Supplementary Information

Access to Steroidal Pyridazines *via* Modified Thiohydrazides

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General Information

NMR spectra were acquired on BrukerAvance 600 and 300 spectrometers at room temperature; the chemical shifts δ were measured in ppm relative to the solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm, DMSO-d_6, δ = 2.50 ppm; ^{13}C: $CDCl_3$, δ = 77.00 ppm, DMSO-d_6, δ = 39.50 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet. The coupling constants (J) are in Hertz. The structures of all compounds were established using 1D NMR (^{1}H, ^{13}C, JMOD) and 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{1}H TOCSY,^{1}H-^{1}H ROESY, ^{13}C-^{1}H HMBC, ^{13}C-^{1}H HSQC, ^{1}H-^{1}H NOESY) spectroscopy. Infrared spectra were measured on a FT-IR spectrometer in KBr pellets. High-resolution and accurate mass spectra were obtained onBrukermicrOTOF-QTM ESI-TOF (Electrospray Ionization/Time of Flight) and Thermo Scientific* LTQ Orbitrap mass spectrometers. Melting points (mp) are uncorrected and were measured on a Boetius capillary melting point apparatus. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254 aluminum supported plates); the visualization was accomplished with an UV lamp (365 nm) and using chemical staining with [$Ce(SO_4)_2/H_2SO_4$]. Column chromatography was performed on silica gel 60 (60-120 mesh, Merck). 3β-Acetate androst-5-en-3β-ol-17-one,17β-hydroxy-17α-methyl-5α-androstan-3-one,17β-hydroxy-5α-androstan-3-one,estrone, phosphorus oxychloride, morpholine and hydrazine hydrate were commercially available and were used without additional purification. All reactions were carried out using freshly distilled and dry solvents. Parent chloroacetanilides were prepared according to published procedures.[1]

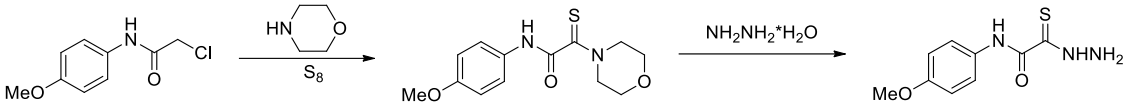
[1]*German Patent* 229409, 1985; *Chem. Abstr*. **1987**, *106*, 8566.

Typical experimental procedures

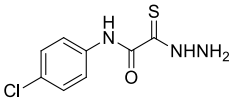
I. Preparation of oxamic acids thiohydrazides

General procedure for the preparation of oxamic acids thiohydrazides: Various oxamic acid thiohydrazidesas substrates were prepared from the corresponding chloroacetanilidesin high yields by the treatment with hydrazine according to the literature procedure.[2]

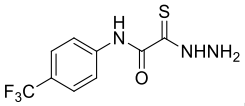
Representative compound:**2-Hydrazinyl-N-(4-methoxyphenyl)-2-thioxoacetamide (3a).**



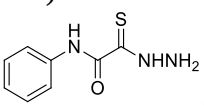
To a solution of sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL),chloroacetanilide (2.0 g, 10.0 mmol)was added with stirring.The reaction mixture was kept overnight at room temperature (TLC monitoring). The mixture was poured into water (70 mL). The precipitate that formed was filtered off, dried, and dissolved in acetone to remove the sulfur excess. The organic fraction was separated, and the solvent was evaporated *in vacuo*. The solid residue was recrystallized from ethanol to give monothiooxamide as a white solid in 95% yield (2.7 g, 9.5 mmol).
To a solution of monothiooxamide (2.7 g, 9.5 mmol) in DMF (10 mL), hydrazine hydrate (2.7 mL, 50 mmol) was added, and the mixture was allowed to stand at room temperature for 10-12 h. After completion of the reaction (TLC monitoring), the reaction mixture was poured into water (40 mL) and the solution was acidified with hydrochloric acid to pH 6. The precipitate was filtered off and recrystallized from ethanol to give thiohydrazides in 62% yield (1.3 g, 5.9 mmol). Mp 159-160ºC (mp_{lit} 161-163ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, OMe); 6.91 (d, *J* = 8.83 Hz, 2H, Ar); 7.70 (d, *J* = 8.83 Hz, 2H, Ar); 10.12 (br.s, 1H, NH).[3]



2-Hydrazinyl-N-(4-chlorophenyl)-2-thioxoacetamide (3b). The general procedure was followed using chloroacetanilide (2.04 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL). Workup afforded analytically pure compound as a pale yellow solid (1.84 g, 85%), mp 169-171ºC (mp_{lit}172-174ºC). The spectral data matched that reported by Krayushkin and coworkers.[21]H NMR ($CDCl_3$, 300 MHz): δ 7.42 (d, 2H, *J* = 8.73 Hz, Ar); 7.86 (d, 2H, *J* = 8.72 Hz, Ar); 10.28 (s, 1H, NH).[3]



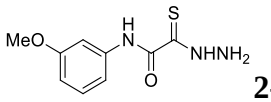
2-Hydrazinyl-N-(4-(trifluoromethyl)phenyl)-2-thioxoacetamide (3c). The general procedure was followed usingchloroacetanilide (2.37 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL). Workup afforded analytically pure compound as a pale yellow solid (1.58 g, 60%), mp 169-170ºC. The spectral data matched that reported by Krayushkin and coworkers.[21]H NMR (DMSO-d_6, 300 MHz): δ 7.70 (d, 2H, *J* = 8.07 Hz, Ar); 8.00 (d, 2H, *J* = 8.07 Hz, Ar); 10.50 (s, 1H, NH).[3]



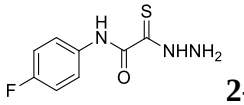
2-Hydrazinyl-N-phenyl-2-thioxoacetamide (3d). The general procedure was followed using chloroacetanilide (1.7 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL). The spectral data matched that reported by Krayushkin and coworkers.[2] Workup afforded analytically pure compound as a white solid (1.53 g, 83%),mp 145-146ºC (mp_{lit} 144-147ºC).[1]H NMR

[2]Yarovenko, V. N.; Shirokov, A. V.; Krupinova, O. N.; Zavarzin, I. V.; Krayushkin, M. M. *Russ. J. Org. Chem.* **2003**, *39*, 1133.
[3] The signals of the NH_2NH groups were not observed in ^{1}H NMR

($CDCl_3$, 300 MHz): δ 7.15-7.16 (m, 1H, Ph); 7.40-7.43 (m, 2H, Ph); 7.64 (d, 2H, *J* = 7.92 Hz, Ph); 10.20 (s, 1H, NH).[3]



2-Hydrazinyl-N-(3-methoxyphenyl)-2-thioxoacetamide (3e). The general procedure was followed using chloroacetanilide (2.00 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL). Workup afforded analytically pure compound as a pale yellow solid (1.62 g, 71%),mp 165-168^{o}C. The spectral data matched that reported by Krayushkin and coworkers.[21]H NMR (DMSO-d_6, 300 MHz): δ 6.75 (d, 1H, *J* = 8.20 Hz, Ar); 7.18-7.45 (m, 3H, Ar); 10.19 (s, 1H, NH).[3]



2-Hydrazinyl-N-(4-fluorophenyl)-2-thioxoacetamide (3f). The general procedure was followed using chloroacetanilide (1.90 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL). Workup afforded analytically pure compound as a pale yellow solid (1.81 g, 85%), mp 170-172^{o}C (mp_{lit} 157-160^{o}C). The spectral data matched that reported by Krayushkin and coworkers.[21]H NMR (DMSO-d_6, 300 MHz): δ 7.22 (dd, 2H, *J* = 8.79 Hz, Ar); 7.80 (dd, 2H, *J* = 4.40, 8.79 Hz, Ar); 10.29 (s, 1H, NH).[3]

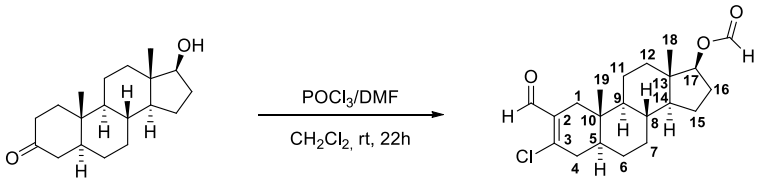
II. Preparation of chlorovinyl aldehydes

General procedure for the preparation of 17-chloro-16-formyl steroids: Various chloroformyl steroid substrates were prepared from the corresponding ketosteroidsin high yield by the treatment with phosphorus oxychloride according to a modified literature procedure.[4]

17α,17β-Dimethyl-2-formyl-3-chloro-18-norandroste-2,13-diene (2).

A flame-dried round bottom flask containing a stir bar and DMF (0.70 mL, 8.9 mmol) in CH_2Cl_2(8 mL) was cooled to 0°C and 0.75 mL of $POCl_3$ (8.1mmol) was added dropwise while stirring. The mixture was stirred for 90 minutes, before a dropwise addition of 17β-hydroxy-17α-methyl-5α-androstan-3-one(0.35 g, 1.2 mmol) solution in CH_2Cl_2 (10 mL). The mixture was warmed to ambienttemperature and stirred for 18 hours. The reaction was deluted with CH_2Cl_2 (20 mL) poured over ice and quenchedwith $NaHCO_3$. Once neutralized, the organic fractionwas washed with water (3×25 mL) and brine (1×20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated toafford the product.The residue was purified by silica gel (60-120 mesh) column chromatography with a petroleum ether – benzene (6:1) as eluent, to give product as white solid (0.23 g, yield 61 %). Mp 116-117ºC.
^{1}HNMR (600 MHz, $CDCl_3$): δ 0.70 (s, 3H, 19-CH_3); 0.97 (s, 6H, 17´-CH_3, 17´´-CH_3); 0.97-1.13 (m, 2H, 9-CH, 7-CH_2); 1.21-1.33 (m, 2H, 6-CH_2, 11-CH_2); 1.54-1.67 (m, 4H, 5-CH, 6-CH_2, 16-CH_2); 1.78 (d, 1H, *J* = 17.40 Hz, 1-CH_2); 1.82-1.89 (m, 1H, 12-CH_2); 1.90-1.97 (m, 2H, 7-CH_2, 11-CH_2); 1.98-2.04 (m, 2H, 8-CH,12-CH_2); 2.04-2.10 (m, 1H, 15-CH_2); 2.21-2.27 (m, 1H, 15-CH_2); 2.35 (dd, 1H, *J* = 3.00, 11.40 Hz, 4-CH_2); 2.45 (dd, 1H, *J* = 4.20, 11.40 Hz, 4-CH_2); 2.63 (d, 1H, 17.40 Hz,1-CH_2); 10.22 (s, 1H, CHO). ^{13}CNMR (125 MHz, $CDCl_3$):δ 11.4 (19-CH_3); 22.1 (12-CH_2); 22.7 (11-CH_2); 26.4 (17´-CH_3); 26.7 (17´´-CH_3); 28.1 (6-CH_2); 29.7 (15-CH_2); 30.6 (7-CH_2); 34.3 (10-C); 36.4 (8-CH); 37.8 (1-CH_2); 39.5 (16-CH_2); 40.3 (4-CH_2); 42.5 (5-CH); 45.4 (17-C); 51.1 (9-CH); 132.2 (2-C); 135.3 (14-C); 141.1 (13-C); 149.9 (3-C); 191.5 (CHO). IR(KBr): 2928, 2858 (CH), 1675(CO), 1623 (C=C).HRMS (ESI) for $C_{21}H_{29}ClONa$ ($[M+Na]^+$): calcd 355.1799, found ($[M+Na]^+$) 355.1797.

17β-Formyloxy-2-formyl-3-chloro-androst-2-ene (6).

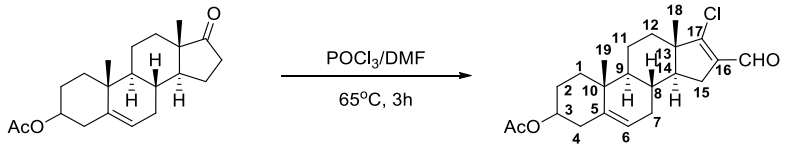


A flame-dried round bottom flask containing a stir bar and DMF (0.87 mL, 11 mmol) in CH_2Cl_2(10 mL) was cooled to 0°C and 0.91 mL of $POCl_3$ (9.8mmol) was added dropwise while stirring. The mixture was stirred for 90 minutes, before a dropwise addition of androstane (0.41 g, 1.4 mmol) solution in CH_2Cl_2 (15 mL). The mixture was warmed to ambienttemperature and stirred for 22 hours. The reaction was deluted with CH_2Cl_2 (20 mL) poured over ice and quenchedwith $NaHCO_3$. Once neutralized, the organic fractionwas washed with water (3×20 mL) and brine (1×20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated toafford the product.The residue was purified by silica gel (60-120 mesh) column chromatography with a benzene as eluent, to give product as white solid (0.31 g, yield 61

[4] Ruiz, A.; Coro, J.; Almagro, L.; Ruiz, J.; Molero, D.; Maroto, E. E.; Filippone, S.; Herranz, M.; Martínez- Álvarez, R.; Sancho-García, J. C.; Meo, F.; Suarez, M.; Martín, N. *J. Org. Chem.* **2013**, *78*, 2819.

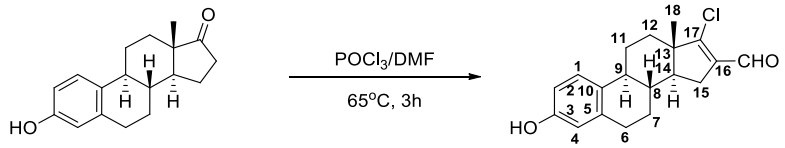
%). Mp 160-161°C.The spectral datamatched previously reported.[51]H NMR (600 MHz, $CDCl_3$): δ 0.74 (s, 3H, 19-CH_3); 0.79 (dt, 1H,*J* = 4.30, 10.90 Hz, 9-CH); 0.82 (s, 3H, 18-CH_3); 0.92 (dq, 1H,*J* = 3.70, 12.20 Hz, 7-CH_2); 1.06 (dt, 1H,*J* = 7.10, 11.70 Hz, 14-CH); 1.17 (dt, 1H,*J* = 4.20, 13.00 Hz, 12-CH_2); 1.25 (dq,1H, *J* = 3.90, 13.10 Hz, 6-CH_2); 1.32 (m, 1H, 15-CH_2); 1.37 (m, 1H, 11-CH_2); 1.40 (m, 1H, 8-CH); 1.52-1.54 (m, 1H, 6-CH_2); 1.55-1.57 (m, 1H, 5-CH); 1.64-1.67 (m, 2H, 11-CH_2, 15-CH_2); 1.70-1.72 (m, 1H, 7-CH_2); 1.73-1.75 (m, 1H, 1-CH_2); 1.80 (dt, 1H,*J* = 3.30, 6.60 Hz, 12-CH_2); 2.19-2.22 (m, 2H, 16-CH_2); 2.34 (dd, 1H, *J* = 12.60, 18.50 Hz, 4-CH_2); 2.45 (dd, 1H, *J* = 5.30, 18.50 Hz, 4-CH_2); 2.54 (d, 1H, *J* = 17.20 Hz, 1-CH_2); 4.69 (t, 1H, *J* = 9.00 Hz, 17-CH); 8.08 (s, 1H, CHO); 10.19 (s, 1H, CHO).

3β-Acetoxy-16-formyl-17-chloro-androsta-5,16-diene (9).



Phosphorus oxychloride (15 mL, 60 mmol) was added dropwise with stirring to a solution of androstane(5.0 g, 15 mmol) in dimethylformamide (40 mL) at 55-60°C. The reaction mixture was allowed to attain 65°C and then heated for 3h. The mixture was poured onto ice-water (100 mL). The crude precipitate was filtered, washed with water (3×50 mL), and dried in air. The product was isolated by crystallization from aqueous methanol as a white solid in 65% yield (3.7 g, 10 mmol). Mp 178-183°C.The spectral datamatched that reported by Lane and coworkers.[61]HNMR (300 MHz, $CDCl_3$): δ 1.03-1.22 (m, 2H, 1-CH_2, 9-CH); 1.01 (s, 3H, 19-CH_3); 1.08 (s, 3H, 18-CH_3); 1.43-1.50 (m, 1H, 12-CH_2); 1.50-1.55 (m, 1H, 2-CH_2); 1.56-1.60 (m, 1H, 14-CH); 1.61-1.66 (m, 2H, 11-CH_2); 1.69-1.70 (m, 1H, 7-CH_2); 1.72-1.82 (m, 2H, 2-CH_2,15-CH_2); 1.85-1.95 (m, 3H, 8-CH, 1-CH_2, 12-CH_2); 2.05 (s, 3H, Ac); 2.07-2.10 (m, 3H, 7-CH_2, 4-CH_2); 2.57 (dd, 1H, *J* = 5.87, 14.67Hz, 15-CH_2); 4.59-4.64 (m, 1H, 3-CH); 5.41-5.42 (m, 1H, 6-CH); 10.01 (1H, CHO).

3-Hydroxy-16-formyl-17-chloro-1,3,5,(10),16-estratetraene (13).



Phosphorus oxychloride (15 mL, 60 mmol) was added dropwise with stirring to a solution of estrone (4.0 g, 15 mmol) in dimethylformamide (40 mL)at 55-60°C. The reaction mixture was allowed to attain 65°C and then heated for 3h. The mixture was poured onto ice-water (100 mL).The crude precipitate was filtered, washed with water (3×50 mL), and dried in air. The product was isolated by crystallization from aqueous methanol as a white solid in 70% yield(3.3 g, 11 mmol). Mp 218-220°C.Thespectraldatamatchedpreviouslyreported.[51]HNMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3H, 18-CH_3); 1.40-1.43 (m, 1H, 7-CH_2); 1.53-1.55 (m, 1H, 11-H); 1.66-1.67 (m, 1H, 12-CH_2); 1.65-1.67 (m, 1H, 8-CH); 1.68-1.69 (m, 1H, 14-CH); 1.81-1.83 (m, 1H, 12-CH_2); 1.93-1.95 (m, 1H, 7-CH_2); 2.22-2.23 (m, 1H, 9-CH); 2.33-2.35 (m, 1H, 11-CH_2); 2.44-2.46 (m, 1H, 6-CH_2); 2.70-2.73 (m, 1H, 6-CH_2); 2.75-2.78 (m, 1H, 15-CH_2); 2.95-2.97 (m, 1H, 15-CH_2); 6.59 (s, 1H, 4-CH); 6.65 (d, 1H, J = 8.4 Hz, 2-CH); 7.13 (d, 1H, J=8.4 Hz, 1-CH), 10.04 (s, 1H, CHO).[7]

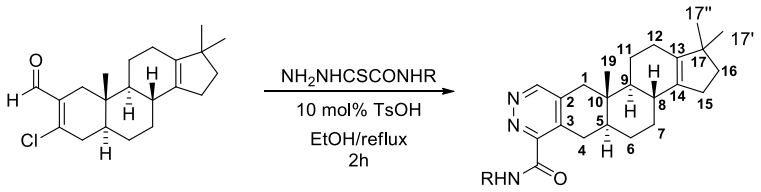
[5]Komkov, A. V.; Komendantova, A. S.; Menchikov, L. G.; Chernoburova, E. I.; Volkova, Y. A.; Zavarzin, I. V. *Org. Lett.***2015**, *17*, 3734−3737.

[6] Lloyd, D.; Gagan, J. M. F.; Lane, A. G. *J. Chem. Soc. C* **1970**, *18*, 2484.

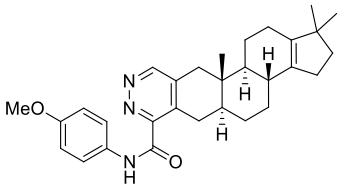
[7] The signal of the OH group was not observed in ^{1}H NMR of 3β-hydroxy-17-chloro-16-formyl-estron-16-ene.

III. Preparation of pyridazines

Synthesis of 17α,17β-Dimethyl-18-nor-5α-androsta-2,13-diene[3,2-d]3′-(N-arylcarbamoyl)pyridazines 4.



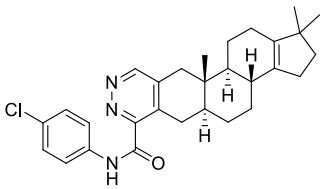
Oxamic acid thiohydrazide (0.17mmol) was added to a solution of the 17α,17β-dimethyl-2-formyl-3-chloro-18-norandroste-2,13-diene (56 mg, 0.17mmol) and p-toluenesulfonic acid monohydrate (3.1 mg, 10 mol%) in ethanol (30 mL). The reaction mixture was refluxed for 2h until the complete conversion of the intermediate hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature and solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) column chromatography withchloroform/MeOH (150:1) as eluent.



17α,17β-Dimethyl-18-nor-5α-androsta-2,13-diene[3,2-d]3′-[N-(4-methoxyphenyl)carbamoyl]pyridazine 4a.

Yield 68% (54 mg).Pale yellow solid, Mp 111-112ºC.

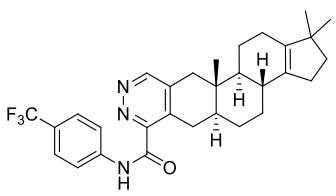
^{1}HNMR (600 MHz, $CDCl_3$):δ 0.75 (s, 3H, 19-CH_3); 0.98 (s, 6H, 17′-CH_3, 17′′-CH_3); 1.02-1.15 (m, 2H, 7-CH_2, 9-CH); 1.29-1.35 (m, 1H, 11-CH_2); 1.38-1.45 (m, 1H, 6-CH_2); 1.53-1.60 (m, 1H, 5-CH); 1.60-1.68 (m, 2H, 16-CH_2); 1.72-1.78 (m, 1H, 6-CH_2); 1.87-1.97 (m, 2H, 11-CH_2,12-CH_2); 1.98-2.12 (m, 4H, 7-CH_2, 8-CH, 12-CH_2, 15-CH_2); 2.23-2.30 (m, 1H, 15-CH_2); 2.53 (d, 1H, *J* = 17.40 Hz, 1-CH_2); 2.88 (dd, 1H,*J* = 12.00, 18.00 Hz, 4-CH_2); 2.94 (d, 1H, *J* = 17.40 Hz, 1-CH_2); 3.54 (dd,1H, *J* = 4.80, 18.00 Hz, 4-CH_2); 3.82 (s, 3H, OMe); 6.92 (d, 2H, *J* = 8.40 Hz,2CH_{arom}); 7.67 (d, 2H, *J* = 8.40 Hz,2CH_{arom}); 8.98 (s, 1H, $CH_{pyridazine}$); 10.15 (s, 1H, NH).^{13}CNMR (125 MHz, $CDCl_3$):δ 11.6 (19-CH_3); 22.2 (12-CH_2); 22.7 (11-CH_2); 26.4 (17′-CH_3); 26.7 (17′′-CH_3); 28.8 (6-CH_2); 29.7 (15-CH_2); 30.3 (4-CH_2); 30.7 (7-CH_2); 34.1 (10-C); 36.5 (8-CH); 39.5 (16-CH_2); 41.0 (1-CH_2); 41.1 (5-CH); 45.4 (17-C); 51.3(9-CH); 55.0 (OMe); 114.3 (2CH_{arom}); 121.6 (2CH_{arom}); 130.8 (C_{arom}); 135.6 (14-C); 140.2 (3-C); 140.6 (13-C); 141.4 (2-C); 150.1 ($C_{pyridazine}$); 153.1 ($CH_{pyridazine}$); 156.7 (C_{arom}); 161.6 (CO). IR(KBr): 3316 (NH), 2949, 2857 (CH), 1685(CO), 1595, 1513 cm^{-1}.HRMS (ESI) for $C_{30}H_{38}N_3O_2$ ([M+H]$^+$): calcd 472.2959, found 472.2949.



17α,17β-Dimethyl-18-nor-5α-androsta-2,13-diene[3,2-d]3′-[N-(4-chlorophenyl)carbamoyl]pyridazine 4b.

Yield 82% (66 mg). Pale yellow solid, Mp 96-97ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76 (s, 3H, 19-CH_3); 0.99 (s, 6H, 17′-CH_3, 17′′-CH_3); 1.02-1.13 (m, 2H, 7-CH_2, 9-CH); 1.29-1.36 (m, 1H, 11-CH_2); 1.38-1.47 (m, 1H, 6-CH_2); 1.53-1.59 (m, 1H, 5-CH); 1.60-1.68 (m, 2H, 16-CH_2); 1.74-1.79 (m, 1H, 6-CH_2); 1.88-1.97 (m, 2H, 11-CH_2, 12-CH_2); 1.99-2.12 (m, 4H, 7-CH_2, 8-CH, 12-CH_2, 15-CH_2); 2.23-2.30 (m, 1H, 15-CH_2); 2.54 (d,1H,*J* = 17.40 Hz, 1-CH_2); 2.87 (dd, 1H,*J* = 12.00, 18.00 Hz, 4-CH_2); 2.95 (d, 1H,*J* = 17.40 Hz, 1-CH_2); 3.52 (dd, 1H,*J* = 4.80, 18.00 Hz, 4-CH_2); 7.35 (d, 2H,*J* = 8.40 Hz,2CH_{arom}); 7.73 (d, 2H, *J* = 8.40 Hz,2CH_{arom}); 8.99 (s, 1H, $CH_{pyridazine}$); 10.30 (s, 1H, NH).^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6 (19-CH_3); 22.2 (12-CH_2); 22.7 (11-CH_2); 26.4 (17′-CH_3); 26.7 (17′′-CH_3); 28.8 (6-CH_2); 29.7 (15-CH_2); 30.3 (4-CH_2); 30.7 (7-CH_2); 34.1 (10-C); 36.5 (8-CH); 39.5 (16-CH_2); 41.0 (1-CH_2); 41.1 (5-CH); 45.4 (17-C); 51.3(9-CH); 121.2 (2CH_{arom}); 129.1 (2CH_{arom}); 129.7 (C_{arom}); 135.5 (14-C); 136.2 (C_{arom}); 140.6 (3-C); 141.0 (13-C); 141.4(2-C); 149.8 ($C_{pyridazine}$); 153.0 ($CH_{pyridazine}$); 161.8 (CO). IR(KBr): 3325 (NH), 2928, 2857 (CH), 1689(CO), 1590, 1520 cm^{-1}. HRMS (ESI) for $C_{29}H_{35}ClN_3O$ ([M+H]$^+$): calcd 476.2463, found 476.2460.

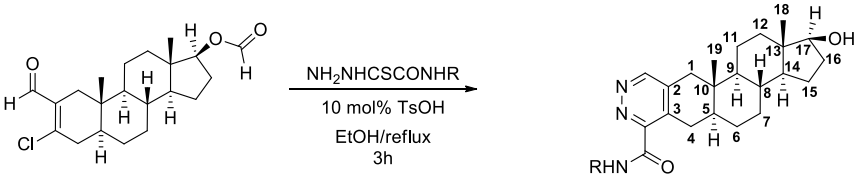


17α,17β-Dimethyl-18-nor-5α-androsta-2,13-diene[3,2-d]3´-[N-(4-trifluoromethylphenyl)carbamoyl]pyridazine 4c.

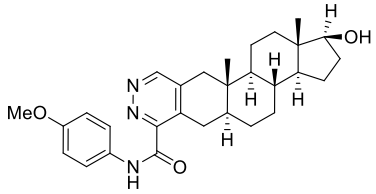
Yield 51% (44 mg).Pale yellow solid,Mp 97-98ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76 (s, 3H, 19-CH_3); 1.00 (s, 6H, 17´-CH_3, 17´´-CH_3); 1.02-1.13 (m, 2H, 7-CH_2, 9-CH); 1.30-1.38 (m, 1H, 11-CH_2); 1.40-1.49 (m, 1H, 6-CH_2); 1.55-1.62 (m, 1H, 5-CH); 1.62-1.71 (m, 2H, 16-CH_2); 1.76-1.81 (m, 1H, 6-CH_2); 1.90-1.97 (m, 2H, 11-CH_2, 12-CH_2); 2.01-2.13 (m, 4H, 7-CH_2, 8-CH,12-CH_2, 15-CH_2); 2.25-2.33 (m, 1H, 15-CH_2); 2.53 (d, 1H,*J* = 17.40 Hz, 1-CH_2); 2.88 (dd, 1H,*J* = 12.60, 19.80 Hz, 4-CH_2); 2.94 (d, 1H, *J* = 17.40 Hz, 1-CH_2); 3.55 (dd, 1H,*J* = 4.80, 19.80 Hz, 4-CH_2); 7.65 (d, 2H,*J* = 8.40 Hz,2CH_{arom}); 7.89 (d, 2H, *J* = 8.40 Hz, 2CH_{arom}); 8.98 (s, 1H, $CH_{pyridazine}$); 10.47 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$):δ 11.6 (19-CH_3); 22.2 (12-CH_2); 22.8 (11-CH_2); 26.4 (17´-CH_3); 26.7 (17´´-CH_3); 28.9 (6-CH_2); 29.8 (15-CH_2); 30.3 (4-CH_2); 30.8 (7-CH_2); 34.1 (10-C); 36.6 (8-CH); 39.6 (16-CH_2); 41.0 (1-CH_2); 41.3 (5-CH); 45.5 (17-C); 51.4 (9-CH); 119.6 (2CH_{arom}); 126.4 (q, J_{C-F} = 3.0 Hz, 2CH_{arom}); 135.6 (14-C); 140.0 (3-C); 140.2 (13-C); 140.7 (2-C); 141.5 (C_{arom}); 149.3 ($C_{pyridazine}$); 153.9 ($CH_{pyridazine}$); 162.4 (CO).[8]IR(KBr): 3326 (NH), 2931, 2859 (CH), 1695(CO), 1616, 1597, 1529, 1324 (CF_3) cm^{-1}.HRMS (ESI) for $C_{30}H_{35}F_3N_3O$ ([M+H]$^+$): calcd 510.2727, found 510.2720.

Synthesis of 17β-Hydroxy-5α-androst-2-eno[3,2-d]3´-(N-arycarbamoyl)pyridazines7.



Oxamic acid thiohydrazide (0.17mmol) was added to a solution of 17β-formyloxy-2-formyl-3-chloro-androst-2-ene(62 mg, 0.17mmol) and p-toluenesulfonic acid monohydrate (3.1 mg, 10 mol%) in ethanol (30 mL). The reaction mixture was refluxed for 3h until the complete conversion of the intermediate hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature and solvent removed under reduced pressure. The crude product was purified by column chromatography using chloroform/MeOH(60:1) as eluent.



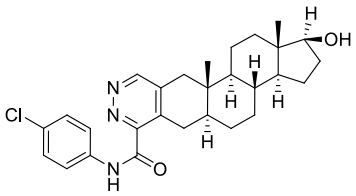
17β-Hydroxy-5α-androst-2-eno[3,2-d]3´-[N-(4-methoxyphenyl)carbamoyl]pyridazine 7a.

Yield 73% (58 mg).). Pale yellow solid, Mp237-238ºC.The spectral data matched previously reported.[5]

^{1}HNMR (600 MHz, $CDCl_3$):δ 0.84 (s, 3H, 19-CH_3); 0.85 (s, 3H, 18-CH_3); 0.86-0.89 (m, 1H, 9-CH); 0.96-0.98 (m, 1H, 7-CH_2); 1.00-1.02 (m 1H, 14-CH); 1.14 (t, 1H, *J* = 13.00 Hz, 12-CH_2); 1.30 (m, 1H, 15-CH_2); 1.38 (m, 1H, 6-CH_2); 1.42-1.44 (m, 1H, 8-CH); 1.45-1.47 (m, 1H, 16-CH_2); 1.48-1.50 (m, 1H, 11-CH_2); 1.52-1.55 (m, 1H, 5-CH); 1.62-1.64 (m, 1H, 15-CH_2); 1.68-1.70 (m, 1H, 11-CH_2); 1.70-1.72 (m, 1H, 6-CH_2); 1.78-1.80 (m, 1H, 7-CH_2); 1.90 (d, 1H, *J* = 12.20 Hz, 12-CH_2); 2.08-2.10 (m, 1H, 16-CH_2); 2.48 (d, 1H, *J* = 16.70 Hz, 1-CH_2); 2.83 (d, 1H, *J* = 16.70 Hz, 1-CH_2); 2.89 (dd, 1H, *J* = 12.60, 18.50 Hz, 4-CH_2); 3.54 (d, 1H, *J* = 18.50 Hz, 4-CH_2); 3.68 (t, 1H, *J* = 8.50 Hz, 17-CH); 3.82 (s, 3H,OMe); 6.92 (d, 2H,*J* = 8.40 Hz,2CH_{arom}); 7.67 (d, 2H,*J* = 8.40 Hz,2CH_{arom}); 8.93 (s, 1H, $CH_{pyridazine}$); 10.11 (s, 1H, NH).[9]^{13}CNMR (125MHz, $CDCl_3$): δ 11.1 (18-CH_3); 11.8 (19-CH_3); 20.7 (11-CH_2); 23.3 (15-CH_2); 28.3 (6-CH_2); 30.4 (4-CH_2);30.5 (16-CH_2);31.1(7-CH_2); 34.1 (10-C); 35.5 (8-CH); 36.6 (12-CH_2); 41.0 (1-CH_2); 41.3 (5-CH); 42.9(13-C); 50.9 (14-CH); 53.7 (9-CH); 55.5 (OMe); 81.8 (17-CH); 114.3(2CH_{arom});121.6 (2CH_{arom}); 130.8(C_{arom}); 139.6 (3-C); 139.8 (2-C); 149.7 ($C_{pyridazine}$); 153.6 ($CH_{pyridazine}$); 156.6(C_{arom}); 161.8 (CO). IR(KBr): 3423 (NH), 2929, 2862 (CH), 1688(CO), 1523, 1514.

[8] The signals of the CF_3 group and C were not observed in ^{13}C NMR spectra.

[9] The signal of the OH group was not observed in ^{1}H NMR.

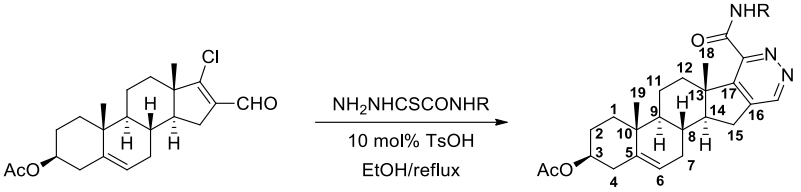


17β-Hydroxy-5α-androst-2-eno[3,2-d]3´-[N-(4-chlorophenyl)carbamoyl]pyridazine 7b.

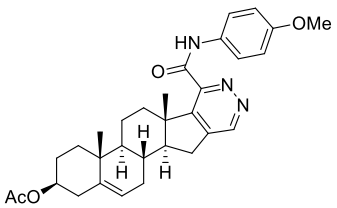
Yield 67% (54 mg).). Pale yellow solid, Mp148-149ºC.

^{1}H NMR (600 MHz, DMSO-d_6): δ 0.65 (s, 3H, 18-CH_3); 0.69 (s, 3H, 19-CH_3); 0.80-0.92 (m, 3H, 7-CH_2, 9-CH, 14-CH); 1.00 (t, 1H,*J* = 9.00 Hz, 12-CH_2); 1.16 (dq, 1H,*J* = 6.00, 12.00 Hz, 15-CH_2); 1.21-1.42 (m, 4H, 6-CH_2, 8-CH,11-CH_2,16-CH_2); 1.45-1.57 (m, 3H, 5-CH, 6-CH_2, 15-CH_2); 1.59-1.68 (m, 2H, 7-CH_2, 11-CH_2); 1.76-1.87 (m, 2H, 12-CH_2, 16-CH_2); 2.43 (d, 1H,*J* = 17.40 Hz, 1H, 1-CH_2); 2.55 (dd, 1H, *J* = 12.00, 19.20 Hz, 4-CH_2); 2.83 (d, 1H,*J* = 17.40 Hz, 1-CH_2); 2.96 (dd, 1H, *J*= 4.80, 19.20 Hz, 4-CH_2); 3.44 (t, 1H,*J* = 6.00 Hz, 17-CH); 4.42 (s, 1H, OH); 7.41 (d, 2H,*J* = 9.00 Hz, 2CH_{arom}); 7.87(d, 2H,*J* = 9.00 Hz, 2CH_{arom}); 9.04 (s, 1H, $CH_{pyridazine}$); 10.93 (s, 1H, NH).^{13}CNMR (125 MHz, DMSO-d_6):δ 11.2 (18-CH_3); 11.4 (19-CH_3); 20.3 (11-CH_2); 23.0 (15-CH_2); 27.7 (6-CH_2); 28.8 (4-CH_2); 29.8 (16-CH_2); 30.6 (7-CH_2); 33.7 (10-C); 35.0 (8-CH); 36.4 (12-CH_2); 39.8 (1-CH_2); 40.2 (5-CH); 42.4(13-C); 50.4 (14-CH); 52.9 (9-CH); 80.0 (17-CH); 121.6 (2CH_{arom}); 127.6 (C_{arom}); 128.6(2CH_{arom}); 135.5 (3-C); 137.5 (C_{arom}); 138.1 (2-C); 152.8 ($C_{pyridazine}$); 153.7 ($CH_{pyridazine}$); 163.6 (CO).IR(KBr): 3328 (NH), 2928, 2870 (CH), 1689(CO), 1590, 1519,1493 cm^{-1}.HRMS (ESI) for $C_{28}H_{35}ClN_3O_2$ ([M+H]$^+$): calcd 480.2412, found 480.2403.

Synthesis of 6'-(N-arylcarbamoyl)-3β-acetoxyandrost-5-eno[16,17-d]pyridazines10a-c.



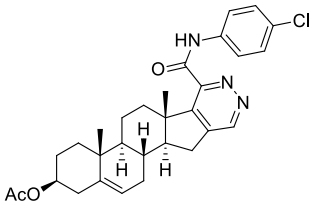
Oxamic acid thiohydrazide (0.17mmol) was added to a solution of the 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene (65 mg, 0.17mmol) and p-toluenesulfonic acid monohydrate (3.1 mg, 10 mol%) in ethanol (30 mL). The reaction mixture was stored at rt for 30 min, diluted with water (30 mL) and extracted with ethyl acetate (3×50 mL). Organic fraction was dried over Na_2SO_4, solvent was removed under reduced pressure and resulting solid hydrazone was resolved in ethanol (10 mL). Solution was refluxed for 1h and cooled to rt. Precipitate formed was filtered for **10d**, in the over cases the crude product was purified by column chromatography using benzene/chloroform (1:1) as eluent.



6'-[N-(4-Methoxyphenyl)carbamoyl]-3β-acetoxyandrost-5-eno[16,17-d]pyridazine 10a.

Yield 73% (65 mg). Pale yellow solid, Mp269-270ºC.

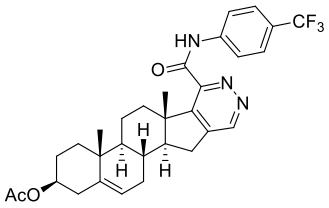
^{1}HNMR (300 MHz, $CDCl_3$): δ 1.03-1.15 (m, 2H, 1-CH_2, 9-CH); 1.10 (s, 3H, 19-CH_3); 1.27 (s, 3H, 18-CH_3); 1.40-1.98 (m, 9H, 1-CH_2, 2-CH_2, 7-CH_2, 8-CH, 11-CH_2, 12-CH_2, 14-CH); 2.03 (s, 3H, Ac); 2.10-2.20 (m, 1H, 7-CH_2); 2.30-2.43 (m, 2H, 4-CH_2); 2.65 (dd, 1H, *J* = 16.00 Hz, 15-CH_2); 2.89 (dd, 1H, *J*= 6.00, 16.00 Hz, 15-CH_2); 3.10-3.14 (m, 1H, 12-CH_2); 3.82 (s, 3H, OMe); 4.60-4.63 (m, 1H, 3-CH); 5.41-5.44 (m, 1H, 6-CH); 6.92 (d, 2H, *J* =8.00 Hz, 2CH_{arom}); 7.68 (d, 2H, *J* = 8.00 Hz, 2CH_{arom}); 9.20 (s, 1H, $CH_{pyridazine}$); 9.98 (s, 1H, NH).^{13}C NMR (125 MHz, DMSO-d_6): δ 16.3 (18-CH_3); 19.0 (19-CH_3); 20.1 (11-CH_2); 21.2 (CO<u>Me</u>); 27.3 (2-CH_2); 29.9 (15-CH_2); 30.3 (8-CH); 31.0 (7-CH_2,); 32.7 (12-CH_2); 36.6 (1-CH_2);37.1 (10-C); 37.8 (4-CH_2); 46.4 (13-C); 49.4 (9-CH); 55.4 (OMe); 56.4 (14-CH); 73.0 (3-CH); 113.9 (2CH_{arom}); 121.7 (2CH_{arom}); 121.7 (6-CH); 131.7 (C_{arom}); 140.0 (5-C); 146.1 (16-C); 150.0 ($CH_{pyridazine}$); 151.7 (17-C); 152.2 ($C_{pyridazine}$); 156.0 (C_{arom}); 163.2 (CO); 170.0 (CO).IR(KBr): 3234 (NH), 2958, 2932, 2905, 2874 (CH), 1727(COO), 1680 (CON), 1597, 1518 cm^{-1}.HRMS (ESI) for $C_{31}H_{38}N_3O_4$ ([M+H]$^+$): calcd 516.2857, found 516.2841.



6'-[N-(4-Chlorophenyl)carbamoyl]-3β-acetoxyandrost-5-eno[16,17-d]pyridazine 10b.

Yield 67% (59 mg). Pale yellow solid, Mp230-231ºC.

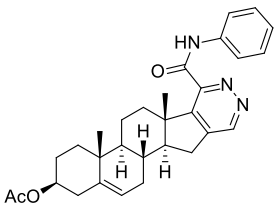
^{1}H NMR (600 MHz, DMSO-d_6): δ 1.01-1.11 (m, 1H, 9-CH); 1.02-1.11 (m, 1H, 1-CH_2); 1.05 (s, 3H, 19-CH_3); 1.15 (s, 3H, 18-CH_3); 1.42-1.48, (m, 1H, 12-CH_2); 1.52-1.59 (m, 1H, 2-CH_2); 1.55-1.63 (m, 1H, 14-CH); 1.58-1.67 (m, 2H, 11-CH_2); 1.67-1.75 (m, 1H, 7-CH_2); 1.75-1.82 (m, 1H, 2-CH_2); 1.77-1.83 (m, 1H, 8-CH); 1.79-1.87 (m, 1H, 1-CH_2); 1.98 (s, 3H, Ac); 2.07-2.13 (m, 1H, 7-CH_2); 2.24-2.34 (m, 2H, 4-CH_2); 2.34-2.40 (m, 1H, 12-CH_2); 2.69 (dd, 1H,*J* = 15.60 Hz, 15-CH_2); 2.86 (dd, 1H,*J* = 6.00, 15.60 Hz, 15-CH_2); 4.42-4.46 (m, 1H, 3-CH); 5.39-5.41 (m, 1H, 6-CH); 7.42 (d, 2H, *J* = 7.80 Hz, 2CH_{arom}); 7.86 (d, 2H, *J* = 7.80 Hz, 2CH_{arom}); 9.34 (s, 1H, $CH_{pyridazine}$); 10.95 (s, 1H, NH).^{13}CNMR (125 MHz, DMSO-d_6):δ 16.0 (18-CH_3); 18.7 (19-CH_3); 19.9 (11-CH_2); 20.9 (CO<u>Me</u>); 27.2 (2-CH_2); 29.5 (15-CH_2); 30.0 (8-CH); 30.8 (7-CH_2); 32.5 (12-CH_2); 36.1 (1-CH_2, 10-C); 37.5 (4-CH_2); 46.2 (13-C); 49.2 (9-CH); 56.2 (14-CH); 73.0 (3-CH); 121.4 (6-CH); 121.5(2CH_{arom}); 127.6(C_{arom}); 128.6 (2CH_{arom}); 137.4(C_{arom}); 139.8 (5-C); 145.1 (16-C); 150.3 ($CH_{pyridazine}$); 150.8 (17-C); 151.4 ($C_{pyridazine}$); 163.7 (CO); 169.5 (CO).IR(KBr): 3235 (NH), 2956, 2933, 2905, 2870 (CH), 1728(COO), 1684 (CON), 1591, 1533, 1518,1495 cm^{-1}.HRMS (ESI) for$C_{30}H_{35}ClN_3O_3$ ([M+H]$^+$): calcd 520.2361, found 520.2356.



6'-[N-(4-(Trifluoromethylphenylphenyl)carbamoyl]-3β-acetoxyandrost-5-eno[16,17-d]pyridazine 10c.

Yield 75% (71 mg). Pale yellowsolid, Mp 214-215ºC.

^{1}H NMR (600 MHz, DMSO-d_6): δ 1.03-1.15 (m, 2H, 1-CH_2, 9-CH); 1.03 (s, 3H, 19-CH_3); 1.17 (s, 3H, 18-CH_3); 1.44-1.52 (m, 1H, 12-CH_2); 1.55-1.62 (m, 1H, 2-CH_2); 1.60-1.67 (m, 1H, 14-CH); 1.60-1.70 (m, 2H, 11-CH_2); 1.73-1.79 (m, 1H, 7-CH_2); 1.77-1.82 (m, 1H, 2-CH_2); 1.80-1.87 (m, 2H, 8-CH, 1-CH_2); 1.98 (s, 3H, Ac); 2.10-2.17 (m, 1H, 7-CH_2); 2.26-2.38 (m, 2H, 4-CH_2); 2.40-2.46 (m, 1H, 12-CH_2); 2.71 (dd, 1H,*J* = 16.20 Hz, 15-CH_2); 2.87 (dd, 1H,*J* = 6.60, 16.20 Hz, 15-CH_2); 4.45-4.48 (m, 1H, 3-CH); 5.40-5.42 (m, 1H, 6-CH); 7.73 (d, 2H, *J* =8.40Hz, 2CH_{arom}); 8.05 (d, 2H, *J* = 8.40 Hz, 2CH_{arom}); 9.35 (s, 1H, $CH_{pyridazine}$); 11.08 (s, 1H, NH).^{13}CNMR (125 MHz, DMSO-d_6):δ 15.9 (18-CH_3); 18.6 (19-CH_3); 19.8 (11-CH_2); 20.6 (CO<u>Me</u>); 27.1 (2-CH_2); 29.4 (15-CH_2); 29.9 (8-CH); 30.6 (7-CH_2); 32.4 (12-CH_2); 36.0 (1-CH_2, 10-C); 37.4 (4-CH_2); 46.1 (13-C); 49.2 (9-CH); 57.0 (14-CH); 72.9 (3-CH); 119.8 (2CH_{arom}); 120.8 (q, $^2J_{C\text{-}F}$ =33.1 Hz, C_{arom}); 121.2 (6-CH); 122.5 (q, $^1J_{C\text{-}F}$ =395.0 Hz, CF_3); 125.7 (2CH_{arom}); 139.7 (5-C); 141.8(C_{arom}); 145.0 (16-C); 150.2 ($CH_{pyridazine}$); 150.8 (17-C); 151.0 ($C_{pyridazine}$); 163.9 (CO); 169.3 (CO).IR(KBr): 3324 (NH), 2942, 2908, 2870 (CH), 1732(COO), 1697 (CON), 1616, 1599, 1529,1510 cm^{-1}. HRMS (ESI) for $C_{31}H_{35}F_3N_3O_3$ ([M+H]$^+$): calcd 554.2625, found 554.2615.



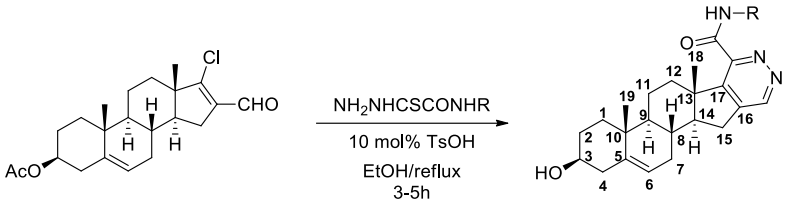
6'-(N-Phenylcarbamoyl)-3β-acetoxyandrost-5-eno[16,17-d]pyridazine 10d.

Yield 82% (68 mg). Colorless solid, Mp282-283ºC.The spectral data matched previously reported.[5]

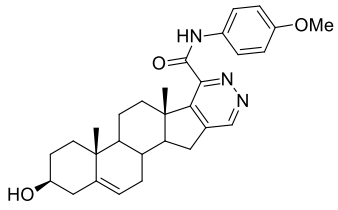
^{1}H NMR (600 MHz, DMSO-d_6): δ 1.03 (s, 3H, 19-CH_3); 1.06-1.09 (m, 1H, 9-CH); 1.07-1.09 (m, 1H, 1-CH_2); 1.16 (s, 3H, 18-CH_3); 1.47-1.49 (m, 1H, 12-CH_2); 1.56-1.58 (m, 1H, 2-CH_2); 1.61-1.63 (m, 1H, 14-CH); 1.64-1.66 (m, 2H, 11-CH_2); 1.74-1.78 (m, 1H, 7-CH_2); 1.79-1.80 (m, 1H, 2-CH_2); 1.81-1.83 (m, 1H, 8-CH); 1.82-1.84 (m, 1H, 1-CH_2); 1.98(s, 3H,Ac); 2.10-2.13 (m, 1H, 7-CH_2); 2.31-2.33 (m, 2H, 4-CH_2); 2.41-2.43 (m, 1H, 12-CH_2); 2.69 (dd, 1H, *J* = 15.60 Hz, 15-CH_2); 2.87 (dd, 1H,*J* = 6.00, 15.60 Hz, 15-CH_2); 4.43-4.46 (m, 1H, 3-CH); 5.39-5.41 (m, 1H, 6-CH); 7.14 (t,1H,*J* = 7.80 Hz, CH_{arom}); 7.37 (t, 2H,*J* = 7.80 Hz, 2CH_{arom}); 7.81 (d, 2H, *J* = 7.80 Hz, 2CH_{arom});9.32 (s, 1H, CH); 10.70 (s, 1H, NH).^{13}C NMR (125 MHz, DMSO-d_6): δ 15.4 (18-CH_3); 18.1 (19-CH_3); 19.3 (11-CH_2); 20.2 (CO<u>Me</u>); 26.6(2-CH_2); 28.9 (15-CH_2); 29.4 (8-CH);30.2 (7-CH_2,);32.0 (12-CH_2); 35.5 (1-CH_2, 10-C); 36.9 (4-CH_2); 45.6(13-C); 48.7 (9-CH); 55.6(14-CH); 72.4 (3-CH);119.3(2CH_{arom});120.7 (6-CH); 123.3 (CH_{arom}); 127.9(2CH_{arom}); 137.8

(C_{arom}); 139.2 (5-C); 144.3 (16-C); 149.4 ($CH_{pyridazine}$); 150.0 (17-C); 151.0 ($C_{pyridazine}$); 152.9(CO);168.8 (CO). IR(KBr): 3423 (NH), 2929, 2862 (CH), 1730 (COO), 1688(CON), 1523 cm^{-1}.

Synthesis of 6'-(N-arylcarbamoyl)-3β-hydroxyandrost-5-ene[16,17-d]pyridazines10a',b',e',f'.



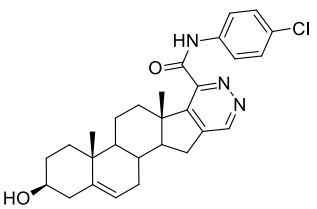
Oxamic acid thiohydrazide (0.17mmol) was added to a solution of the 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene (64 mg, 0.17mmol) and p-toluenesulfonic acid monohydrate (3.1 mg, 10 mol%) in ethanol (30 mL). The reaction mixture was refluxed for 3-5h until the complete conversion of the intermediate hydrazone (TLC monitoring). The resulted mixture was cooled to room temperature and poured onto ice-water (40 mL). The resulting off-white precipitate was filtered, washed with water (3×15 mL) and heptane (3×15 mL), and dried in air. The crude product was purified by column chromatography using petroleum ether/ethyl acetate (1:1)as eluent.



6'-[N-(4-Methoxyphenyl)carbamoyl]-3β-hydroxyandrost-5-eno[16,17-d]pyridazine 10a'.

Yield 85% (68 mg). Pale yellow solid, Mp220-224ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93-1.09 (m, 2H, 1-CH_2, 9-CH); 1.11 (s, 3H, 19-CH_3); 1.26 (s, 3H, 18-CH_3); 1.40-1.92 (m, 9H, 1-CH_2, 2-CH_2, 7-CH_2, 8-CH,11-CH_2, 12-CH_2,14-CH); 2.08-2.12 (m, 1H, 7-CH_2);2.24-2.39 (m, 2H, 4-CH_2); 2.65 (dd, 1H, *J*=13.21, 15.57 Hz, 15-CH_2); 2.89 (dd, 1H, *J*= 6.30, 15.57 Hz, 15-CH_2); 3.12-3.16 (m, 1H, 12-CH_2); 3.50-3.53 (m, 1H, 3-CH);3.82 (s, 3H, OMe); 5.39-5.41 (m, 1H, 6-CH); 6.92 (d, 2H, *J* = 9.16 Hz, 2CH_{arom}); 7.66 (d, 2H, *J* = 9.16 Hz, 2CH_{arom}); 9.19 (s, 1H, $CH_{pyridazine}$); 9.98 (s, 1H, NH).[1013]C NMR (75 MHz, DMSO-d_6): δ 15.5 (18-CH_3); 19.5 (19-CH_3); 20.2 (11-CH_2); 30.6 (15-CH_2);31.0 (8-CH); 31.7 (2-CH_2); 31.7 (12-CH_2); 33.9 (7-CH_2); 36.8 (1-CH_2); 37.1(10-C); 42.3 (4-CH_2); 48.2 (13-C); 50.2 (9-CH); 55.6 (14-CH); 57.1 (OMe);71.7 (3-CH); 114.4 (2CH_{arom}); 120.7 (6-CH); 121.7(2CH_{arom}); 131.0 (C_{arom}); 141.6 (5-C); 146.4 (16-C); 149.7 ($C_{pyridazine}$); 150.5 ($CH_{pyridazine}$); 154.0 (17-C); 156.7 (C_{arom}); 161.4 (CO).IR (KBr): 3310 (NH), 2956, 2933, 2922,2894 (CH), 1686 (CON), 1665, 1598, 1527, 1514, 1457, 1437, 1415, 1236 cm^{-1}. HRMS (ESI) for $C_{29}H_{36}N_3O_3$ ($[M+H]^+$):calcd 474.2751, found 474.2759.



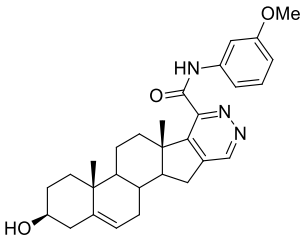
6'-[N-(4-Chlorophenyl)carbamoyl]-3β-hydroxyandrost-5-eno[16,17-d]pyridazine10b'.

Yield 92% (74 mg). Pale yellowsolid, Mp279-282ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91-1.12 (m, 2H, 1-CH_2, 9-CH); 1.10 (s, 3H, 19-CH_3); 1.25 (s, 3H, 18-CH_3); 1.40-1.93 (m, 9H, 1-CH_2, 2-CH_2, 7-CH_2, 8-CH, 11-CH_2,12-CH_2, 14-CH); 2.10-2.18 (m, 1H, 7-CH_2); 2.27-2.33 (m, 2H, 4-CH_2); 2.65 (dd,1H,*J*=14.02, 16.48 Hz, 15-CH_2); 2.87 (dd,1H,*J*= 6.41, 16.48 Hz, 15-CH_2); 3.09-3.14 (m, 1H, 12-CH_2); 3.50-3.57 (m, 1H, 3-CH); 5.38-5.40 (m, 1H, 6-CH); 7.35 (d, 2H, *J* = 8.24 Hz, 2CH_{arom}); 7.75 (d, 2H, *J* = 8.24 Hz, 2CH_{arom}); 9.20 (s, 1H, $CH_{pyridazine}$); 10.13 (s, 1H, NH).[1013]C NMR (75 MHz, DMSO-d_6): δ 15.4 (18-CH_3); 19.3 (19-CH_3); 20.7 (11-CH_2); 30.6 (15-CH_2);31.0 (8-CH); 31.8 (2-CH_2);32.0(12-CH_2); 33.8 (7-CH_2); 36.7 (10-C); 37.1 (1-CH_2); 42.2 (4-CH_2); 48.2 (13-C); 50.1 (9-CH); 57.0 (14-CH);71.6 (3-

[10] The signal of the OH group was not observed in ^{1}H NMR.

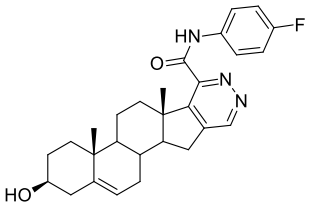
CH); 120.6 (6-CH); 121.2(2CH_{arom});129.1(2CH_{arom}); 129.5 (C_{arom}); 136.3 (C_{arom});141.5 (5-C); 146.6 (16-C); 150.5 ($C_{pyridazine}$); 150.5 ($CH_{pyridazine}$); 154.2 (17-C); 161.4 (CO).HRMS (ESI) for $C_{28}H_{33}ClN_3O_2$ ($[M+H]^+$): calcd 478.2256, found 478.2246.



6'-[N-(3-Methoxyphenyl)carbamoyl]-3β-hydroxyandrost-5-eno[16,17-d]pyridazine10e'.

Yield 86% (69 mg). Pale yellowsolid, Mp179-180°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93-1.13 (m, 2H, 1-CH_2, 9-CH); 1.12 (s, 3H, 19-CH_3); 1.26 (s, 3H, 18-CH_3); 1.44-1.95 (m, 9H, 1-CH_2, 2-CH_2, 7-CH_2, 8-CH, 12-CH_2, 11-CH_2, 14-CH); 2.28-2.32 (m, 1H, 7-CH_2); 2.25-2.39 (m, 2H, 4-CH_2); 2.64 (dd, 1H,*J* = 13.19, 15.39 Hz, 15-CH_2); 2.86 (dd, 1H, *J* = 6.60, 15.39 Hz, 15-CH_2); 3.13-3.17 (m, 1H, 12-CH_2); 3.51-3.58 (m, 1H, 3-CH); 3.86 (s, 3H, OMe); 5.39-5.41 (m, 1H, 6-CH); 6.70-6.73 (m, 2H, 2CH_{arom}); 7.25-7.30 (m, 1H, CH_{arom});7.44-7.45 (m, 1H, CH_{arom}); 9.19 (s, 1H, $CH_{pyridazine}$); 10.05 (s, 1H, NH).^{1013}CNMR (75 MHz, DMSO-d_6):δ 15.5 (18-CH_3); 19.4 (19-CH_3); 20.8 (11-CH_2); 30.8 (15-CH_2); 31.2 (8-CH); 31.7 (2-CH_2); 31.7 (12-CH_2); 32.8 (7-CH_2); 36.8 (10-C); 37.2 (1-CH_2); 42.1 (4-CH_2); 48.2 (13-C); 50.3 (9-CH); 55.4 (14-CH); 57.1 (OMe); 71.7 (3-CH); 106.0 (CH_{arom}); 110.5(CH_{arom}); 112.5 (CH_{arom}); 120.6 (6-CH); 129.8 (CH_{arom}); 139.0 (C_{arom}); 141.7 (5-C); 146.3 (16-C); 150.5 ($CH_{pyridazine}$); 150.5 ($C_{pyridazine}$); 154.7 (17-C); 160.5 (C_{arom});161.6 (CO).IR (KBr): 3312 (NH), 2935, 2918, 2897 (CH), 1680 (CON), 1660, 1598, 1524, 1435, 1415 cm^{-1}. HRMS (ESI) for $C_{29}H_{36}N_3O_3$ ($[M+H]^+$):calcd 474.2751, found 474.2754.

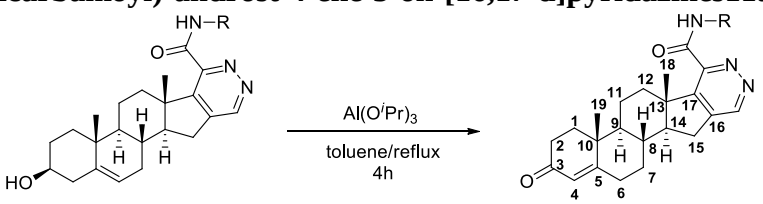


6'-(N-(4-Fluorophenyl)carbamoyl)-3β-hydroxyandrost-5-eno[16,17-d]pyridazine 10f'.

Yield 92% (72 mg). Pale yellowsolid, Mp295-297°C.

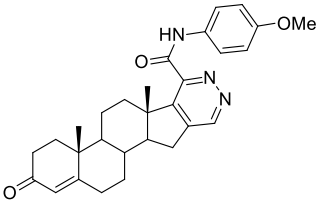
^{1}H NMR (600 MHz, DMSO-d_6): δ 0.95-1.09 (m, 2H, 1-CH_2, 9-CH); 1.02 (s, 3H, 19-CH_3); 1.18 (s, 3H, 18-CH_3); 1.40-1.81 (m, 9H, 1-CH_2, 2-CH_2, 7-CH_2, 8-CH, 12-CH_2, 11-CH_2, 14-CH); 2.04-2.06 (m, 1H, 7-CH_2); 2.13-2.17 (m, 2H, 4-CH_2);2.39-2.41 (m, 1H, 12-CH_2); 2.67 (dd, 1H, *J* = 13.90, 15.73 Hz, 15-CH_2); 2.85 (dd, 1H, *J* = 6.39, 15.73 Hz, 15-CH_2); 3.20-3.25 (m, 1H, 3-CH); 4.75 (s, 1H, OH);5.30-5.31 (m, 1H, 6-CH); 7.17-7.19 (m, 2H, 2CH_{arom}); 7.83-7.85 (m, 2H, 2CH_{arom}); 9.32 (s, 1H, $CH_{pyridazine}$); 10.81 (s, 1H, NH).^{13}CNMR (150MHz, DMSO-d_6):δ 16.1 (18-CH_3); 18.9 (19-CH_3); 19.2 (11-CH_2); 29.6 (15-CH_2); 30.1 (8-CH); 30.6 (7-CH_2); 31.2 (2-CH_2); 32.8 (12-CH_2); 36.0 (10-C); 37.2 (1-CH_2); 42.0 (4-CH_2); 46.2 (13-C); 49.4 (9-CH); 56.3 (14-CH); 69.8 (3-CH); 115.1 (d, J_{C-F} = 22.2 Hz, 2CH_{arom}); 119.6 (6-CH); 121.7 (d, J_{C-F} = 7.6 Hz, 2CH_{arom}); 134.8 (C_{arom}); 141.5 (5-C); 145.0 (16-C); 150.7 (17-C); 150.2 ($CH_{pyridazine}$); 151.4 ($C_{pyridazine}$); 158.5 (d, J_{C-F} = 240.6Hz, C_{arom}); 163.4 (CO).IR (KBr): 3316 (NH), 2961, 2936, 2904, 2819 (CH), 1696 (CON), 1535, 1522 cm^{-1}.HRMS (ESI) for $C_{28}H_{33}FN_3O_2$ ($[M+H]^+$):calcd 462.2551, found 462.2552.

Synthesis of 6'-(N-arylcarbamoyl)-androst-4-ene-3-on-[16,17-d]pyridazines11a,f.



Aluminiumisopropoxide(0.12 mL, 0.6mmol) was added to a solution of the 3β-hydroxyandrost-5-ene[16,17-d]pyridazines **10a',f'** (0.1mmol) and cyclohexanone (2.4 mL, 26mmol) in dry toluene(4 mL). The reaction mixture was refluxed for 4h until the complete conversion of the starting material (TLC

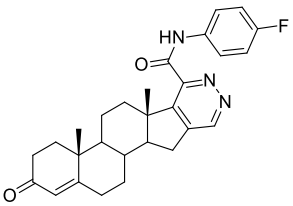
monitoring). The resulted mixture was cooled to room temperature and poured onto AcOH(30% water solution, 8 mL). Organic fraction was washed with saturated solution of $NaHCO_3$, water fraction was extracted with $CHCl_3$ (3x7 mL). Combined organic fraction was washed with water till pH 7. Solvent was removed under reduced pressure. An excess ofcyclohexanone was removed by steam distillation.The crude product was purified by column chromatography using petroleum ether/ethyl acetate (1:1) as eluent.



6'-[N-(4-Methoxyphenyl)carbamoyl]-androst-4-ene-3-on[16,17-d]pyridazine11a.

Yield 58% (27 mg). Pale yellow solid, Mp208-210^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 3H, 19-CH_3); 1.27 (s, 3H, 18-CH_3); 0.93-3.17 (m, 17H); 3.82 (s, 3H,OMe); 5.77 (s, 1H, 4-CH); 6.92 (d, 2H, J = 9.05 Hz, 2CH_{arom}); 7.67 (d, 2H, J = 9.05 Hz, 2CH_{arom}); 9.20 (s, 1H, $CH_{pyridazine}$); 9.99 (s, 1H, NH).^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6 (19-CH_3); 17.3 (11-CH_2); 20.8 (18-CH_3); 29.7 (8-CH); 30.9 (7-CH_2); 31.5 (6-CH_2); 32.6 (2-CH_2); 33.7 (1-CH_2); 33.9 (15-CH_2); 35.5 (12-CH_2); 38.2 (10-C); 48.2 (13-C); 53.7 (9-CH); 55.6 (OMe); 56.3 (14-CH); 114.4 (2CH_{arom}); 121.7 (2CH_{arom}); 124.2 (4-CH); 130.9 (C_{arom}); 145.9 (16-C); 149.4 ($CH_{pyridazine}$); 150.4 (17-C); 153.6 ($C_{pyridazine}$); 156.7 (C_{arom}); 161.3 (CO); 170.1 (5-C); 199.4 (3-C). IR (KBr): 3356, 3423,3326 (NH), 2936, 2881 (CH), 1673 (CON), 1664 (CO), 1531, 1513, 1266, 1233, 1184 cm^{-1}. HRMS (ESI) for $C_{29}H_{34}N_3O_3$ ([M+H]$^{+}$):calcd 472.2595, found 474.2598.

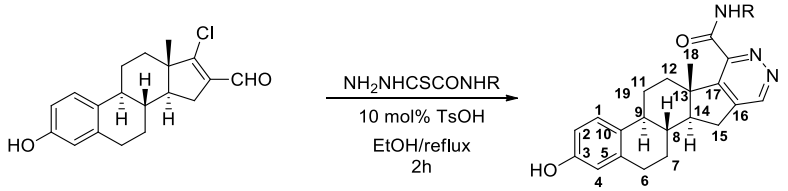


6'-[N-(4-Fluorophenyl)carbamoyl]-androst-4-ene-3-on[16,17-d]pyridazine11f.

Yield 60% (28 mg). Pale yellow solid, Mp253^{o}C.

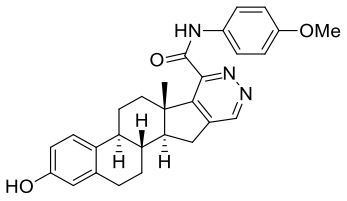
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H, 19-CH_3); 1.30 (s, 3H, 18-CH_3); 0.86-3.18 (m, 17H); 5.77 (s, 1H, 4-CH);7.06-7.12 (m, 2H, 2CH_{arom}); 7.70-7.75 (m, 2H, 2CH_{arom}); 9.21 (s, 1H, $CH_{pyridazine}$); 10.11 (s, 1H, NH).^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3 (19-CH_3); 19.4 (11-CH_2); 20.8 (18-CH_3); 29.8 (8-CH); 31.0 (7-CH_2); 31.6 (6-CH_2); 32.6 (2-CH_2); 33.7 (1-CH_2); 34.0 (15-CH_2); 35.6 (12-CH_2); 37.1 (10-C); 50.1 (13-C); 53.7 (9-CH); 56.3 (14-CH); 115.6 (d, J_{C-F} = 21.0 Hz, 2CH_{arom}); 120.7 (4-CH); 121.7 (d, J_{C-F} = 7.9 Hz, 2CH_{arom}); 133.8 (C_{arom}); 146.1 (16-C); 149.2 ($CH_{pyridazine}$); 150.6 (17-C); 153.7 ($C_{pyridazine}$); 161.5 (CO); 158.7 (d, J_{C-F} = 240.6 Hz, C_{arom}); 170.0 (5-C); 199.3 (3-C).IR (KBr): 3312 (NH), 2930, 2862 (CH), 1673 (CON), 1647 (CO), 1538, 1527, 1508, 1407, 1231, 1207 cm^{-1}. HRMS (ESI) for $C_{28}H_{31}FN_3O_2$ ([M+H]$^{+}$): calcd 460.2395, found 460.2393.

Synthesis of 6'-(N-arylcarbamoyl)-1,3,5-estratriene[16,17-d]pyridazines 14.



Oxamic acid thiohydrazide (0.17mmol) was added to a solution of 3-hydroxy-16-formyl-17-chloro-1,3,5,(10),16-estratetraene (53 mg, 0.17mmol) and p-toluenesulfonic acid monohydrate (3.1 mg, 10 mol%) in ethanol (30 mL). The reaction mixture was refluxed for 2 h until the complete conversion of the intermediate hydrazone (TLC monitoring). The resulted mixture was cooled to room temperature and

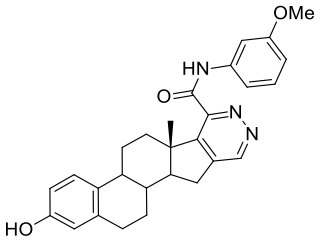
poured onto ice-water (40 mL). The resulting off-white precipitate was filtered, washed with water (3×15 mL) and heptane (3×15 mL), and dried in air. The crude product was purified by column chromatography using petroleum ether/ethyl acetate (1:1)as eluent.



6'-[N-(4-Methoxyphenyl)carbamoyl]-3β-hydroxyestra1,3,5(10)trieno[16, 17-d]pyridazine 14a.

Yield 79% (61 mg). Pale yellowsolid, Mp260ºC.The spectral data matched previously reported.[5]

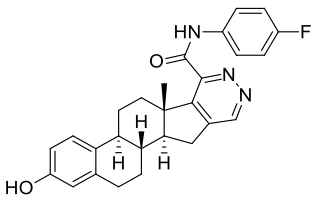
^{1}HNMR (600 MHz, DMSO-d_6): δ 1.12 (s, 3H, 18-CH_3); 1.41-1.43 (m, 1H, 7-CH_2); 1.50-1.54 (m, 1H, 11-CH_2); 1.62-1.64 (m, 1H, 12-CH_2); 1.65-1.67 (m, 1H, 8-CH); 1.77-1.79 (m, 1H, 14-CH); 1.91-1.93 (m, 1H, 7-CH_2); 2.22-2.24 (m, 1H, 9-CH); 2.32-2.35 (m, 1H, 11-CH_2); 2.40-2.42 (m, 1H, 12-CH_2); 2.74-2.76 (m, 1H, 6-CH_2); 2.75-2.78 (m, 1H, 15-CH_2); 2.79-2.81 (m, 1H, 6-CH_2); 2.97-2.99 (m, 1H, 15-CH_2); 3.74 (s, 3H, OMe); 6.44 (d, 1H, *J*= 1.86 Hz, 4-CH); 6.46 (dd, 1H, *J*= 1.86, 8.80 Hz, 2-CH); 6.93 (d, 2H, *J* = 8.80 Hz, 2CH_{arom}); 7.05 (d, 1H, *J*= 8.80 Hz, 1-CH); 7.72 (d, 2H, *J* = 8.80 Hz, 2CH_{arom}); 9.32 (s, 1H, $CH_{pyridazine}$); 10.59 (s, 1H, NH).^{1013}CNMR (125 MHz, DMSO-d_6): δ 16.4 (18-CH_3); 25.8 (11-CH_2); 27.3 (7-CH_2); 29.0 (6-CH_2); 29.6 (15-CH_2); 36.9 (8-CH); 32.8 (12-CH_2); 43.3 (9-CH); 46.7 (13-C); 55.2 (OMe); 55.6 (14-CH); 112.8 (2-CH); 114.0 (2CH_{arom}); 115.0 (4-CH); 122.0 (2CH_{arom}); 125.9 (1-CH); 130.0 (10-C); 131.8 (C_{arom}); 137.0 (5-C); 146.0 (16-C); 150.3 ($CH_{pyridazine}$); 150.9 ($C_{pyridazine}$); 151.9 (17-C); 155.1 (3-C); 155.8 (C_{arom}); 163.4 (CO).



6'-[N-(3-Methoxyphenyl)carbamoyl]-3β-hydroxyestra-1,3,5(10)trieno[16,17-d]pyridazine 14e.

Yield 83% (64 mg). Pale yellowsolid, Mp178-180ºC.

^{1}H NMR (300 MHz, DMSO-d_6):δ 1.15 (s, 3H, 18-CH_3); 1.41-1.43 (m, 1H, 7-CH_2); 1.40-1.54 (m, 1H, 11-CH_2); 1.62-1.65 (m, 1H, 12-CH_2); 1.65-1.69 (m, 1H, 8-CH); 1.77-1.80 (m, 1H, 14-CH); 1.91-1.99 (m, 1H, 7-CH_2); 2.23-2.26 (m, 1H, 9-CH); 2.32-2.36 (m, 1H, 11-CH_2); 2.40-2.43 (m, 1H, 12-CH_2); 2.70-2.72 (m, 1H, 15-CH_2); 2.75-2.78 (m, 1H, 6-CH_2); 2.93-2.98 (m, 1H, 15-CH_2); 3.77 (s, 3H, OMe); 6.48 (d, 1H, *J* = 1.95 Hz, 4-CH); 6.50 (dd, 1H, *J* = 1.95, 8.65 Hz, 2-CH);6.75 (dd, 1H, *J* = 1.86, 8.37 Hz, CH_{arom}); 7.03 (d, 1H, *J* = 8.65 Hz, 1-CH);7.28 (dd, 1H, *J* = 8.37 Hz, CH_{arom}); 7.42 (d, 1H, *J* = 8.37 Hz, CH_{arom}); 7.51 (d, 1H, *J* = 1.86 Hz, CH_{arom});9.02 (br.s, 1H, OH); 9.36 (s, 1H, $CH_{pyridazine}$);10.83 (s, 1H, NH).^{13}C NMR (75 MHz, DMSO-d_6): δ 16.4 (18-CH_3); 25.7 (11-CH_2); 27.2 (7-CH_2); 28.9 (6-CH_2); 29.3 (15-CH_2); 37.0 (8-CH); 32.7 (12-CH_2); 43.2 (9-CH); 46.6 (13-C); 55.0 (OMe); 55.6 (14-CH);105.7 (CH_{arom}); 109.5 (CH_{arom}); 112.2 (CH_{arom}); 112.7 (2-CH);114.9 (4-CH); 125.8 (1-CH); 129.6 (CH_{arom}); 129.9 (10-C); 136.9 (5-C); 139.8 (C_{arom}); 145.1 (16-C); 150.4 ($CH_{pyridazine}$); 151.0 ($C_{pyridazine}$);151.7 (17-C); 155.0 (3-C); 159.5 (C_{arom}); 163.8 (CO).IR (KBr): 3323 (NH), 3136, 2935, 2869 (CH), 1694 (CON), 1606, 1535, 1524, 1495, 1464, 1287, 1252, 1154 cm^{-1}. HRMS (ESI) for $C_{28}H_{30}N_3O_3$ ($[M+H]^+$):calcd 456.2282, found 456.2288.



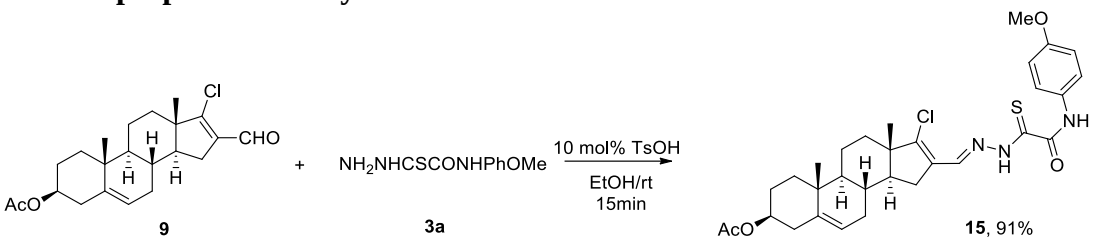
6'-[N-(4-Fluorophenyl)carbamoyl]-3β-hydroxyestra-1,3,5(10)trieno[16,17-d]pyridazine 14f.

Yield 91% (68 mg). Colorless solid, Mp232ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (s, 3H, 18-CH_3); 1.41-1.43 (m, 1H, 7-CH_2); 1.52-1.57 (m, 1H, 11-CH_2); 1.62-1.67 (m, 1H, 12-CH_2); 1.67-1.70 (m, 1H, 8-CH); 1.77-1.79 (m, 1H, 14-CH); 1.93-1.96 (m, 1H, 7-CH_2); 2.23-2.27 (m, 1H, 9-CH); 2.32-2.35 (m, 1H, 11-CH_2); 2.40-2.44 (m, 1H, 12-CH_2); 2.73-2.76 (m, 1H, 6-CH_2); 2.75-2.78 (m, 1H, 15-CH_2);

2.80-2.86 (m, 1H, 6-CH_2); 2.95-2.99 (m, 1H, 15-CH_2); 6.48 (d, 1H, *J* = 1.86 Hz, 4-CH); 6.53 (dd, 1H, *J* = 1.86, 8.80 Hz, 2-CH); 7.04 (d, 1H, *J* = 8.80 Hz, 1-CH); 7.24 (dd, 2H, *J* = 8.80, 8.87 Hz, $2CH_{arom}$); 7.89 (dd, 2H, *J* = 5.08, 8.80 Hz, $2CH_{arom}$); 9.05 (br.s, 1H, OH); 9.38 (s, 1H, $CH_{pyridazine}$); 10.95 (s, 1H, NH).[13]CNMR (75 MHz, DMSO-d_6): δ 16.3 (18-CH_3); 26.0 (11-CH_2); 27.3 (7-CH_2); 29.0 (6-CH_2); 29.8 (15-CH_2); 36.9 (8-CH); 32.8 (12-CH_2); 43.3 (9-CH); 46.7 (13-C); 55.6 (14-CH); 112.8 (2-CH); 115.0 (4-CH); 115.2 (d, J_{C-F} = 22.5 Hz, $2CH_{arom}$); 122.0 (d, J_{C-F} = 7.6 Hz, $2CH_{arom}$); 125.9 (1-CH); 129.9 (10-C); 135.0 (C_{arom}); 136.9 (5-C); 145.2 (16-C); 150.5 ($CH_{pyridazine}$); 151.2 (17-C); 151.6 ($C_{pyridazine}$); 155.0 (3-C);159.3 (d, J_{C-F} = 239.3 Hz, C_{arom}); 163.7 (CO).HRMS (ESI) for $C_{27}H_{27}FN_3O_2$ ($[M+H]^+$): calcd 444.2082, found 444.2071.

Procedure for the preparation of hydrazone 15.



Oxamic acid thiohydrazide (25 mg, 0.11 mmol) was added to a solution of the 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene (38 mg, 0.11 mmol) and p-toluenesulfonic acid monohydrate (1.9 mg, 10 mol%) in ethanol (30 mL). The reaction mixture was stored at rt for 30-40 min. The precipitate formed was filtered, washed with ethanol, and dried *in vacuo* to obtain product **15** as a yellow solid, mp 247-250ºC, in 91% yield (58 mg, 0.091 mmol).

^{1}H NMR (600 MHz, DMSO-d_6, for the mixture of *E*-**14**-thione/**14**-thiadiazoline, 1:1)[11] δ 0.83-2.28 (m, 34H, *E*-**14**-thione+**14**-thiadiazoline); 0.94 (s, 6H, 19-CH_3, *E*-**14**-thion+**14**-thiadiazoline); 1.01 (s, 6H, 18-CH_3, *E*-**14**-thione+**14**-thiadiazoline); 1.96 (s, 6H, OAc, *E*-**14**-thione+**14**-thiadiazoline); 3.72 (s, 6H, OCH_3, *E*-**14**-thione+**14**-thiadiazoline); 4.44 (m, 2H, 3-CH, *E*-**14**-thione+**14**-thiadiazoline); 5.35-5.38 (m, 2H, 6-CH, *E*-**14**-thione+**14**-thiadiazoline); 6.31 (br.s, 1H, CH, **14**-thiadiazoline); 6.86 (d, *J* = 8.6 Hz, 4H, 4-$MeOC_6H_4$, **14**-thione+**14**-thiadiazoline); 7.64 (d, 4H, *J* = 8.6 Hz, 4H, 4-$MeOC_6H_4$, **14**-thione+**14**-thiadiazoline); 8.81 (s, 1H, CH, **14**-thione); 8.87 (br.s., 1H, NH, **14**-thiadiazoline); 10.09 (s, 1H, NHCO, **14**-thione); 10.36 (s, 1H, NHCO, **14**-thiadiazoline); 13.74 (s, 1H, NHCS, **14**-thion).[13]C NMR (125 MHz, DMSO-d_6 for the mixture of *E*-**14**-thione/**14**-thiadiazoline/*Z*-**14**-thiol) δ 14.7, 14.7, 16.0, 18.7, 19.8, 19.9, 20.9, 27.2, 28.8, 29.2, 29.6, 29.7, 29.8, 30.0, 30.2, 30.3, 30.8, 32.5, 32.8, 33.0, 36.2, 37.5, 39.1, 39.2, 39.4, 39.5, 39.6, 39.8, 49.2, 49.4, 49.5, 53.0, 53.2, 55.1, 56.2, 67.9, 73.0, 113.6, 113.8, 113.8, 113.9, 114.1, 121.3, 121.4, 121.5, 121.6, 130.5, 131.2, 132.9, 139.7, 143.2, 149.9, 150.4, 155.5, 155.6, 157.3, 157.6, 169.5, 184.8, 193.1. HRMS (ESI) for $C_{31}H_{38}ClN_3NaO_4S$ ($[M+Na]^+$): calcd 606.2164, found 606.2161.

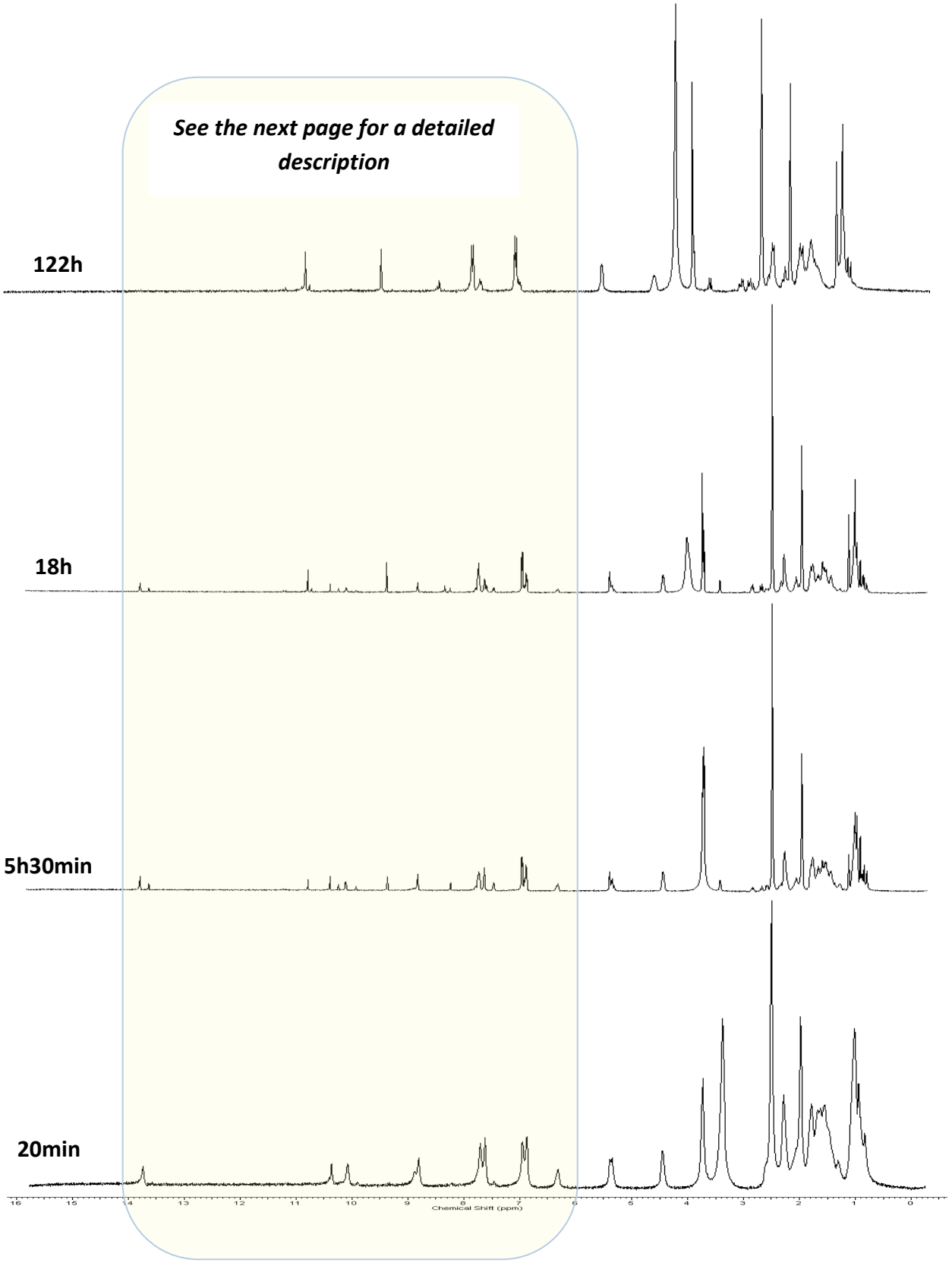
[11] In ^{1}H NMR of compound **15**, the characteristic signals of *Z*-**15**-thione form are observed at σ 13.58 (CONH), 10.22 (NHCS) and 8.22 (CH=) ppm.

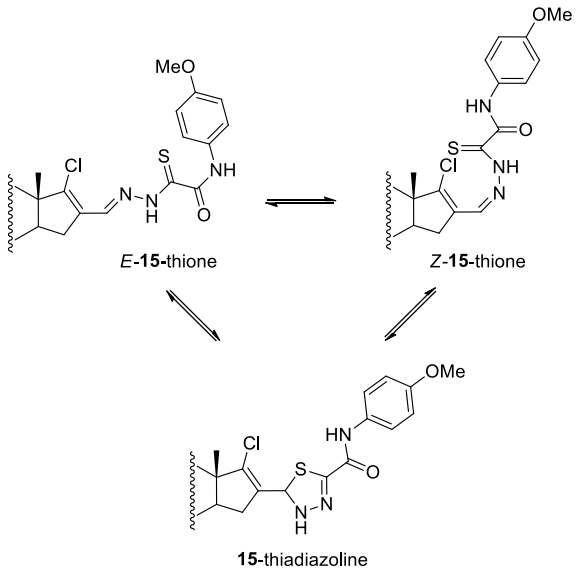
Biology

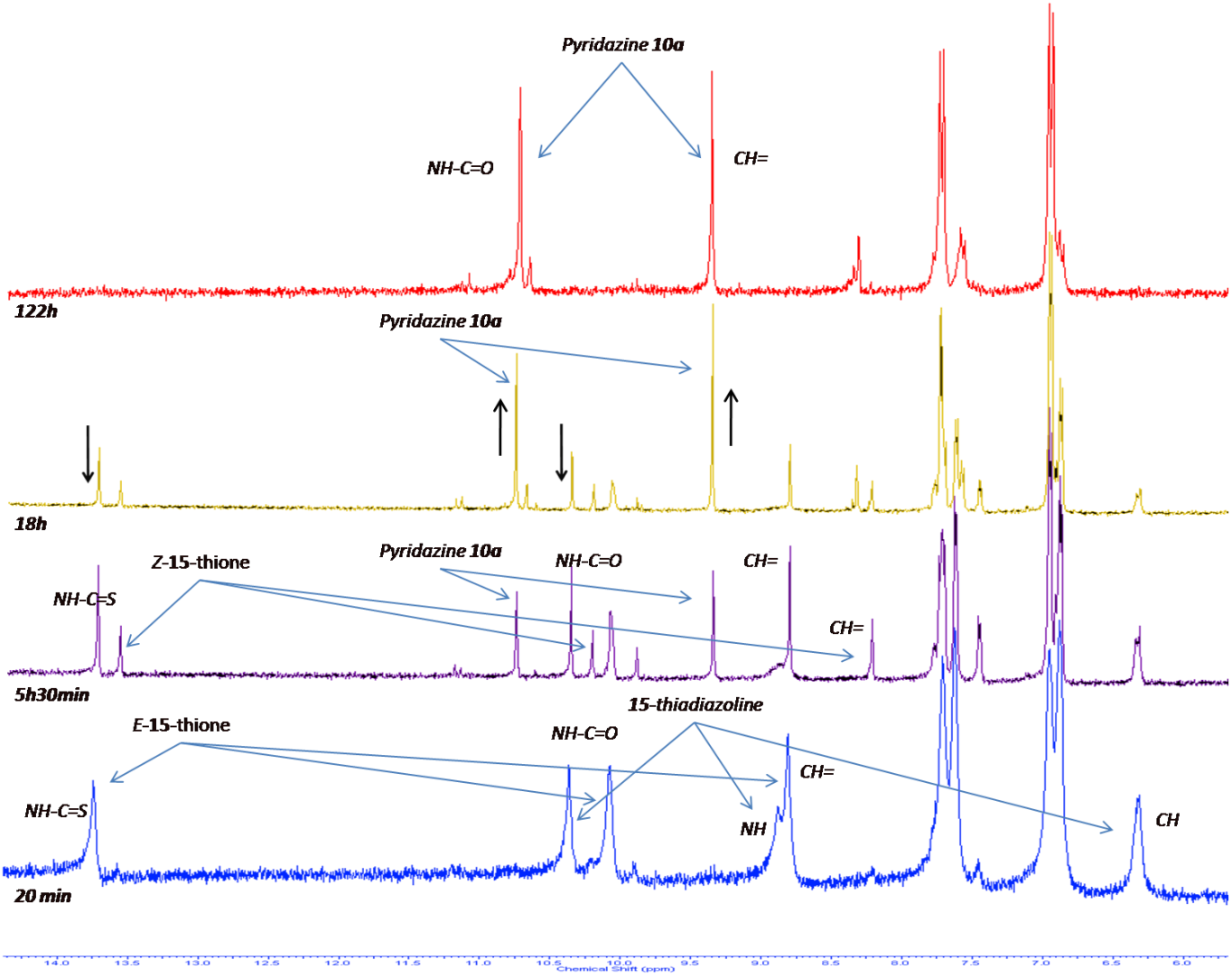
Cell cultures and evaluation of the inhibitory activity

The human breast cells, hormone dependent MCF-7 and hormone independent MDA-MB-231, were purchased from ATCC collection (USA) and stored in the cryobank of N.N. Blokhin Cancer Research Center (Moscow, Russia) until the present analysis. Cells were cultured in standard high glucose DMEM medium (PanEco, Russia) supplemented with 10% fetal calf serum (FCS) (HyClone, USA) and 0,1 mg/ml sodium pyruvate (Santa Cruz, USA) at 37°C, 5% CO_2 and 80-85% humidity (NuAir CO_2 incubator). The cell growth was evaluated by the MTT-test based on the accumulation of a MTT reagent (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) (Applichem, USA) by living cells. Briefly, the cells were seeded with 10^4 cells per well in 24-well plates (Corning, USA) in 900 μL of medium. The tested compounds were dissolved in DMSO (Applichem, USA) to 5 mM before experiments and then were diluted in medium to required concentrations. Compounds with different concentrations in 100 μL of medium were added in 24 h after seeding and the cells were grown for 72 hours. After incubation with compounds medium was removed and MTT reagent dissolved in medium was added at a final concentration of 0.2 mg/ml to each well and incubated for 3 h. Then the cell supernatants were removed and the MTT formazan purple crystals were dissolved in 100% DMSO (350 μL per well). Plates were gently shaken and the density of absorbance was measured at 571 nm on MultiScan reader (ThermoFisher, USA). Viability of the cells was expressed after subtraction of blank value (the density of absorbance in the well w/o cells) from all wells.Dose-response curves were analyzed by regression analysis using sigmoid curves (Log(concentration) vs normalized density of absorbance). In this study, concentrations that inhibited half cell growth (IC_{50} values)were provided using GraphPad Prism (USA).

Monitoring of Chemical Reaction **9** with **3a** in Real Time with ^{1}H NMR Spectroscopy in DMSO-d_6




MeO
Cl
S
NH
N
N
H
O
E-15-thione
OMe
HN
O
S
Cl
NH
N
Z-15-thione
OMe
HN
Cl
S
O
N
N
H
15-thiadiazoline


Pyridazine 10a
NH-C=O
CH=
122h
Pyridazine 10a
18h
Z-15-thione
Pyridazine 10a
NH-C=O
CH=
NH-C=S
CH=
5h30min
15-thiadiazoline
E-15-thione
NH-C=O
CH=
NH-C=S
NH
CH
20 min
Chemical Shift (ppm)

Monitoring of Chemical Reaction **9** with **3a** in Real Time with ^{1}H NMR Spectroscopy in $CDCl_3$

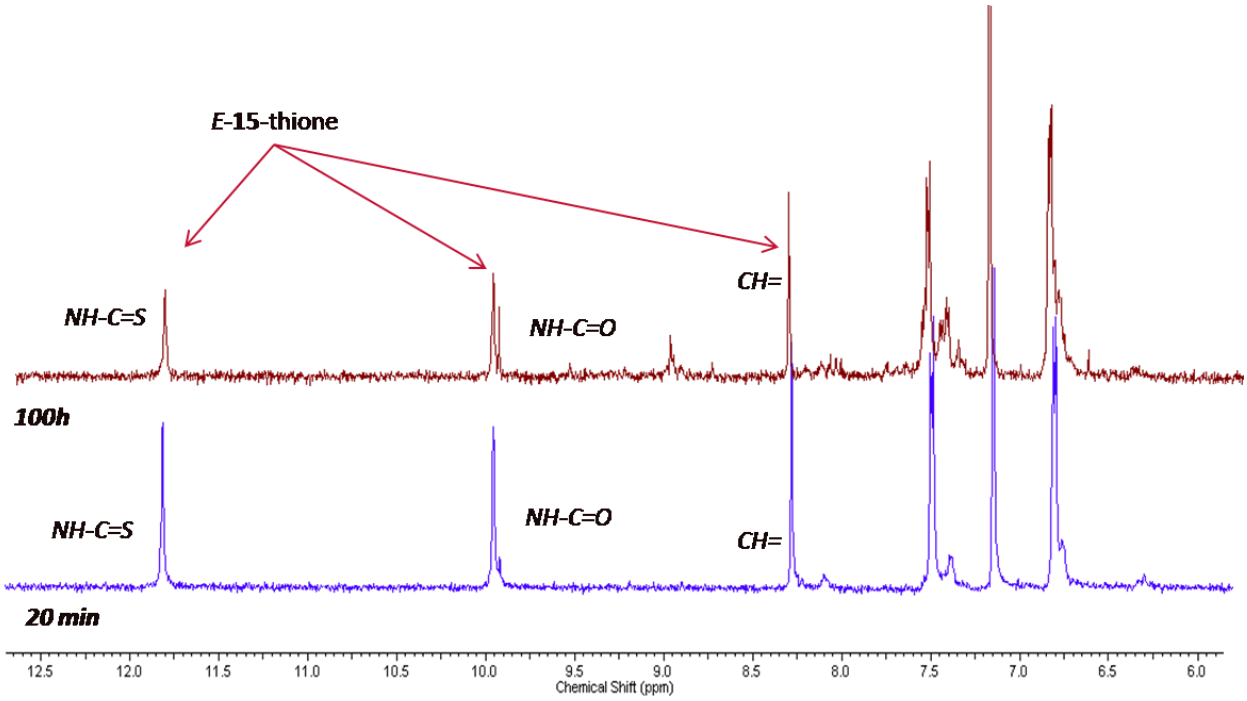
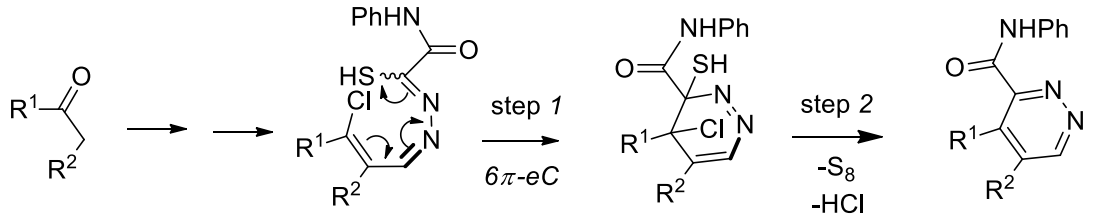


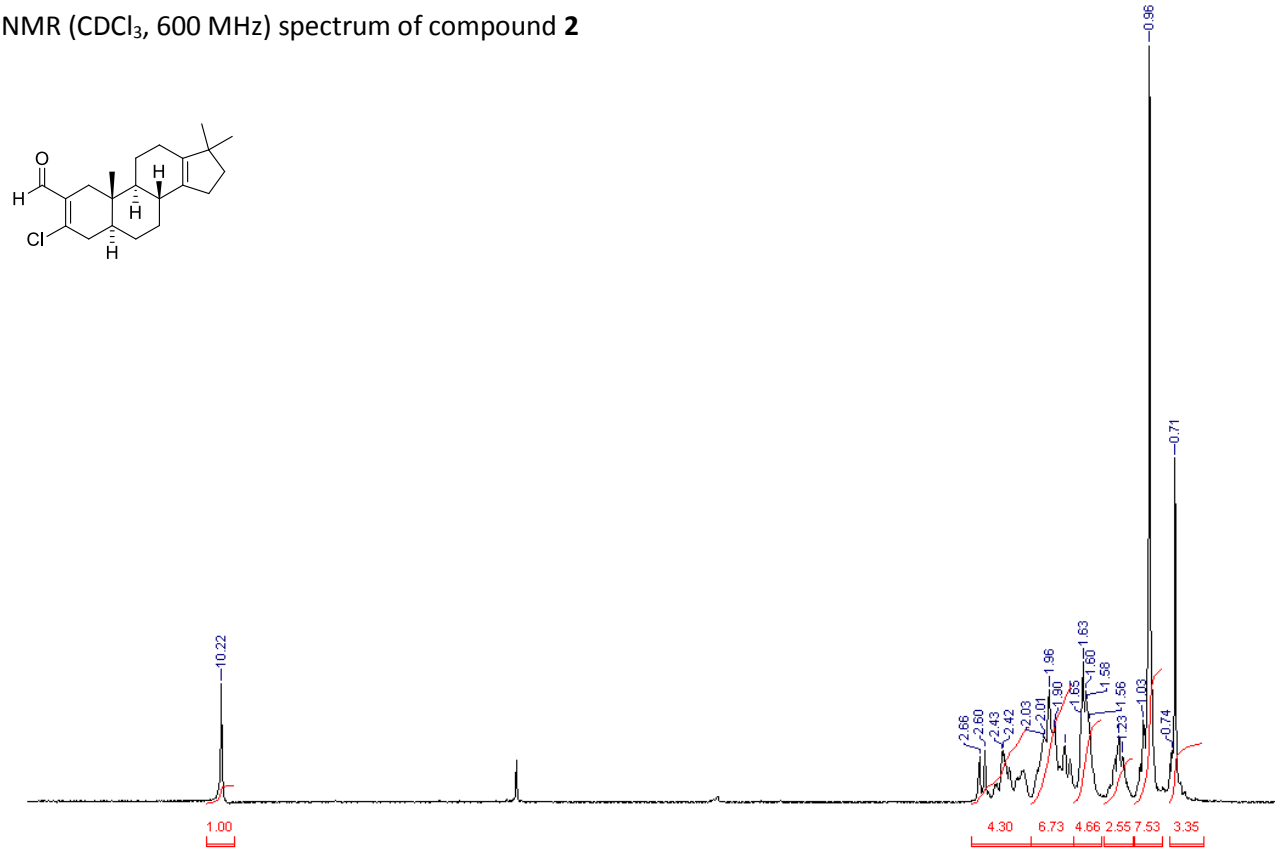
Table 1. Heat of reactions and Activation energy of disrotatory reaction (Kcal/Mol) calculated by semi-empirical quantum chemistry method PM6[12]



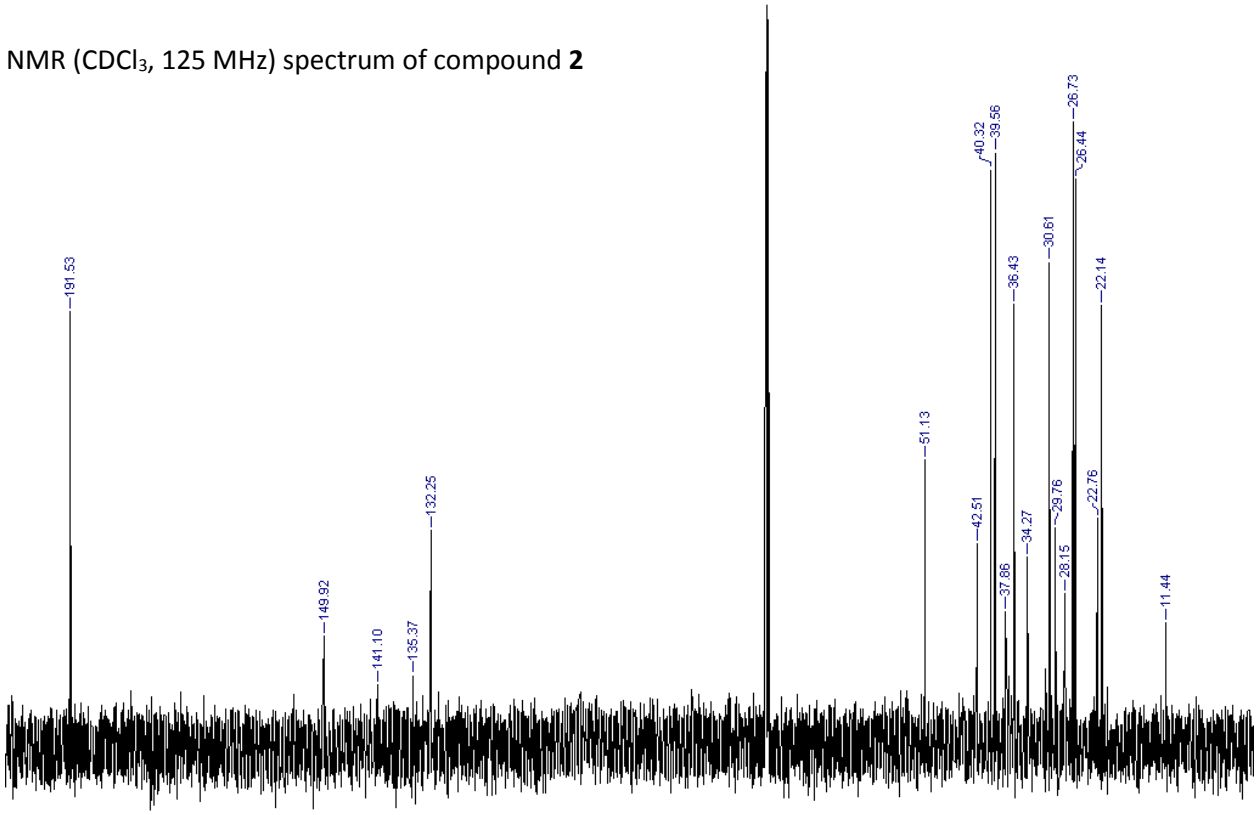
Startingketone (**A**)	Step*1* 6π-electrocyclization		Step*2* aromatization	Step*1*+ Step*2*
	ΔH_{react}	$E^{\neq}_{act}$	ΔH_{react}	ΔH_{react}
Cyclohexanone	-11.63	8.24	-19.49	-31.12
1	-7.31	5.72	-22.89	-30.2
5	-7.32	5.72	-22.90	-30.22
Cyclopentanone	-12.39	9.12	-19.18	-31.57
8	-4.51	3.22	-27.38	-31.89
12	-3.32	2.54	-27.58	-30.9

[12] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.

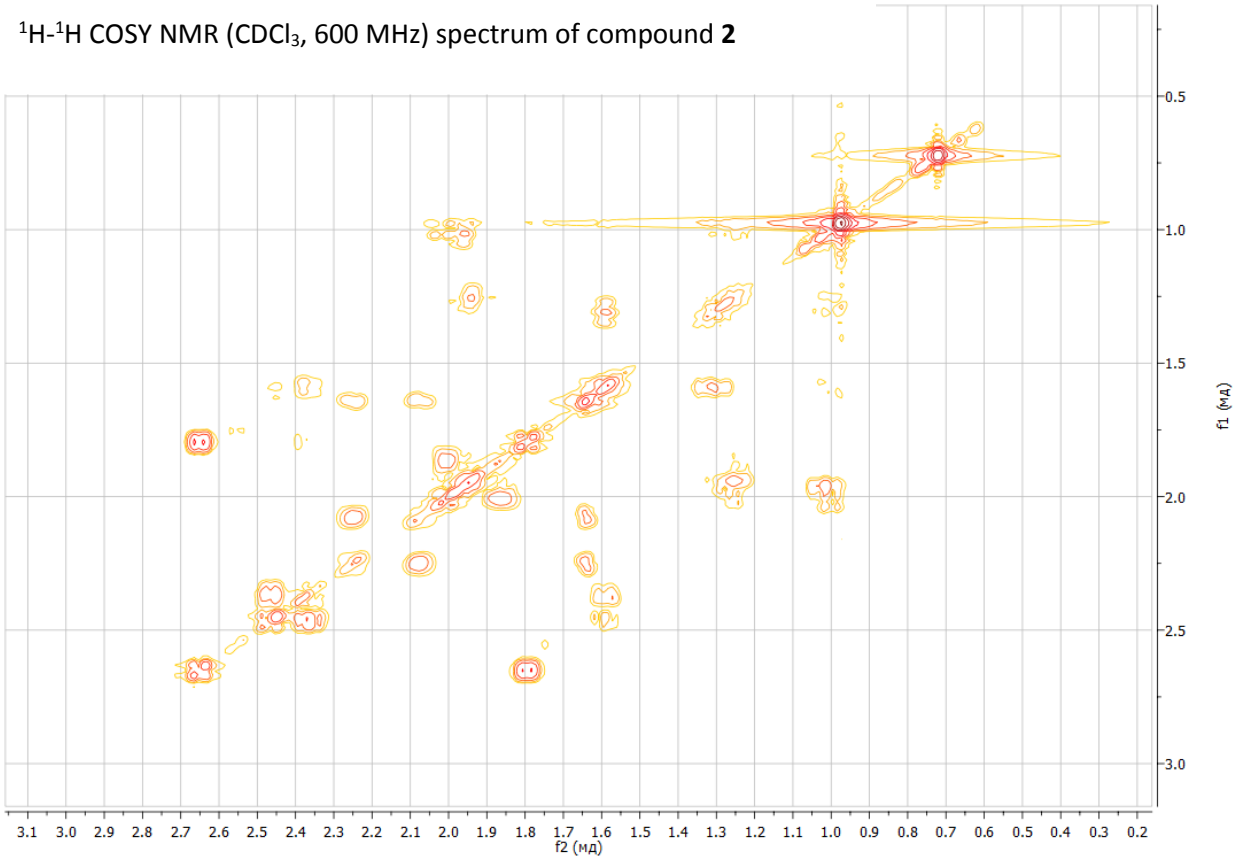
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **2**



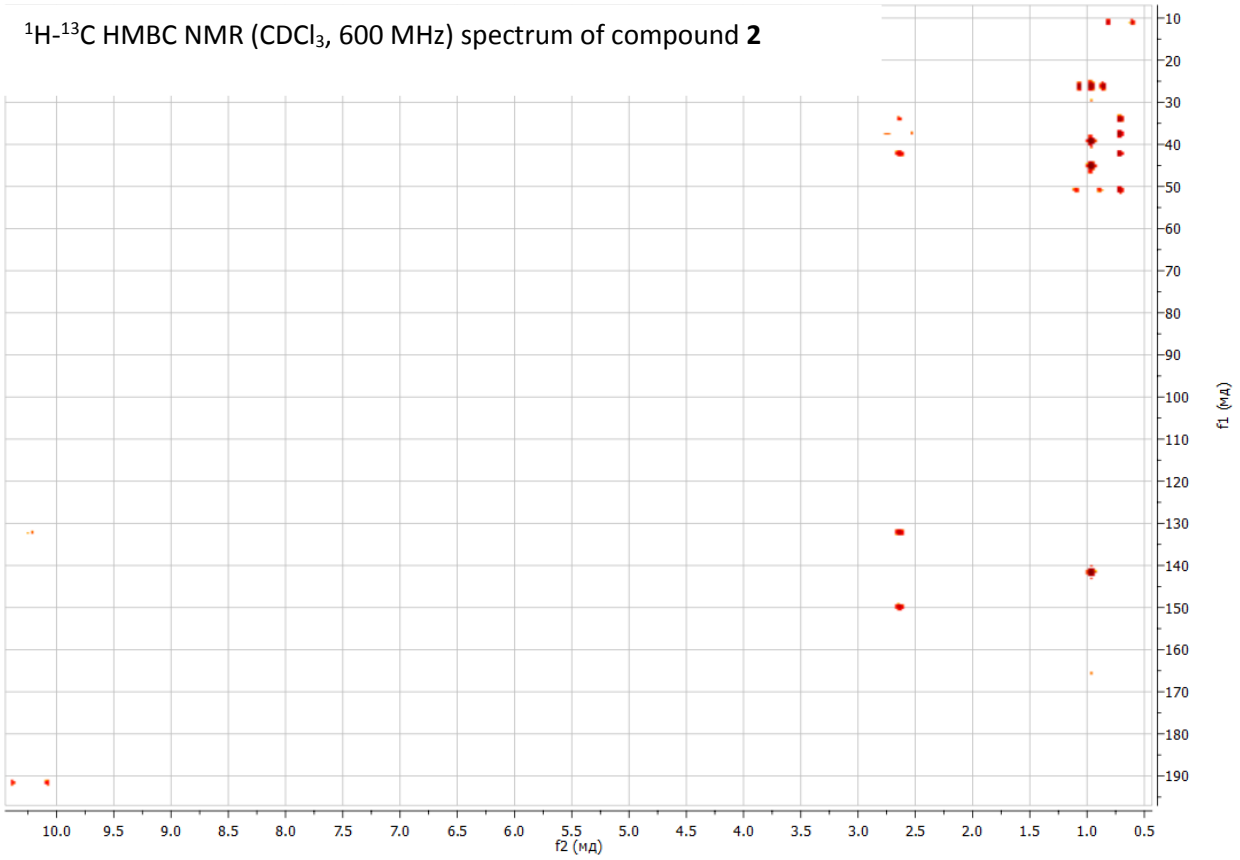
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of compound **2**



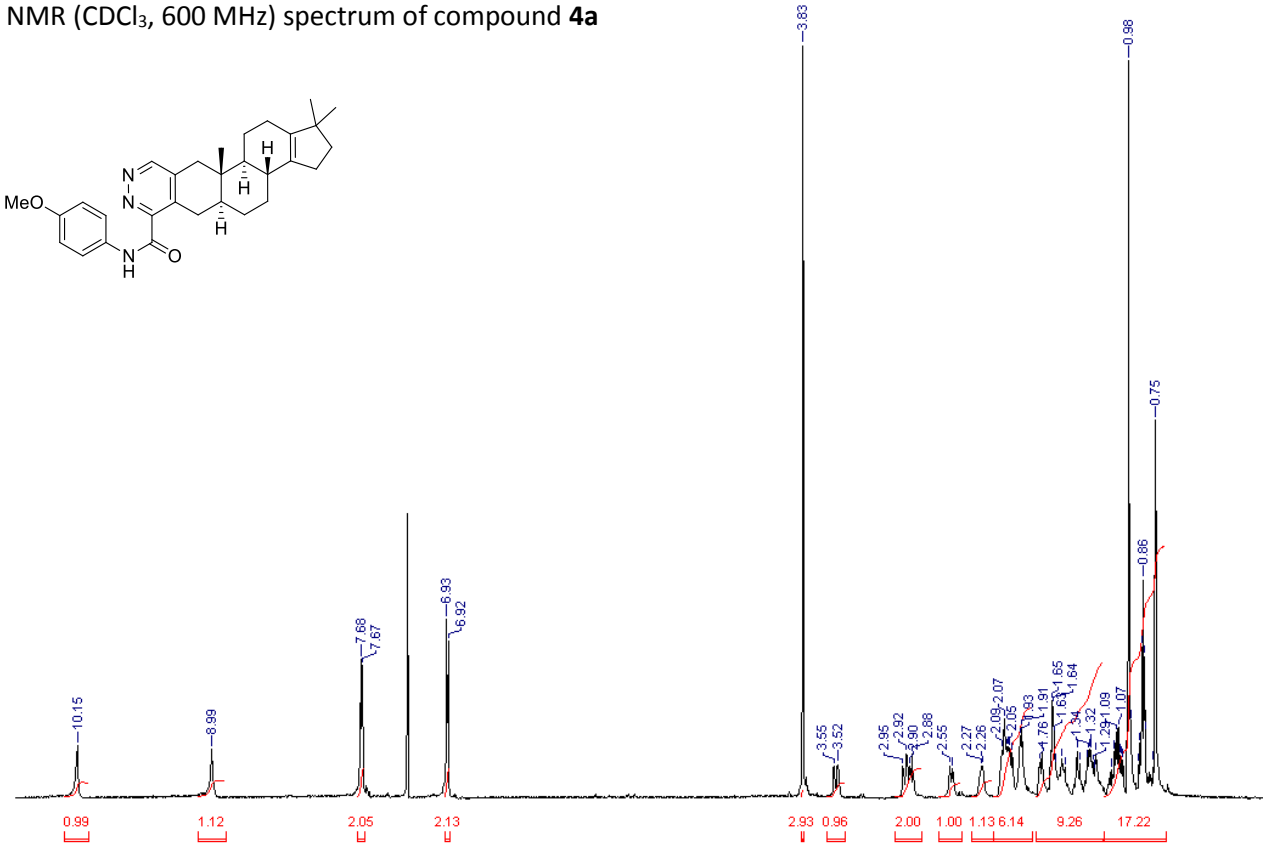
^{1}H-^{1}H COSY NMR ($CDCl_3$, 600 MHz) spectrum of compound **2**



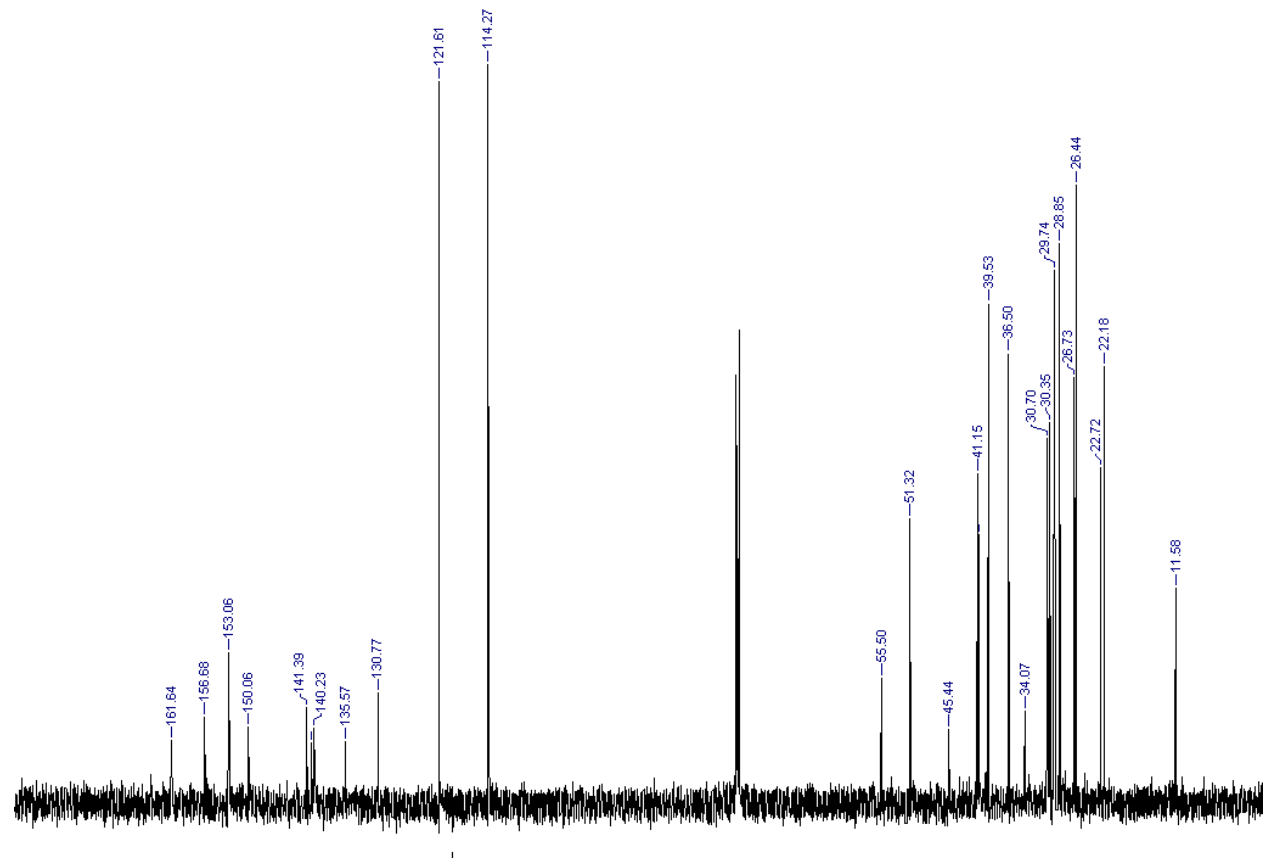
^{1}H-^{13}C HMBC NMR ($CDCl_3$, 600 MHz) spectrum of compound **2**



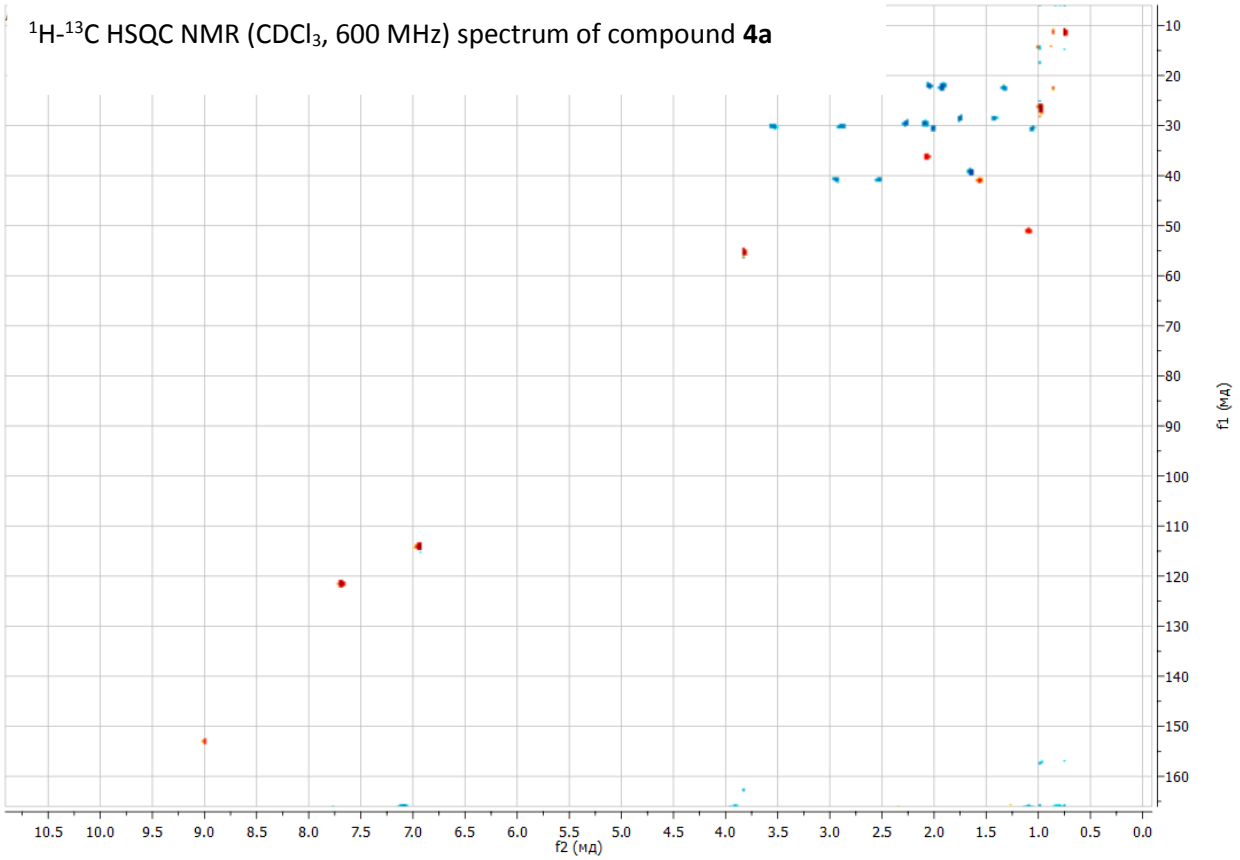
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4a**



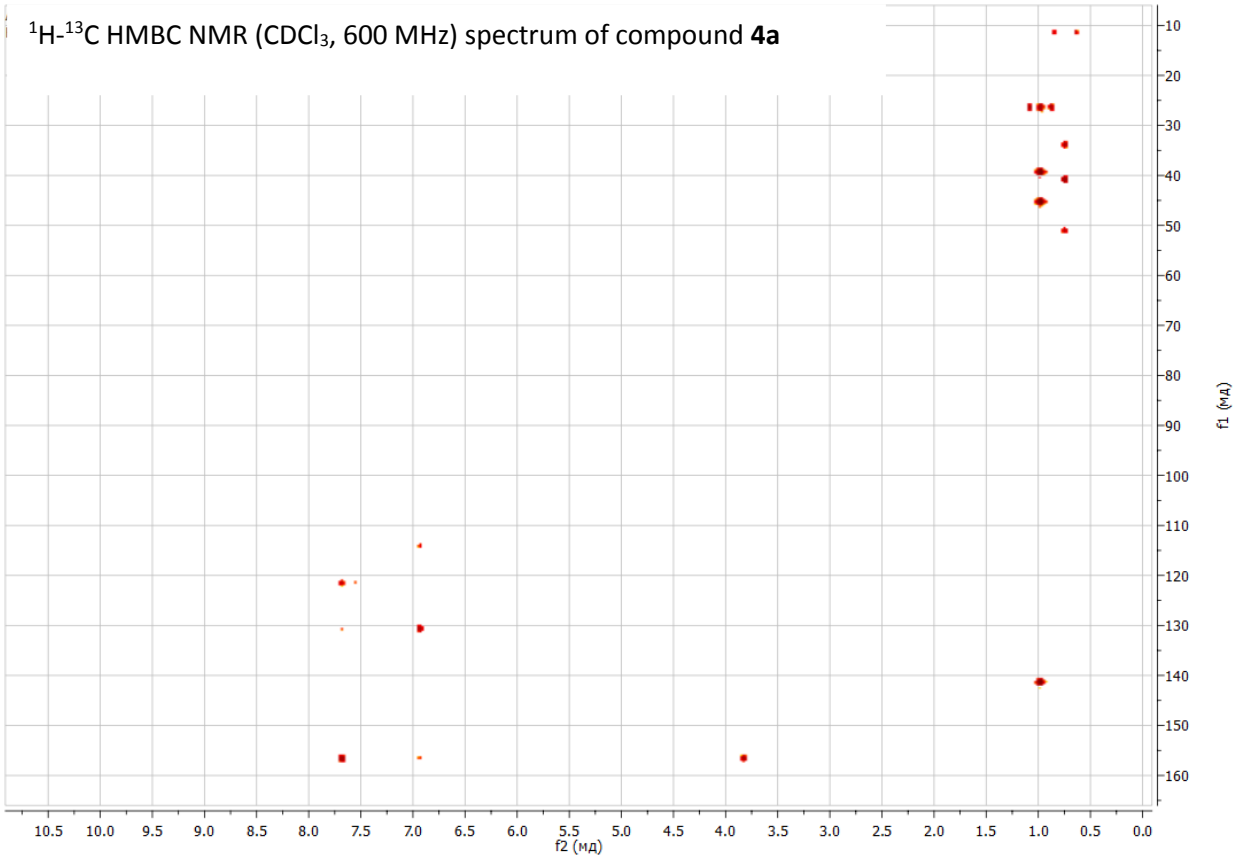
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of compound **4a**



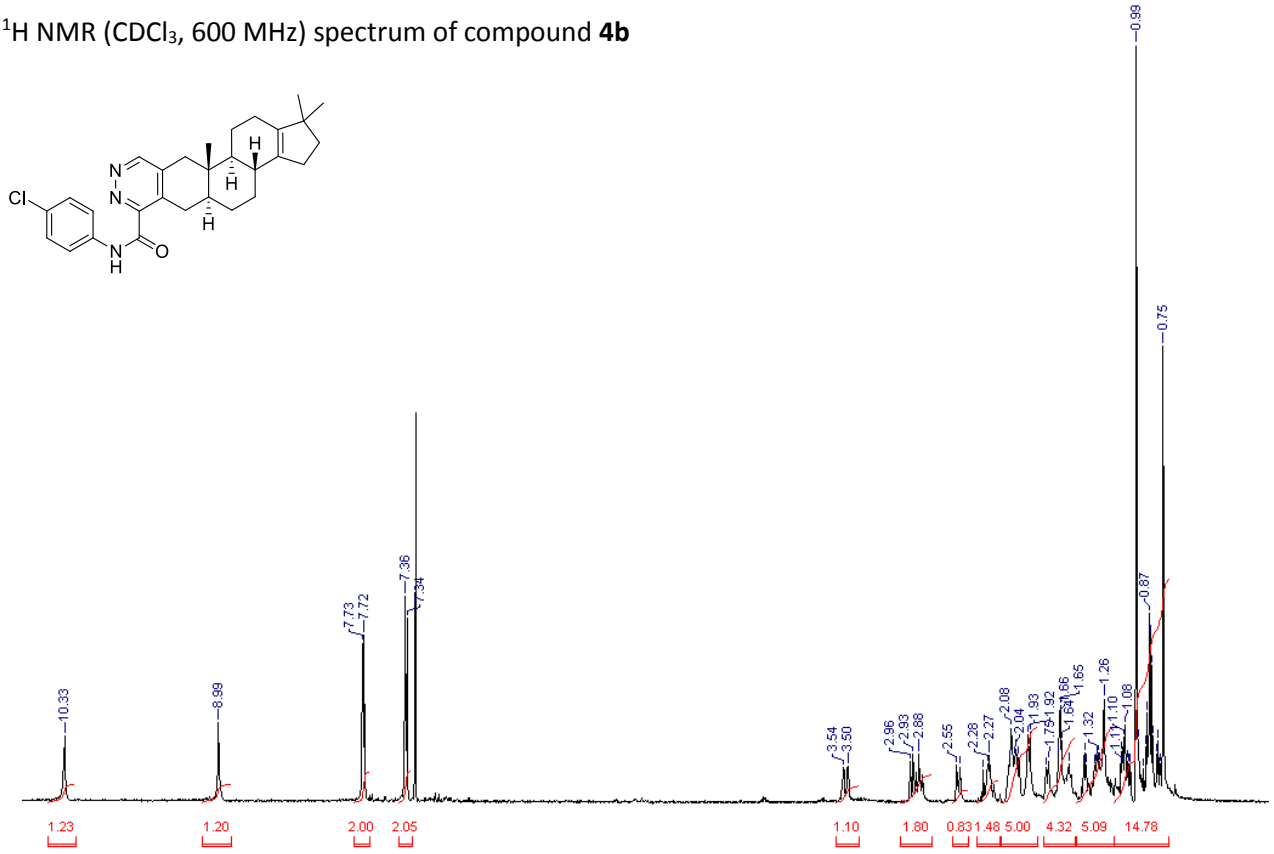
^{1}H-^{13}C HSQC NMR ($CDCl_3$, 600 MHz) spectrum of compound **4a**



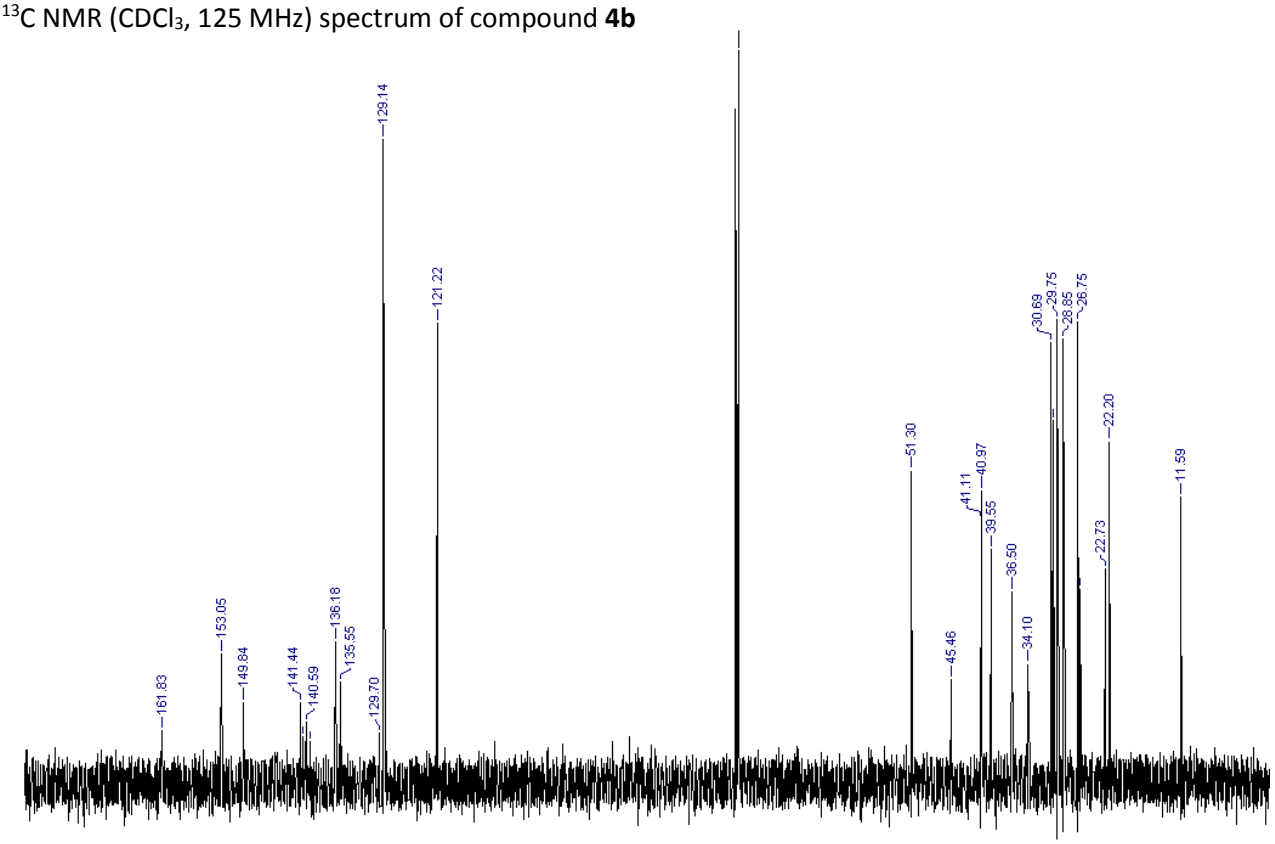
^{1}H-^{13}C HMBC NMR ($CDCl_3$, 600 MHz) spectrum of compound **4a**



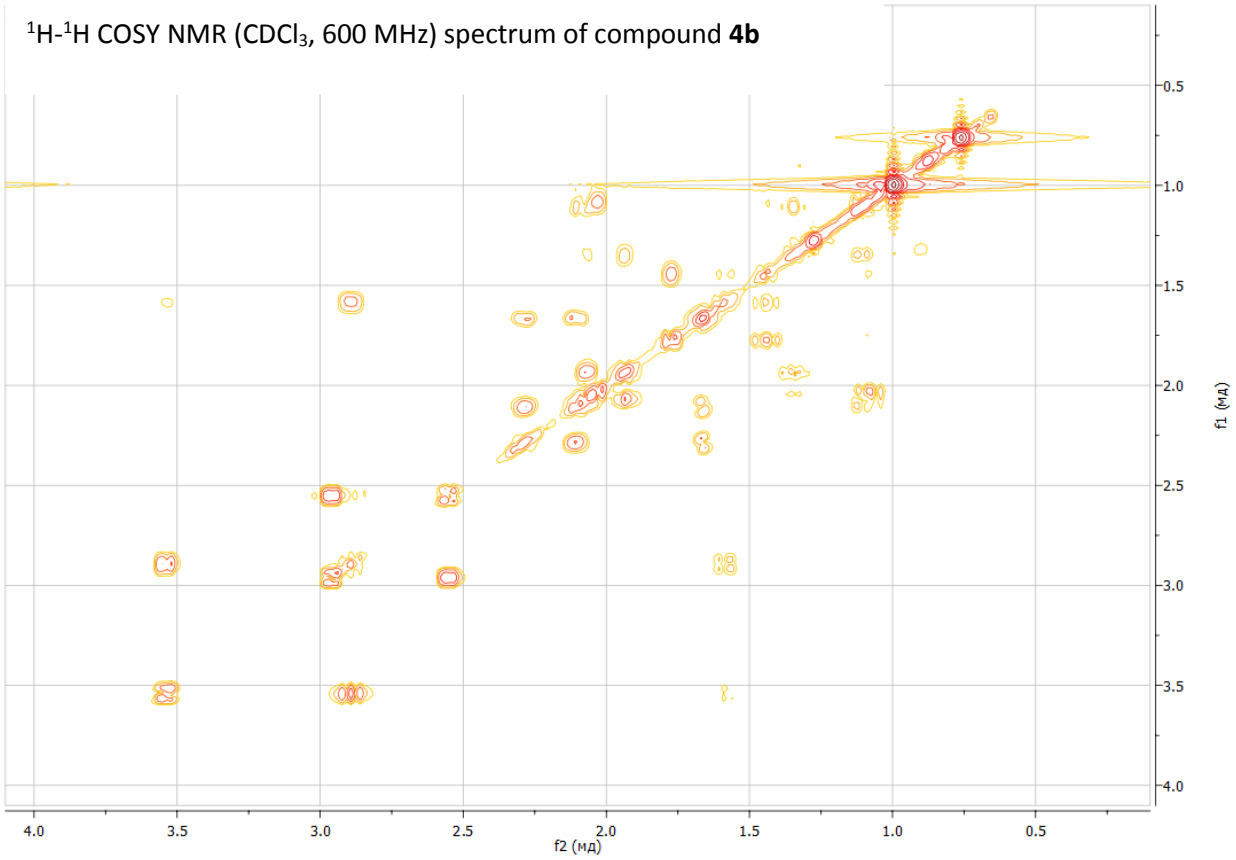
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4b**



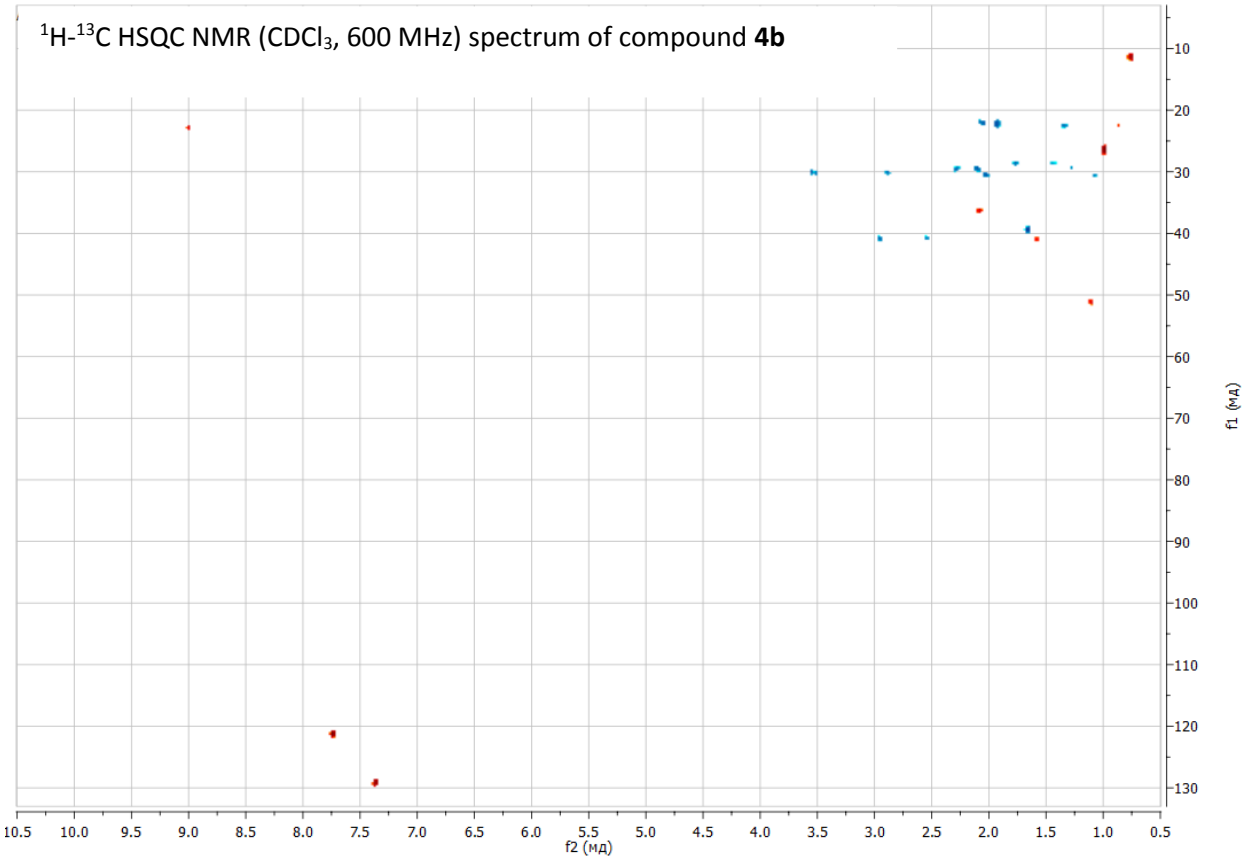
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of compound **4b**



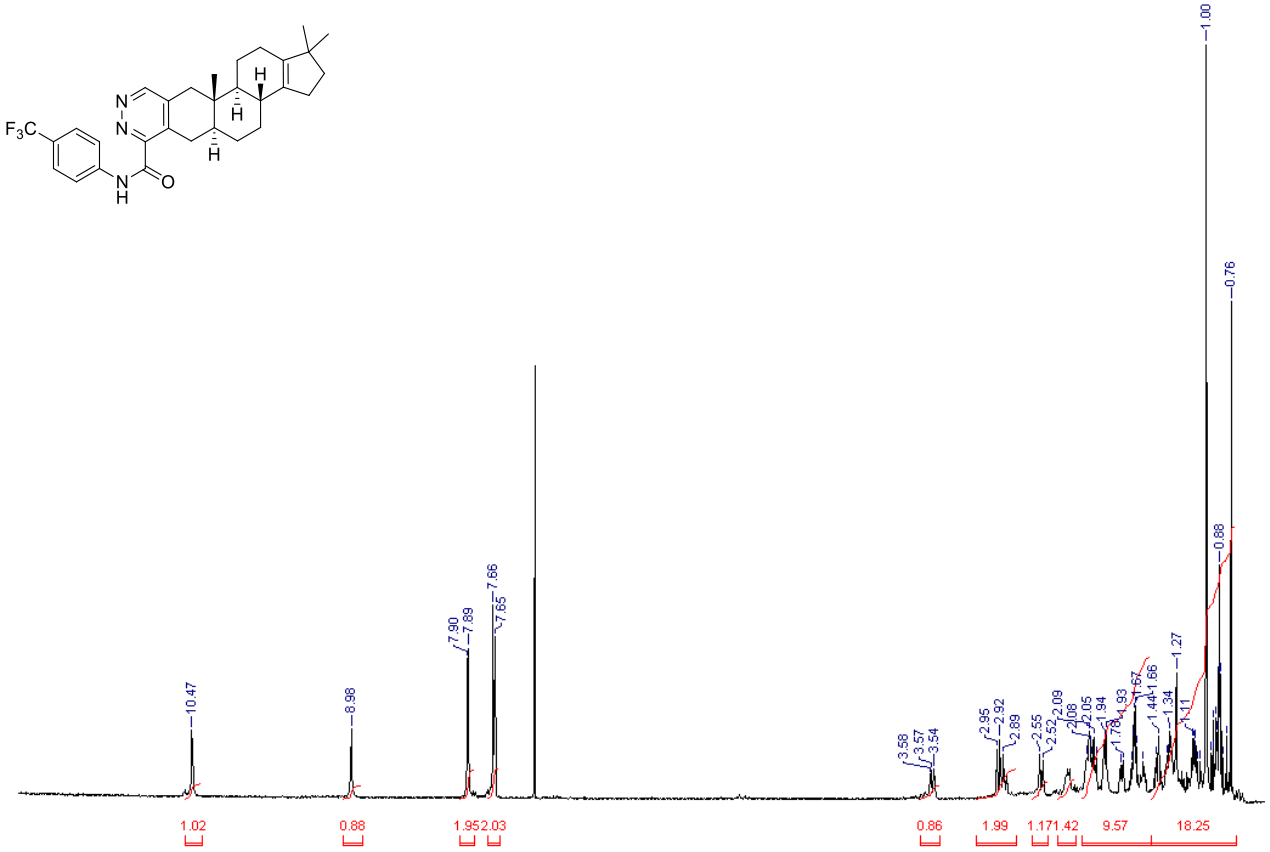
^{1}H-^{1}H COSY NMR ($CDCl_3$, 600 MHz) spectrum of compound **4b**



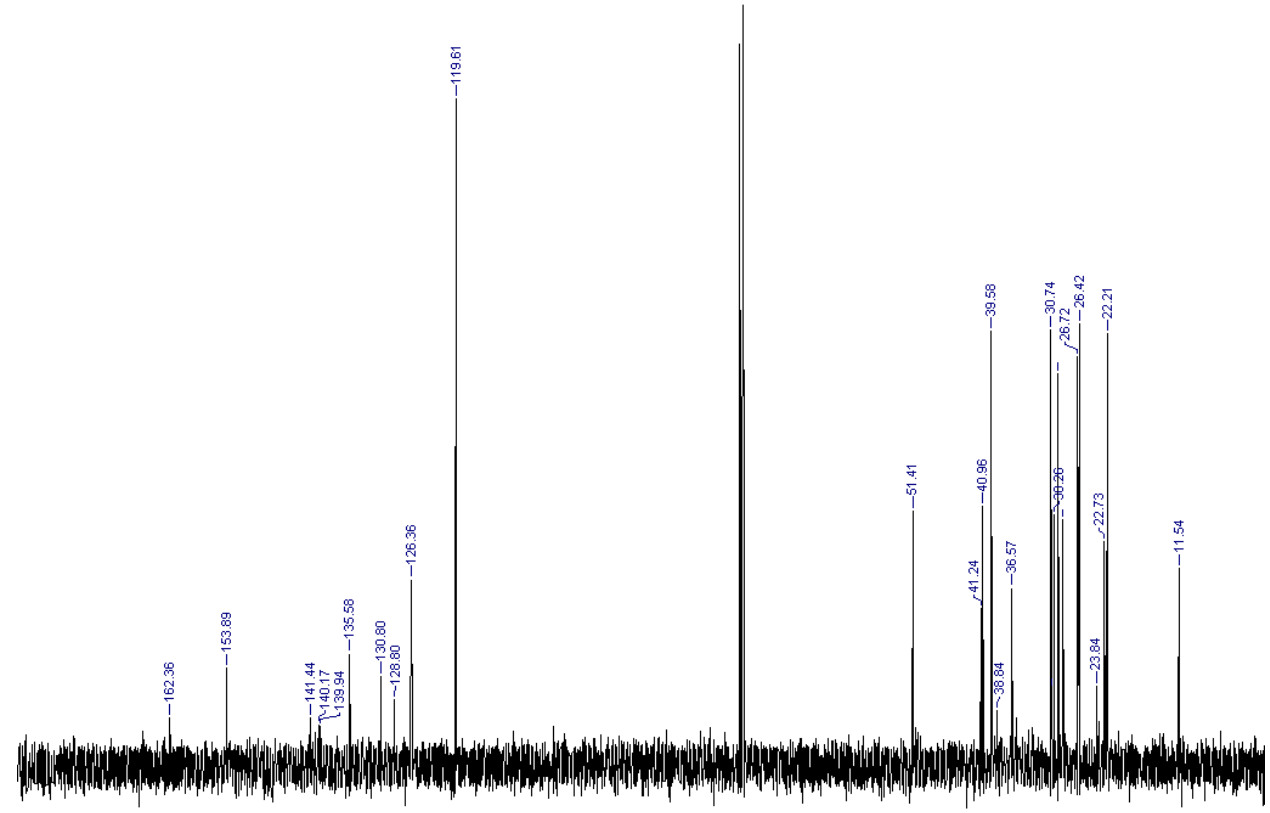
^{1}H-^{13}C HSQC NMR ($CDCl_3$, 600 MHz) spectrum of compound **4b**



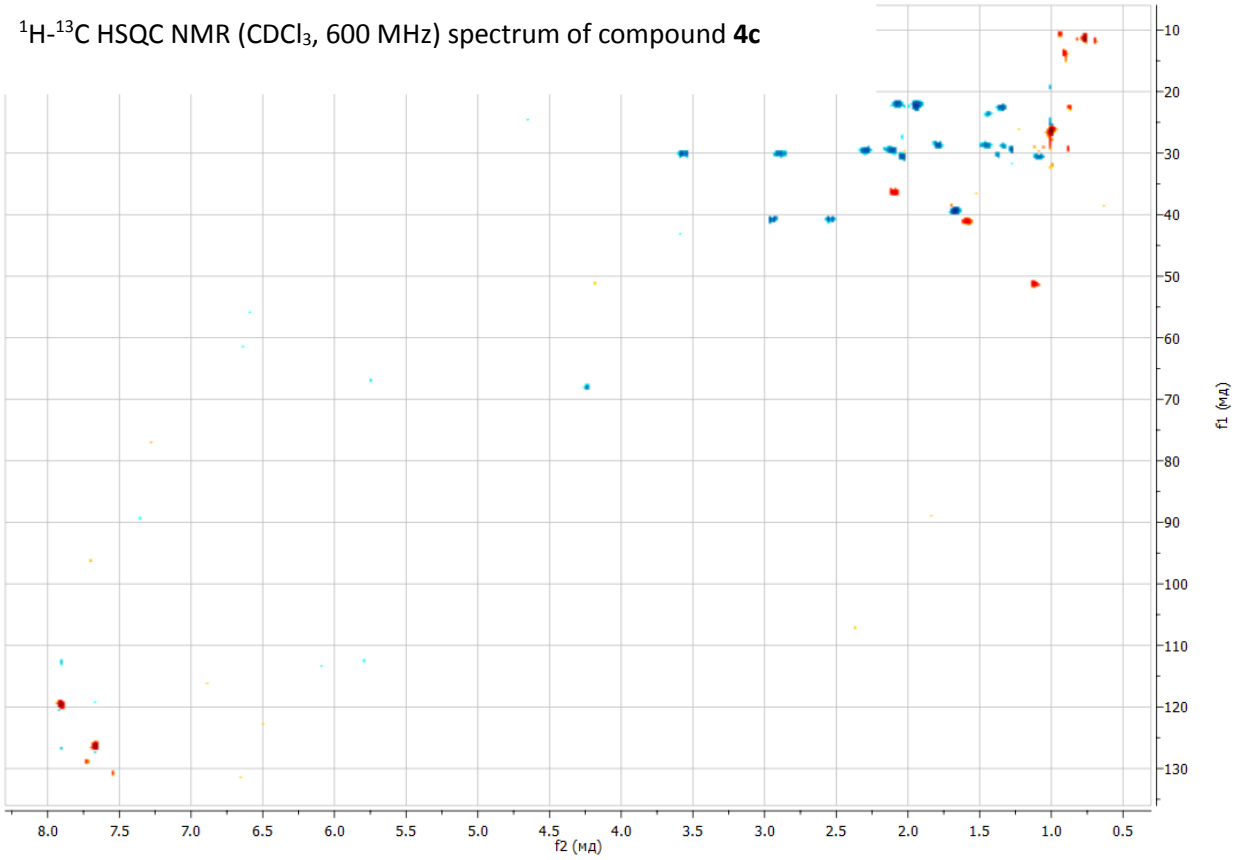
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4c**



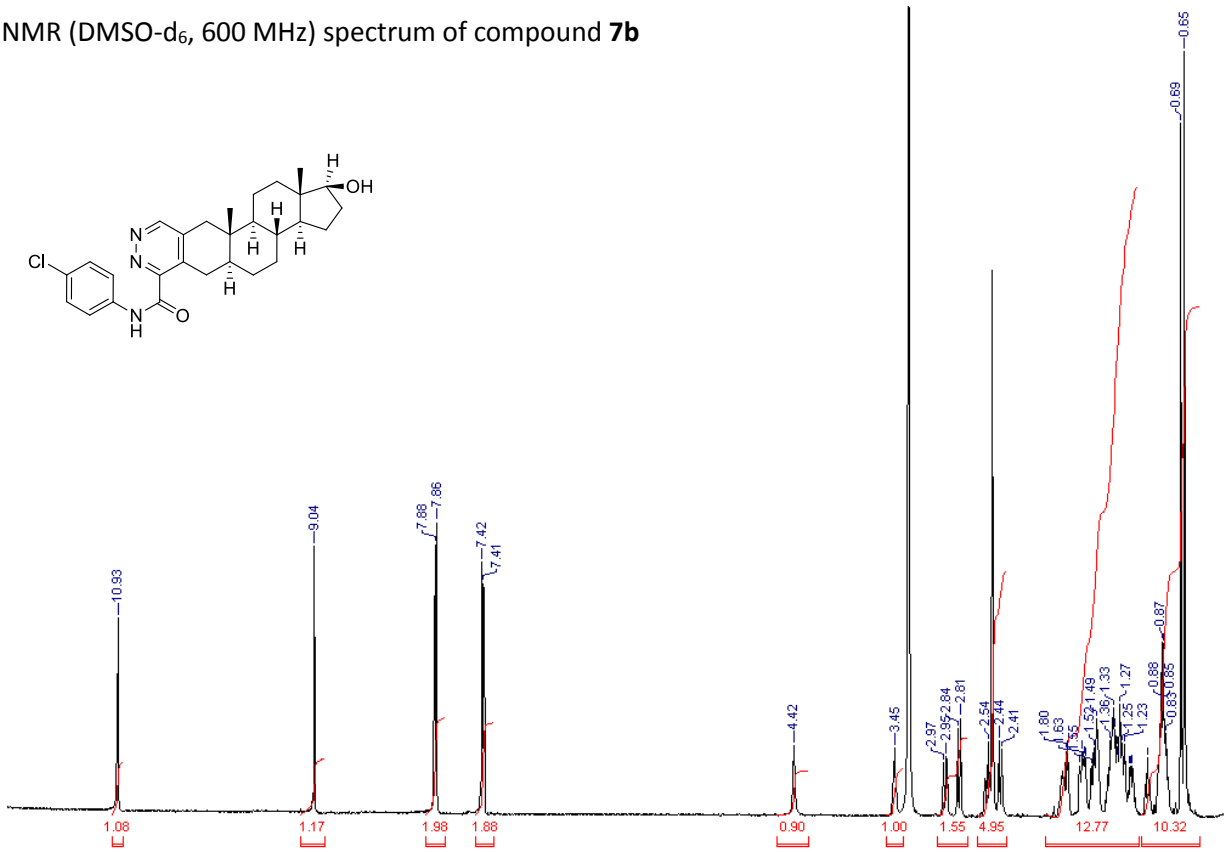
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of compound **4c**



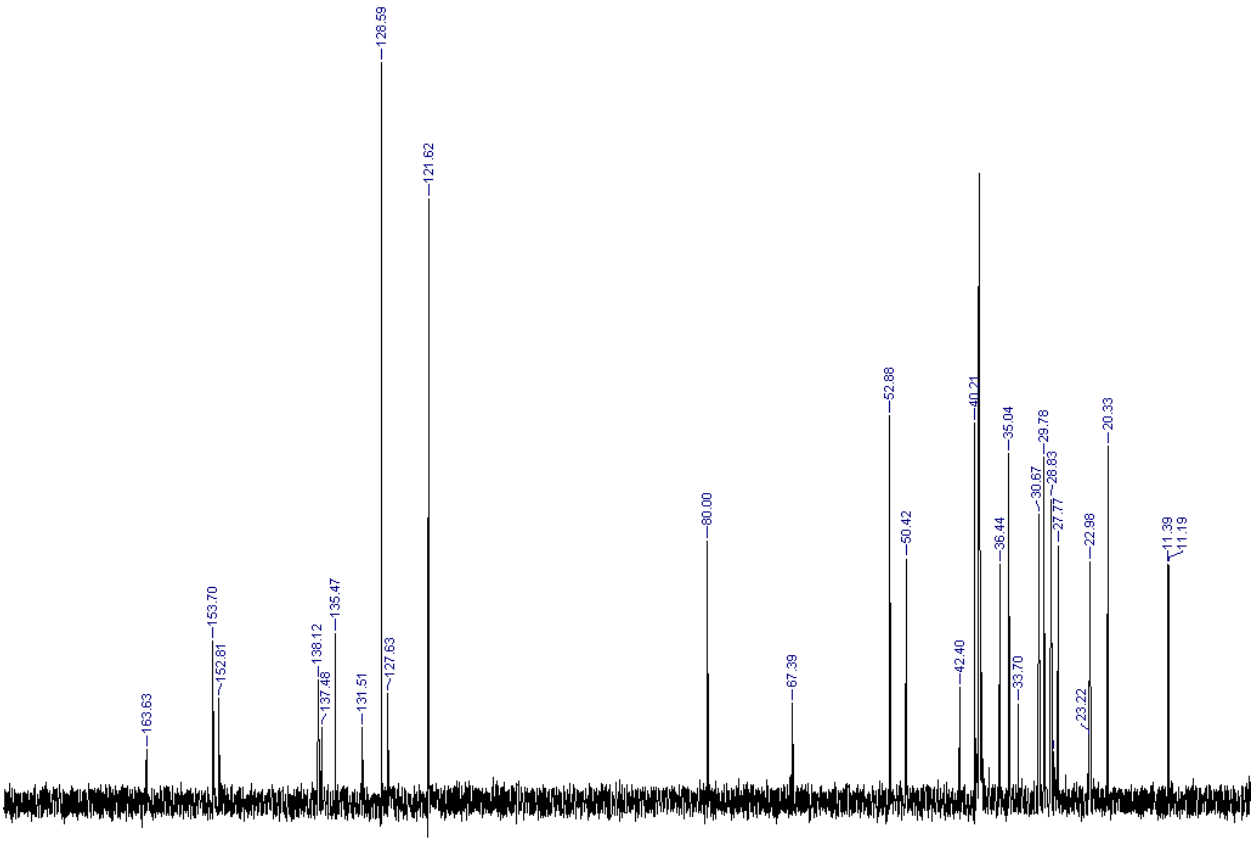
^{1}H-^{13}C HSQC NMR ($CDCl_3$, 600 MHz) spectrum of compound **4c**



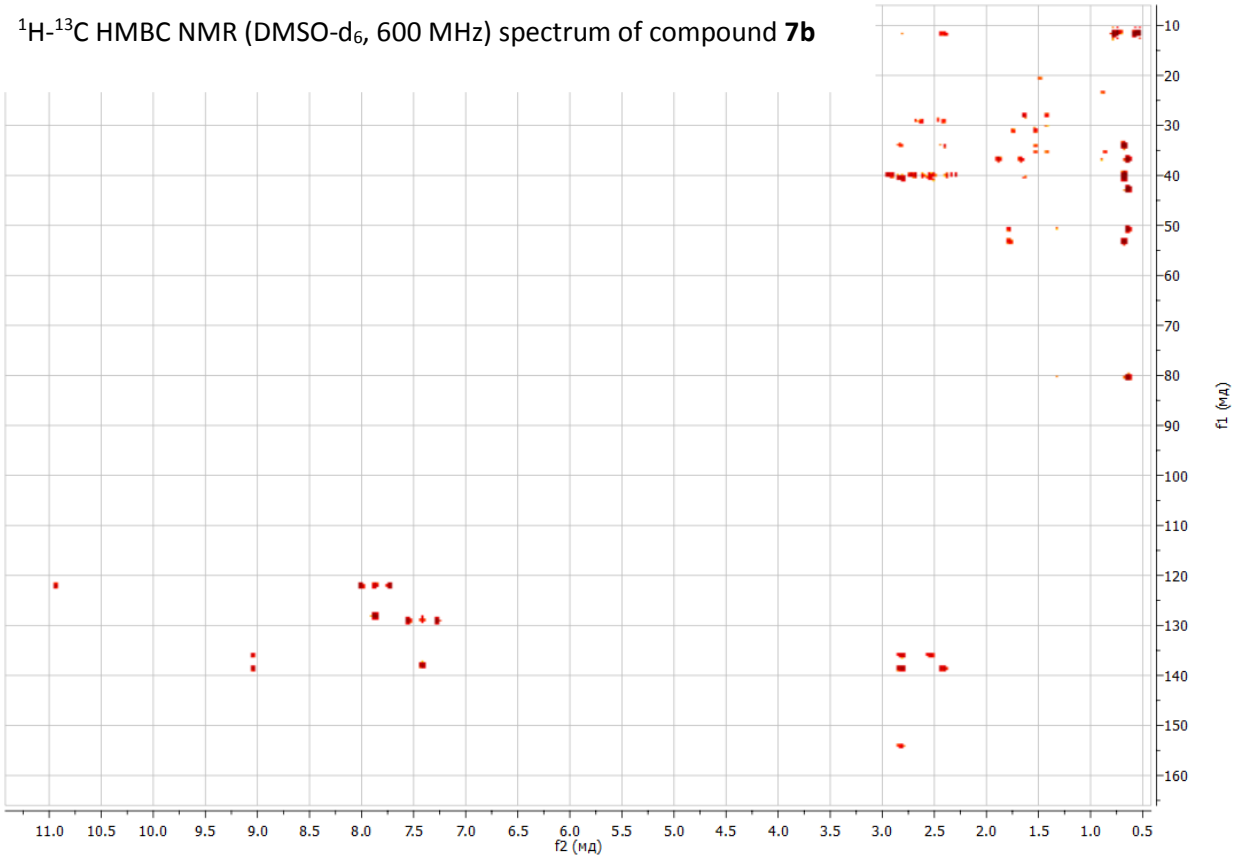
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **7b**



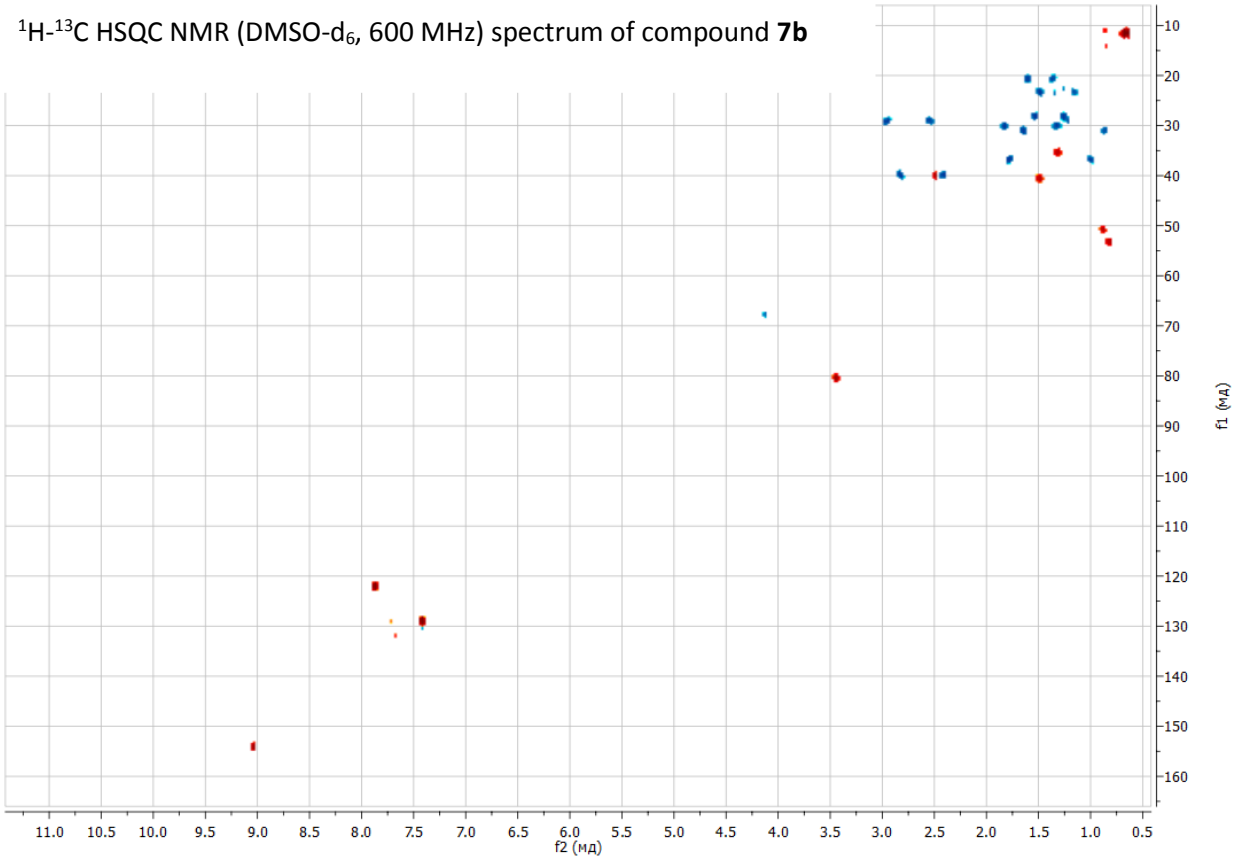
^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of compound **7b**



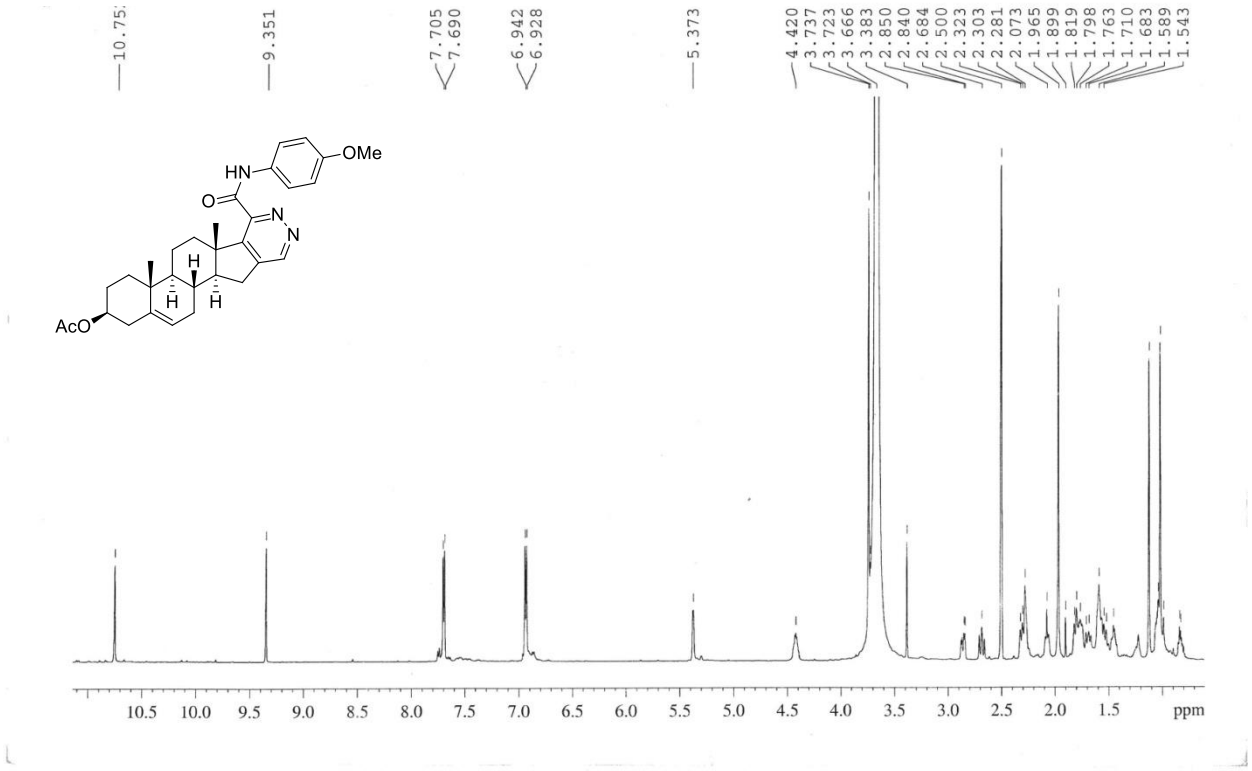
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 600 MHz) spectrum of compound **7b**



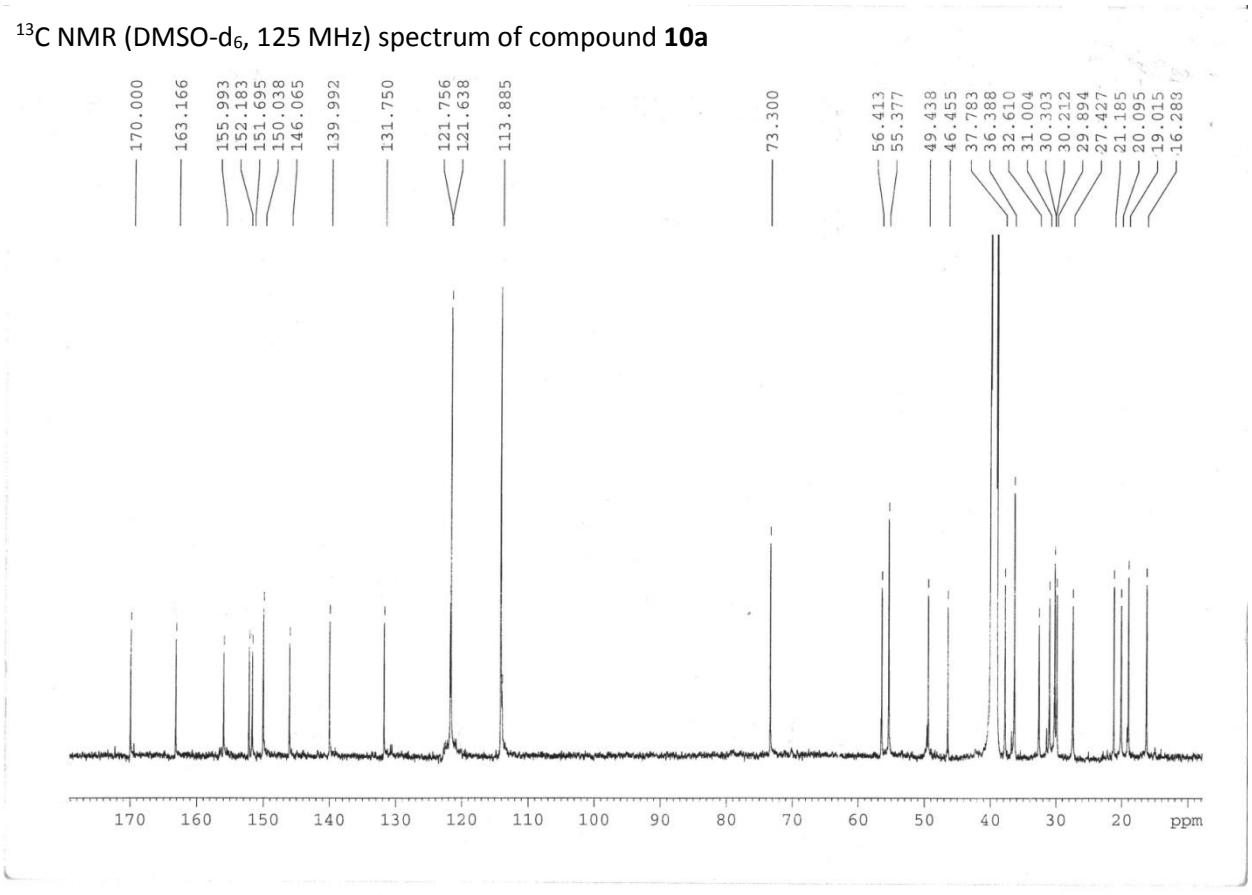
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 600 MHz) spectrum of compound **7b**



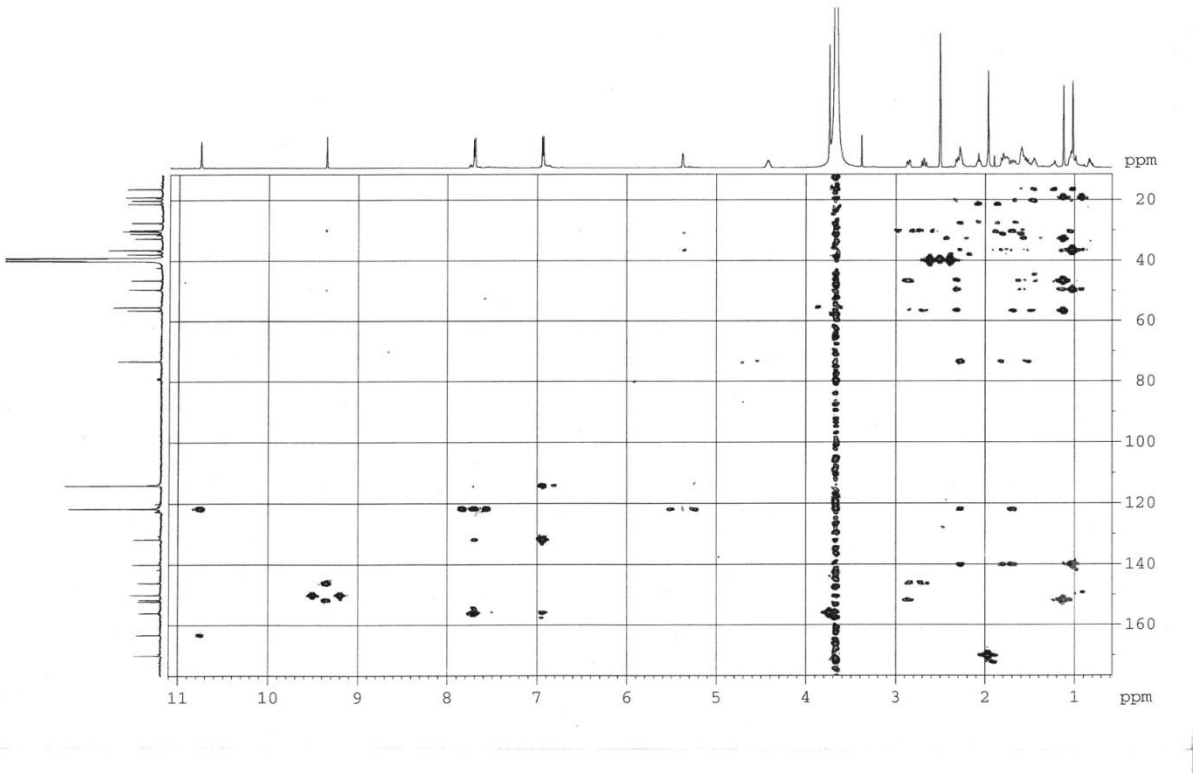
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **10a**



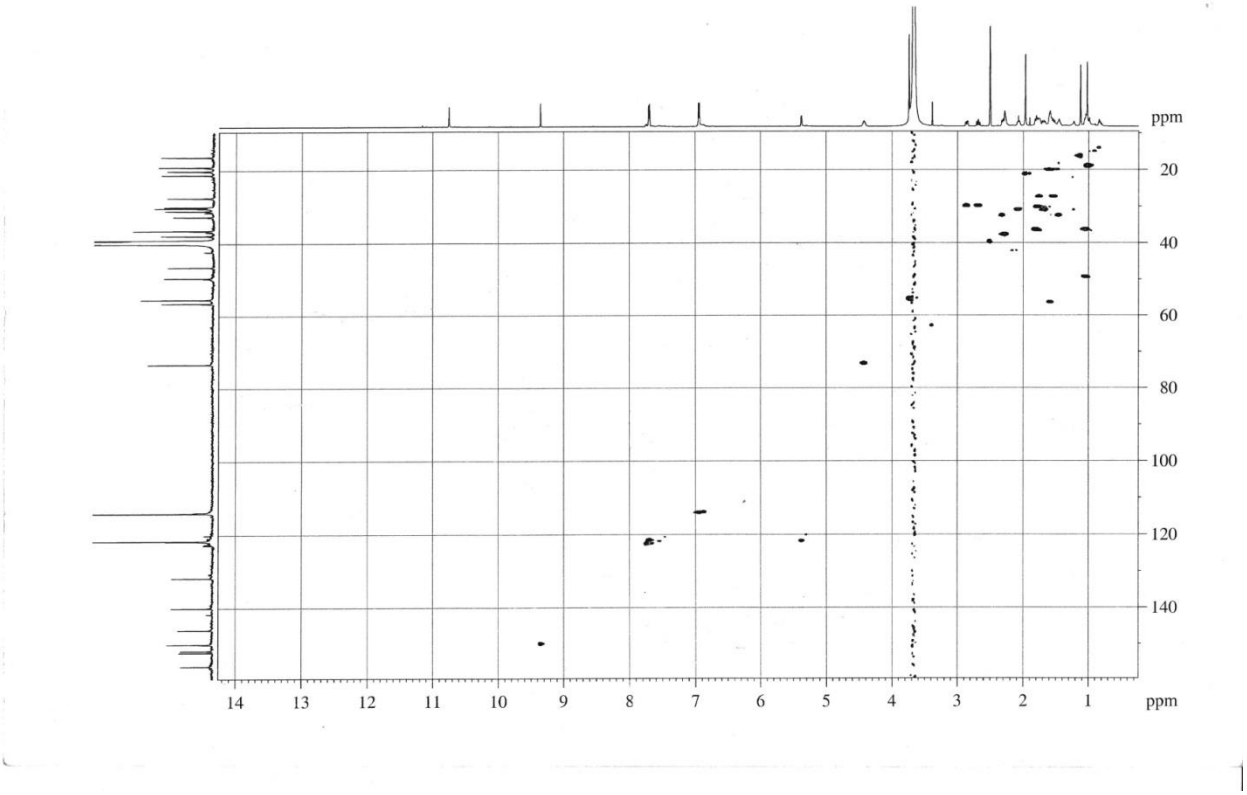
^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of compound **10a**



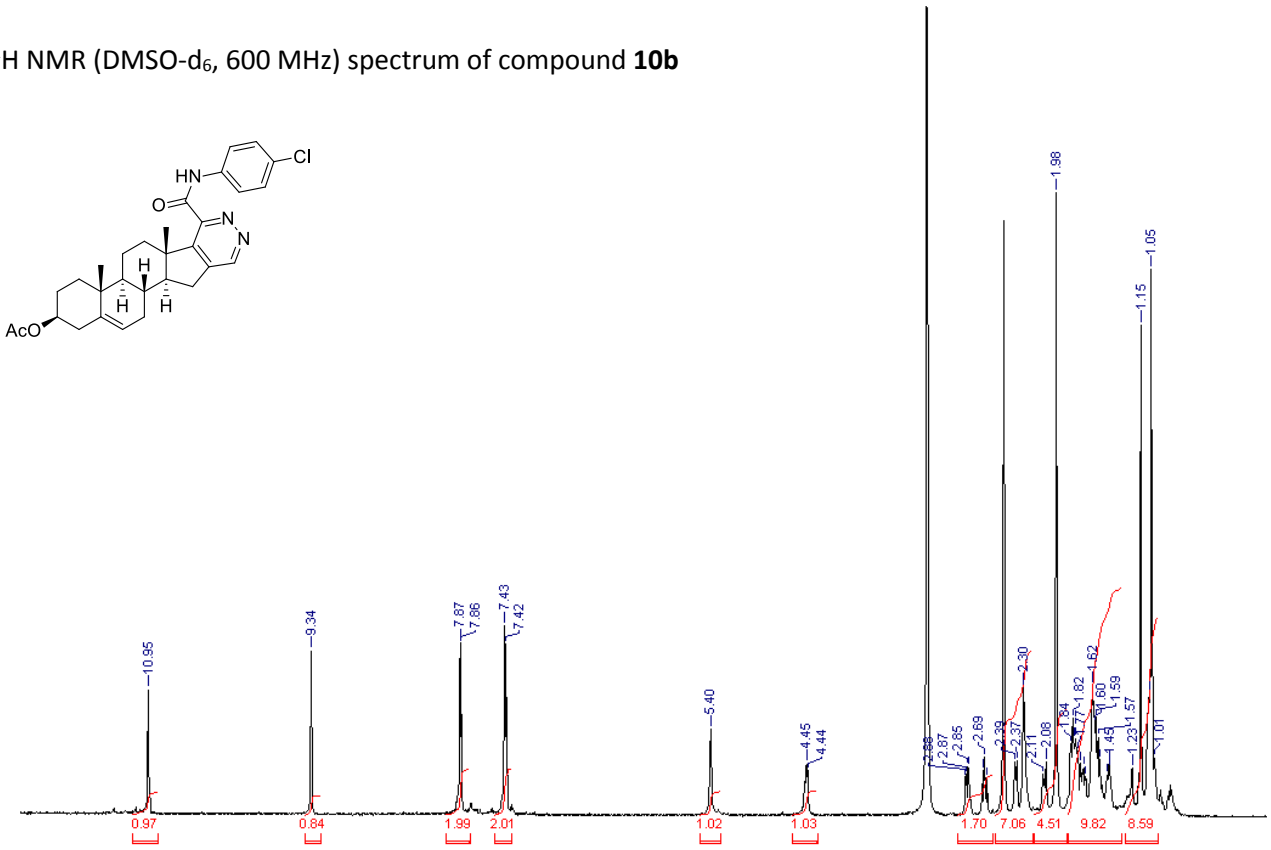
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 600 MHz) spectrum of compound **10a**



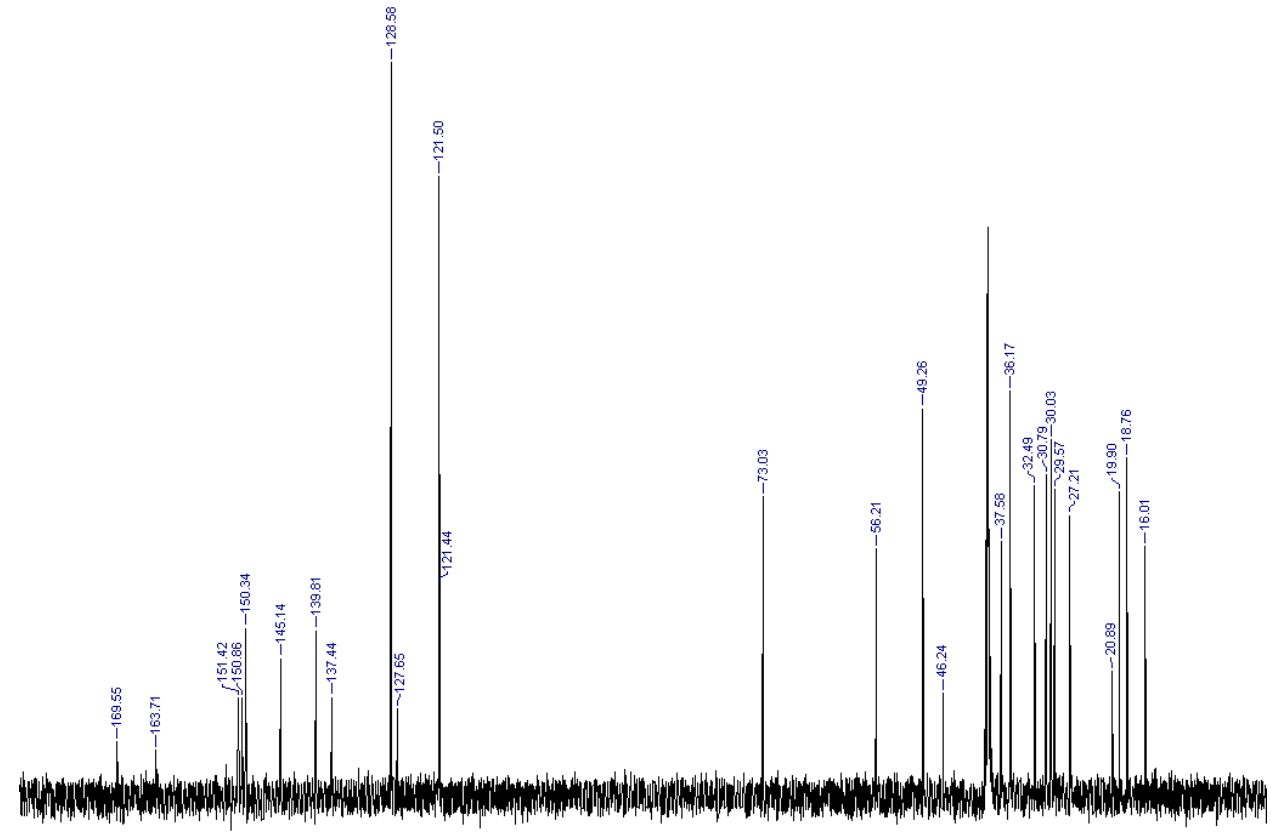
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 600 MHz) spectrum of compound **10a**



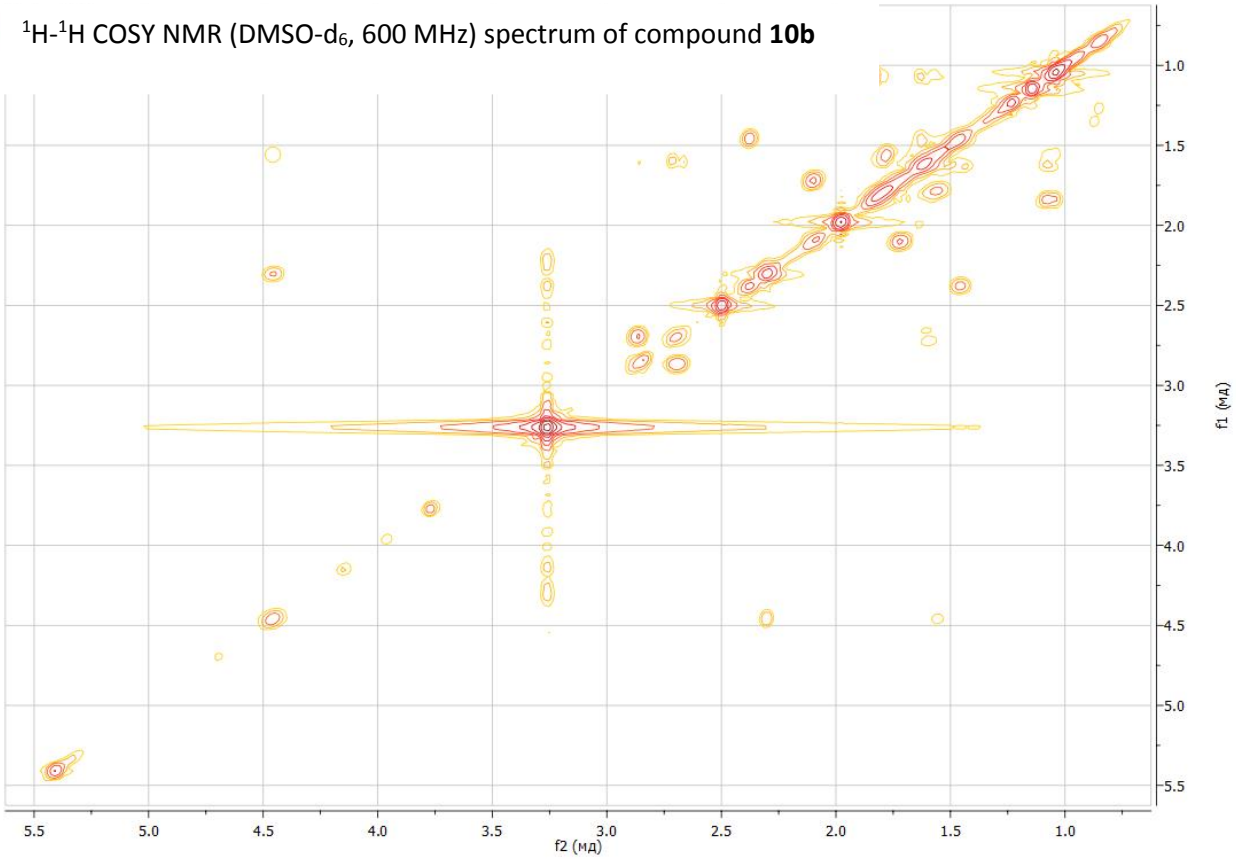
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **10b**



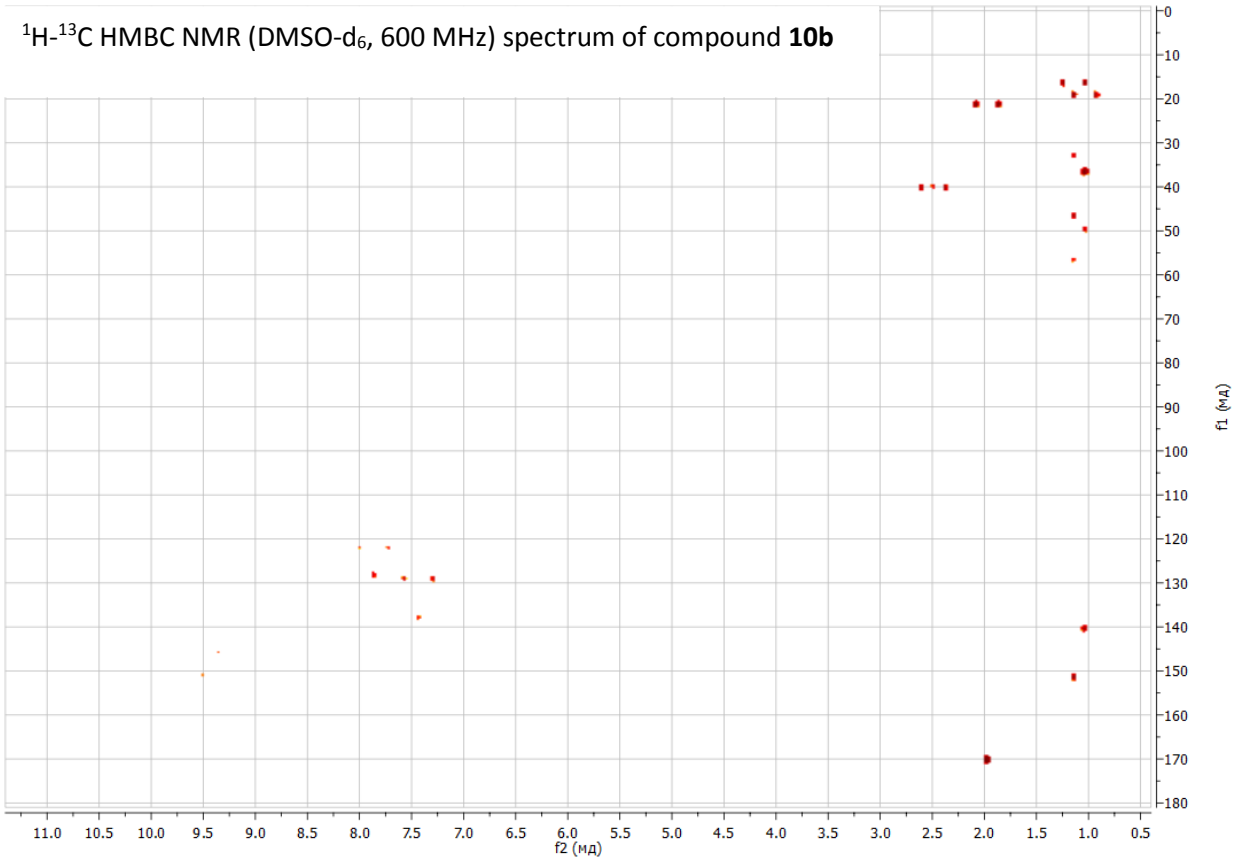
^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of compound **10b**



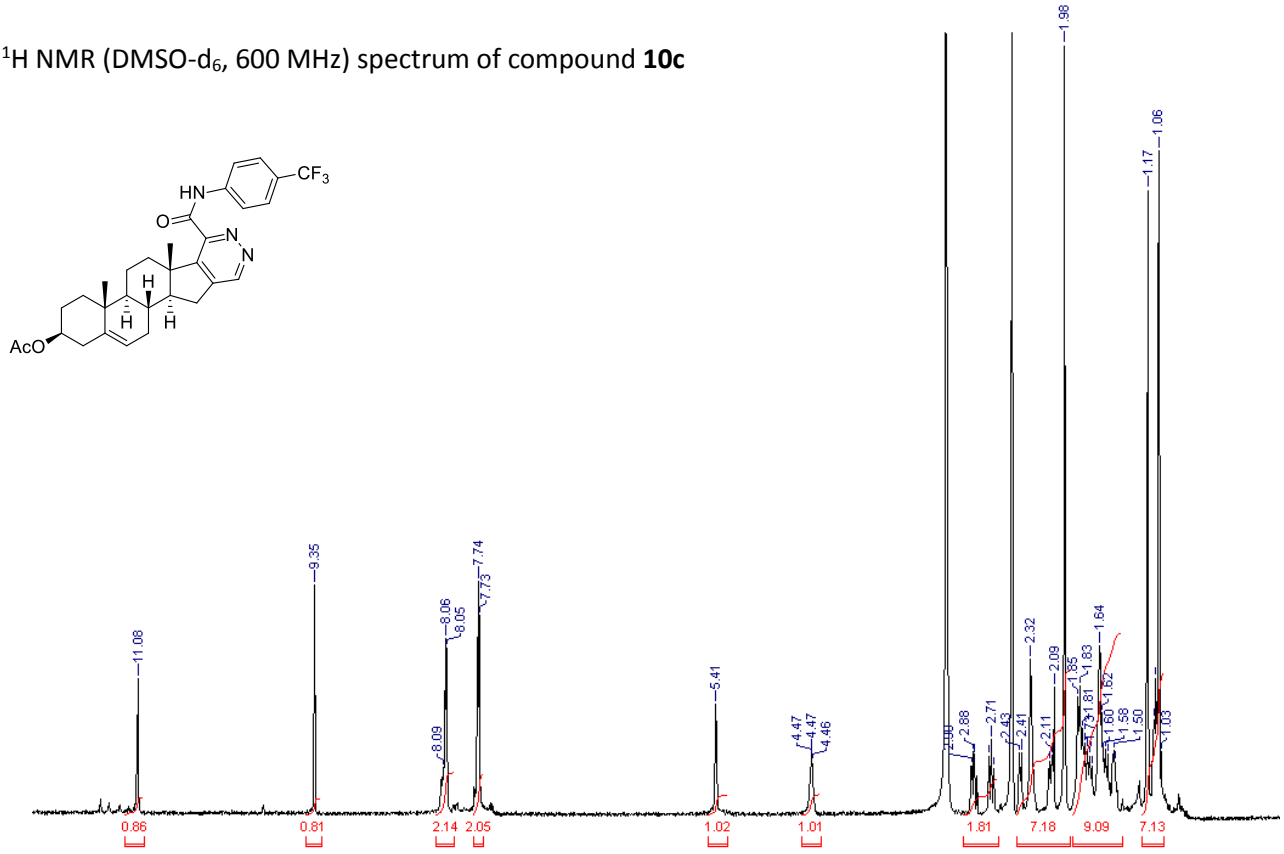
^{1}H-^{1}H COSY NMR (DMSO-d$_6$, 600 MHz) spectrum of compound **10b**



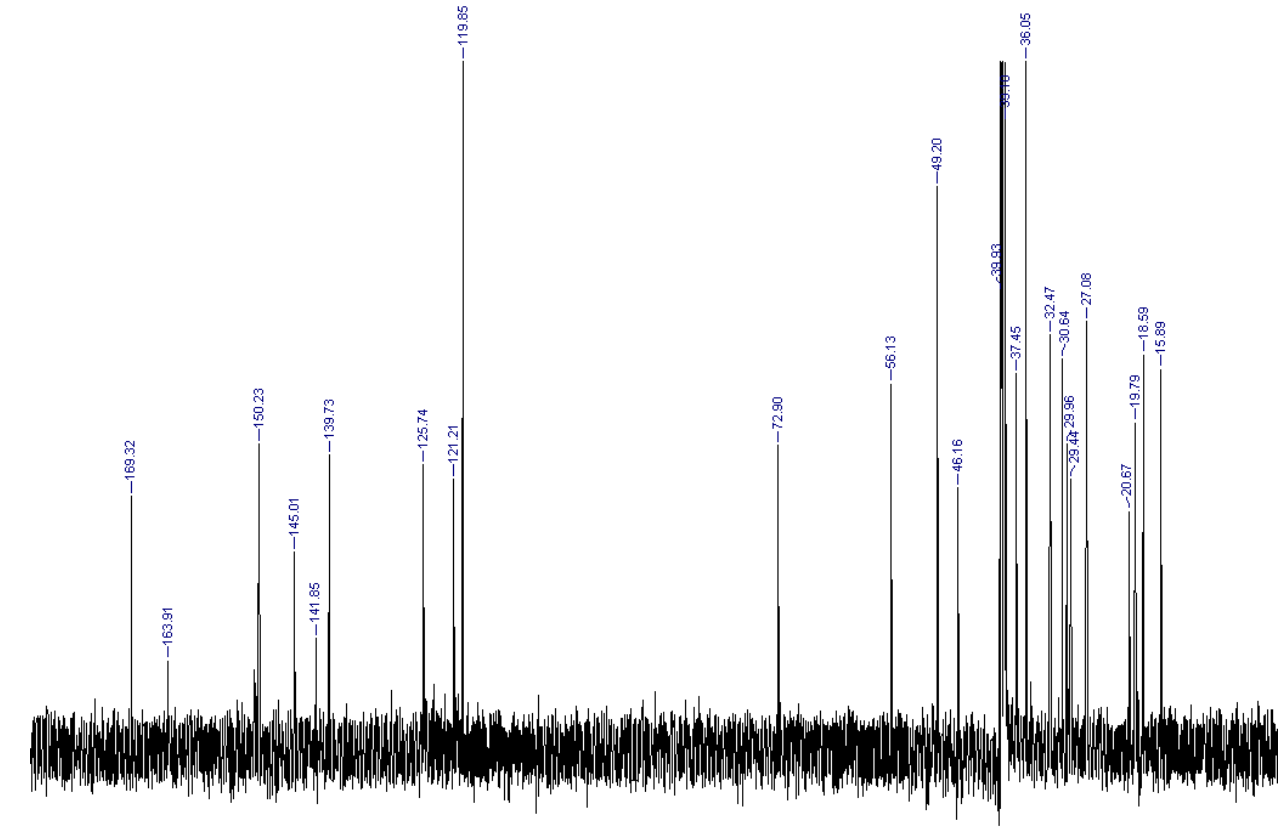
^{1}H-^{13}C HMBC NMR (DMSO-d$_6$, 600 MHz) spectrum of compound **10b**



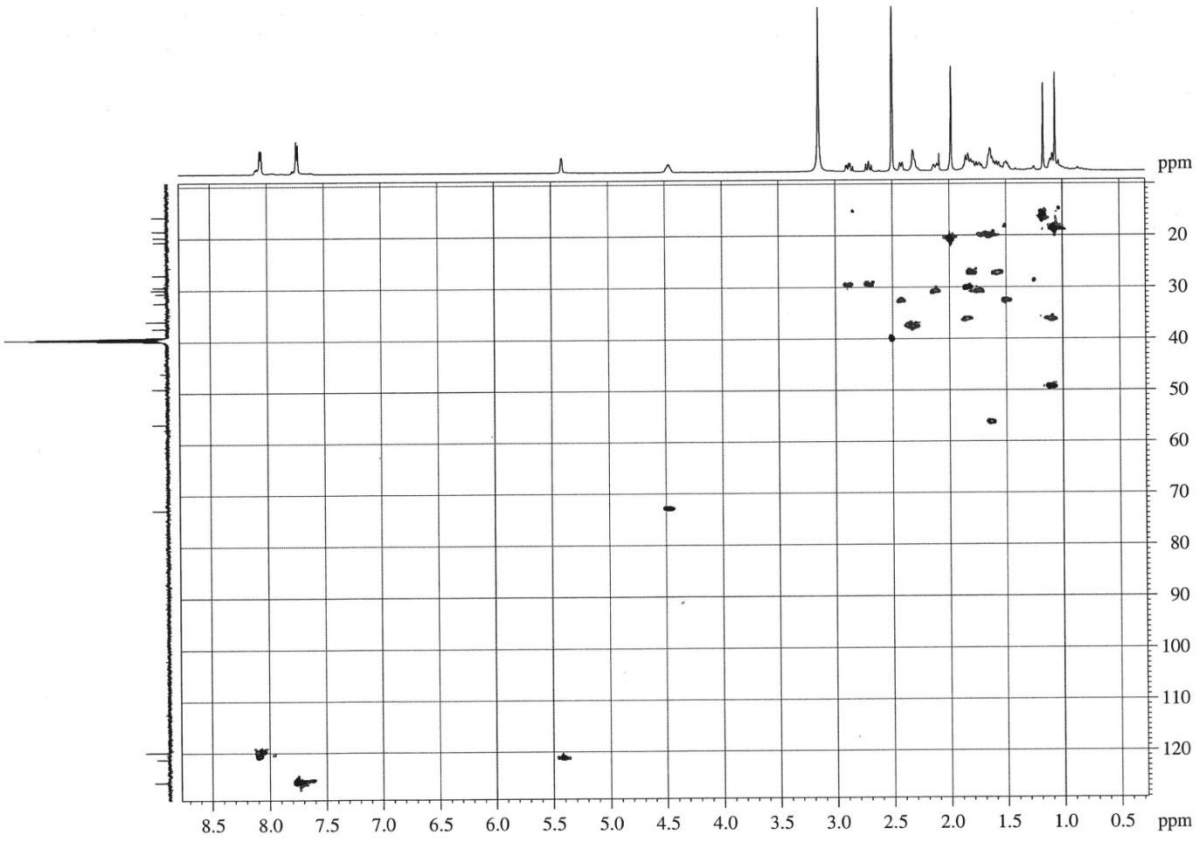
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **10c**



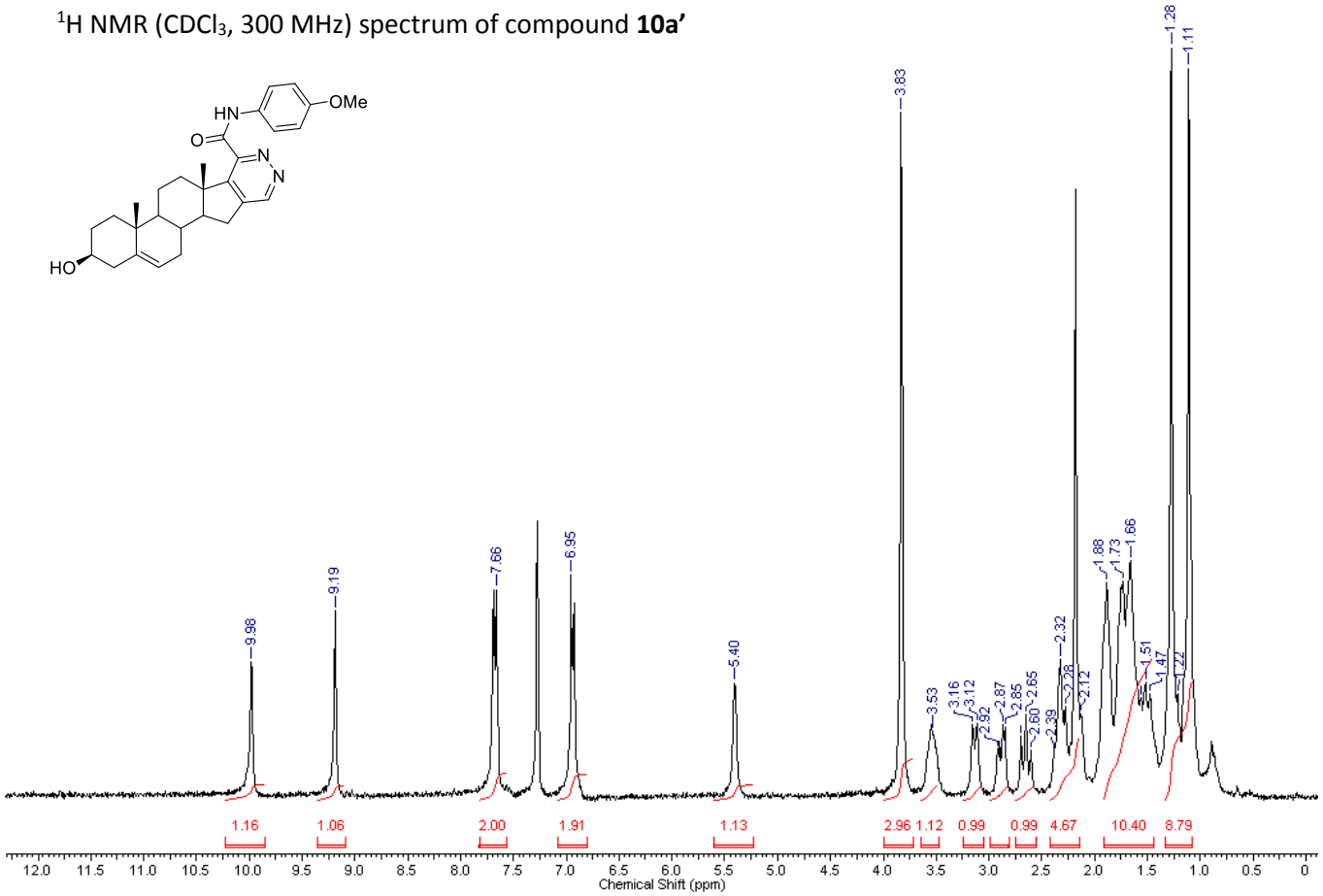
^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of compound **10c**



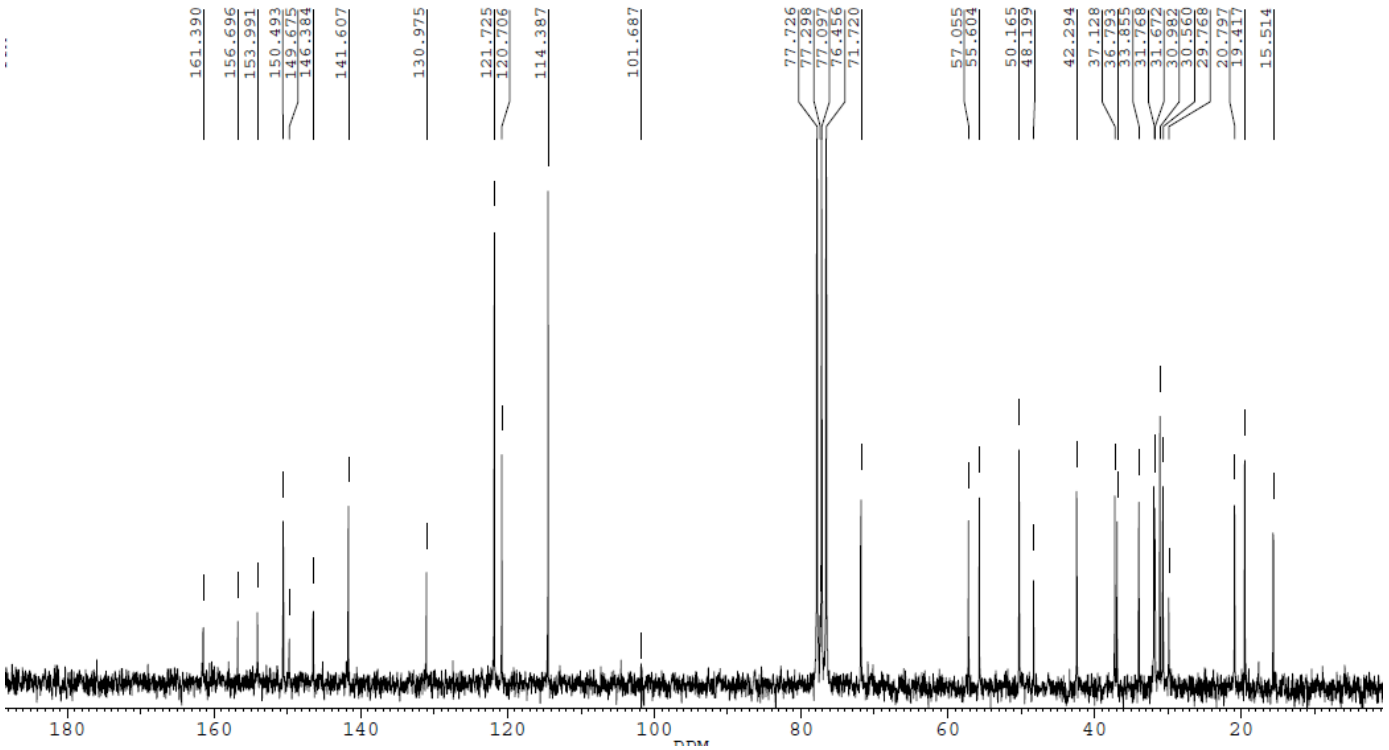
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 600 MHz) spectrum of compound **10c**



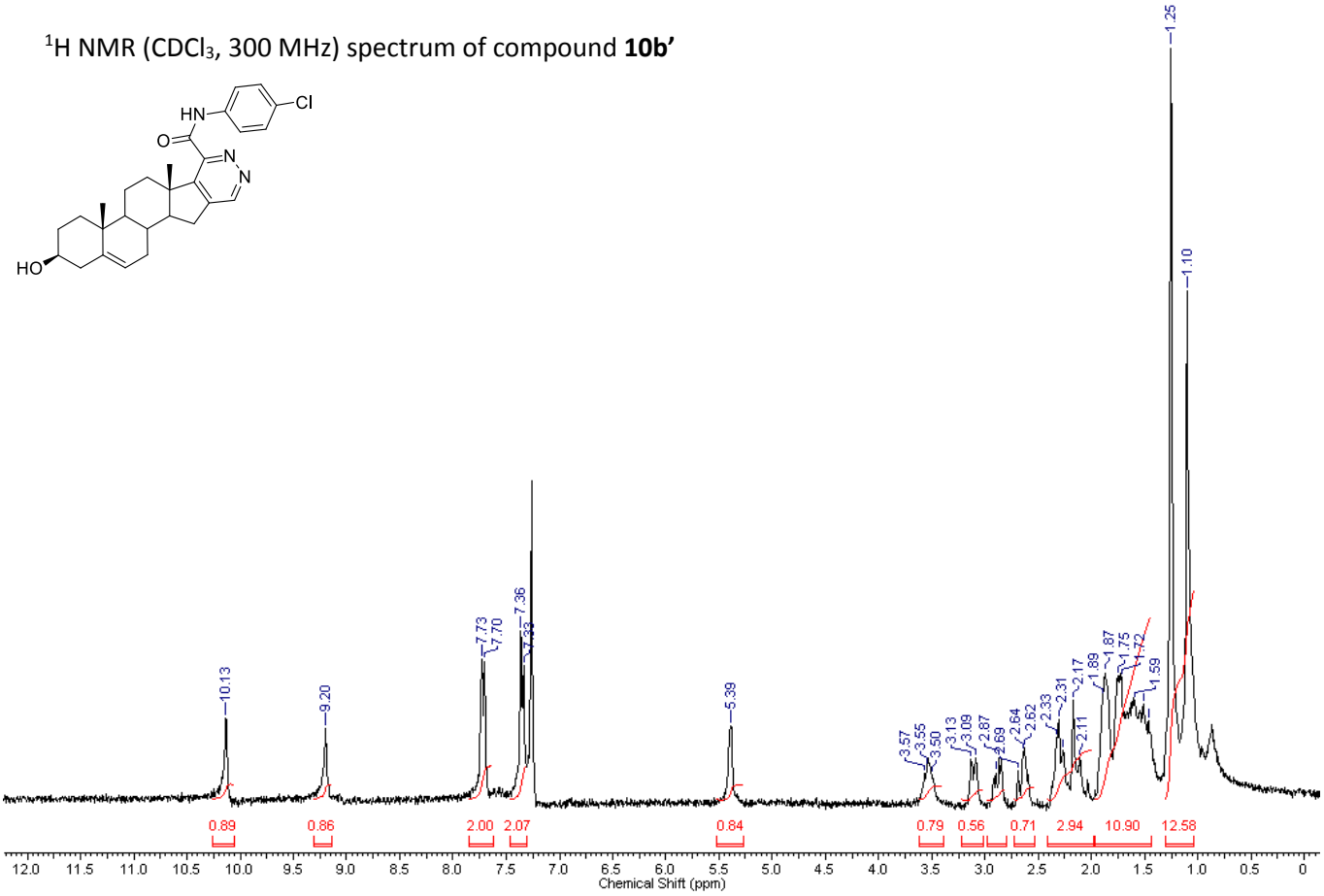
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **10a'**



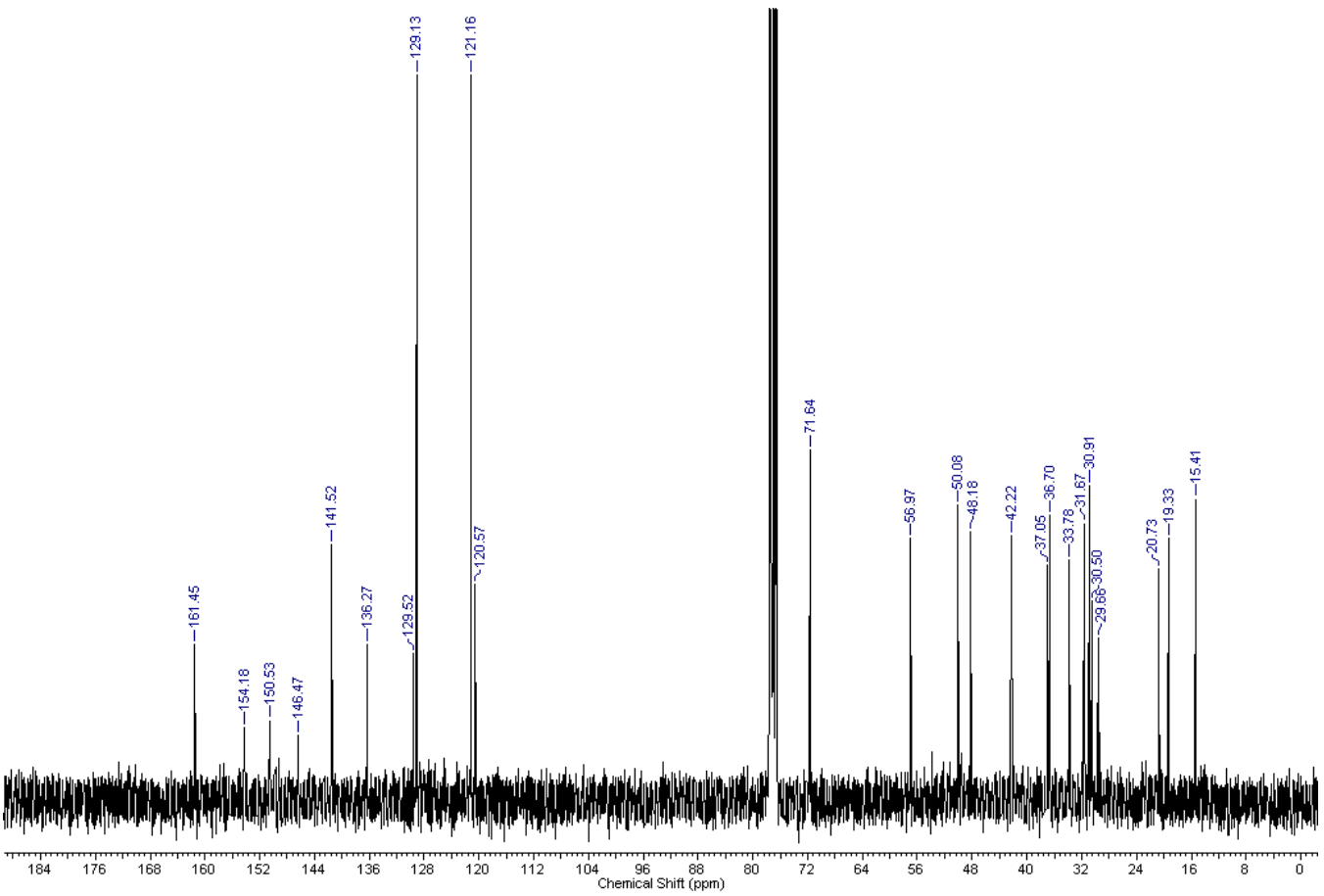
^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **10a'**



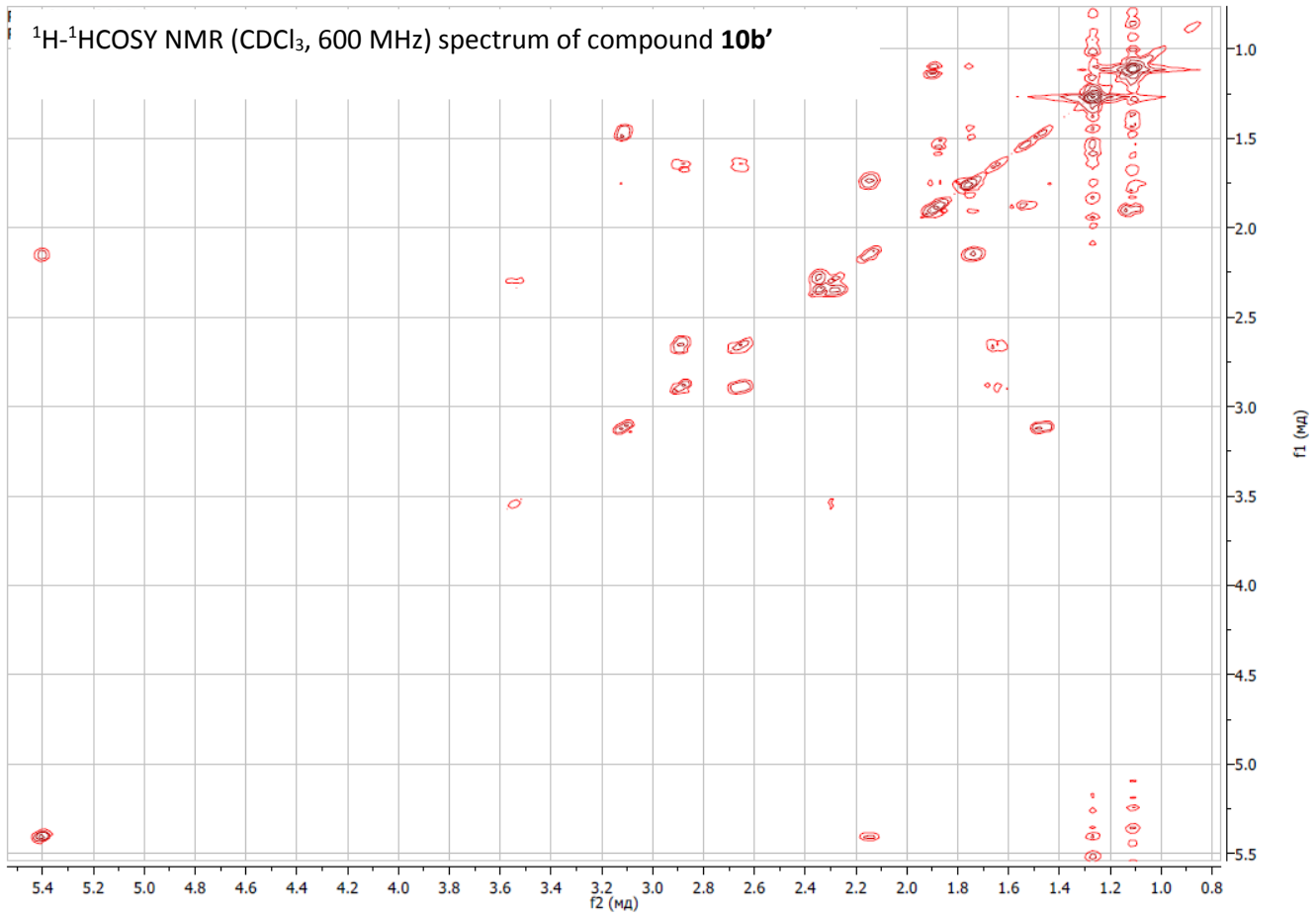
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **10b'**



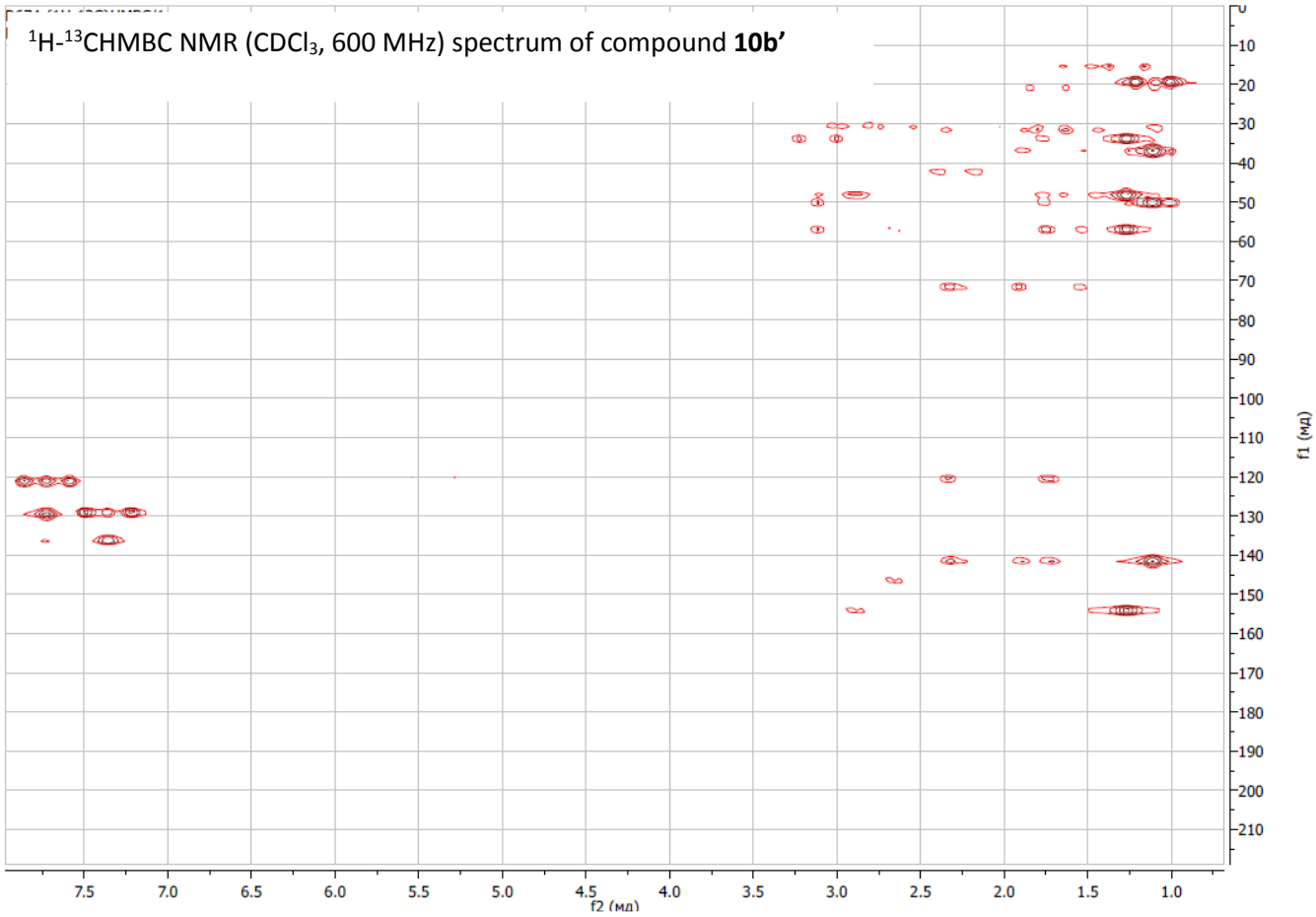
^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **10b'**

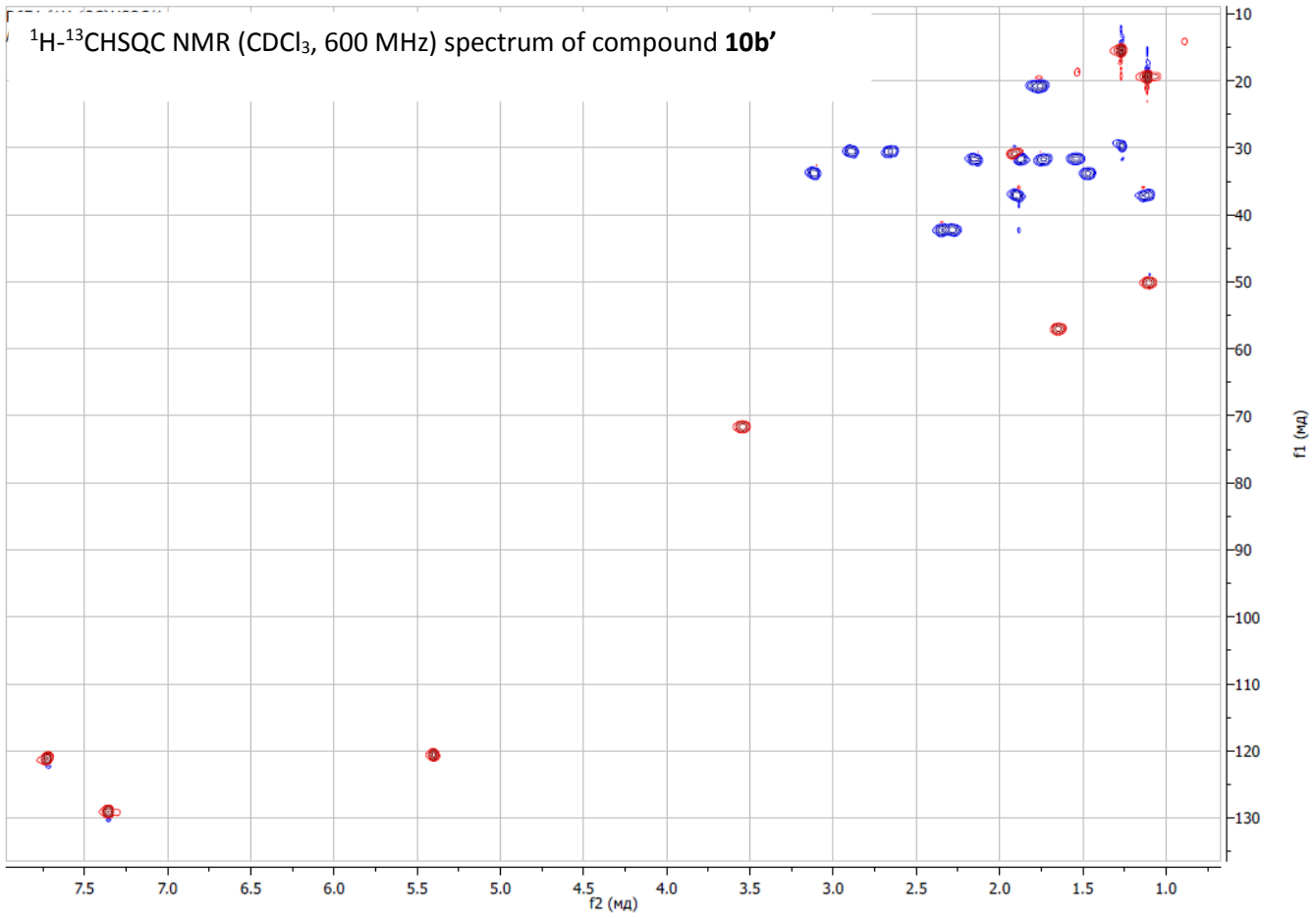


^{1}H-^{1}HCOSY NMR ($CDCl_3$, 600 MHz) spectrum of compound **10b'**

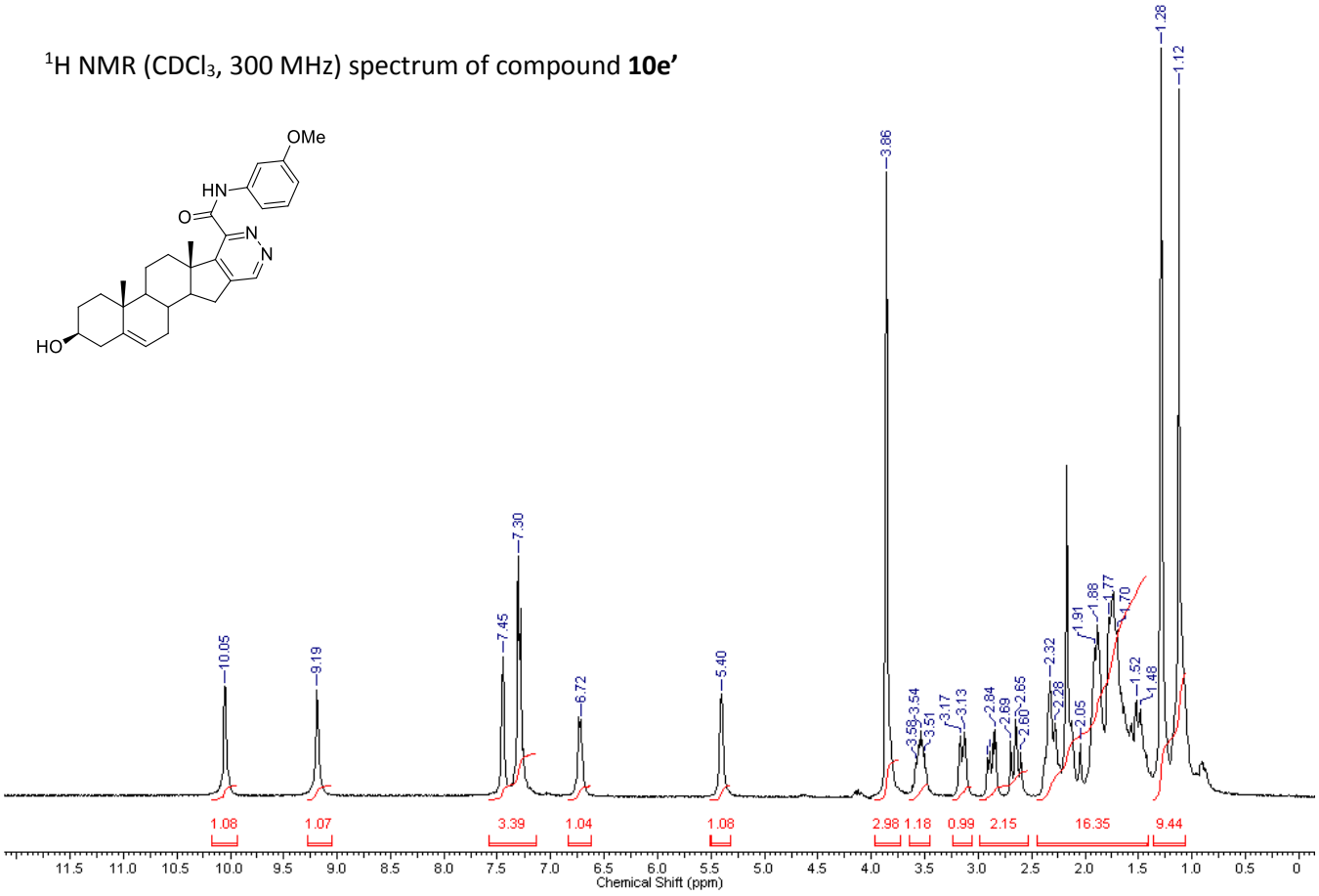


^{1}H-^{13}CHMBC NMR ($CDCl_3$, 600 MHz) spectrum of compound **10b'**

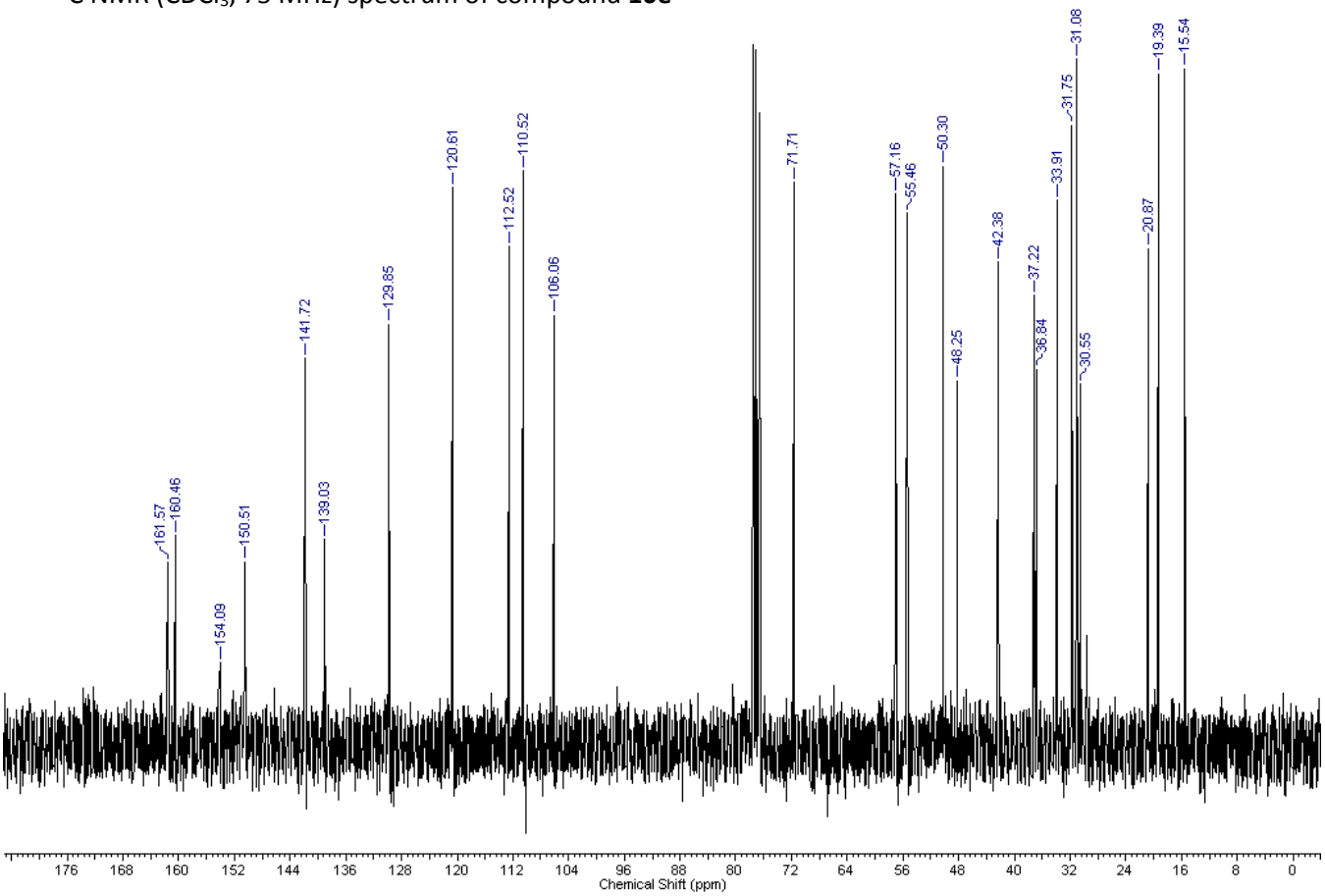



^{1}H-^{13}CHSQC NMR ($CDCl_3$, 600 MHz) spectrum of compound **10b'**
f2 (мд)
f1 (мд)

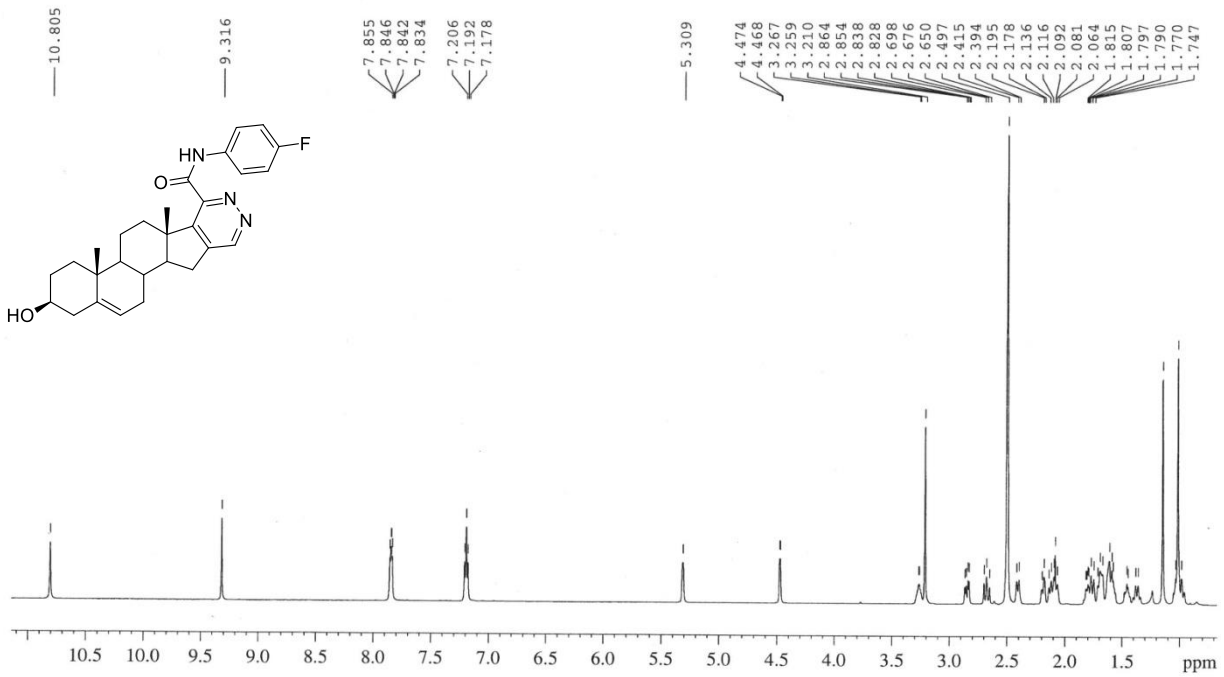
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **10e'**



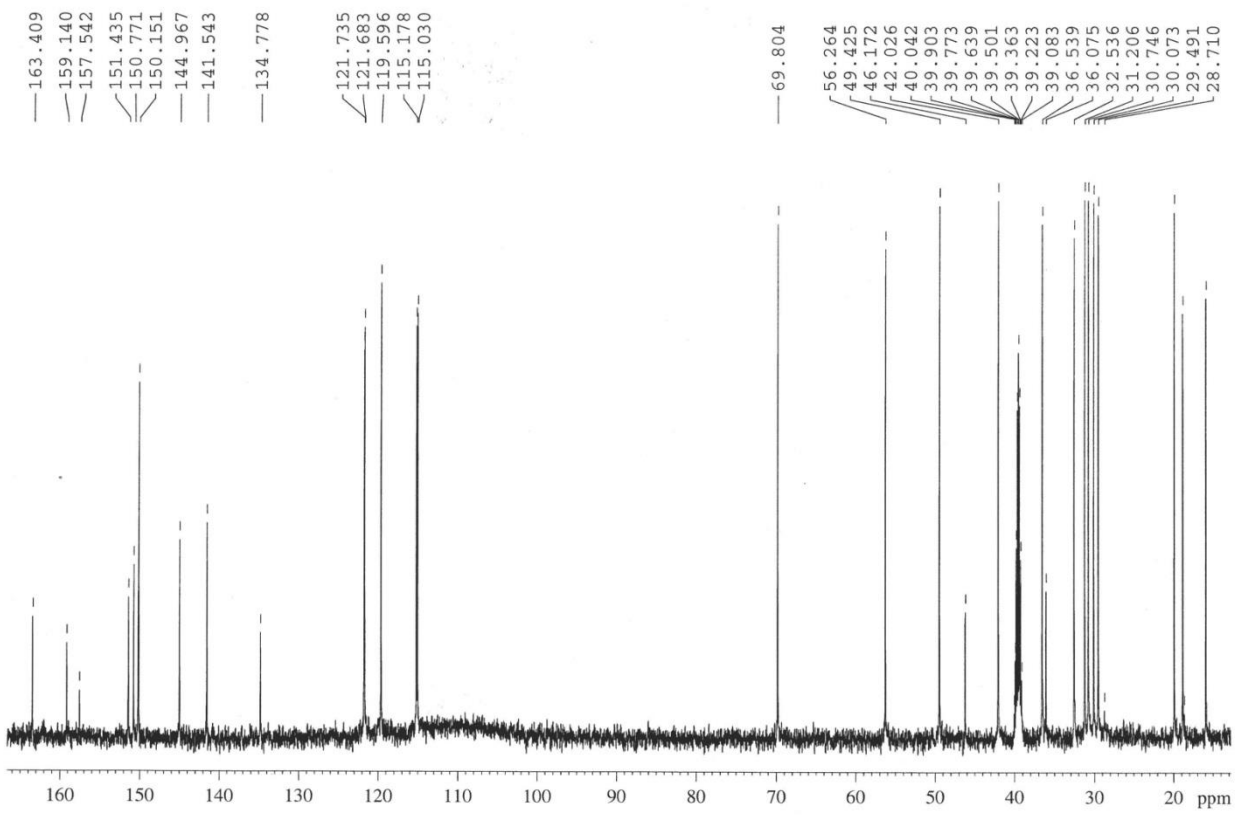
^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **10e'**



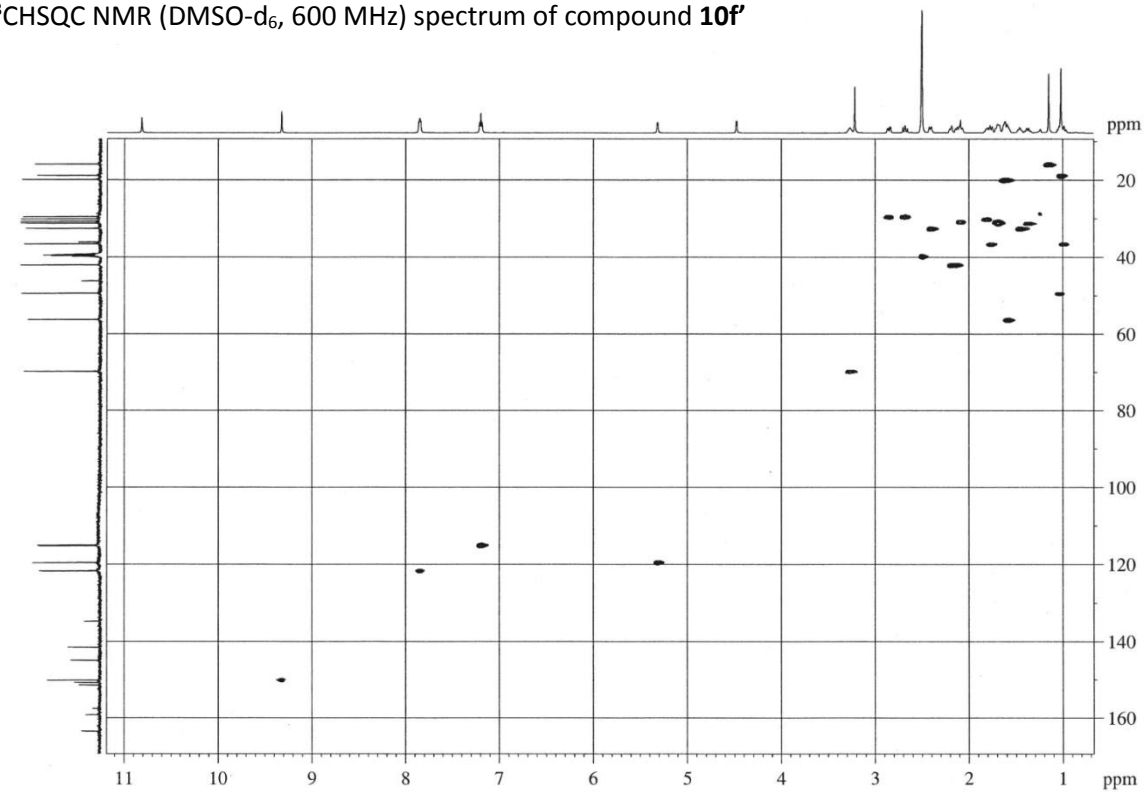
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **10f'**



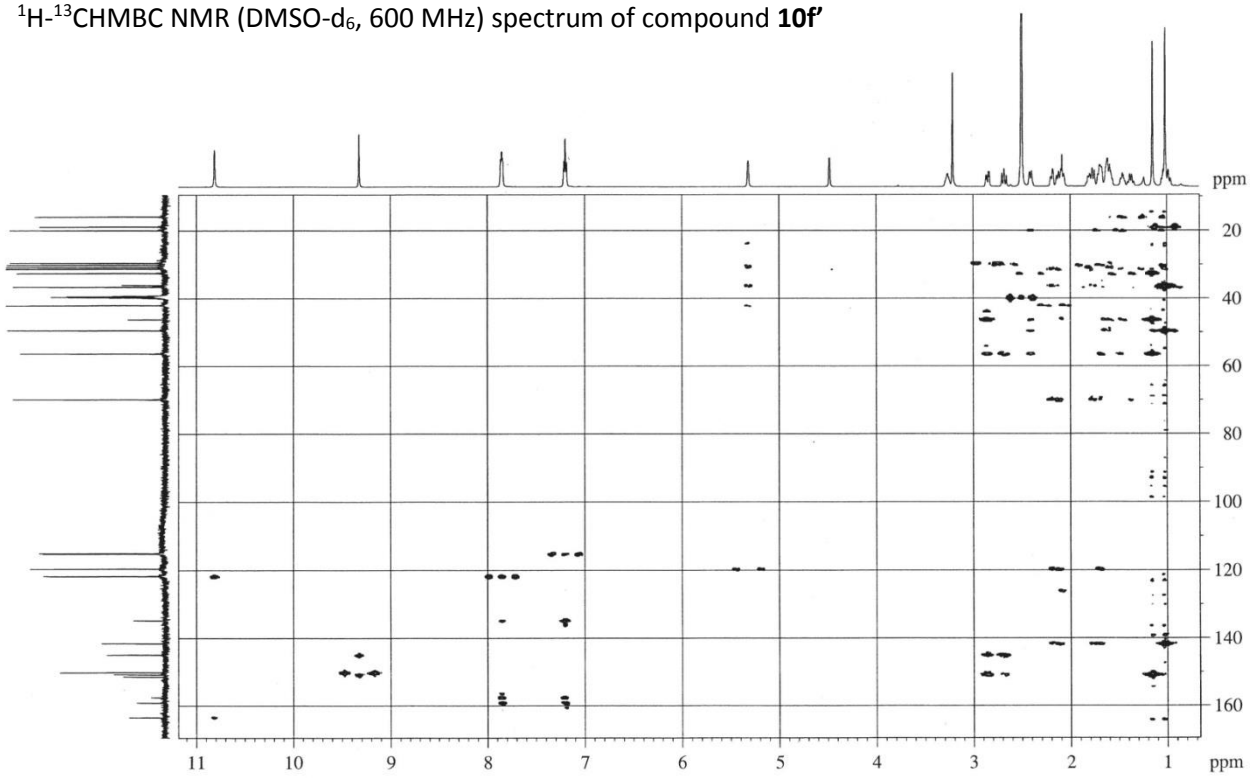
^{13}C NMR (DMSO-d_6, 150 MHz) spectrum of compound **10f'**



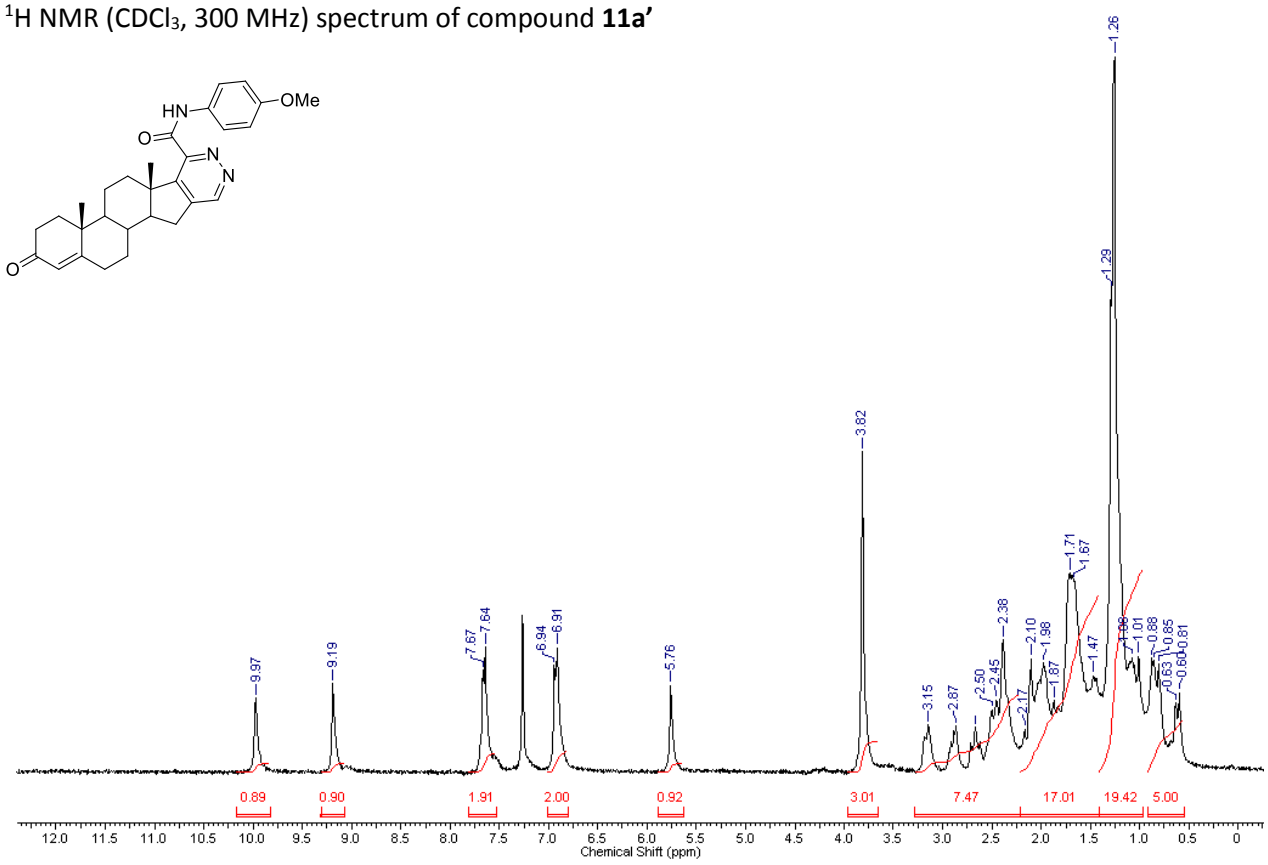
^{1}H-^{13}CHSQC NMR (DMSO-d_6, 600 MHz) spectrum of compound **10f'**



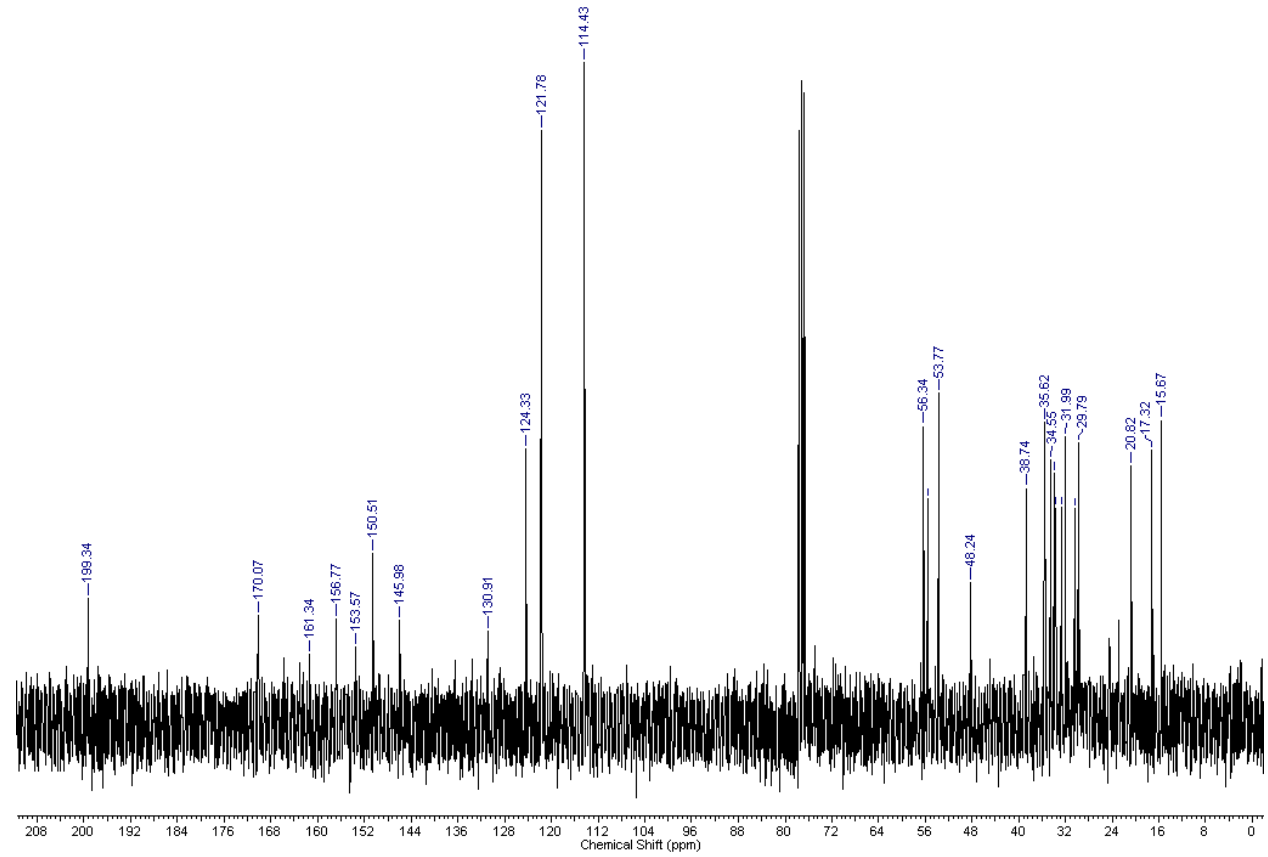
^{1}H-^{13}CHMBC NMR (DMSO-d_6, 600 MHz) spectrum of compound **10f'**



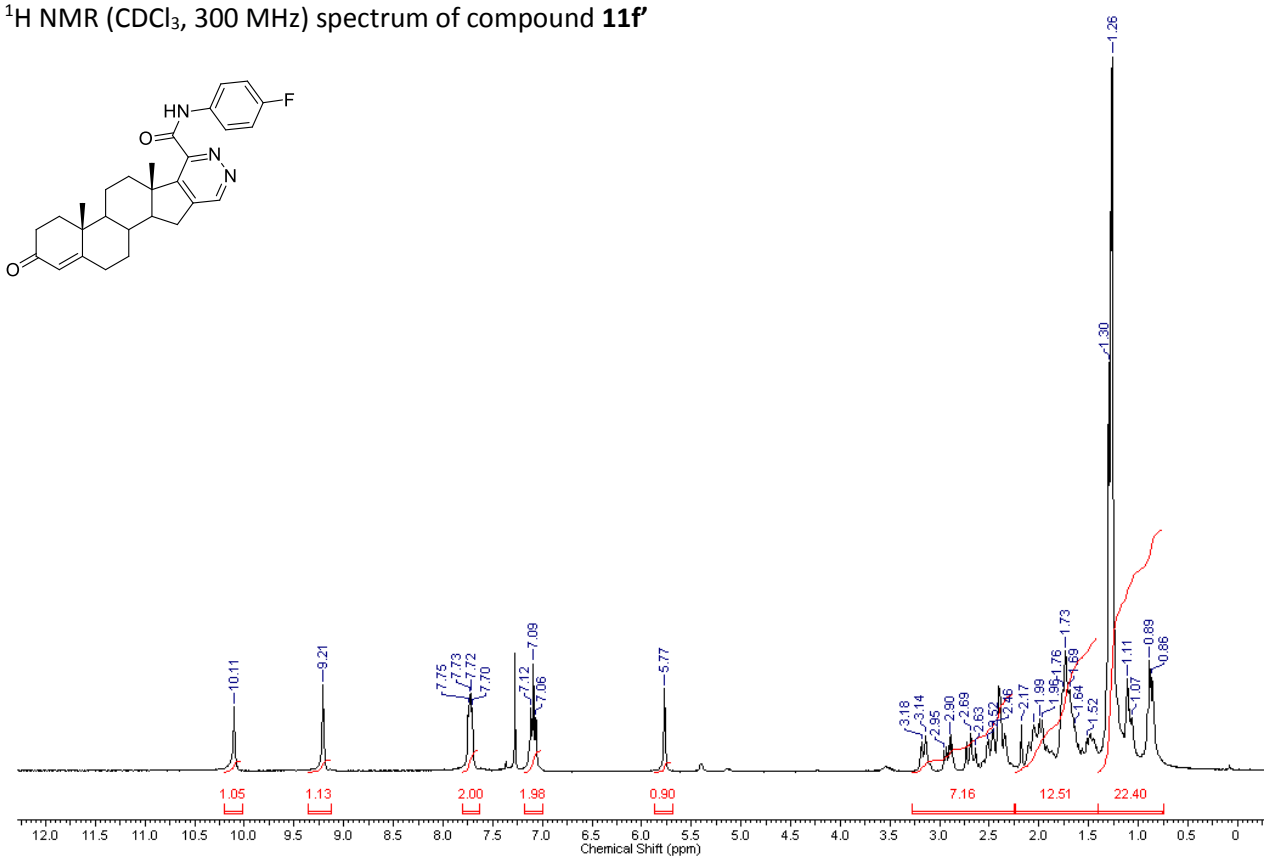
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **11a'**



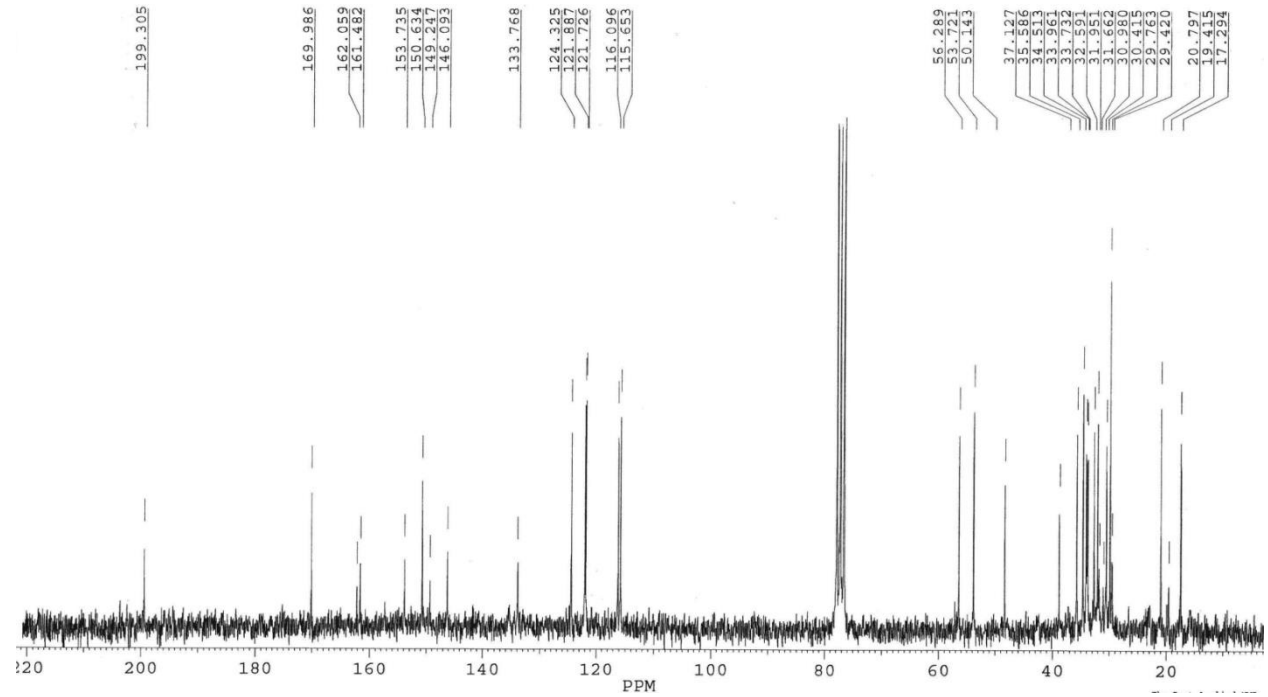
^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **11a'**



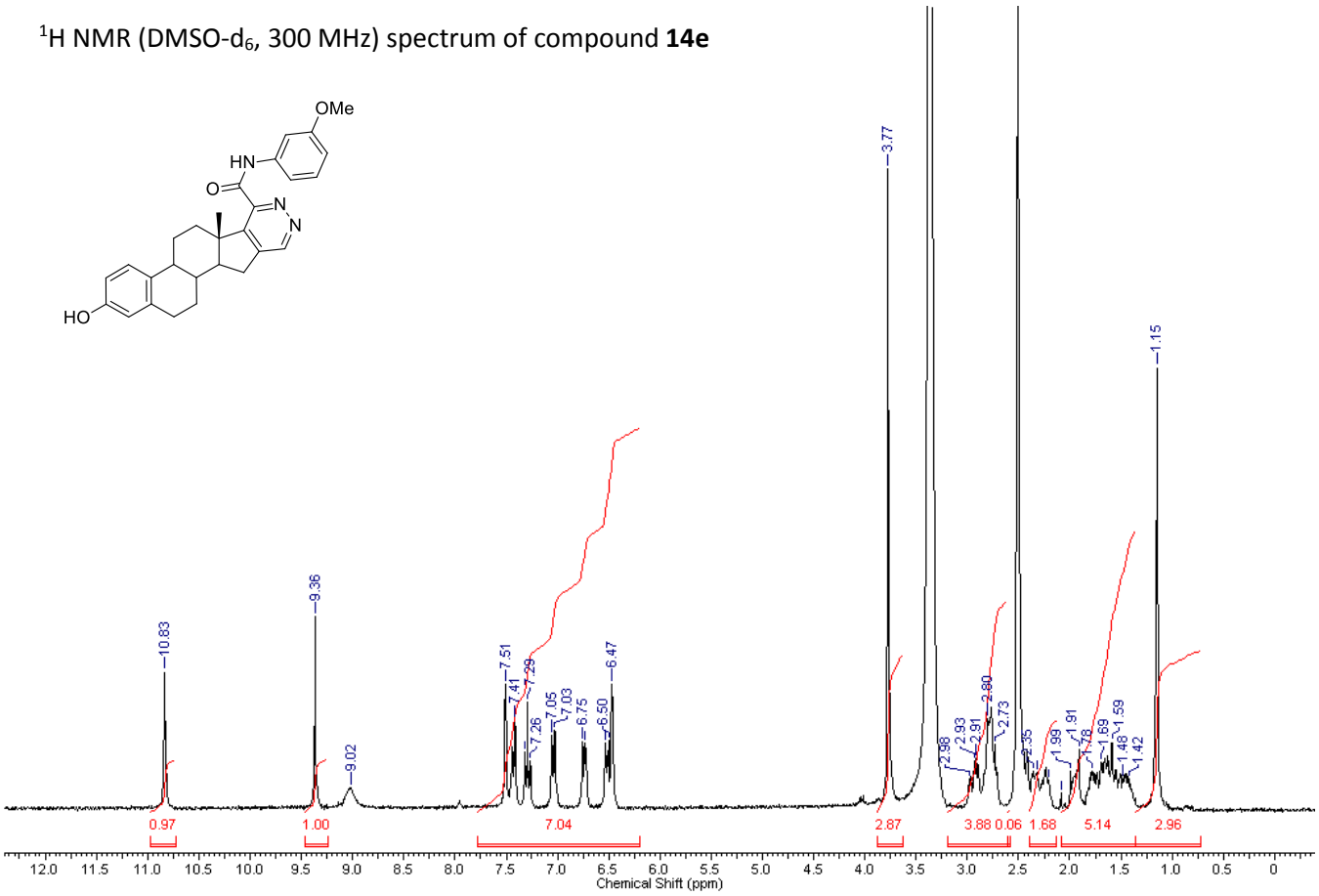
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **11f'**



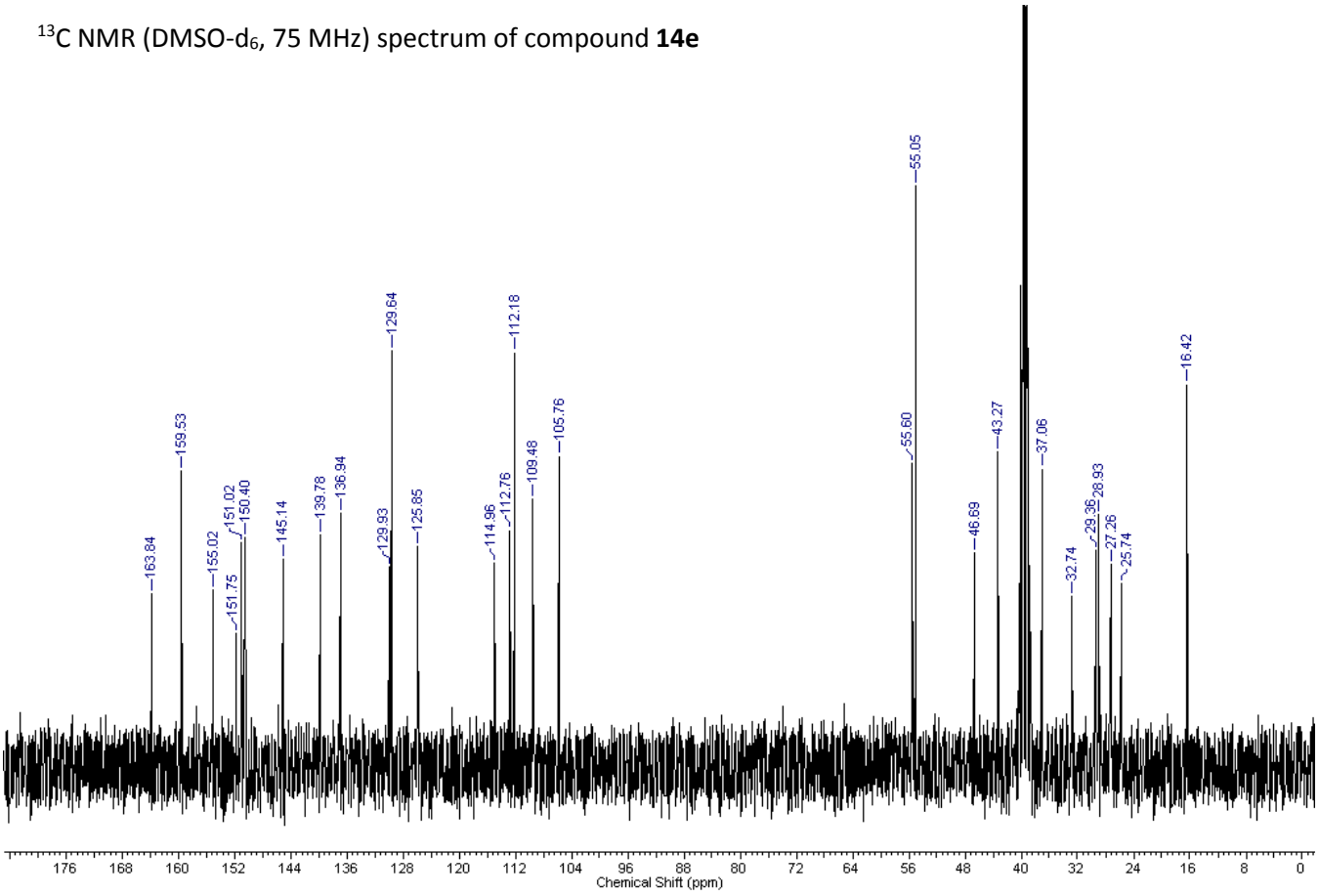
^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **11f'**



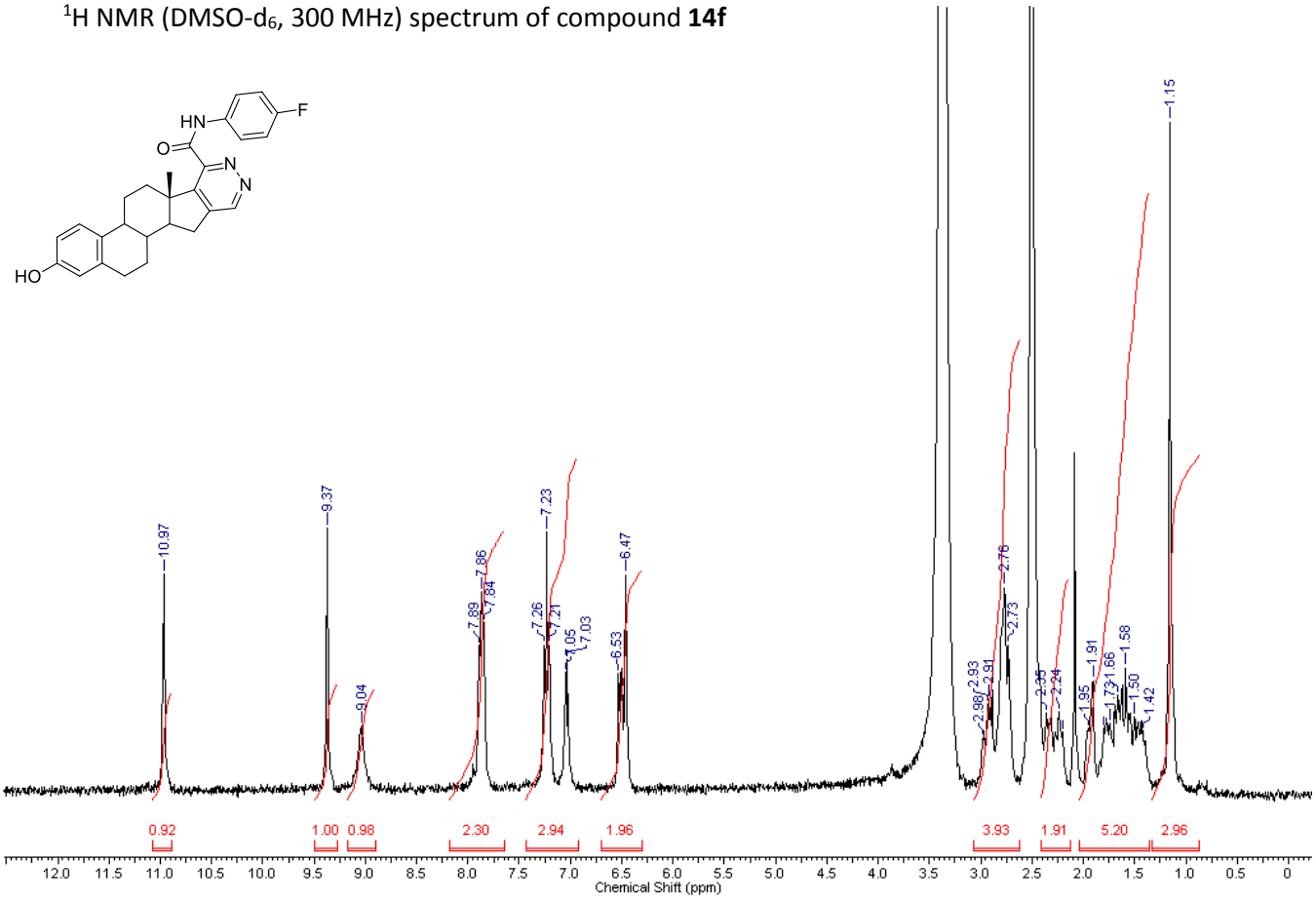
^{1}H NMR (DMSO-d$_6$, 300 MHz) spectrum of compound **14e**



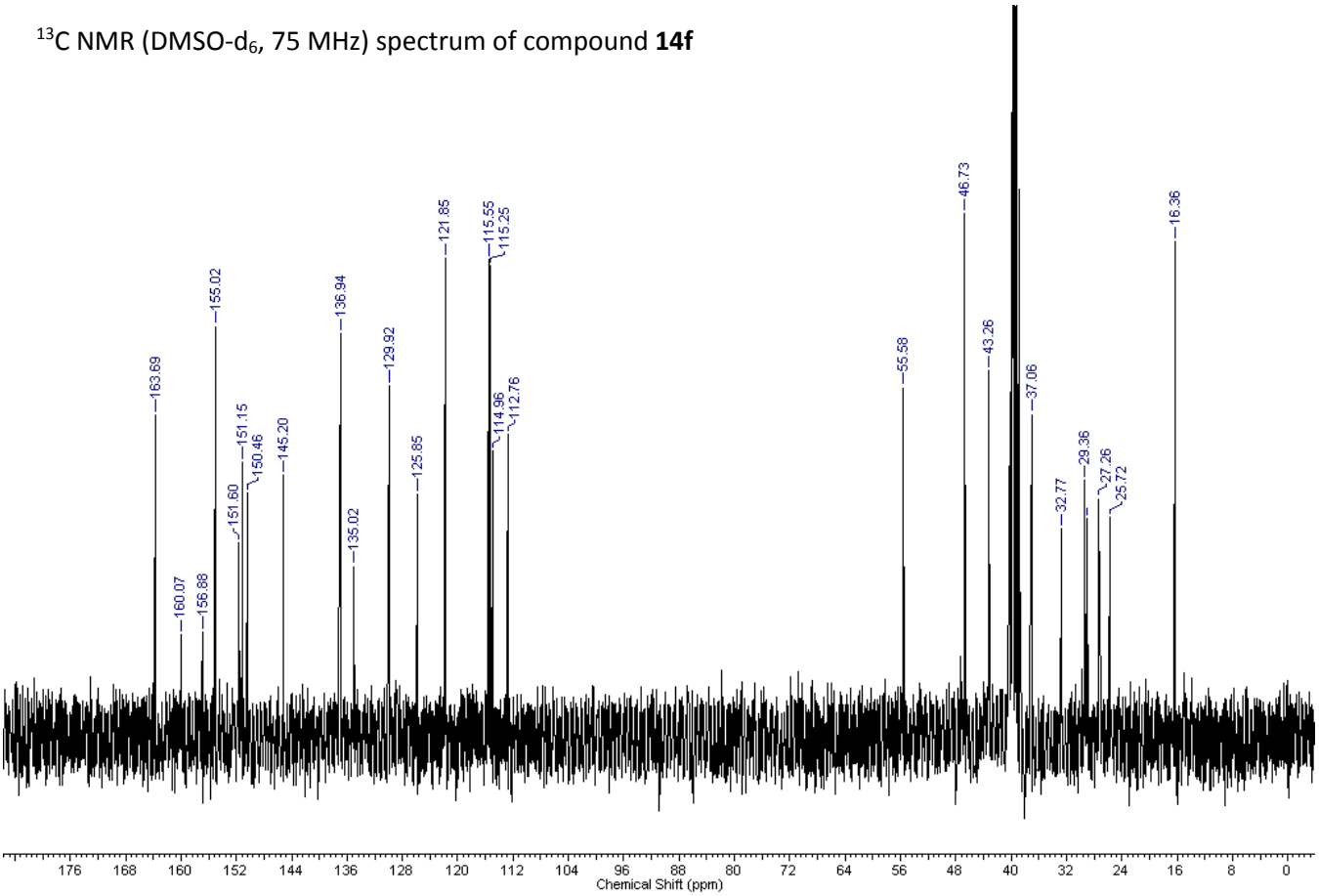
^{13}C NMR (DMSO-d$_6$, 75 MHz) spectrum of compound **14e**



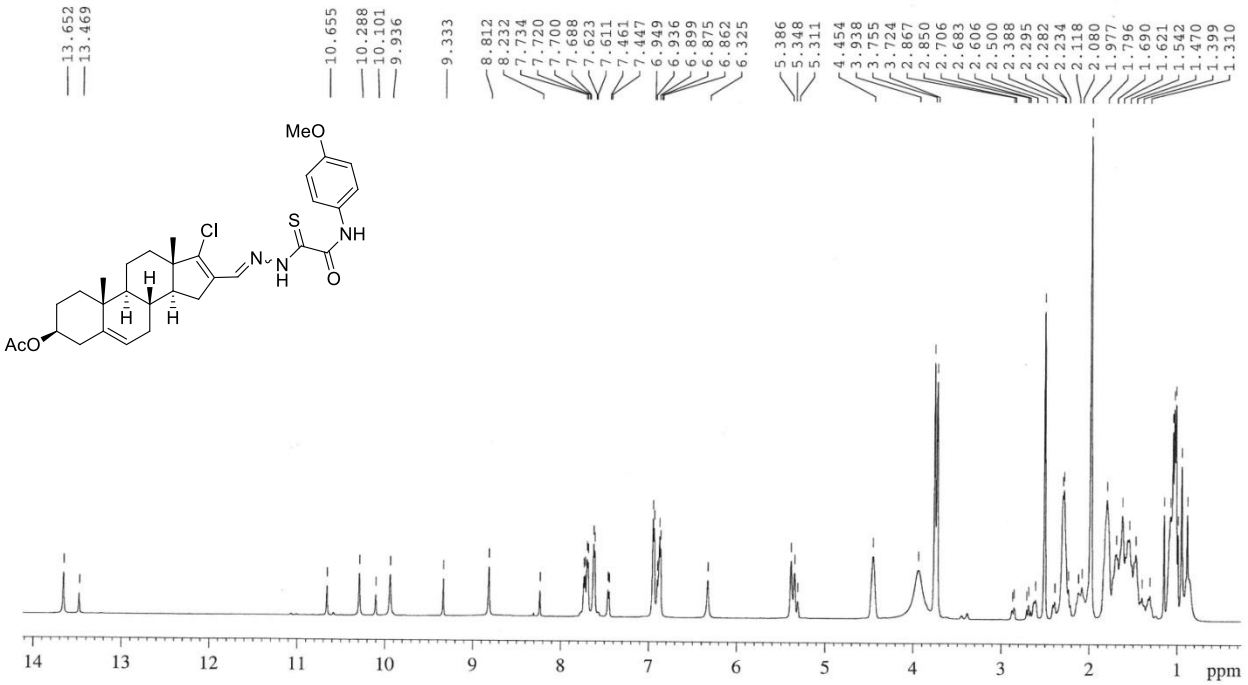
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **14f**



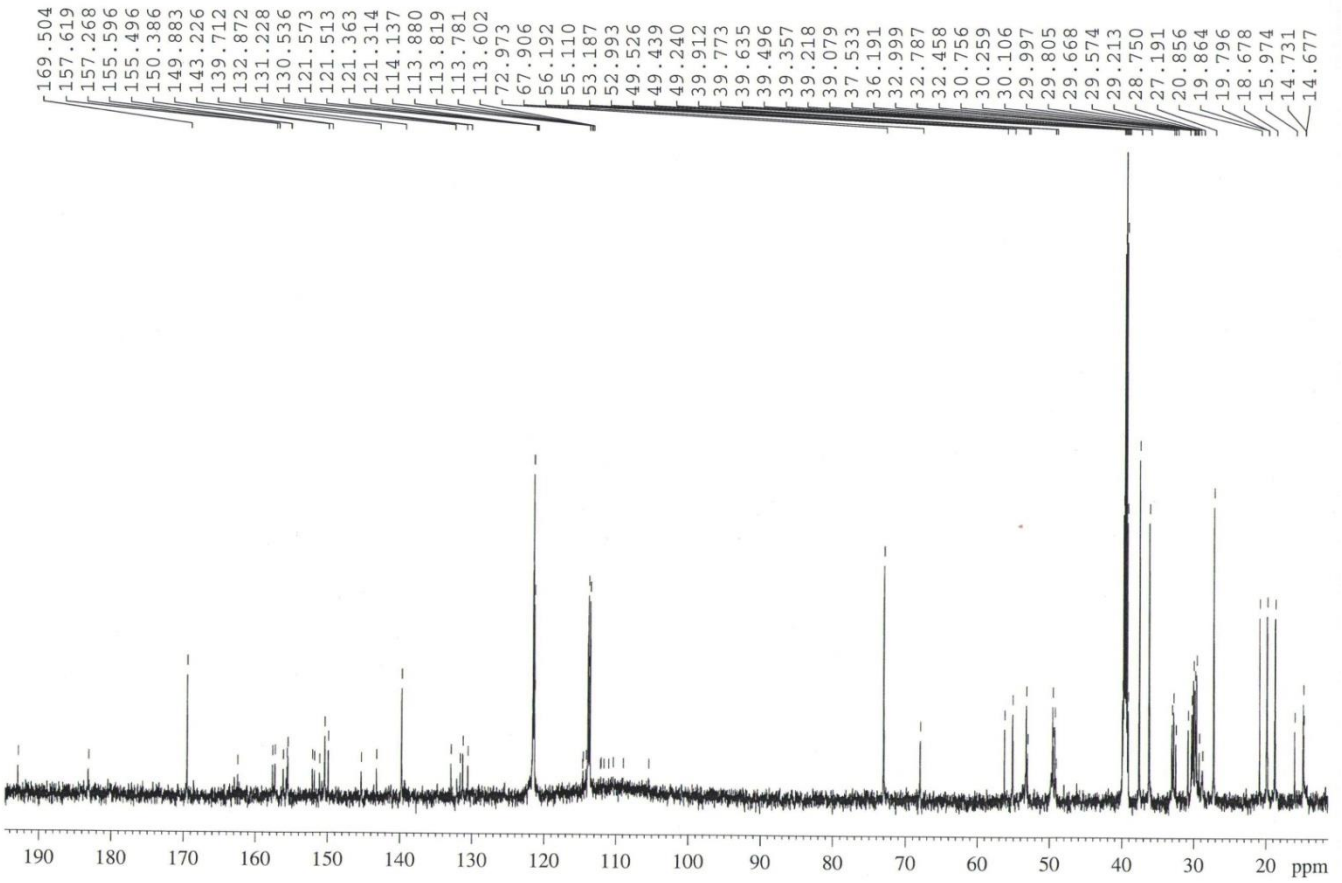
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **14f**



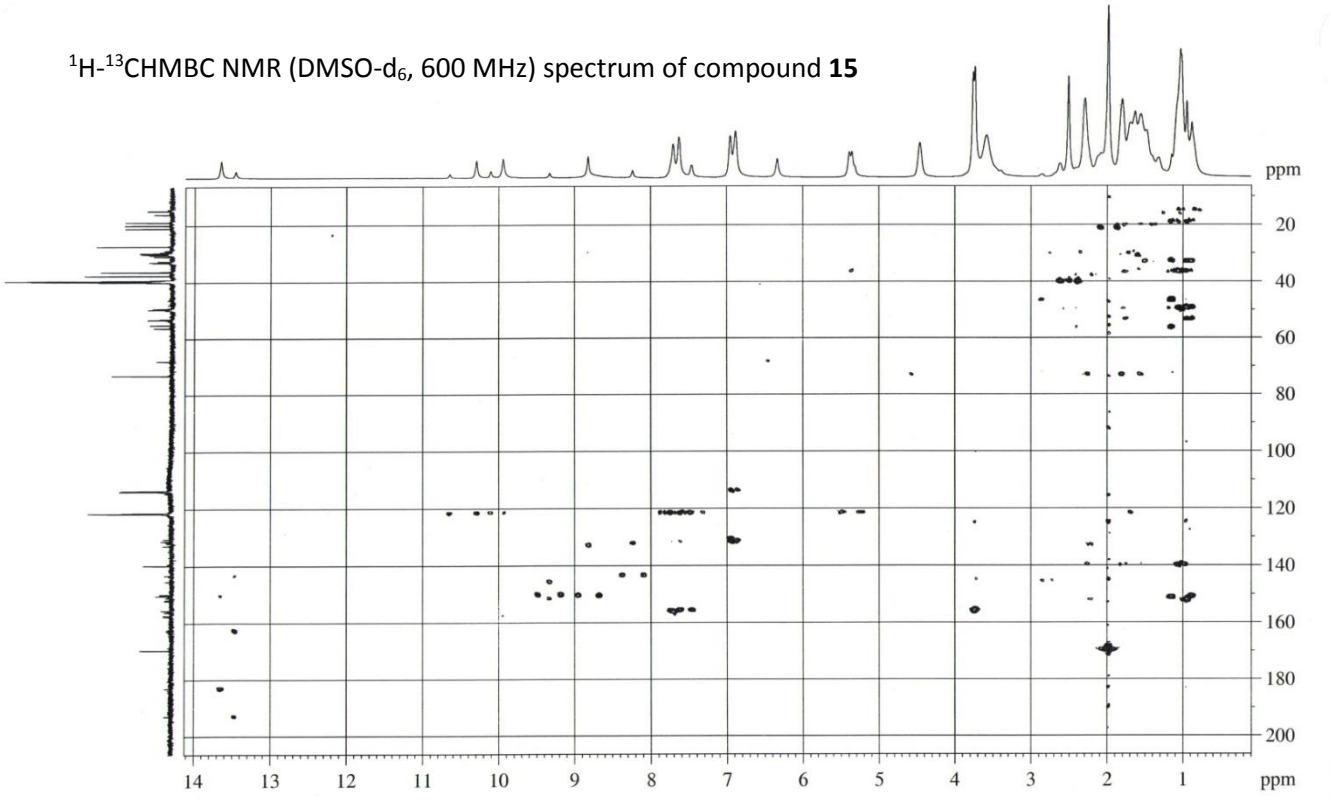
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **15**



^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of compound **15**



^{1}H-^{13}CHMBC NMR (DMSO-d_6, 600 MHz) spectrum of compound **15**



^{1}H-^{13}CHSQC NMR (DMSO-d_6, 600 MHz) spectrum of compound **15**