Supplementary Information 1

Synthesis and bioactivity of benzothiazaphosphepines and relevant phosphonates as antioxidant/antidiabetic agents

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EXPERIMENTAL SECTION

General data:

Melting points were determined with an open capillary tube on an Electrothermal (variable heater) melting point apparatus. Later on, the used thermometer was calibrated by using standard compounds of known mps and the melting points of the new compounds were corrected exclusively. IR spectra were recorded on a JASCO FT-IR 6100 using KBr the bromide disc. NMR spectra were measured using JEOL E.C.A-500 MHz (^{1}H: 500.7 MHz, ^{13}C: 125.4 MHz, ^{31}P: 200.7 MHz) spectrometer. The mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. Elemental analysis of the products was carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, using Elemental C, H, N analyzer Vario EL II I Germany. The purity of all new samples was verified by microchemical analysis (C/H/N/P/S) and spectroscopy. TLC: Merck 0.2 mm silica gel 60 F254 analytic aluminum plates. All international principles and local regulations concerning the care and use of laboratory animals were considered during the pharmacological screening.

Synthesis

The substrates 2-[(2-mercaptophenyl)imino]methyl]phenol (**1a**) and 2-(4-(dimethylamino) benzylideneamino)benzenethiol (**1b**) were synthesized according to the reported methods from the condensation of *o*-aminothiophenol with the proper aldehyde in ethanol.[11,12]

Reactions of 1a and 1b with Wadsworth-Horner-Emmons (WHE) reagents 2, 5, and 8a-8d

Synthesis of **4a**, **4b**, **7a**, **7b**, *and* **10a-10h**. *General method*: A solution of dry DMF (20 mL) containing 3.9 mmol of LiH and 1.3 mmol of diethyl vinylphosphonate (**2**), diethyl 2-methallyl-phosphonate (**5**), methyl diethyl phosphonoacetate (**8a**), triethyl phosphonoacetate (**8b**), diethyl methylthiomethyl- (**8c**), or diethyl 2-amino-2-thioxoethyl-phosphonate (**8d**) was treated, under stirring, with 1 mmol of **1a** or **1b** in DMF (15 mL) in one portion at r.t. The suspension was further heated under reflux for the proper time (18-25 h, TLC). The reaction mixture was poured into distilled water (100 mL), acidified with HCl (1*N*), and extracted with AcOEt. The combined organic phase was washed, dried over anhydrous sodium sulfate, followed by removal of the solvents under reduced pressure. The resulting residue was collected,

and crystallized from the proper solvent to give the benzothiazaphosphepines **4a**, **4b**, **10a-10h** or the phosphonates **7a** and **7b**.

4-(3-Ethoxy-2-methyl-3-oxido-2,3-dihydro-1,5,3-benzothiazaphosphepin-4-yl)phenol (4a) was obtained as yellow crystals (0.25 g, 72%); mp 138 °C (EtOH); ν_{max}/cm^{-1} 3417, 1574, 1241, 1078; δ_H (500.7 MHz, $CDCl_3$) 1.17 (dt, J_{H-H} = 6.6 Hz, $^4J_{P-H}$ = 4.6 Hz, 3H, *Me*CO), 1.29 (dd, J_{HH} = 8.7 Hz, J_{P-H} = 8.9 Hz, 3H, *Me*), 4.19 (dq, J_{H-H} = 6.6 Hz, $^3J_{P-H}$ = 5.7 Hz, 2H, H_2C), 5.05 (dq, J_{H-H} = 8.7 Hz, $^2J_{P-H}$ = 14.7 Hz, 1H, *H*C), 7.02-7.96 (m, 8H, *H*-Ar), 12.5 (s, 1H, *H*O); δ_C (125.4 MHz, $CDCl_3$) 191.4 (d, J_{P-C} = 78.5 Hz, *C*-4), 160.9, 152.2, 134.8, 133.2, 129.7, 127.0, 126.3, 126.0, 125.2, 121.7, 117.9, 112.0 (*C*-Ar), 62.4 (d, $^2J_{P-C}$ = 10.5 Hz, CH_2OP), 32.4 (d, $^1J_{P-C}$ = 68.8 Hz, *C*HMe), 16.7 (d, $^3J_{P-C}$ = 6.9 Hz, *Me*COP), 15.7 (d, $^2J_{P-C}$ = 11.8 Hz, C-2-*Me*); δ_P (200.7 MHz, $CDCl_3$) 14.2; *m/z* (%) 346 (11) [M^+-1], 238 (100). Anal. Calcd for $C_{17}H_{18}NO_3PS$ (347.3): C, 58.78; H, 5.22; N, 4.03; P, 8.92; S, 9.23. Found: C, 58.86; H, 5.13; N, 3.98; P, 8.98; S, 9.38.

[4-(3-Ethoxy-2-methyl-3-oxido-2,3-dihydro-1,5,3-benzothiazaphosphepin-4-yl)phenyl]-dimethylamine (4b) was obtained as yellow crystals (0.28 g, 75%); mp 157 °C (EtOH); ν_{max}/cm^{-1} 1559, 1263, 1047; δ_H (500.7 MHz, $CDCl_3$) 1.23 (dt, ^{3} J_{H-H} = 6.4 Hz, $^4J_{P-H}$ = 4.8 Hz, 3H, *Me*), 1.29 (dd, J_{H-H} = 4.7 Hz, $^3J_{P-H}$ = 8.8 Hz, 3H, *Me*), 3.13 (s, 6H, Me_2N), 4.19 (dq, J_{H-H} = 6.3 Hz, $^3J_{P-H}$ = 5.9 Hz, 2H, H_2C), 5.14 (dq, J_{H-H} = 6.3 Hz, $^2J_{P-H}$ = 14.9 Hz, 1H, *H*C-P), 6.89-8.34 (m, 8H, *H*-Ar); δ_C (125.4 MHz, , $CDCl_3$) 187.1 (d, J_{P-C} = 76.3 Hz, *C*-4), 153.8, 151.0, 129.7, 129.4, 128.5, 127.7, 127.0, 126.2, 126, 125.2, 113.7 (*C*-Ar), 62.4 (d, $^2J_{P-C}$ = 9.8 Hz, CH_2OP), 39.6 (Me_2N), 33.6 (d, $^1J_{P-C}$ = 66.7 Hz, *C*HMe), 16.5 (d, $^3J_{P-C}$ = 6.5 Hz, *Me*COP), 14.9 (d, $^2J_{P-C}$ = 10.2 Hz, C-2-*Me*); δ_P (200.7 MHz, , $CDCl_3$) 14.8; *m/z* (%) 373 (14) [M^+-1], 238 (100). Anal. Calcd for $C_{19}H_{23}N_2O_2PS$ (374.4): C, 60.95; H, 6.19; N, 7.48; P, 8.27; S, 8.56. Found: C, 61.09; H, 6.12; N, 7.43; P, 8.36; S, 8.68.

Diethyl 4-(2-hydroxybenzyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-3-yl-phosphonate (7a) was obtained as colorless crystals (0.27 g, 64%); mp 144 °C (cyclohexane); ν_{max}/cm^{-1} 3431, 1605, 1256, 1095; δ_H (500.7 MHz, $CDCl_3$) 1.13 (dt, J_{H-H}= 6.7 Hz, $^4J_{P-H}$ = 4.9 Hz, 2 × 3H, *Me*COP), 1.53, 1.87 (2d, $^4J_{P-H}$ = 4.2 Hz, 2 × 3H, 2*Me*), 4.09 (dq, J_{H-H} = 6.7 Hz, $^3J_{P-H}$ = 6.2 Hz, 2 × 2H, H_2COP), 7.26-8.31 (m, 8H, *H*-Ar), 9.55 (s, 1H, *H*N), 11.74 (s, 1H, *H*O); δ_C (125.4 MHz, $CDCl_3$) 154.4 (d, $^2J_{P-C}$ = 31.3 Hz, *C*-4), 155.6, 145.1, 130.6, 130.2, 126.4, 125.9, 125.7, 123.3, 121.0, 119.4 (*C*-Ar), 112.5 (d, $^1J_{P-C}$ = 80.5 Hz, *C*-P), 61.6 (d, $^2J_{P-C}$ = 10.7 Hz, CH_2), 47.2 (d, $^2J_{P-C}$ = 14.2 Hz, *C*-2), 33.2, 31.0 (2d, $^3J_{P-C}$ = 7.8 Hz, 2*Me*), 15.9 (d, $^3J_{P-C}$ = 5.6 Hz, *Me*); δ_P (200.7 MHz, $CDCl_3$) 27.8; *m/z* (%) 418 (17) [M^+-1], 234 (100). Anal. Calcd for $C_{21}H_{26}NO_4PS$ (419.4): C, 60.13; H, 6.25; N, 3.34; P, 7.38; S, 7.64. Found: C, 60.25; H, 6.37; N, 3.29; P, 7.51, S, 7.52.

Diethyl 4-(4-(dimethylamino)benzyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-3-ylphosphonate (7b) was obtained as colorless crystals (0.30 g, 68%); mp 168 °C (CH_2Cl_2); ν_{max}/cm^{-1} 1599, 1259, 1079; δ_H (500.7 MHz, $CDCl_3$) 1.09 (dt, J_{H-H} = 7.1 Hz, $^4J_{P-H}$ = 4.7 Hz, 2 × 3H, *Me*COP), 1.67, 1.84 (2d, $^4J_{P-H}$ = 4.2 Hz, 2 × 3H, 2*Me*), 3.03 (s, 6H, Me_2N), 4.12 (dq, $^3J_{H-H}$ = 6.7 Hz, $^3J_{P-H}$ = 5.8 Hz, 2 × 2H, 2H_2COP), 7.26-8.11 (m, 8H, *H*-Ar), 10.49 (s, 1H, *H*N), ; δ_C (125.4 MHz, $CDCl_3$) 155.8 (d, $^2J_{P-C}$ = 33.5 Hz, *C*-4), 150.1, 143.8, 130.4, 130.2, 127.4, 126.4, 123.2, 121.4, 121.0, 114.2 (*C*-Ar), 111.7 (d, $^1J_{P-C}$ = 84.4 Hz, *C*-P), 63.2 (d, $^2J_{P-C}$ = 10.2 Hz, CH_2), 47.3 (d, $^2J_{P-C}$ = 20.6 Hz, *C*-Me_2), 40.2 (Me_2N), 32.6 (2d, $^3J_{P-C}$ 5.8 Hz, 2*Me*), 15.5 (d, $^3J_{P-C}$ 4.9 Hz, *Me*); δ_P (200.7 MHz, $CDCl_3$) 28.4; *m/z* (%) 445 (15) [M^+-1], 234 (100). Anal. Calcd for

$C_{23}H_{31}N_2O_3PS$ (446.5): C, 61.86; H, 7.00; N, 6.27; P, 6.94; S, 7.18. Found: C, 61.98; H, 7.07; N, 6.18; P, 7.08; S, 7.28.

Methyl 2-ethoxy-4-(4-hydroxyphenyl)-2,5-dihydro-1,5,2-benzothiazaphosphepine-3-carboxylate 2-oxide (10a) was obtained as str. yellow crystals (0.27 g, 69%); mp 150 °C (CH_2Cl_2); ν_{max}/cm^{-1} 3434, 1697, 1256, 1087; δ_H (500.7 MHz, $CDCl_3$) 1.24 (dt, $^3J_{H-H}$ = 6.7 Hz, $^4J_{P-H}$ = 4.3 Hz, 3H, *Me*COP), 3.61 (s, 3H, H_3C, ester), 4.39 (dq, J_{H-H} = 6.7 Hz, $^3J_{P-H}$ = 6.7 Hz, 2H, H_2COP), 6.91-8.01 (m, 8H, *H*-Ar), 9.56 (s, 1H, *H*N), 12.56 (br, 1H, *H*O); δ_C (125.4 MHz, $CDCl_3$) 166.6 (d, J_{P-C} = 11.4 Hz, *C*-4), 160.4 (d, $^2J_{P-C}$ = 7.6 Hz, *C*=O), 156.6, 141.3, 130.8, 130.3, 129.1, 126.9, 126.3, 123.9, 119.7, 118.9, 118.7 (*C*-Ar), 91.3 (d, $^1J_{P-C}$ = 123.1 Hz, *C*-P), 61.5 (d, $^2J_{P-C}$ = 10.4 Hz, CH_2), 52.2 (*Me*), 15.8 (d, J_{PC} = 7.5 Hz, *Me*COP); δ_P (200.7 MHz, $CDCl_3$) 13.2; *m/z* (%) 390 (9) [M^+-1], 282 (100). Anal. Calcd for $C_{18}H_{18}NO_5PS$ (391.3): C, 55.24; H, 4.64; N, 3.58; P, 7.91; S, 8.19. Found: C, 55.30; H, 4.59; N, 3.54; P, 7.97; S, 8.06.

Ethyl 2-ethoxy-4-(4-hydroxyphenyl)-2,5-dihydro-1,5,2-benzothiazaphosphepine-3-carboxylate 2-oxide (10b) was obtained as str. yellow crystals (0.27 g, 68%); mp 141 °C (CH_2Cl_2); ν_{max}/cm^{-1} 3411, 1685, 1253, 1080; δ_H (500.7 MHz, $CDCl_3$) 1.23 (t, J_{H-H} = 6.8 Hz, 3 H, *Me*), 1.28 (dt, $^3J_{H-H}$ = 6.5 Hz, $^4J_{P-H}$ = 4.5 Hz, 3H, *Me*), 3.67 (q, J_{H-H} = 6.8 Hz, 2H, H_2C, ester), 4.43 (dq, $^3J_{H-H}$ = 6.5 Hz, $^3J_{P-H}$ = 5.9 Hz, 2H, H_2COP), 7.11-7.97 (m, 8H, *H*-Ar), 9.52, 12.39, (2br, 2 × 1H, *H*N, *H*O); δ_C (125.4 MHz, $CDCl_3$) 167.2 (d, $^2J_{P-C}$ = 9.5 Hz, *C*-4), 160.7 (d, $^2J_{P-C}$ = 8.9 Hz *C*=O), ester), 156.8, 142.2, 130.5, 130.1, 129.5, 126.5, 126.2, 124.2, 123.1, 119.9, 118.9, (*C*-Ar), 91.5 (d, $^1J_{P-C}$ = 125.3 Hz, *C*-P), 61.9 (d, $^2J_{P-C}$ = 9.5 Hz, CH_2OP), 59.3 (CH_2), 16.0 (d, $^3J_{P-C}$ = 6.2 Hz, *Me*), 14.1 (*Me*); δ_P (200.7 MHz, $CDCl_3$) 13.7; *m/z* (%) 404 (13) [M^+-1], 296 (100). Anal. Calcd for $C_{19}H_{20}NO_5PS$ (405.4): C, 56.29; H, 4.97; N, 3.45; P, 7.64; S, 7.91. Found: C, 56.21; H, 5.06; N, 3.36; P, 7.62; S, 7.66.

2-[2-Ethoxy-3-(methylthio)-2-oxido-2,5-dihydro-1,5,2-benzothiazaphosphepin-4-yl]-phenol (10c) was obtained as yellow crystals (0.26 g, 69%); mp 127 °C (CH_2Cl_2); ν_{max}/cm^{-1} 3673-3404, 1241, 1078; δ_H (500.7 MHz, $CDCl_3$) 1.21 (dt, J_{H-H} = 6.9 Hz, $^4J_{P-H}$ = 4.9 Hz, 3H, *Me*), 2.28 (d, $^4J_{P-H}$ = 4.4 Hz, 3H, *Me*S), 4.33 (dq, J_{H-H} = 6.9 Hz, $^3J_{P-H}$ = 5.8 Hz, 2H, H_2C), 7.1-8.0 (m, 8H, *H*-Ar), 9.63, 12.35 (2s, 2 × 1H, *H*N & *H*O); δ_C (125.4 MHz, $CDCl_3$) 149.7 (d, J_{P-C} = 12.5 Hz, *C*-4), 155.4, 141.8, 130.7, 130.4, 129.0, 125.8, 124.4, 122.8, 121.1, 119.7, 118.2 (*C*-Ar), 105.6 (d, $^1J_{P-C}$ = 134.4 Hz, *C*-P), 62.3 (d, J_{P-C} = 10.8 Hz, CH_2), 15.7 (d, J_{P-C} = 7.5 Hz, *Me*), 14.5 (*Me*S); δ_P (200.7 MHz, $CDCl_3$) 15.3; *m/z* (%) 378 (10) [M^+-1], 255 (100). Anal. Calcd for $C_{17}H_{18}NO_3PS_2$ (379.4): C, 53.97; H, 4.78; N, 3.69; P, 8.16; S, 16.90. Found: C, 53.97; H, 4.69; N, 3.62; P, 8.09; S, 16.84.

2-Ethoxy-4-(2-hydroxyphenyl)-2,5-dihydro-1,5,2-benzothiazaphosphepine-3-carbothioamide 2-oxide (10d) was obtained as yellow crystals (0.27 g, 71%); mp 174 °C (CH_2Cl_2); ν_{max}/cm^{-1} 3459, 3424, 1257, 1082; δ_H (500.7 MHz, $CDCl_3$) 1.27 (dt, $^3J_{H-H}$ = 6.7 Hz, $^4J_{P-H}$ = 4.9 Hz, 3H, *Me*), 4.36 (dq, $^3J_{H-H}$ = 6.7 Hz, $^3J_{P-H}$ = 5.2 Hz, 2H, H_2C), 6.99-7.49 (m, 8H, *H*-Ar), 9.78 (br, 2H, H_2N), 9.96 (br, 1H, *H*N), 11.02 (s, 1H, *H*O); δ_C (125.4 MHz, $CDCl_3$) 208.4 (*C*=S), 171.2 (d, $^2J_{P-C}$ = 11.5 Hz, *C*-4), 157.2, 142.5, 132.5, 131.9, 130.0, 127.9, 124.6, 123.9, 121.6, 120.9, 119.5 (*C*-Ar), 116.2 (d, $^1J_{P-C}$ = 128.5 Hz, *C*-P), 62.3 (d, J_{P-C} = 11.5 Hz, CH_2), 15.3 (d, J_{P-C} 7.5 Hz, *Me*); δ_P (200.7 MHz, $CDCl_3$) 13.6; *m/z* (%) 391 (26) [M^+-1], 283 (100). Anal. Calcd for $C_{17}H_{17}N_2O_3PS_2$ (392.4): C, 52.03; H, 4.37; N, 7.14; P, 7.89; S, 16.34. Found: C, 51.97; H, 4.31; N, 7.09; P, 7.93; S, 16.27.

Methyl 2-ethoxy-4-(4-(dimethylamino)phenyl)-2,5-dihydro-1,5,2-benzothiazaphosphephine-3-carboxylate 2-oxide (10e) was obtained as str. yellow crystals (0.28 g, 69%); mp 178 ^{o}C ($CHCl_3$); ν_{max}/cm^{-1} 3359, 1697, 1256, 1087; δ_H (500.7 MHz, $CDCl_3$) 1.28 (dt, $J_{H\text{-}H}$ = 6.7 Hz, $^4J_{P\text{-}H}$ = 4.3 Hz, 3H, *Me*CO), 3.17 (s, 6H, *Me*$_2$N), 3.91 (s, 3H, *Me*O), 4.27 (dq, $J_{H\text{-}H}$ = 6.7 Hz, $^3J_{P\text{-}H}$ = 5.7 Hz, 2H, *H*$_2$C), 6.89-8.12 (m, 8H, *H*-Ar), 12.30 (s, 1H, *H*N); δ_C (125.4 MHz, $CDCl_3$) 167.0 (d, $^2J_{P\text{-}C}$ = 11.8 Hz *C*-4), 161.4 (d, $^2J_{P\text{-}C}$ = 9.5 Hz *C*=O), 149.8, 142.1, 132.5, 129.7, 128.9, 123.9, 123.5, 119.8, 118.4, 114.3 (*C*-Ar), 90.5 (d, $^1J_{P\text{-}C}$ = 127.5 Hz, *C*-P), 61.9 (d, $^2J_{P\text{-}C}$ = 10.2 Hz, *C*H$_2$), 53.2, 40.5 (*Me*, *Me*$_2$N), 14.6 (d, $^3J_{P\text{-}C}$ = 6.2 Hz, *Me*); δ_P (200.7 MHz, $CDCl_3$) 13.8; *m/z* (%) 417 (9) [M$^+$-1], 282 (100). Anal. Calcd for $C_{20}H_{23}N_2O_4PS$ (418.4): C, 57.41; H, 5.54; N, 6.69; P, 7.40; S, 7.66. Found: C, 57.46; H, 5.50; N, 6.63; P, 7.44; S, 7.61.

Ethyl 2-ethoxy-4-(4-(dimethylamino)phenyl)-2,5-dihydro-1,5,2-benzothiazaphosphephine-3-carboxylate 2-oxide (10f) was obtained as str. yellow crystals (0.30 g, 70%); mp 166 ^{o}C ($CHCl_3$); ν_{max}/cm^{-1} 3448, 1230, 1183; δ_H (500.7 MHz, $CDCl_3$) 1.27 (t, $J_{H\text{-}H}$ = 7.4 Hz, 3H, *Me*), 1.27 (dt, $J_{H\text{-}H}$ = 6.5 Hz, $^4J_{P\text{-}H}$ = 4.3 Hz, 3H, *Me*COP), 3.03 (s, 6H, *Me*$_2$N), 4.27 (q, $J_{H\text{-}H}$ = 7.4 Hz, 2H, *H*$_2$C), 4.45 (dq, $^3J_{H\text{-}H}$ = 6.5 Hz, $^3J_{P\text{-}H}$ = 5.9 Hz, 2H, *H*$_2$C), 6.95-7.99 (m, 8H, *H*-Ar), 12.31 (br, 1H, *H*N); δ_C (125.4 MHz, $CDCl_3$) 167.5 (d, $^2J_{P\text{-}C}$ = 11.5 Hz *C*-4), 160.8 (d, $^2J_{P\text{-}C}$ = 9.4 Hz *C*=O), 149.9, 140.5, 131.8, 129.6, 128.7, 124.5, 123.2, 120.2, 118.5, 115.2 (*C*-Ar), 91.1 (d, $^1J_{P\text{-}C}$ = 132.2 Hz, *C*-P), 63.0 (d, $^2J_{P\text{-}C}$ = 9.5 Hz, *C*H$_2$OP), 59.3 (*C*H$_2$), 38.6 (*Me*$_2$N), 16.2 (d, $^3J_{P\text{-}C}$ = 5.6 Hz, *Me*), 14.5 (*Me*); δ_P (200.7 MHz, $CDCl_3$) 15.8; *m/z* (%) 431 (21) [M$^+$-1], 296 (100). Anal. Calcd for $C_{21}H_{25}N_2O_4PS$ (432.4): C, 58.32; H, 5.83; N, 6.48; P, 7.16; S, 7.41. Found: C, 58.47, H, 5.73; N, 6. 39; P, 7.26; S, 8.03.

4-[4-(Dimethylamino)phenyl)-2-oxido-2,5-dihydro-1,5,2-benzothiazaphosphepin-4-yl]-phenol (10g) was obtained as yellow crystals (0.28 g, 70%); mp 152 ^{o}C (CH_2Cl_2); ν_{max}/cm^{-1} 3364, 1223, 1078; δ_H (500.7 MHz, $CDCl_3$) 1.24 (dt, $^3J_{H\text{-}H}$ = 6.9 Hz, $^4J_{P\text{-}H}$ = 4.9 Hz, 3H, *Me*), 2.71 (d, $^4J_{P\text{-}H}$ = 4.6, 3H, *Me*S), 3.02 (s, 6H, *Me*$_2$N), 4.32 (dq, $J_{H\text{-}H}$ = 6.9 Hz, $J_{P\text{-}H}$ = 5.8 Hz, 2H, *H*$_2$C), 6.76-8.03 (m, 8H, *H*-Ar), 10.55 (br, 1H, *H*N); δ_C (125.4 MHz, $CDCl_3$) 150.1 (*C*-4), 150.0, 140.6, 130.7, 128.8, 127.4, 124.5, 123.2, 121.6, 119.5, 114.3 (*C*-Ar), 104.6 (d, $^1J_{P\text{-}C}$ = 130.4 Hz, *C*-P), 62.4 (d, $^2J_{P\text{-}C}$ = 9.8 Hz, *C*H$_2$OP), 40.2 (*Me*$_2$N), 15.2 (d, $^3J_{P\text{-}C}$ = 6.5 Hz, *C*H$_3$), 14.5 (*Me*-S); δ_P

, $CDCl_3$) 1.28 (dt, $^3J_{H\text{-}H}$ = 6.9 Hz, $^4J_{P\text{-}H}$ = 4.9 Hz, 3H, *Me*CO), 3.09 (s, 6H, *Me*$_2$N), 4.15 (dq, $^3J_{H\text{-}H}$ = 6.9 Hz, $^3J_{P\text{-}H}$ = 5.1 Hz, 2H, *H*$_2$COP), 6.83-8.26 (m, 8H, *H*-Ar), 10.18, 11.55 (2br, 2H, 1H, *H*$_2$N, *H*N); δ_C (125.4 MHz, $CDCl_3$) 208.7 (*C*=S), 171.4 (*C*-4), 151.4, 142.3, 131.5, 129.9, 128.2, 124.5, 123.6, 122.4, 121.4, 115.4, (*C*-Ar), 115.3 (d, $^1J_{P\text{-}C}$ = 129.5 Hz, *C*-P), 60.9 (d, $^2J_{P\text{-}C}$ = 10.2 Hz, *C*H$_2$), 40.2 (*Me*$_2$N), 14.5 (d, $^3J_{P\text{-}C}$ = 5.6 Hz, *Me*COP); δ_P (200.7 MHz, $CDCl_3$) 14.1; *m/z* (%) 418 (18) [M$^+$-1], 283 (100). Anal. Calcd for $C_{19}H_{22}N_3O_2PS_2$ (419.5): C, 54.40; H, 5.29; N, 10.02; P, 7.38; S, 15.29. Found: C, 54.33; H, 5.18; N, 9.95; P, 7.44; S, 15.37.

(200.7 MHz, $CDCl_3$) 15.8; *m/z* (%) 405 (7) [M$^+$-1], 255 (100). Anal. Calcd for $C_{19}H_{23}N_2O_2PS_2$ (406.5): C, 56.14; H, 5.70; N, 6.89; P, 7.62; S, 15.78. Found: C, 56.07; H, 5.64; N, 6.74; P, 7.74; S, 15.88

4-[4-(Dimethylamino)phenyl]-2-ethoxy-2,5-dihydro-1,5,2-benzothiazaphosphepine-3-carbothioamide 2-oxide (10h) was obtained as yellow crystals (0.30 g, 72%); mp 184 ^{o}C (CH_2Cl_2); ν_{max}/cm^{-1} 3423 (br), 1232, 1061; δ_H (500.7 MHz

Bioscreening assays

Animals: Adult Swiss albino rats (90 days) were used in this study. The rats were fed a standard pellet diet and given water ad libitum. Animals were maintained under proper temperature (25-30 °C), ventilation, and hygienic conditions. They were exposed to 12 h each of light and dark.

Antioxidant evaluation

Reagents: DNA (Type 1, calf thymus, bleomycin sulfate, butylated hydroxyanisol (BHA), and L-ascorbic acid were obtained from Sigma. AAPH and ABTS were purchased from Wak. All other chemicals were of high quality available.

Assay for erythrocyte hemolysis: Blood was obtained from rats by cardiac puncture and collected in heparinized tubes. Erythrocytes were separated from plasma and the buffy coat was washed three times with 10 volume of 0.15 M NaCl. During the last washing, the erythrocytes were centrifuged at 2500 rpm for 10 min to obtain a constantly packed cell preparation. Erythrocyte hemolysis was mediated by proxyl radicals in this assay system.[25] 10% Suspension of erythrocyte in pH 7.4 phosphate-buffered saline (PBS) was added to the same volume of 200 mM of 2,2`-Azobis-(2-amidino-propane)dihydrochloride (AAPH) containing samples to be tested vitamin C (**Y**) **1b, 4a, 4b**, **7a**, **7b**, or **10a-10h** (2 mM). The mixture was shaken gently while being incubated at 37 °C for ≈ 1 h; then removed, diluted with eight times of PBS and centrifuged at 2500 rpm for 10 min. The absorbance *A* of the supernatant was read at 540 nm. Similarly, the mixture was treated with eight volumes of distilled water to achieve complete hemolysis, and the absorbance *B* of the supernatant obtained after centrifugation was measured at 540 nm; data were expressed as mean standard deviation. The percentage of hemolysis was calculated using the equation: $[(1 - A/B) \times 100]$. The result of the antioxidant assay by erythrocyte hemolysis was presented in Table 1.

***Antioxidant activity screening assay-ABTS method*:-**

For each of the investigated compounds, 2 mL of 2,2`-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) solution (60 mm) was added to 3 M MnO_2 solution (25 μg/mL) all prepared in PBS (pH 7.0). The mixture was shaken, centrifuged, filtered, and the absorbance ($A_{control}$) of the resulting green-blue solution (ABTS radical solution) was adjusted at *ca* 0.5 at λ 734 nm. Then 50 mL of (2 mM) solution of the tested compound **Y**, **1b, 4a, 4b**, **7a**, **7b**, or **10a-10h** in spectroscopic grade EtOH/PBS (1:1) was added. The absorbance (A_{test}) was measured and the reduction in color intensity was expressed as %inhibition. The % inhibition for each compound is calculated from the following equation:[26] % Inhibition = $\{[A_{control} - A_{test}] / A_{control}\} \times 100$; blank sample was run without ABTS and using EtOH/PBS (1:1) instead of sample. Negative control sample was run with EtOH/phosphate buffer (1:1) instead of the tested compound. The result of the antioxidant assay by ABST method was displayed in Table 2.

Bleomycin-dependent DNA damage:

The assay was done according to the reported method.[27] The reaction mixture (0.5 mL) contained DNA (0.5 mg/mL), bleomycin sulfate (0.05 mg/mL), $MgCl_2$ (5 mM), $FeCl_3$ (50 mM), and selected samples to be tested **Y, 4b**, **7a**, **7b**, or **10a, 10b, 10g,** or **10h** (2 mM). The mixture was incubated at 37 °C for 1 h, and the reaction was terminated by addition of 0.05 mL ethylenediamine-tetraacetic acid (EDTA) (0.1 M). The color was developed by adding 0.5 mL thiobarbituric acid (TBA) (1% v/v) and 0.5 mL HCl (25% v/v), followed by heating at 80 °C for 10 min. After centrifugation, the extent of DNA damage was measured by the increase in

absorbance at 532 nm. The result of the assay for protection of bleomycin/DNA damage was displayed in Table 3.

Antidiabetic evaluation
Materials and methods

Diabetes was induced in rats (5 groups, 8 rats in each group) by the intraperitoneally (i.p.) injection of Streptozocin (STZ) dissolved in freshly prepared phosphate buffer saline (PBS). Seven days after the injection, the blood glucose levels were measured. The animal with a blood glucose concentration level above 250 mg/dL was considered to be diabetic and used in the experiments. To prevent the hypoglycemia which could occur during the 24 h following the STZ administration, 15% glucose solution was orally given to the diabetic rats. In all experiments, rats were fasted for 16 h prior to streptozocin (STZ) injection.

The tested samples glibenclamide (**Z**, standard drug), **1b, 4a, 4b**, **7a**, **7b**, or **10a-10h** at a dose 50 mg/kg b.w. were dissolved in ethanol and administered orally by using a gastric gavage needle. Blood glucose levels were determined after the administration of the tested samples to check the antidiabetic activity of the compounds. Fasting blood glucose level was measured after 7 days of EtOH solution of the tested compound administration from the animals of all groups. Blood was collected from the tip of the tail vein and fasting blood glucose level was measured using a single touch glucometer. The results were expressed in terms of mg/dL of the blood. The results of Blood glucose levels of diabetic rats treated with thiaphosphepines **4a, 4b, 10a-10h,** phosphonates **7a, 7b**, substrate **1b,** and **Z** (glibenclamide) were displayed in Table 4.

Table 1. Antioxidant assay[a)] by erythrocyte hemolysis;

(1 - *A*/*B* × 100)

Cmpd.	Absorb./ samples (*A*)	Hemolysis (%)	Cmpd.	Absorb./ samples (*A*)	Hemolysis (%)
% Hemolysis/Distill. H_2O (*B*)				0.782	--
Y[b]	0.028	96.42	**10c**	0.030	96.16
4a	0.028	96.42	**10d**	0.029	96.29
4b	0.035	96.52	**10e**	0.024	96.93
7a	0.264	66.24	**10f**	0.022	97.19
7b	0.362	53.71	**10g**	0.019	97.57
10a	0.037	95.27	**10h**	0.017	97.83
10b	0.038	95.14	**1b**	0.574	26.60

[a)] The data for hemolysis percentage was expressed as mean ± standard deviation.
[b)] **Y:** Vitamin C

Table 2. Antioxidant assay by ABST method

[Abs (control) - Abs (test)/Abs (control) × 100]

Cmpd	Absorb	%Inhibitn	Cmpd	Absorb	%Inhibitn
Control/ABTS				0.67	-
Y	0.07	89.55	**10c**	0.09	86.57
4a	0.18	73.13	**10d**	0.08	88.06
4b	0.23	65.67	**10e**	0.13	80.60
7a	0.34	49.25	**10f**	0.07	89.55
7b	0.38	43.28	**10g**	0.06	91.04
10a	0.27	59.70	**10h**	0.05	92.54
10b	0.31	53.73	**1b**	0.58	13.43

Table 3. Assay for protection of bleomycin/DNA damage

Cmpds.	Absorb.	Cmpds	Absorb.
Y	0.022	**10a**	0.032
4b	0.162	**10b**	0.035
7a	0.020	**10g**	0.028
7b	0.023	**10h**	0.026

Table 4. Blood glucose levels of diabetic rats treated with thiaphosphepines **4a, 4b, 10a-10h,** phosphonates **7a, 7b**, substrate **1b,** and **Z** (glibenclamide)

Cmpd	G. Initial (mg/dL)	G. Final (mg/dL)	Cmpd.	G. Initial (mg/dL)	G. Final (mg/dL)
Diabetic/control				424.6 ± 11.0	520.26 ± 6.1
4a	388. 58 ± 5.7	187.53 ± 10.3	**10c**	412.6 ± 9.6	152.86 ± 4.3
4b	402.54 ± 9.8	180.72 ± 4.4	**10d**	388.5 ± 4.7	160.42 ± 7.8
7a	417.62 ± 11.2	203.73 ± 7.4	**10e**	386.37 ± 10.8	155.88 ± 9.4

7b	398.36 ± 12.3	196.67 ± 7.2	**10f**	378.62 ± 10.2	165.64 ± 5.6
10a	406.26 ± 8.6	172.75 ± 3.8	**10g**	358.46 ± 11.5	146.63 ± 8.5
10b	408.75 ± 8.4	188.32 ± 6.6	**10h**	372.42 ± 11.0	144.50 ± 9.4
Z	414.66 ± 12.4	140.74 ± 3.54	**1b**	408.15 ± 10.4	394.24±13.2

Synthesis and bioactivity of benzothiazaphosphepines and relevant phosphonates as antioxidant/antidiabetic agents

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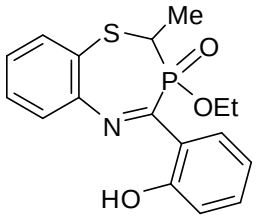
Supplementary Information 2

Full Spectra of the new compounds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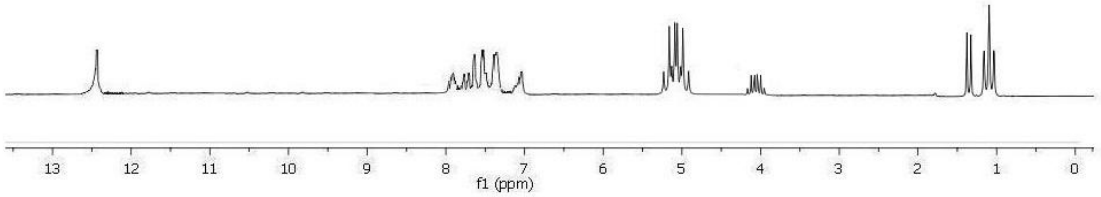
OEt
N
HO

4a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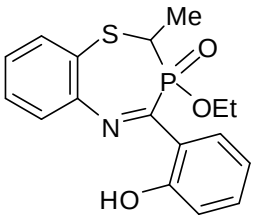
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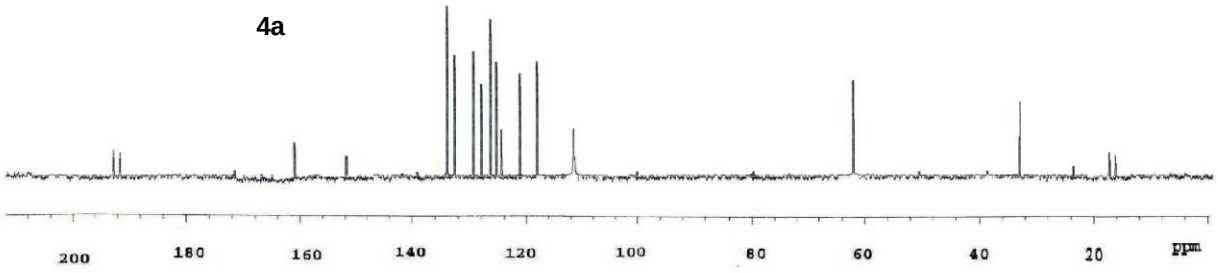
HO

4a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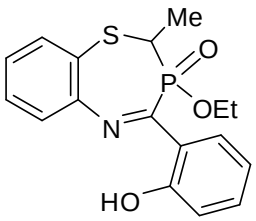
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4a

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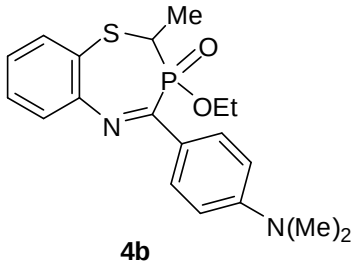
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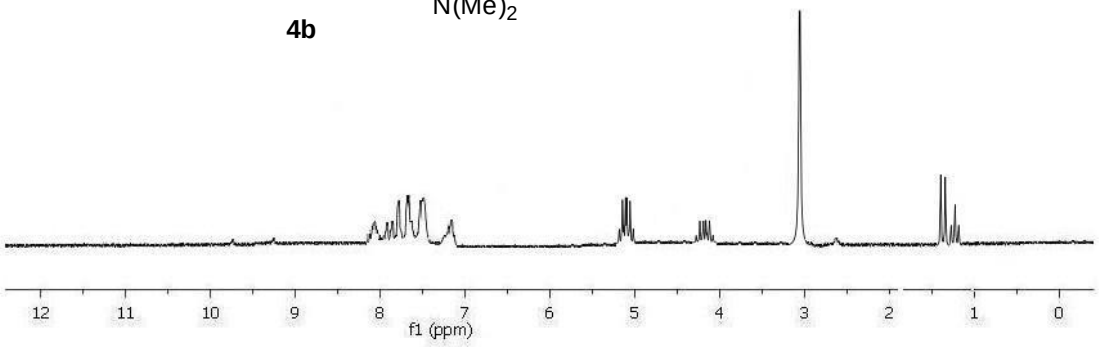
O
P
OEt
N
N(Me)2

4b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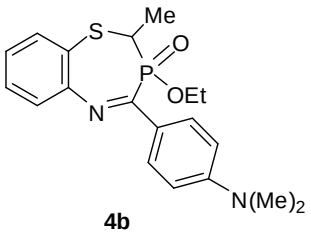
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P
OEt
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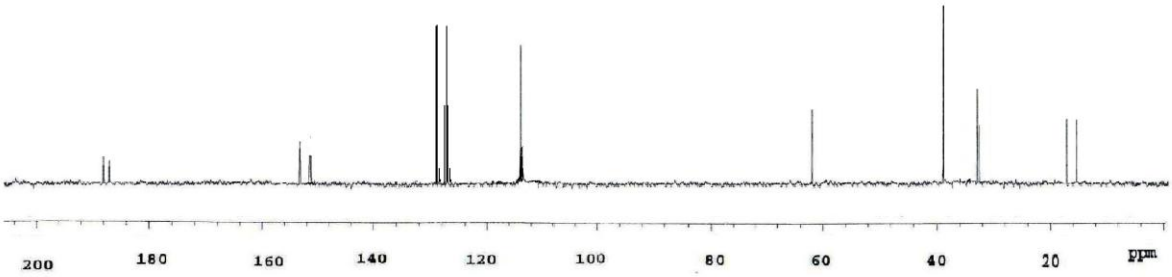
N(Me)2

4b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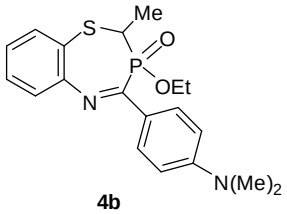
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N
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4b

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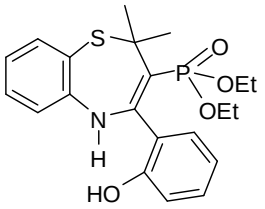
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P
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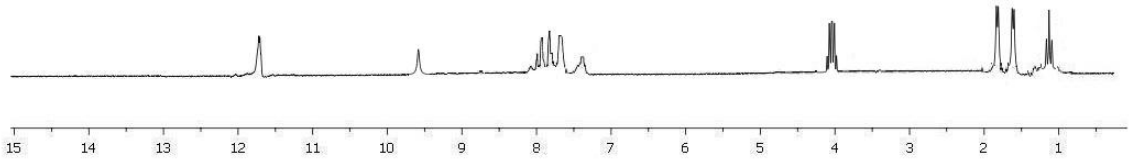
OEt
N
H
HO

7a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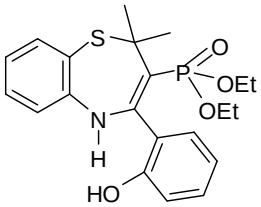
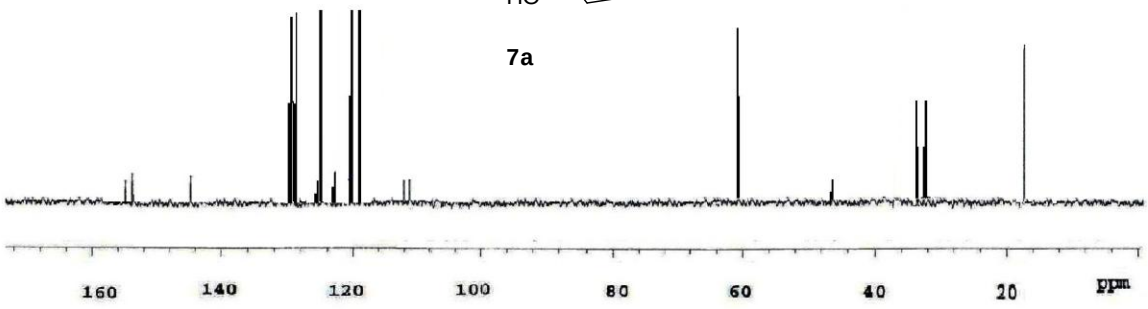

S
O
P
OEt
OEt
N
H
HO

7a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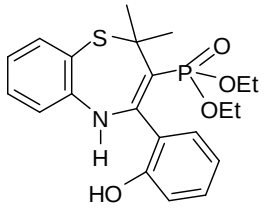
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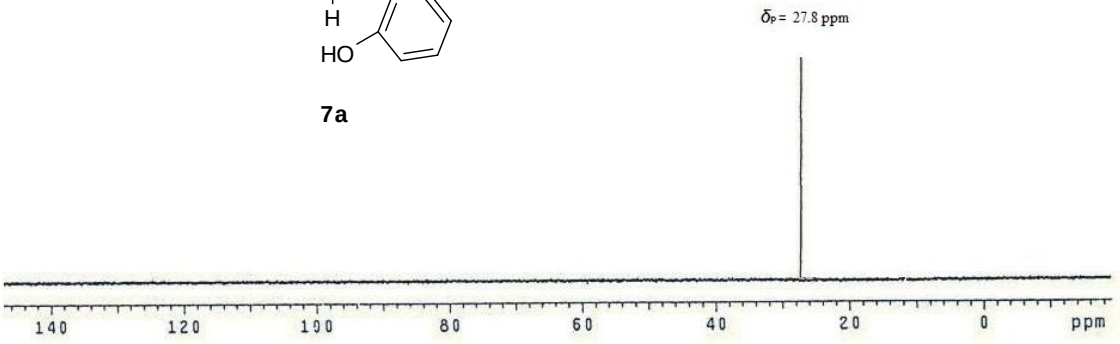
OEt
N
H
HO

7a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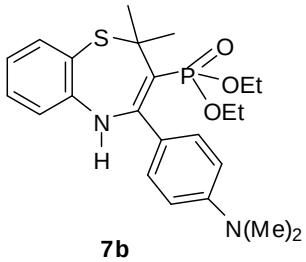
S
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7b

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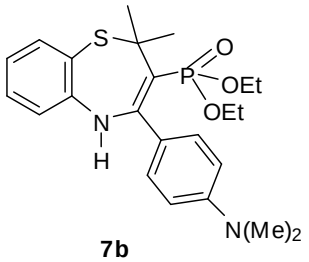
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OEt
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H
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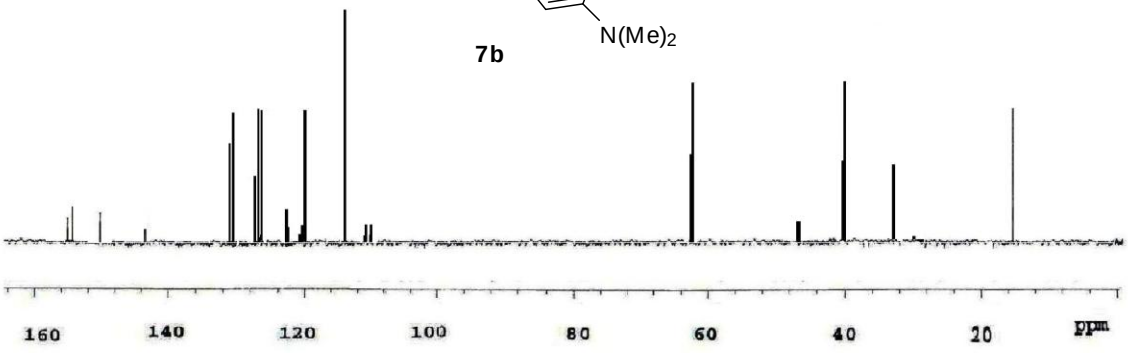
7b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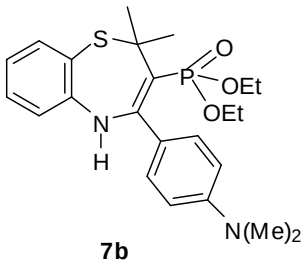
S
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OEt
OEt
N
H
N(Me)2

7b

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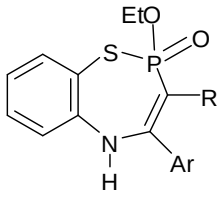
ppm



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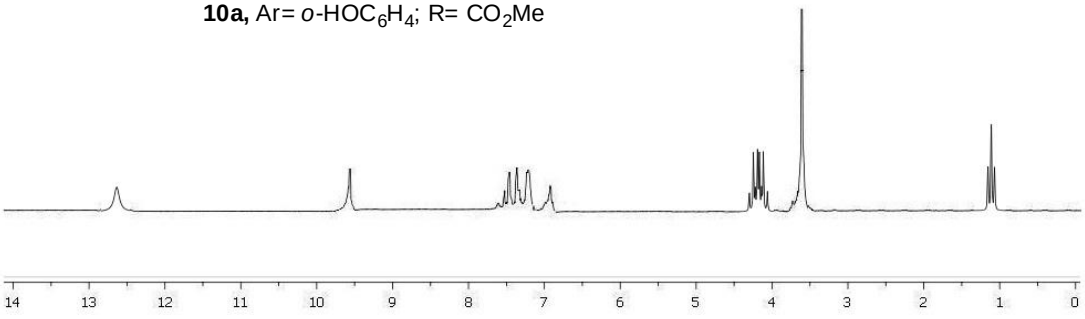

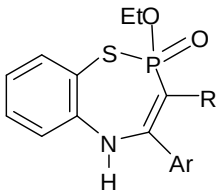

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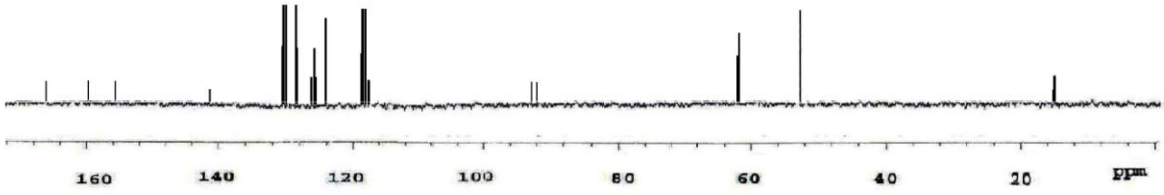

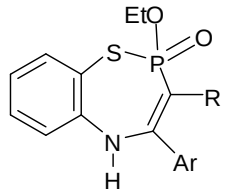

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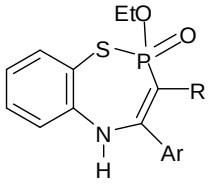

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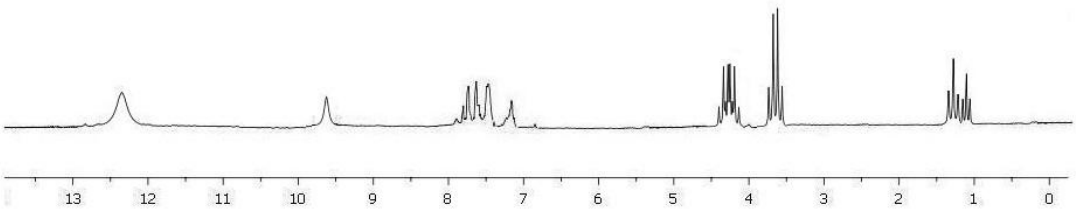

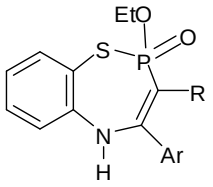

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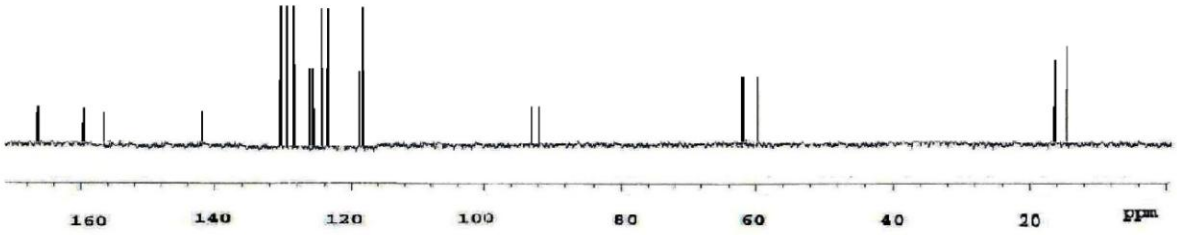

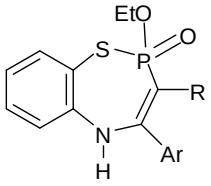

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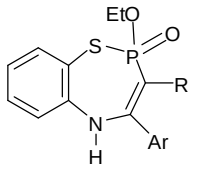

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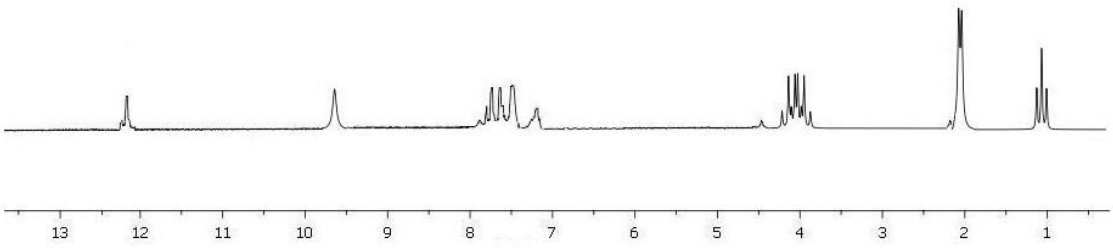

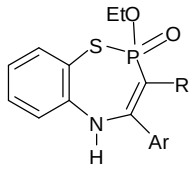

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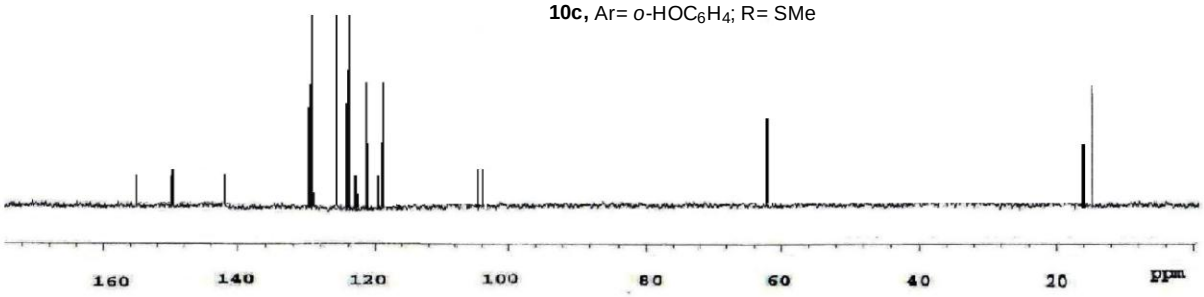
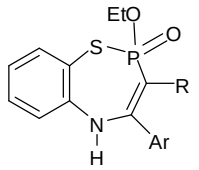
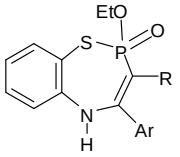
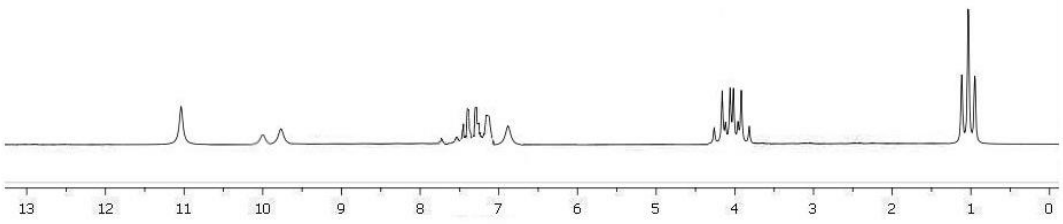


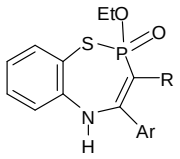


10c, Ar= *o*-HOC_6H_4; R= SMe

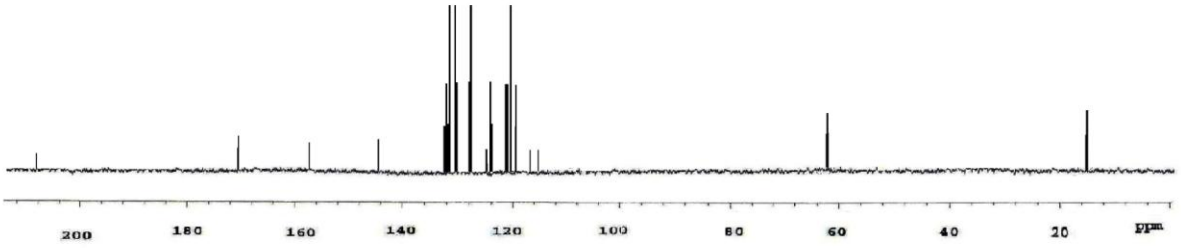


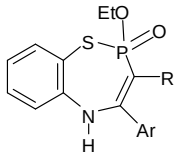
10d, Ar= *o*-HOC_6H_4; R= $C(S)NH_2$



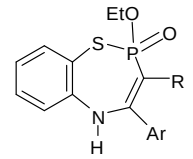


10d, Ar= *o*-HOC_6H_4; R= $C(S)NH_2$

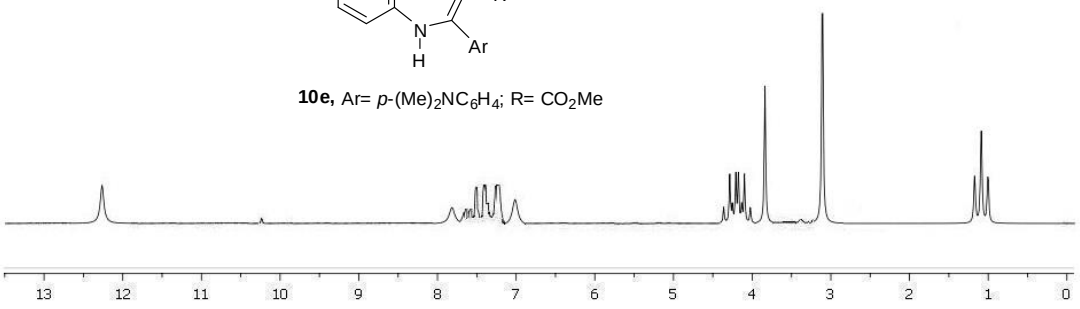


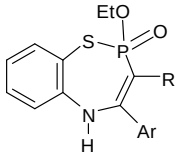


10d, Ar= *o*-HOC_6H_4; R= $C(S)NH_2$



10e, Ar= *p*-$(Me)_2NC_6H_4$; R= CO_2Me





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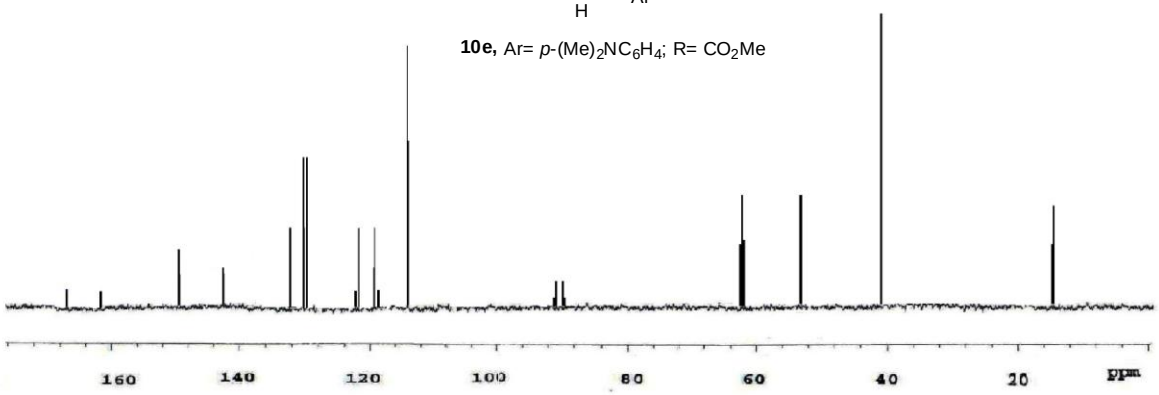
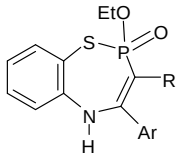
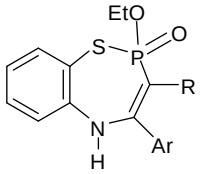




10e, Ar= *p*-$(Me)_2NC_6H_4$; R= CO_2Me



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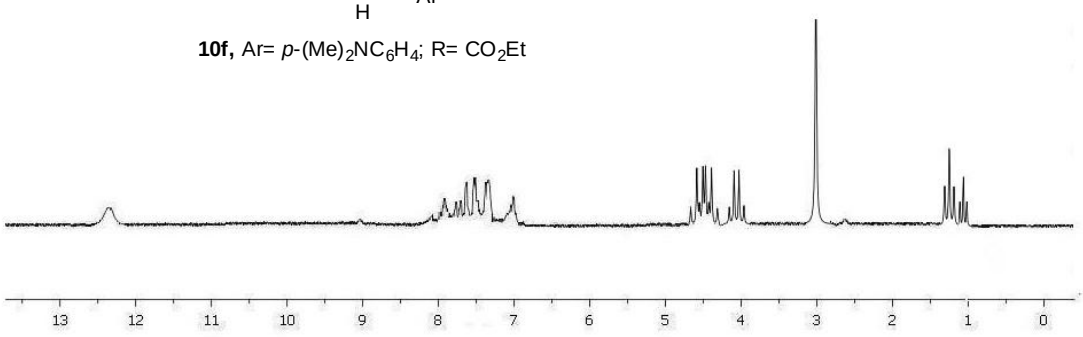
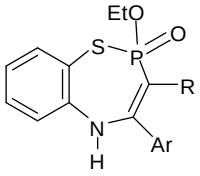
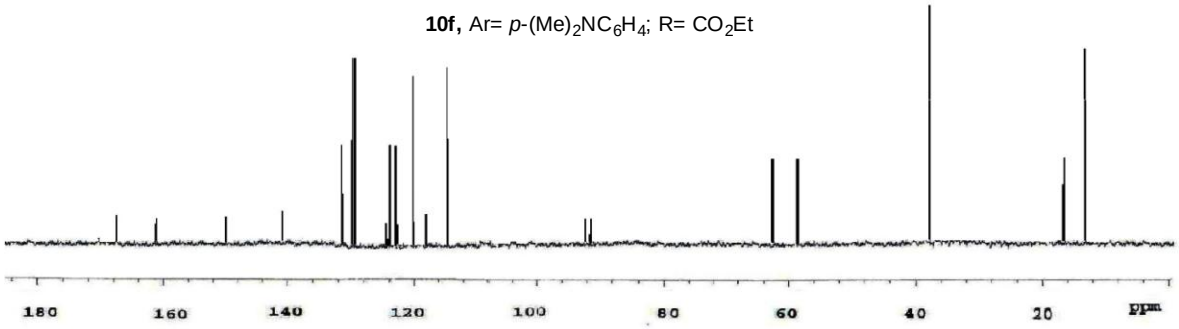
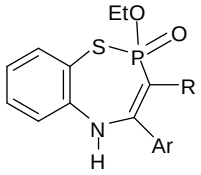


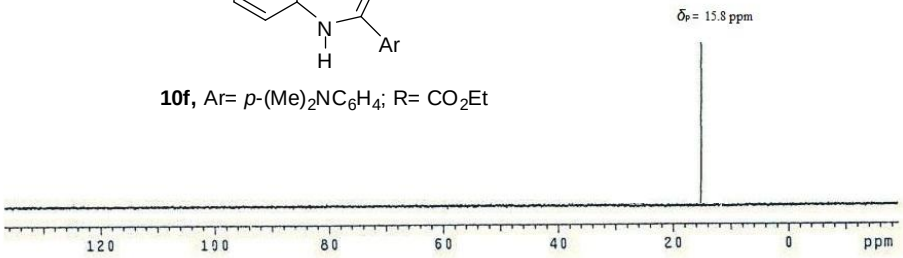


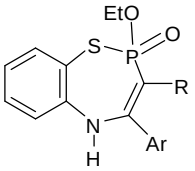
10f, Ar= *p*-$(Me)_2NC_6H_4$; R= CO_2Et



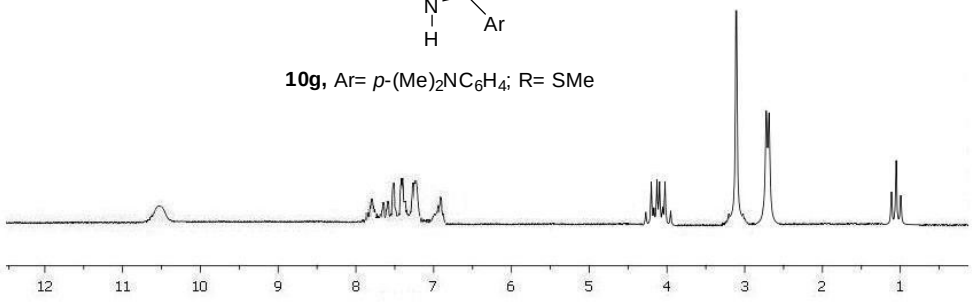


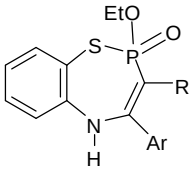
10f, Ar= *p*-$(Me)_2NC_6H_4$; R= CO_2Et





10g, Ar= *p*-$(Me)_2NC_6H_4$; R= SMe





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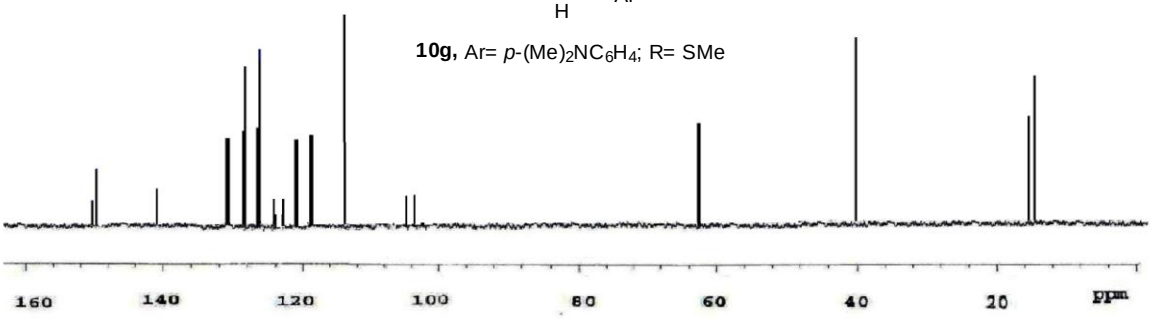

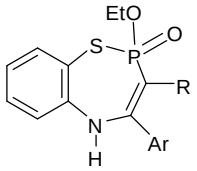

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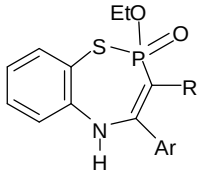

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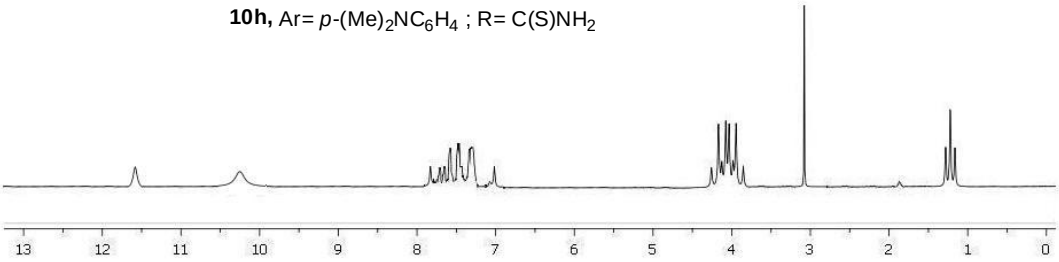

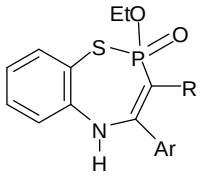

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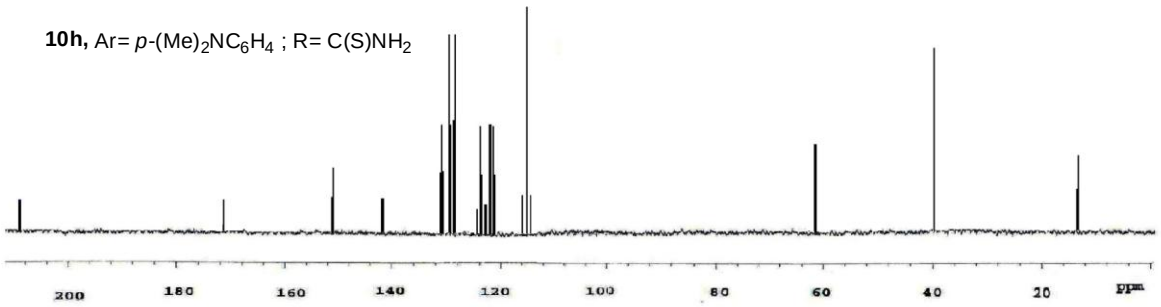

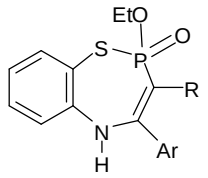

10h, Ar= *p*-$(Me)_2NC_6H_4$; R= $C(S)NH_2$