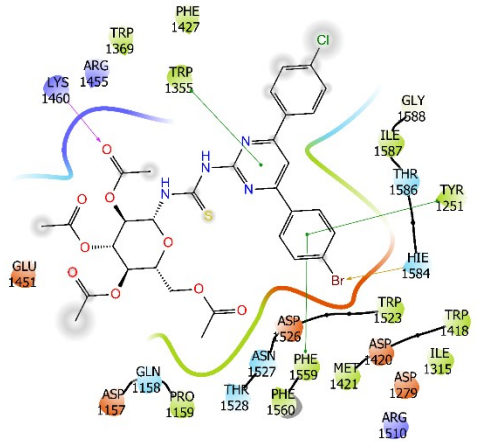
H (**8a**), G_{score} = –9.456 kcal/mol, IC_{50} = 17.52 ± 1.15 µM



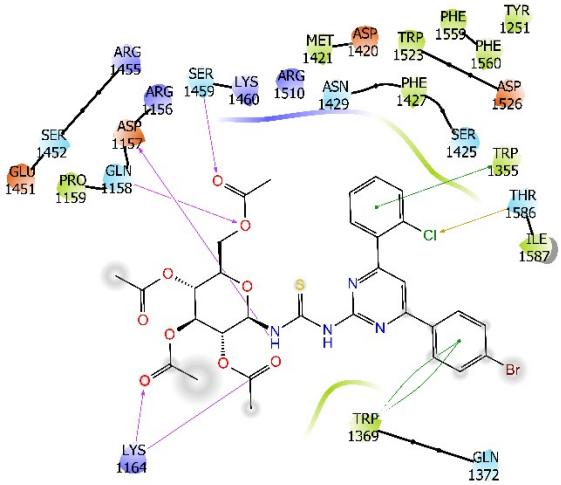
4-F (**8b**), G_{score} = –9.150 kcal/mol, IC_{50} = 27.45 ± 1.12 µM



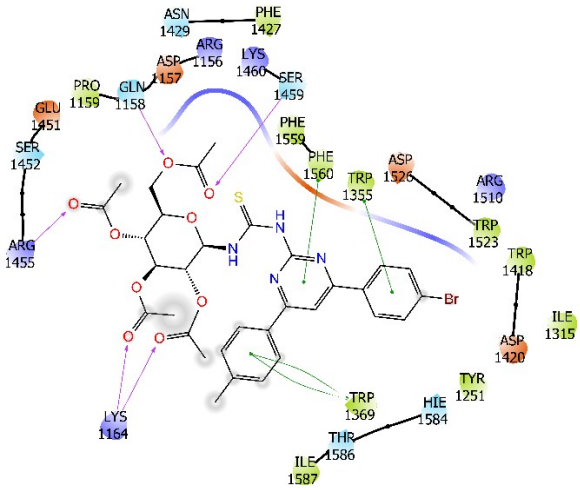
4-Cl (**8c**), G_{score} = –6.929 kcal/mol, IC_{50} = 56.52 ± 1.12 μM



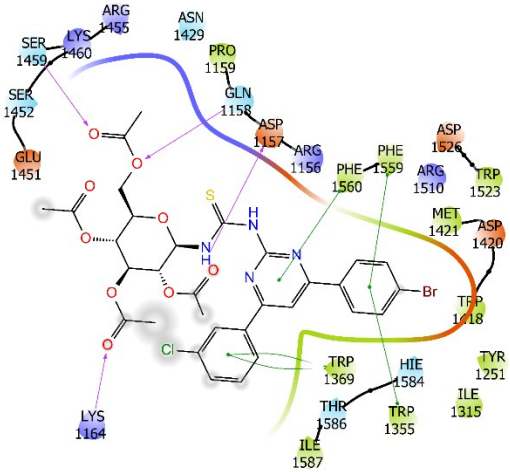
2-Cl (**8e**), G_{score} = –9.911 kcal/mol, IC_{50} = 10.64 ± 0.85 μM



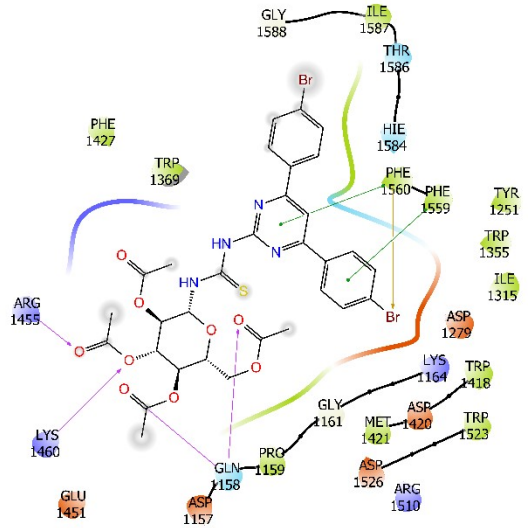
4-Me (**8g**), G_{score} = –8.807 kcal/mol, IC_{50} = 36.52 ± 1.12 μM



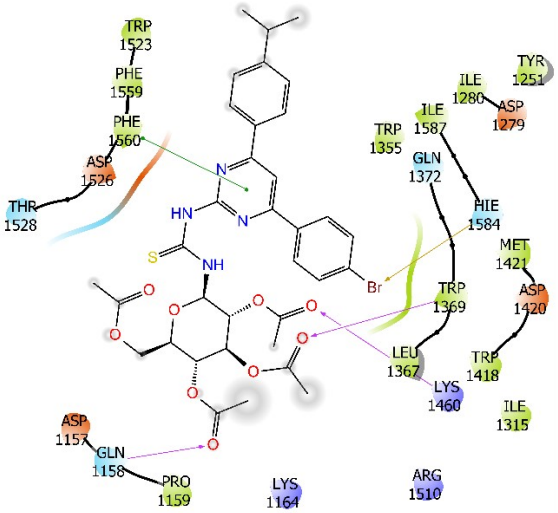
3-Cl (**8d**), G_{score} = –9.730 kcal/mol, IC_{50} = 14.45 ± 0.84 μM



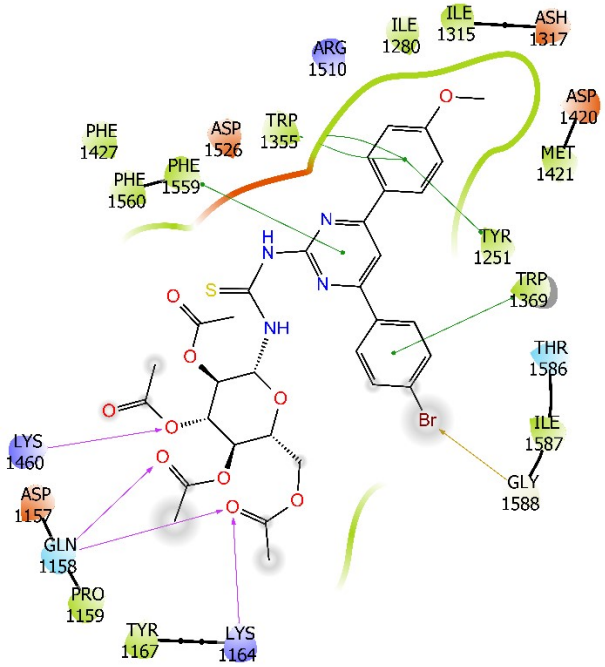
4-Br (**8f**), G_{score} = –9.275 kcal/mol, IC_{50} = 23.62 ± 1.15 μM



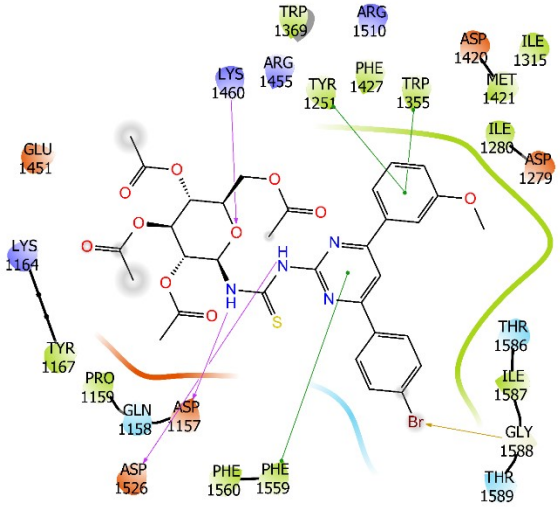
4-^{i}Pr (**8h**), G_{score} = –8.482 kcal/mol, IC_{50} = 47.51 ± 1.12 μM



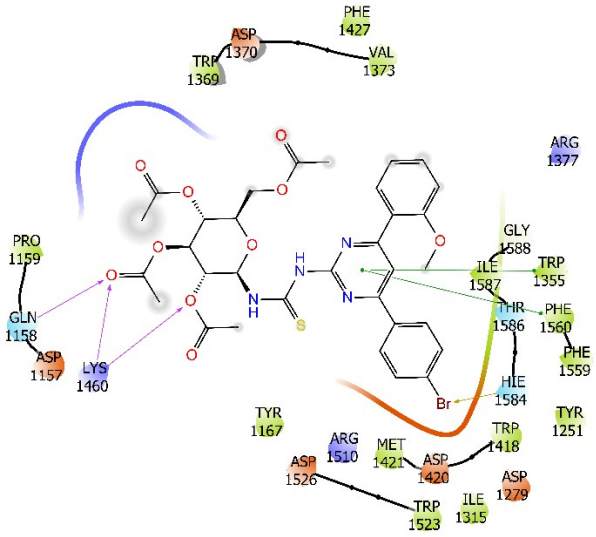
4-OMe (**8i**), G_{score} = –9.929 kcal/mol, IC_{50} = 9.73 ± 0.72 µM



3-OMe (**8j**), G_{score} = –10.175 kcal/mol, IC_{50} = 8.35 ± 0.88 µM



2-OMe (**8k**), G_{score} = –8.667 kcal/mol, IC_{50} = 43.63 ± 1.15 µM



4-NMe$_2$ (**8l**), G_{score} = –9.334 kcal/mol, IC_{50} = 21.16 ± 1.12 µM

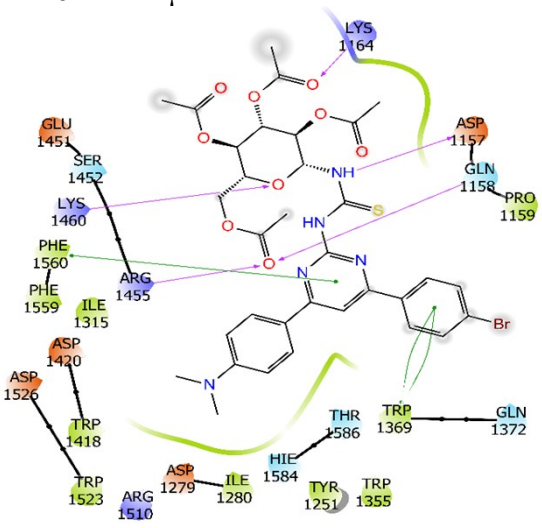


Fig. 3S The mode of interaction in the 2D-presentation of ligand **8a-l** in the active pocket of enzyme 3TOP 4W93 indicated the H bond, stacking π-π and lipophilic interactions of each ligand corresponding to the residues..

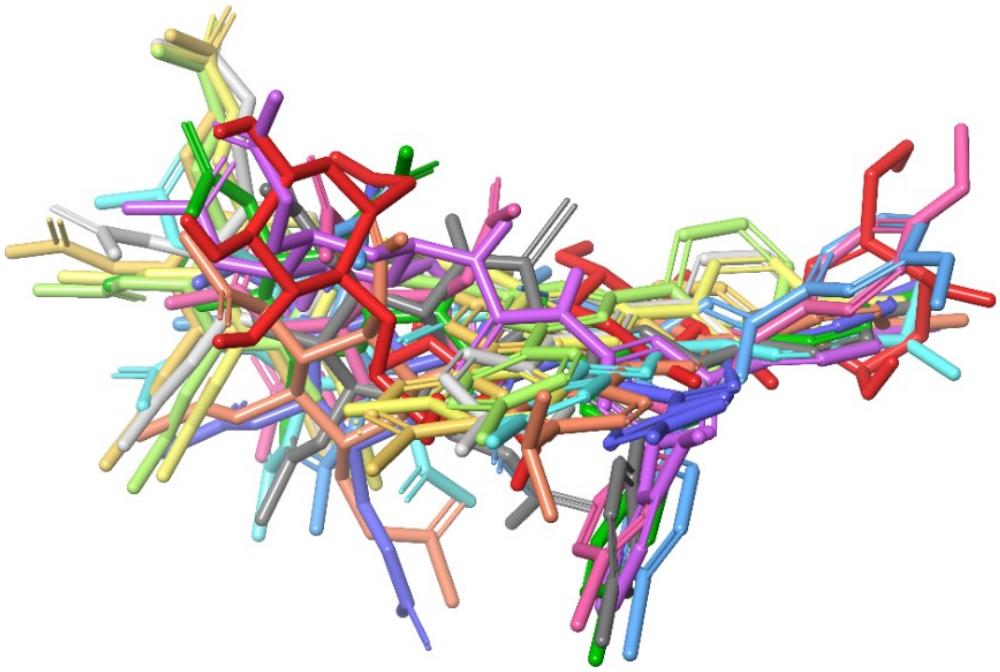
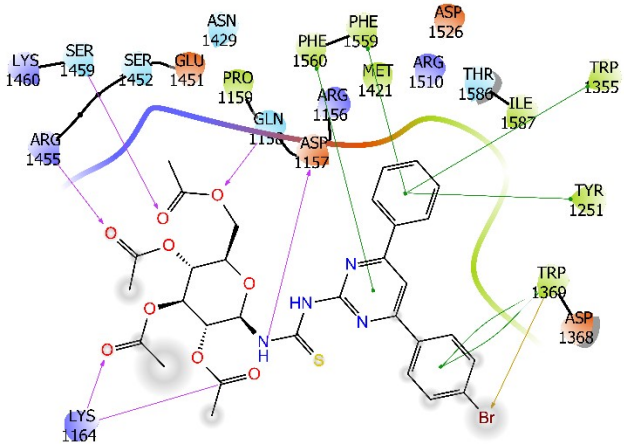


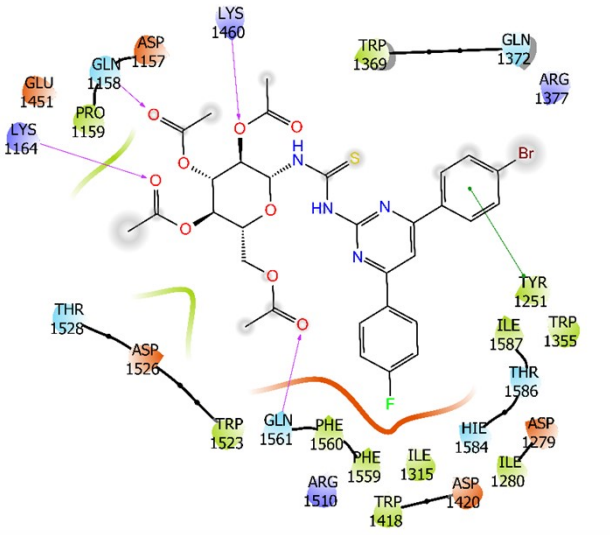
Fig. 4S Superimposing of ligands **8a-l** in active pocket of enzyme 3TOP, where, compound **8a** (R=H, faded orange colour), **8b** (R=4-F, blue colour), **8c** (R=4-Cl, dark grey colour), **8d** (R=3-Cl, yellow colour), **8e** (R=2-Cl, faded yellow-green colour), **8f** (R=4-Br, green colour), **8g** (R=4-Me, grey colour), **8h** (R=4-^{i}Pr, faded red-orange colour), **8i** (R=4-OMe, magenta colour), **8j** (R=3-OMe, faded azure colour), **8k** (R=2-OMe, violet colour), **8l** (R=4-NMe_2, cyan colour). Co-crystal, acarbose was in red colour.

3.3. For dipeptidyl peptidase-4 on enzyme 3W2T

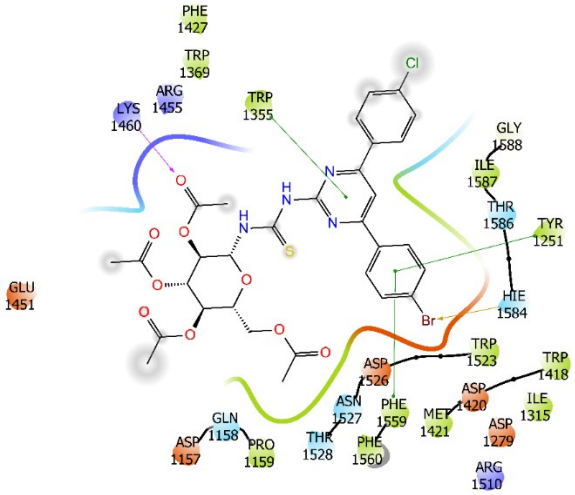
H (**8a**), G_{score} = –7.983 kcal/mol, IC_{50} = 5.52 ± 0.13 µM



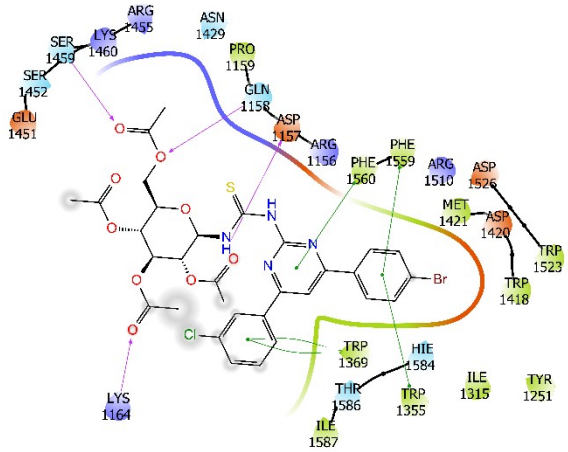
4-F (**8b**), G_{score} = –6.042 kcal/mol, IC_{50} = 45.23 ± 2.32 µM



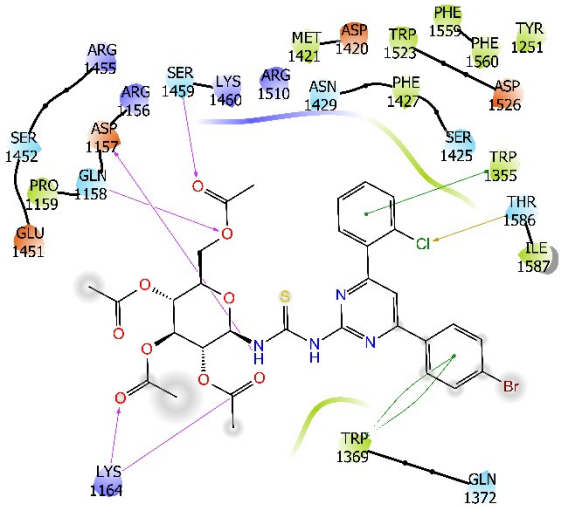
4-Cl (**8c**), G_{score} = –6.940 kcal/mol, IC_{50} = 12.78 ± 0.23 μM



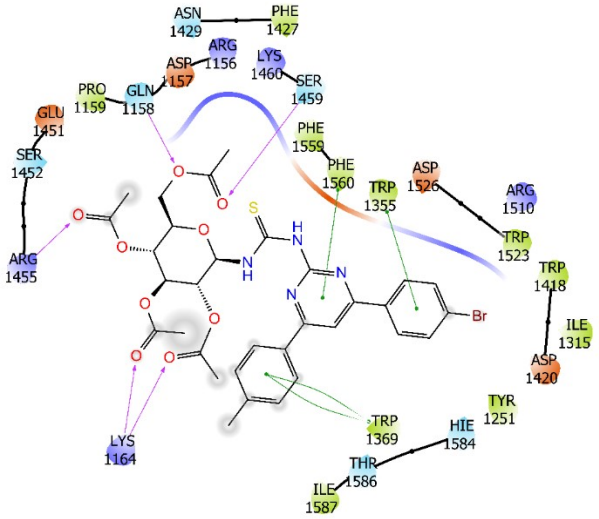
3-Cl (**8d**), G_{score} = –6.895 kcal/mol, IC_{50} = 17.31 ± 0.32 μM



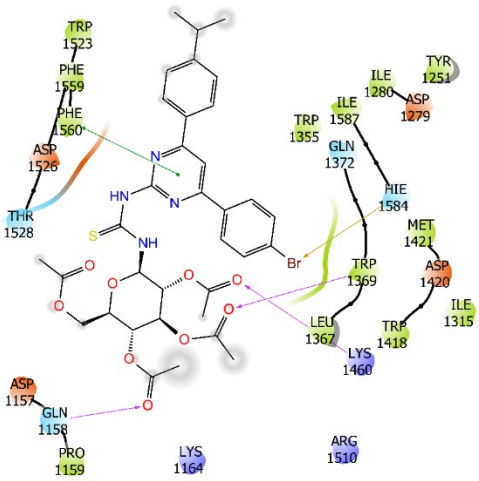
2-Cl (**8e**), G_{score} = –6.594 kcal/mol, IC_{50} = 41.57 ± 2.21 μM



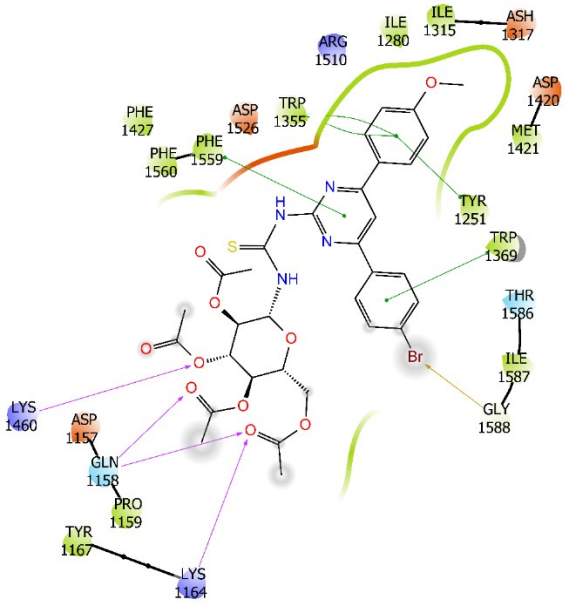
4-Me (**8g**), G_{score} = –9.660 kcal/mol, IC_{50} = 4.62 ± 0.14 μM



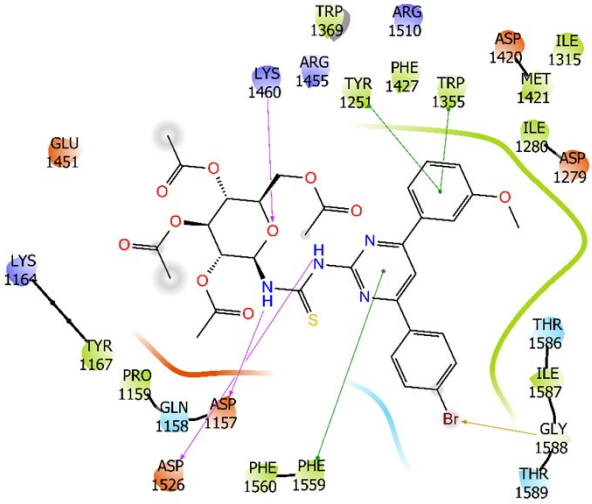
4-^{i}Pr (**8h**), G_{score} = –7.031 kcal/mol, IC_{50} = 8.19 ± 0.14 μM



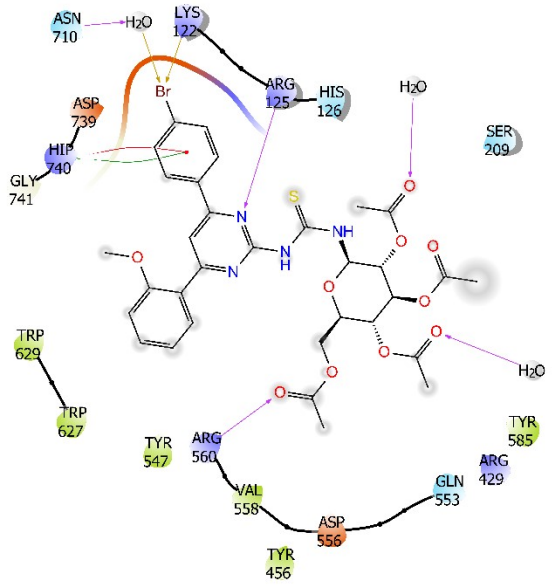
4-OMe (**8i**), G_{score} = –6.611 kcal/mol, IC_{50} = 35.71 ± 0.23 µM



3-OMe (**8j**), G_{score} = –6.704 kcal/mol, IC_{50} = 25.71 ± 0.32 µM



2-OMe (**8k**), G_{score} = –6.727 kcal/mol, IC_{50} = 24.32 ± 0.51 µM



4-NMe$_2$ (**8l**), G_{score} = –5.173 kcal/mol, IC_{50} = 64.27 ± 2.11 µM

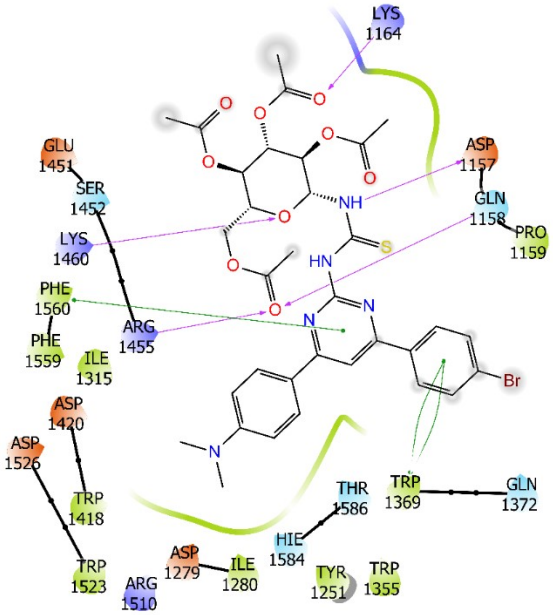


Fig. 5S. The mode of interaction in the 2D-presentation of ligand **8a-l** in the active pocket of enzyme 3W2T 4W93 indicated the H bond, stacking π-π and lipophilic interactions of each ligand corresponding to the residues.

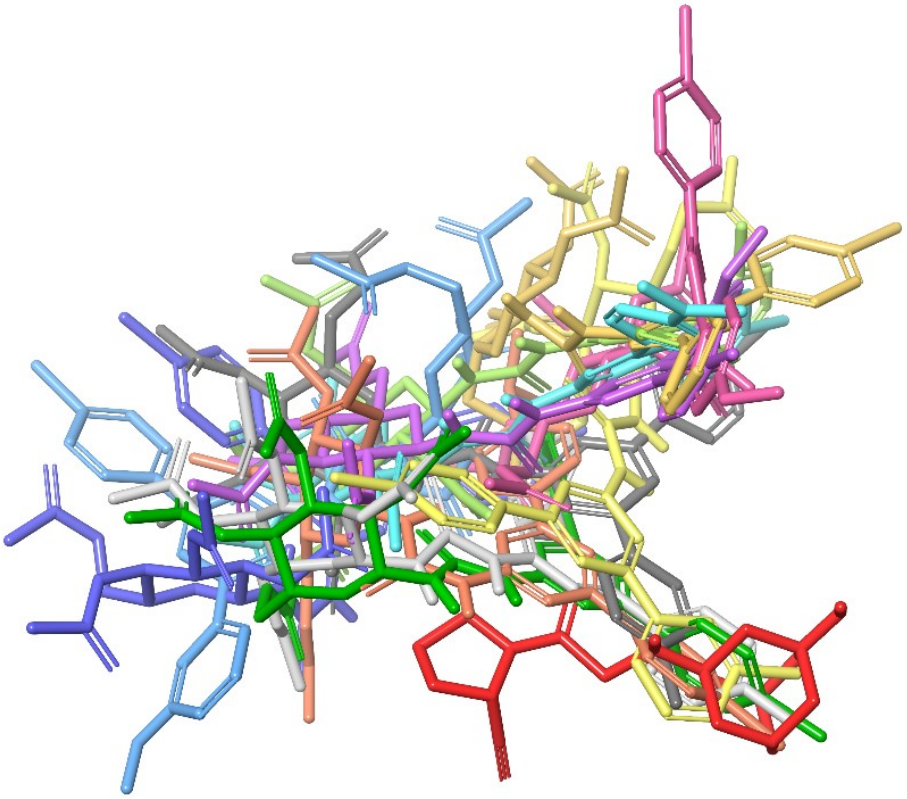
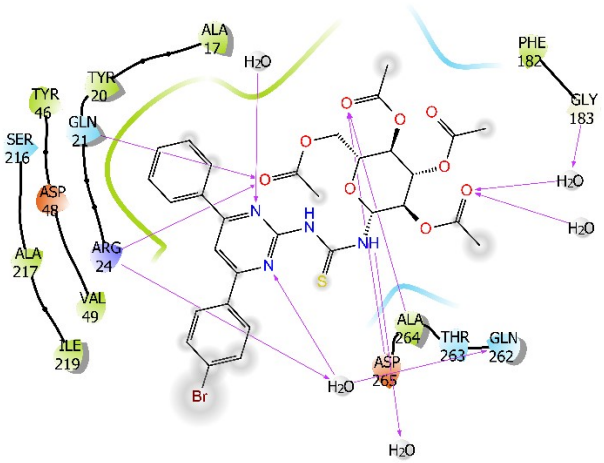


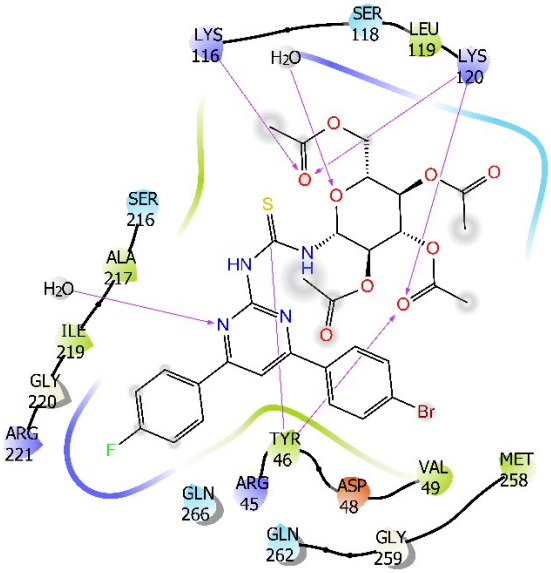
Fig. 6S Superimposing of ligands **8a-l** in active pocket of enzyme 3W2T, where, compound **8a** (R=H, faded orange colour), **8b** (R=4-F, blue colour), **8c** (R=4-Cl, dark grey colour), **8d** (R=3-Cl, yellow colour), **8e** (R=2-Cl, faded yellow-green colour), **8f** (R=4-Br, green colour), **8g** (R=4-Me, grey colour), **8h** (R=4-^{i}Pr, faded red-orange colour), **8i** (R=4-OMe, magenta colour), **8j** (R=3-OMe, faded azure colour), **8k** (R=2-OMe, violet colour), **8l** (R=4-NMe_2, cyan colour). Co-crystal, vildagliptin was in red colour.

3.4. For protein tyrosine phosphatase 1B on enzyme 1NNY

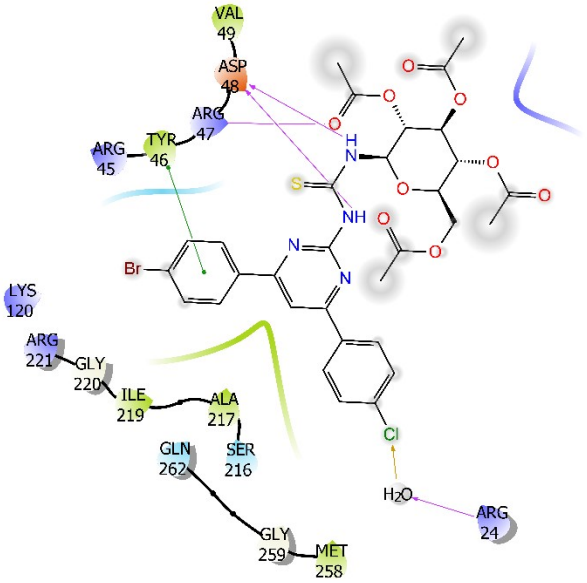
H (**8a**), G_{score} = –8.468 kcal/mol, IC_{50} = 8.72 ± 0.23 µM



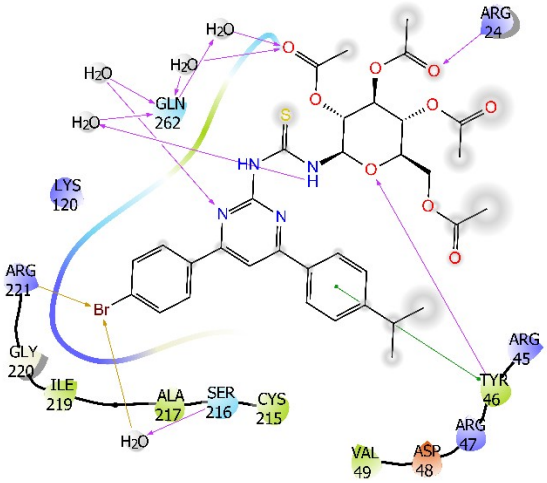
4-F (**8b**), G_{score} = –8.594 kcal/mol, IC_{50} = 7.12 ± 0.14 µM



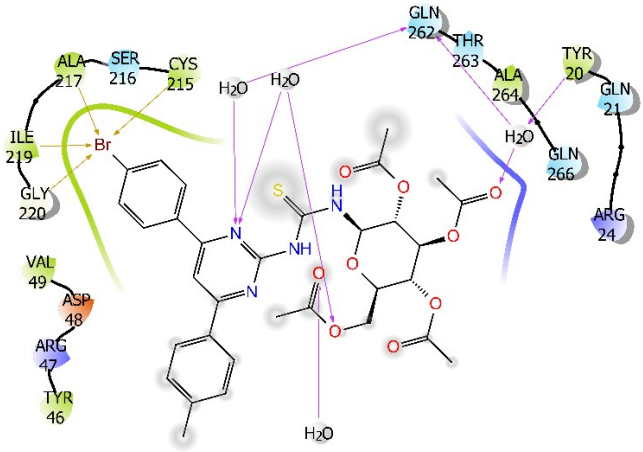
4-Cl (**8c**), G_{score} = –6.483 kcal/mol, IC_{50} = 38.43 ± 1.13 µM



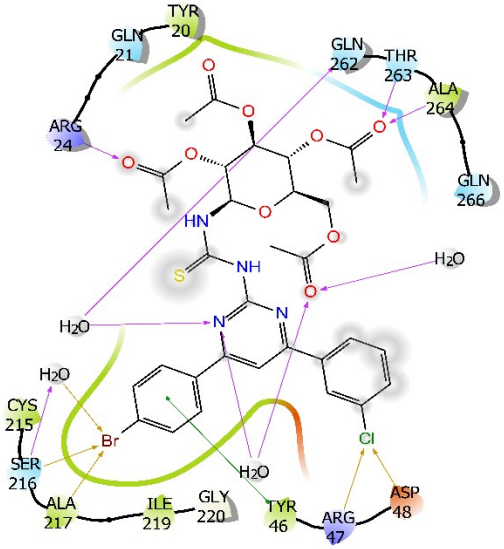
2-Cl (**8e**), G_{score} = –6.971 kcal/mol, IC_{50} = 25.24 ± 0.37 µM



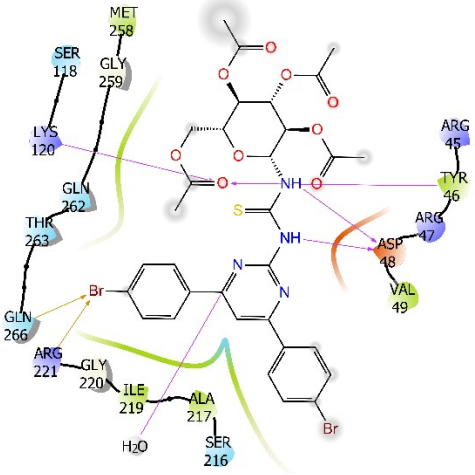
4-Me (**8g**), G_{score} = –5.924 kcal/mol, IC_{50} = 58.32 ± 1.16 µM



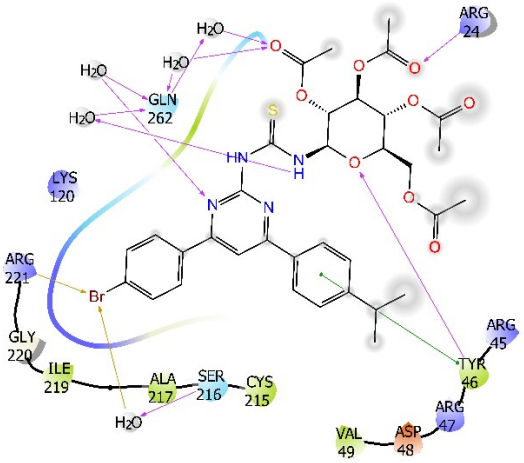
3-Cl (**8d**), G_{score} = –8.755 kcal/mol, IC_{50} = 5.31 ± 0.14 µM



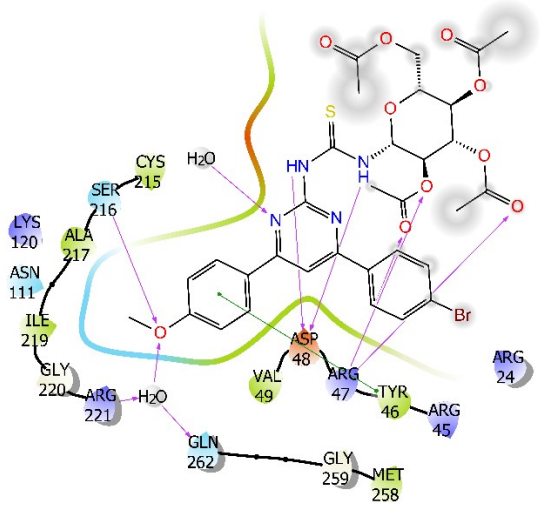
4-Br (**8f**), G_{score} = –8.724 kcal/mol, IC_{50} = 5.62 ± 0.13 µM



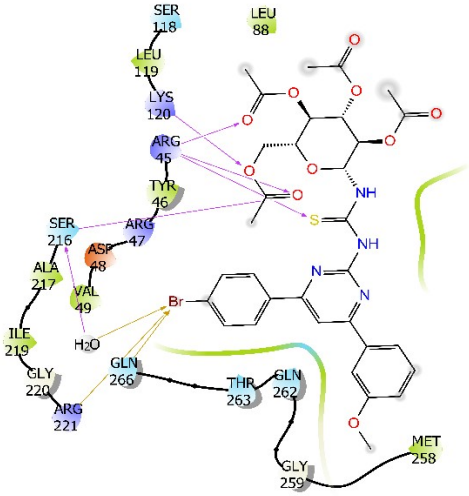
4-^{i}Pr (**8h**), G_{score} = –9.184 kcal/mol, IC_{50} = 2.74 ± 0.03 µM



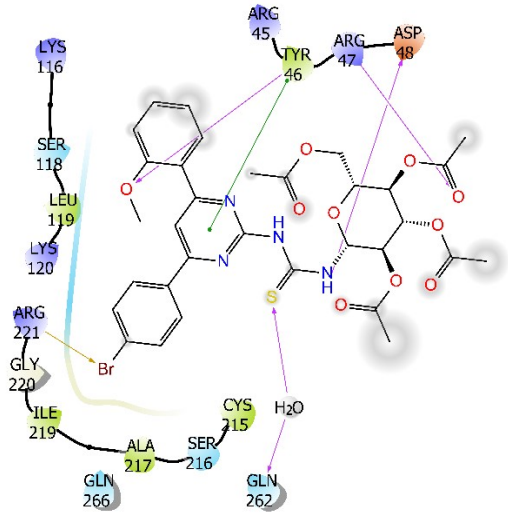
4-OMe (**8i**), G_{score} = –8.327 kcal/mol, IC_{50} = 10.31 ± 0.36 µM



3-OMe (**8j**), G_{score} = –8.272 kcal/mol, IC_{50} = 12.17 ± 0.54 µM



2-OMe (**8k**), G_{score} = –6.592 kcal/mol, IC_{50} = 31.22 ± 1.41 µM



4-NMe$_2$ (**8l**), G_{score} = –8.153 kcal/mol, IC_{50} = 14.13 ± 0.22µM

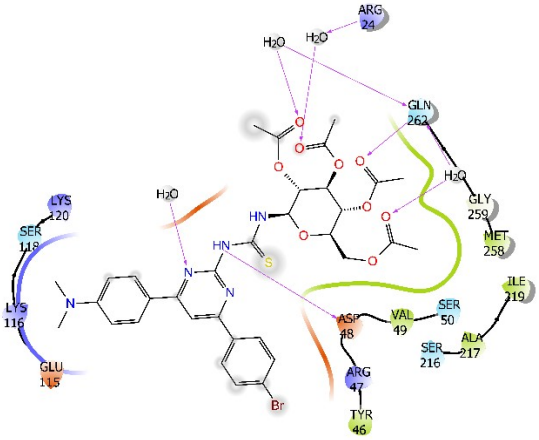


Fig. 7S. The mode of interaction in the 2D-presentation of ligand **8a-l** in the active pocket of enzyme 1NNY 4W93 indicated the H bond, stacking π-π and lipophilic interactions of each ligand corresponding to the residues.

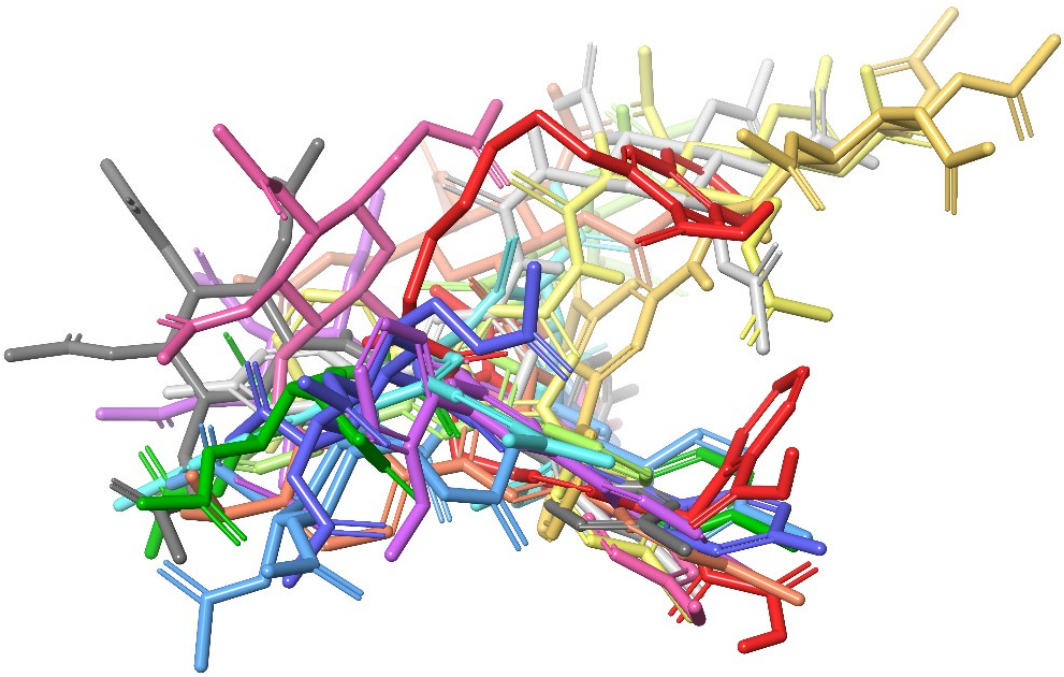
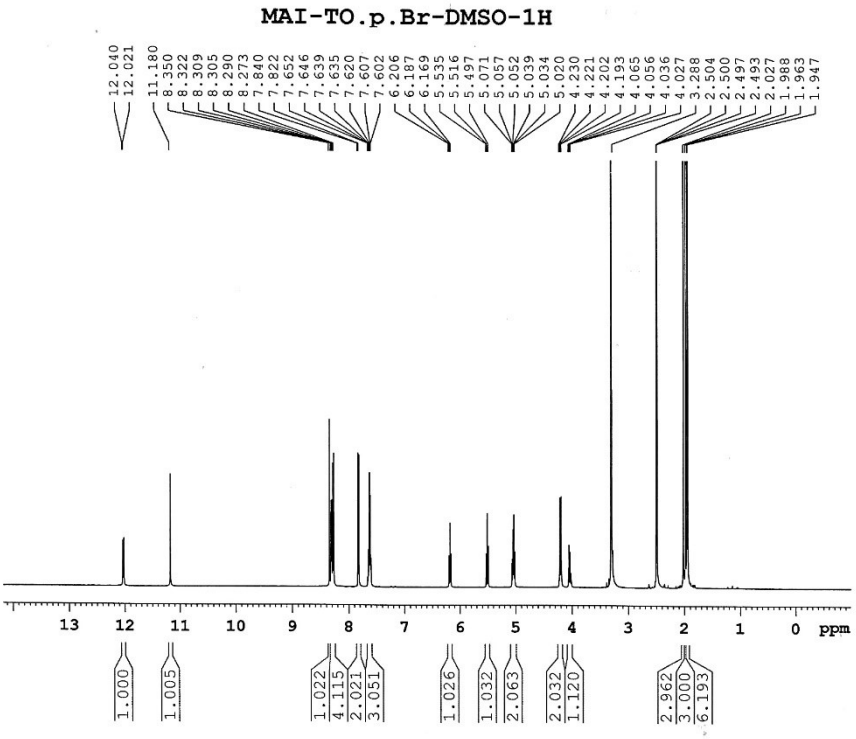
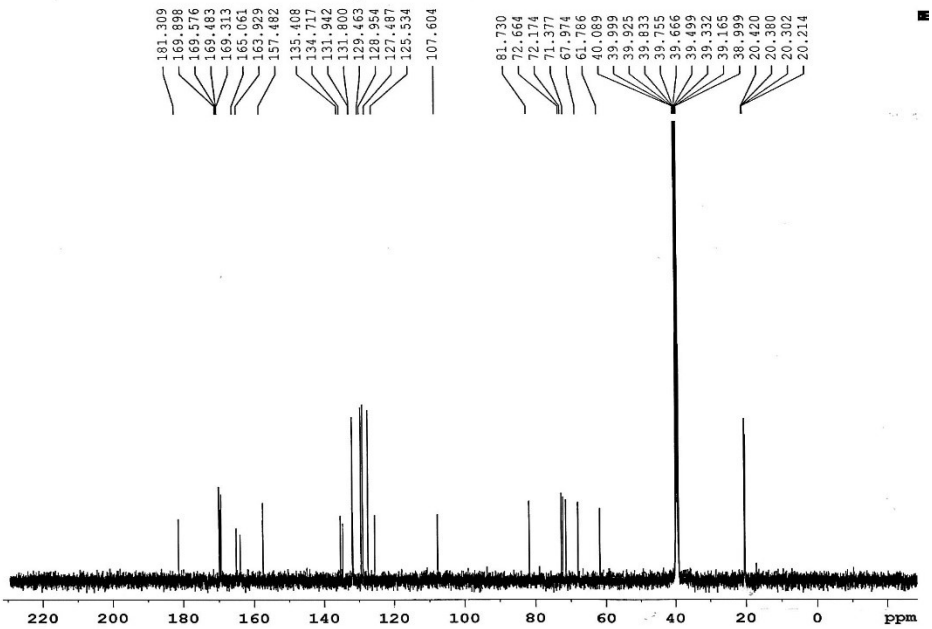


Fig. 8S Superimposing of ligands **8a-l** in active pocket of enzyme 1NNY, where, compound **8a** (R=H, faded orange colour), **8b** (R=4-F, blue colour), **8c** (R=4-Cl, dark grey colour), **8d** (R=3-Cl, yellow colour), **8e** (R=2-Cl, faded yellow-green colour), **8f** (R=4-Br, green colour), **8g** (R=4-Me, grey colour), **8h** (R=4-^{i}Pr, faded red-orange colour), **8i** (R=4-OMe, magenta colour), **8j** (R=3-OMe, faded azure colour), **8k** (R=2-OMe, violet colour), **8l** (R=4-NMe_2, cyan colour). Co-crystal, ursolic acid was in red colour.

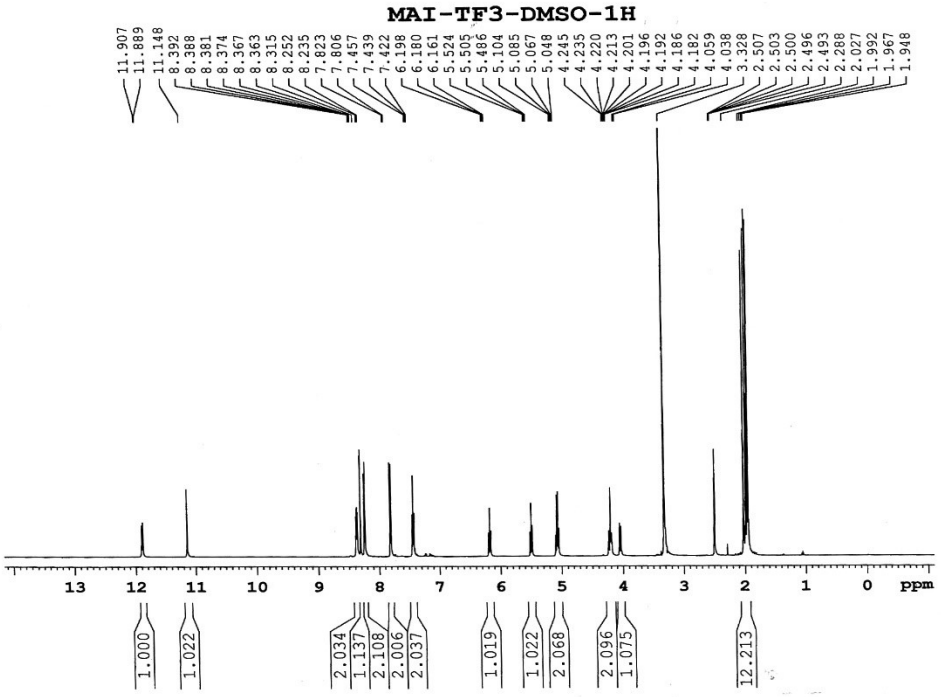
4. NMR & MS Spectra

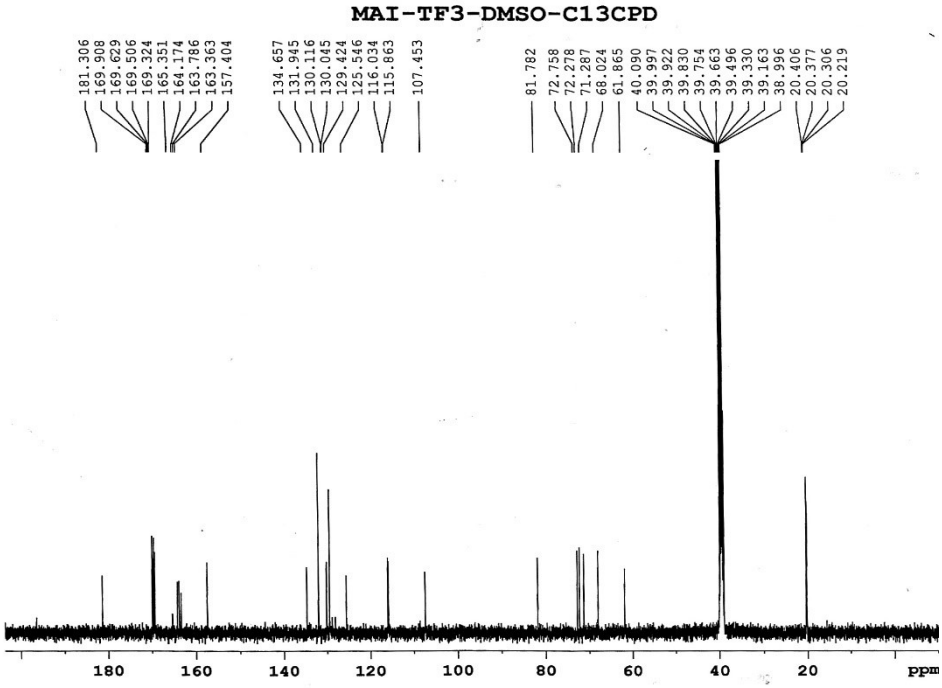
4.1. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(phenyl)-6-(4-bromophenyl)pyrimidin-2-yl]thiourea (8a)



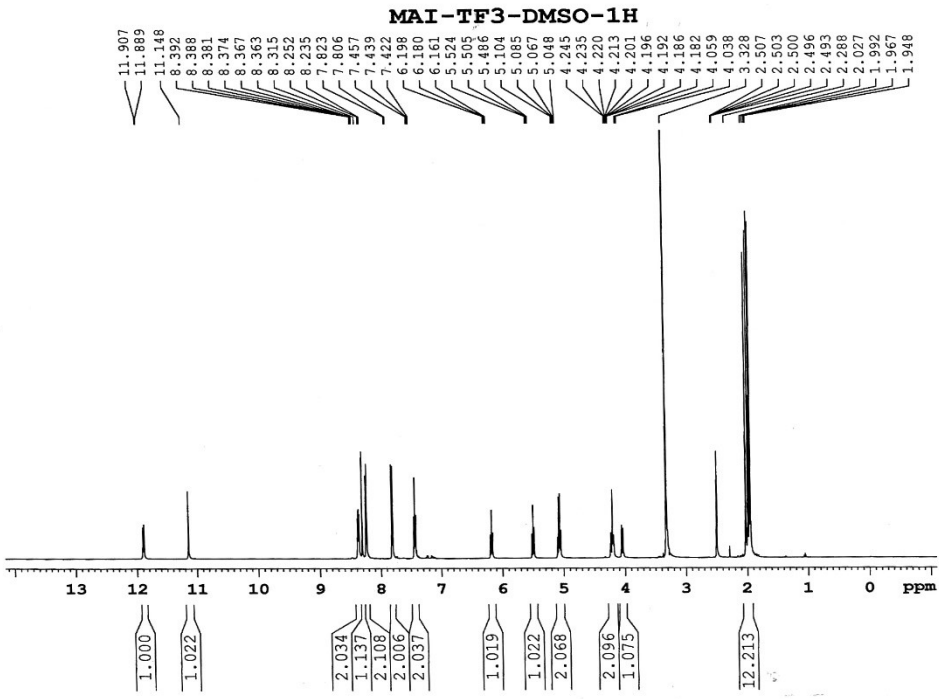


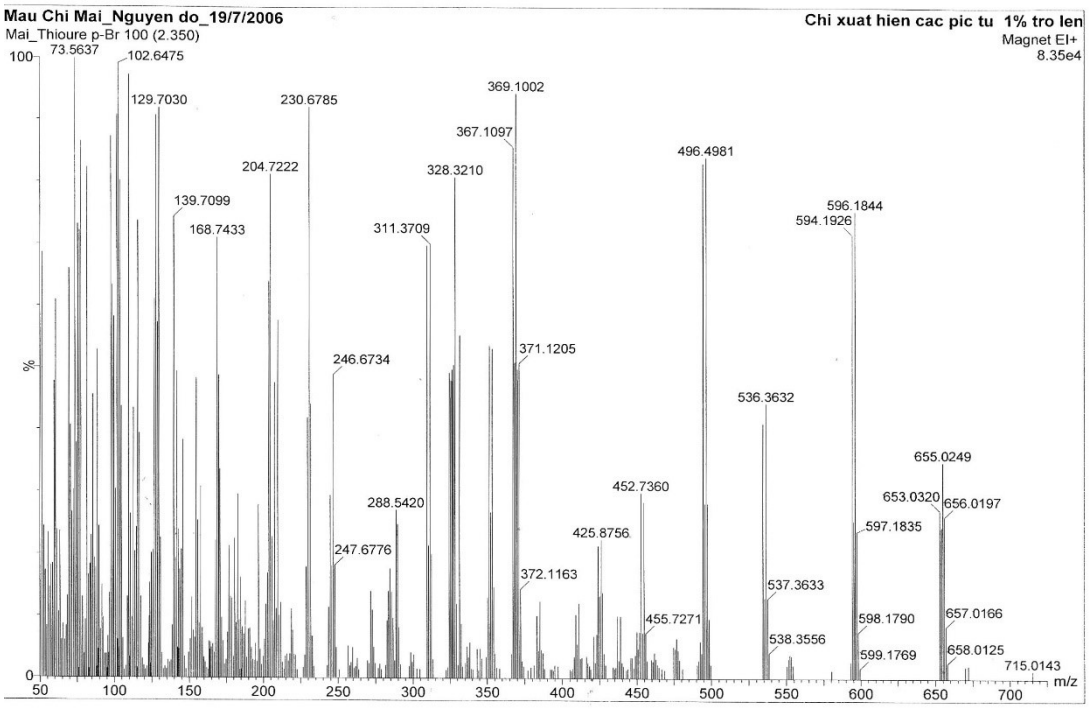
4.2. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-fluorophenyl)pyrimidin-2-yl]thiourea (8b)



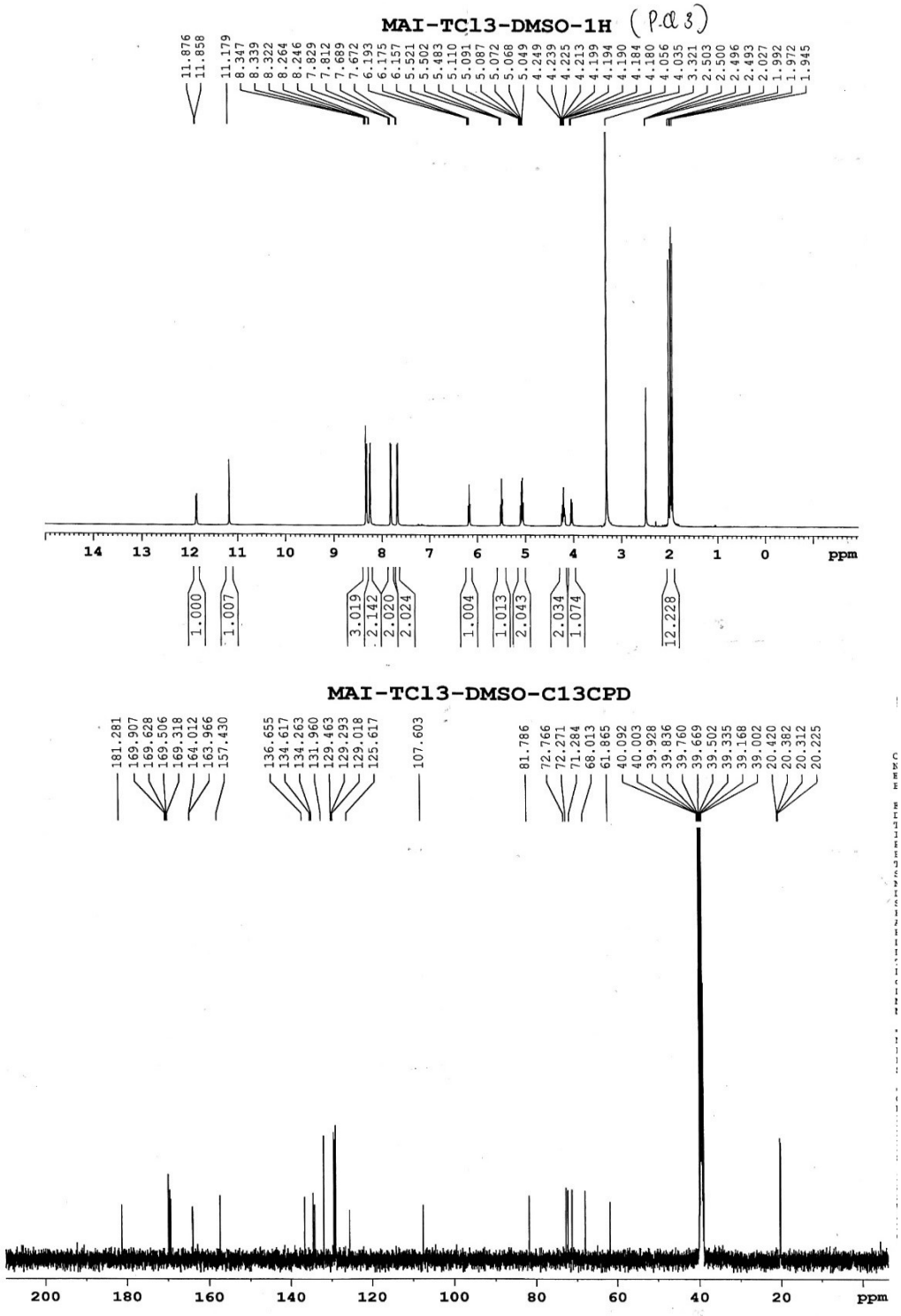


4.3. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-fluorophenyl)pyrimidin-2-yl]thiourea (8b)

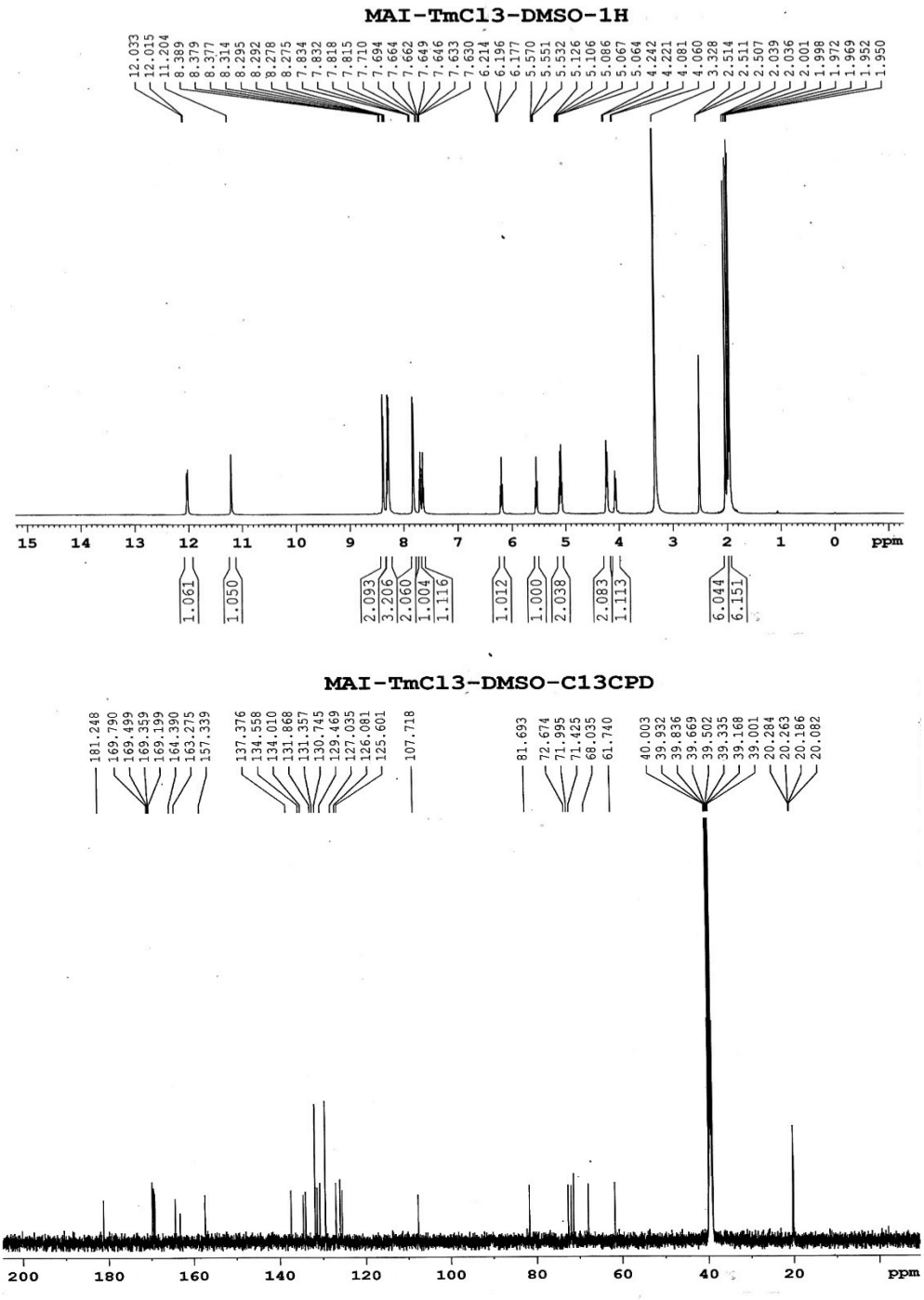



Mau Chi Mai_Nguyen do_19/7/2006
Mai_Thioure p-Br 100 (2.350)
Chi xuat hien cac pic tu 1% tro len
Magnet EI+
8.35e4
100
%
0
73.5637
102.6475
129.7030
230.6785
369.1002
367.1097
496.4981
204.7222
328.3210
139.7099
168.7433
311.3709
596.1844
594.1926
371.1205
246.6734
536.3632
655.0249
452.7360
653.0320
656.0197
288.5420
425.8756
597.1835
247.6776
372.1163
537.3633
455.7271
598.1790
657.0166
538.3556
599.1769
658.0125
715.0143
50
100
150
200
250
300
350
400
450
500
550
600
650
700
m/z

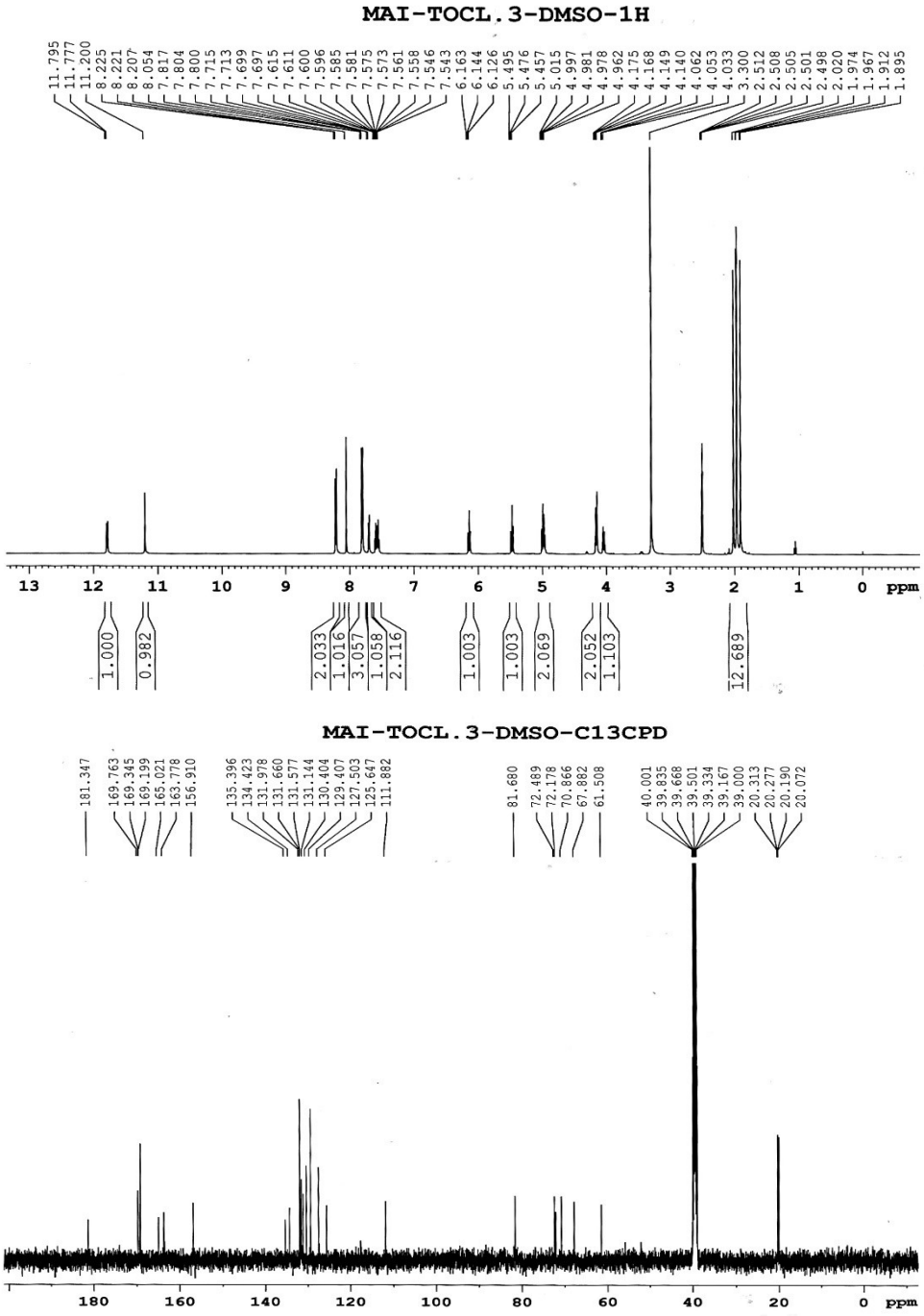
4.3. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-chlorophenyl)pyrimidin-2-yl]thiourea (8c)



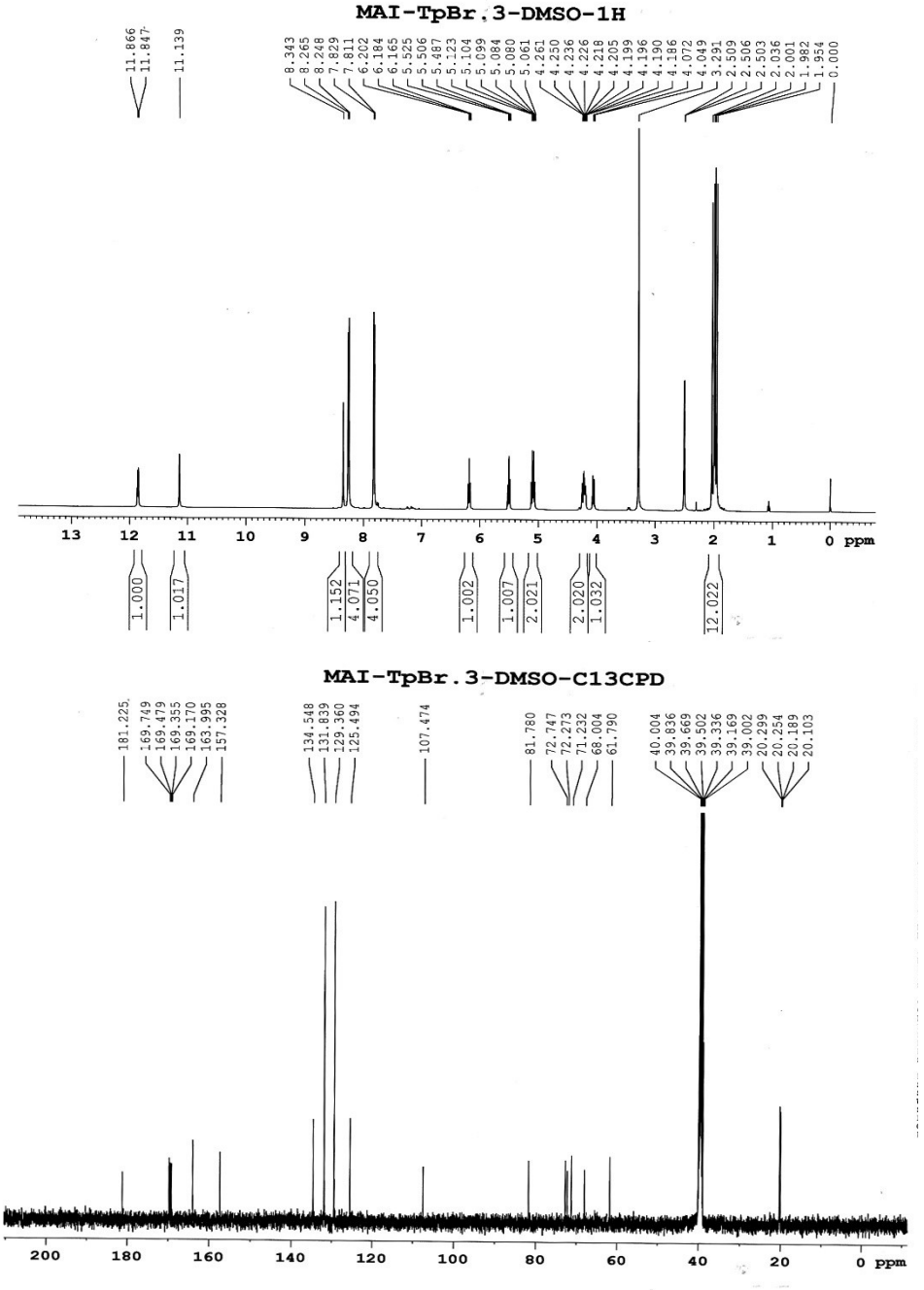
4.4. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(3-chlorophenyl)pyrimidin-2-yl]thiourea (8d)



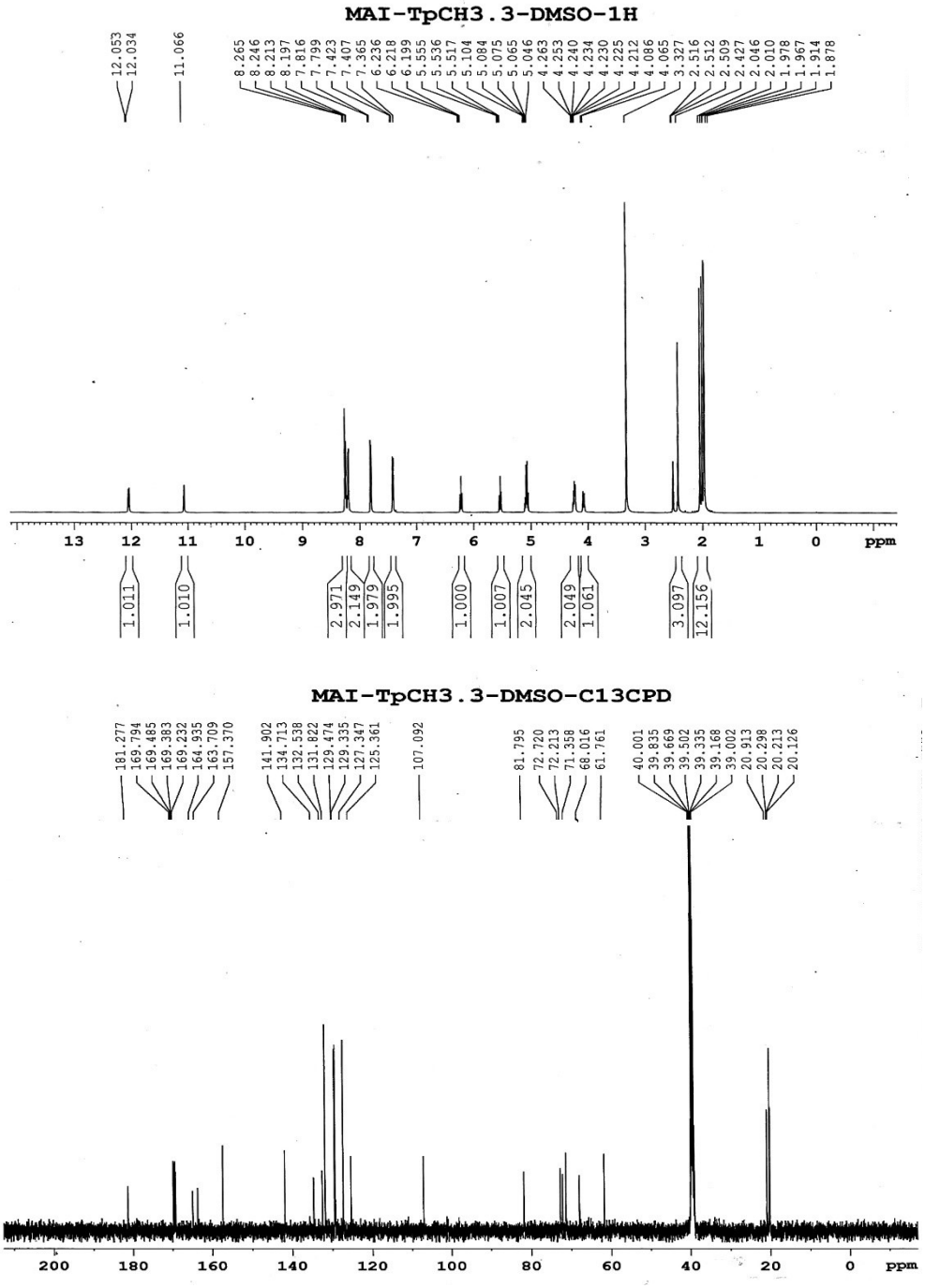
4.5. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(2-chlorophenyl)pyrimidin-2-yl]thiourea (8e)



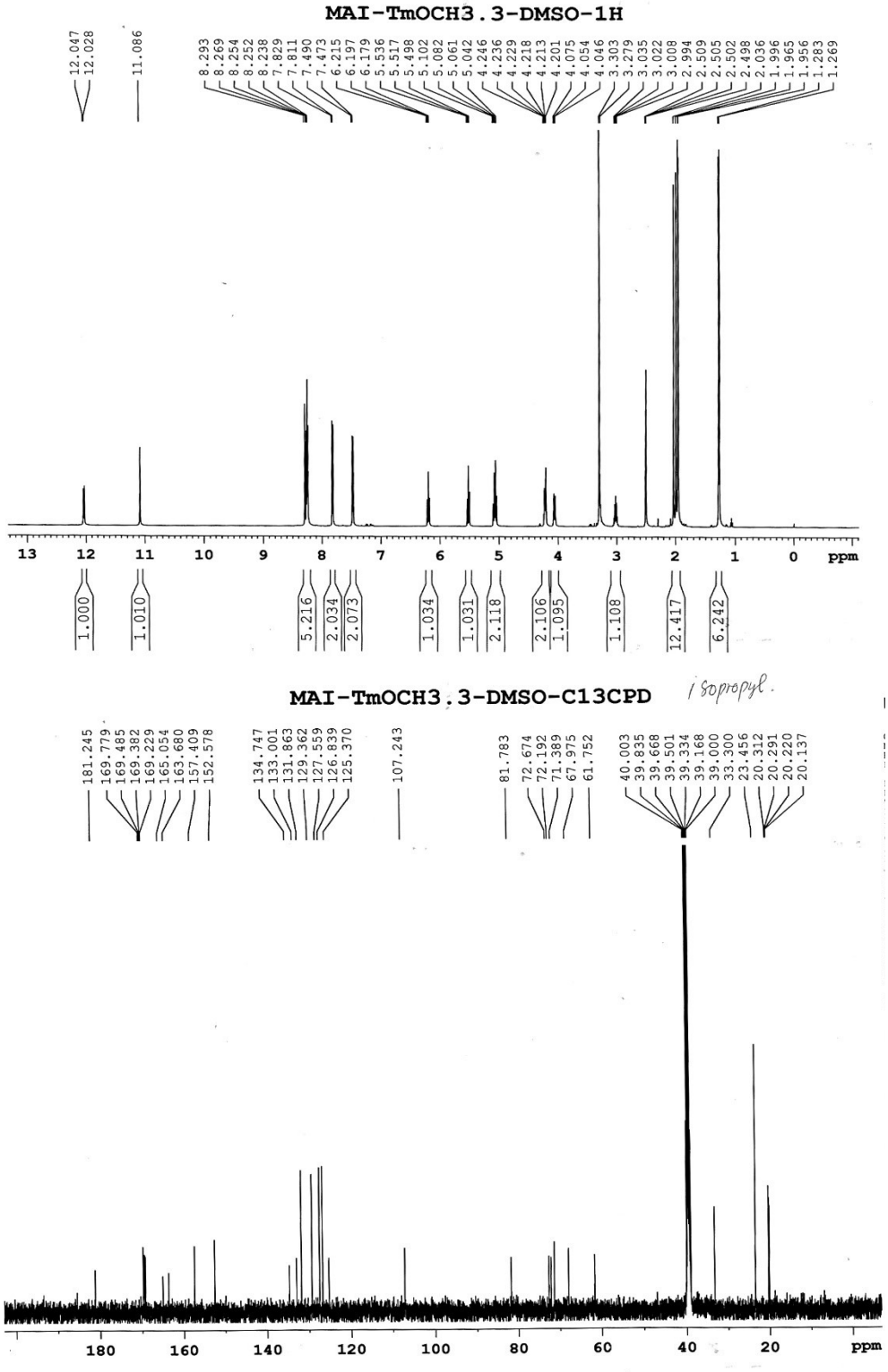
4.6. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4,6-bis(4-bromo-phenyl)pyrimidin-2-yl]thiourea (8f)



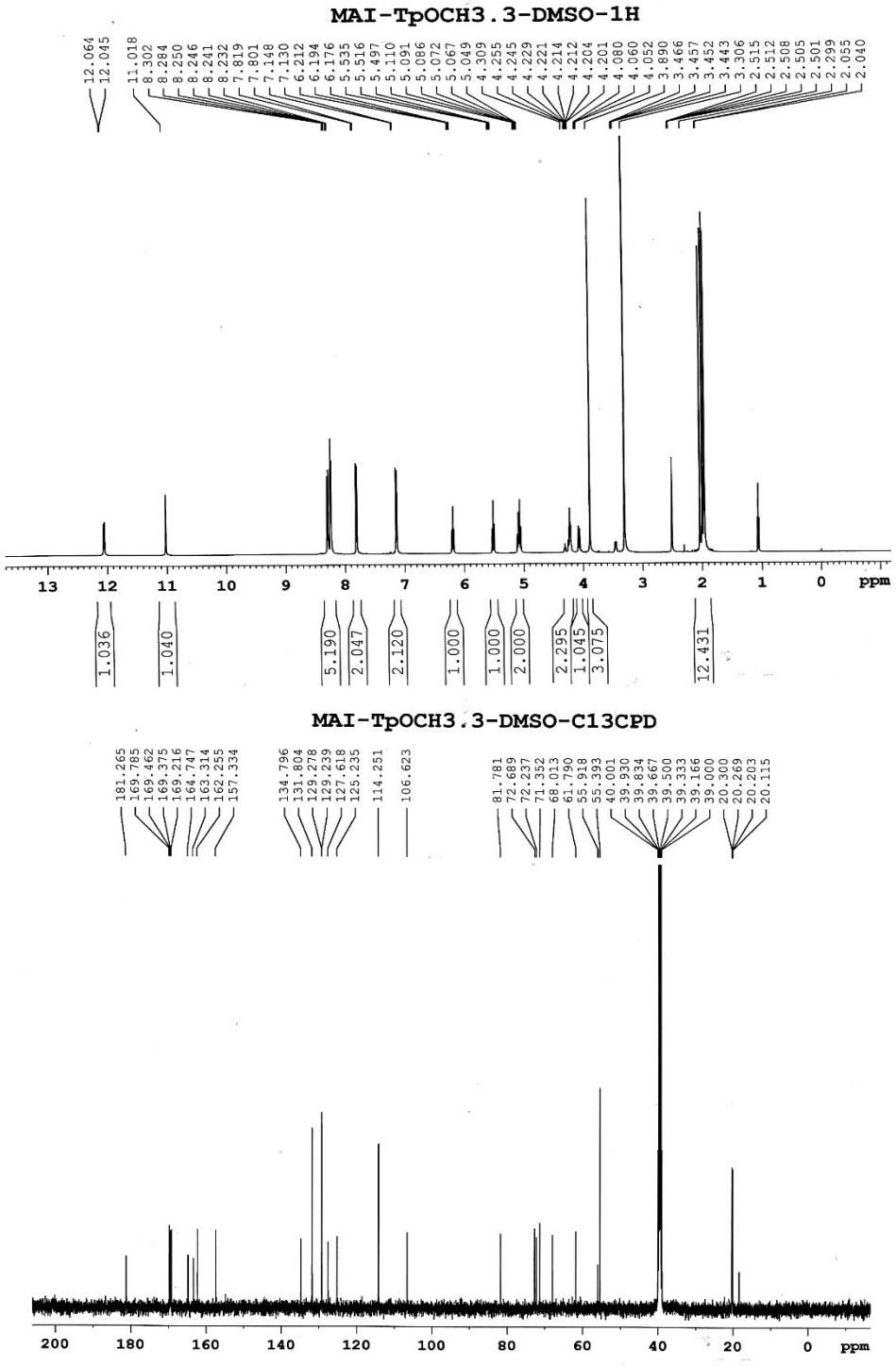
4.7. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-methylphenyl)pyrimidin-2-yl]thiourea (8g)



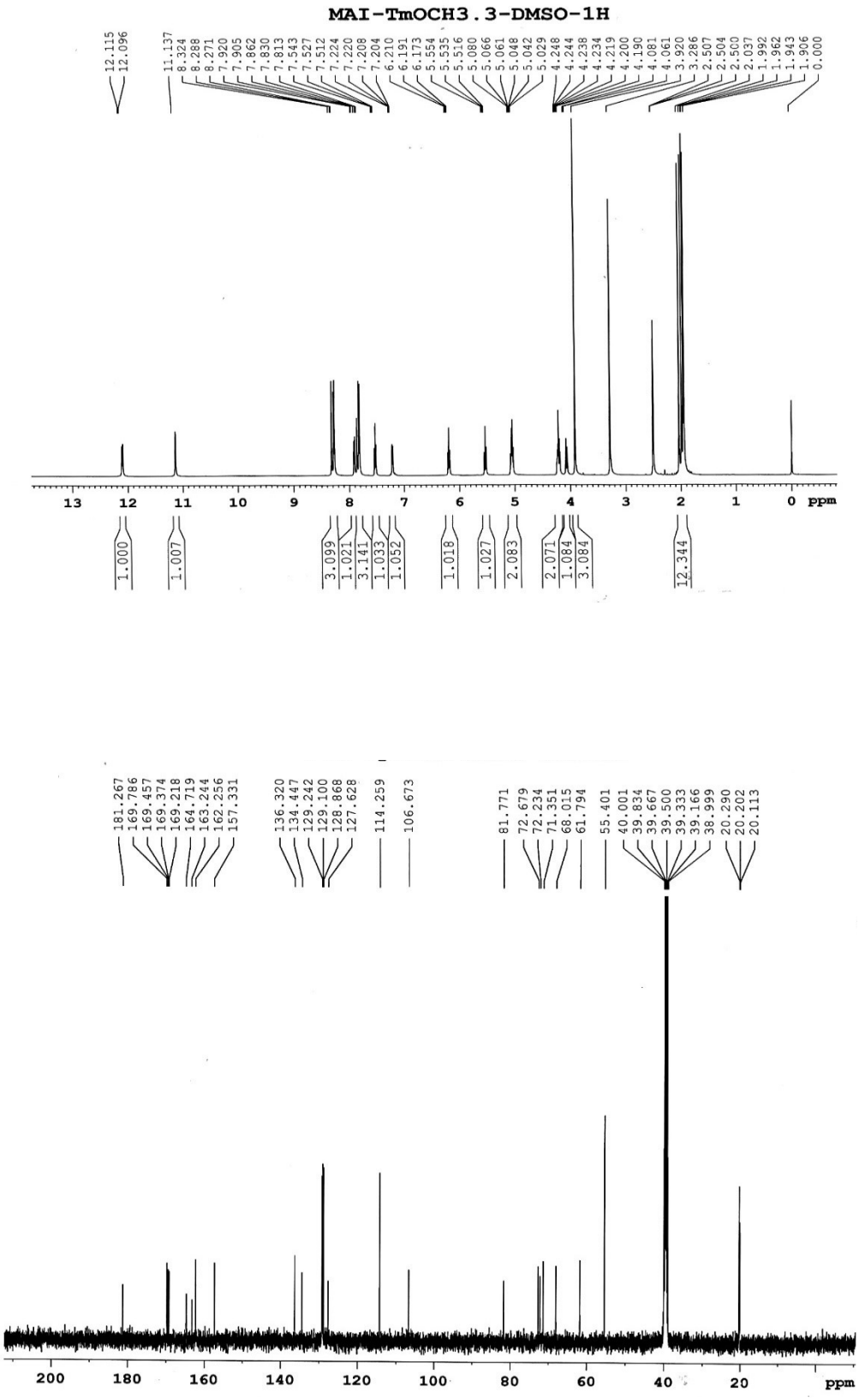
4.8. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-isopropylphenyl)pyrimidin-2-yl]thiourea (8h)



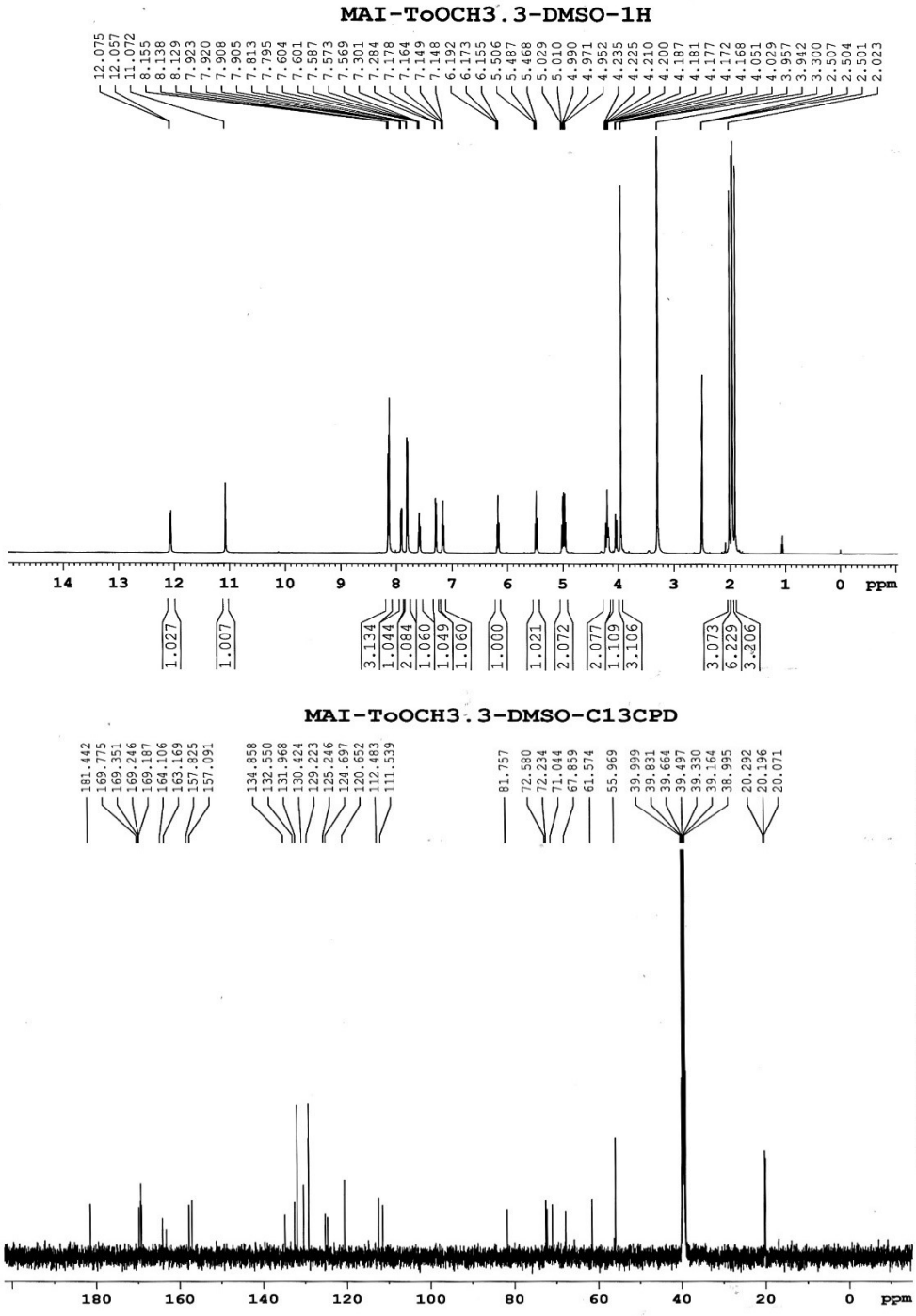
4.9. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-metoxyphenyl)pyrimidin-2-yl]thiourea (8i)



4.10. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(3-metoxyphenyl)pyrimidin-2-yl]thiourea (8j)



4.11. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(2-metoxyphenyl)pyrimidin-2-yl]thiourea (8k)



4.12. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-[4-(4-bromophenyl)-6-(4-dimetylaminephenyl)pyrimidin-2-yl]thiourea (8l)