Design and synthesis of phosphoryl-substituted steroidal pyridazines (Pho-STPYRs) as potent estrogen receptor alpha inhibitors: targeted treatment of hormone-dependent breast cancer cells

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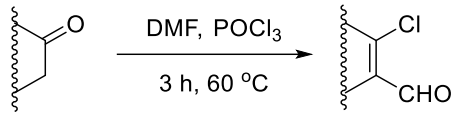
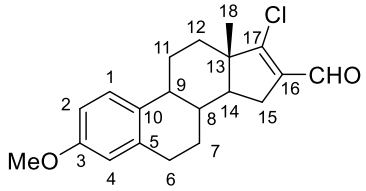
Steroidal β-chlorovinylaldehydes 4**, 13, 25**, and **29** were prepared from the corresponding steroidal ketones by the treatment with $POCl_3$/DMF mixture according to the literature procedure.[1]

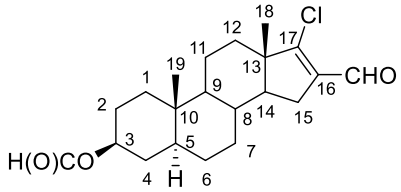
General procedure for the synthesis of steroidal β-chlorovinylaldehydes 3, 21, and 25.



A flame-dried round bottom flask containing a stir bar and DMF (2.0 mL, 26.0 mmol, 17.8 equiv) was cooled to 0°C and $POCl_3$ (1.35 mL, 14.6 mmol, 10.0 equiv) was added dropwise while stirring. The mixture was stirred for 30 minutes, before a dropwise addition of steroidal ketone (1.46 mmol, 1.0 equiv) solution in DMF (1.5 mL). The mixture was warmed to ambient temperature and stirred at 60°C for 3 hours. The reaction mixture was poured into iced water (50 mL). Formed suspension was allowed to stay 1 hour at 5°C, precipitate was filtered off, dried and filtered through pad of silica gel (eluent: benzene).

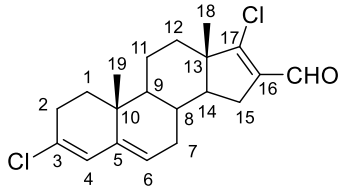


17-Chloro-3-methoxy-16-formyl-$\Delta^{1,3,5(10),16}$-estratetraene (3). Obtained according to general procedure from 0.401 g of 3-methoxyestone as white solid (73%, 0.350 g), m.p. 124-125°C. ^{1}H NMR (400 MHz, 100 MHz, 150 MHz, ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HSQC, DMSO-d_6): δ 0.95 (s, 3H, 18-CH_3), 1.28 – 1.41 (m, 1H, 7-CH_2), 1.42 – 1.65 (m, 3H, 8-CH, 11-CH_2, 12-CH_2), 1.66 – 1.77 (m, 1H, 14-CH), 1.81 – 1.93 (m, 2H, 7-CH_2, 12-CH_2), 2.15 (dd, *J* = 14.4, 11.7 Hz, 1H, 15-CH_2), 2.20 – 2.30 (m, 1H, 9-CH), 2.35 – 2.44 (m, 1H, 11-CH_2), 2.45 – 2.49 (m, 1H, 15-CH_2), 2.75 – 2.86 (m, 2H, 6-CH_2), 3.69 (s, 3H, OCH_3), 6.63 (d, *J* = 2.8 Hz, 1H, 4-CH), 6.69 (dd, *J* =8.6, 2.8 Hz, 1H, 2-CH), 7.16 (d, *J* = 8.6 Hz, 1H, 1-CH), 9.92 (s, 1H, CHO). ^{13}C NMR (101 MHz, DMSO-d_6): δ 14.9 (18-CH_3), 25.5 (11-CH_2), 26.4 (7-CH_2), 27.8 (15-CH_2), 29.0 (6-CH_2), 32.5 (12-CH_2), 36.7 (8-CH), 43.4 (9-CH), 50.4 (13-C), 52.3 (14-CH), 54.9 (OCH_3), 111.5 (2-CH), 113.5 (4-CH), 125.9 (1-CH), 131.6 (10-C), 136.2 (16-C), 137.3 (5-C), 157.2 (3-C), 160.9 (17-C), 187.6 (CHO). HRMS (ESI) for $C_{20}H_{24}ClO_2$ ([M+H]$^+$): calcd 331.1459, found 331.1451.



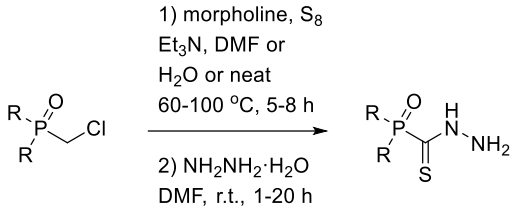
3β-Formyloxy-16-formyl-17-chloro-5α-16-androstene (21). Obtained according to general procedure from 0.424 g of 3β-hydroxy-5α-androstane as white solid (62%, 0.330 g), m.p. 151-152°C. ^{1}H NMR (600 MHz, 150 MHz, ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HSQC, DMSO-d_6): δ 0.76 – 0.82 (m, 1H, 9-CH), 0.83 (s, 3H, 19-CH_3), 0.92 (s, 3H, 18-CH_3), 0.94 – 0.99 (m, 1H, 7-CH_2), 1.03 (td, *J* = 13.9, 4.2 Hz, 1H, 1-CH_2), 1.16 – 1.31 (m, 3H, 5-CH, 6-CH_2), 1.31 – 1.42 (m, 3H, 4-CH_2, 11-CH_2, 14-CH_2), 1.43 – 1.52 (m, 2H, 2-CH_2, 14-CH), 1.52 – 1.60 (m, 2H, 4-CH_2, 8-CH), 1.61 – 1.71 (m, 3H, 1-CH_2, 7-CH_2, 11-CH_2), 1.72 – 1.80 (m, 2H, 2-CH_2, 12-CH_2), 2.04 (dd, *J* = 14.8, 11.5 Hz, 1H, 15-CH_2), 2.37 (dd, *J* = 14.8, 6.3 Hz, 1H, 15-CH_2), 4.68 (tt, *J* = 10.9, 4.9 Hz, 1H, 3-CH), 8.17 (s, 1H, OCHO), 9.89 (s, 1H, CHO). ^{13}C NMR (150 MHz, DMSO-d_6): δ 11.8 (19-CH_3), 14.9 (18-CH_3), 20.2 (11-CH_2), 27.1 (2-CH_2), 27.7 (6-CH_2),

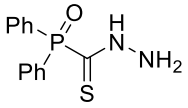
28.0 (15-CH_2), 30.4 (7-CH_2), 32.4 (12-CH_2), 33.4 (8-CH), 33.6 (10-C), 35.7 (1-CH_2), 44.0 (5-CH), 50.2 (13-C), 52.9 (14-CH), 53.5 (9-CH), 72.8 (3-CH), 136.2 (16-C), 160.7 (17-C), 161.7 (OCHO), 187.5 (CHO). HRMS (ESI) for $C_{21}H_{30}ClO_3$ ([M+H]$^+$): calcd 365.1878, found 365.1871.



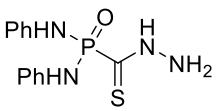
16-Formyl-3,17-dichloro-androst-3,5,16-triene (25). Obtained according to general procedure from 0.411 g of 4-androstene-3,17-dione as white solid (40%, 0.206 g), m.p. 132-133°C. ^{1}H NMR (400 MHz, 100 MHz, ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HSQC, DMSO-*d*$_6$): δ 0.97 (s, 3H, 19-CH_3), 1.00 (s, 3H, 18-CH_3), 1.02 – 1.20 (m, 1H, 9-CH), 1.27 (td, *J* = 12.3, 6.2 Hz, 1H, 1-CH_2), 1.40 – 1.64 (m, 3H, 11-CH_2, 12-CH_2, 14-CH), 1.69 – 1.91 (m, 5H, 1-CH_2, 7-CH_2, 8-CH, 11-CH_2, 12-CH_2), 2.13 (dd, *J* = 14.7, 11.5 Hz, 1H, 15-CH_2), 2.24 (dt, *J* = 18.3, 5.3 Hz, 1H, 7-CH_2), 2.32 – 2.37 (m, 1H, 2-CH_2), 2.45 (dd, *J* = 14.7, 6.5 Hz, 1H, 15-CH_2), 2.50 – 2.58 (m, 1H, 2-CH_2), 5.54 – 5.57 (m, 1H, 6-CH), 6.15 (d, *J* = 2.3 Hz, 1H, 4-CH), 9.93 (s, 1H, CHO). ^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 14.8 (18-CH_3), 18.5 (19-CH_3), 20.0 (11-CH_2), 28.0 (15-CH_2), 29.7 (8-CH), 29.9 (7-CH_2), 30.2 (2-CH_2), 32.3 (12-CH_2), 34.0 (1-CH_2, 10-C), 47.4 (9-CH), 50.1 (13-C), 52.9 (14-CH), 123.9 (6-CH), 126.7 (4-CH), 129.8 (3-C), 136.3 (16-C), 140.2 (5-C), 160.5 (17-C), 187.5 (CHO). HRMS (ESI) for $C_{20}H_{25}Cl_2O$ ([M+H]$^+$): calcd 351.1277, found 351.1266.

General procedure for the synthesis of phosphorylthioformic acid hydrazides 5





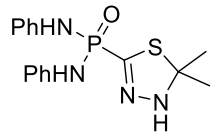
(Diphenylphosphoryl)methanethiohydrazide (5a).[2, 3] Morpholine (1.7 mL, 19.2 mmol, 1.2 equiv) was added to the mixture of compound **1c** (4.0 g, 16.0 mmol, 1.0 equiv), trimethylamine (6.7 mL, 48 mmol, 3.0 equiv), and sulfur (1.54 g, 48.0 mmol, 3.0 equiv) in DMF (12 mL). The mixture was stirred at 60 °C for 8 h until the complete conversion of phosphinic chloride (TLC monitoring). The resulted mixture was cooled to room temperature and diluted with water (100 mL), carefully acidified with conc. HCl to pH 2-3. Precipitate was filtered off, redissolved in acetone (30 ml), and the undissolved fraction of the precipitate was filtered. Filtrate was concentrated under reduced pressure to get 3.4 g of diphenylphosphoryl thiomorpholide, which was used in the next step without additional purification. Next, hydrazine hydrate (3.3 mL, 6.7 mmol, 1.5 equiv) was added to diphenylphosphoryl thiomorpholide (3.4 g, 10.4 mmol, 1.0 equiv) in DMF (70 mL). Resulting solution was stirred for 20 h at r.t., diluted with water (350 mL), and carefully acidified with conc. HCl to pH 6. Precipitate formed was filtered off and air dried to give 2.1 g (7.3 mmol, 45% yield) of product. Creamy solid, m.p. 187-189°C, R_f 0.45 (CH_2Cl_2 – MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 – 7.89 (m, 4H, 4 × CH), 7.68 – 7.55 (m, 2H, 2 × CH), 7.55 – 7.37 (m, 4H, 4 × CH), signals of $NHNH_2$ group were not observed. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (d, $^1J_{C\text{-}P}$ = 163.5 Hz, C=S), 132.7 (d, $^4J_{C\text{-}P}$ = 2.8 Hz, 2 × CH), 132.6 (d, $^2J_{C\text{-}P}$ = 9.8 Hz, 4 × CH), 129.1 (d, $^1J_{C\text{-}P}$ = 111.0 Hz, 2 × C), 128.4 (d, $^3J_{C\text{-}P}$ = 12.7 Hz, 4 × CH). ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.79. IR (KBr) 3358, 3281, 3128, 3052, 3023 (CH), 1547, 1480, 1437 (C=C), 1362, 1311, 1172, 1117, 1016, 849, 824, 746, 728, 707, 689, 676, 575, 557, 479 cm^{-1}. HRMS (ESI) for $C_{13}H_{13}N_2OPS^+$ $[M+H]^+$: calcd 277.0559, found 277.0569.



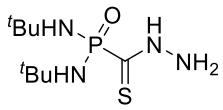
***P*-(Hydrazinocarbonothioyl)-*N,N'*-diphenylphosphonic diamide (5b) complex with hydrazine. [2, 3]** Morpholine (5.2 mL, 60.4 mmol, 5.0 equiv) was added to the suspension of compound **1a** (3.4 g, 12.1 mmol, 1.0 equiv), and sulfur (1.1 g, 21.3 mmol, 3.0 equiv) in water (70 mL). The mixture was refluxed for 5 h until the complete conversion of phosphinic chloride (TLC monitoring). The resulted mixture was cooled to room temperature. Precipitate was filtered off and subjected to column chromatography (eluent: petroleum ether – EtOAc, 1 : 1) to get 3.6 g of *N,N'*-diphenyl-phosphonic diamide thiomorpholide. Next, hydrazine hydrate (1.7 mL, 35.0 mmol, 3.5 equiv) was added to *N,N'*-diphenyl-phosphonic diamide thiomorpholide (3.6 g, 10.0 mmol, 1.0 equiv) in 14 mL dry dioxane. Resulting solution was stirred for 1 hour at r.t., diluted with Et_2O (30 mL). Precipitate formed was filtered off to give 3.2 g (8.3 mmol, 69% yield) of complex

5b·2NH_2NH_2·H_2O. White solid, m.p. 89-90°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.59 (br. s, 2H, 2 × NH), 7.22 – 6.92 (m, 8H, 8 × CH), 6.81 – 6.64 (m, 2H, 2 × CH), 5.21 (br. s, 13H, H_2O, NH_2, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.1 (d, $^1J_{C\text{-}P}$ = 196.2 Hz, C=S), 142.6 (2 × C), 128.9 (4 × CH), 119.8 (4 × CH), 117.63 (d, $^3J_{C\text{-}P}$ = 6.3 Hz, 2 × CH). ^{31}P NMR (121 MHz, DMSO-d_6): δ 0.12. IR (KBr) 3300, 2600, 1601, 1498, 1475, 1379, 1286, 1190, 1163, 1120, 1078, 1018, 947, 910, 869, 751, 691, 619, 509, 466 cm^{-1}. HRMS (ESI) for $C_{13}H_{16}N_4OPS^+$ $[M+H]^+$: calcd 307.0777, found 307.0777. Elemental analysis for $C_{13}H_{25}N_8O_2PS$: calcd, %: C, 40.20; H, 6.49; N, 28.85. Found, % C, 39.87; H, 6.39; N, 29.01.

(5,5-Dimethyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)di(phenylamino)phosphine oxide (5b').[4] A mixture of



complex **5b**∗2NH_2NH_2∗H_2O (3.2 g, 8.3 mmol, 1.0 equiv) and acetone (550 mL) was refluxed for 5 min and additionally stirred at r.t. for 1 h. Acetone was removed under reduced pressure. Residue was washed with Et_2O (275 mL) to give product as a pale yellow solid (2.7 g, 91%), m.p. 186 – 187 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.43 (s, 1H, NH), 7.99 (d, 2H, $J_{H\text{-}P}$ = 11.0 Hz, 2 × NH), 7.30-7.10 (m, 8H, 2 × CH), 6.90-6.80 (m, 2H, 2 × CH), 1.50 (s, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 141.0 (2 × C), 139.1 (d, $^1J_{C\text{-}P}$ = 193.2 Hz, C-P), 128.7 (4 × CH), 120.7 (2 × CH), 118.0 (d, $^3J_{C\text{-}P}$ = 6.4 Hz, 4 × CH), 81.6 (C), 28.8 (2 × CH_3). ^{31}P NMR (243 MHz, DMSO-d_6): δ -1.01.



[Di (*tert*-butylamino)phosphoryl]methanethiohydrazide (5c). [2, 3] Morpholine (43.2 mL, 500 mmol, 20.0 equiv) was added to the mixture of compound **1b** (6.0 g, 24.9 mmol, 1.0 equiv), and sulfur (2.4 g, 74.7 mmol, 3.0 equiv). The mixture was stirred at 65 °C for 8 h until the complete conversion of phosphinic chloride (TLC monitoring). The resulted mixture was cooled to room temperature, diluted with water (300 mL), carefully acidified with conc. HCl to pH 2-3 and extracted with CH_2Cl_2 (3 × 90 mL). Combined organic layers dried over Na_2SO_4, solvent was removed under reduced pressure. Purification by column chromatography (eluent: petroleum ether – EtOAc, 1 : 1) afforded 3.6 g of *N,N'*-di-*tert*-butyl-phosphonic diamide thiomorpholide. Next, hydrazine hydrate (33 mL, 67.0 mmol, 6.0 equiv) was added to *N,N'*-di-*tert*-butyl-phosphonic diamide thiomorpholide (3.6 g, 11.1 mmol, 1.0 equiv) in DMF (50 mL). Resulting solution was stirred for 8 h at r.t., diluted with water (300 mL), and carefully acidified with conc. HCl to pH 4. Reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). Combined organic layers were dried over Na_2SO_4, and solvent was removed under reduced pressure. Purification by column chromatography (eluent: CH_2Cl_2 – MeOH, 50 : 1) afforded 0.7 g (2.9 mmol, 11% yield) of product. Pale green-yellow solid, m.p. 193-195°C, R_f 0.11 (CH_2Cl_2 – MeOH, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22 (br. s, 2H, 2 × NH), 1.32 (s, 18H, 6 × CH_3), signals of $NHNH_2$ group were not observed. ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.5 (d, $^1J_{C\text{-}P}$ = 144.0 Hz, C=S), 52.1 (d, $^2J_{C\text{-}P}$ = 0.8 Hz, 2 × C), 31.57 (d, $^3J_{C\text{-}P}$ = 4.4 Hz, 6 × CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.48. IR (KBr) 3364, 3260, 3143, 2969, 2908, 1561, 1542, 1475, 1411, 1389, 1363, 1240, 1224, 1188, 1110, 1055, 1028, 1008, 882, 854, 729, 667, 611, 556 cm^{-1}. HRMS (ESI) for $C_9H_{24}N_4OPS^+$ $[M+H]^+$: calcd 267.1403, found 267.1403.

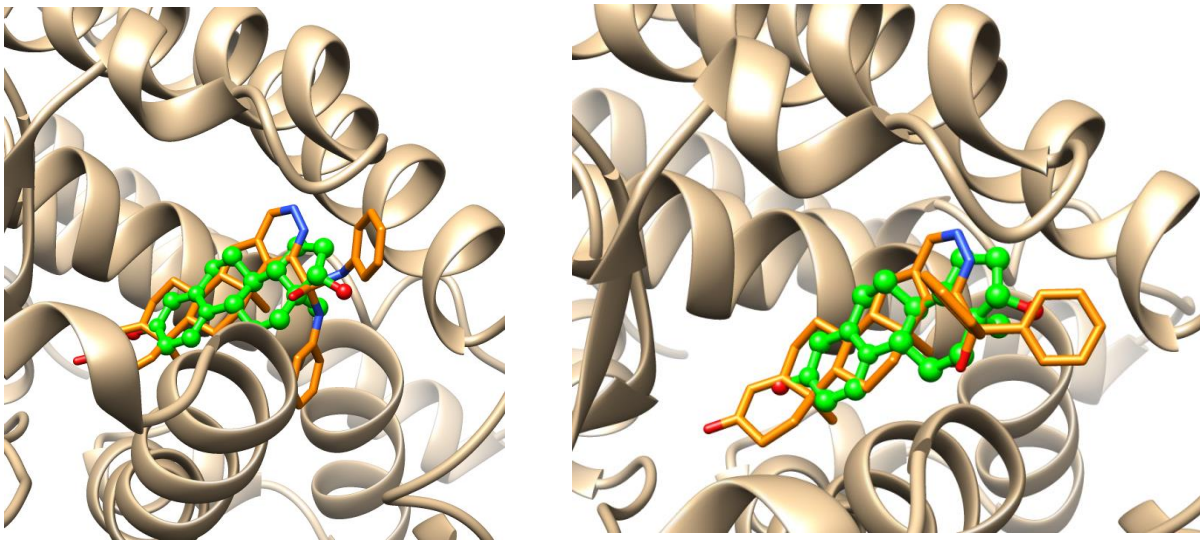


Figure S1. Left panel: a fragment of the binding site of ERα in complexes with estradiol (green) and compound **34** (orange); right panel: a fragment of the binding site of ERα in complexes with estradiol (green) and compound **33** (orange).

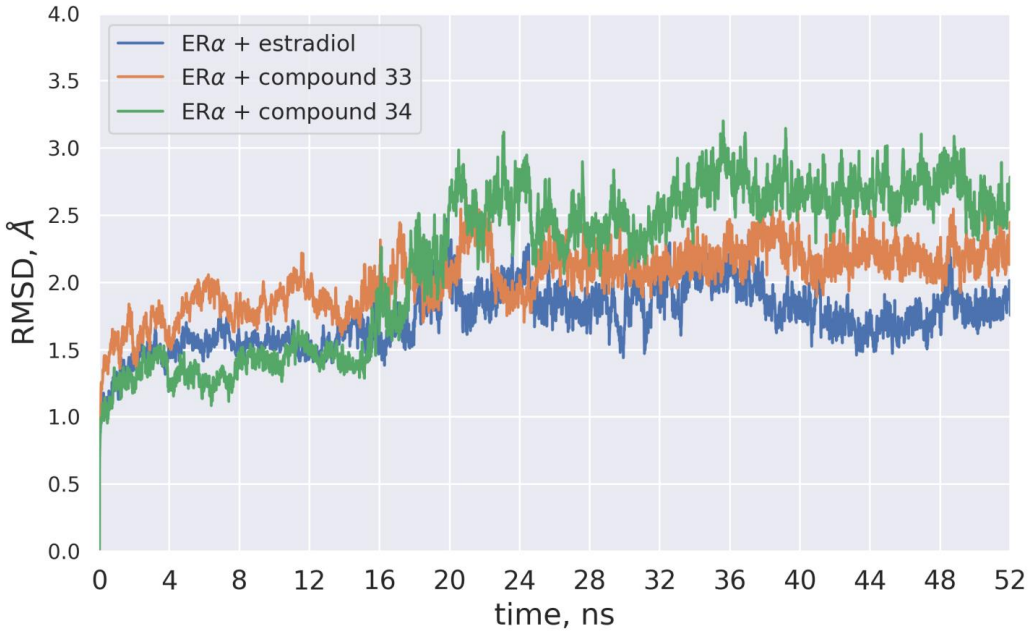


Figure S2. Root-mean-square deviations of the backbone Cα atoms of the estrogen receptor in complexes with different ligands.

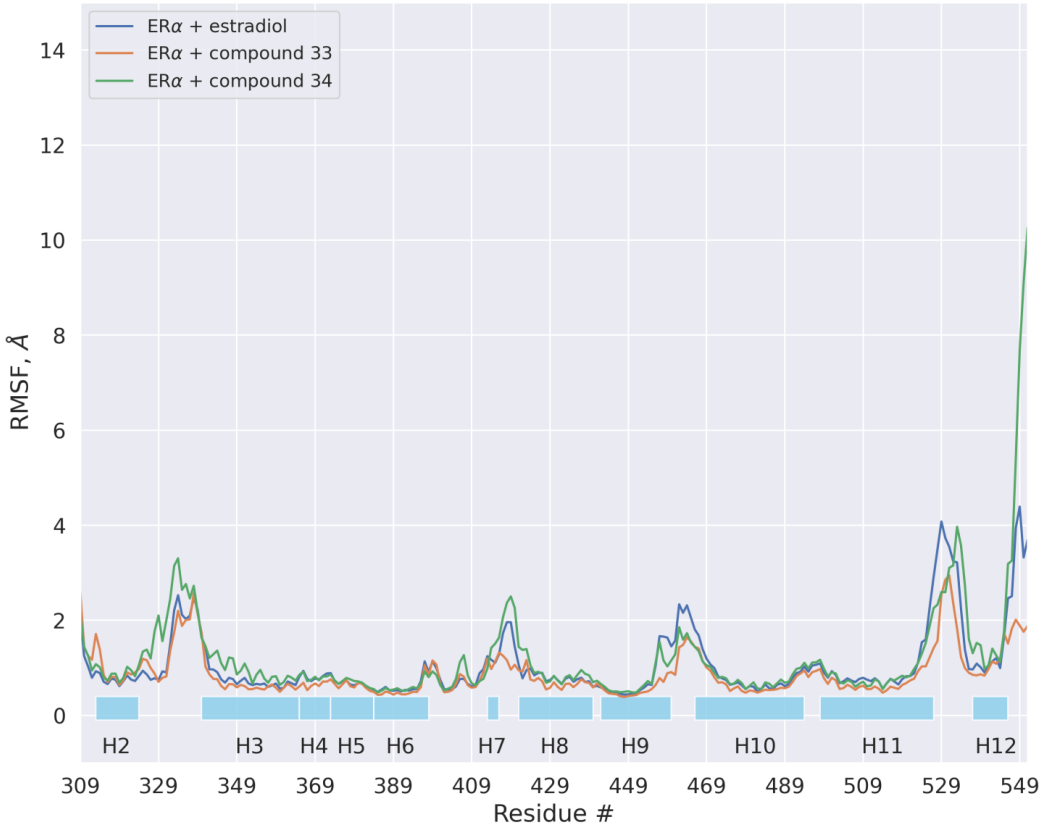


Figure S3. Root-mean-square fluctuations of the backbone Cα atoms of the estrogen receptor in complexes with different ligands.

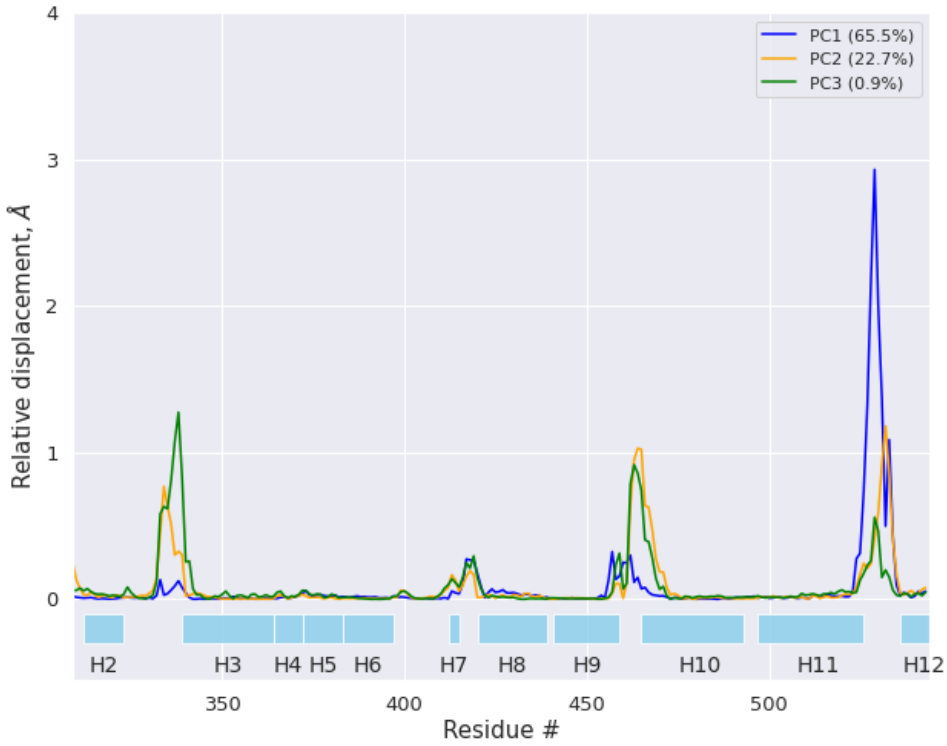


Figure S4. Projection of the displacements of the protein backbone Cα atoms onto the first three principal components during molecular dynamics simulations of ERα in complex with estradiol.

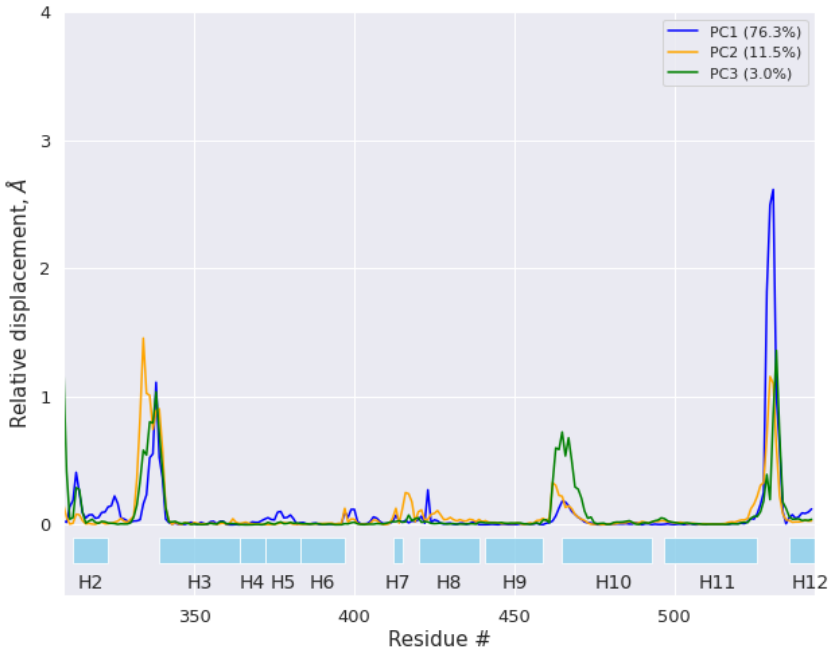


Figure S5. Projection of the displacements of the protein backbone Cα atoms onto the first three principal components during molecular dynamics simulations of ERα in complex with compound **33**.

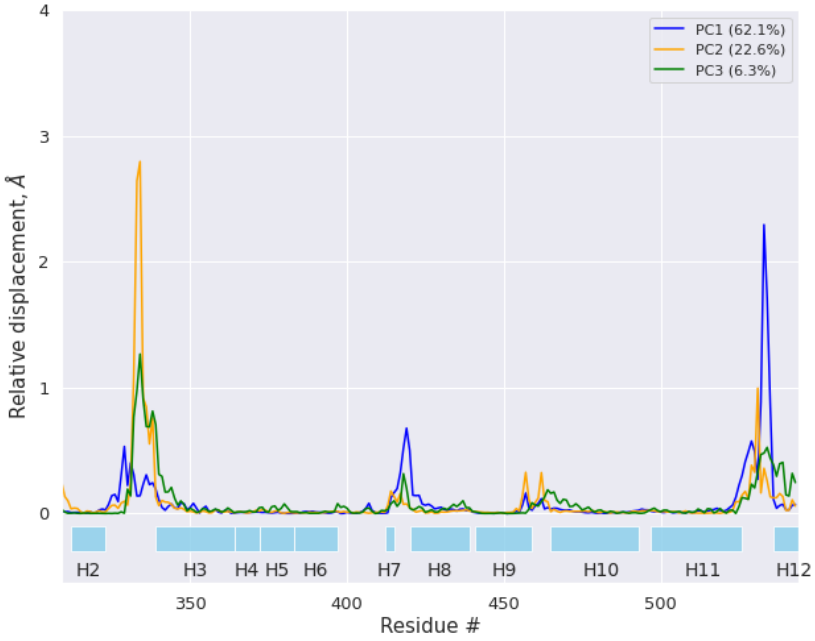


Figure S6. Projection of the displacements of the protein backbone Cα atoms onto the first three principal components during molecular dynamics simulations of ERα in complex with compound **34**.

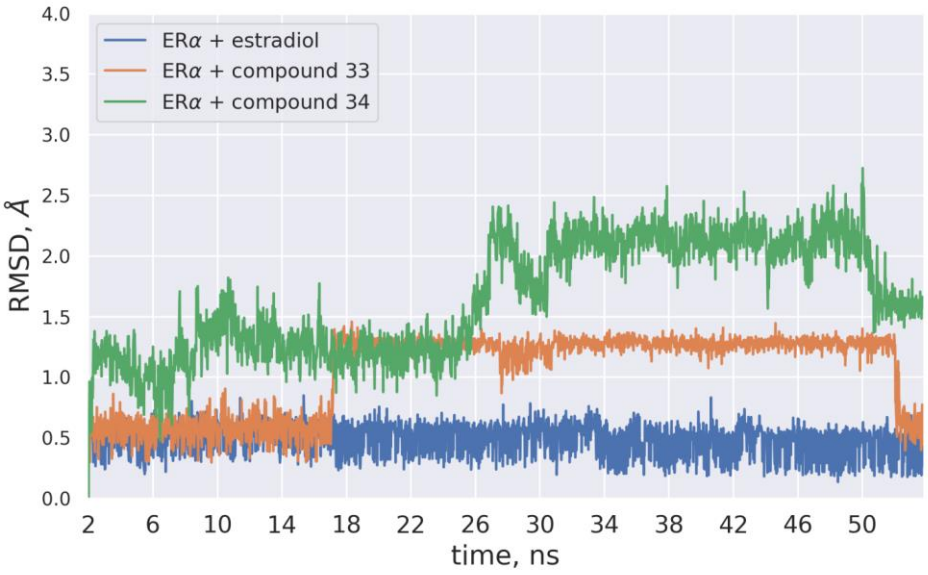


Figure S7. Root-mean-square deviations of the ligand atoms during 50 ns of free molecular dynamics simulations

A **B**

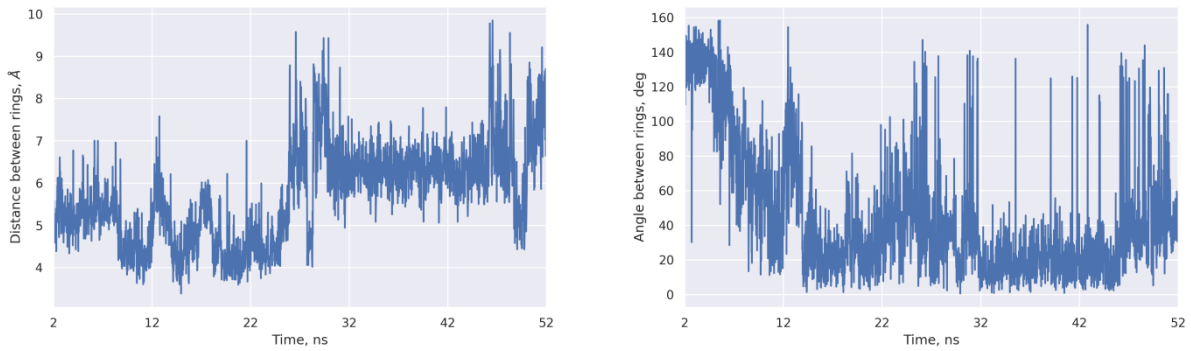


Figure S8. Plots of the distances (A) and angles (B) between the planes of the aromatic system of ligand **34** and His524 during 50 ns of free molecular dynamics simulations.

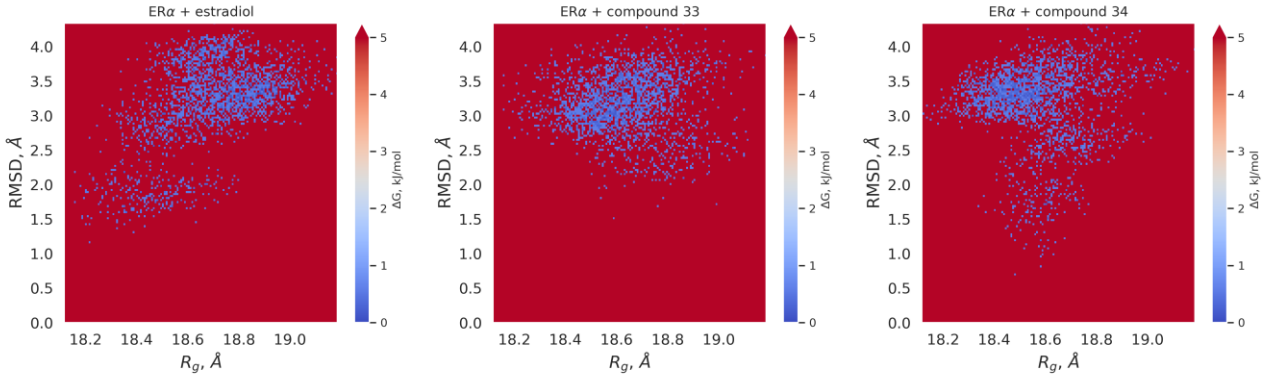


Figure S9. Free energy surfaces built for the complexes of the estrogen receptor alfa with estradiol and compounds **33**, **34**.

Table S1. Analysis of intermolecular interactions (van der Waals interactions) of compounds **33**, **34**, and estradiol with amino acid residues of ERβ.

Compound	Amino acid residues involved in interactions during >95% of the molecular dynamics trajectory	E_{bind}, kcal/mol (AutoDock Vina scoring function)
17β-estradiol	MET295, LEU298, THR299, LEU301, ALA302, GLU305, MET336, LEU339, MET340, GLY342, LEU343, ARG346, PHE356, ILE373, ILE376, LEU380, LYS471, GLY472, MET473, HIS475, LEU476, MET479, LEU500	-10.1
33	ILE282, LEU298, THR299, LEU301, ALA302, GLU305, TRP335, MET336, LEU339, MET340, GLY342, LEU343, ARG346, PHE356, ALA357, LEU360, GLU371, GLY372, ILE373, LEU380, GLY472, HIS475, LEU476, MET479, LEU491, LEU500	-13.8
34	ILE282, MET294, MET295, LEU298, LEU301, ALA302, GLU305, MET336, LEU339, MET340, GLY342, LEU343, ARG346, PHE356, LEU362, VAL370, ILE373, ILE376, PHE377, LEU380, GLY472, HIS475, LEU476, LEU500	-13.8

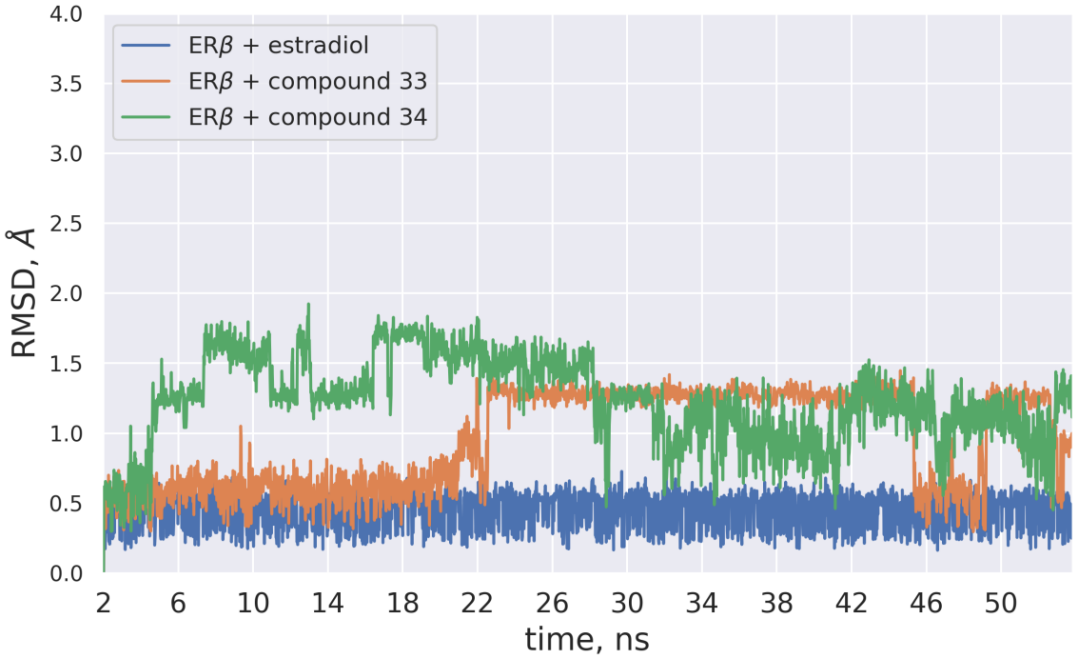


Figure S10. Root-mean-square deviations of the ligand atoms during 50 ns of free molecular dynamics simulations.

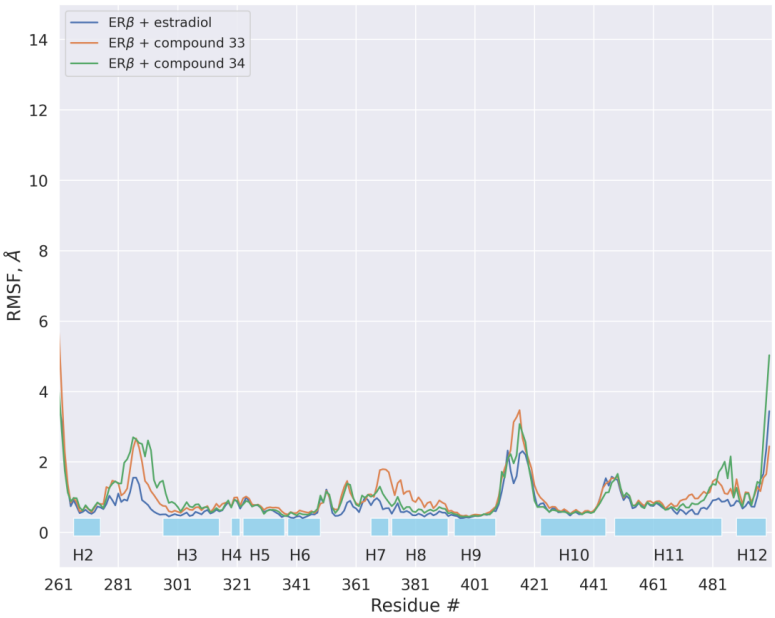


Figure S11. Root-mean-square fluctuations of the backbone Cα atoms of the estrogen receptor beta in complexes with different ligands.

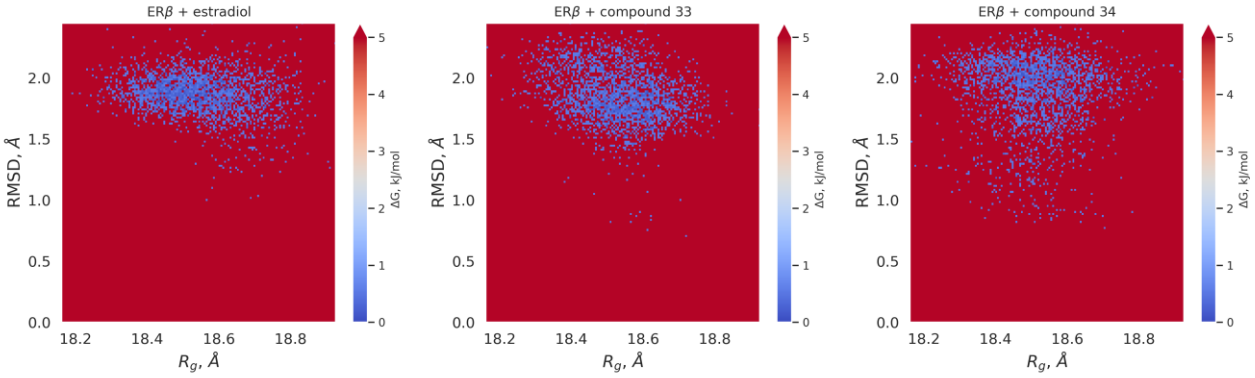
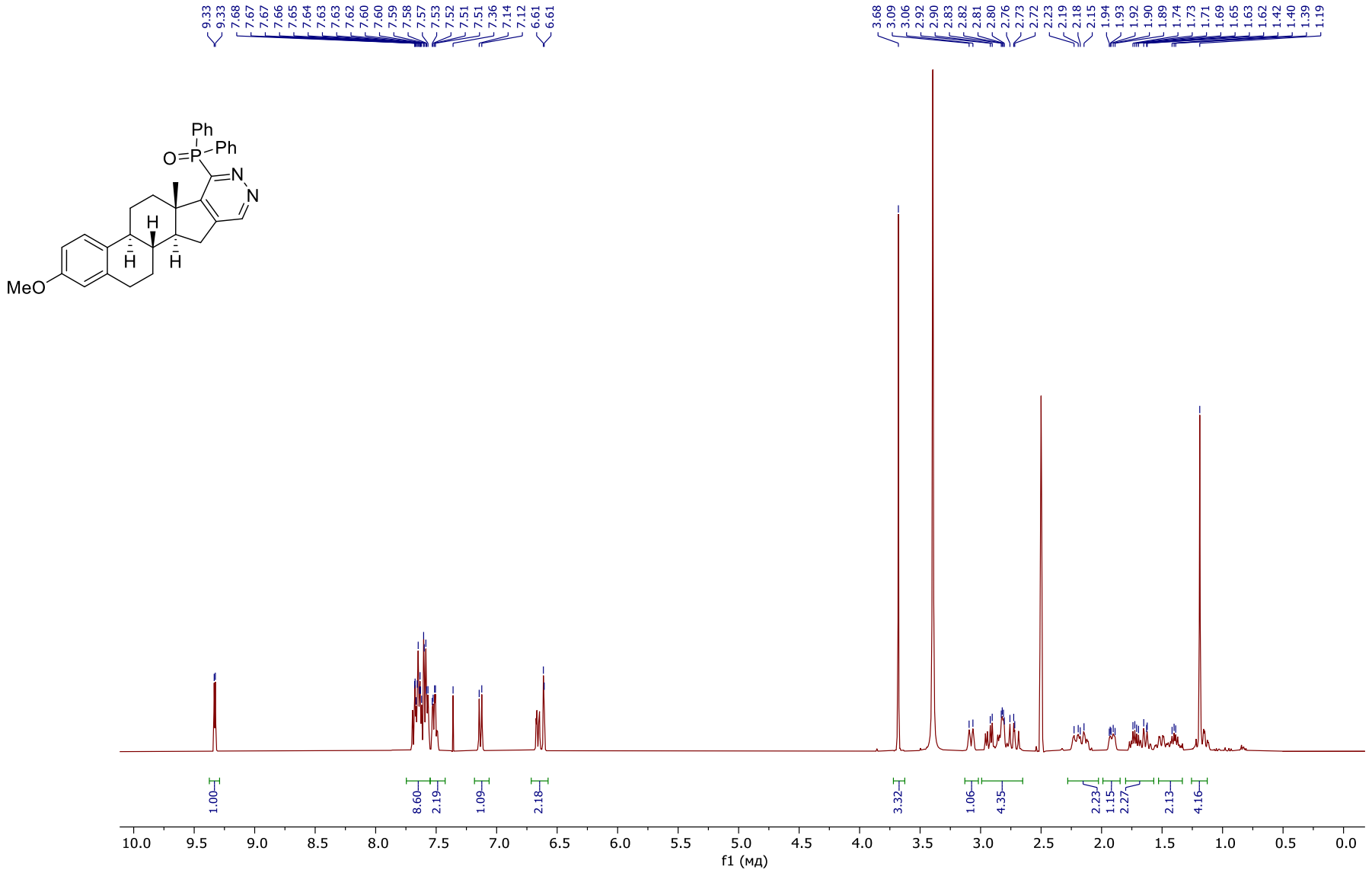
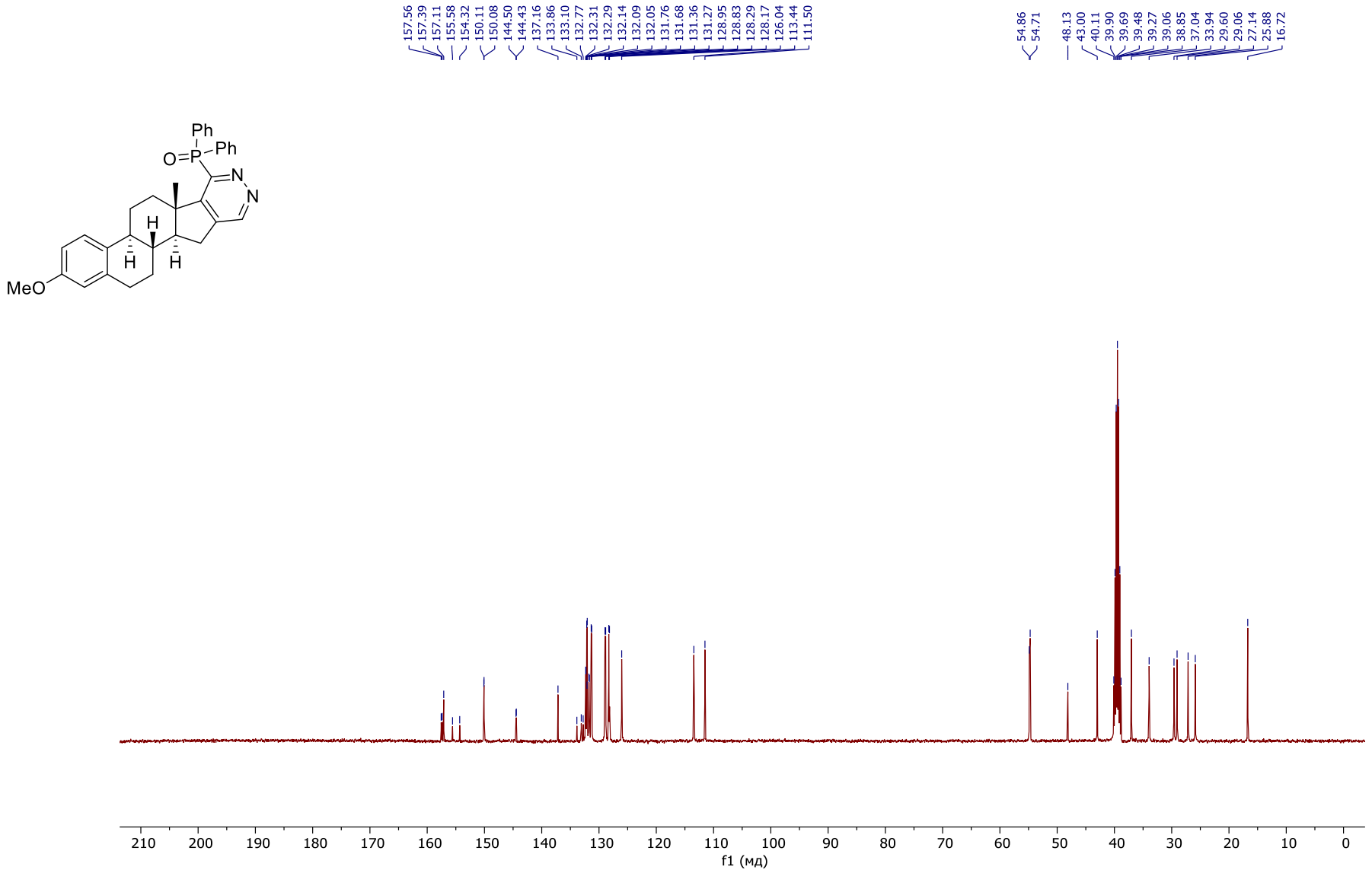


Figure S12. Free energy surfaces built for the complexes of the estrogen receptor beta with 17β-estradiol and compounds **33, 34**.

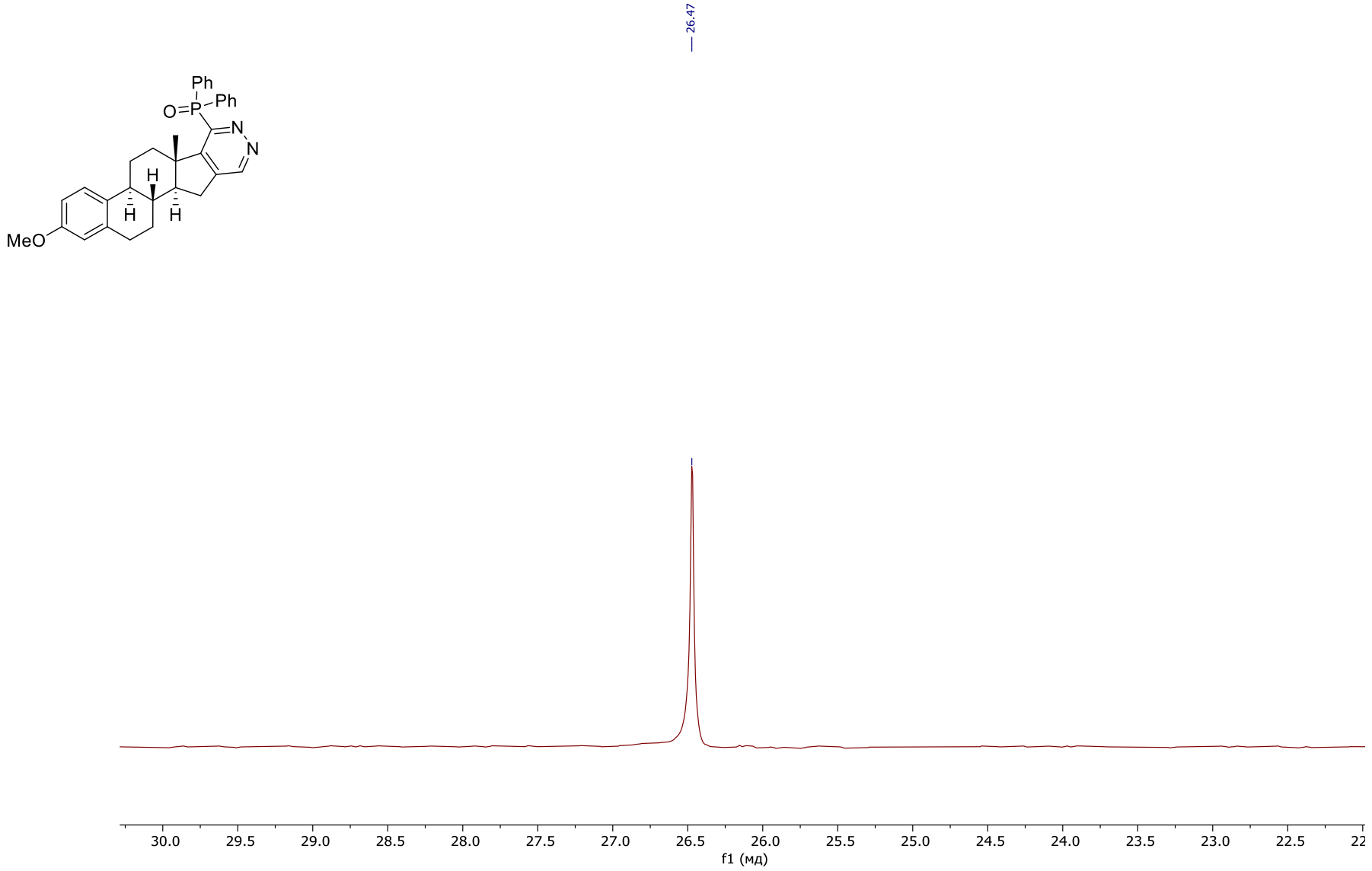
^{1}H NMR (400 MHz, DMSO-d_6) of (3-methoxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (6).



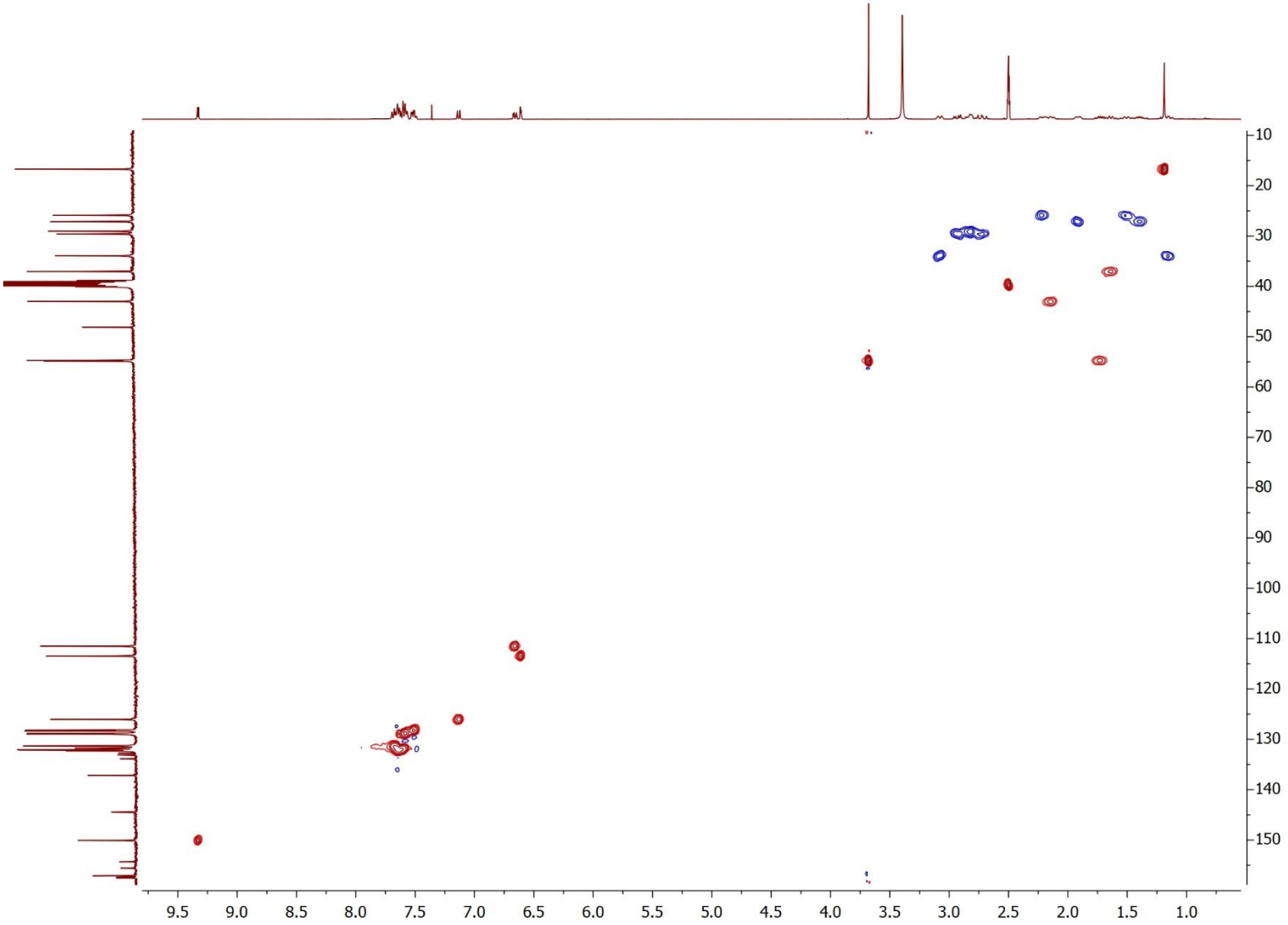
^{13}C NMR (101 MHz, DMSO-d_6) of (3-methoxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (6).



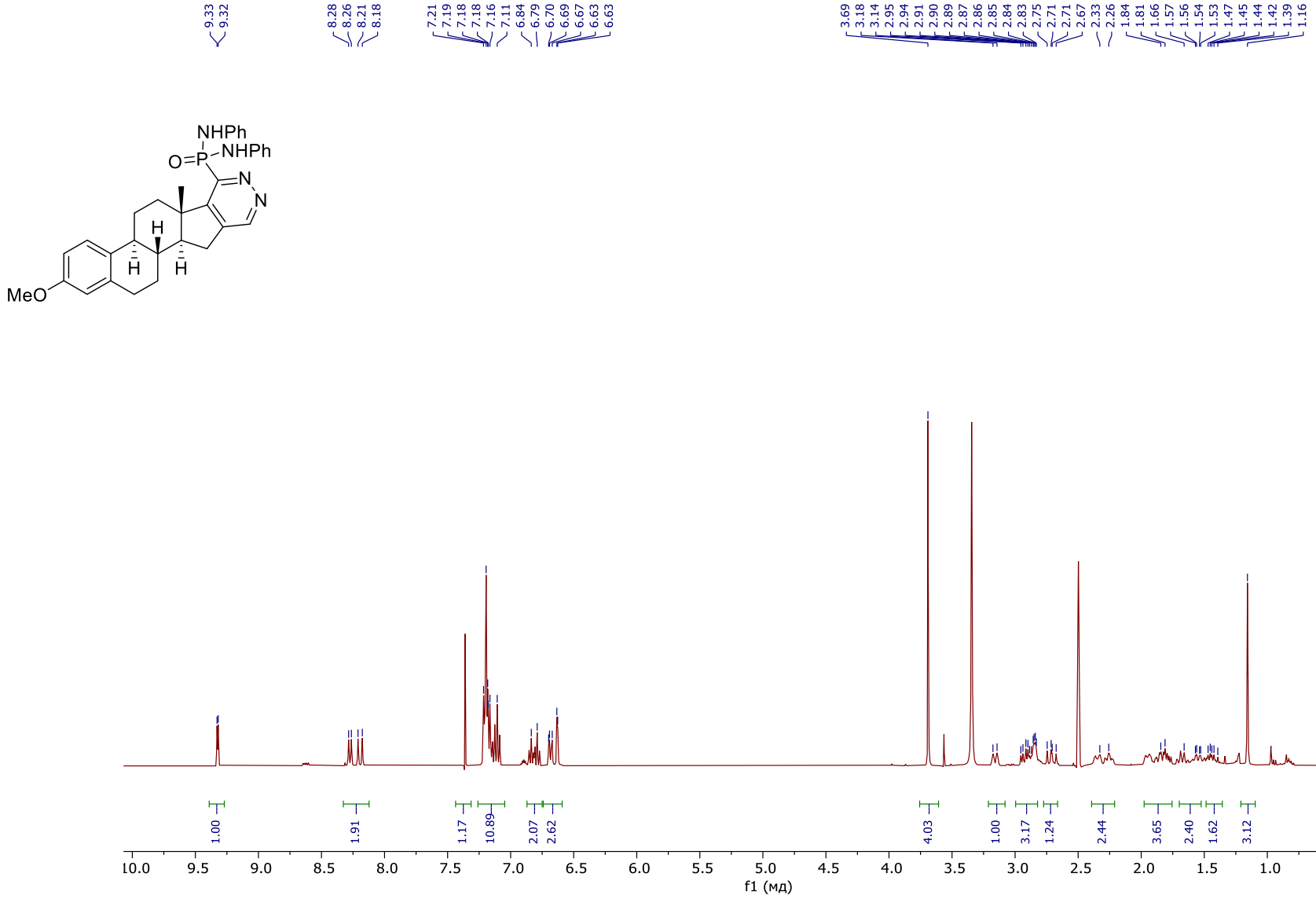
^{31}P NMR (162 MHz, DMSO-d_6) of (3-methoxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (6).



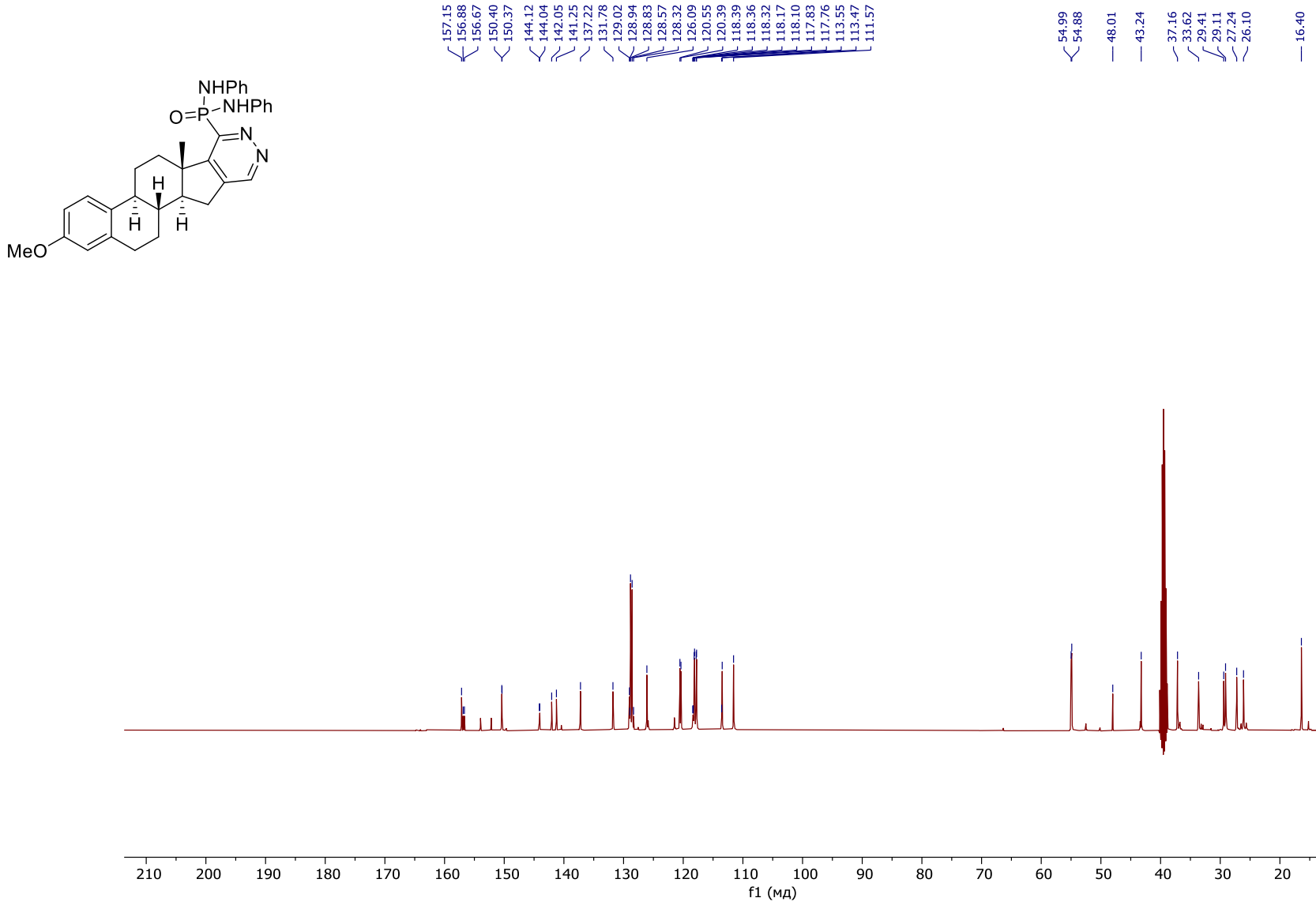
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of (3-methoxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (6).



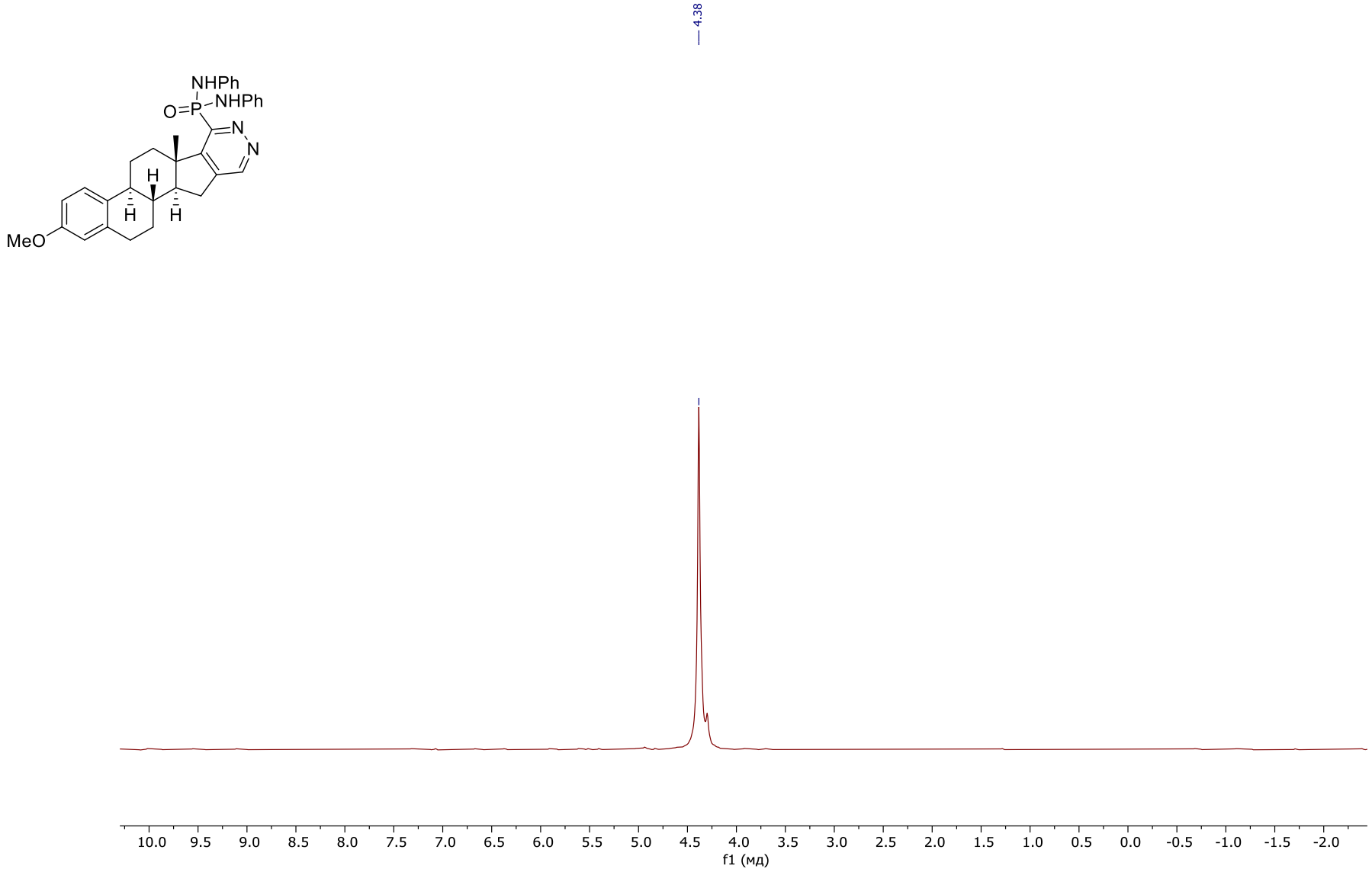
^{1}H NMR (400 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (7).



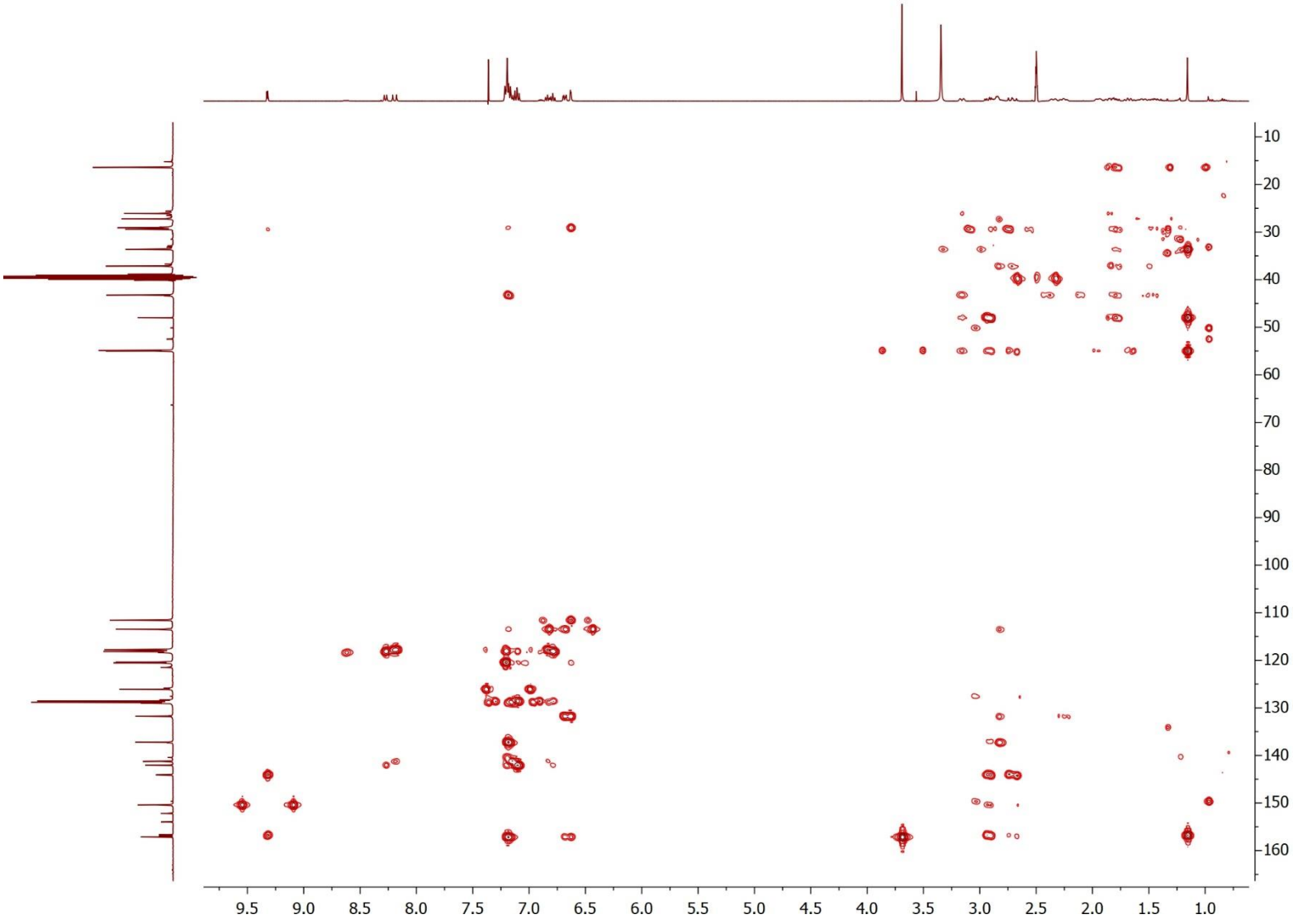
^{13}C NMR (101 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (7).



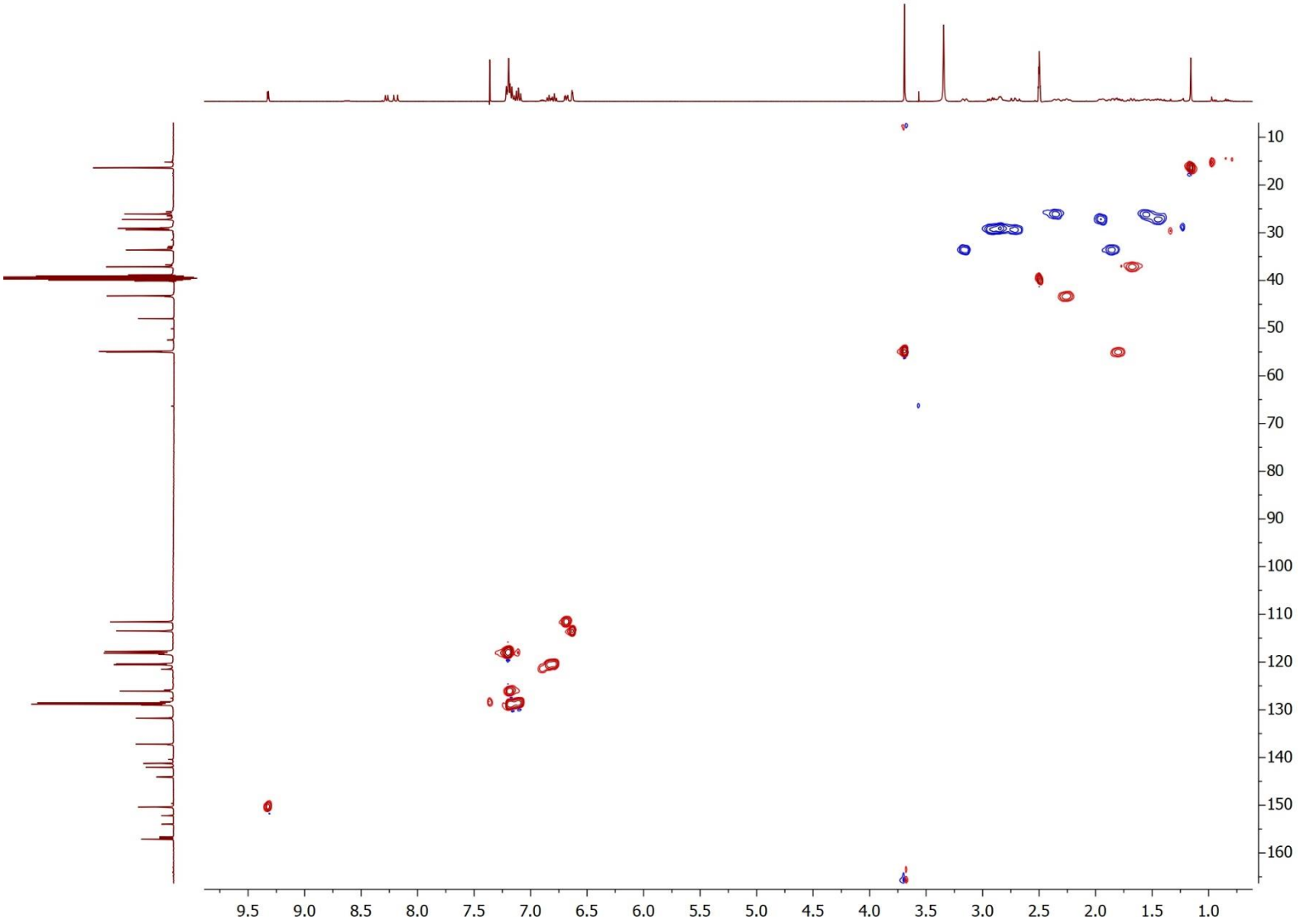
^{31}P NMR (162 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (7).



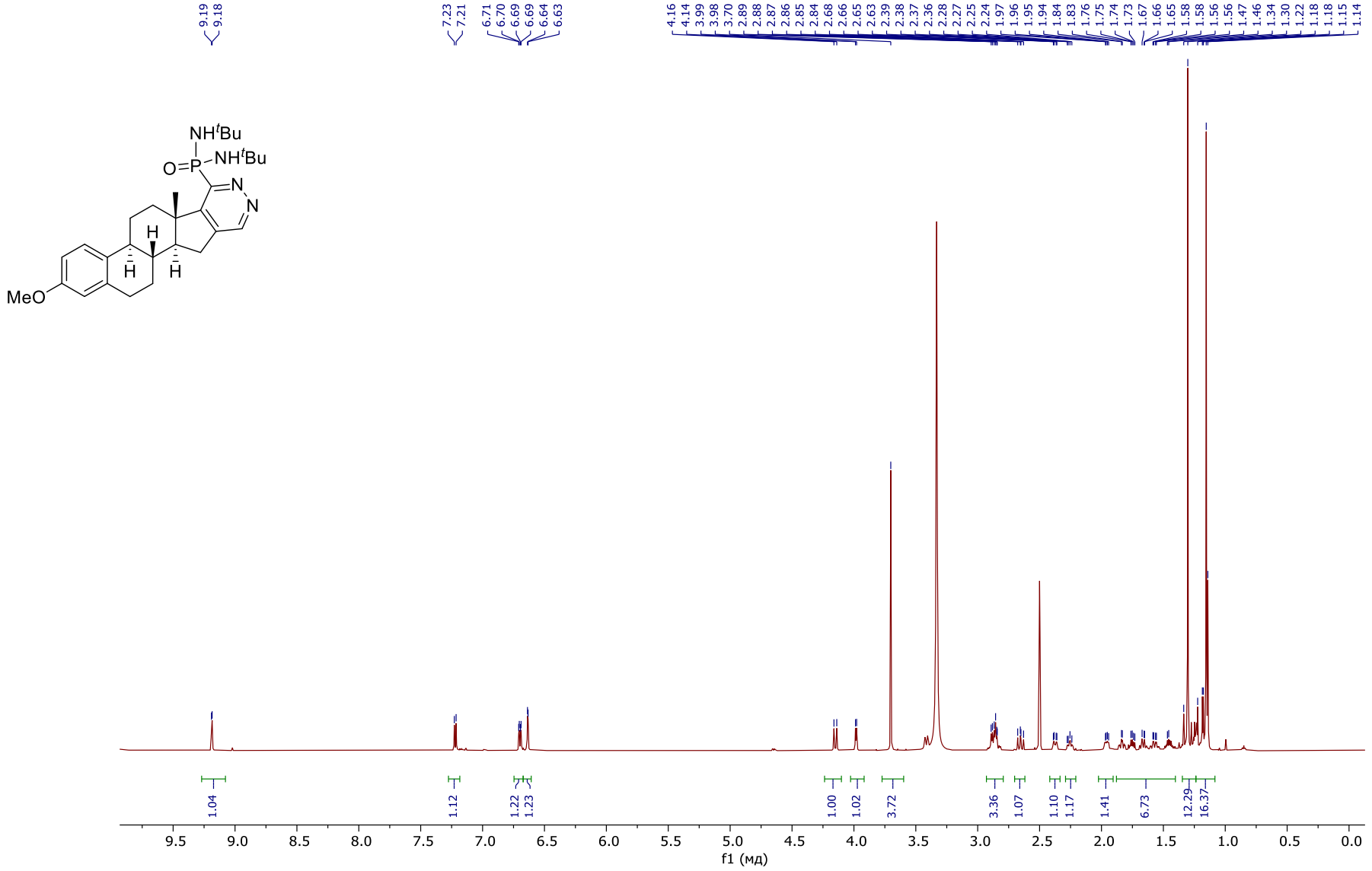
^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (7).



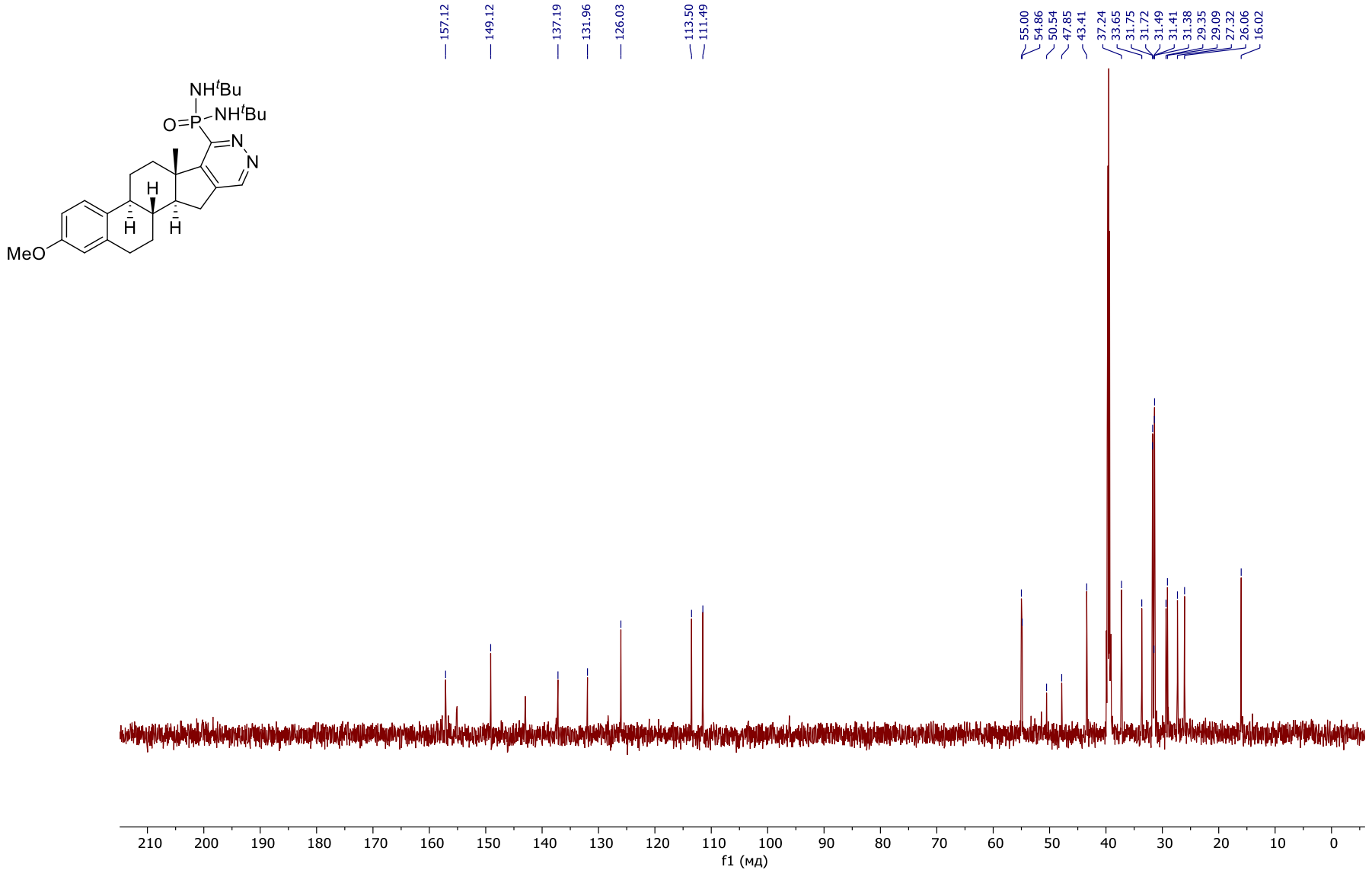
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (7).



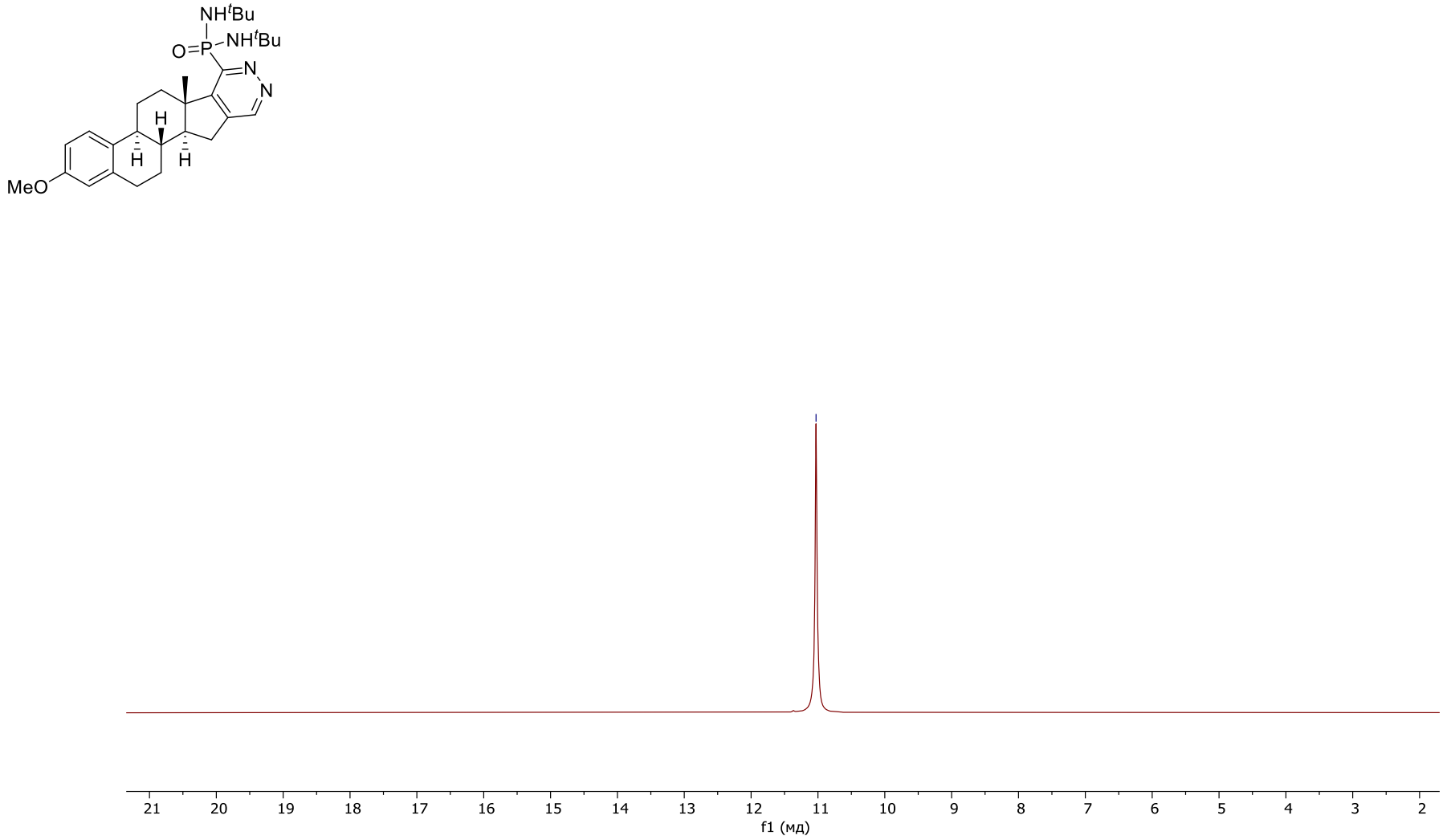
^{1}H NMR (600 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (8).



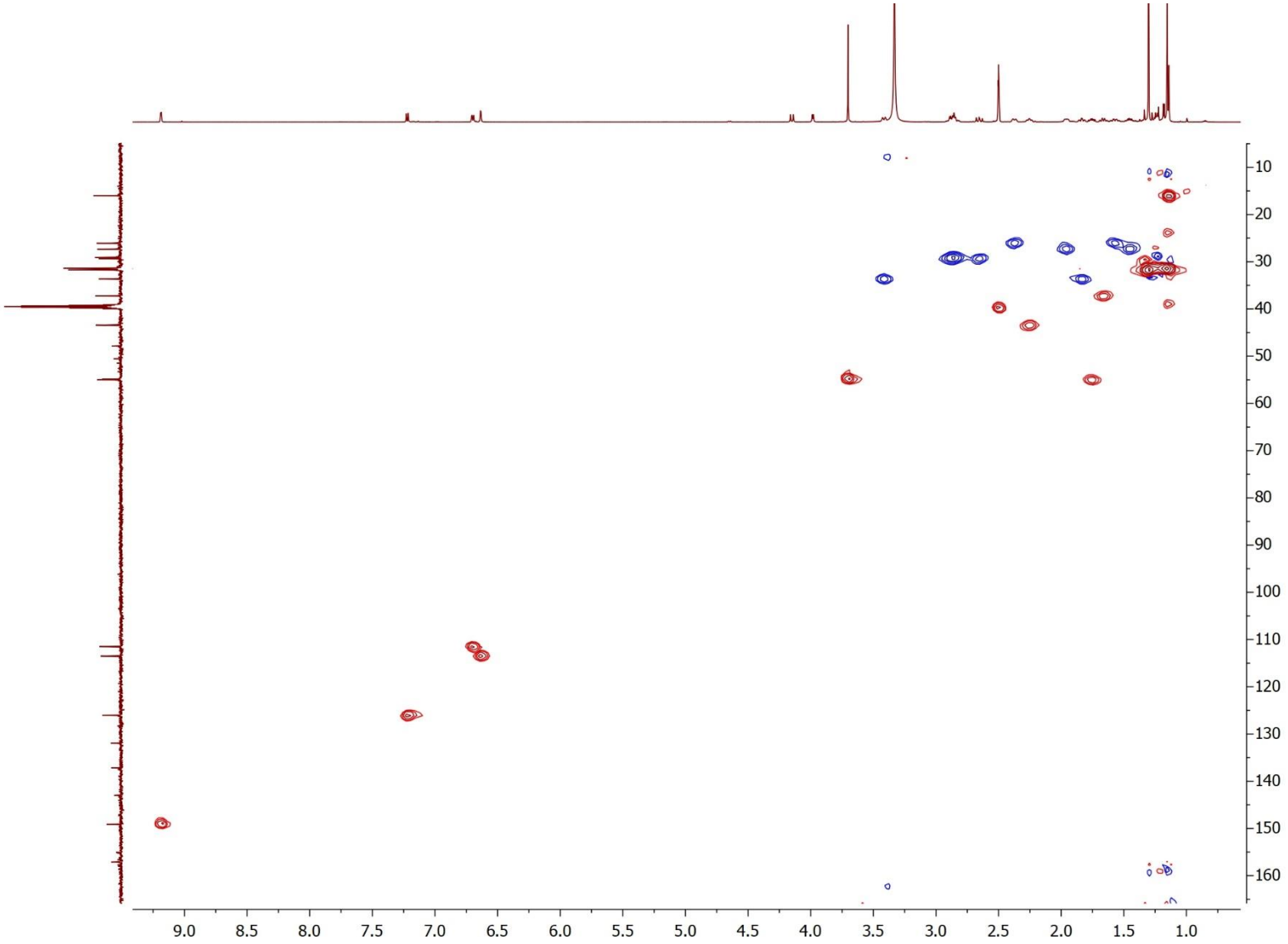
^{13}C NMR (150 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (8).



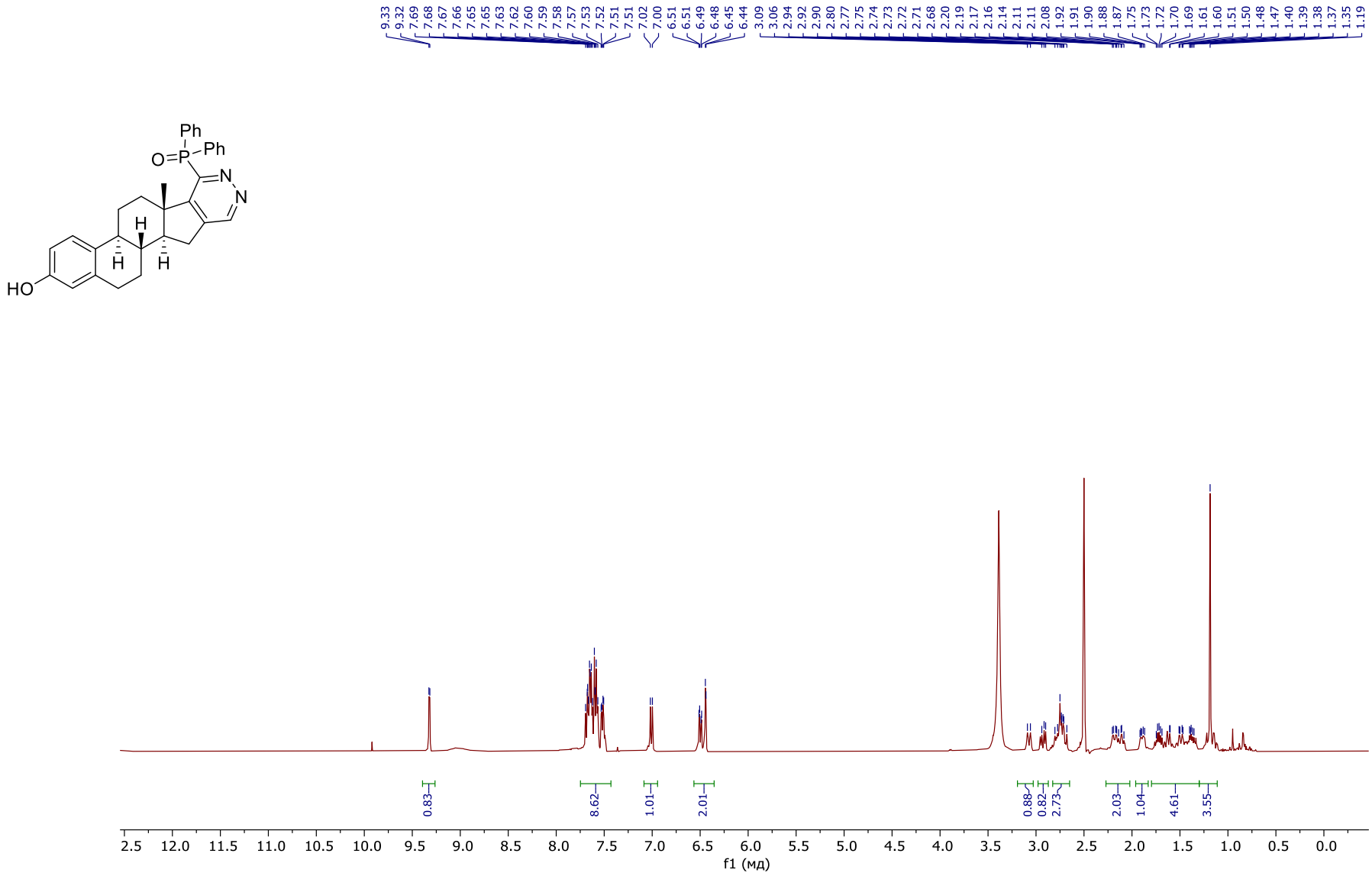
^{31}P NMR (243 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (8).



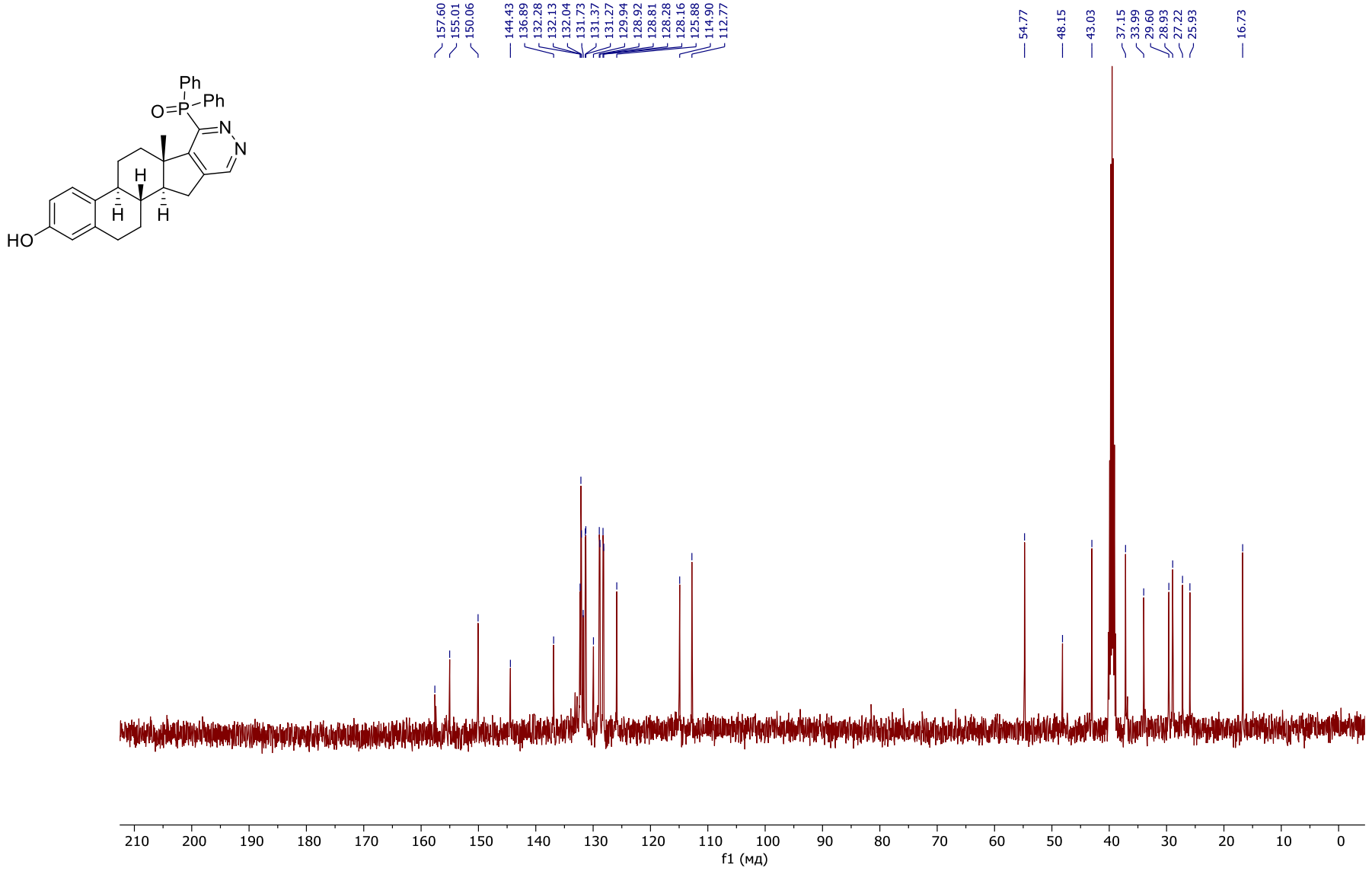
^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3-methoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (8).



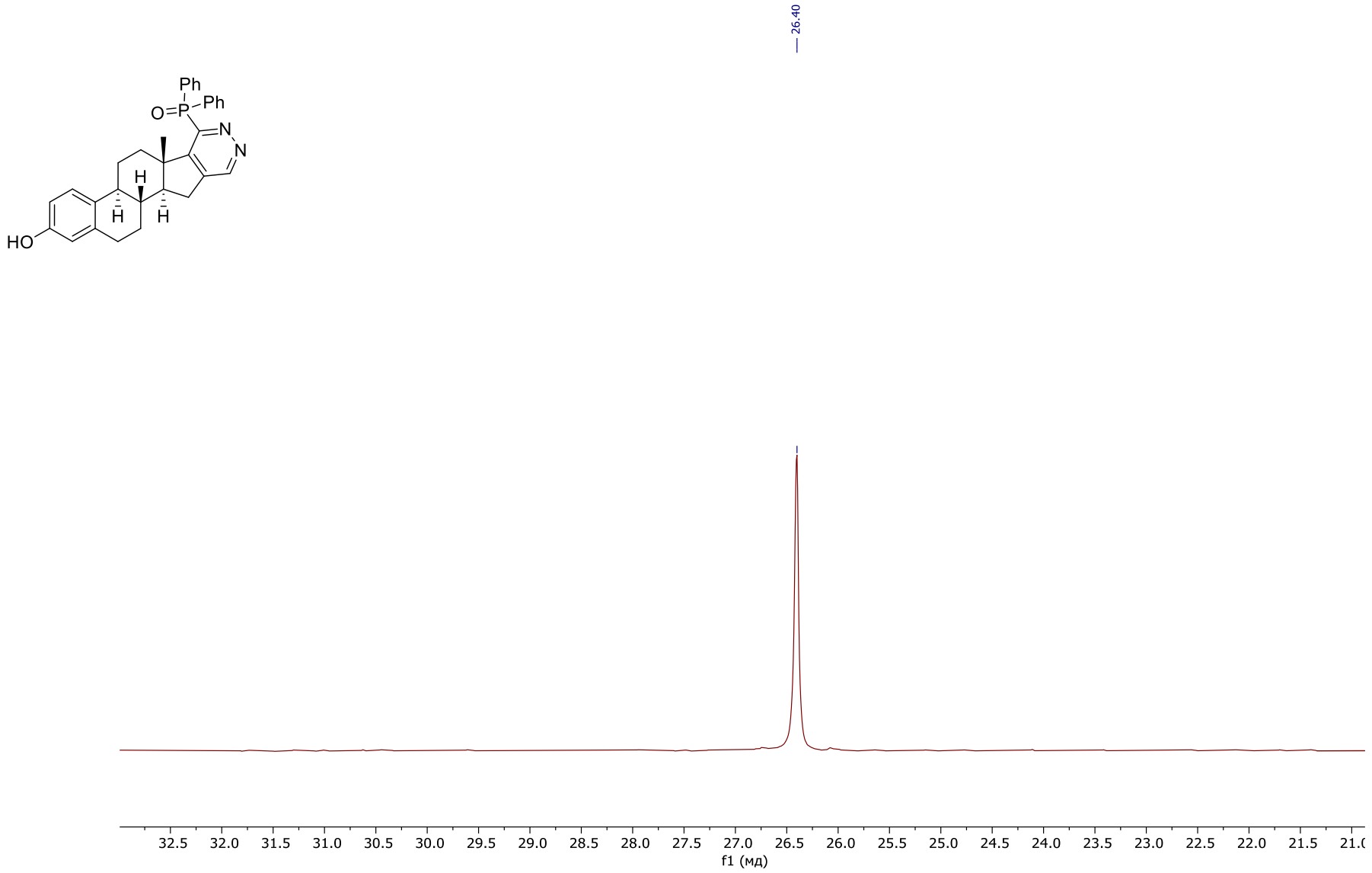
^{1}H NMR (400 MHz, DMSO-d_6) of (3-hydroxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (9).



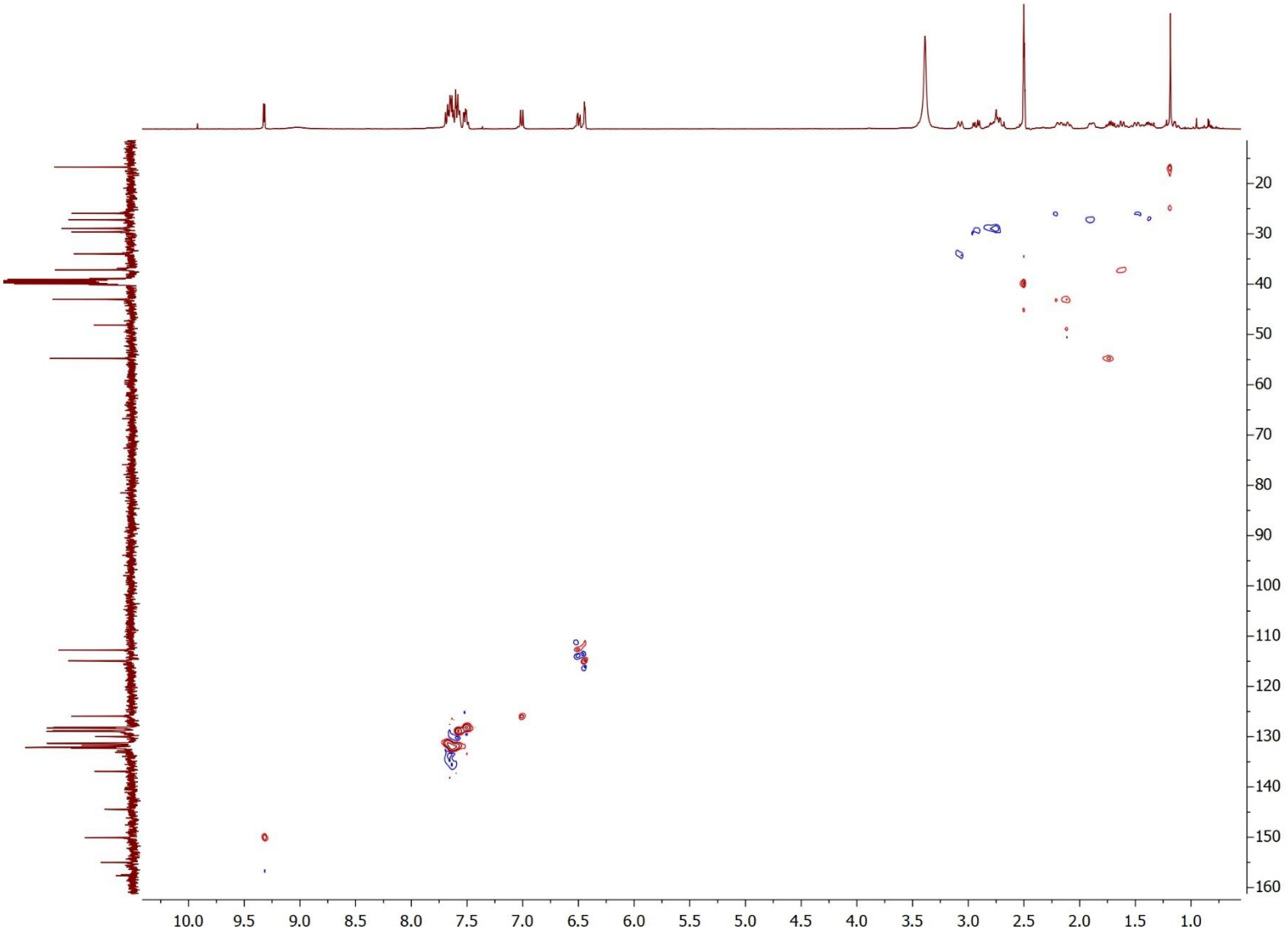
^{13}C NMR (101 MHz, DMSO-d_6) of (3-hydroxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (9).



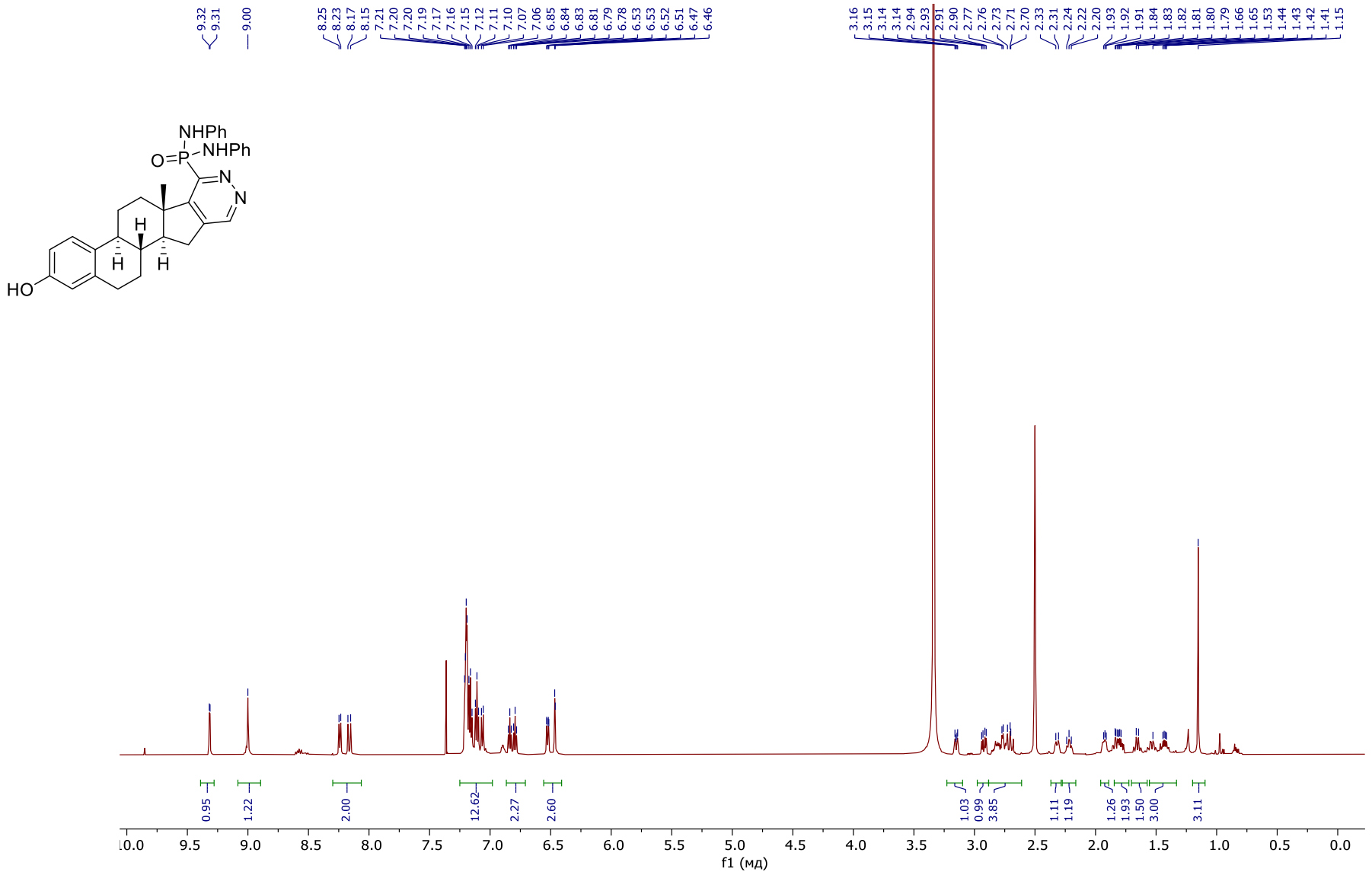
^{31}P NMR (162 MHz, DMSO-d_6) of (3-hydroxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (9).



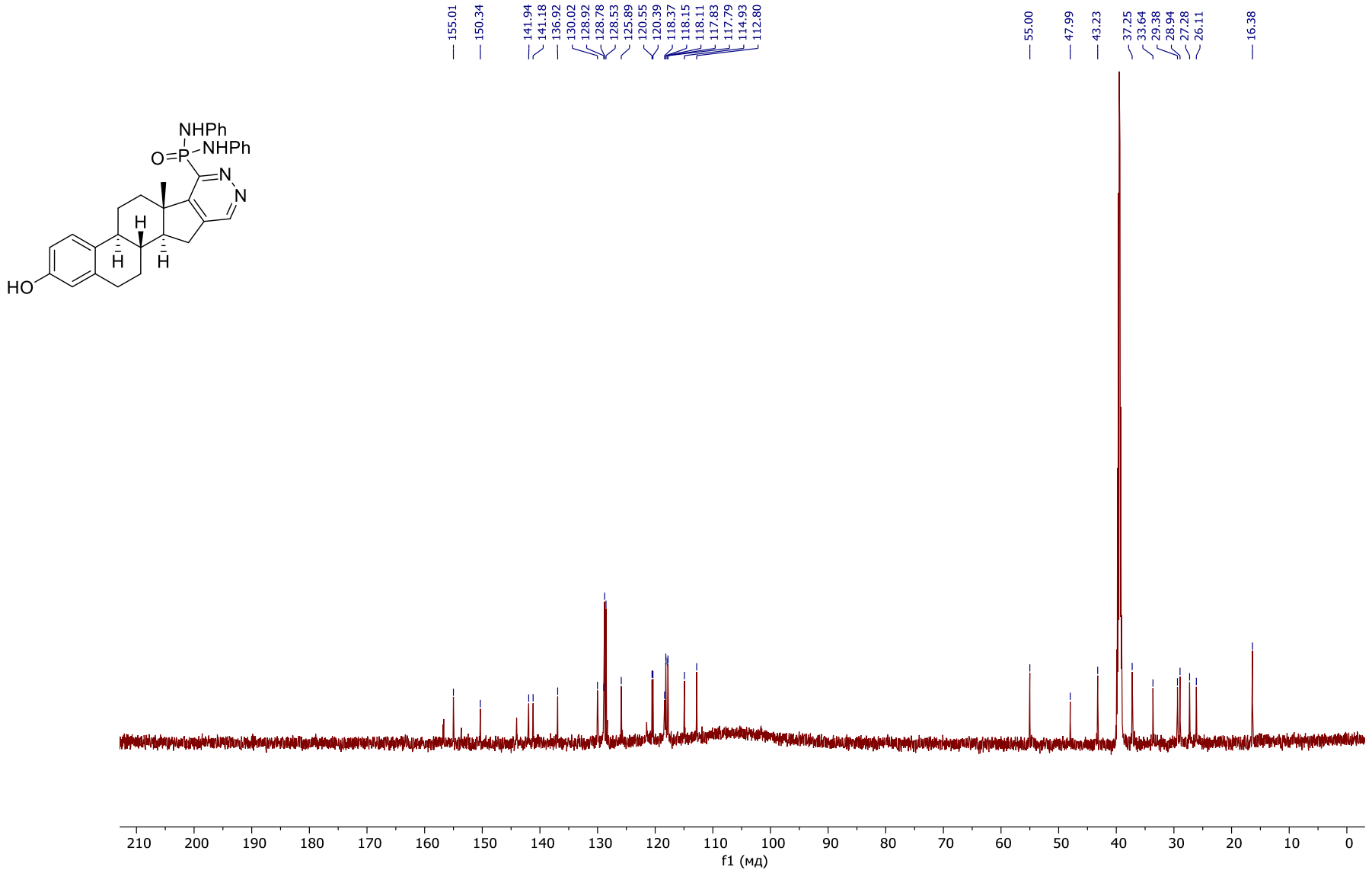
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of (3-hydroxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (9).



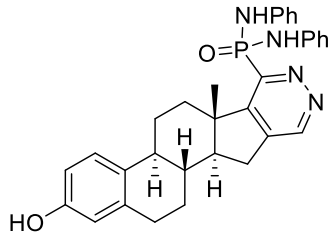
^{1}H NMR (600 MHz, DMSO-*d*$_6$) of 3-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-Δ$^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (10).



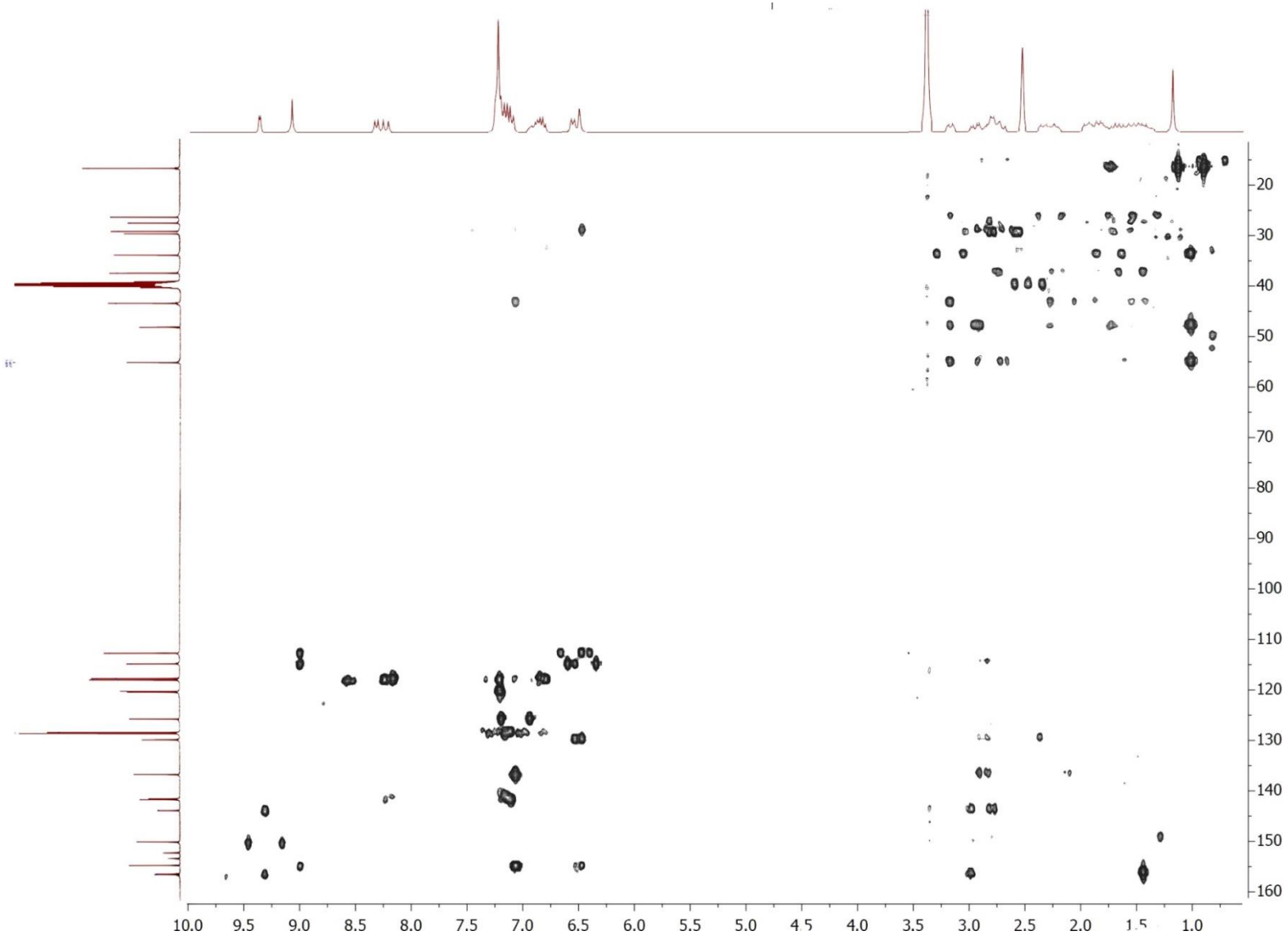
^{13}C NMR (150 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (10).



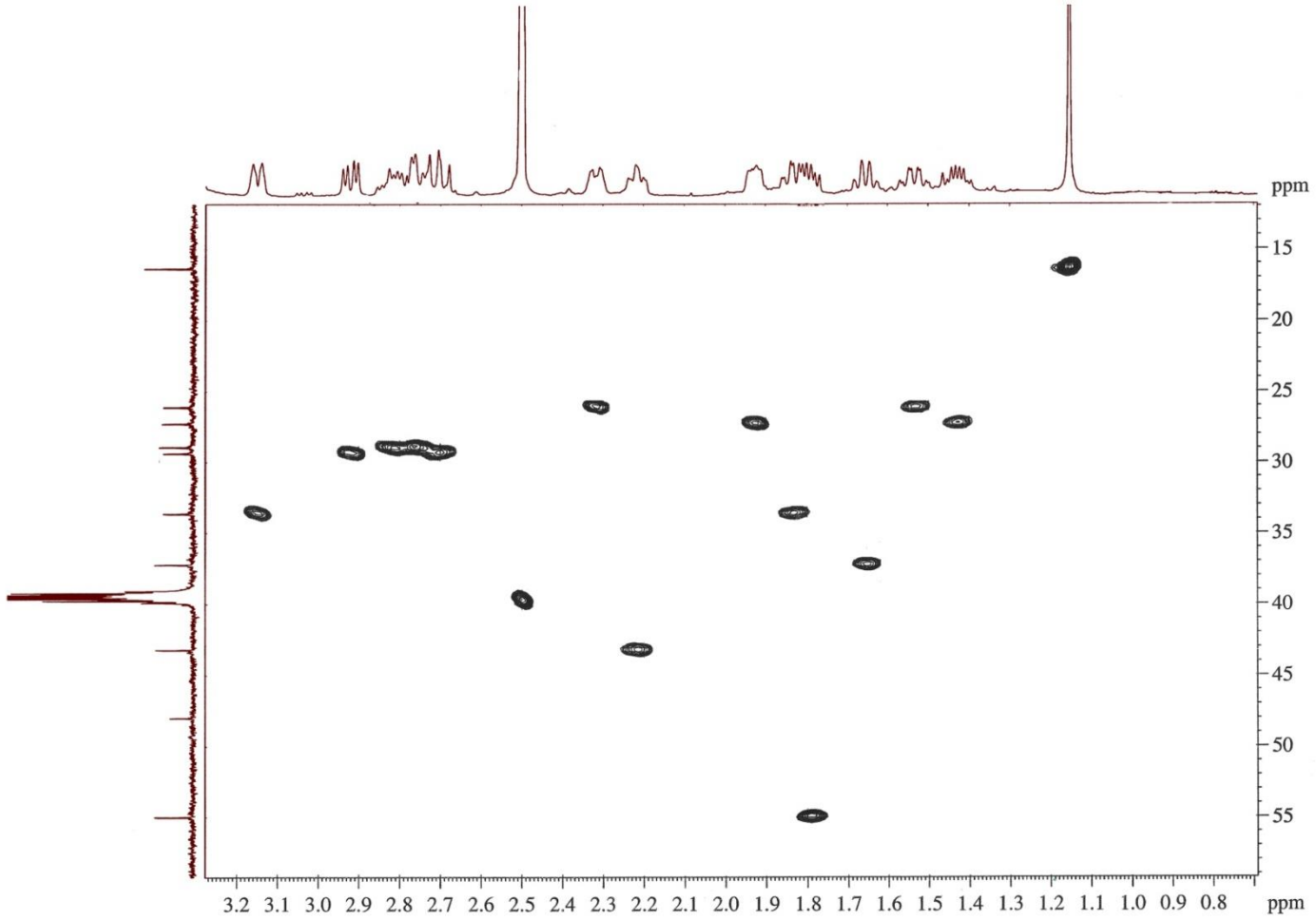
^{31}P NMR (243 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (10).

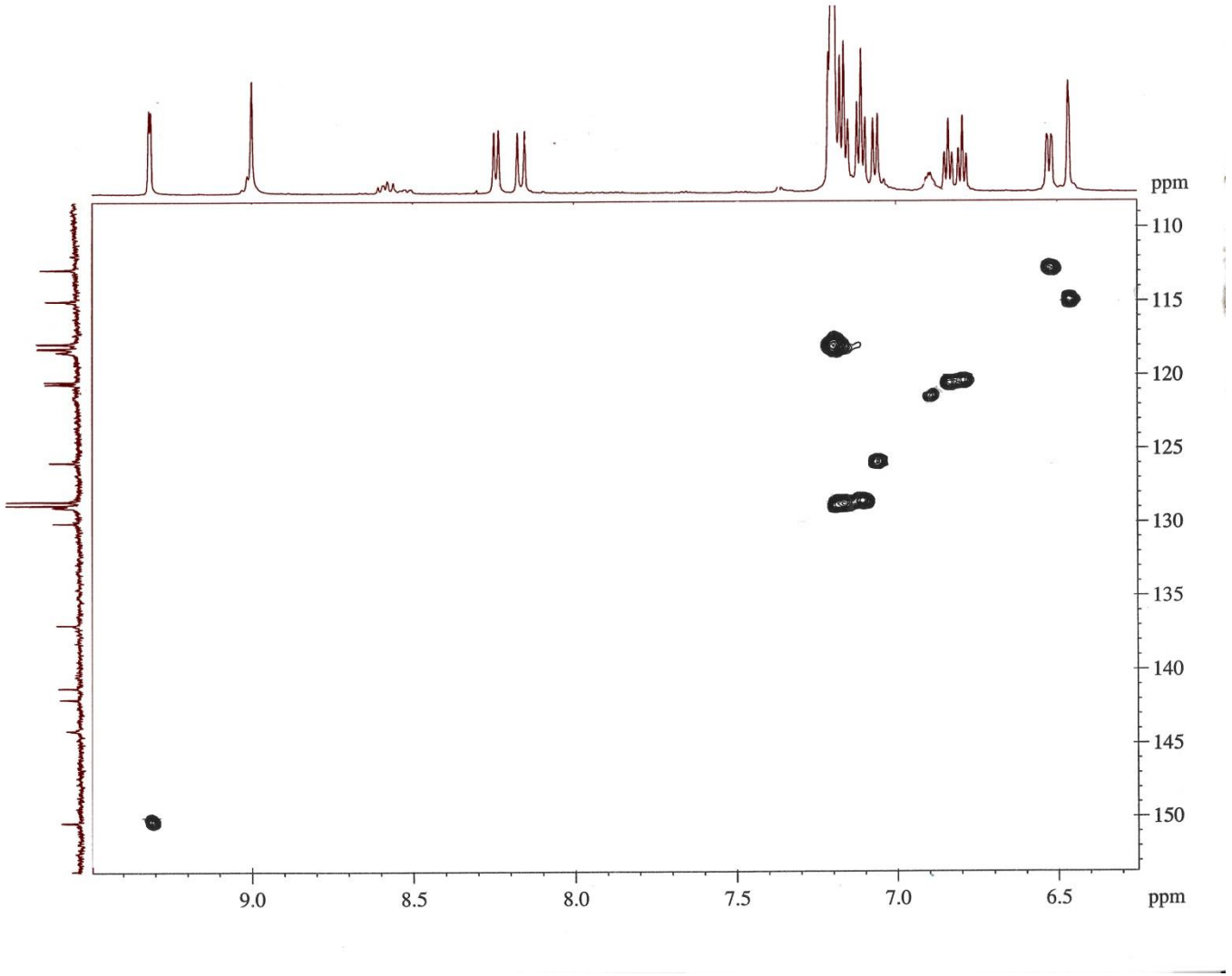


^{1}H-^{13}C HMBC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (10).

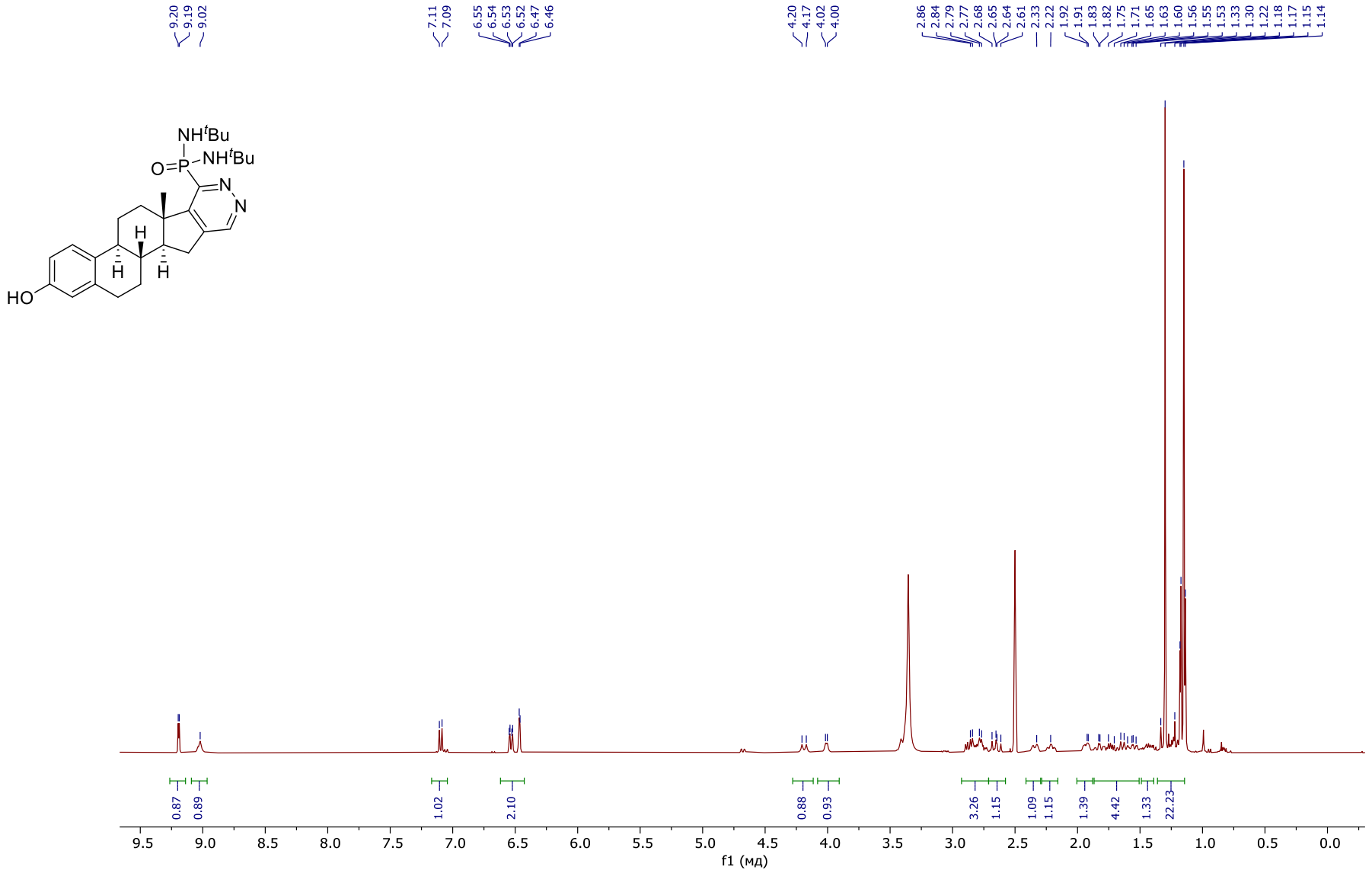


^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (10).

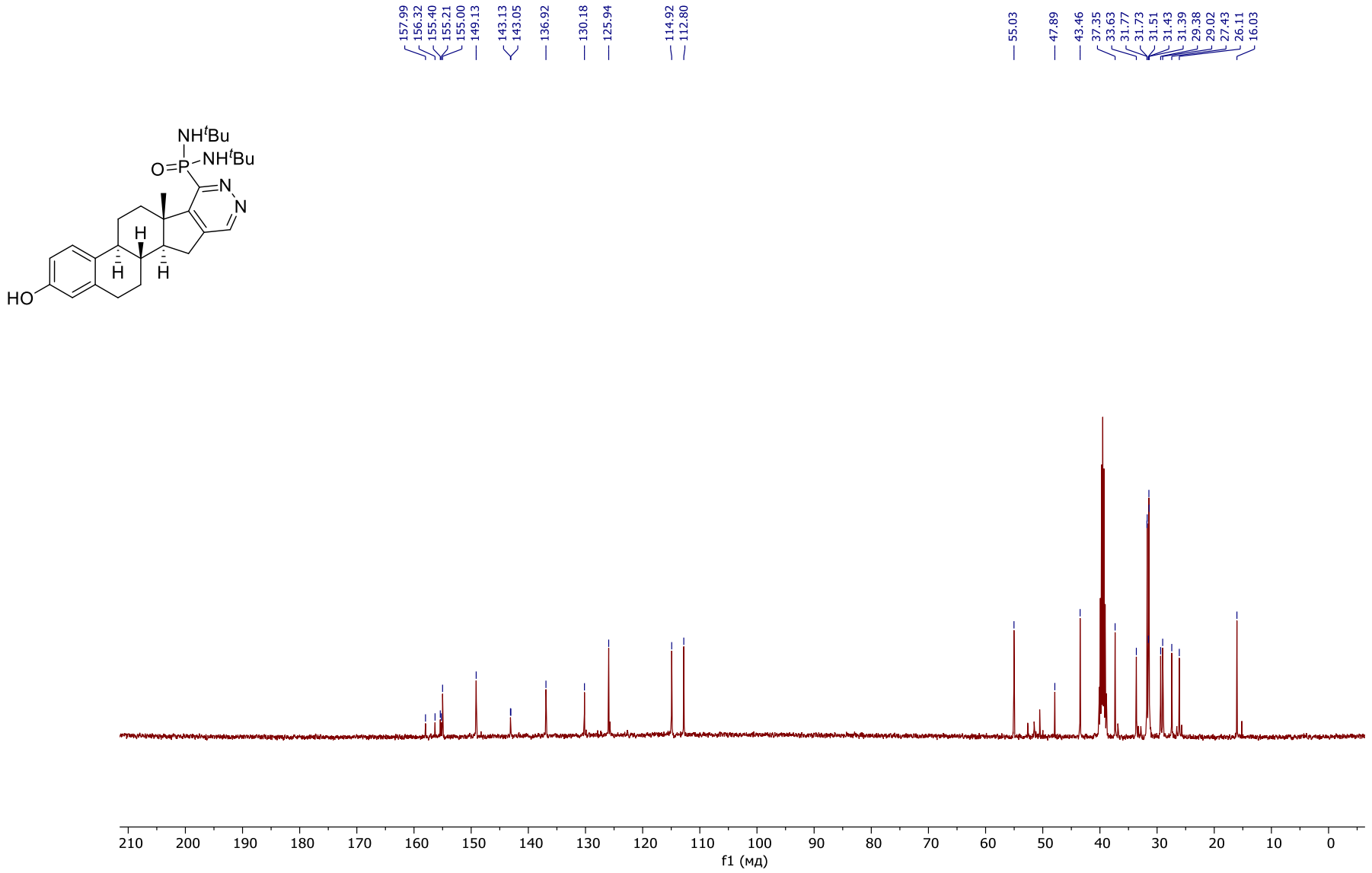



ppm
110
115
120
125
130
135
140
145
150
9.0
8.5
8.0
7.5
7.0
6.5
ppm

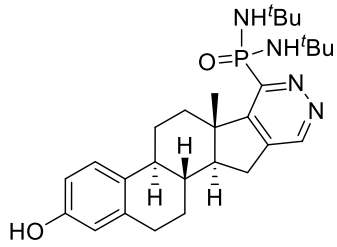
^{1}H NMR (400 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (11).



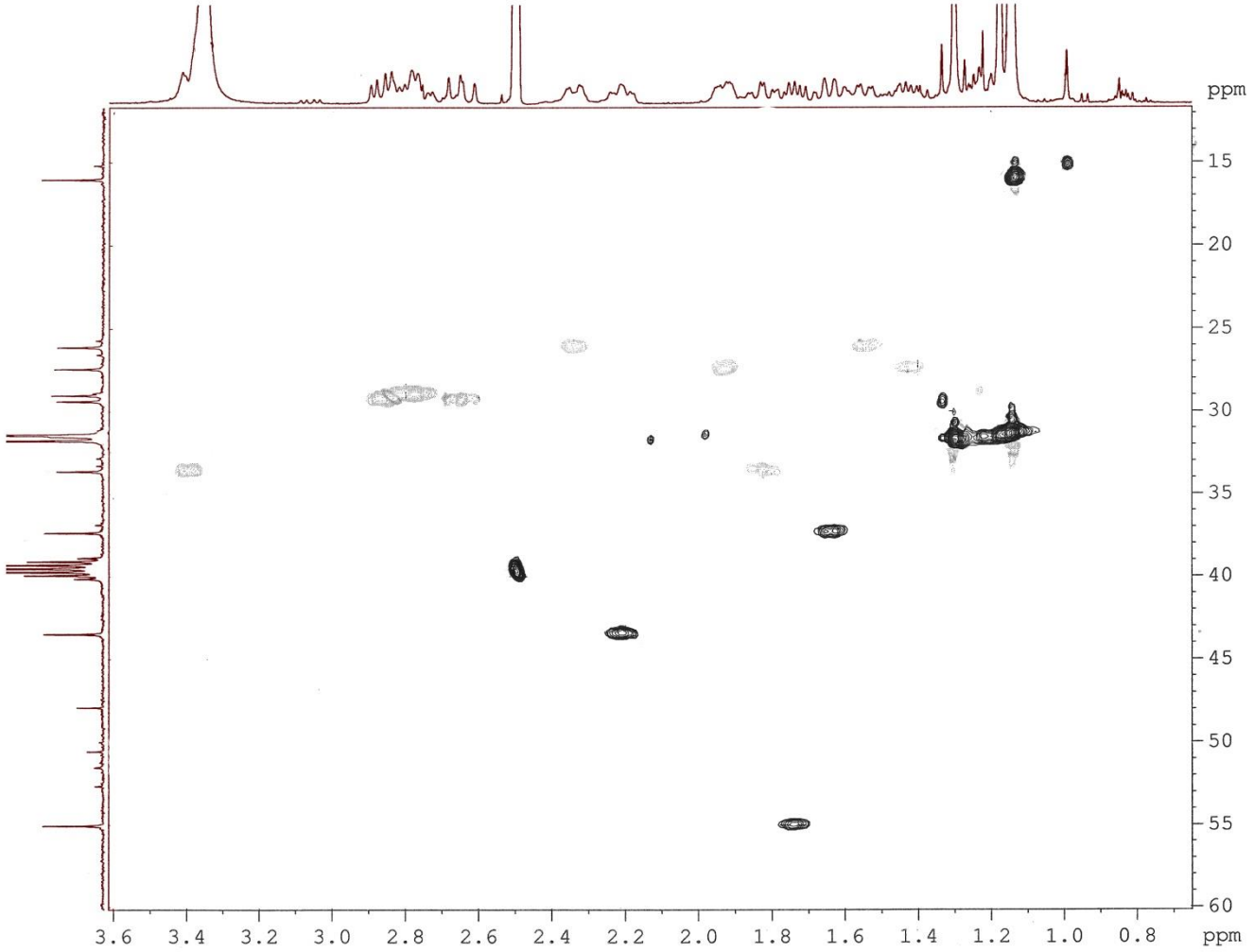
^{13}C NMR (101 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (11).



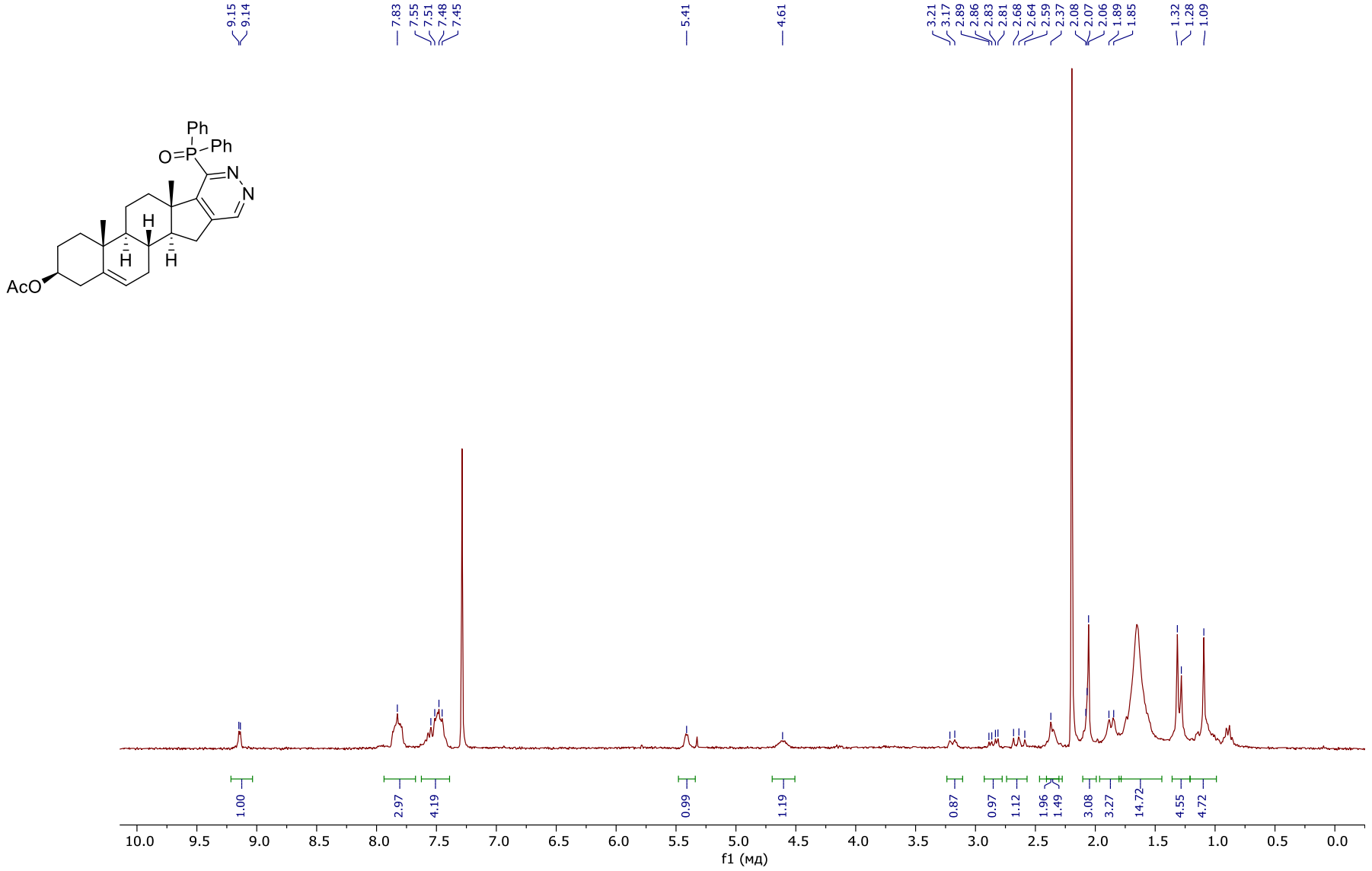
^{31}P NMR (162 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (11).



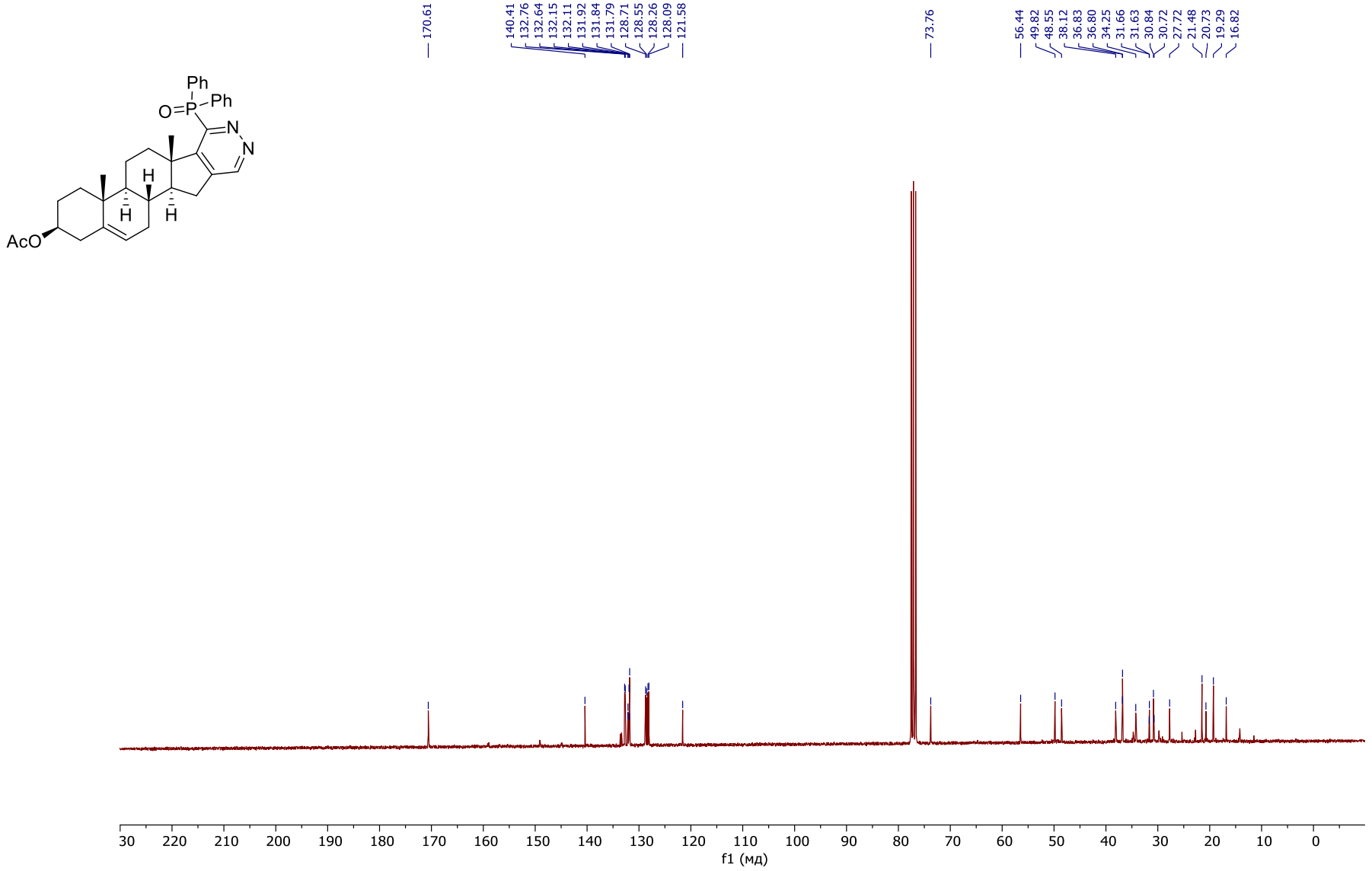
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (11).



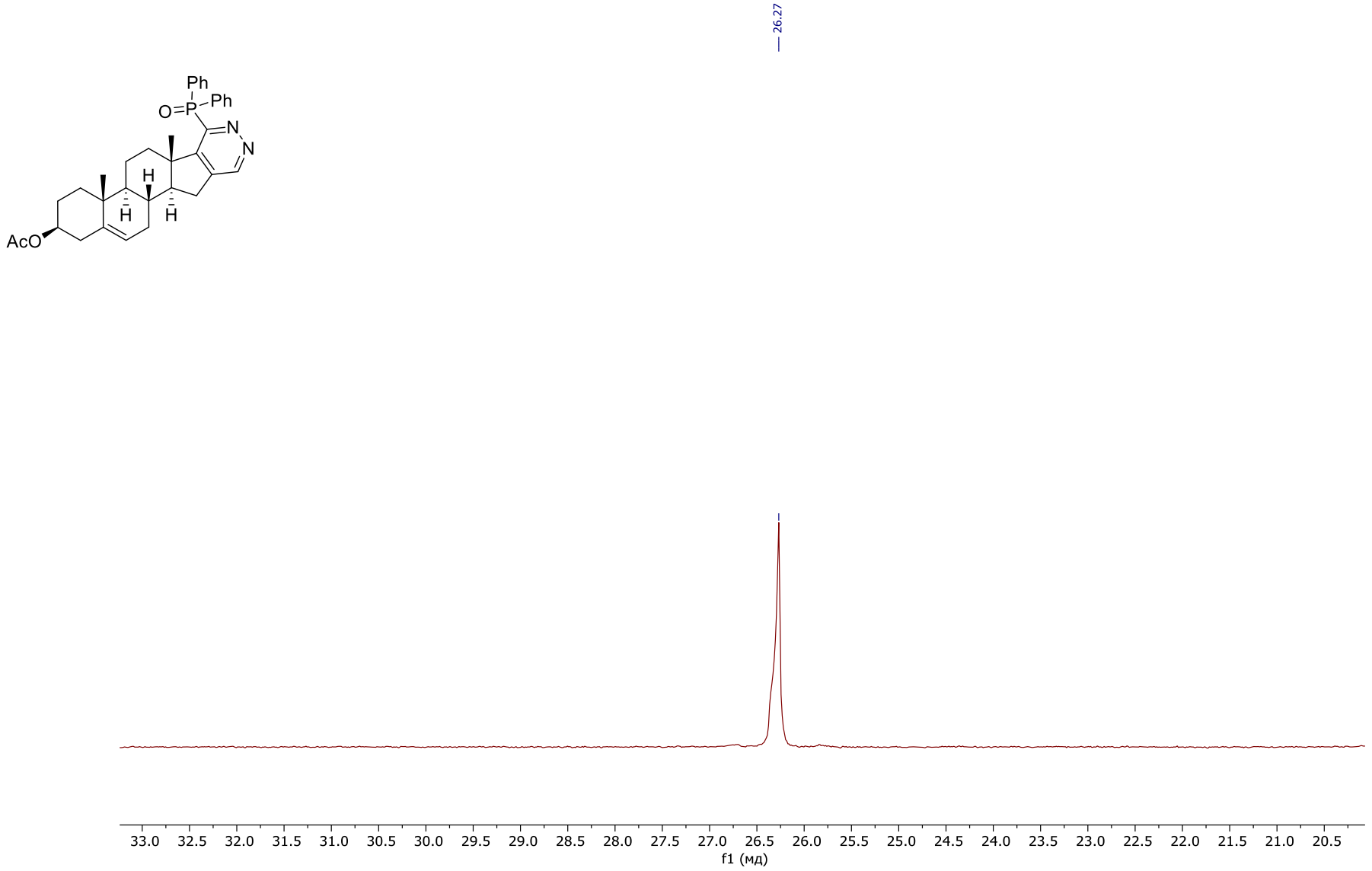
^{1}H NMR (300 MHz, $CDCl_3$) of (3β-acetoxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (14).



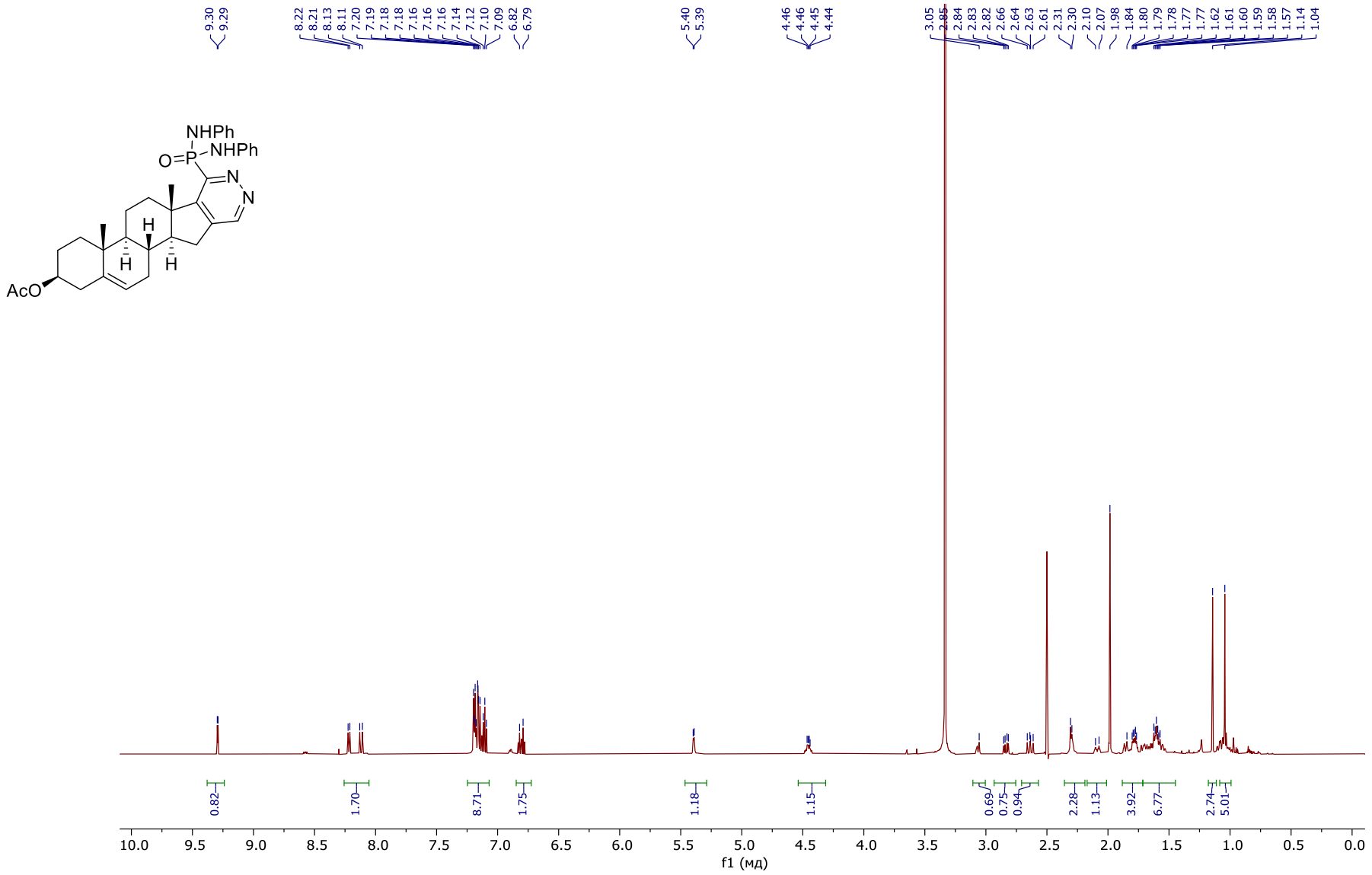
^{13}C NMR (75 MHz, $CDCl_3$) of (3β-acetoxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (14).



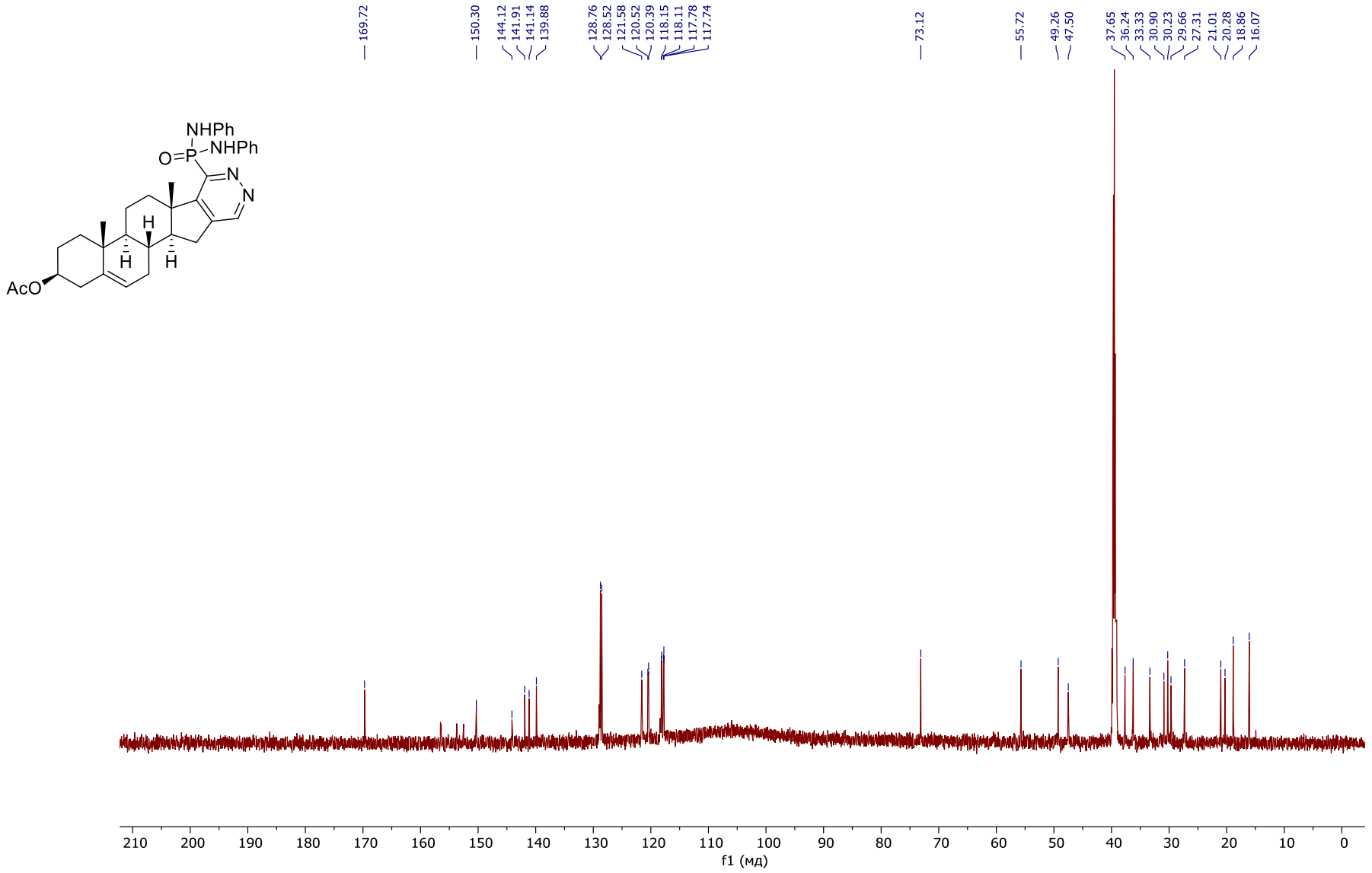
^{31}P NMR (121 MHz, $CDCl_3$) of (3β-acetoxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (14).



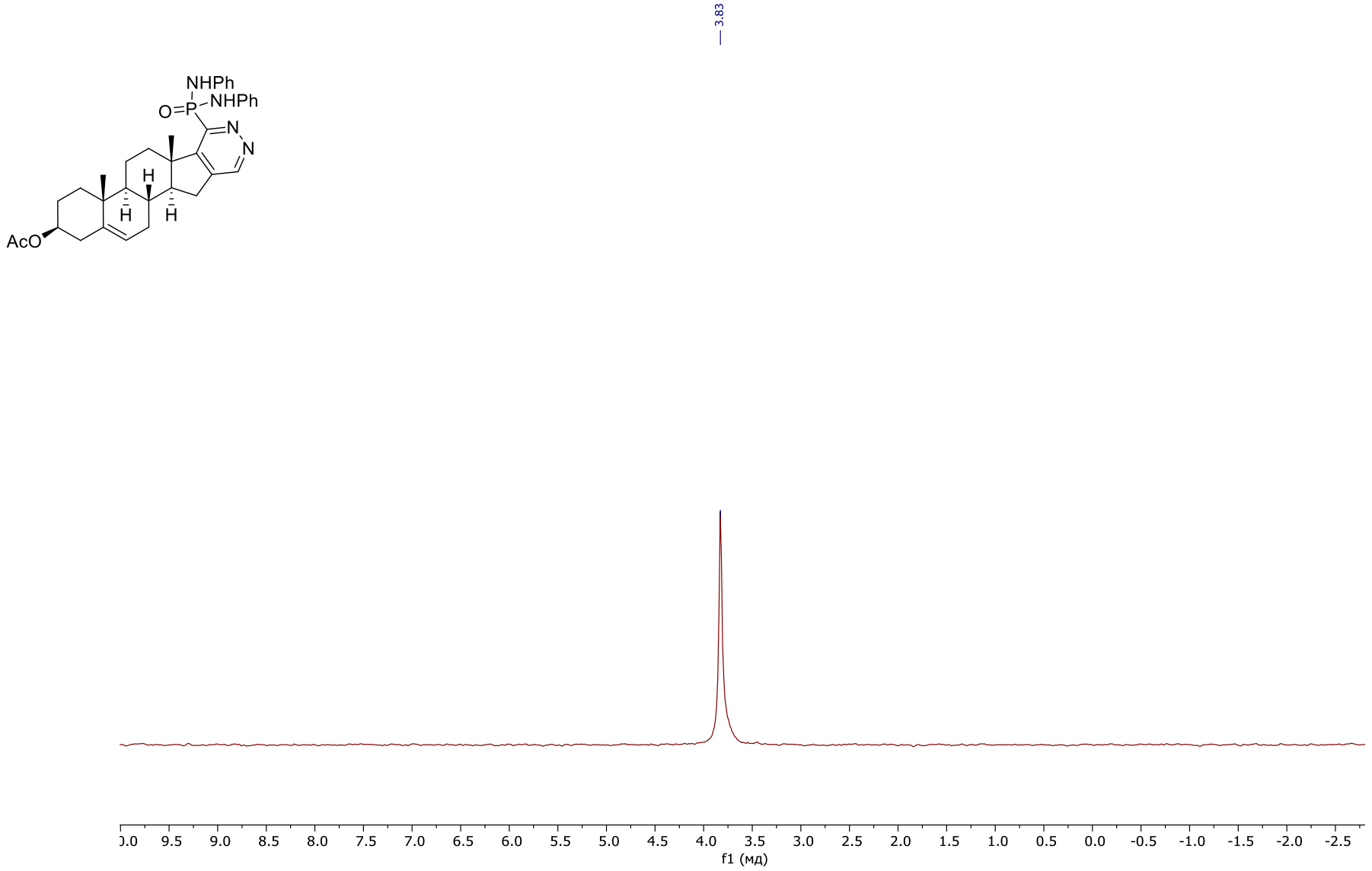
^{1}H NMR (600 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (15).



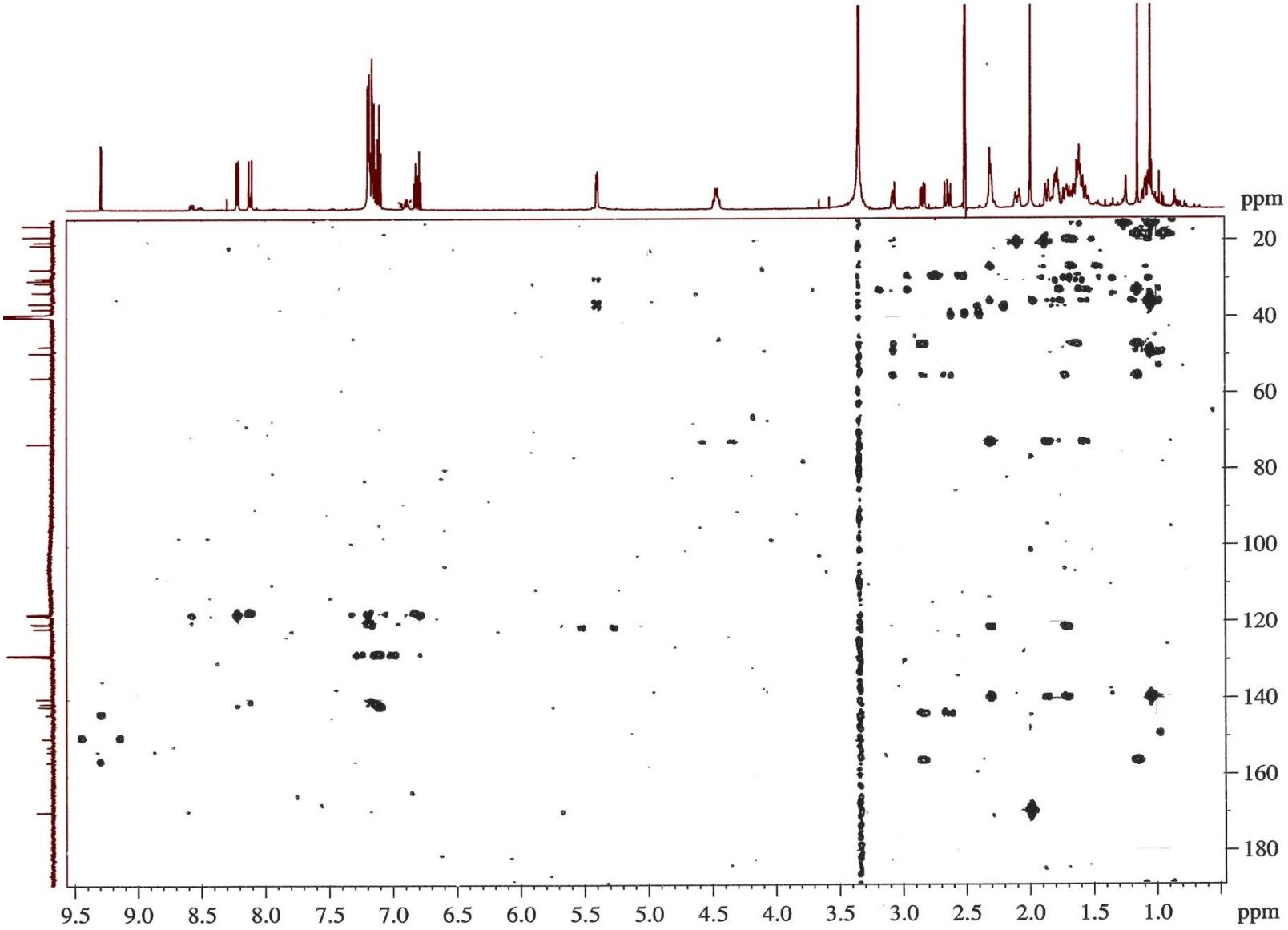
^{13}C NMR (150 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (15).



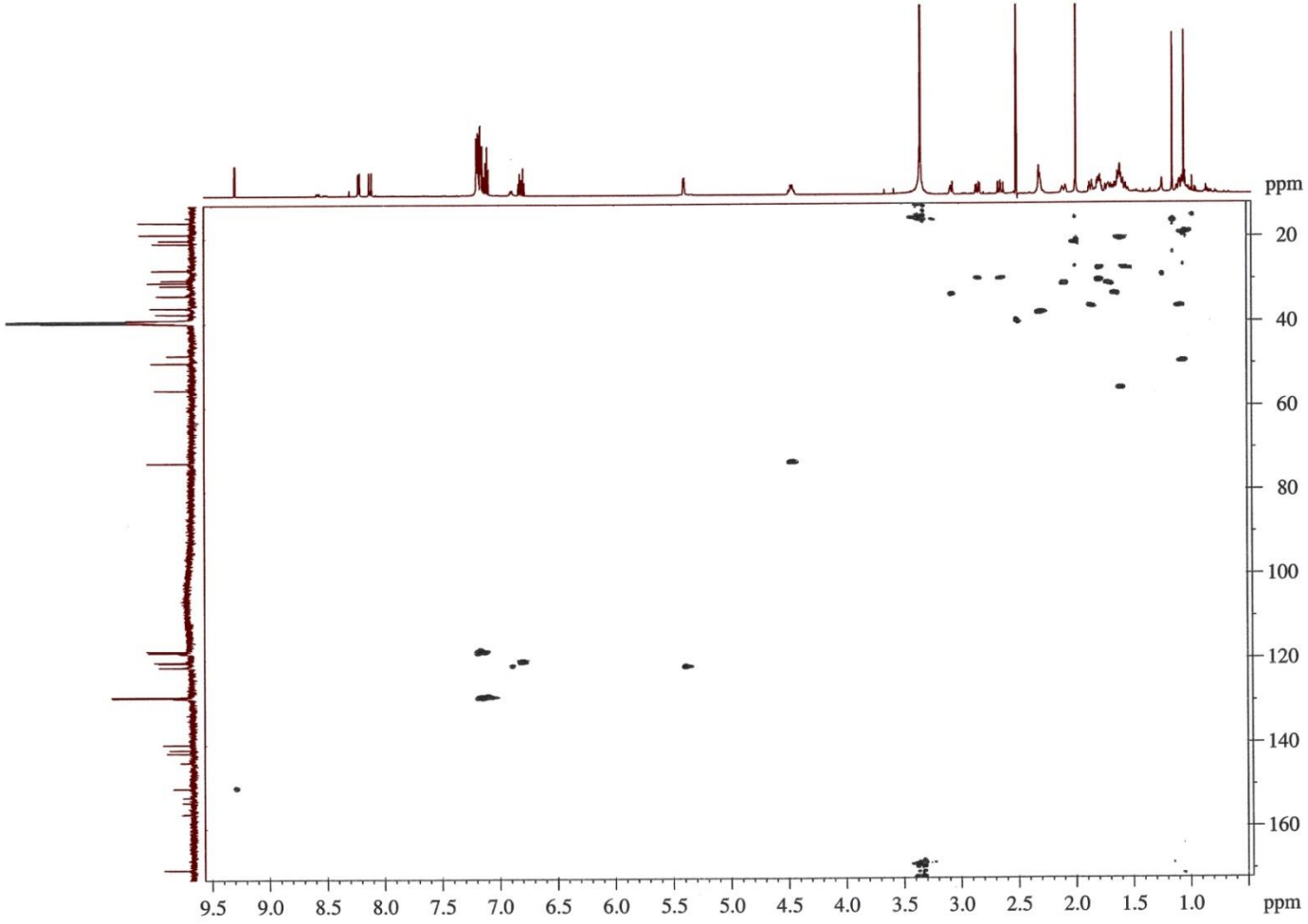
^{31}P NMR (243 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (15).



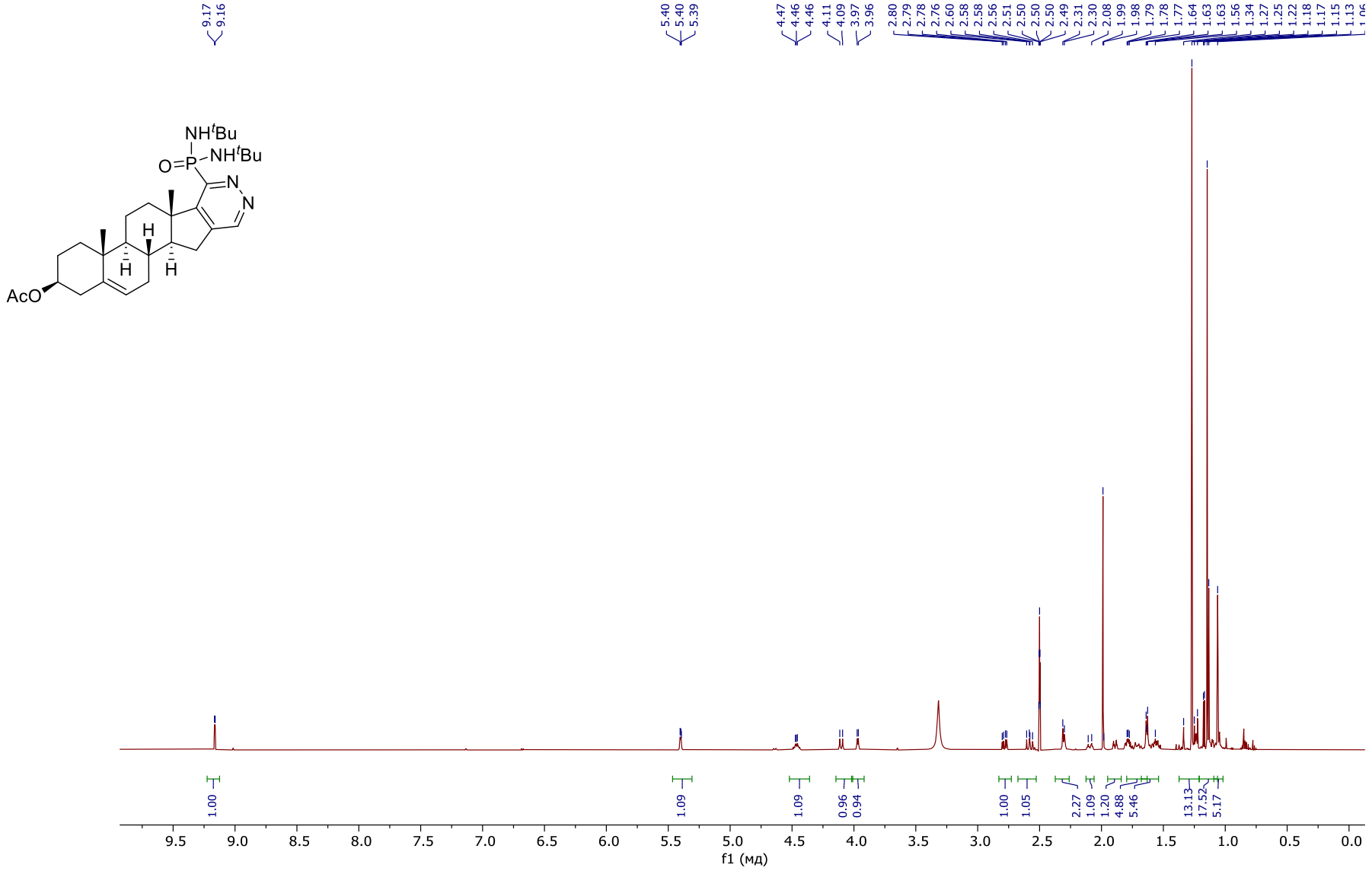
^{1}H-^{13}C HMBC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (15).



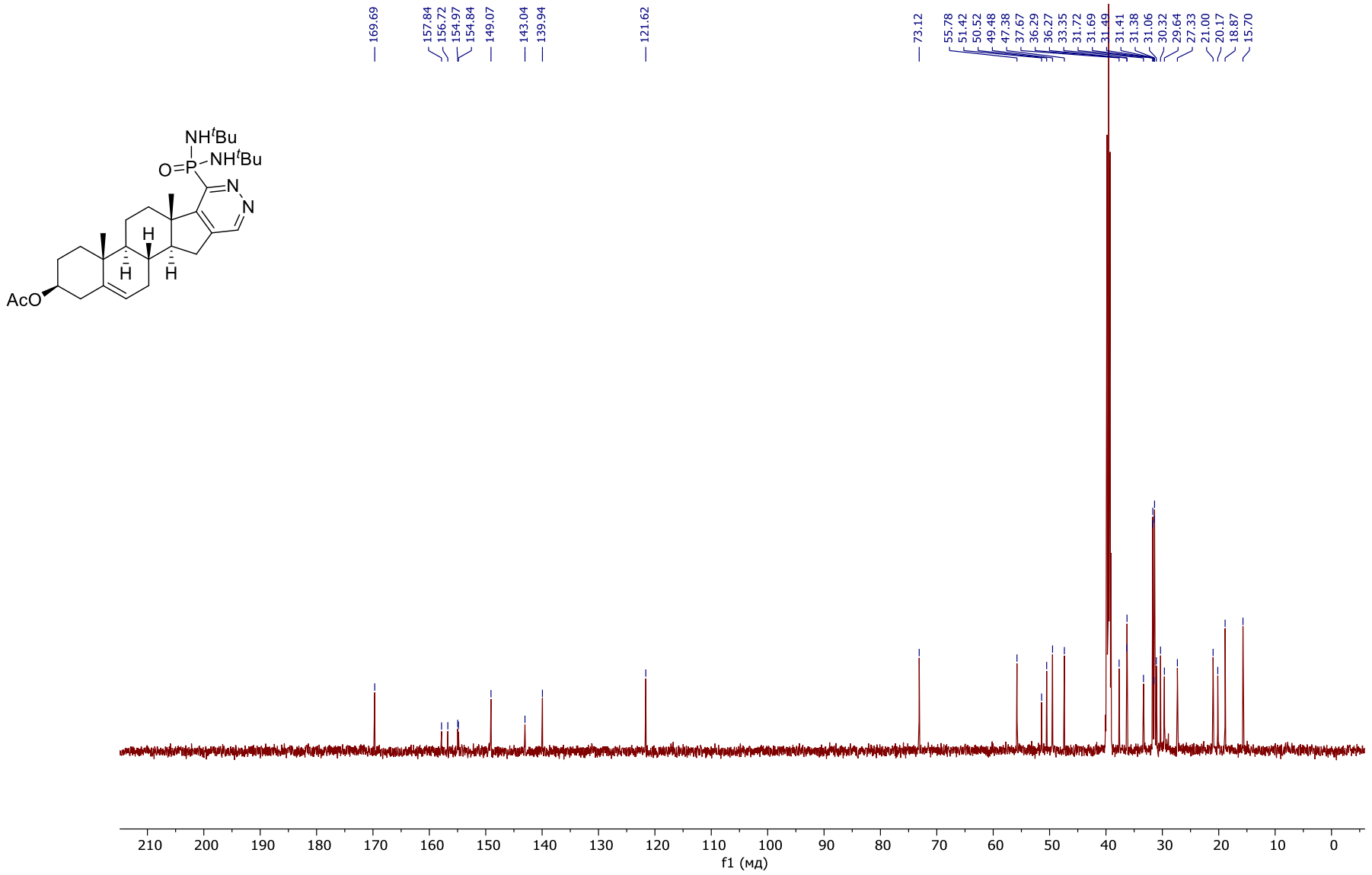
^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (15).



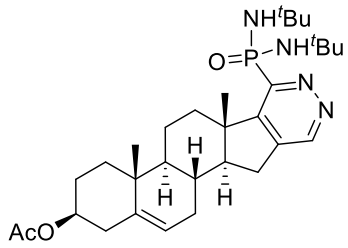
^{1}H NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (16).



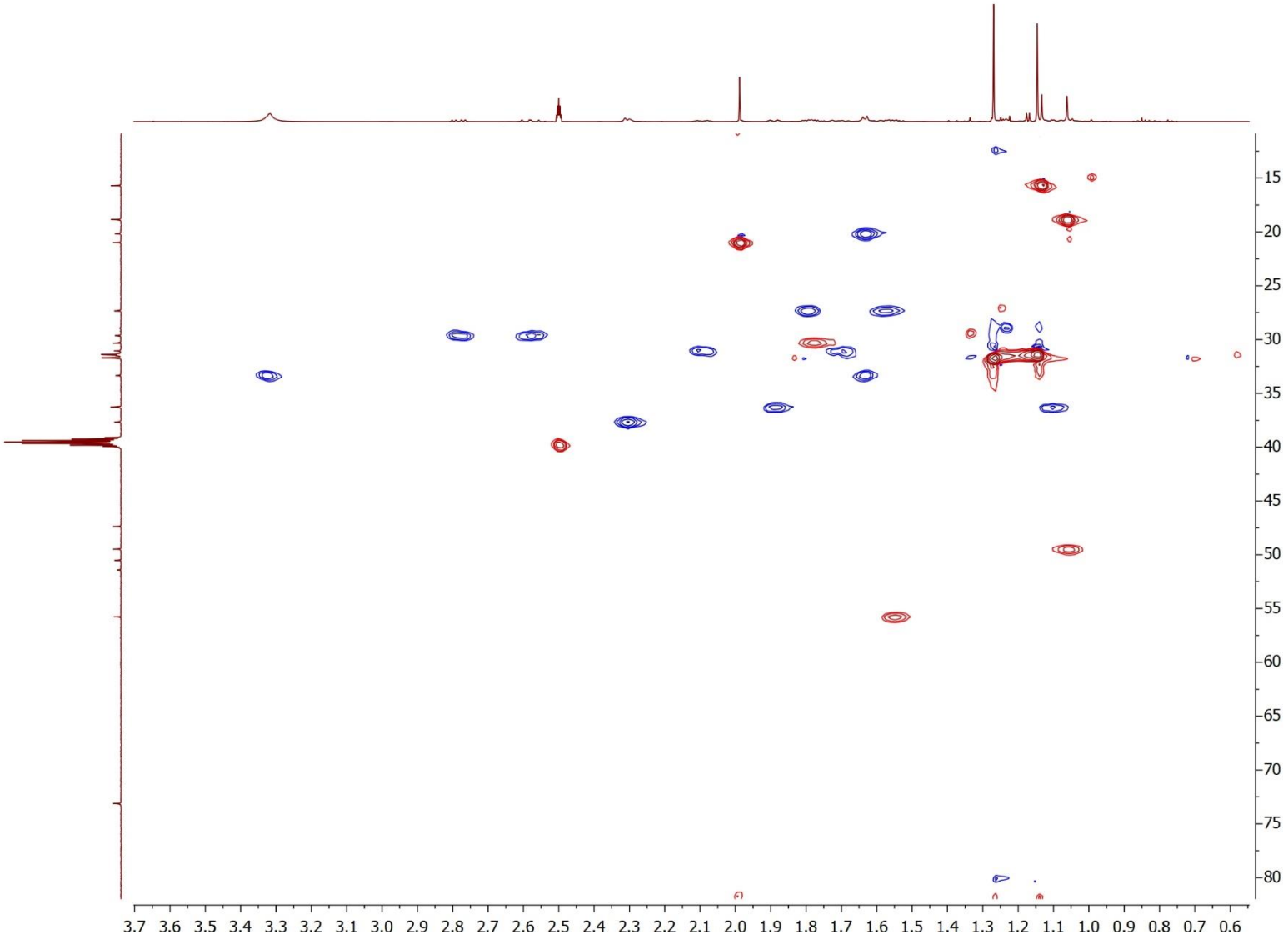
^{13}C NMR (150 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (16).



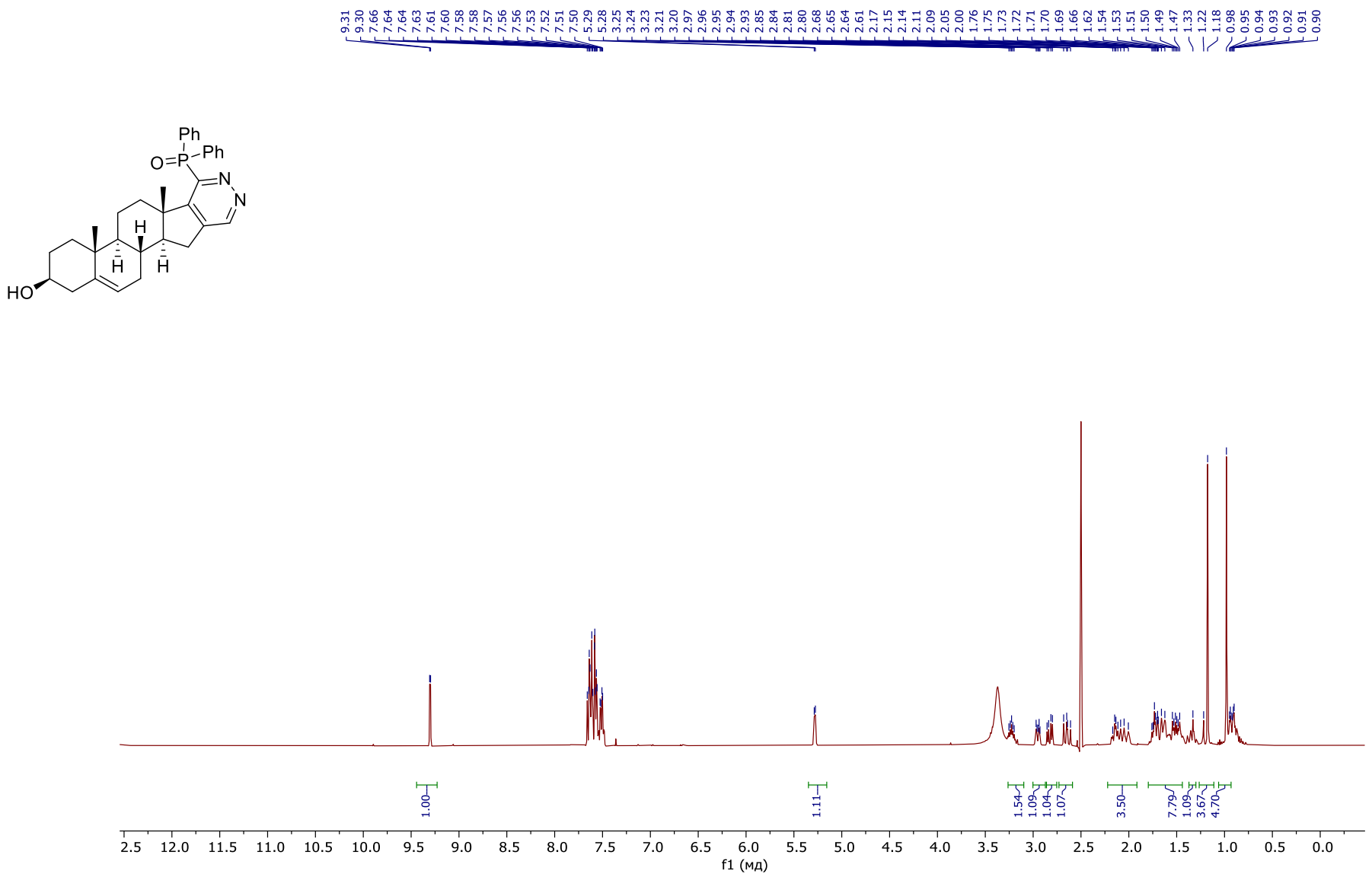
^{31}P NMR (243 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (16).



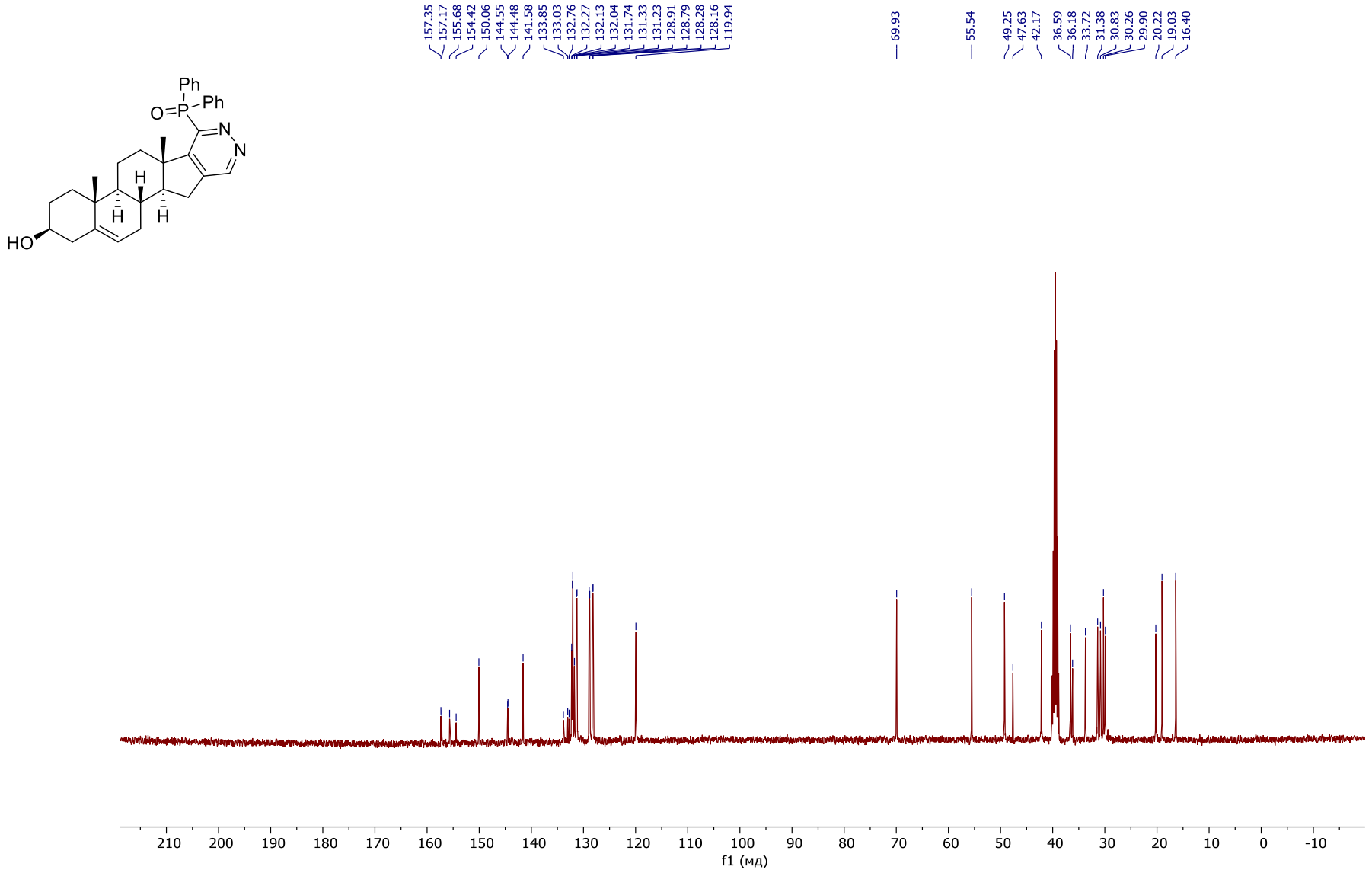
^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-acetoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (16).



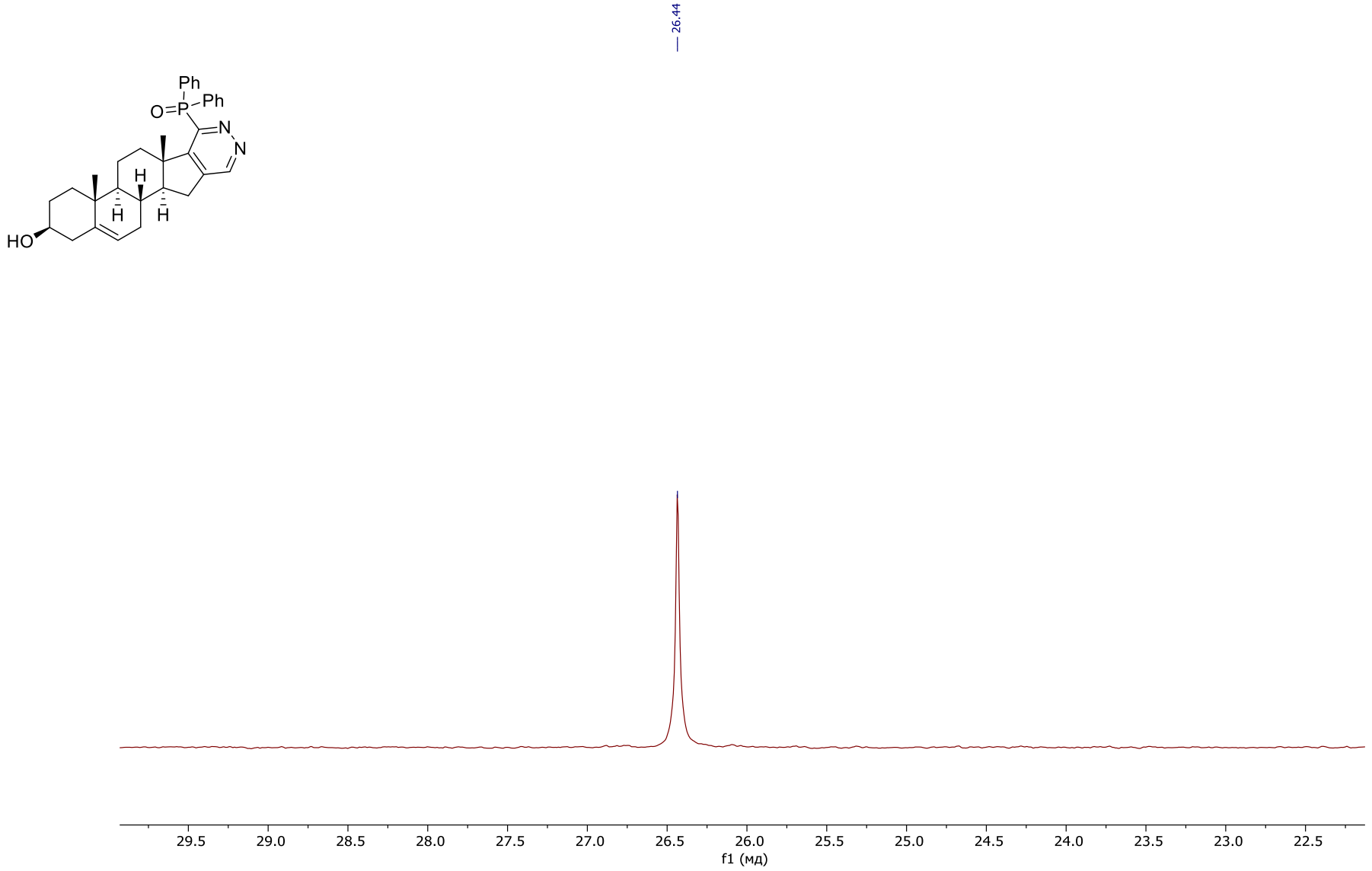
^{1}H NMR (400 MHz, DMSO-d_6) of (3β-hydroxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (17).



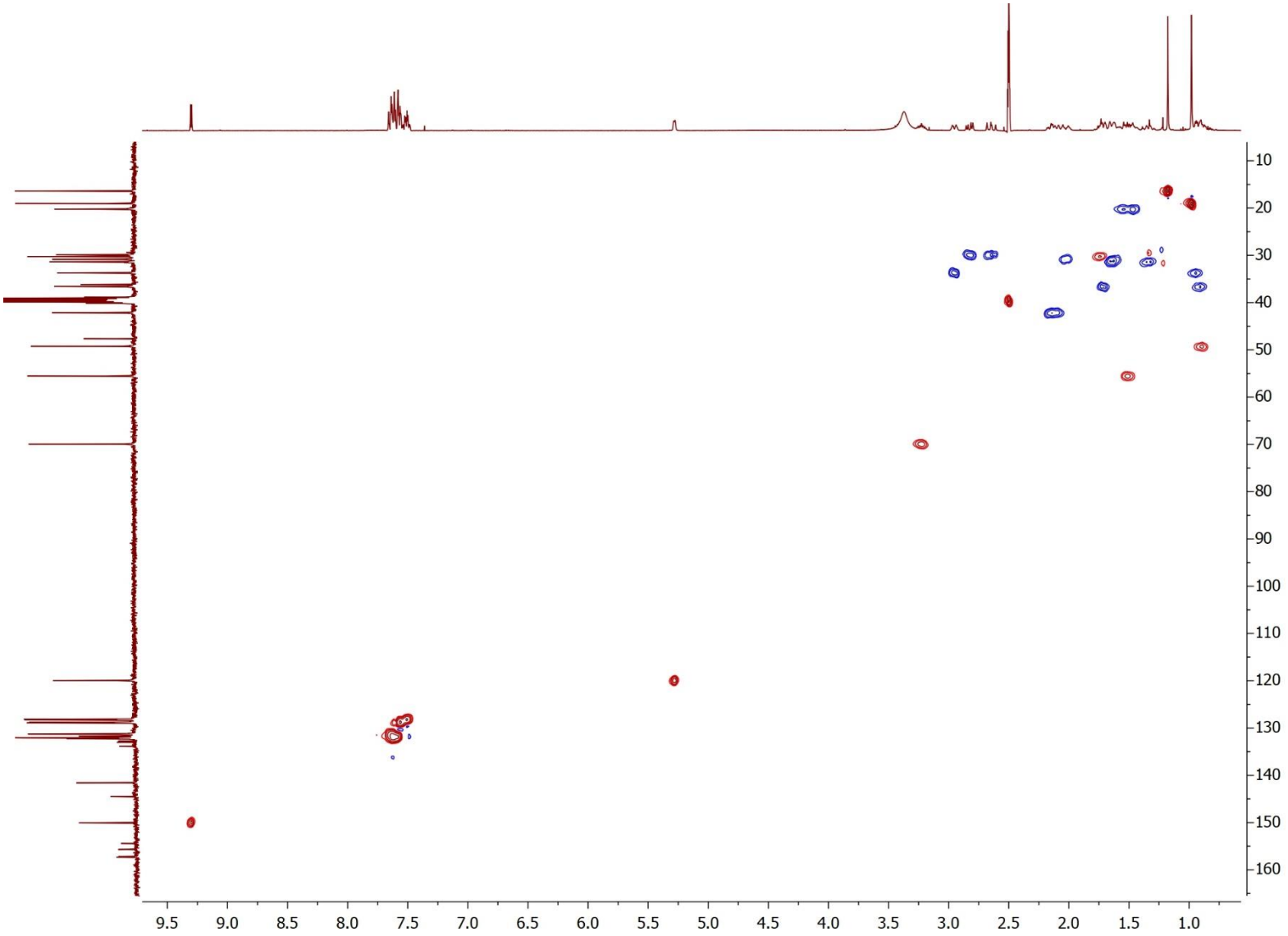
^{13}C NMR (101 MHz, DMSO-d_6) of (3β-hydroxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (17).



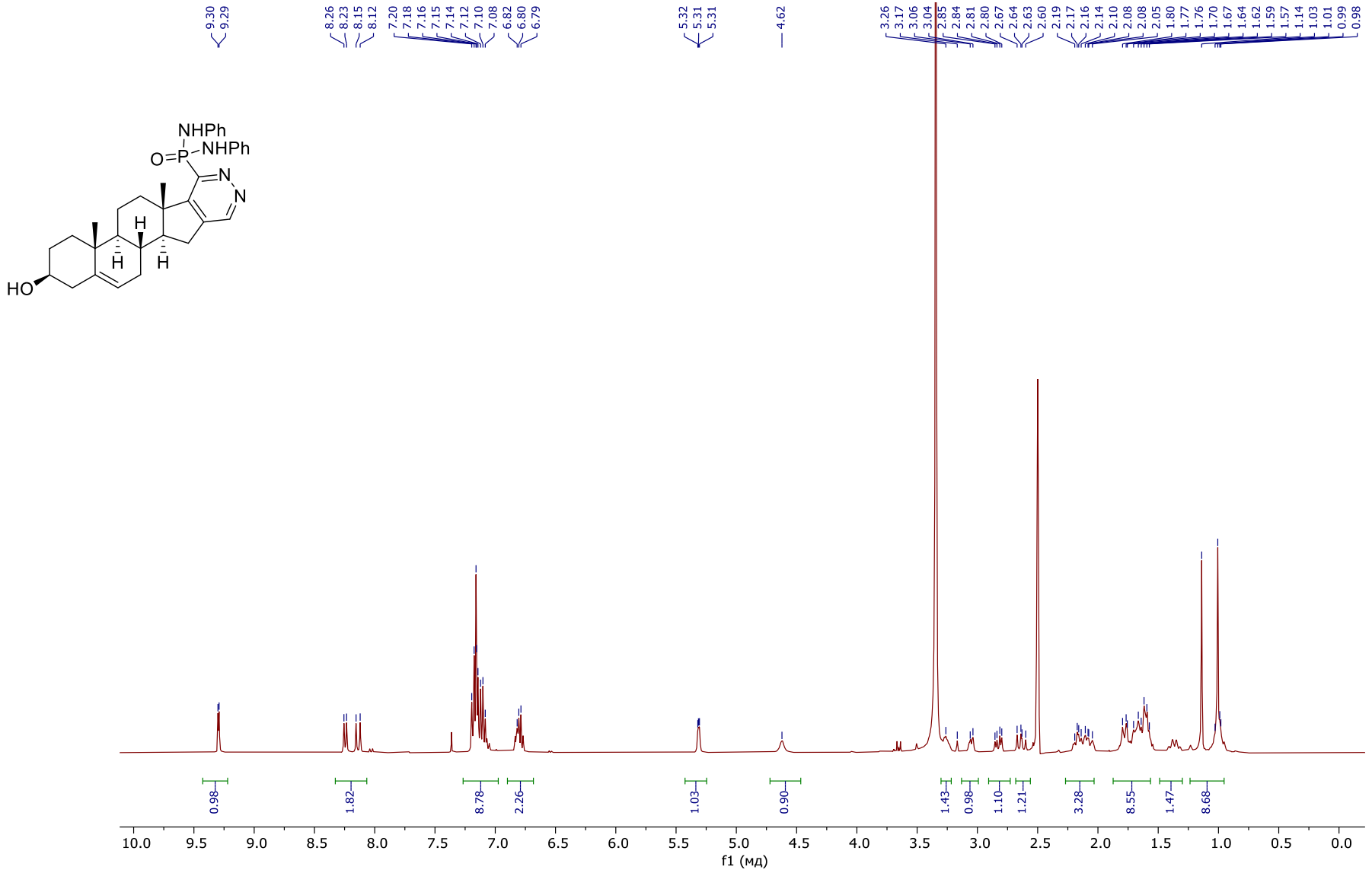
^{31}P NMR (162 MHz, DMSO-d_6) of (3β-hydroxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (17).



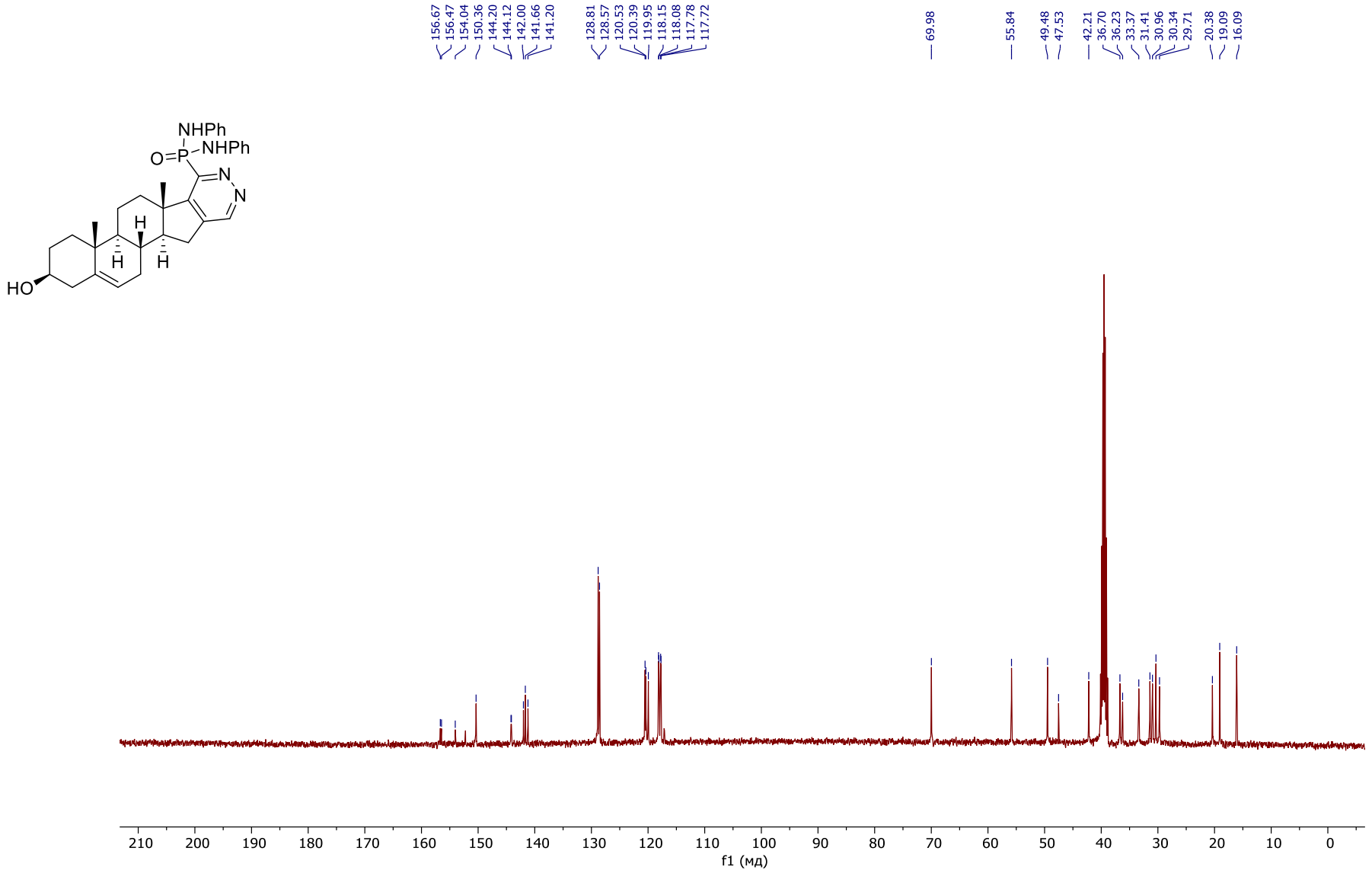
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of (3β-hydroxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (17).



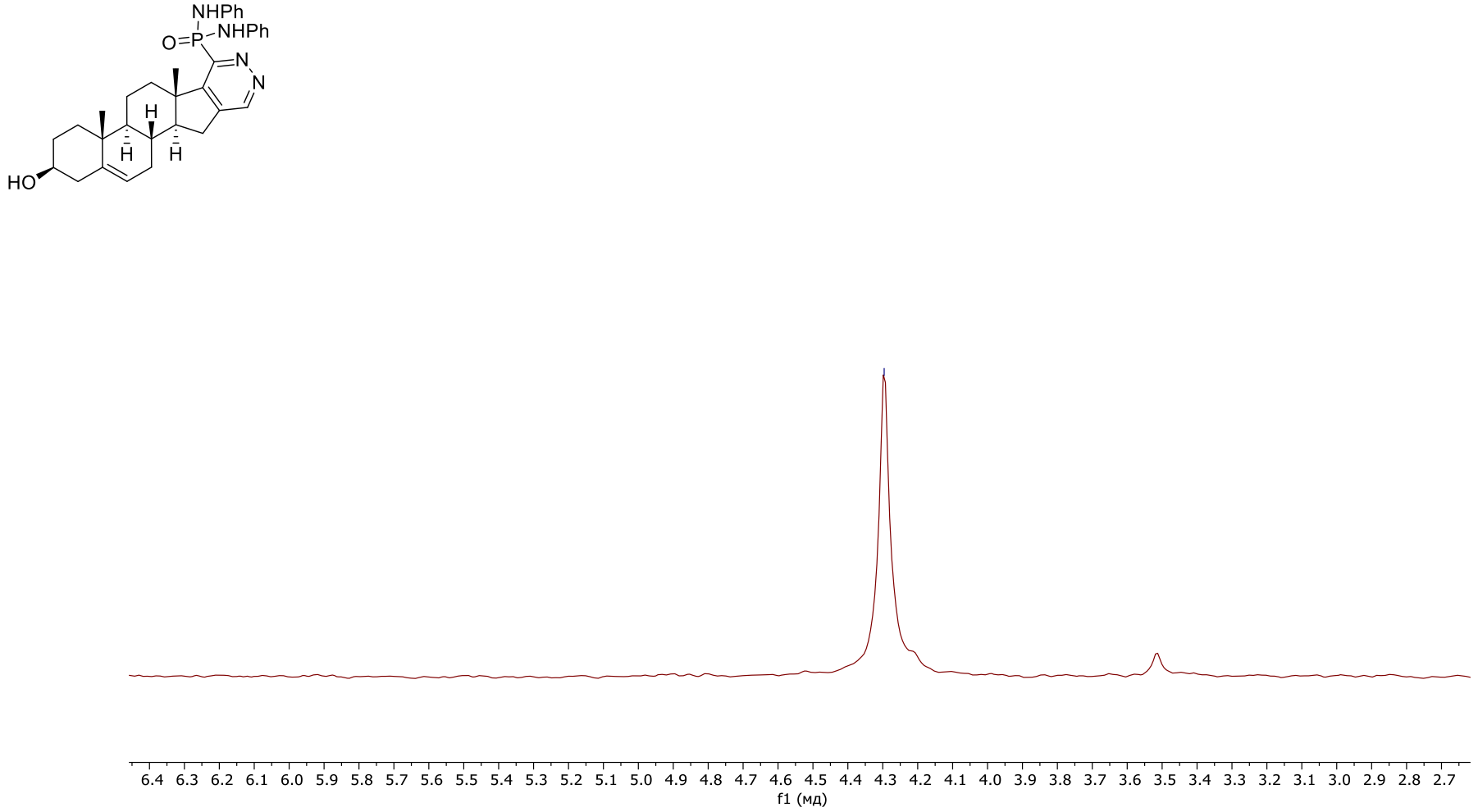
^{1}H NMR (400 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (18).



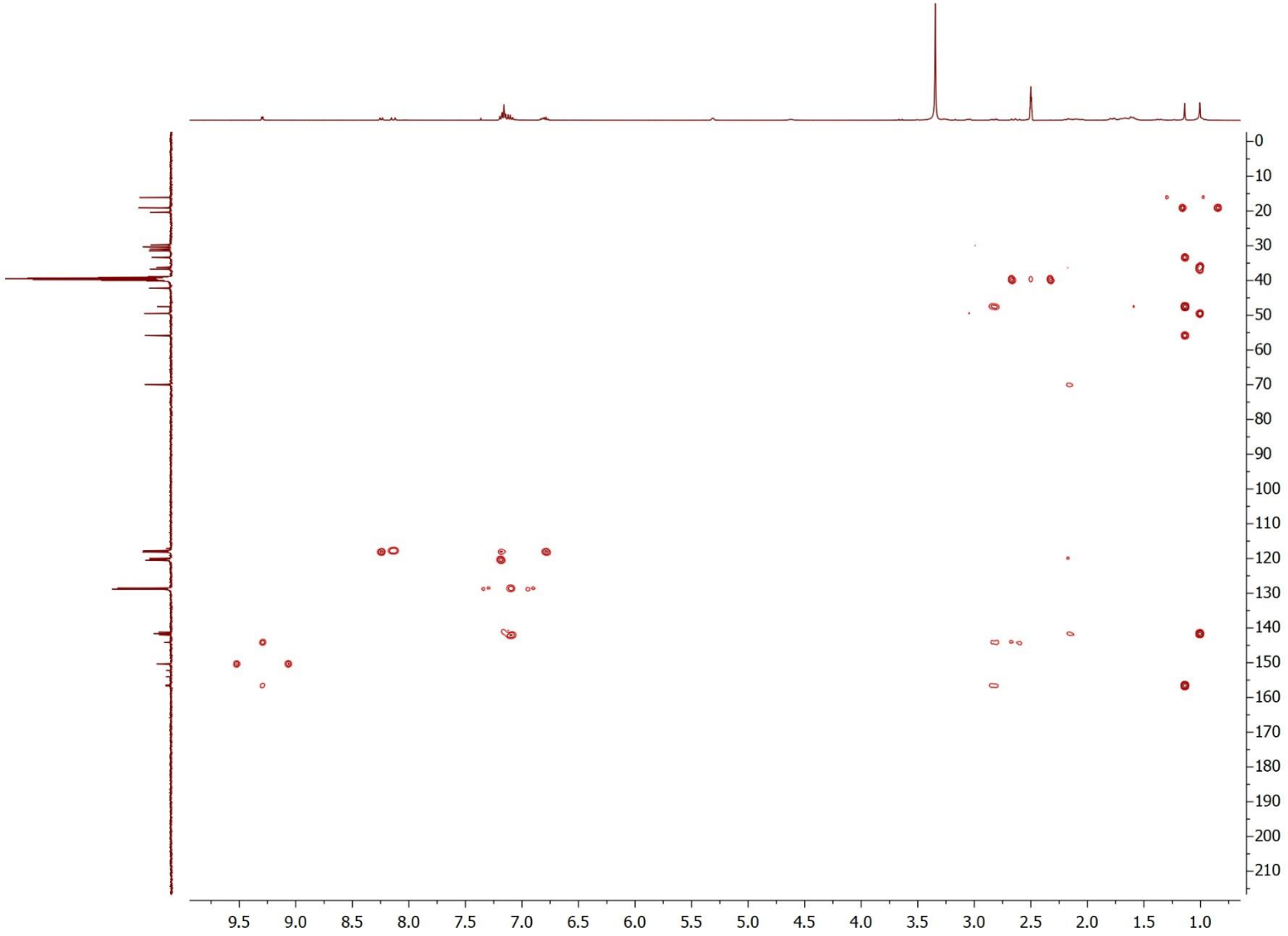
^{13}C NMR (101 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (18).



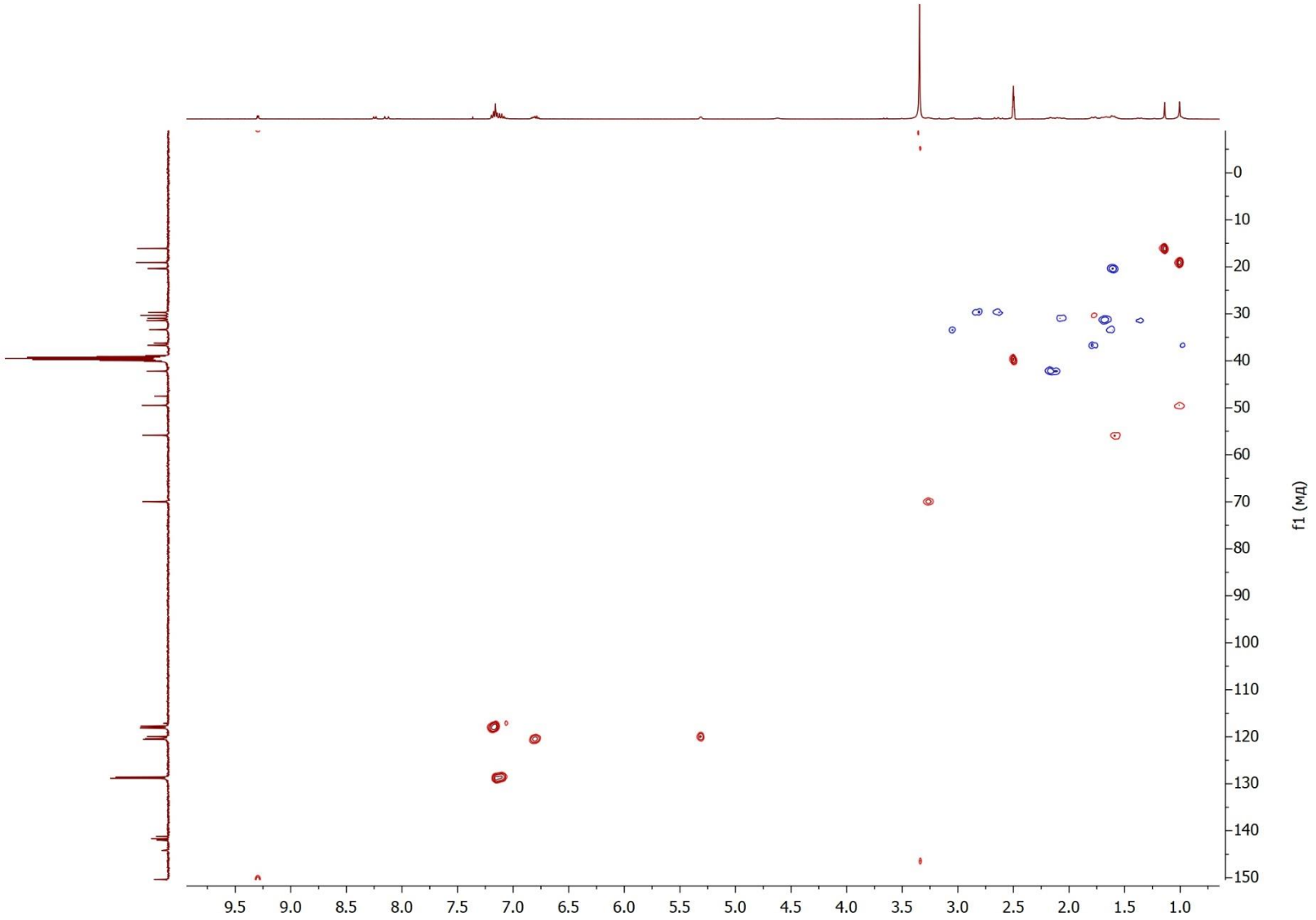
^{31}P NMR (162 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (18).



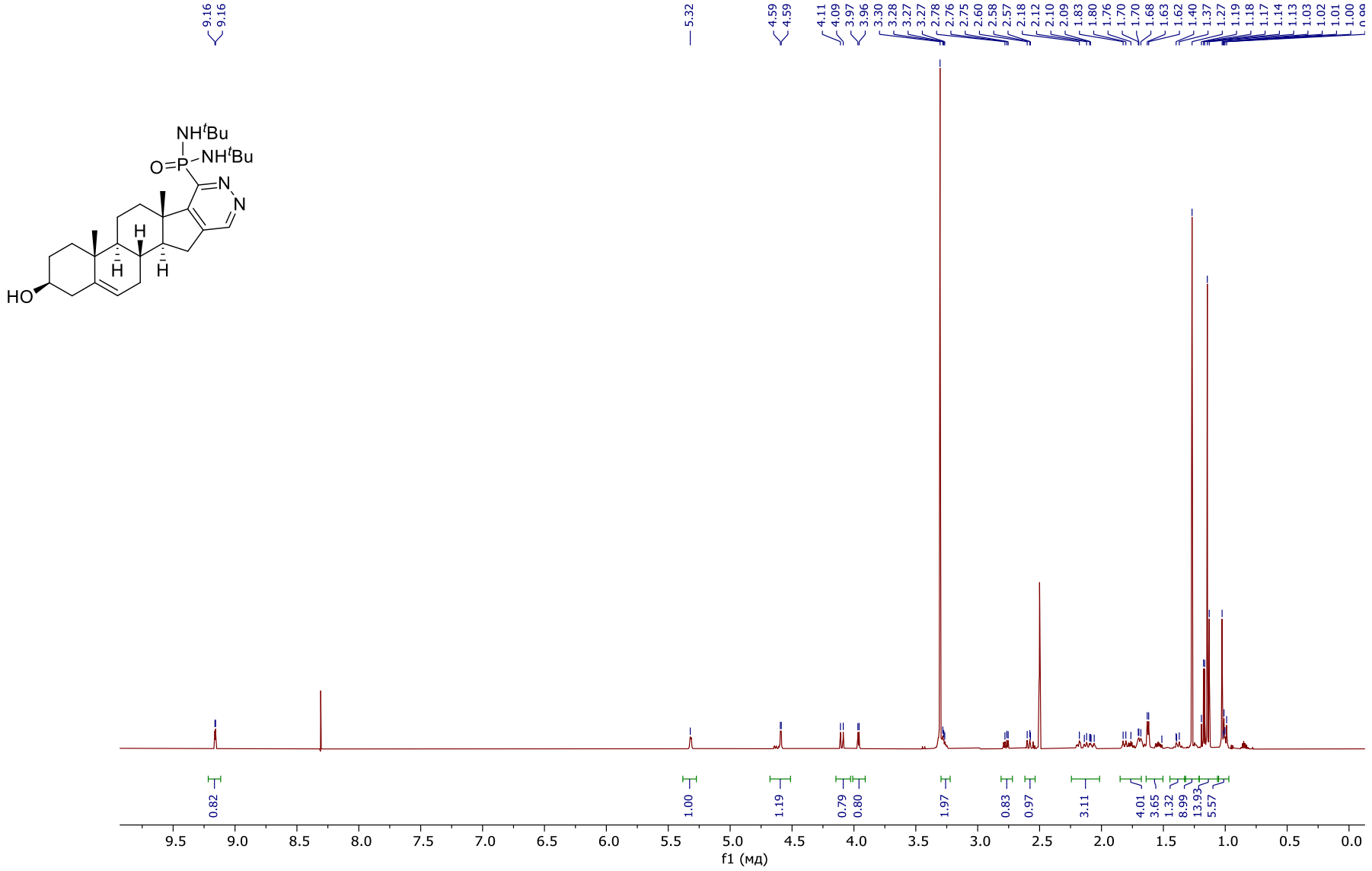
^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (18).



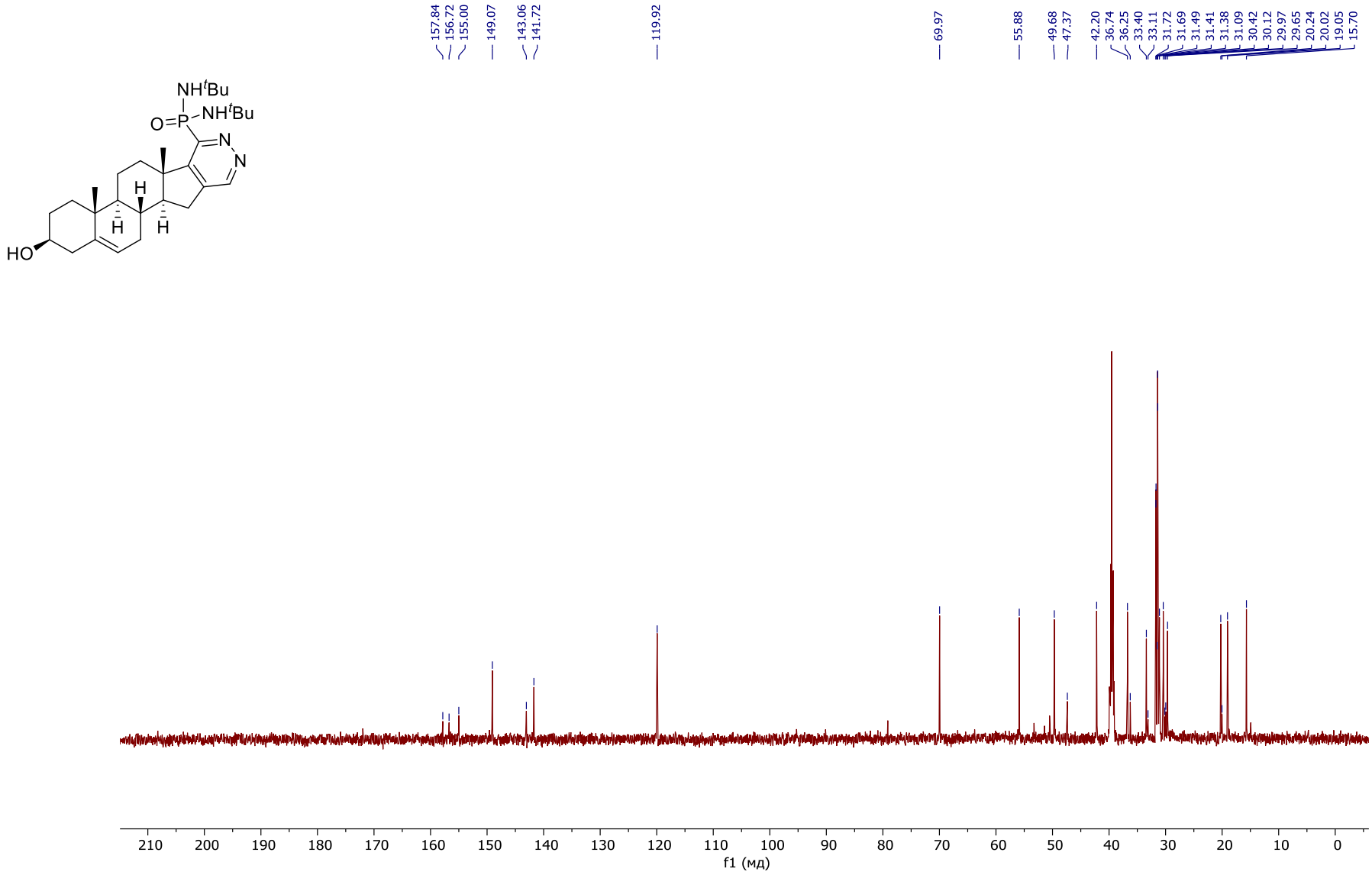
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (18).



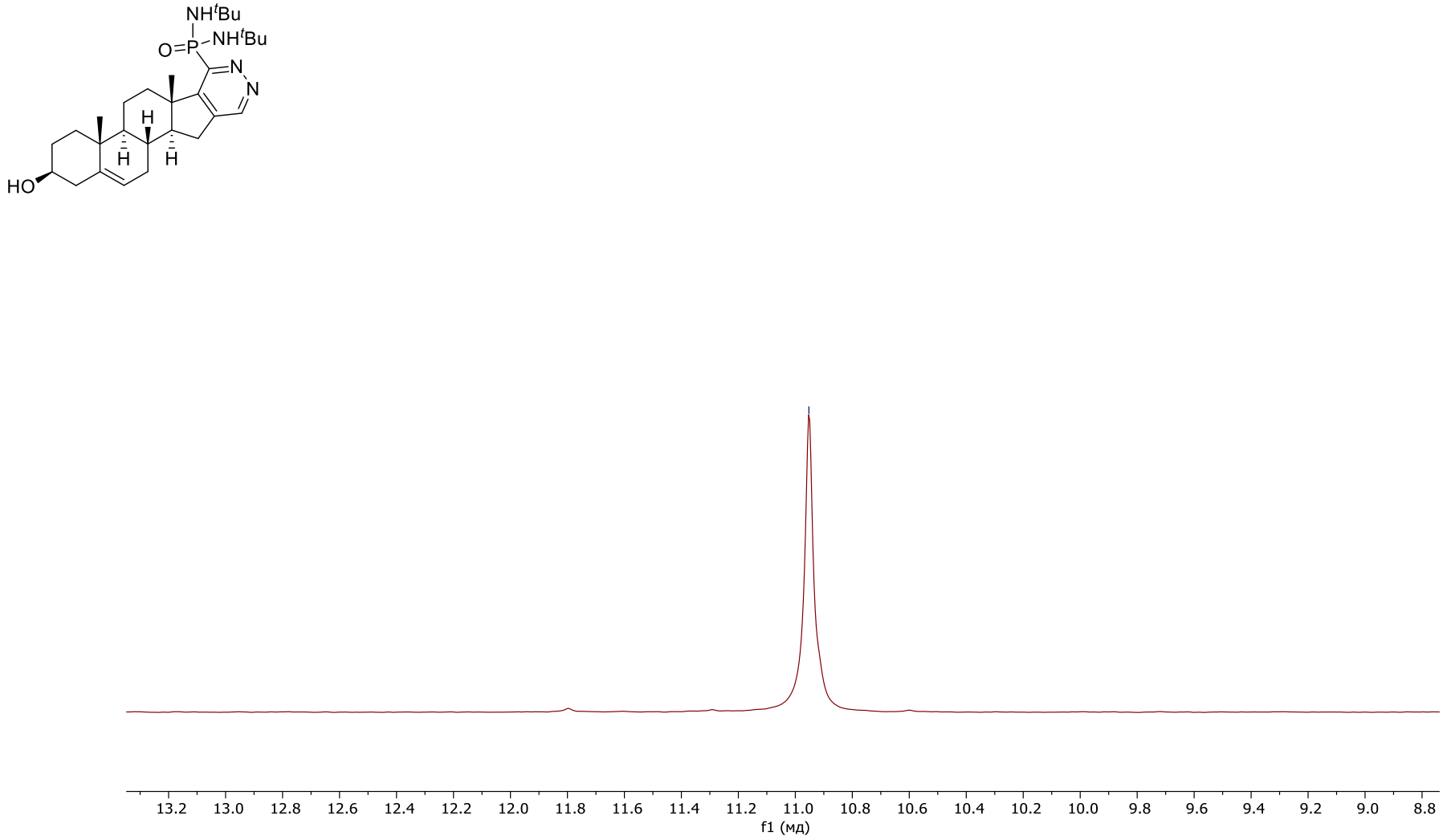
^{1}H NMR (600 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (19).



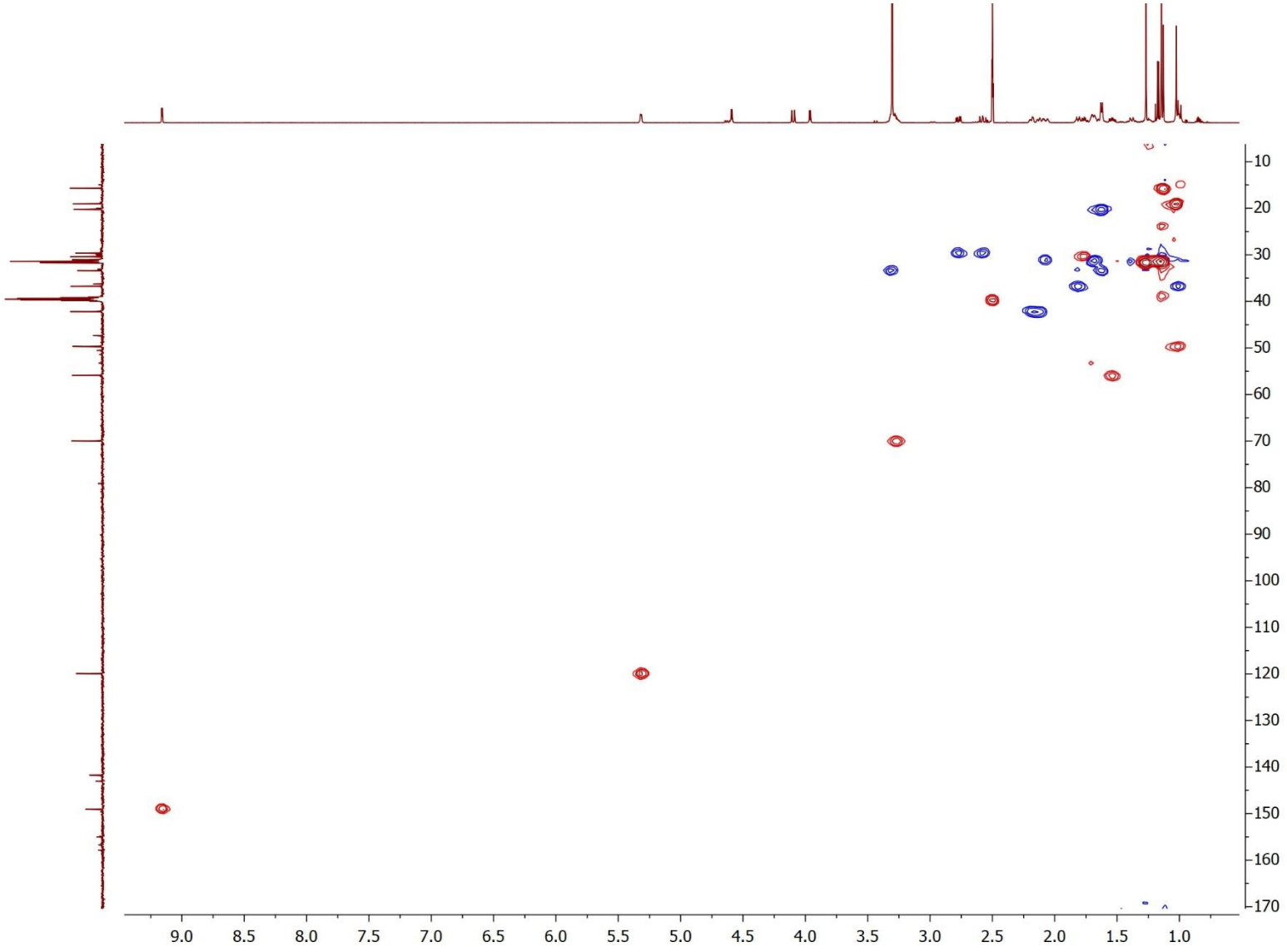
^{13}C NMR (150 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (19).



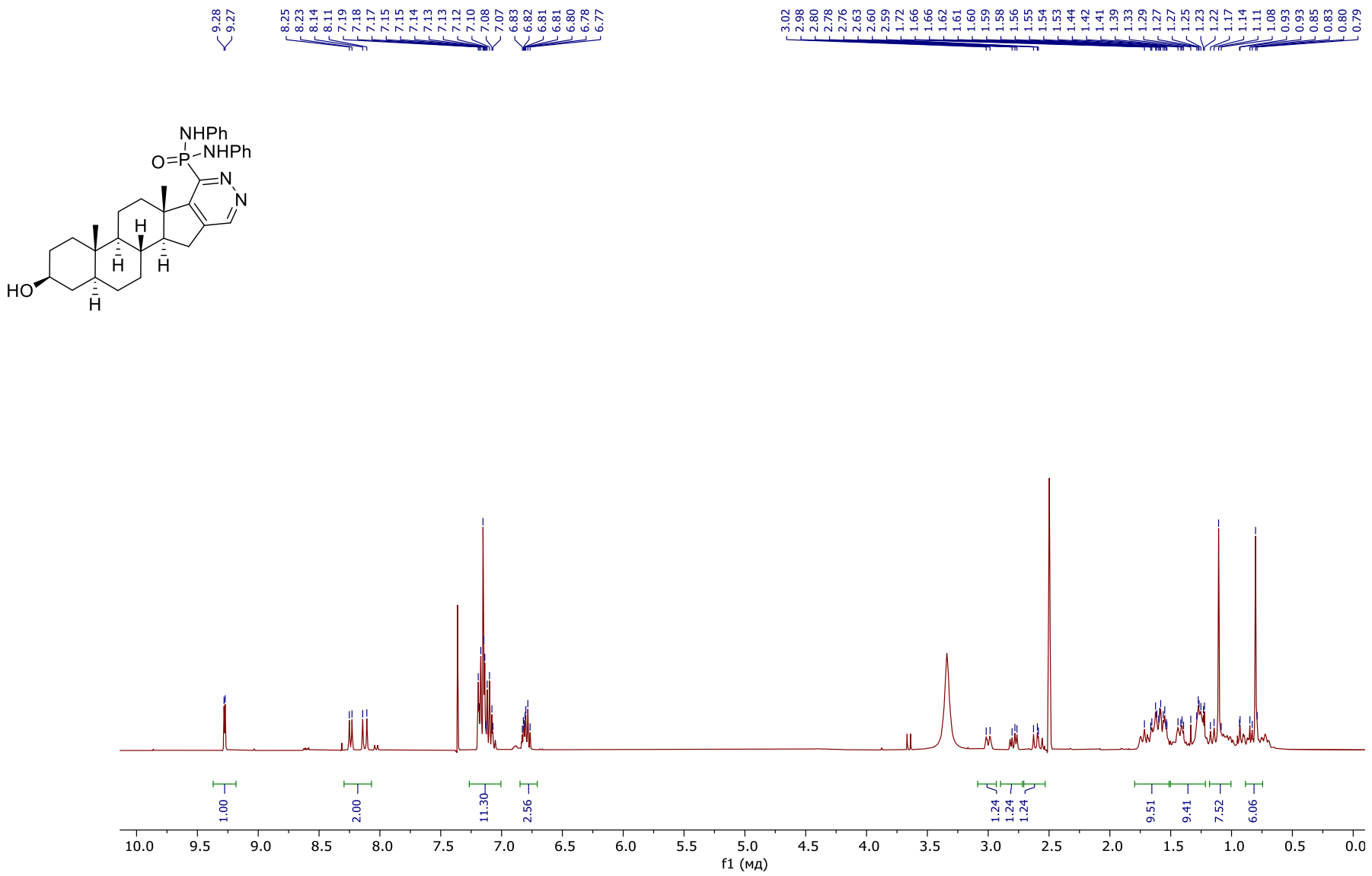
^{31}P NMR (243 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (19).



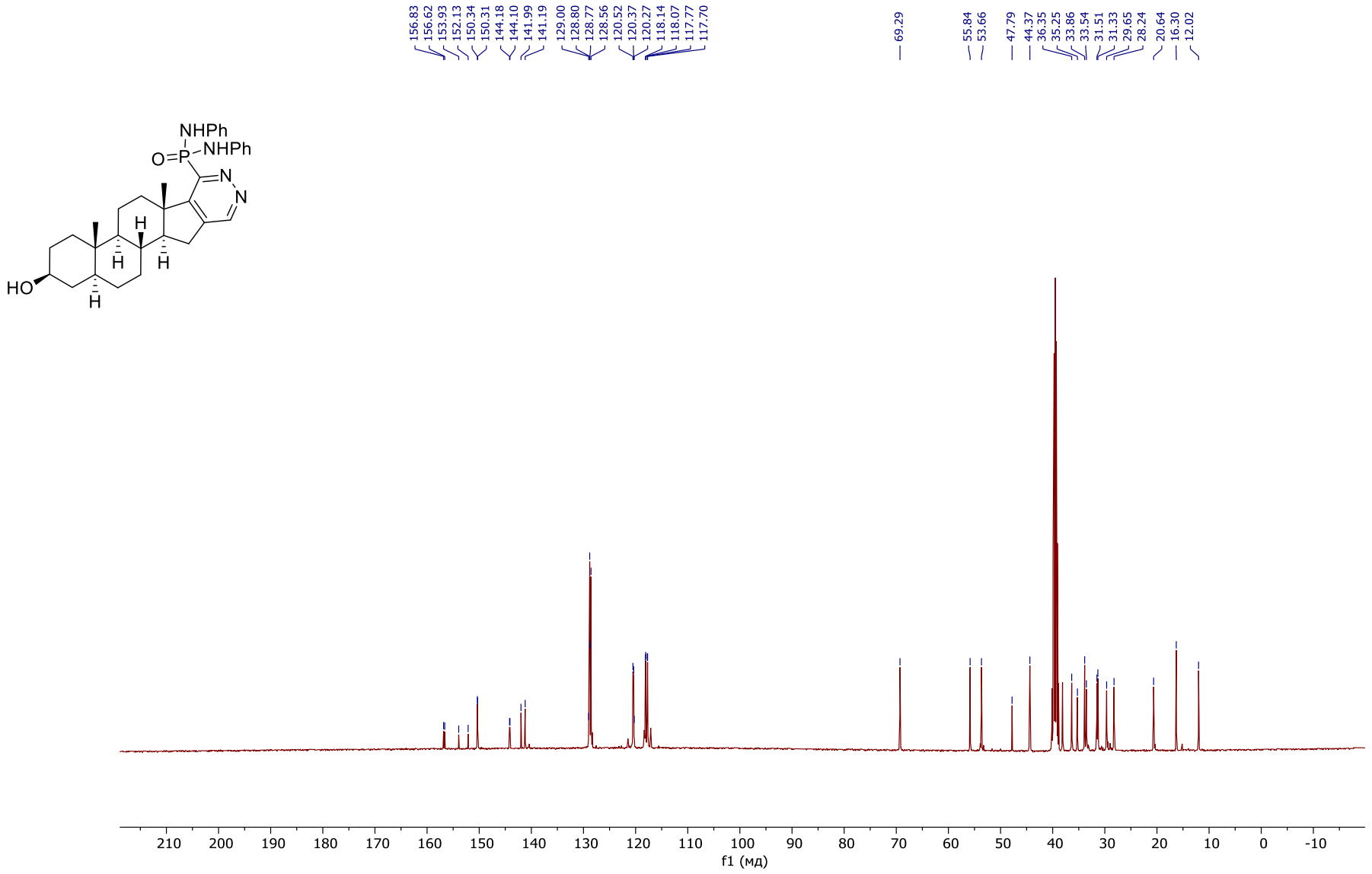
^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (19).



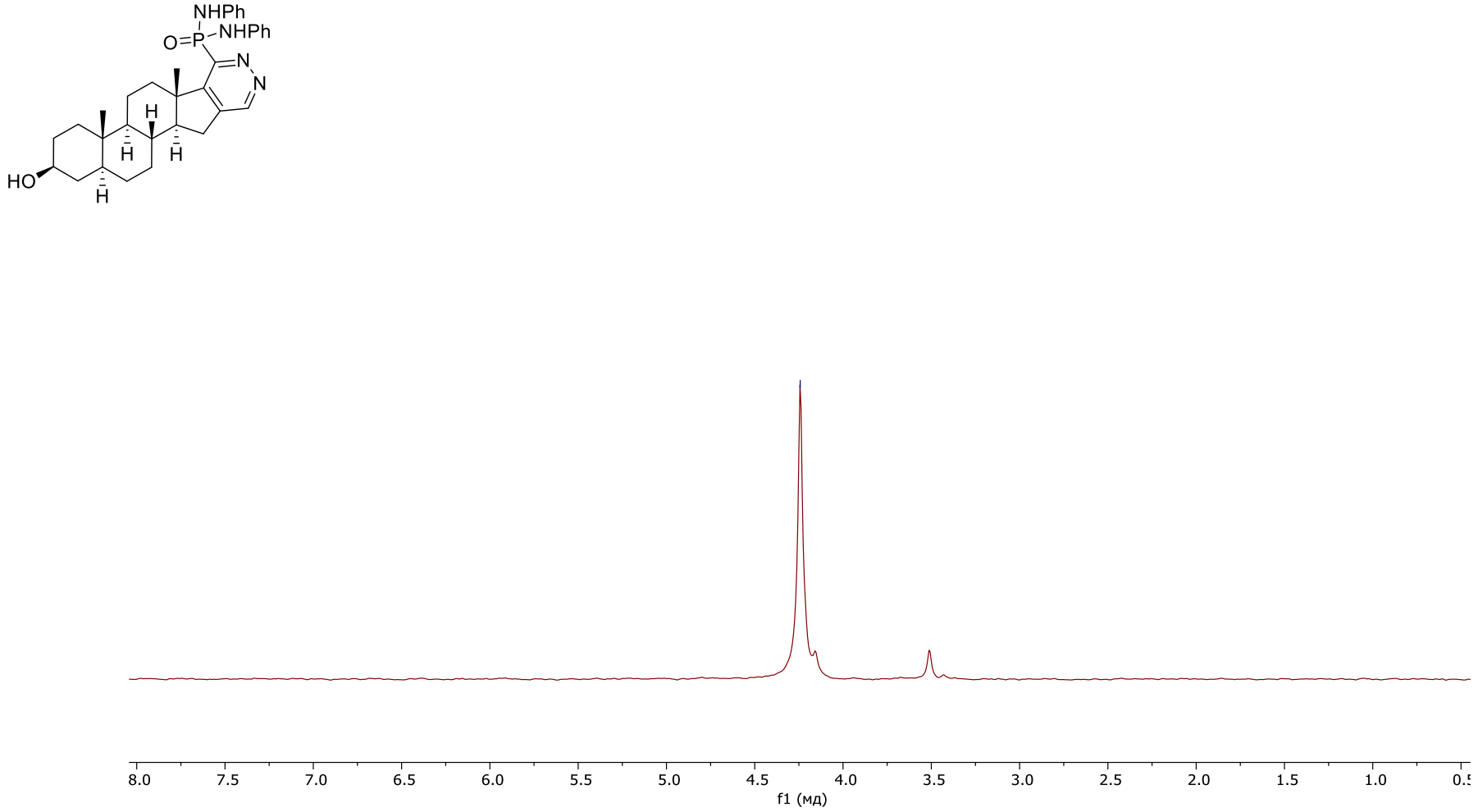
^{1}H NMR (400 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androst[16,17-d]pyridazine (22).



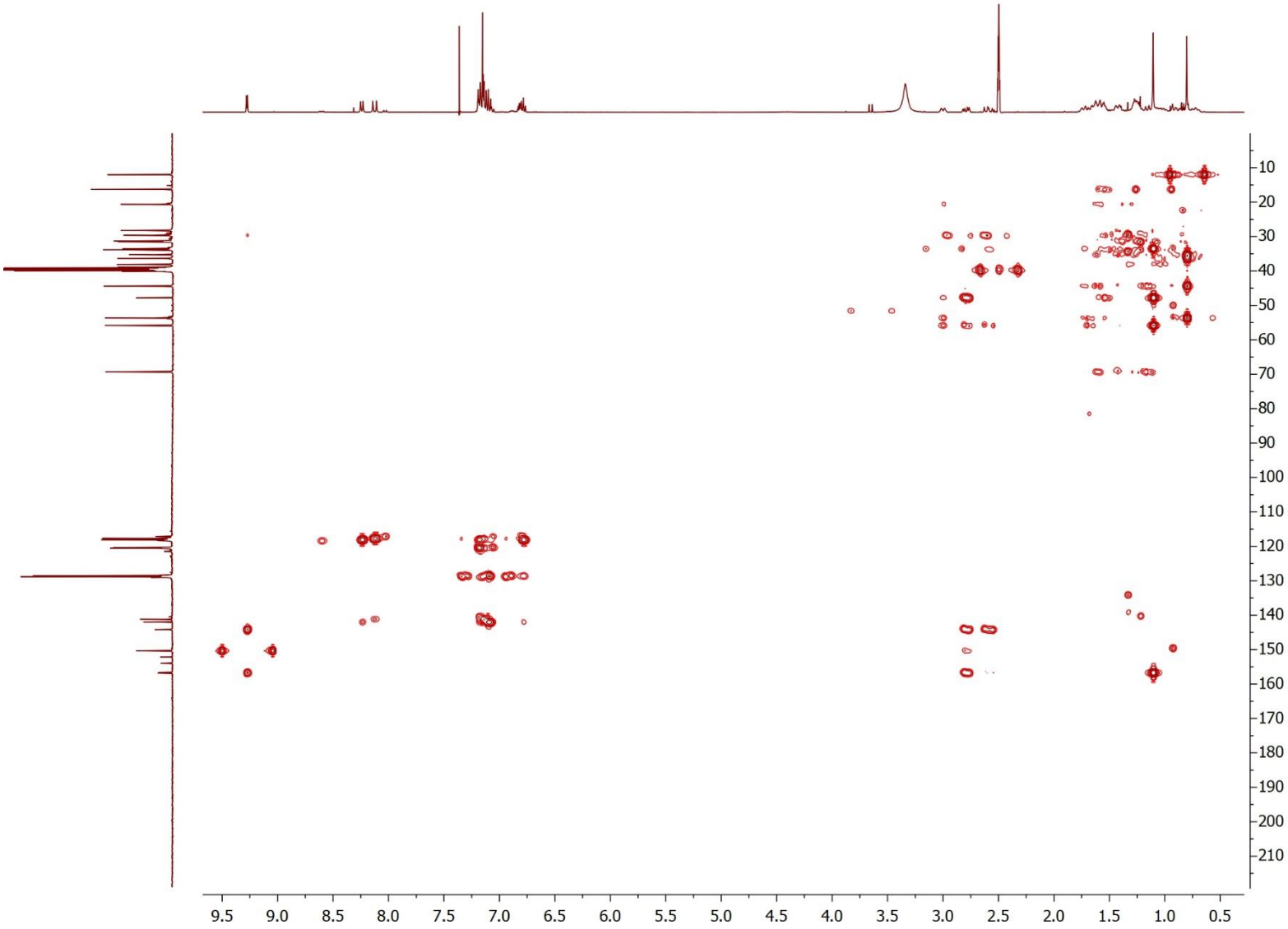
^{13}C NMR (101 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androst[16,17-d]pyridazine (22).



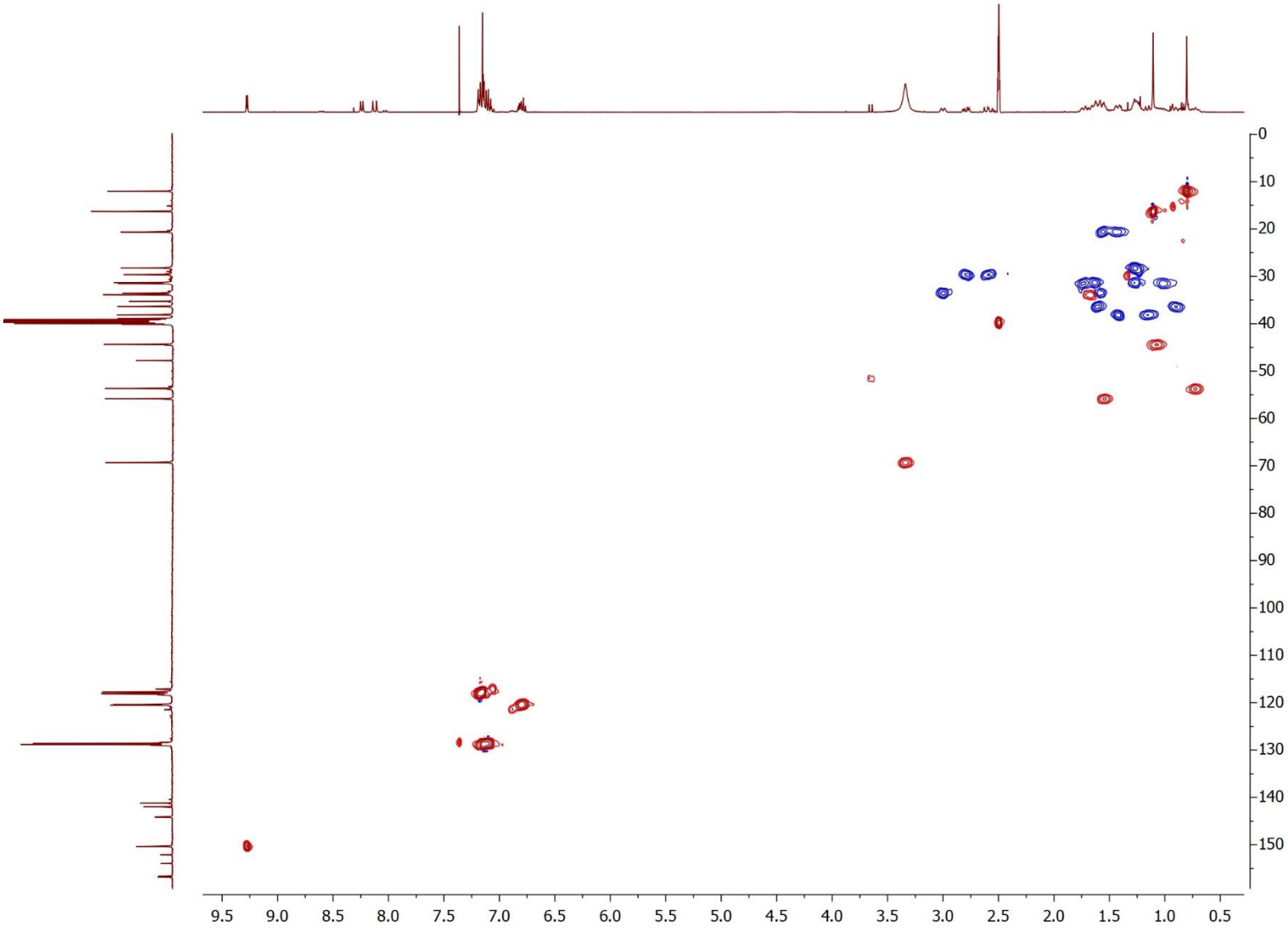
^{31}P NMR (162 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androst[16,17-d]pyridazine (22).



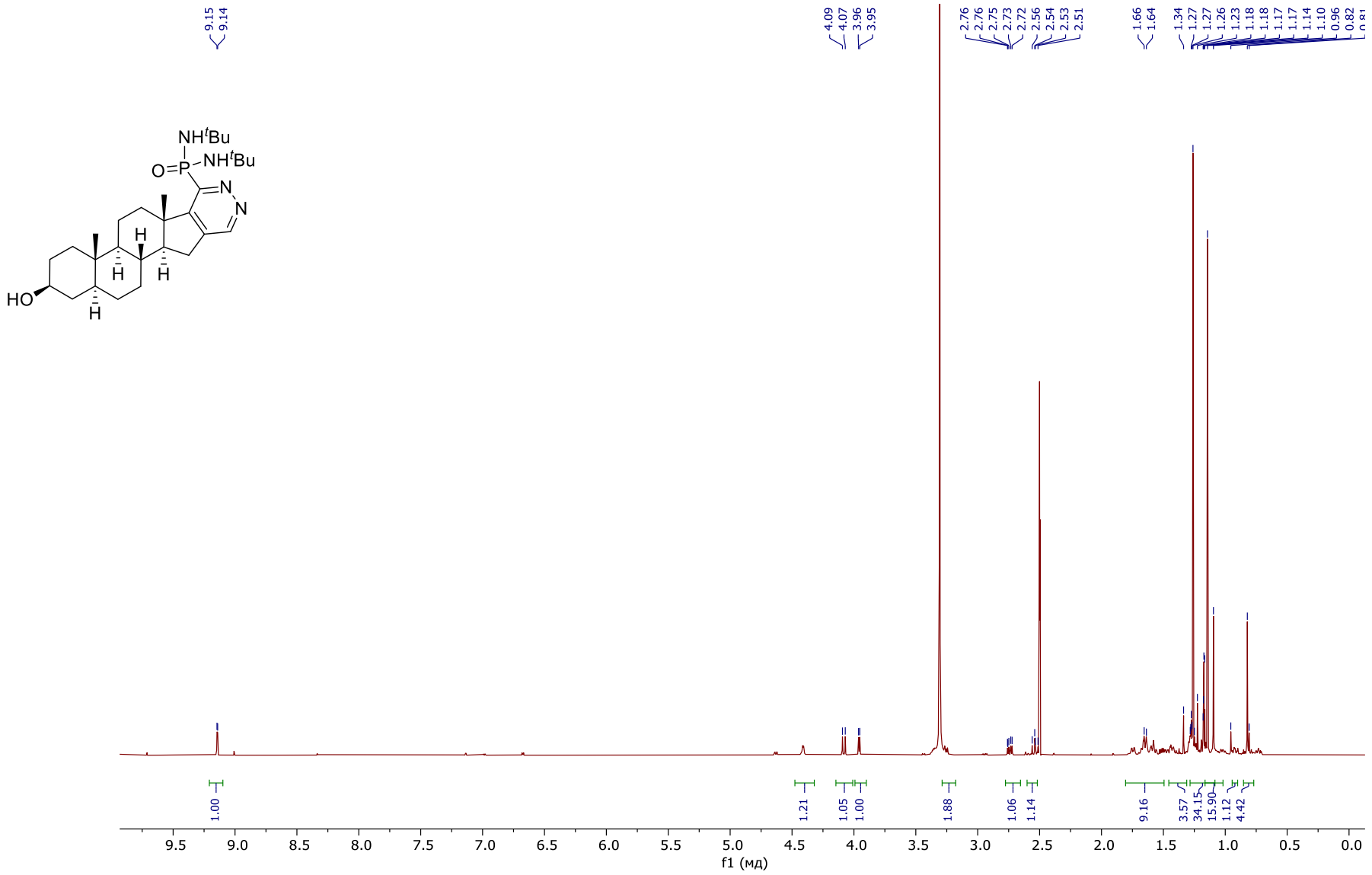
^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androst[16,17-d]pyridazine (22).



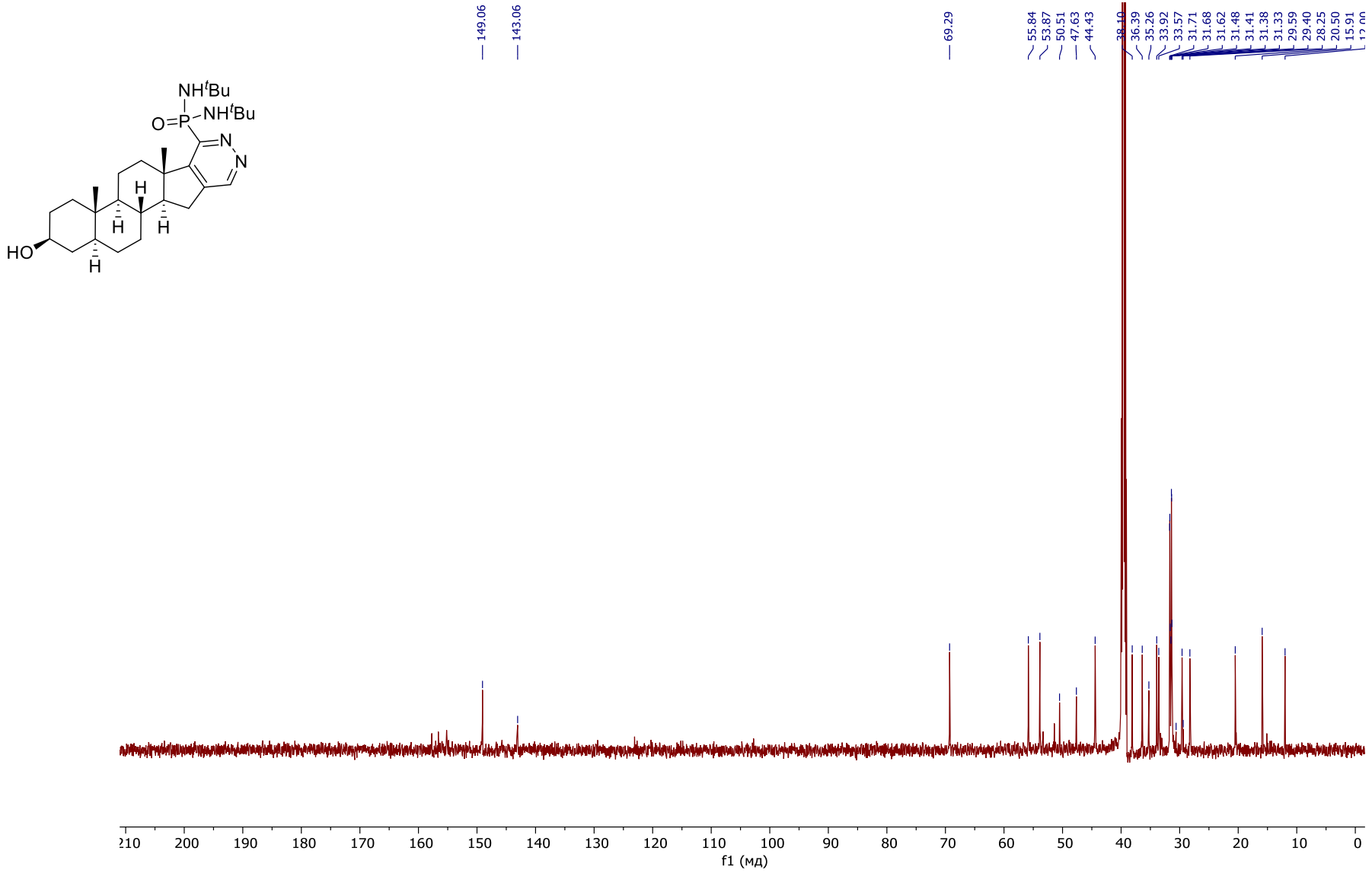
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androst[16,17-d]pyridazine (22).



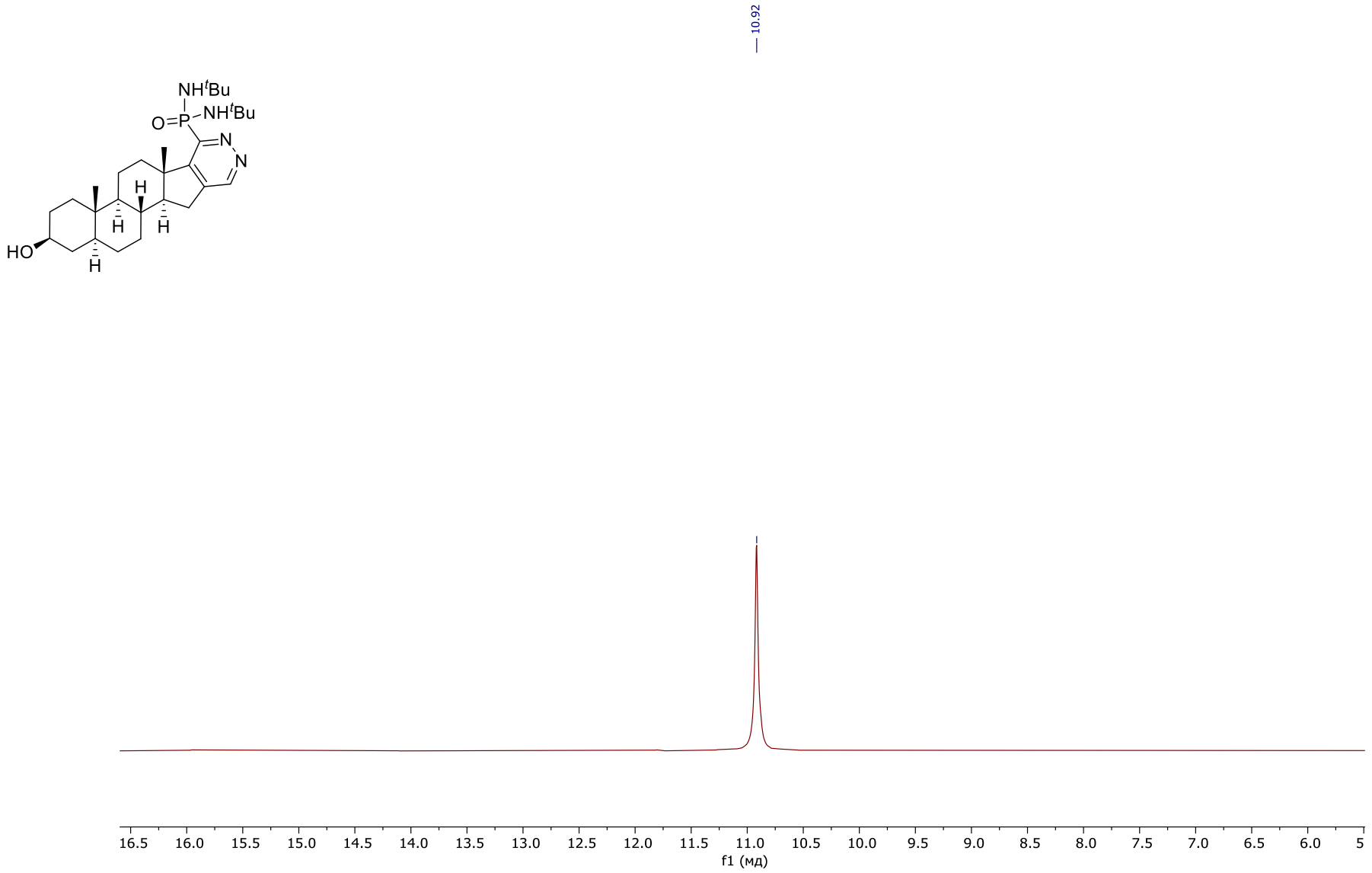
^{1}H NMR (600 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst[16,17-d]pyridazine (23).



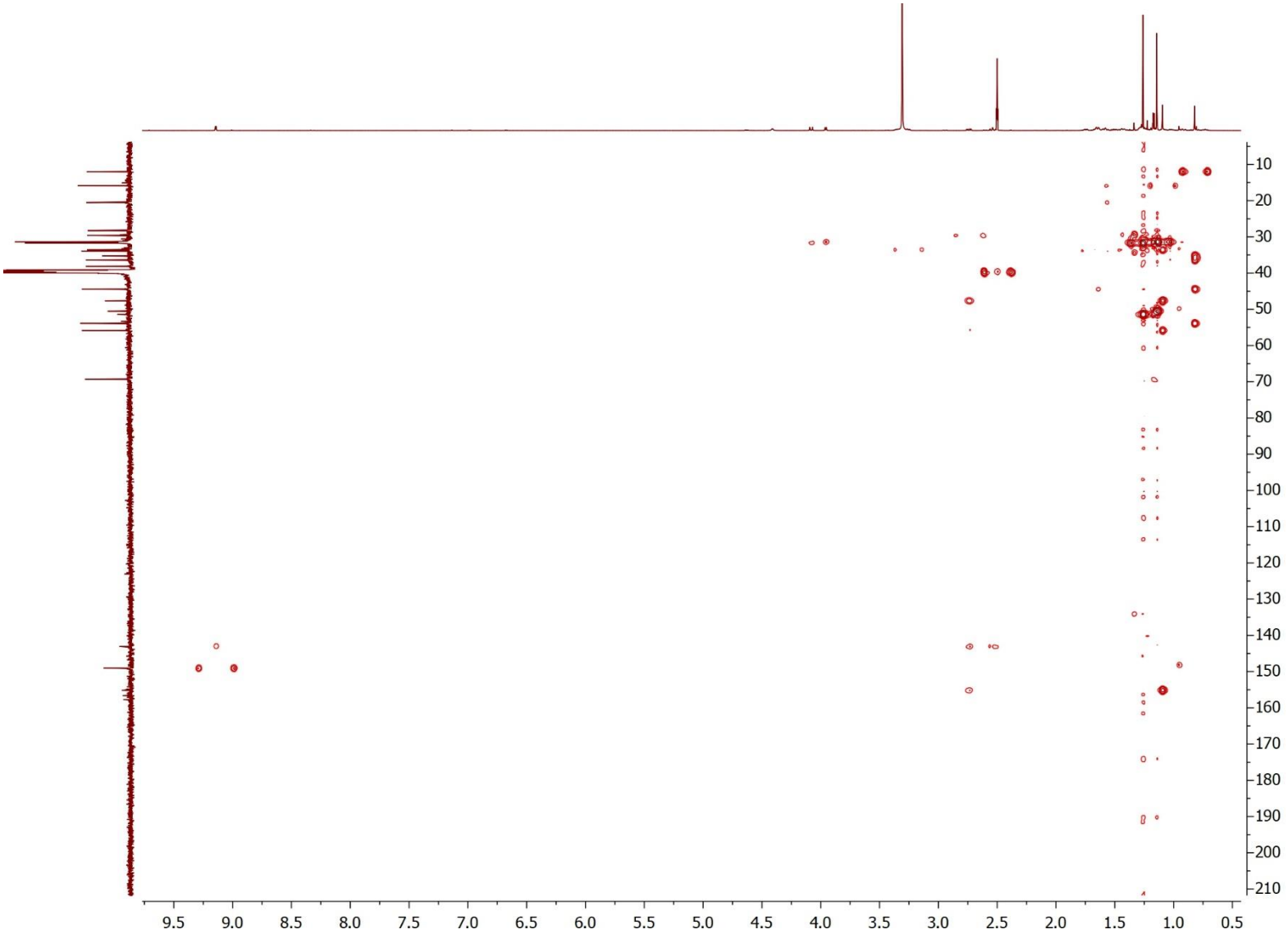
^{13}C NMR (150 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst[16,17-d]pyridazine (23).



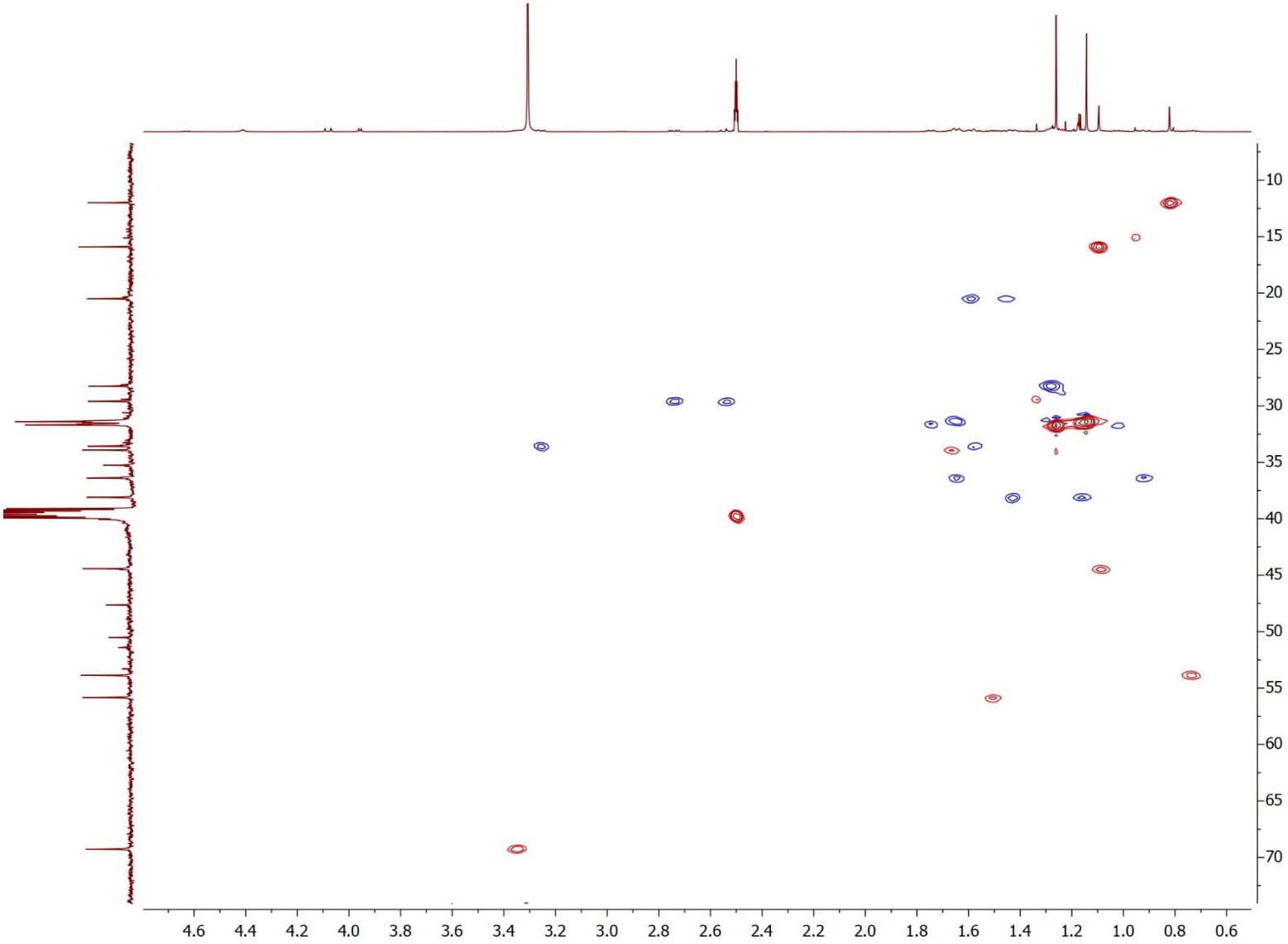
^{31}P NMR (243 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst[16,17-d]pyridazine (23).



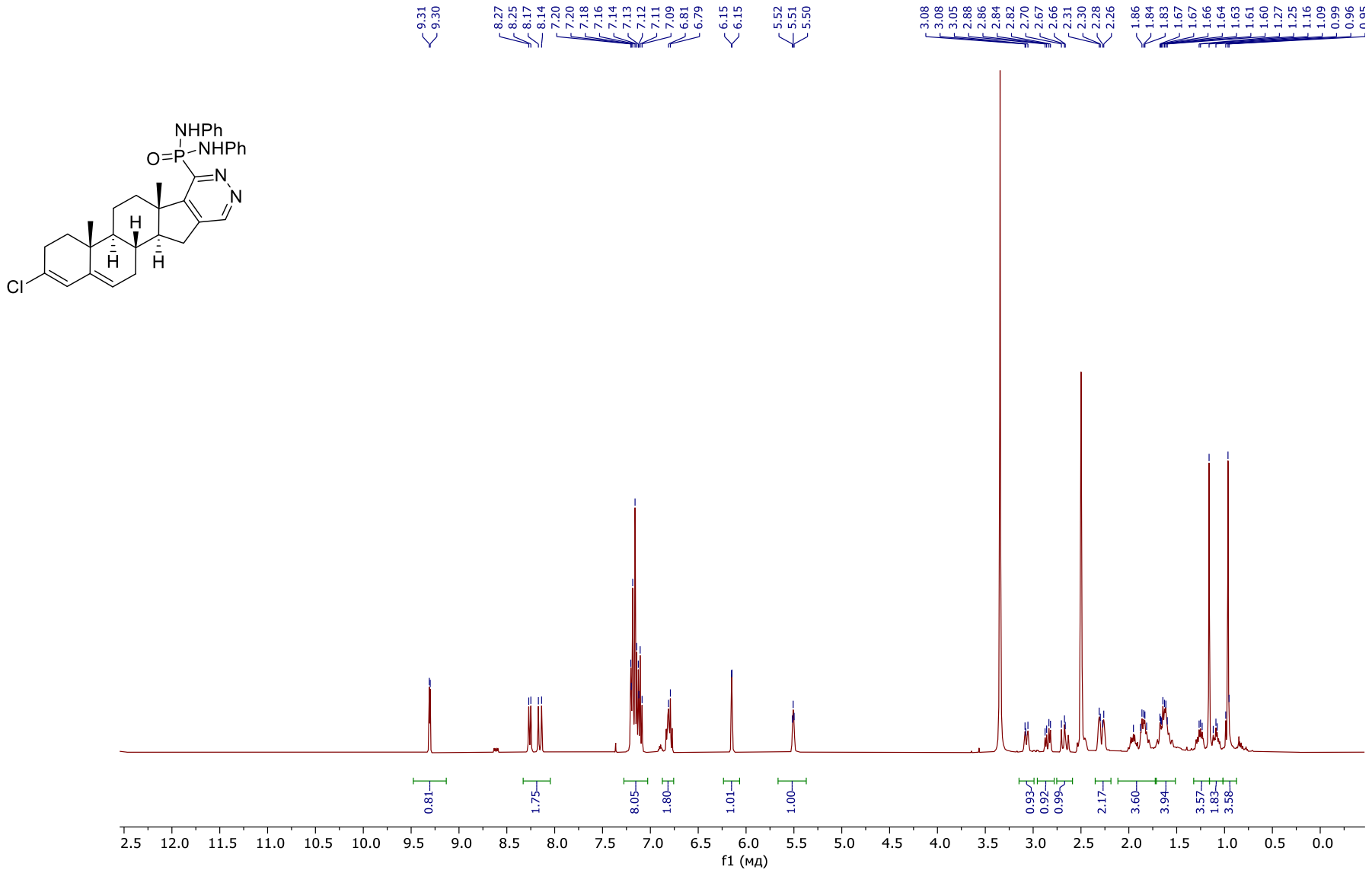
^{1}H-^{13}C HMBC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst[16,17-d]pyridazine (23).



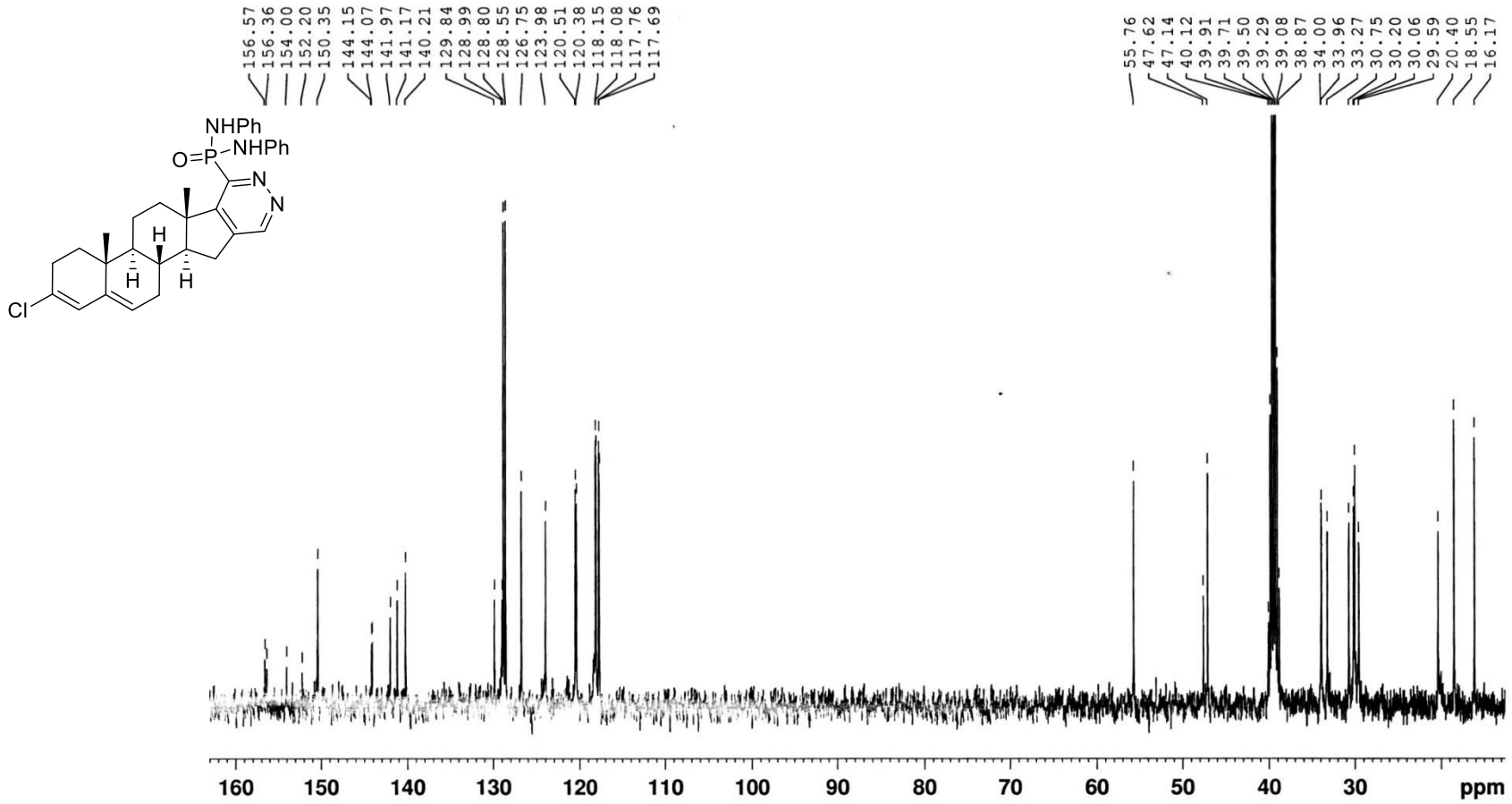
^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 3β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst[16,17-d]pyridazine (23).



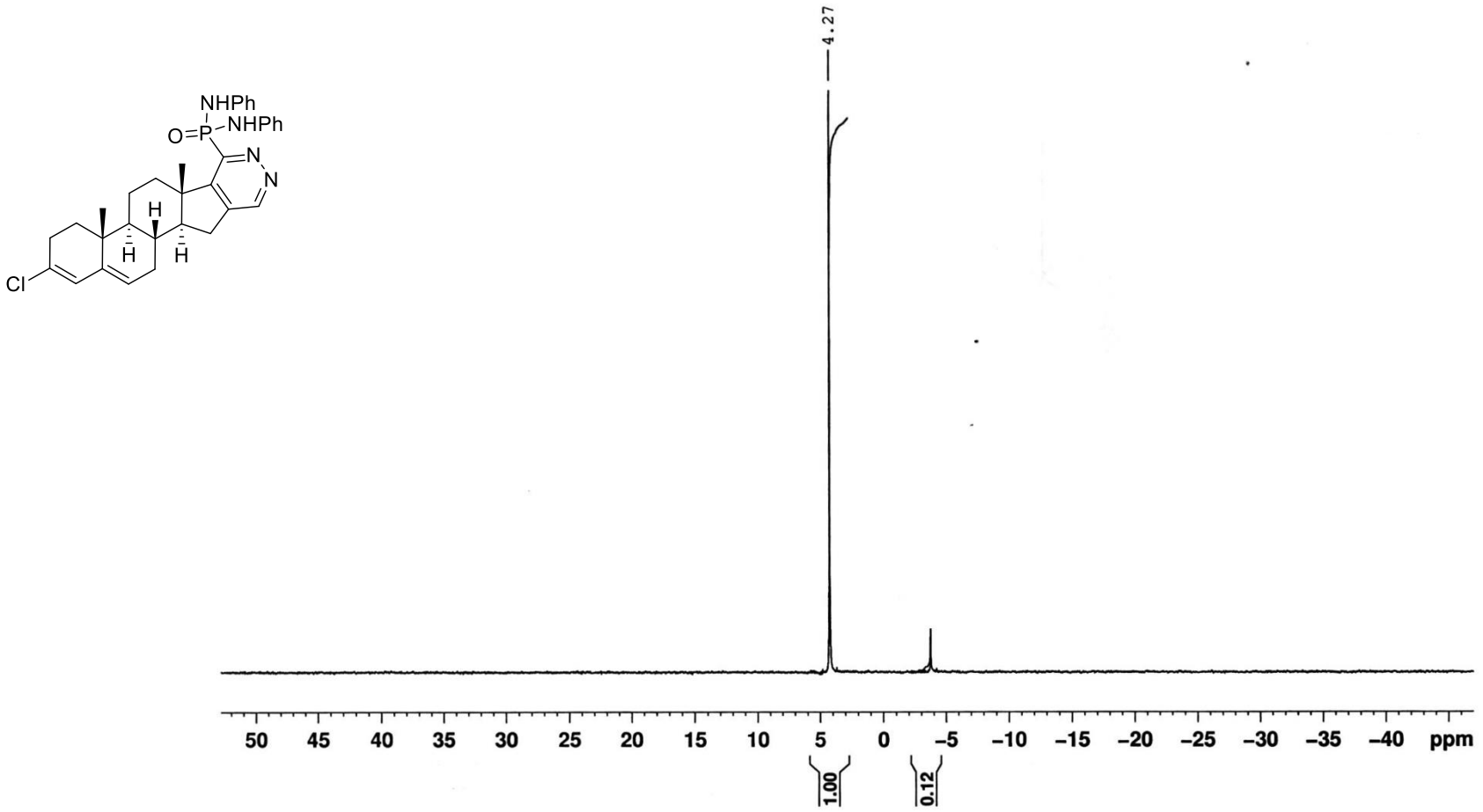
^{1}H NMR (400 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-diphenylphosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (26).



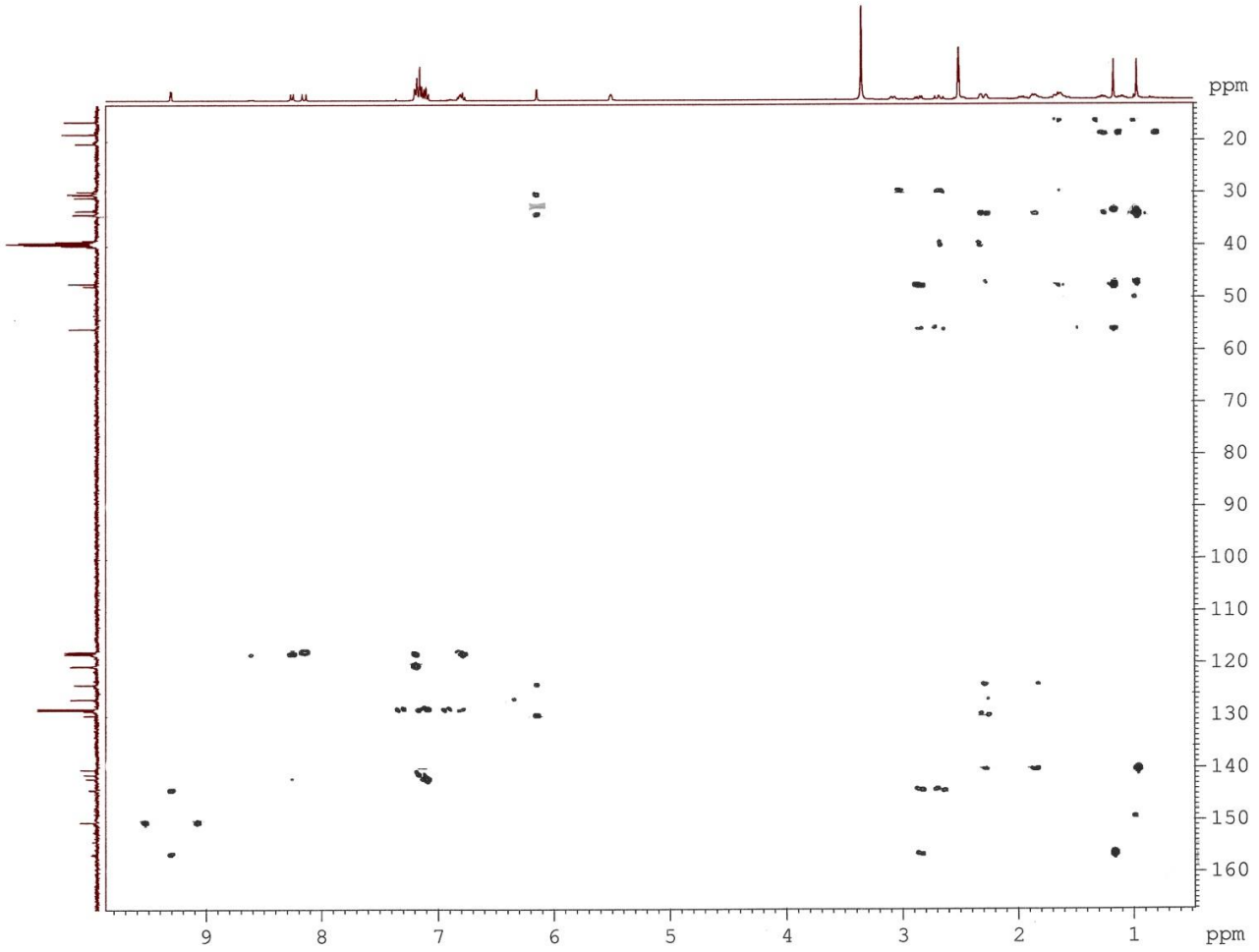
^{13}C NMR (101 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-diphenylphosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (26).



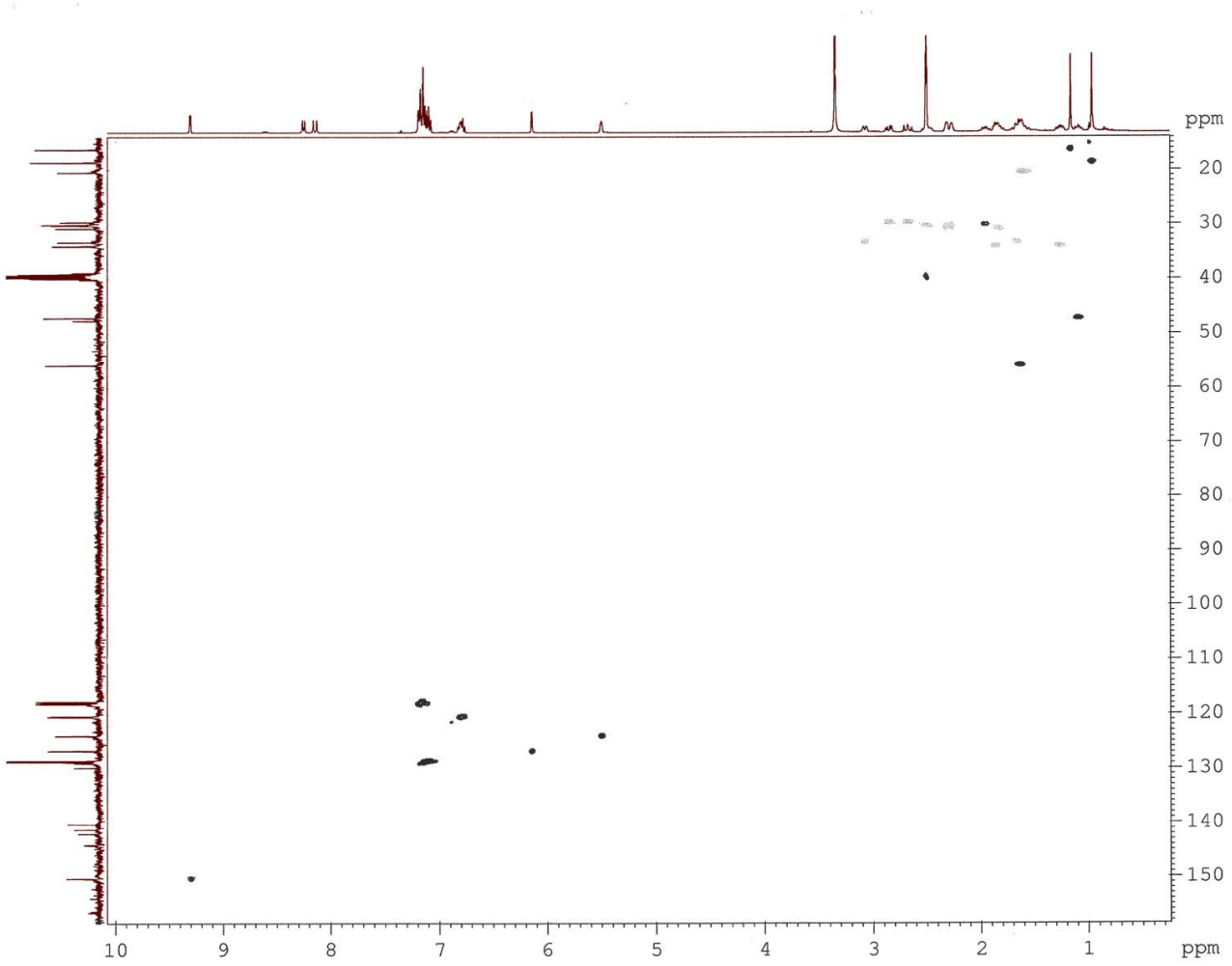
^{31}P NMR (162 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-diphenylphosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (26).



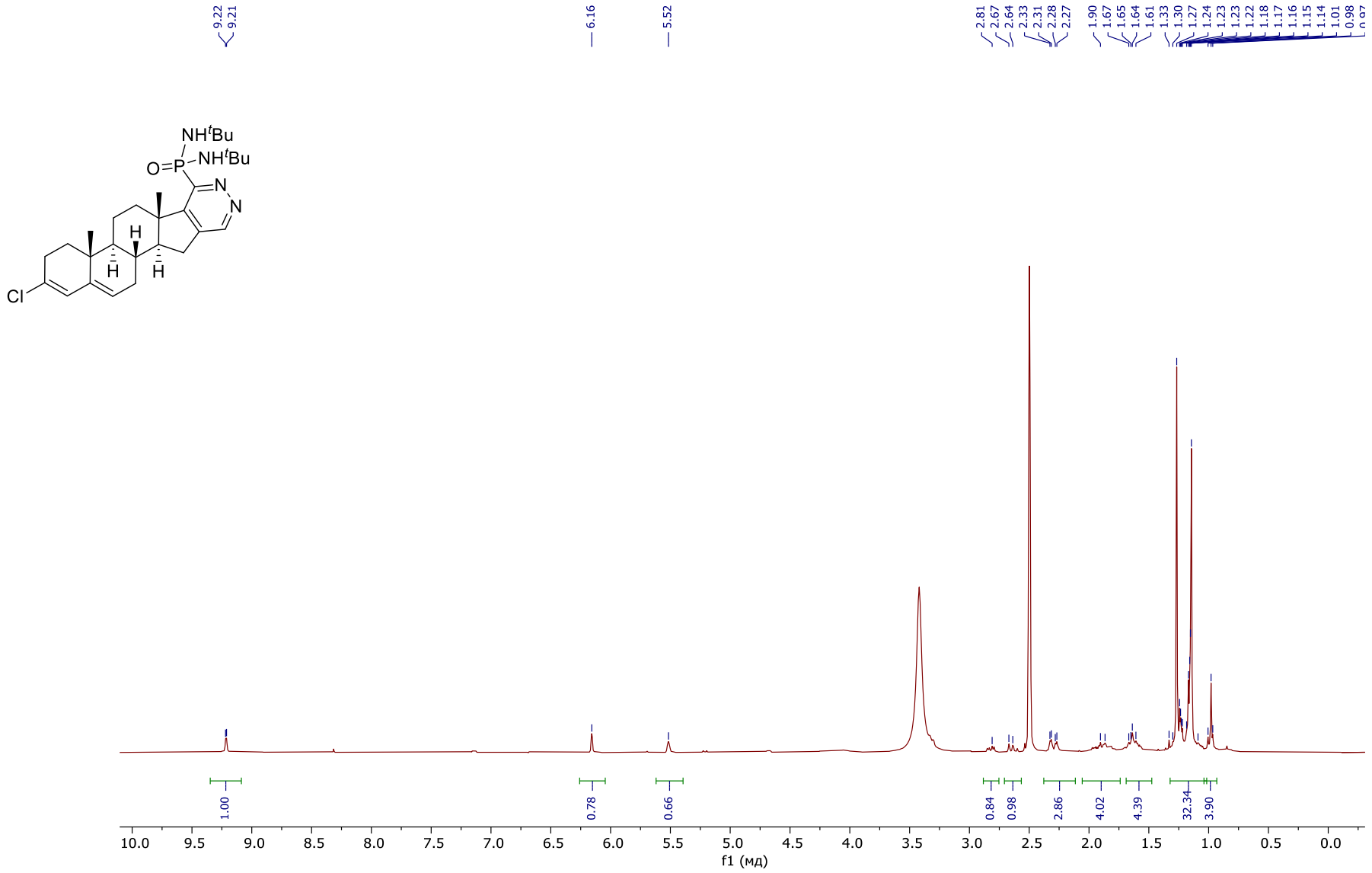
^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-diphenylphosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (26).



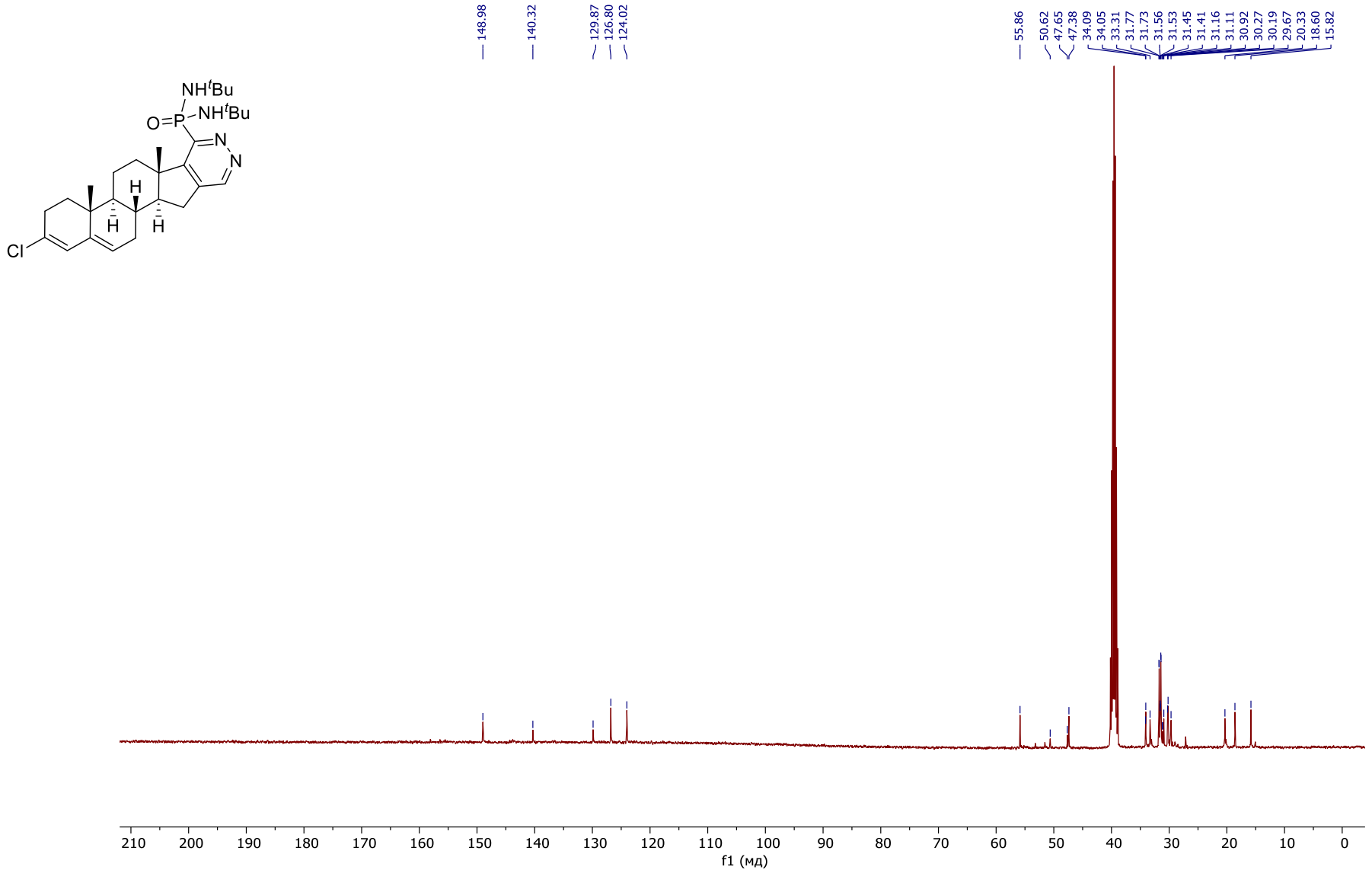
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-diphenylphosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (26).



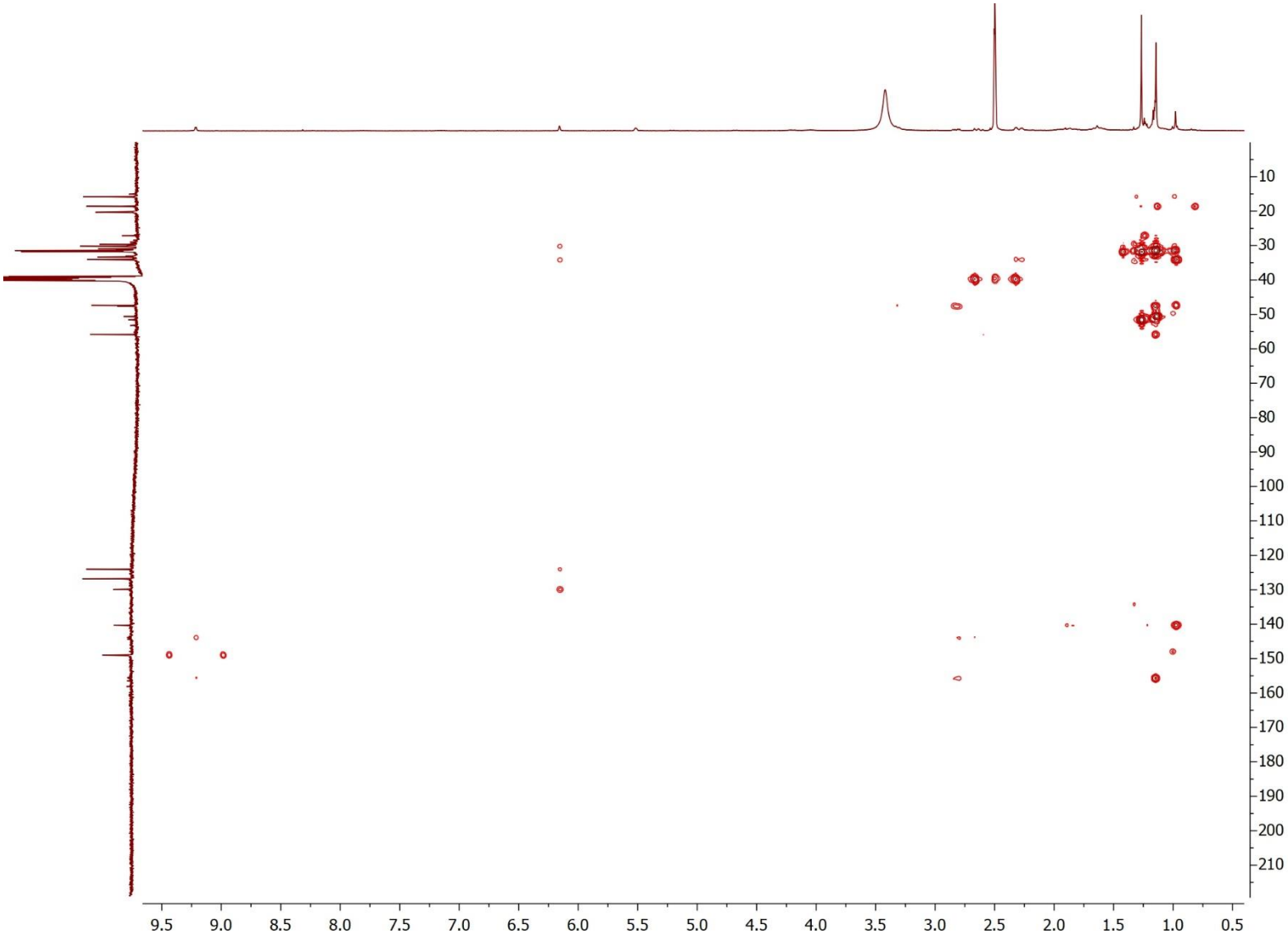
^{1}H NMR (400 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (27).



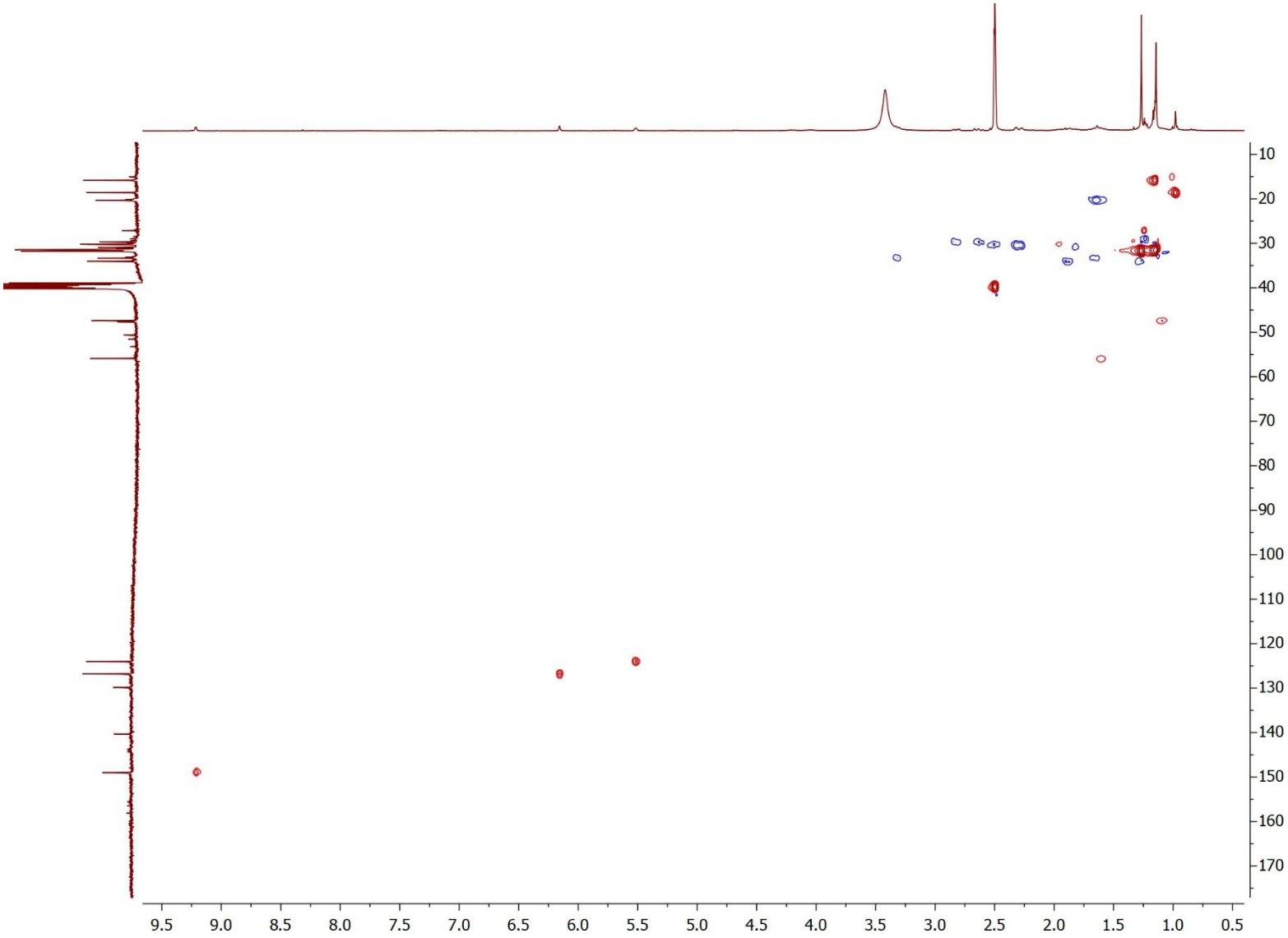
^{13}C NMR (101 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (27).



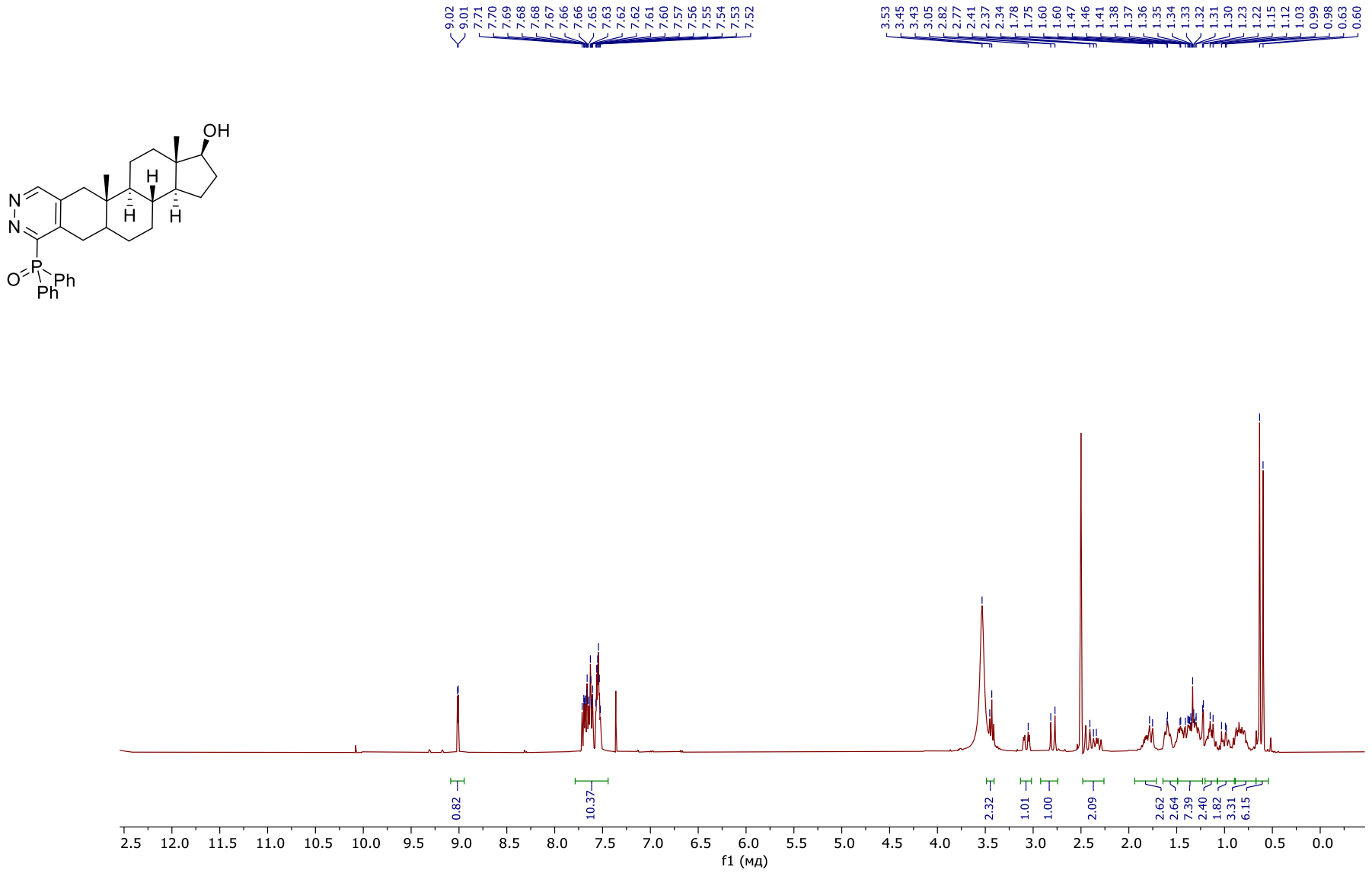
^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (27).



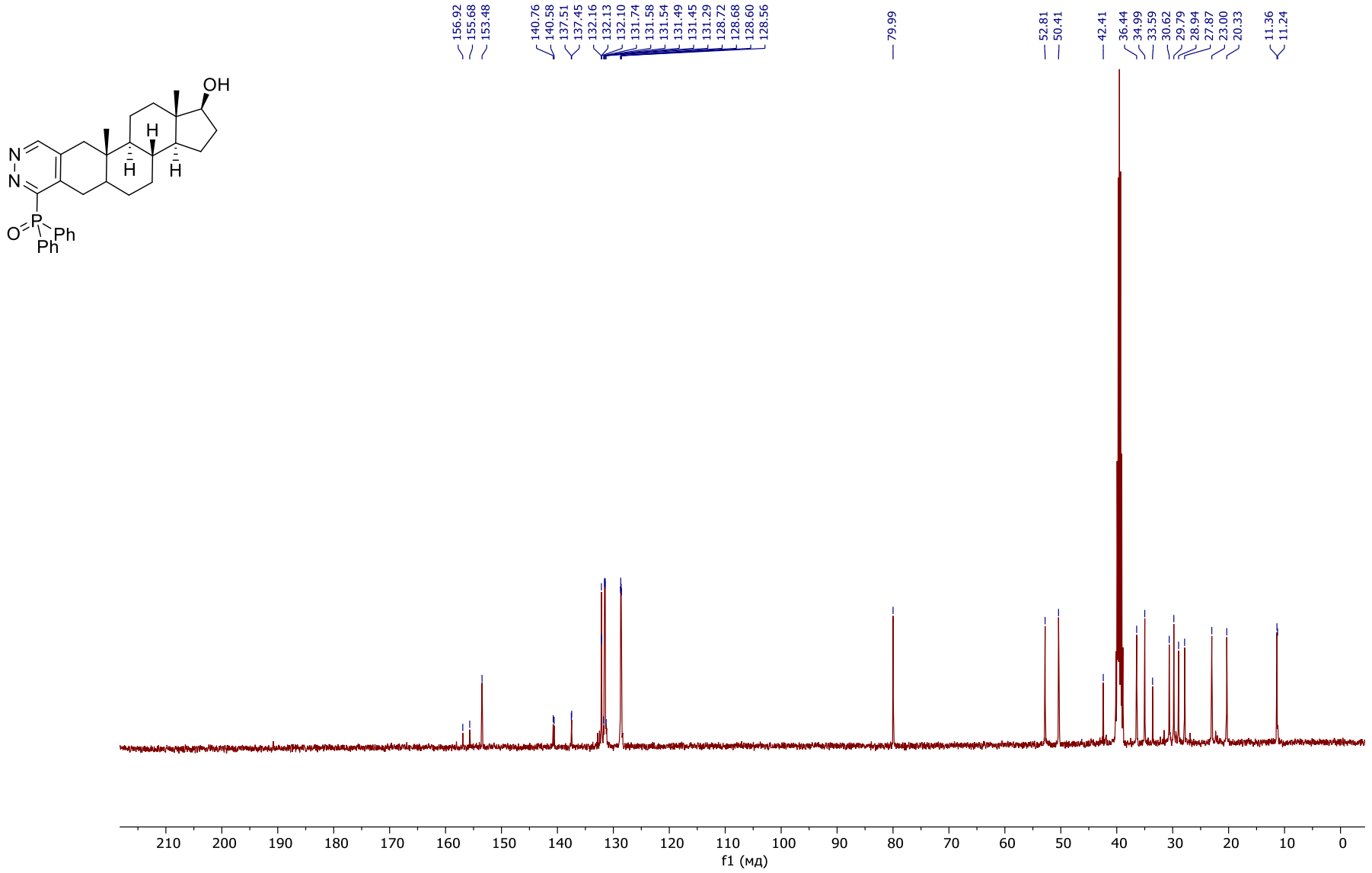
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 3-chloro-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (27).



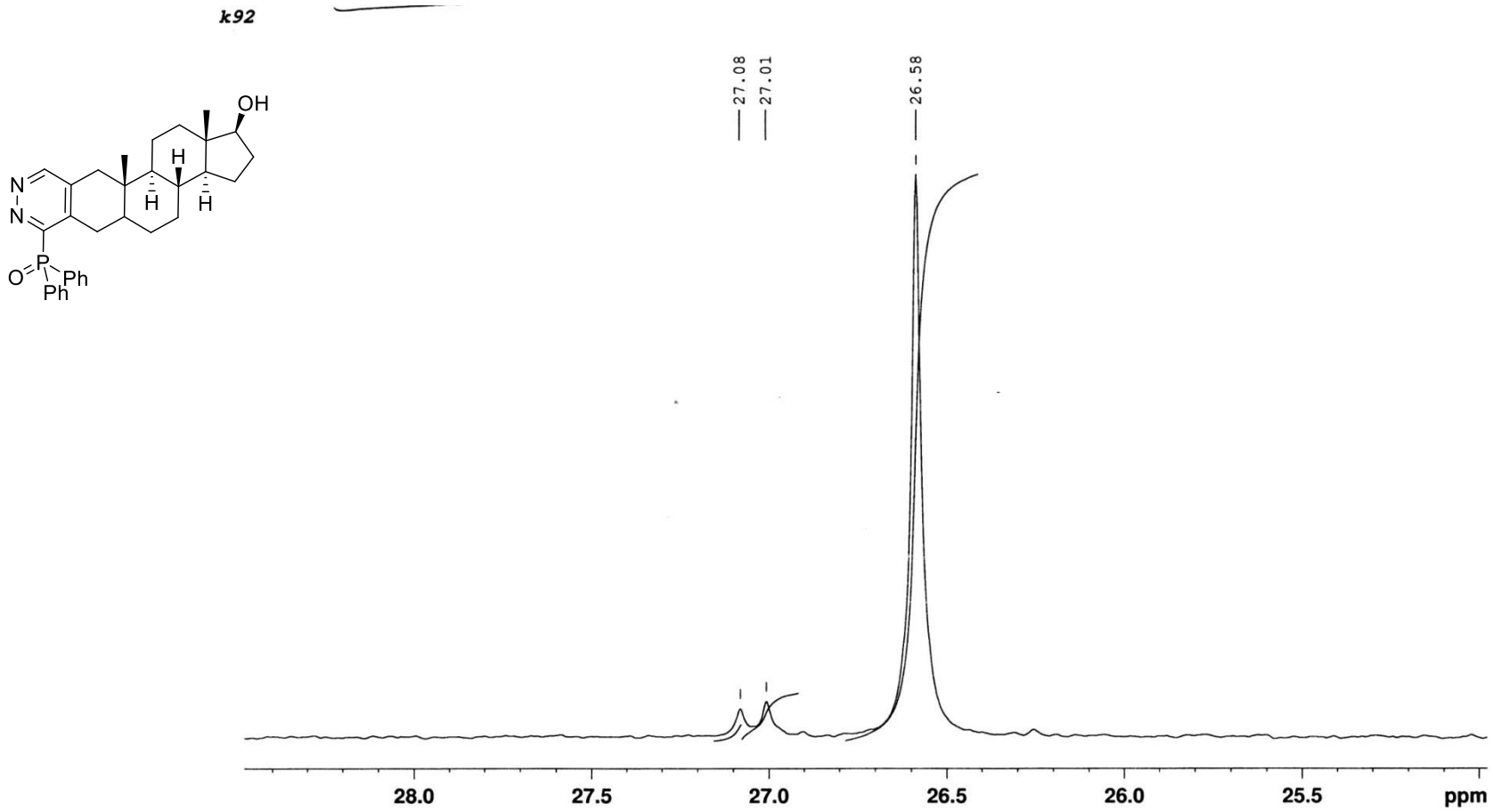
^{1}H NMR (400 MHz, DMSO-d_6) of (17β-hydroxy-5α-androst[3,2-d]pyridazine-1'-yl)diphenylphosphine oxide (30).



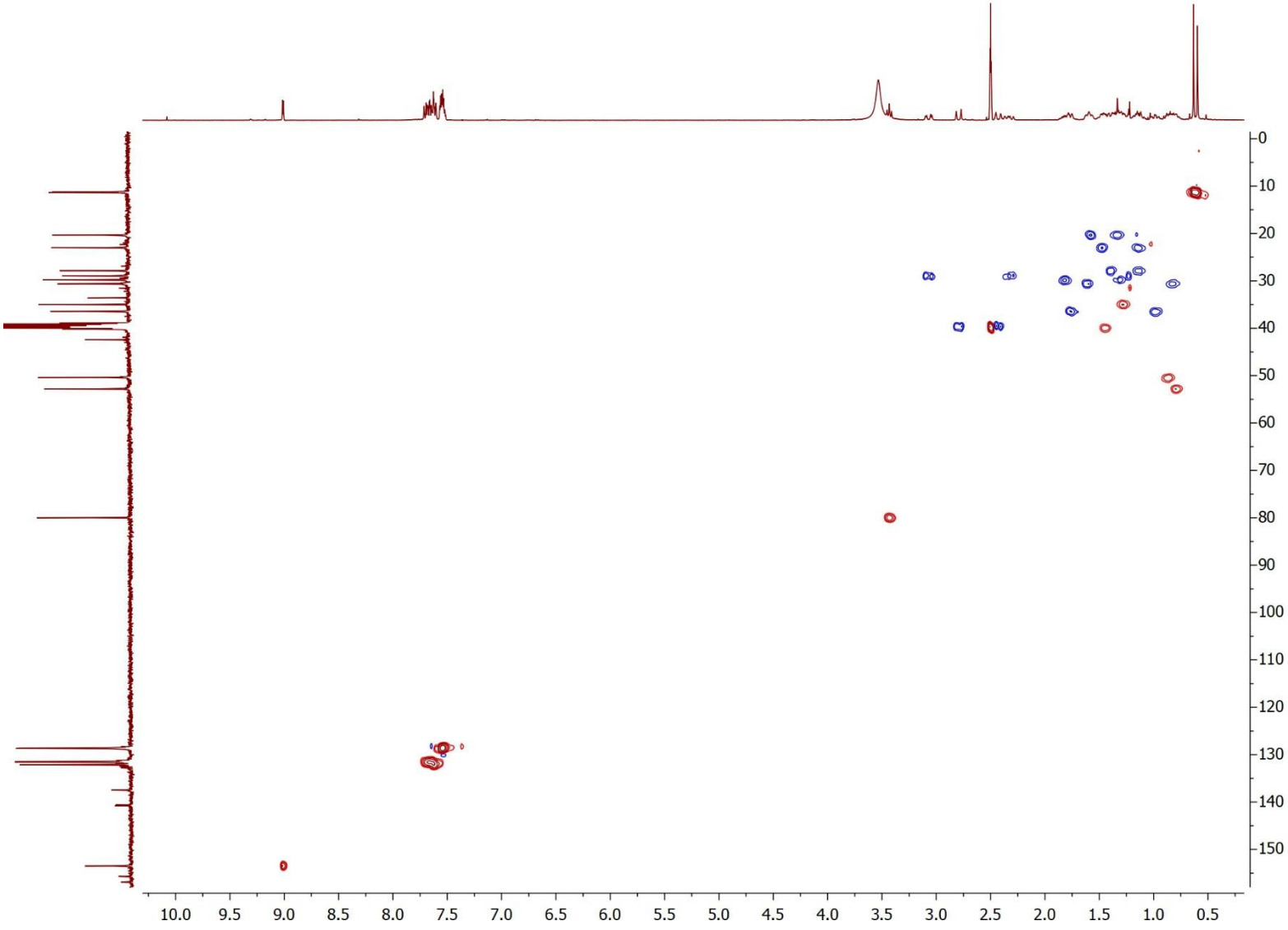
^{13}C NMR (101 MHz, DMSO-d_6) of (17β-hydroxy-5α-androst[3,2-d]pyridazine-1'-yl)diphenylphosphine oxide (30).



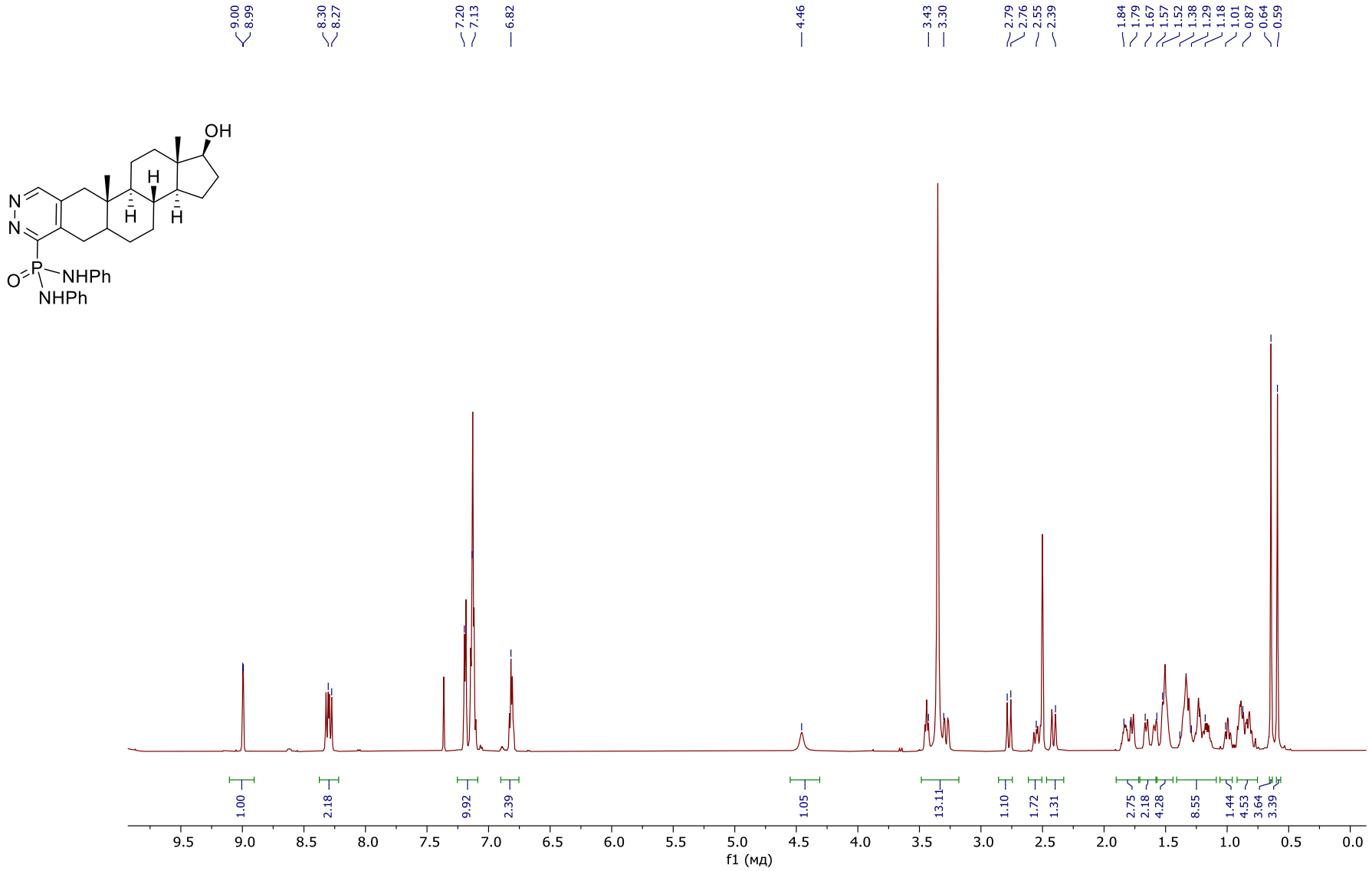
^{31}P NMR (162 MHz, DMSO-d_6) of (17β-hydroxy-5α-androst[3,2-d]pyridazine-1'-yl)diphenylphosphine oxide (30).



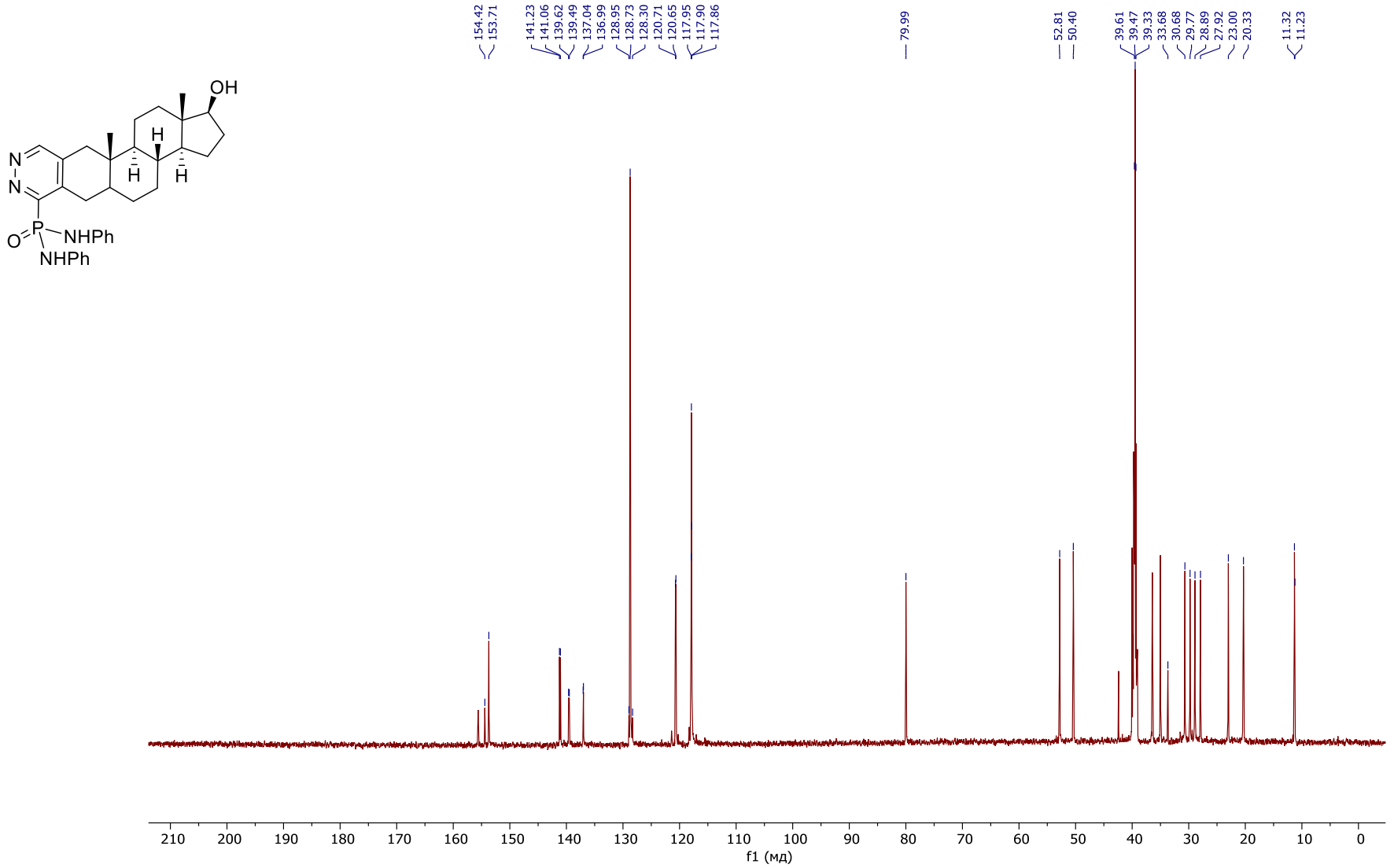
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of (17β-hydroxy-5α-androst[3,2-d]pyridazine-1'-yl)diphenylphosphine oxide (30).



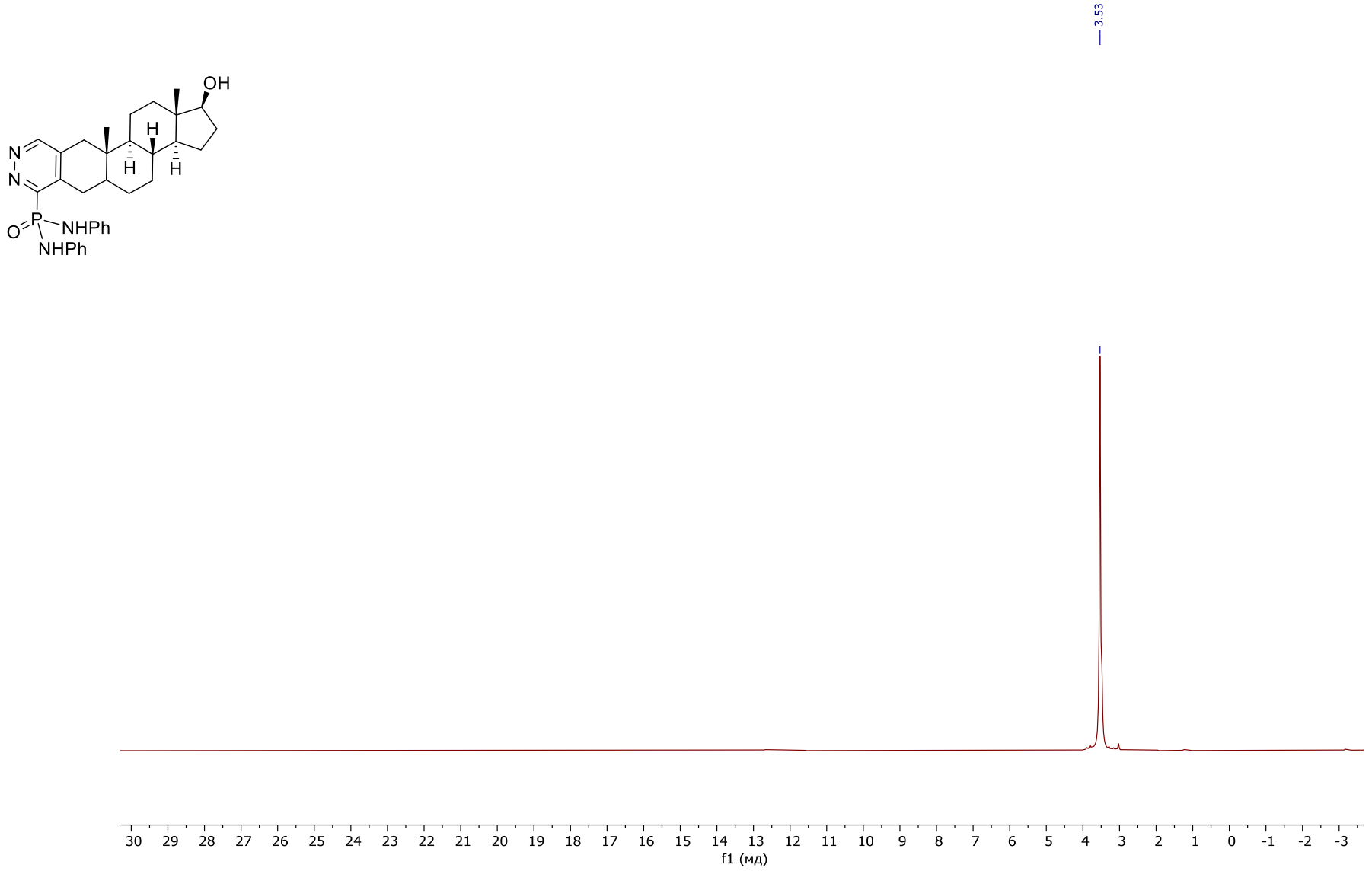
^{1}H NMR (600 MHz, DMSO-*d*$_6$) of 17β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5α-androst[3,2-d]pyridazine (31).



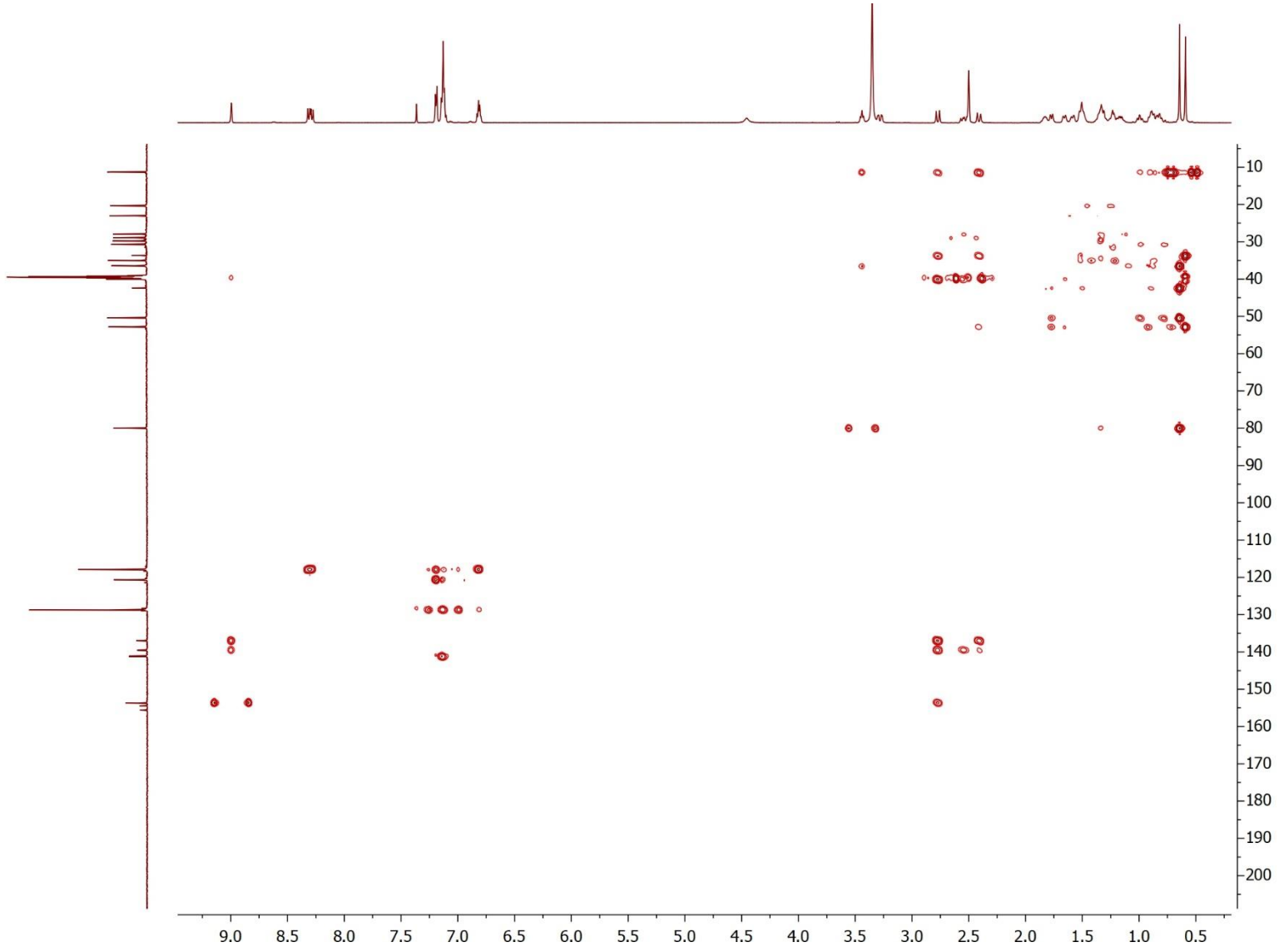
^{13}C NMR (150 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5α-androst[3,2-d]pyridazine (31).



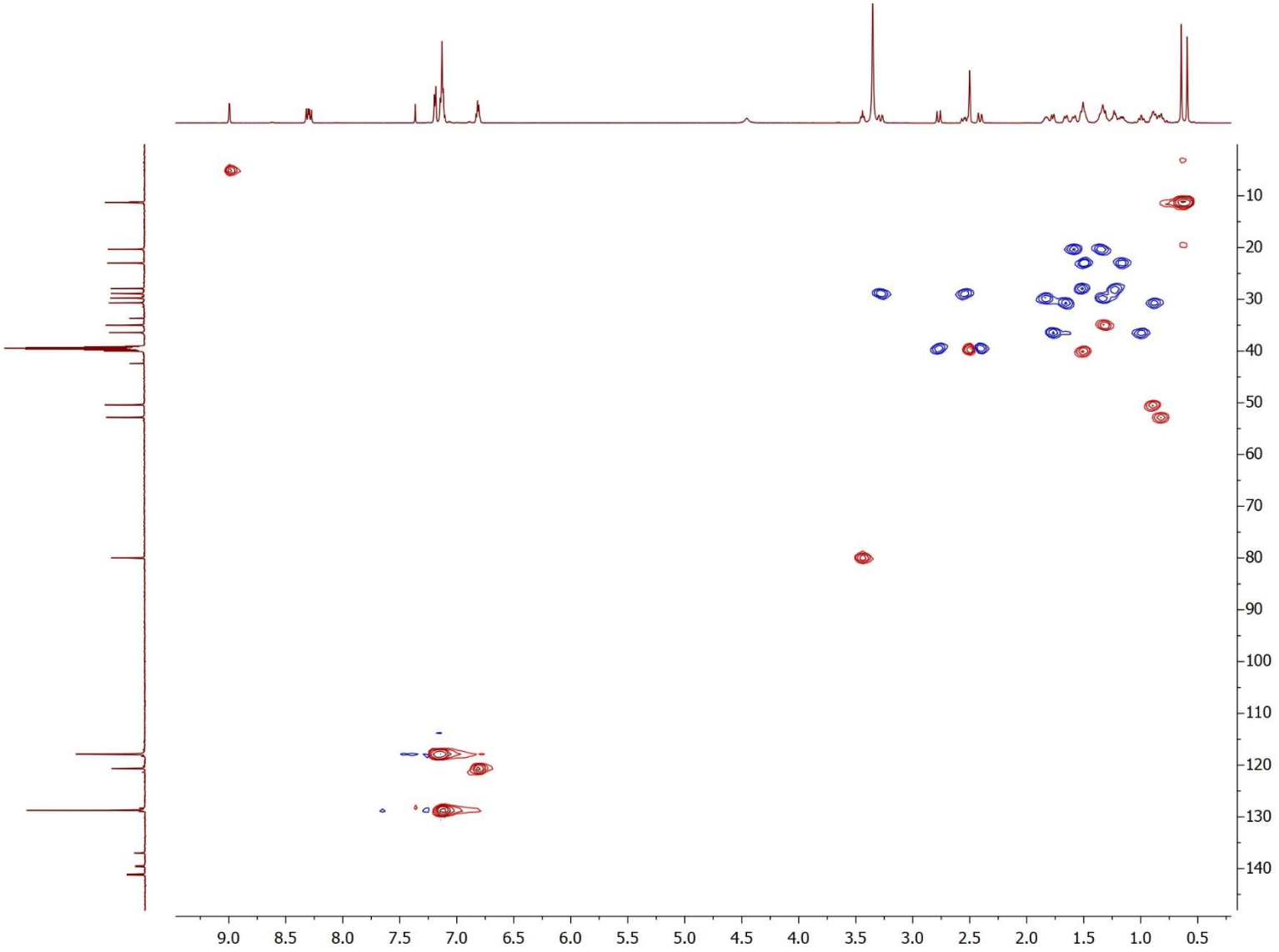
^{31}P NMR (243 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5α-androst[3,2-d]pyridazine (31).



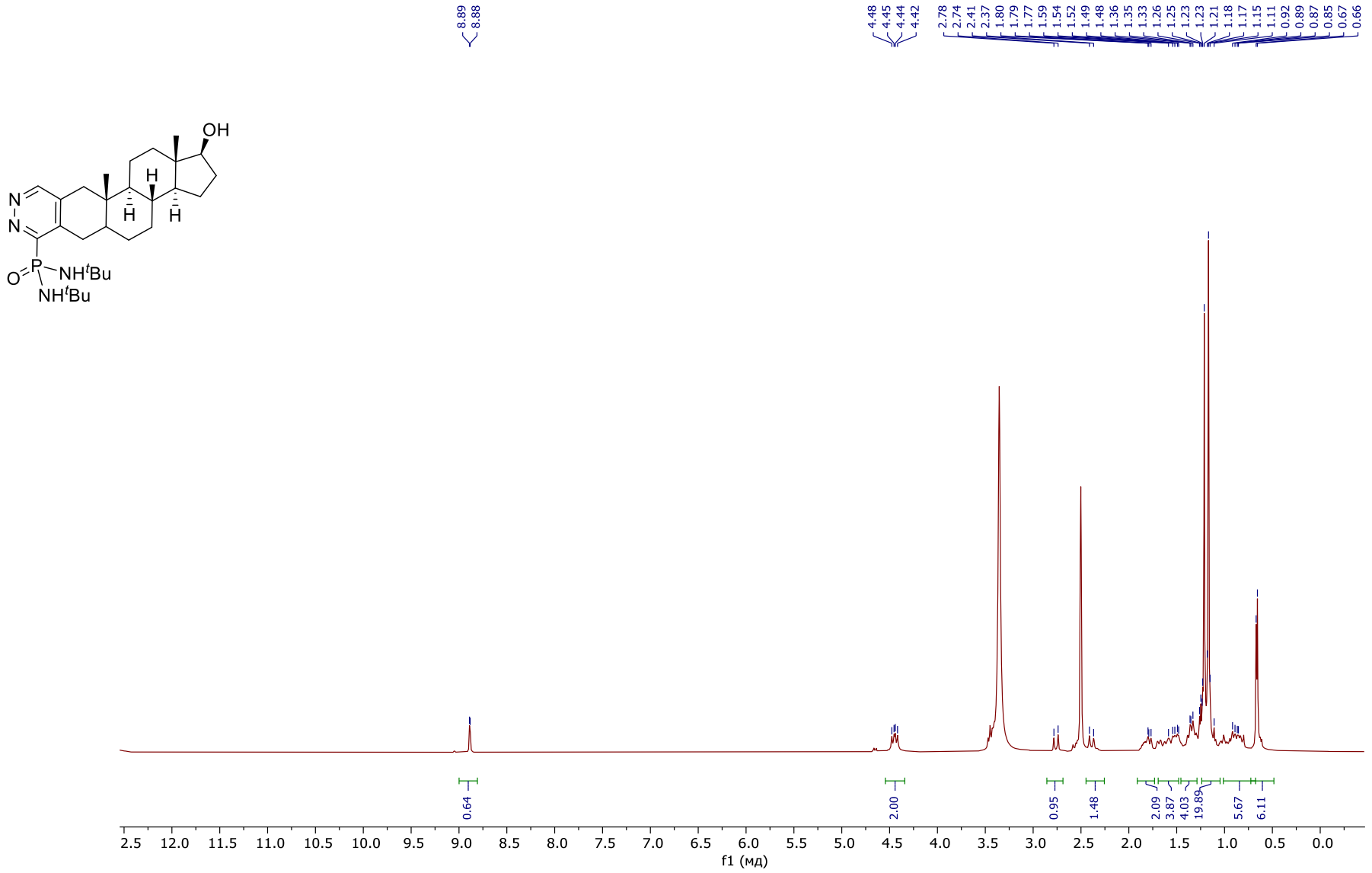
^{1}H-^{13}C HMBC NMR (600 MHz, 150 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5α-androst[3,2-d]pyridazine (31).



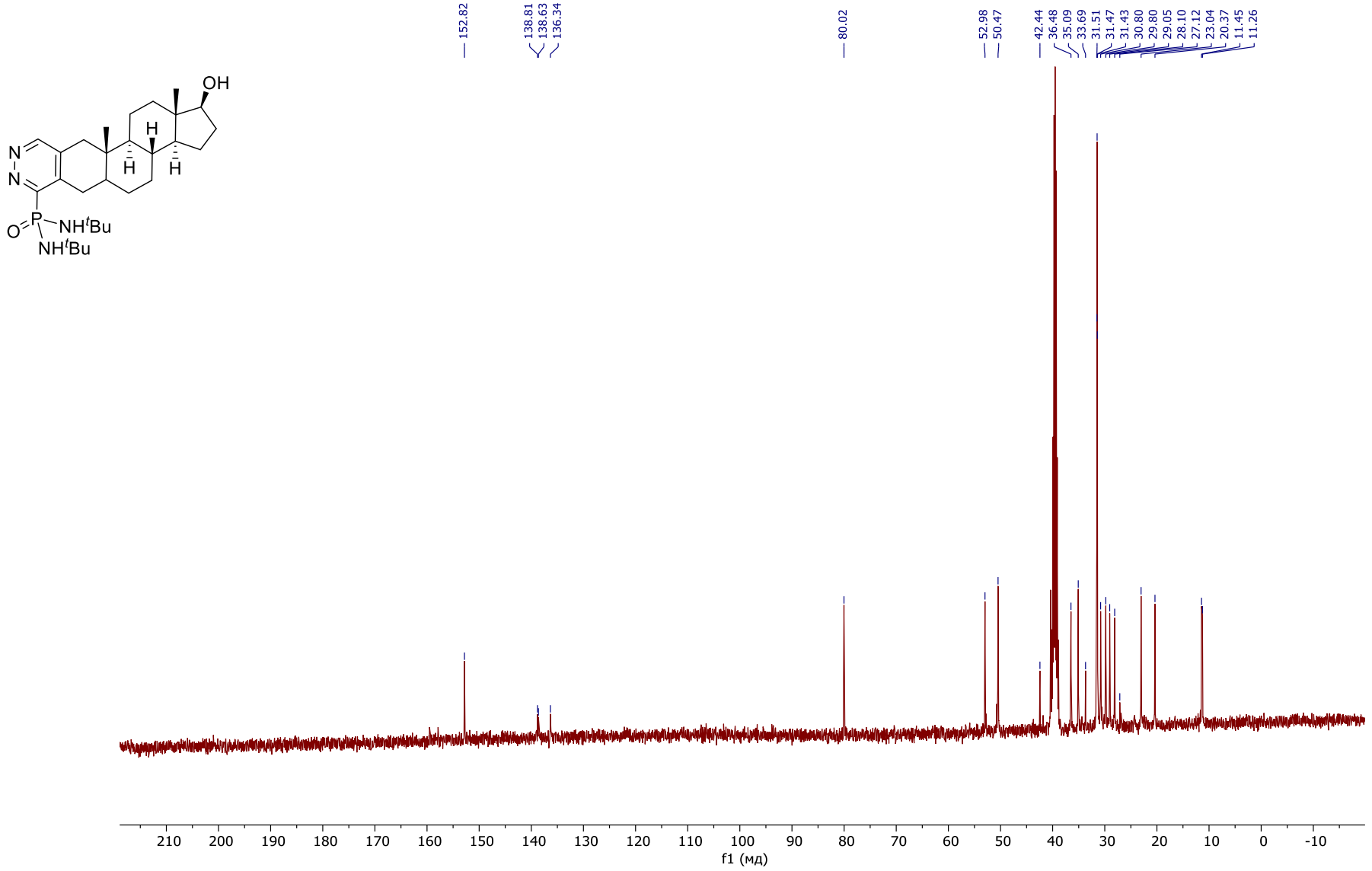
^{1}H-^{13}C HSQC NMR (600 MHz, 150 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5α-androst[3,2-d]pyridazine (31).



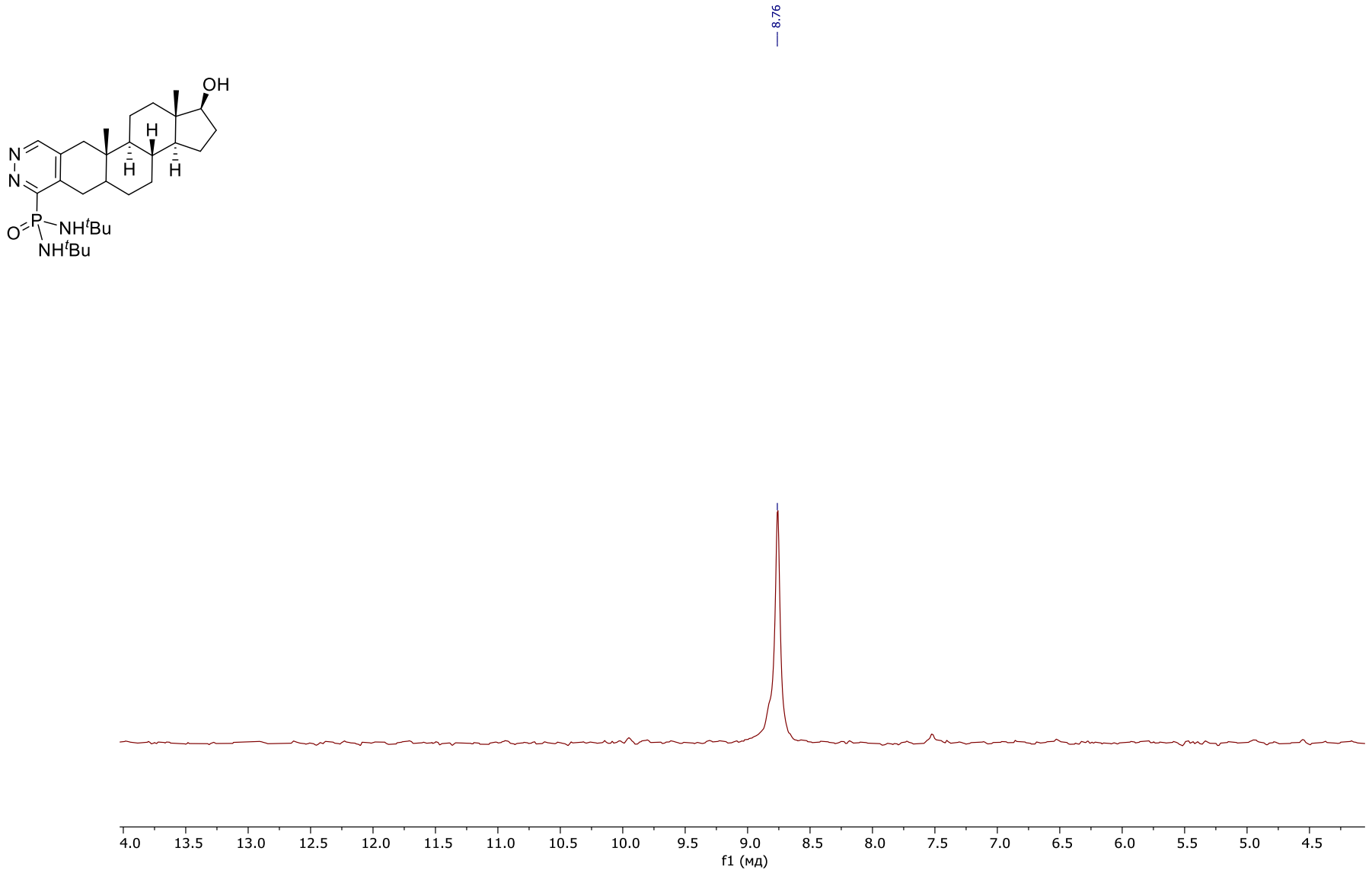
^{1}H NMR (400 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5α-androst[3,2-d]pyridazine (32).



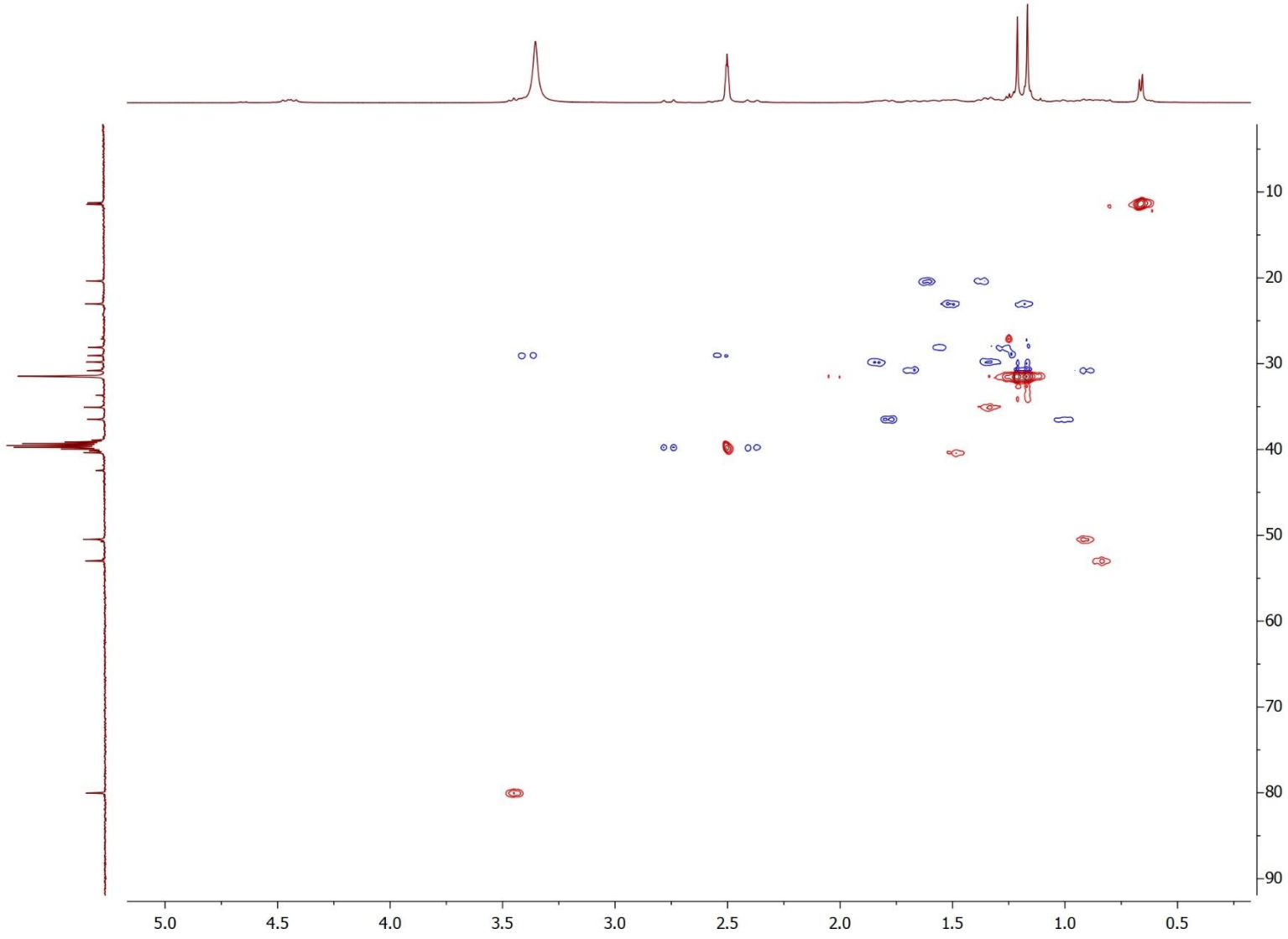
^{13}C NMR (101 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5α-androst[3,2-d]pyridazine (32).



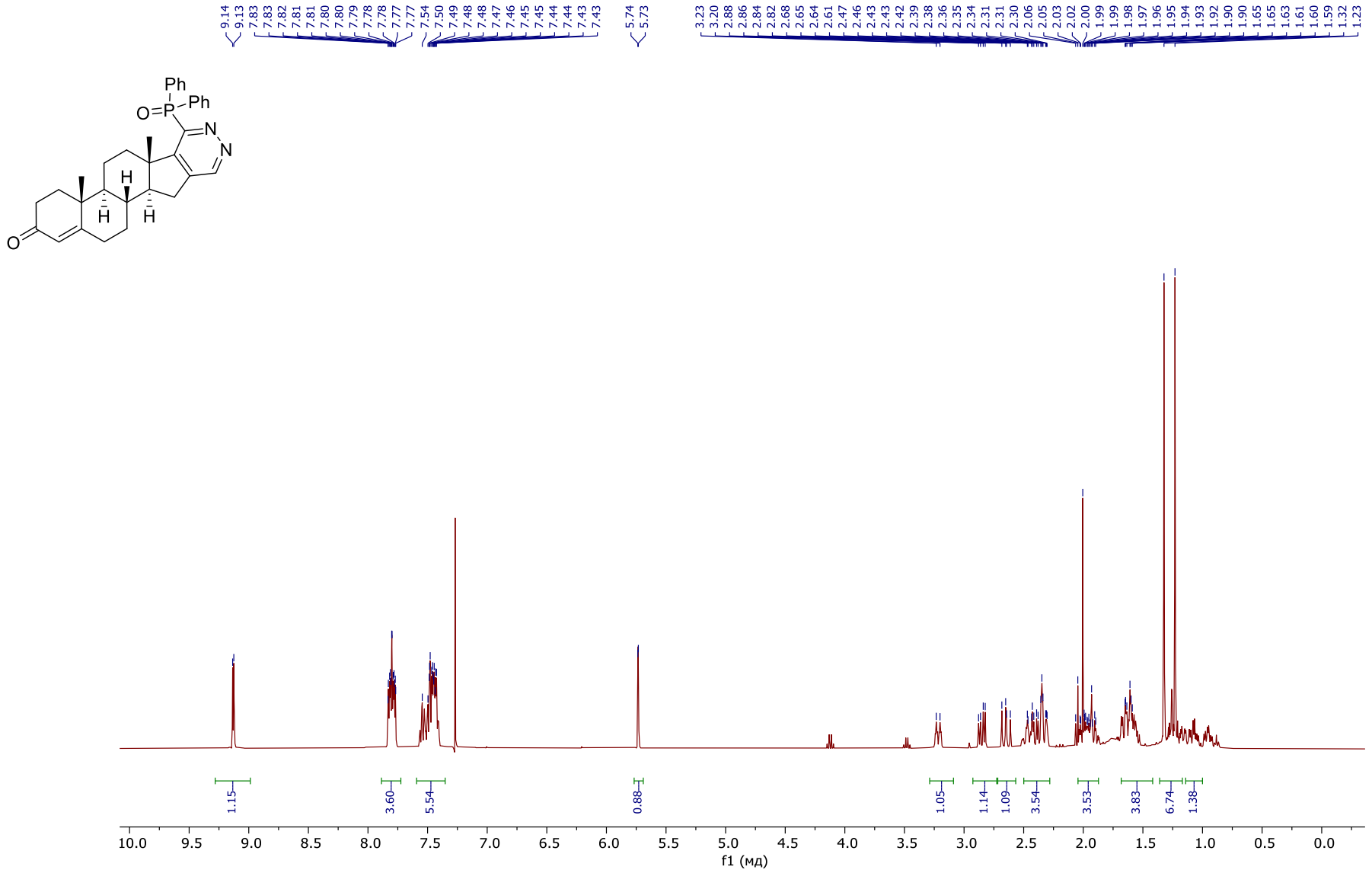
^{31}P NMR (162 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5α-androst[3,2-d]pyridazine (32).



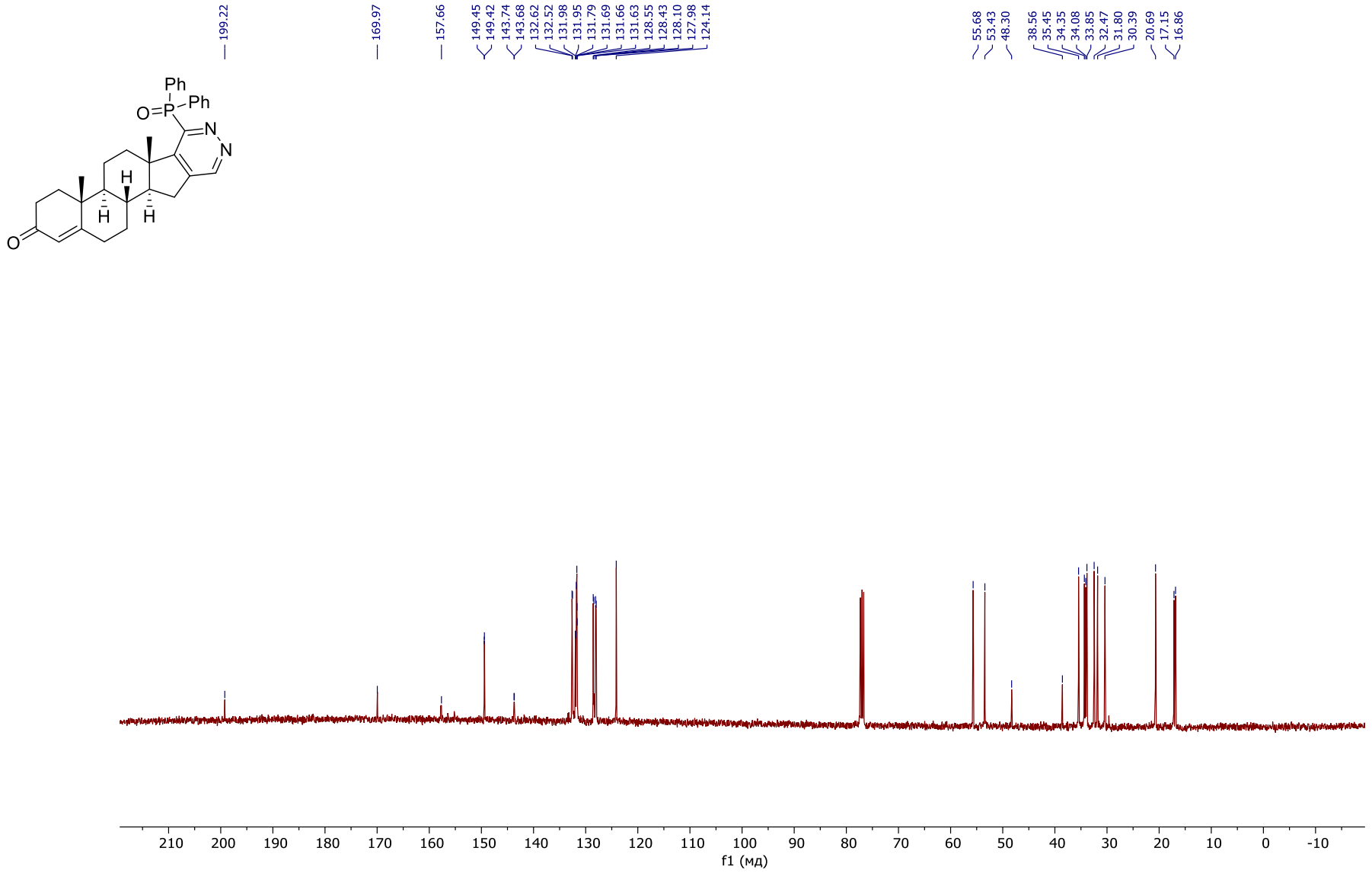
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, DMSO-d_6) of 17β-hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5α-androst[3,2-d]pyridazine (32).



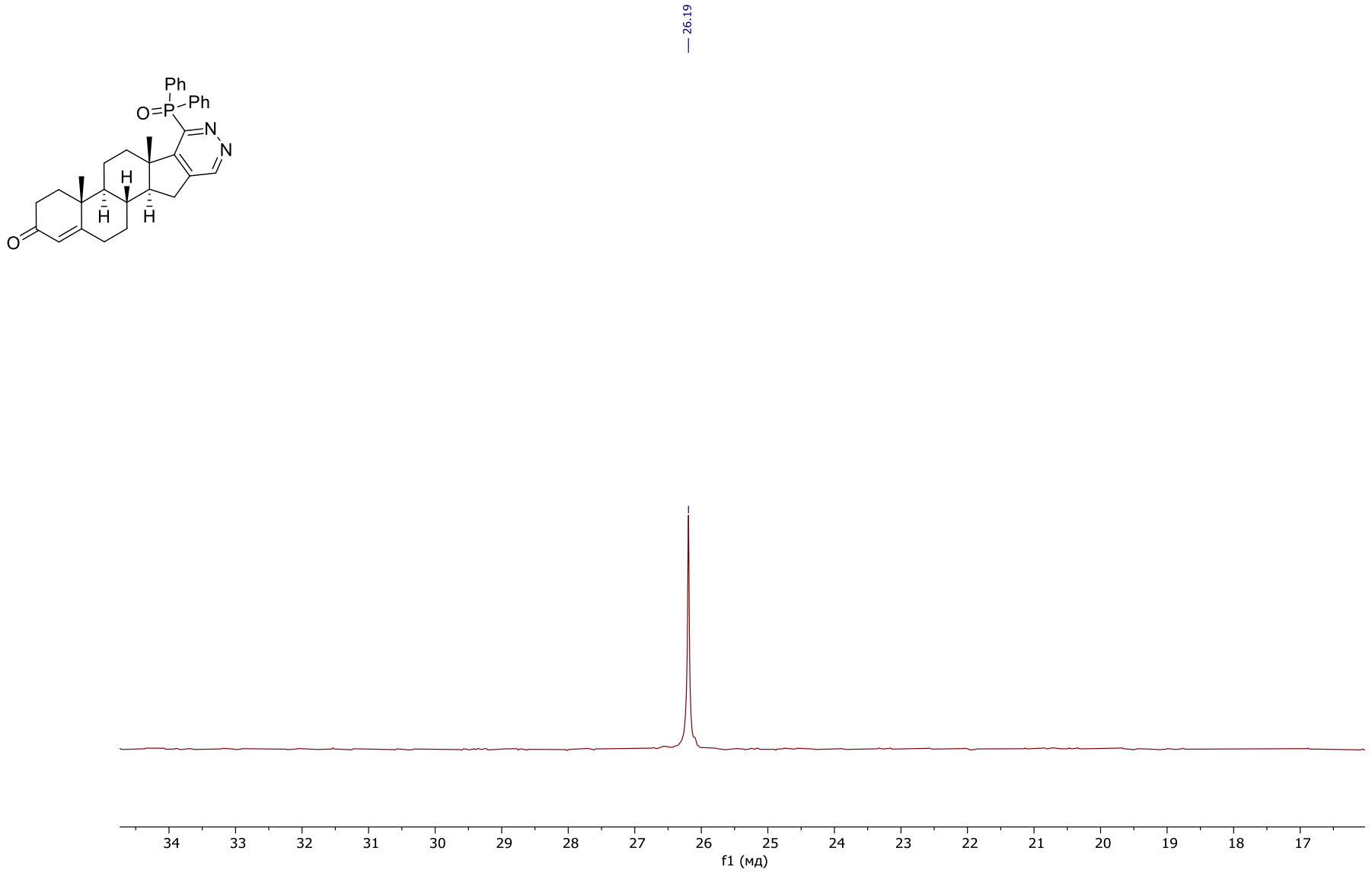
^{1}H NMR (400 MHz, $CDCl_3$) of 3-oxa-1'-(diphenylphosphinoxido)-4-androsteno[16,17-d]pyridazine (33).



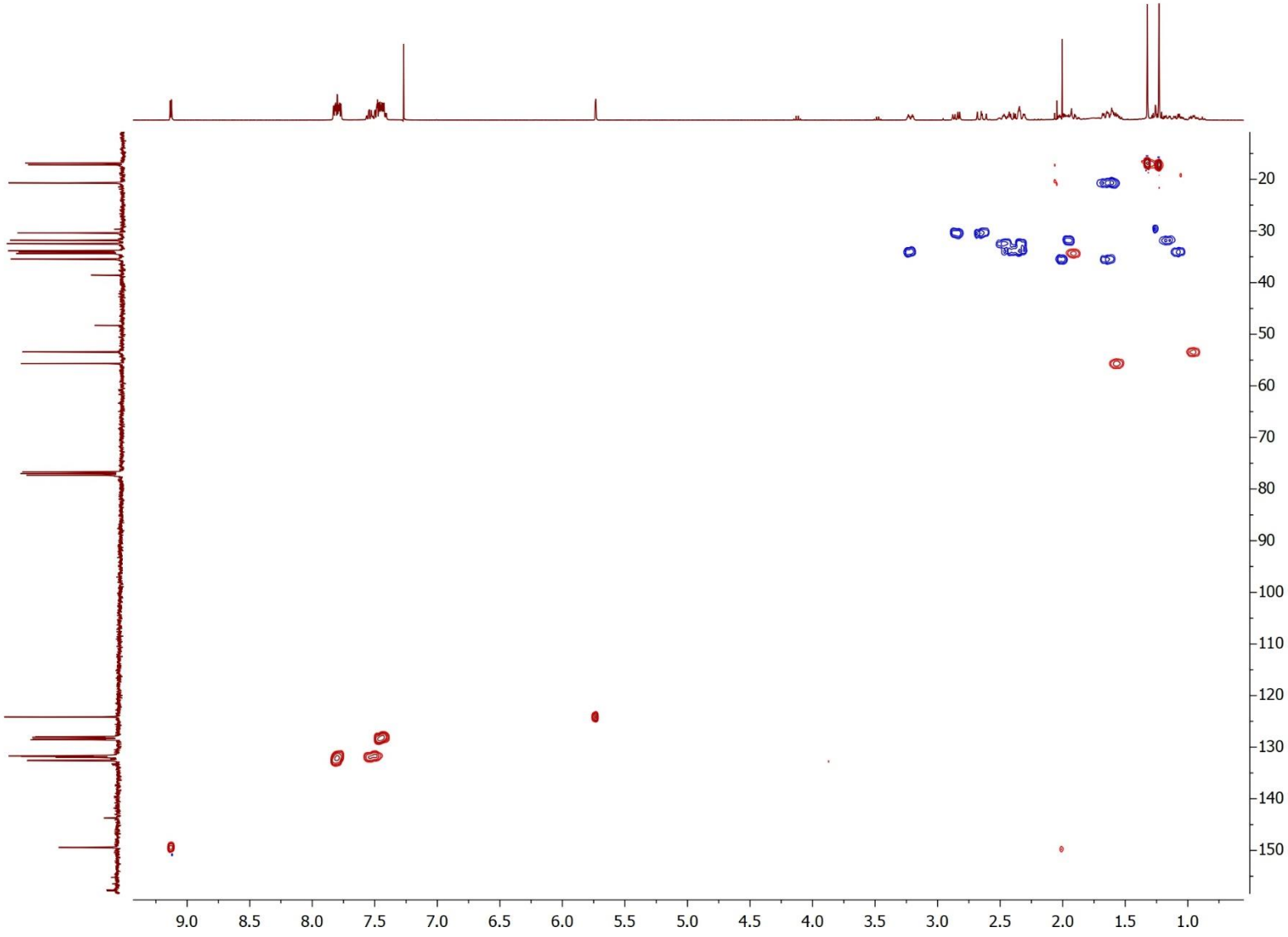
^{13}C NMR (101 MHz, $CDCl_3$) of 3-oxa-1'-(diphenylphosphinoxido)-4-androsteno[16,17-d]pyridazine (33).



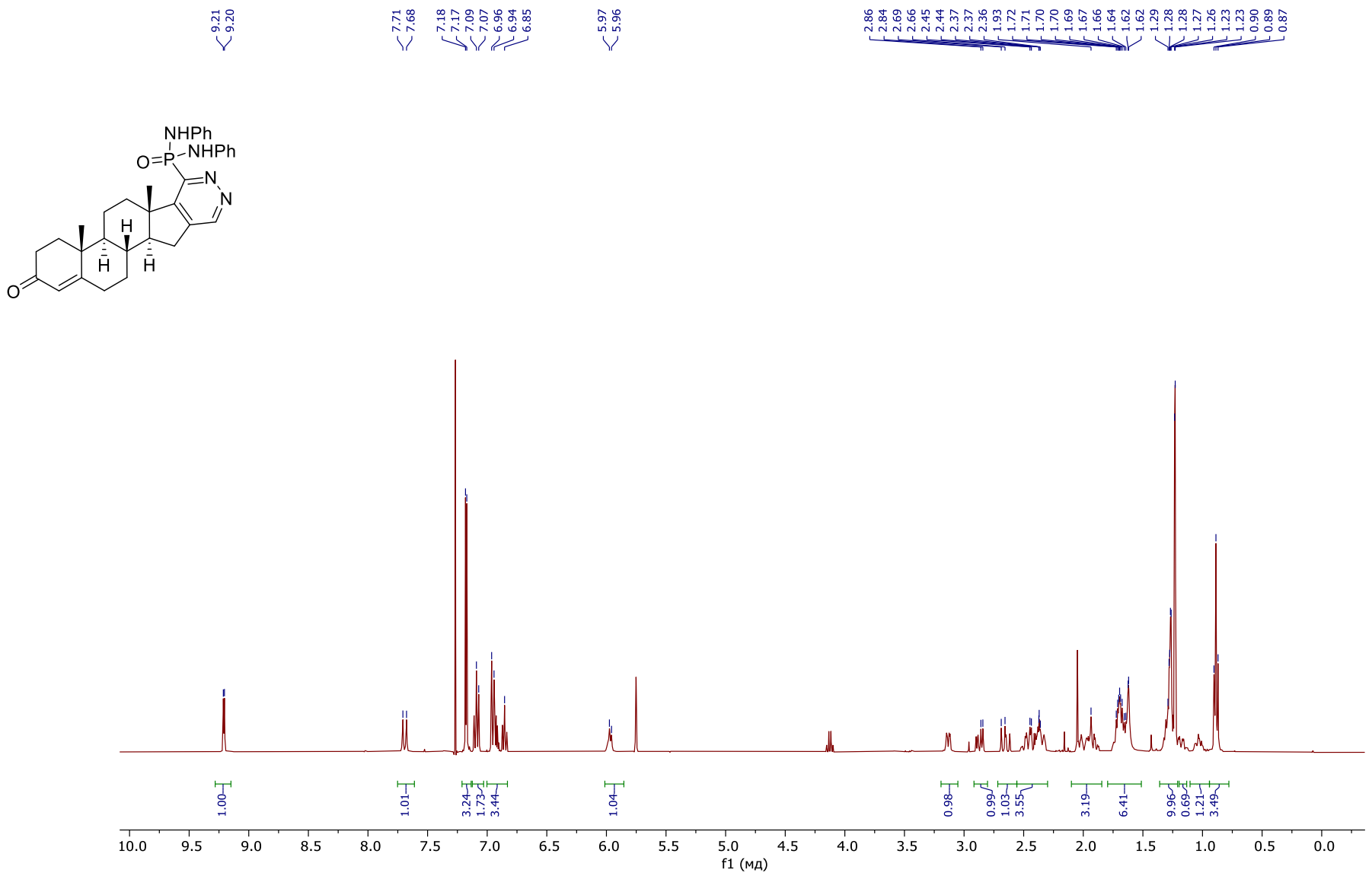
^{31}P NMR (162 MHz, $CDCl_3$) of 3-oxa-1'-(diphenylphosphinoxido)-4-androsteno[16,17-d]pyridazine (33).



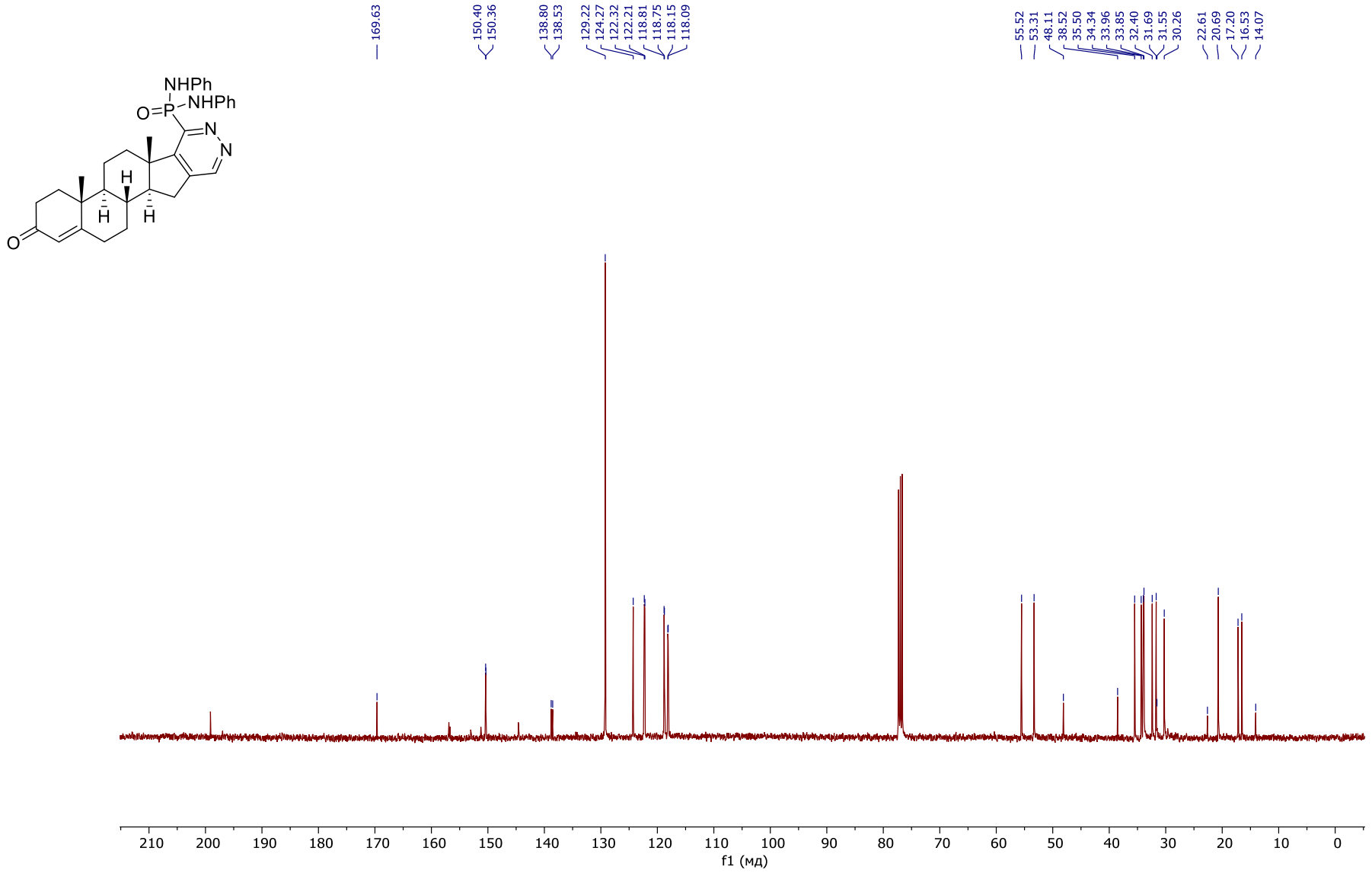
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, $CDCl_3$) of 3-oxa-1'-(diphenylphosphinoxido)-4-androsteno[16,17-d]pyridazine (33).



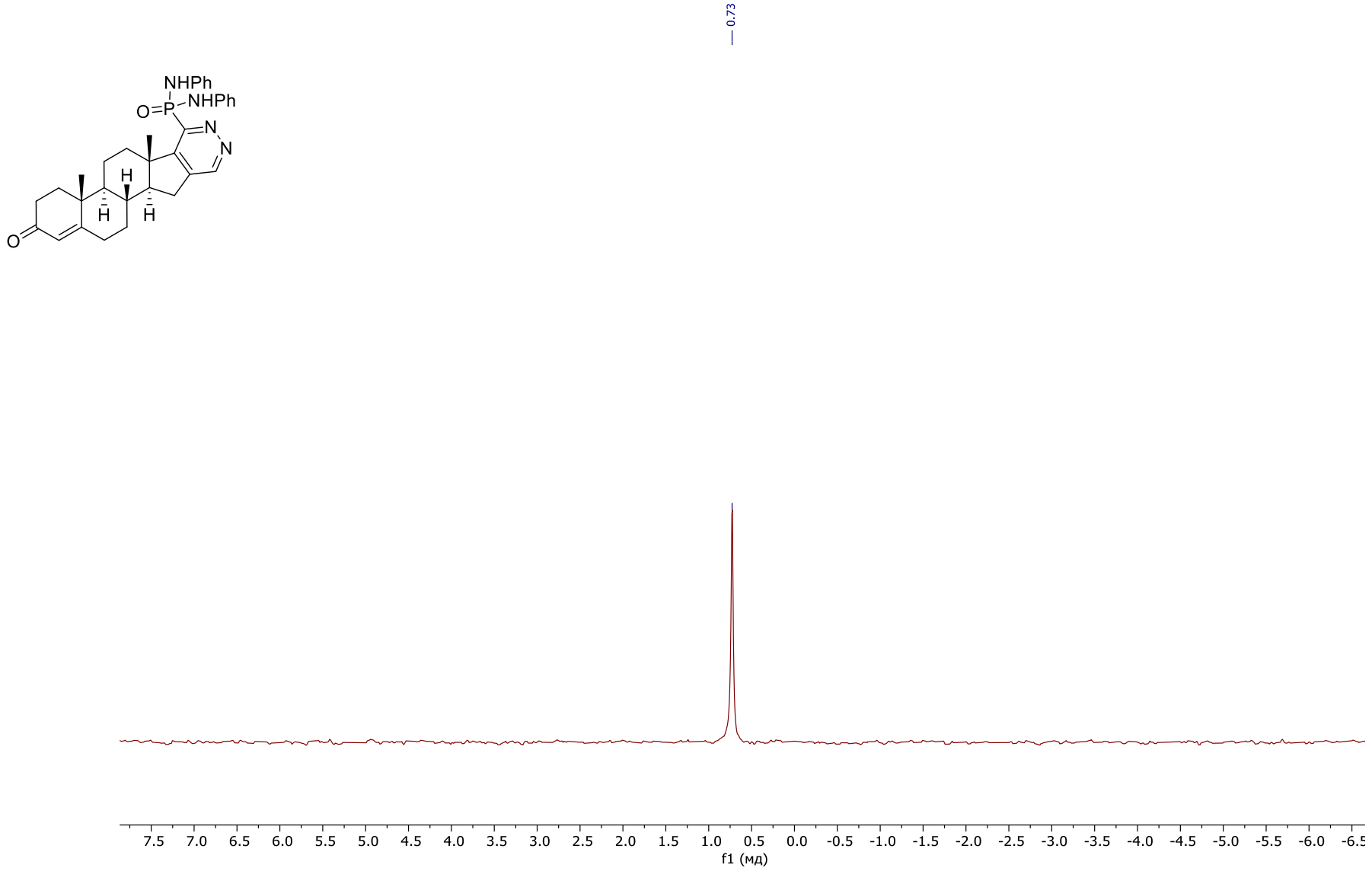
^{1}H NMR (400 MHz, $CDCl_3$, contains traces of ethyl acetate) of 3-oxa-1'-(*N,N'*-diphenylphosphorylamido)-4-androsteno[16,17-d]pyridazine (34).



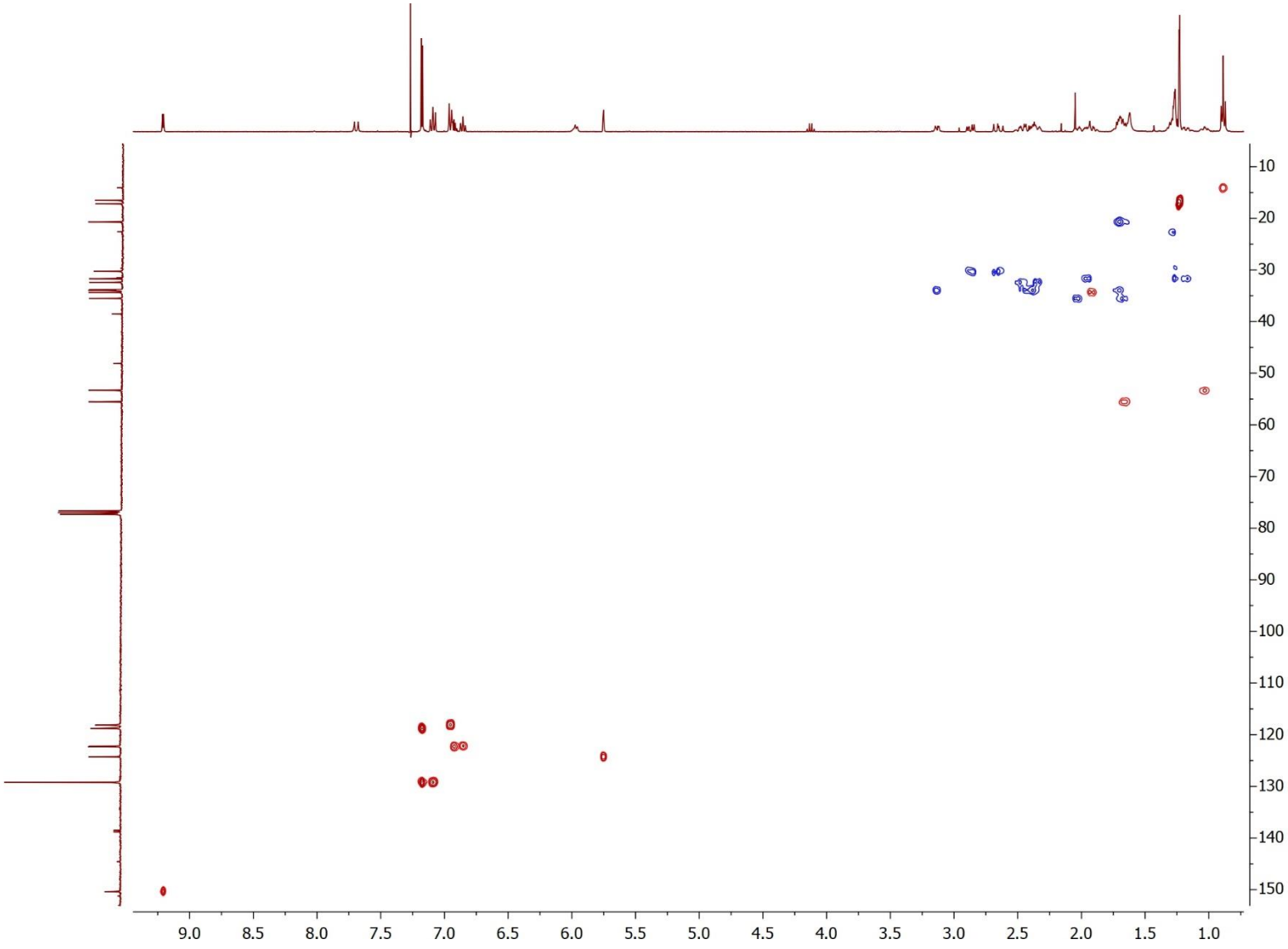
^{13}C NMR (101 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-diphenylphosphorylamido)-4-androsteno[16,17-d]pyridazine (34).



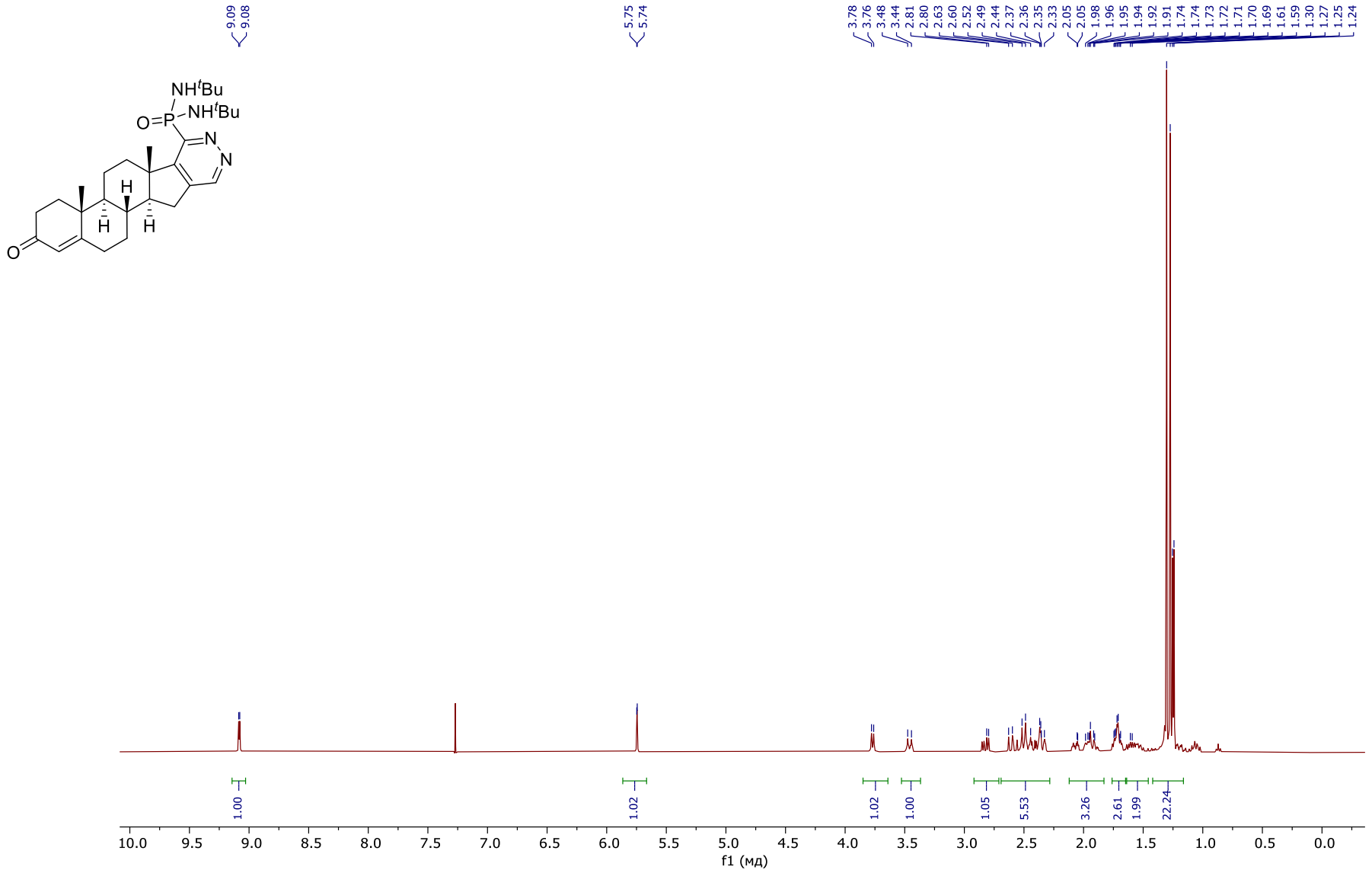
^{31}P NMR (162 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-diphenylphosphorylamido)-4-androsteno[16,17-d]pyridazine (34).



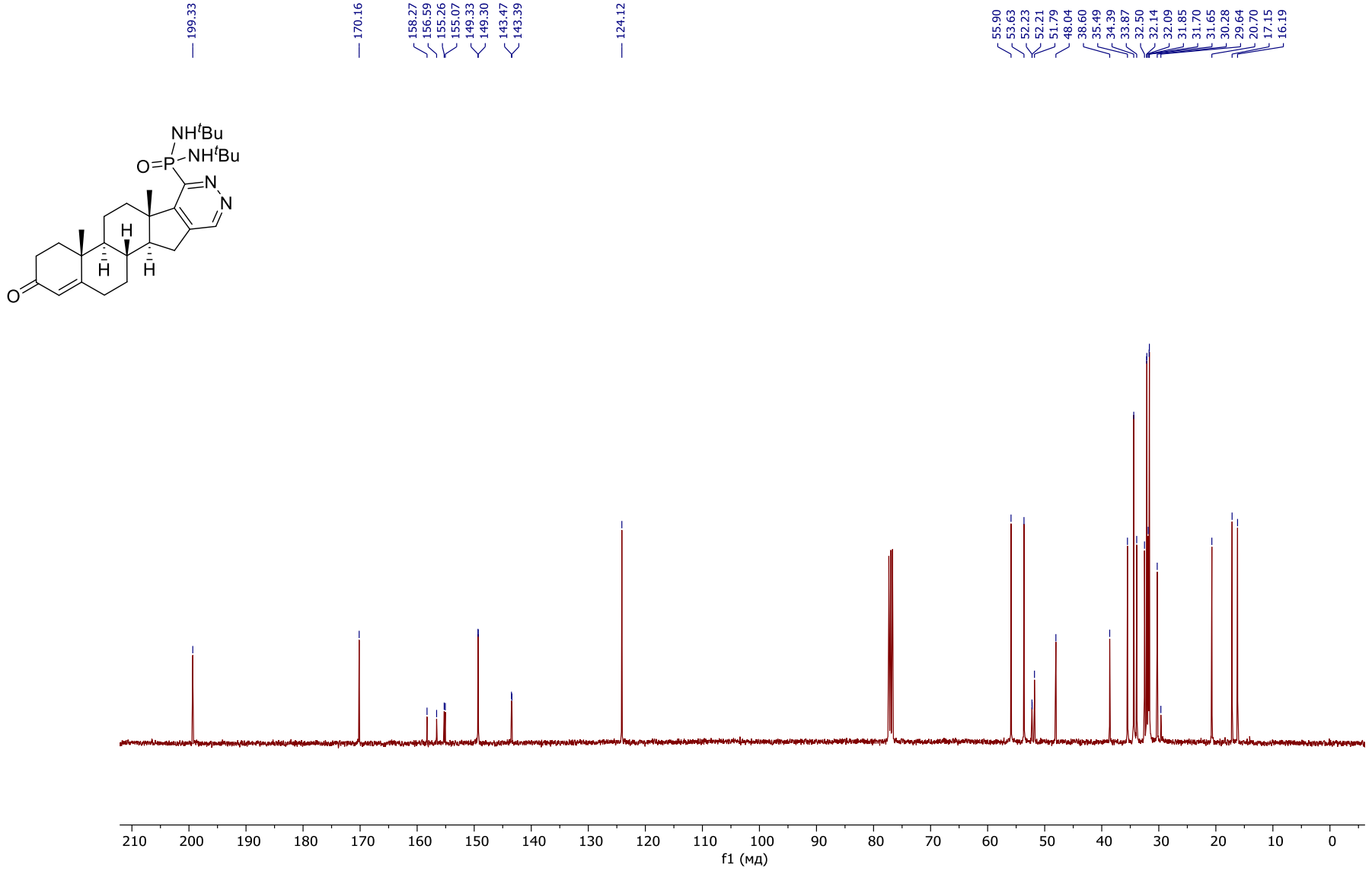
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-diphenylphosphorylamido)-4-androsteno[16,17-d]pyridazine (34).



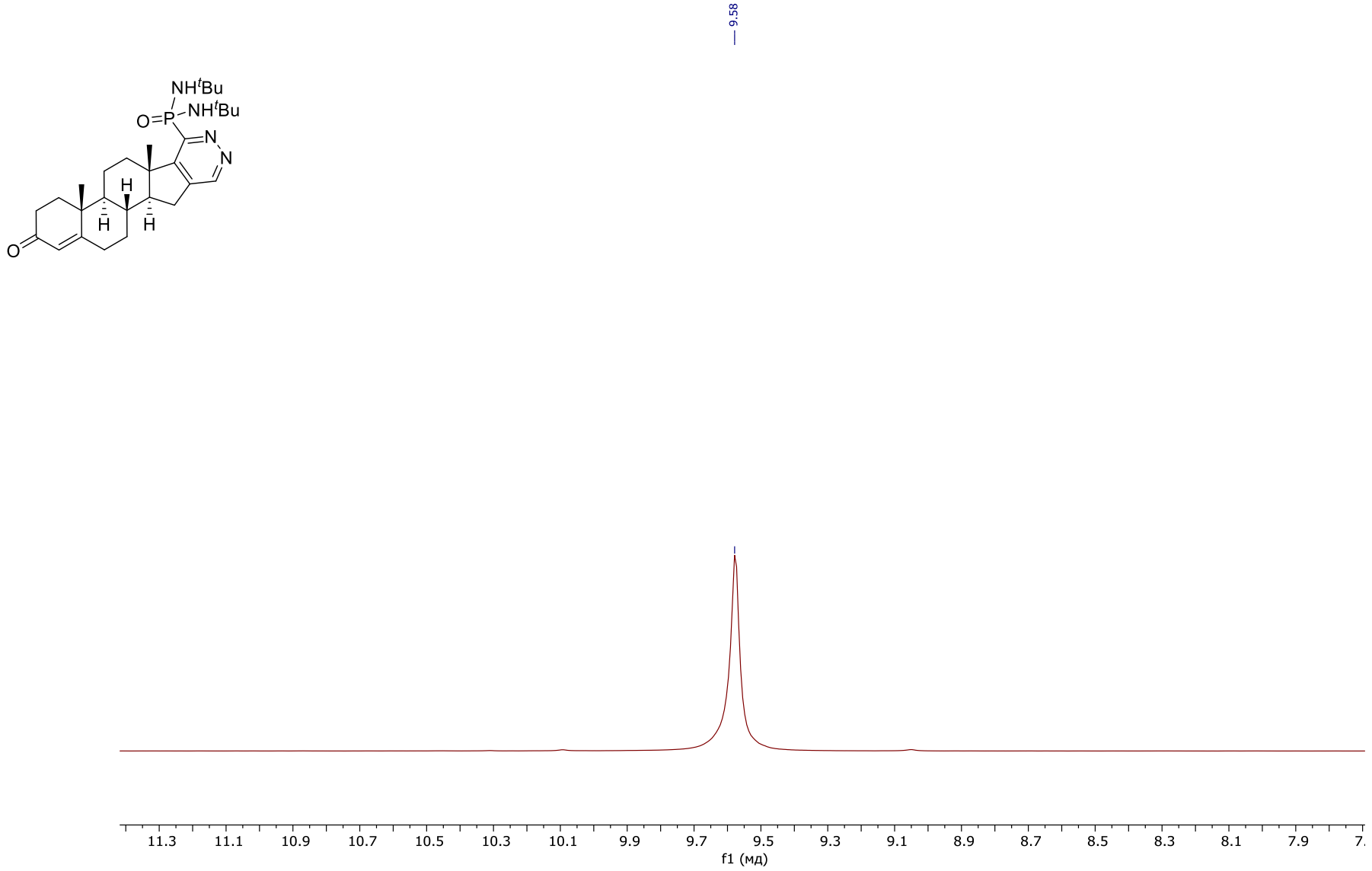
^{1}H NMR (400 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-4-androsteno[16,17-d]pyridazine (35).



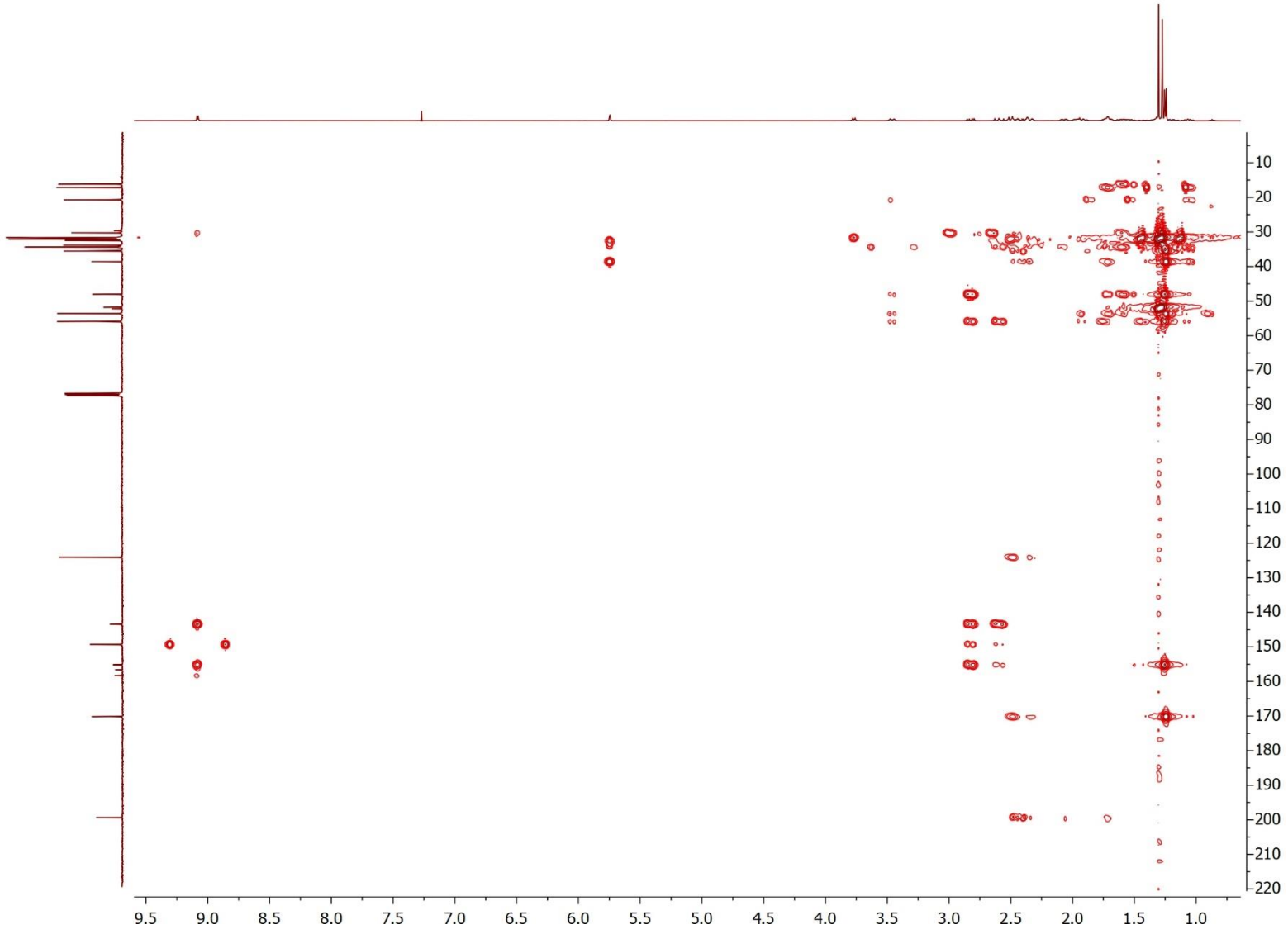
^{13}C NMR (101 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-4-androsteno[16,17-d]pyridazine (35).



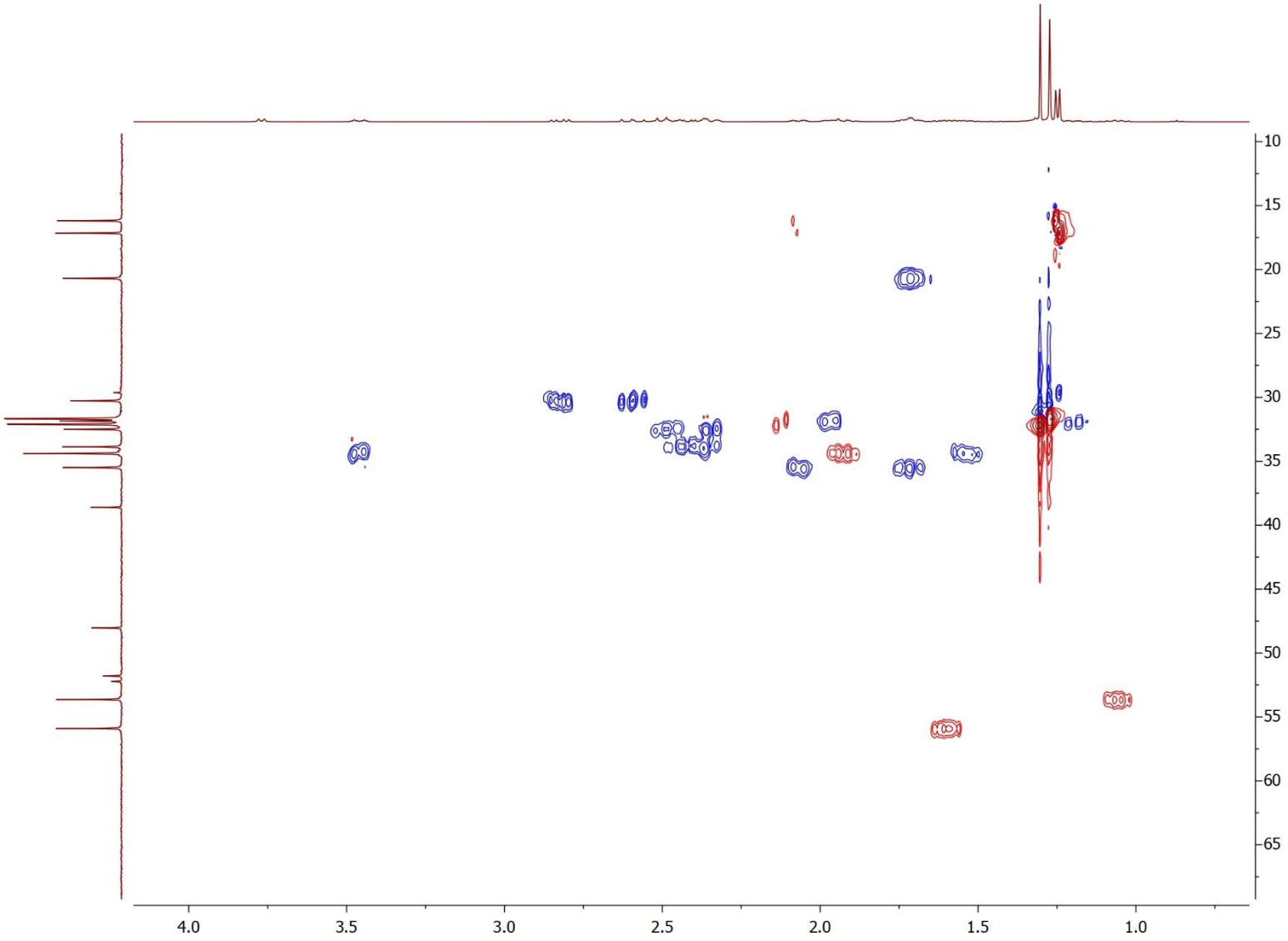
^{31}P NMR (162 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-4-androsteno[16,17-d]pyridazine (35).



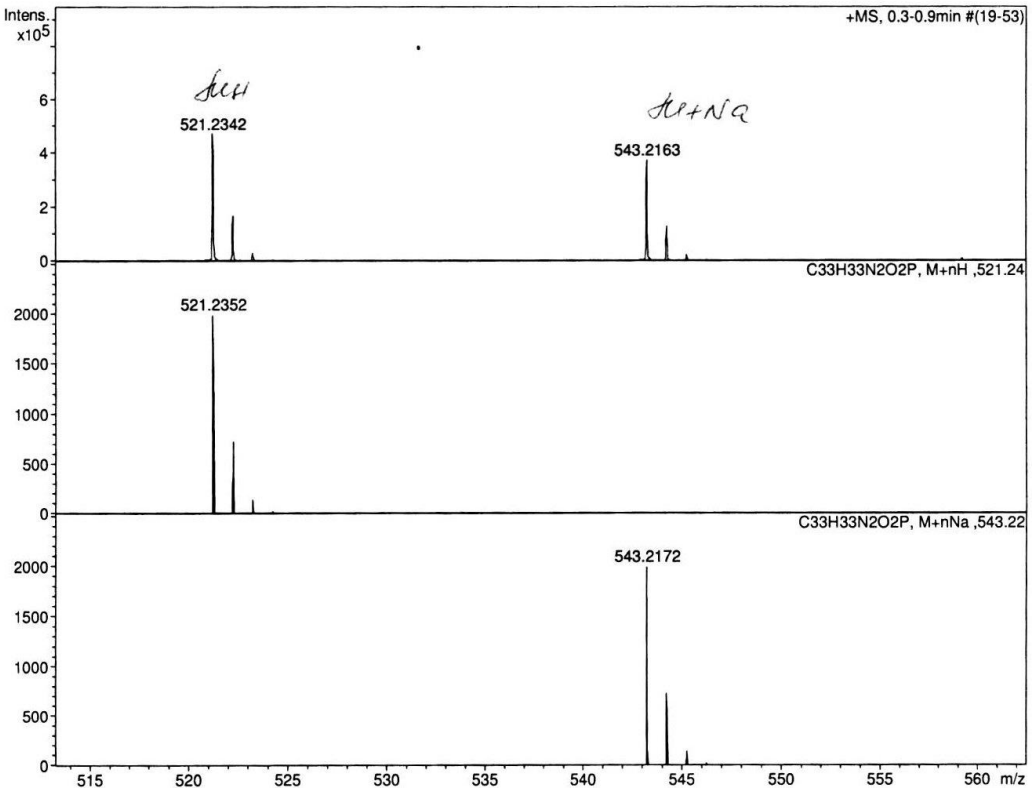
^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-4-androsteno[16,17-d]pyridazine (35).



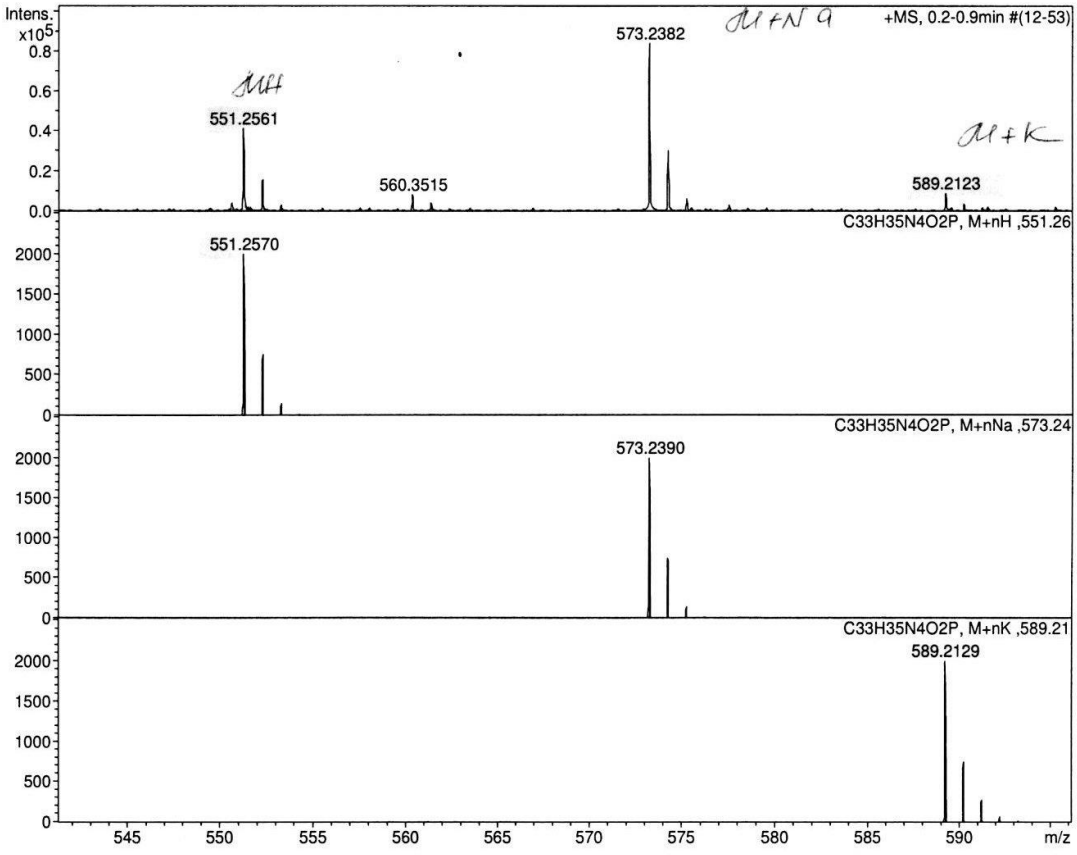
^{1}H-^{13}C HSQC NMR (400 MHz, 101 MHz, $CDCl_3$) of 3-oxa-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-4-androsteno[16,17-d]pyridazine (35).



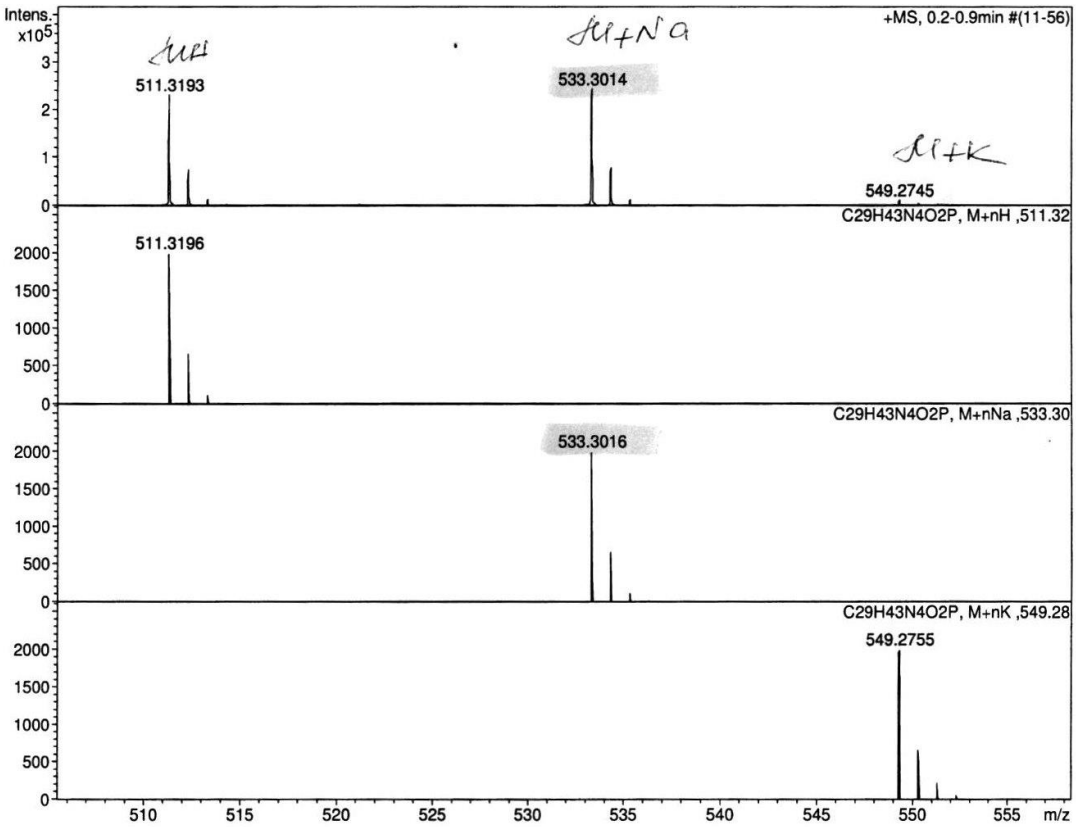
(3-Methoxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (6).



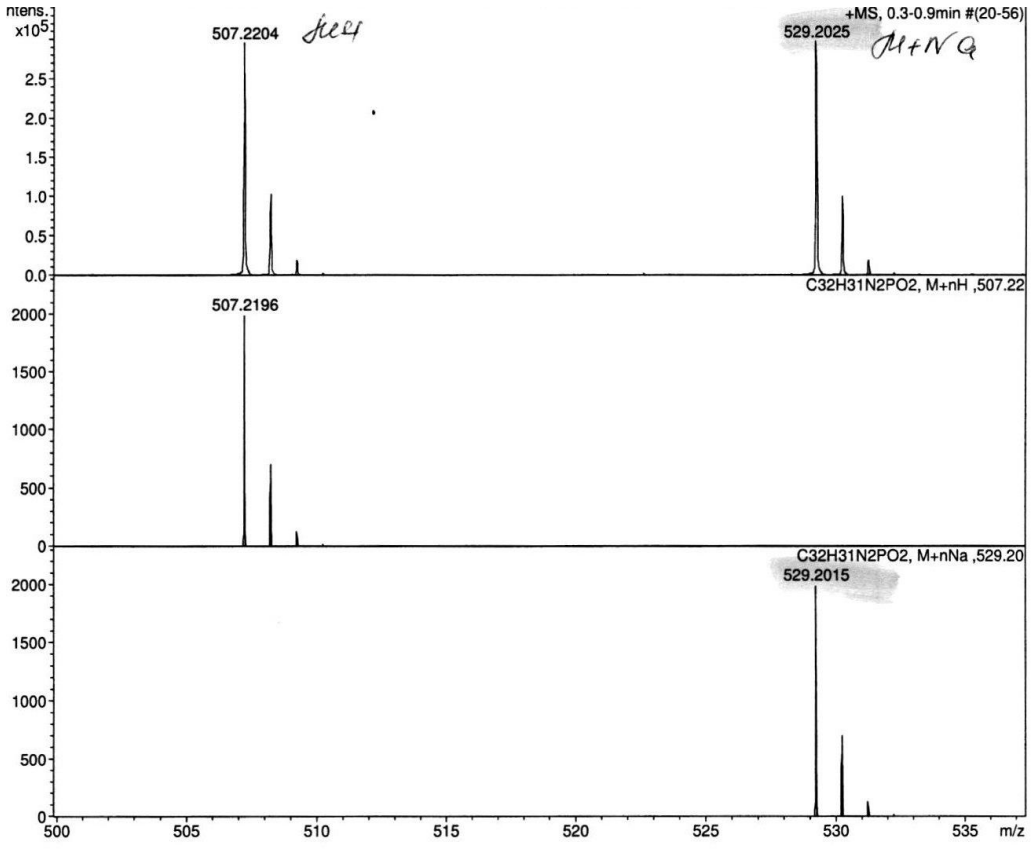
3-Methoxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (7).



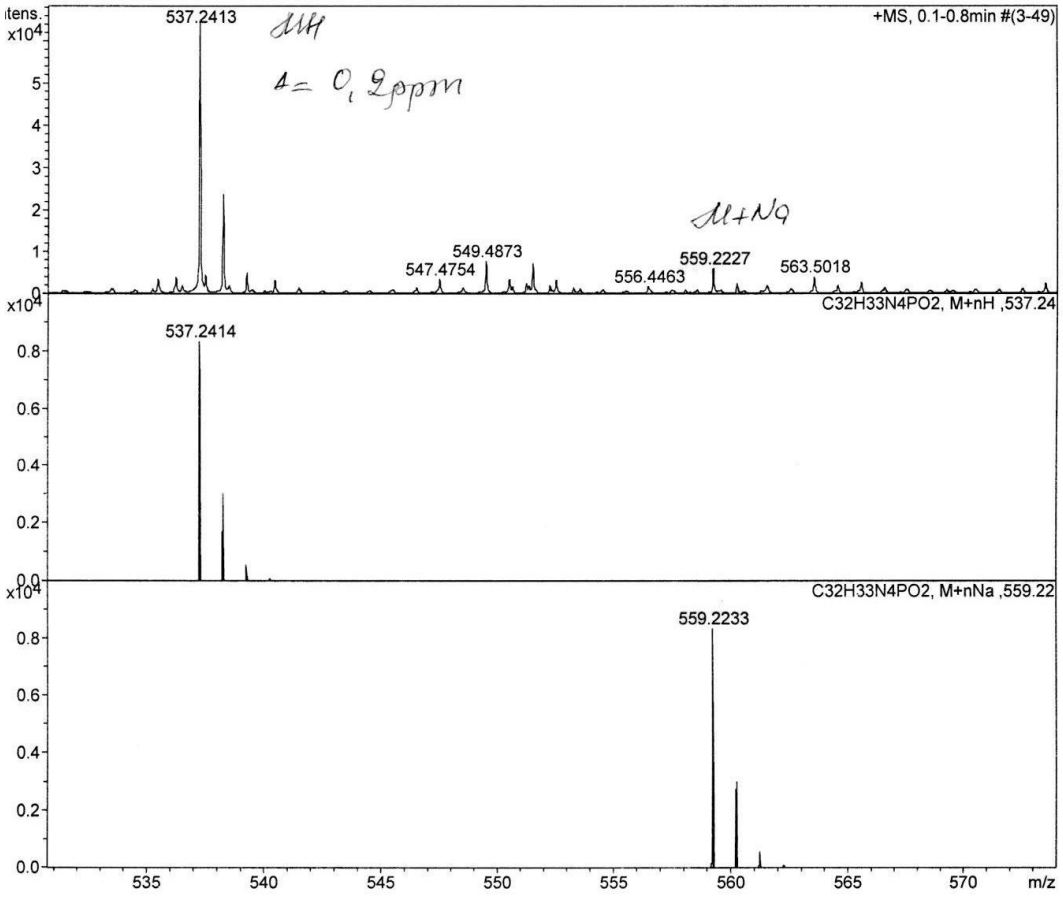
3-Methoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (8).



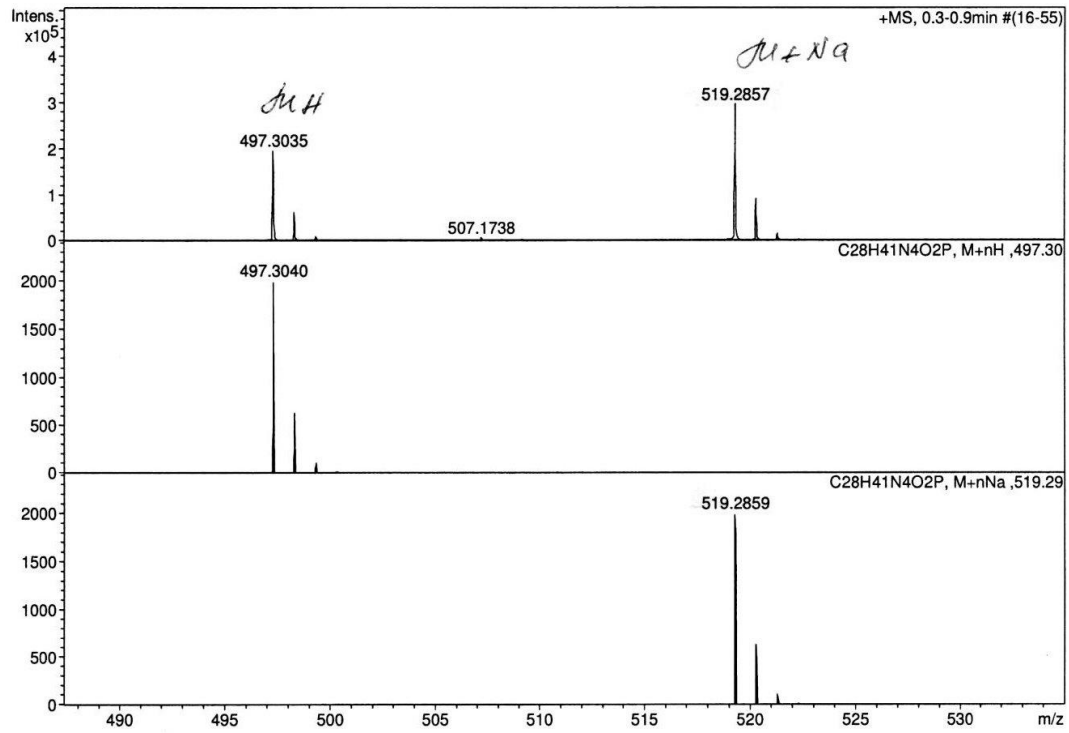
(3-Hydroxy-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine-1'-yl)diphenylphosphine oxide (9).



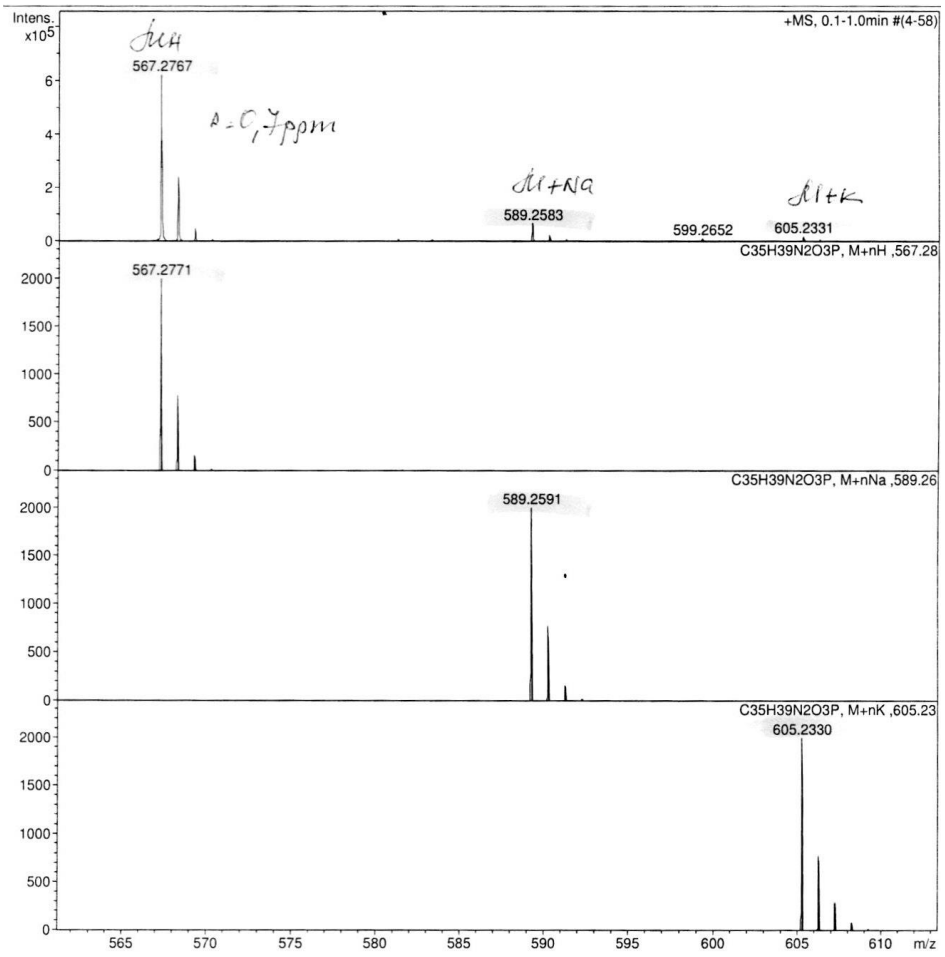
3-Hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (10).



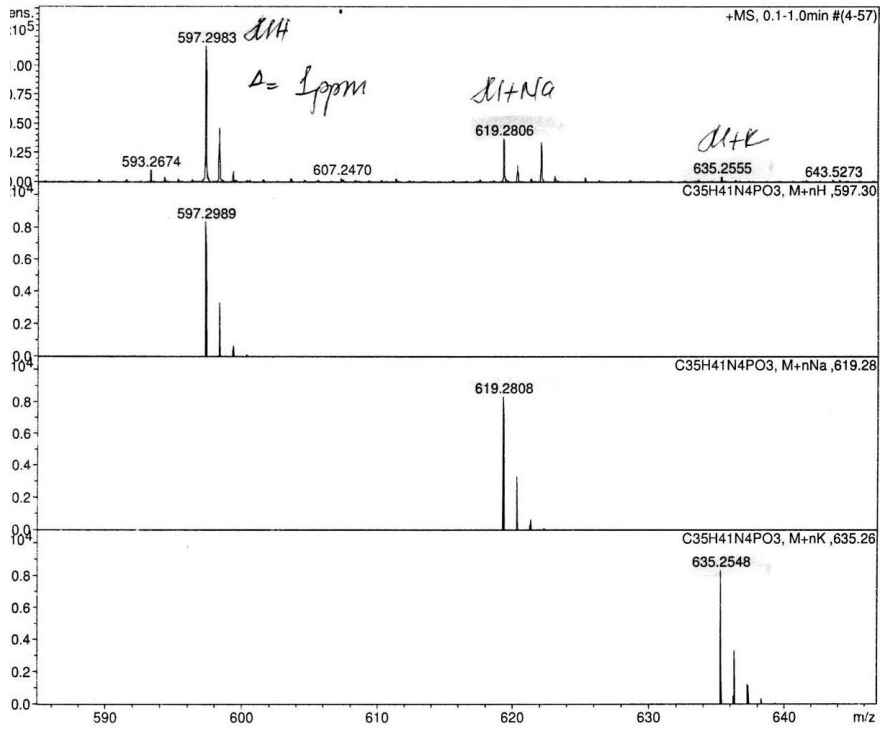
3-Hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-$\Delta^{1,3,5(10)}$-estratrieno[16,17-d]pyridazine (11).



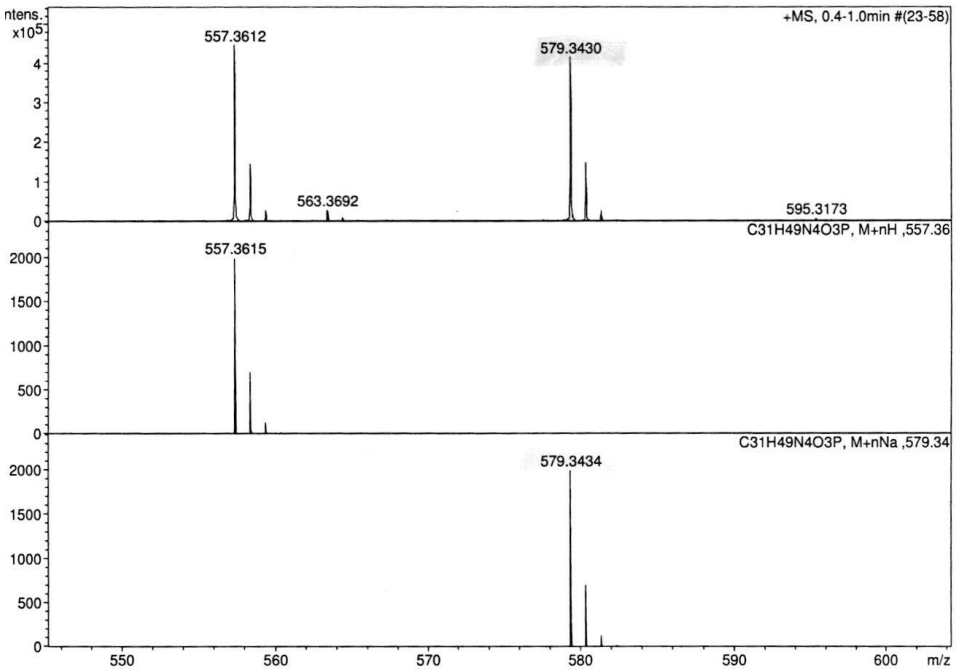
(3β-Acetoxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (14).



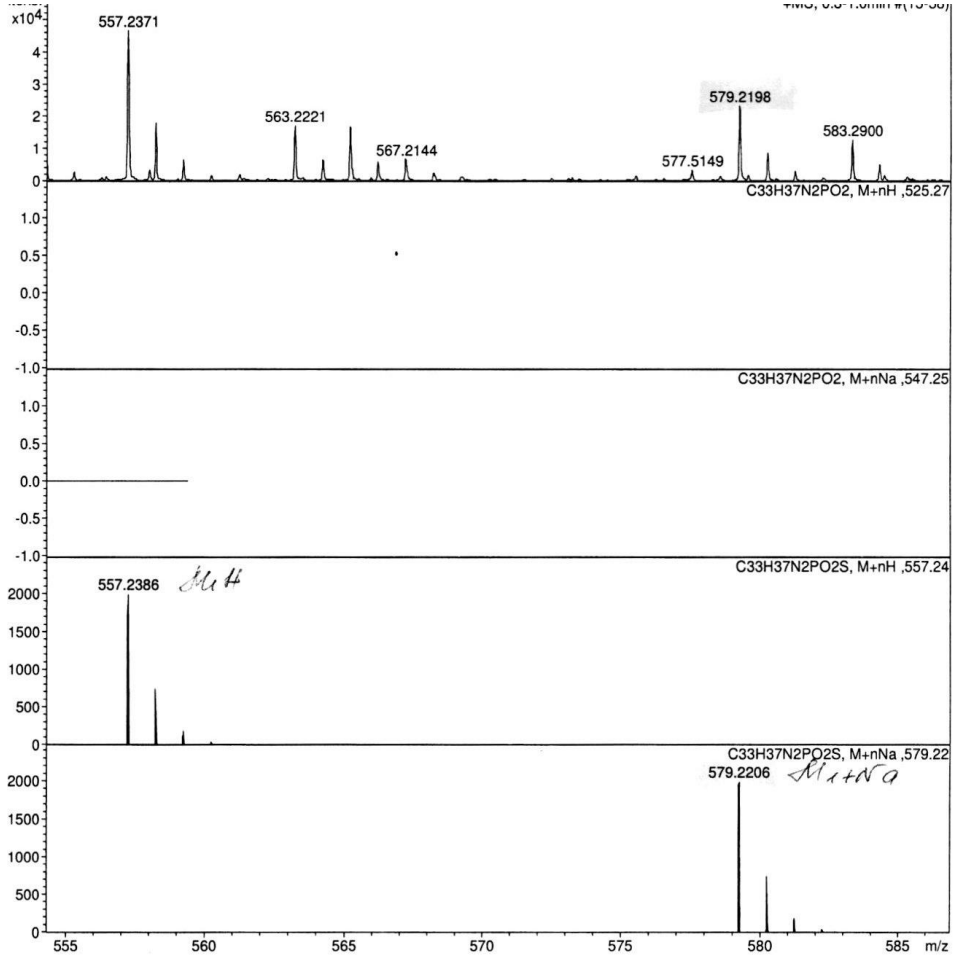
3β-Acetoxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androsteno[16,17-d]pyridazine (15).



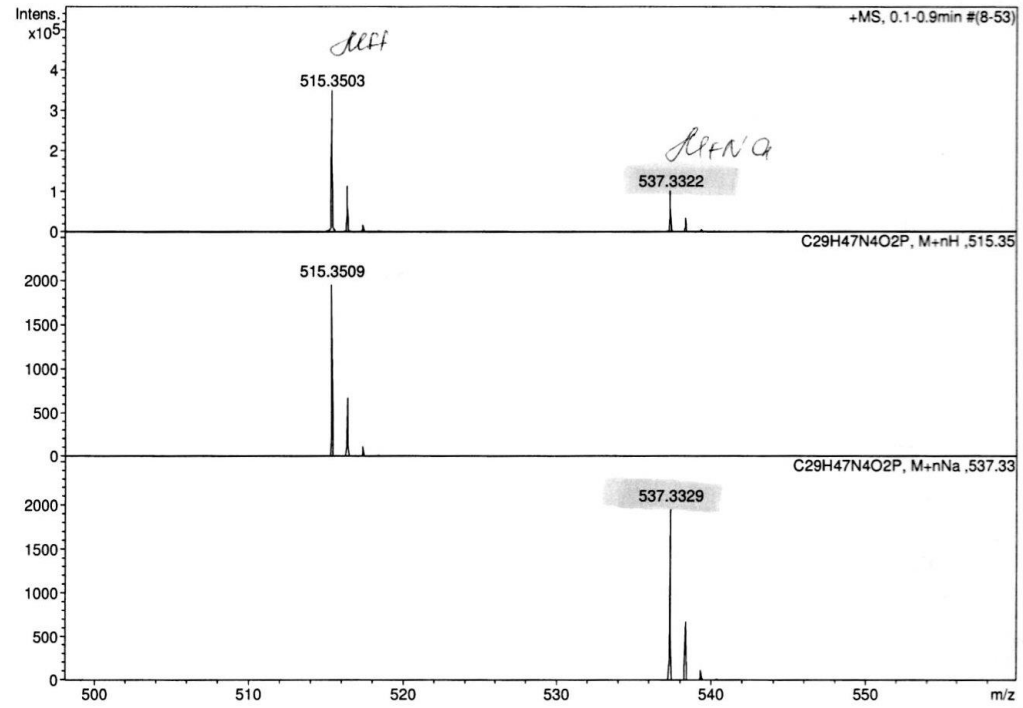
3β-Acetoxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (16).



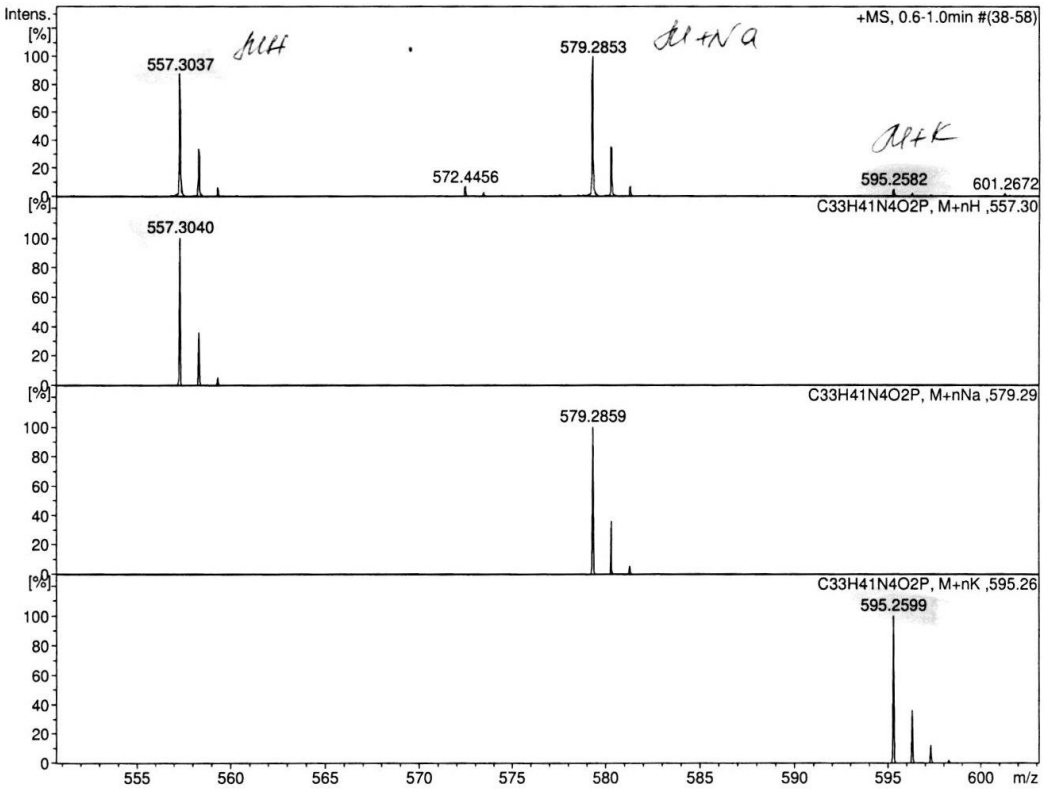
(3β-Hydroxy-5-androsteno[16,17-d]pyridazin-1'-yl)diphenylphosphine oxide (17).



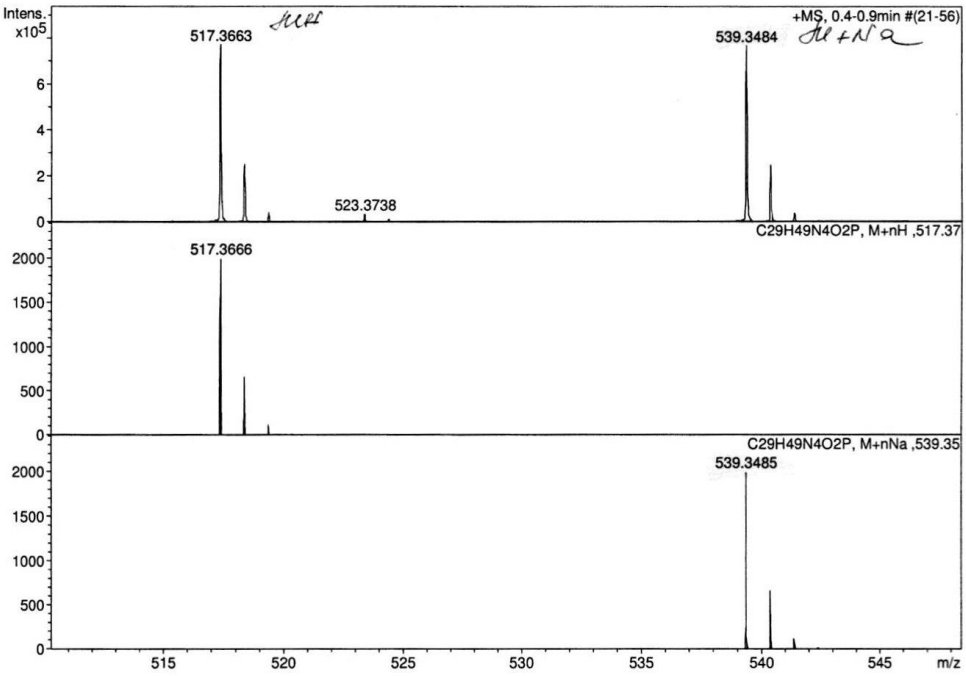
3β-Hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androsteno[16,17-d]pyridazine (19).



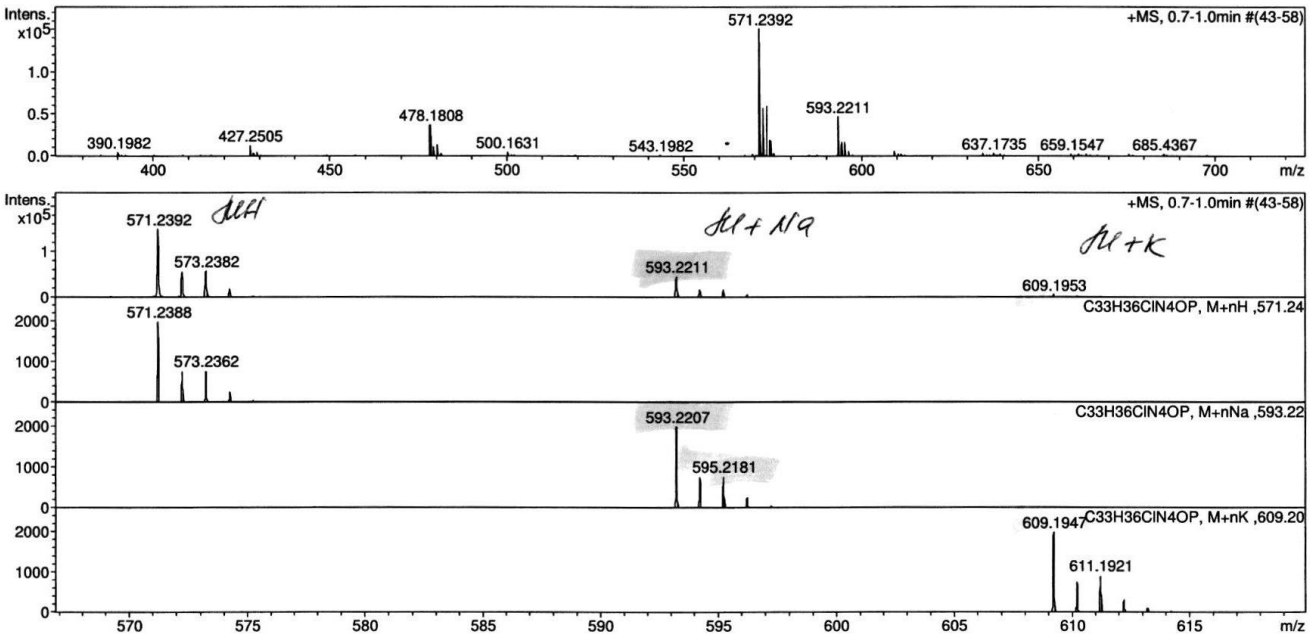
3β-Hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5-androst[16,17-d]pyridazine (22).



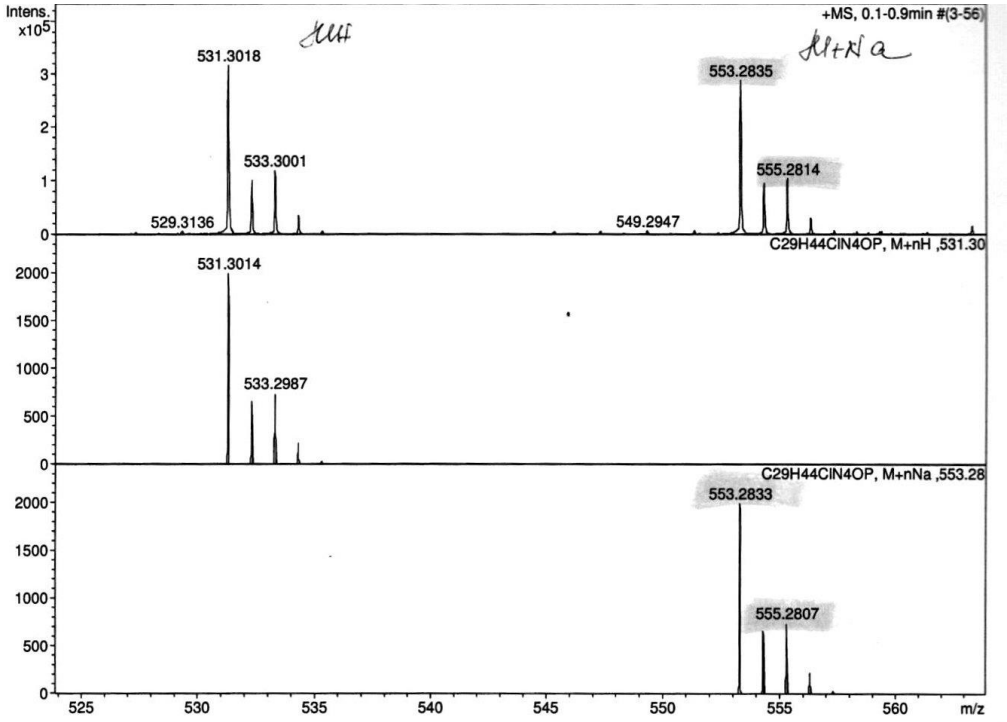
3β-Hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst[16,17-d]pyridazine (23).



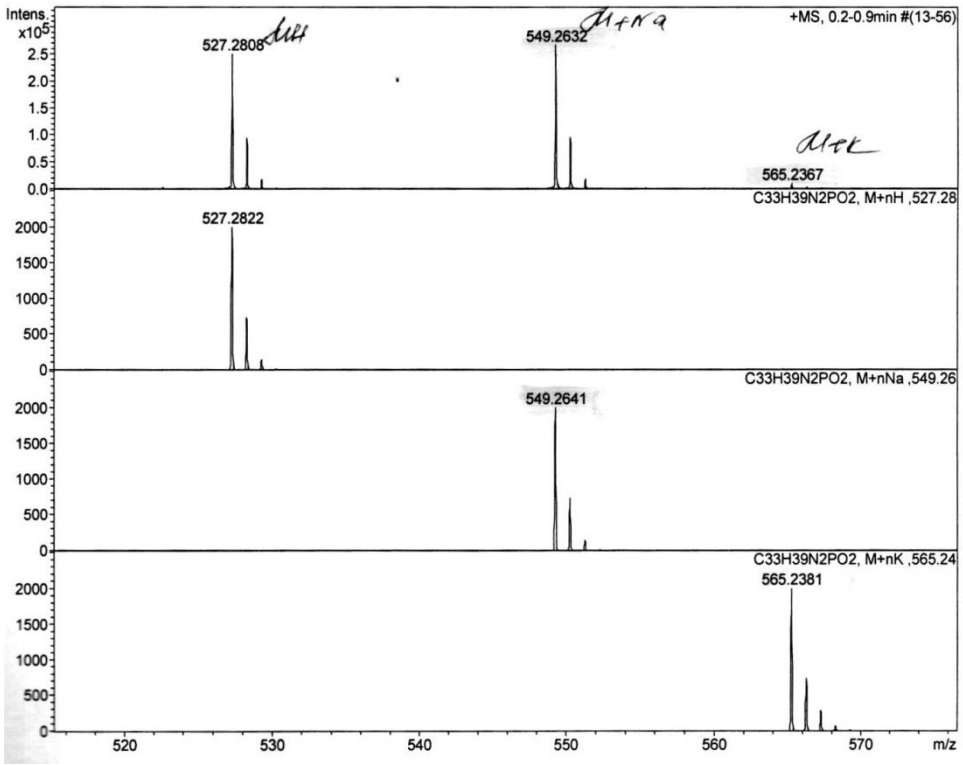
3-Chloro-1'-(*N,N'*-diphenylphosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (26).



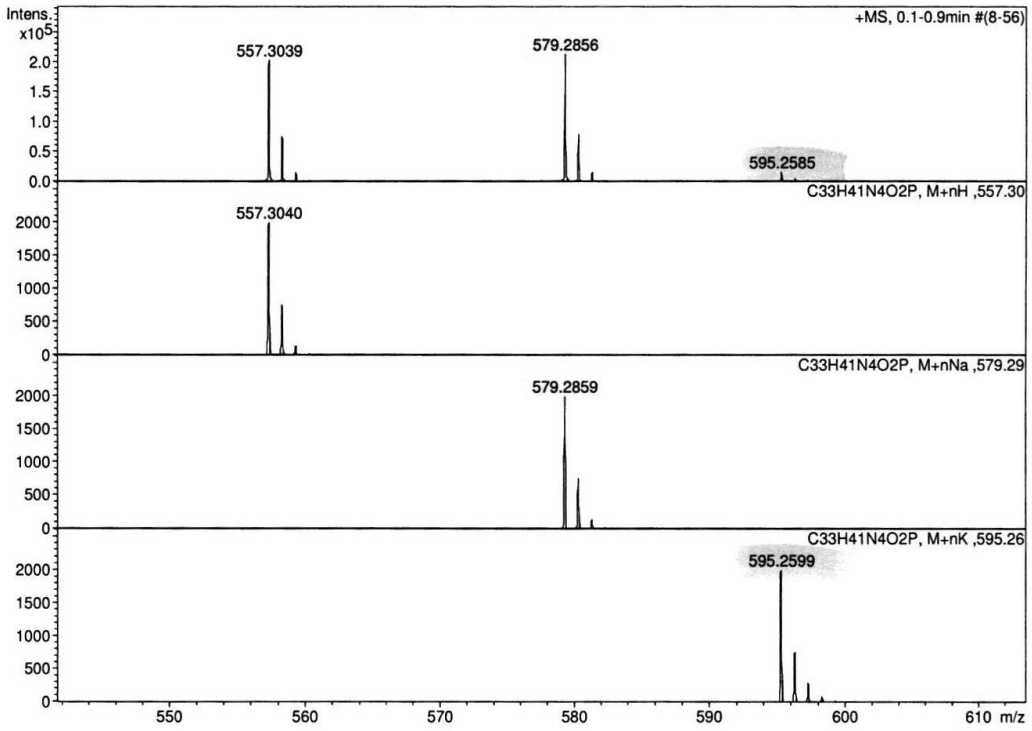
3-Chloro-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5-androst-3,5-dieno[16,17-d]pyridazine (27).



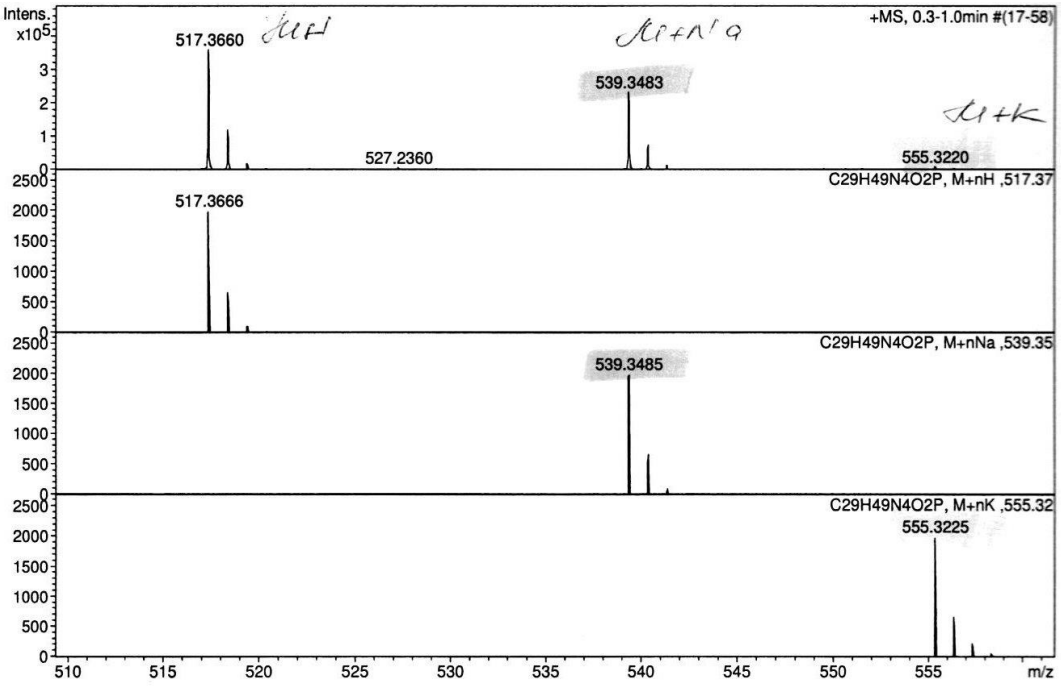
(17β-Hydroxy-5α-androst[3,2-d]pyridazine-1'-yl)diphenylphosphine oxide (30).



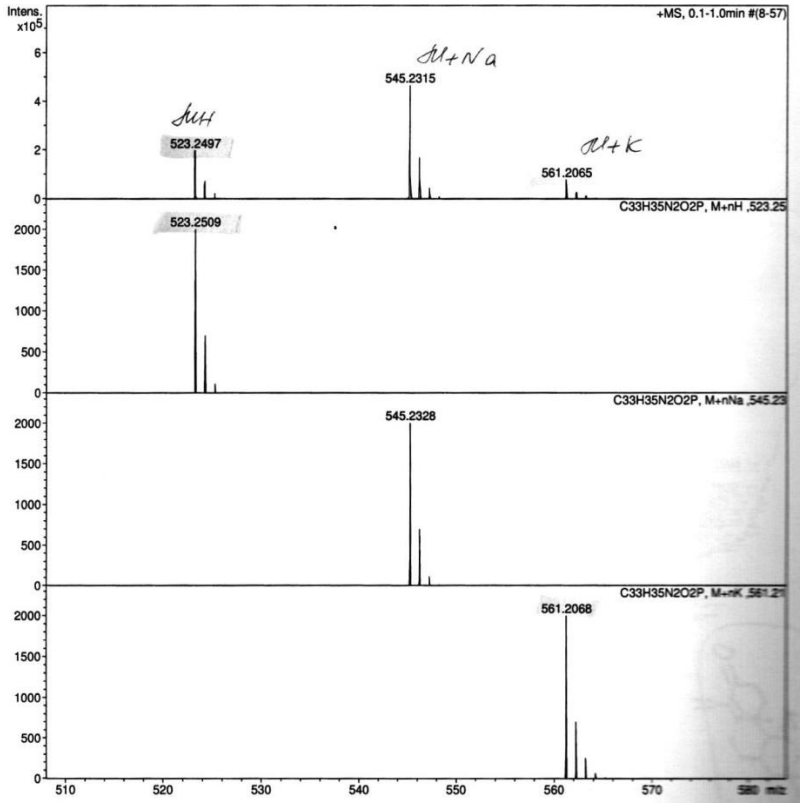
17β-Hydroxy-1'-(*N,N'*-diphenylphosphorylamido)-5α-androst[3,2-d]pyridazine (31).



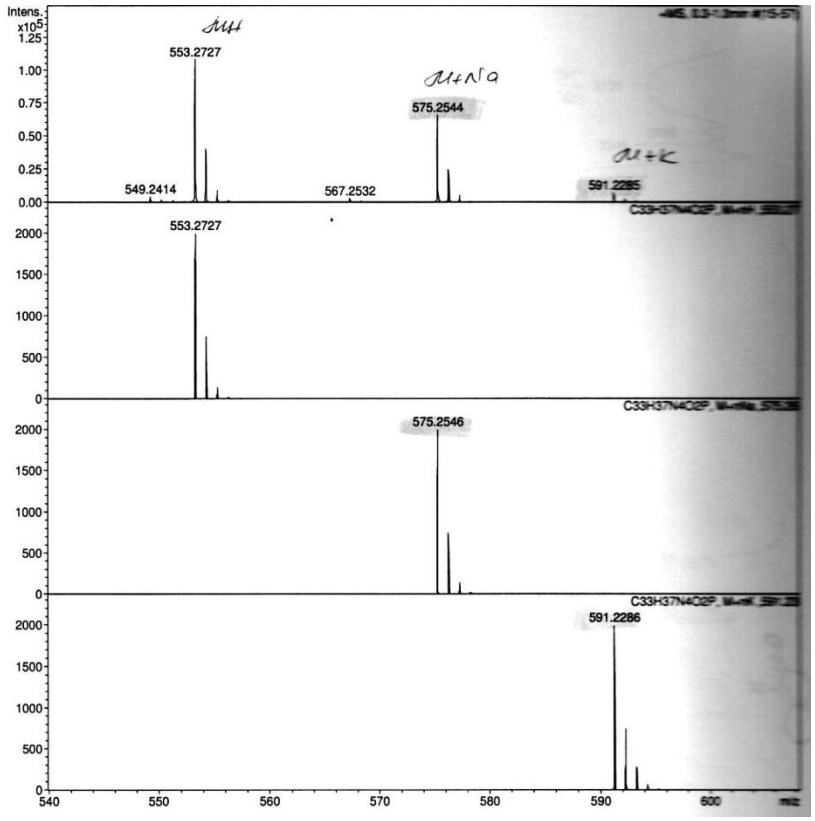
17β-Hydroxy-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-5α-androst[3,2-d]pyridazine (32).



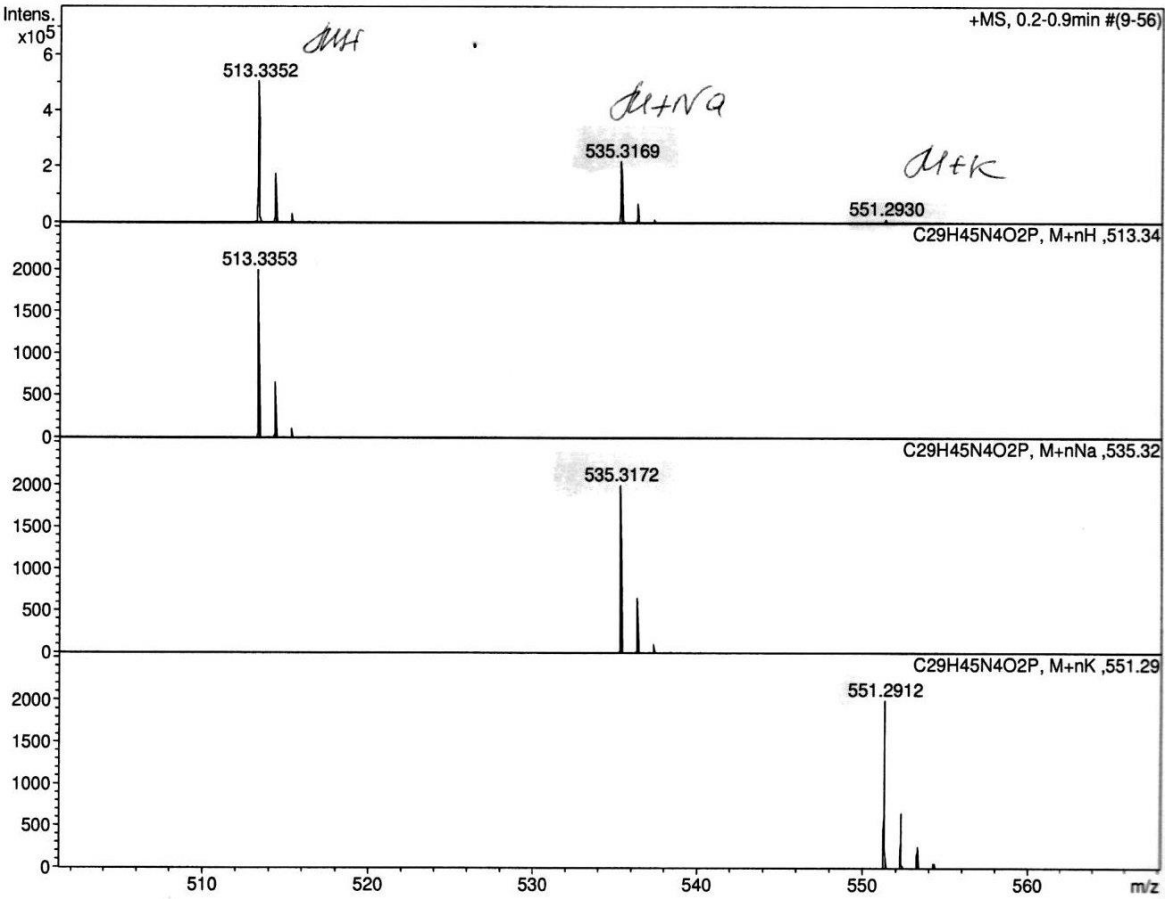
3-Oxa-1'-(diphenylphosphinoxido)-4-androsteno[16,17-d]pyridazine (33).



3-Oxa-1'-(*N,N'*-diphenylphosphorylamido)-4-androsteno[16,17-d]pyridazine (34).



3-Oxa-1'-(*N,N'*-di(*tret*-butyl)phosphorylamido)-4-androsteno[16,17-d]pyridazine (35).



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1. Volkova, Y.A., et al., *Access to steroidal pyridazines via modified thiohydrazides.* RSC Advances, 2016. **6**(49): p. 42863-42868.
2. Kozlov, M., Y. Volkova, and I. Zavarzin, *Synthesis of 5-phosphoryl-substituted 1, 3, 4 (3 H)-thiadiazolones.* Russian Chemical Bulletin, 2019. **68**(11): p. 2105-2107.
3. Kozlov, M., Y. Volkova, and I. Zavarzin, *New transformations of phosphorylthioformic acid morpholides.* Russian Chemical Bulletin, 2020. **69**(8): p. 1604-1606.
4. Kozlov, M., et al., *Simple approach towards phosphorus-substituted spiro 1,3,4-thiadiazolines.* Tetrahedron, 2024. **150**: p. 133746.