Supporting Information

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Nano-ZnO catalyzed microwave synthesis of novel α-aminophosphonates: anti-diabetic potential via molecular docking, ADMET analysis, and α-amylase inhibition studies

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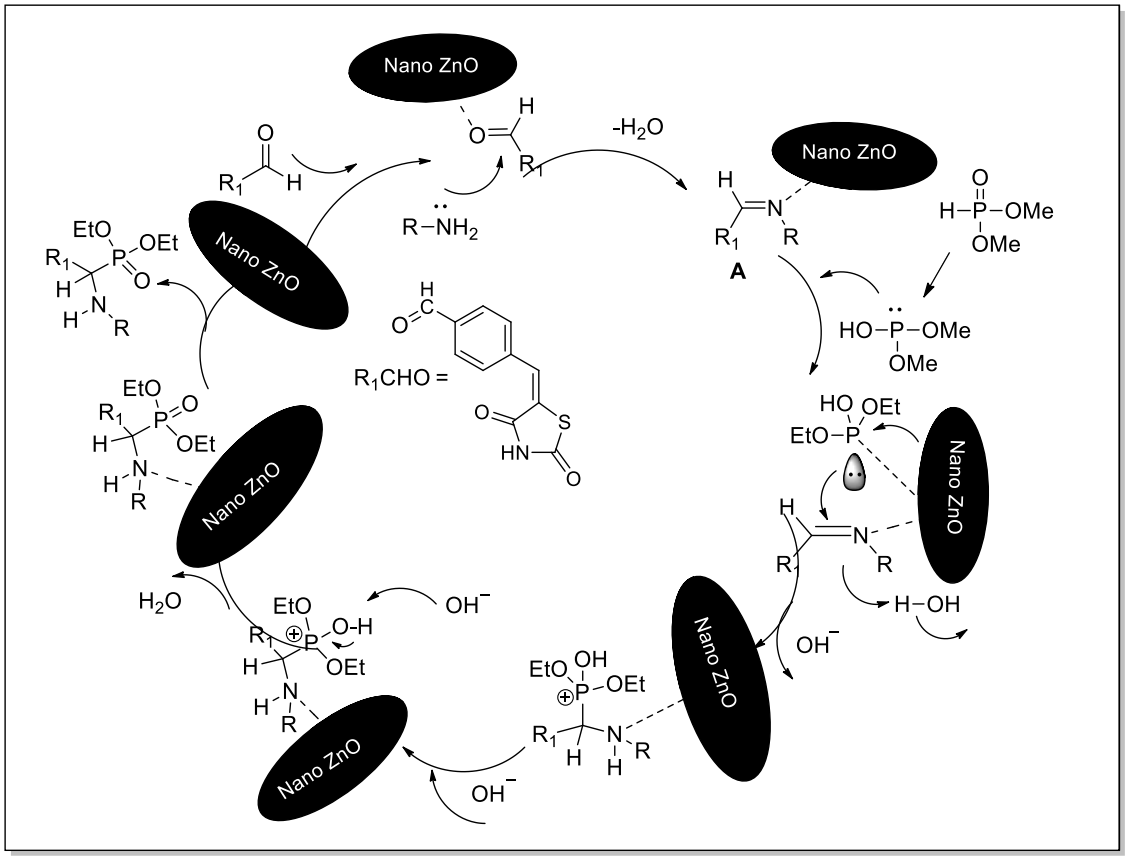
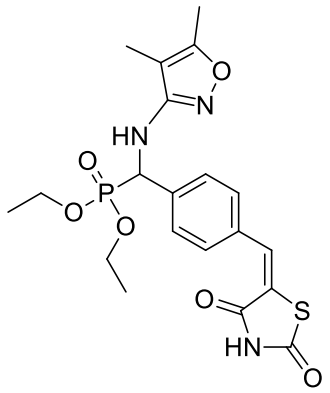


Figure S 1: Mechanism for the nano ZnO catalyzed synthesis of **8a-j**

Materials and characterization techniques

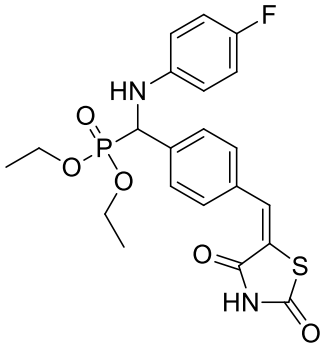
The Auto Dock Vina docking algorithm-powered 1-Click docking program was used to conduct the in silico molecular docking study. All of the compounds' structures were shown, refined, and formatted using Marvin View software. IC50 values were computed and biological activity graphs were generated using Excel software. Only a small portion of the chemicals, which were acquired from Sd. Fine Chem. Ltd. in India, were refined using traditional methods. Sigma Aldrich in India provided the commercially accessible nano ZnO (nanopowder, particle size <100 nm). A magnetic agitator that functioned as a hot plate was used for all of the reactions. The purity of the compounds was assessed using TLC on an Al sheet of silica gel. NMR spectra peaks were identified by the symbols 's' for singlet, 'd' for doublet, 't' for triplet, and'm' for multiplet. For MW irradiation studies, the catalyst microwave reactor-SSMW1 model was employed. The NMR spectra of ^{31}P (161.9 MHz), ^{1}H (400 MHz), and ^{13}C (100 MHz) were recorded using a Bruker AMX spectrometer. The SHIMADZU 2010A was used to record L.C. MS, and the T. F. Flash 1112 device was used to do CHN analysis. An FTIR spectrometer (Bruker IFS 55, Equinox) was used to record the IR spectra in KBr. The values of the chemical shift (δ) and coupling constants (J) are expressed in ppm and Hz, respectively.

*Spectral data of compounds **8b-j***



Compound **8b**

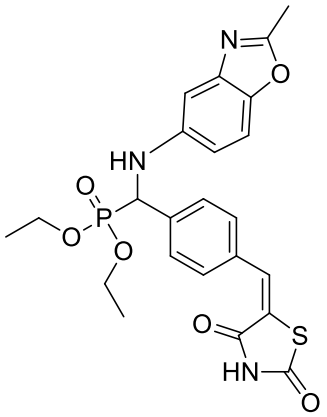
*(E)-diethyl (((4,5-dimethylisoxazol-3-yl)amino)(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)methyl)phosphonate (**8b**):* solid. M.P. 173-175 °C. Yield: 95%. δ_H (DMSO-d_6): 11.64 (s, 1H, Imide-H), 7.66 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.27 (d, *J*=7.2 Hz, 2H, Ar-H), 2.54 (s, 3H, -CH_3), 2.67 (s, 3H, -CH_3), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.28 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.06 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.93 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.23 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 149.34 (C-1'), 101.15 (C-2'), 157.46 (C-3'), 7.62 (C-4'), 10.45 (C-5'); δ_P (DMSO-d_6): 19.6 ppm; IR (KBr) (ν_{max} cm^{-1}): 3247, 3124 (NH), 1727 (C=O), 1210 (P=O), 1006 (P-O-C_{alip}); LCMS (m/z, %): 466 ($M+H^+$, 100); Anal. Calcd. for $C_{20}H_{24}N_3O_6PS$: C, 51.61; H, 5.20; N, 9.03%; found: C, 51.73; H, 5.08; N, 9.14%.



Compound **8c**

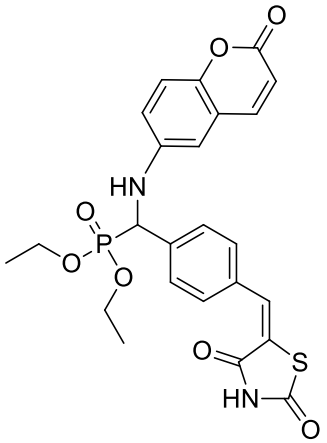
*(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)((4-fluorophenyl)amino)methyl)phosphonate (**8c**):* solid. M.P. 165-167 °C. Yield: 93%. δ_H (DMSO-d_6): 11.67 (s, 1H, Imide-H), 7.68 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.28 (d, *J*=7.2 Hz, 2H, Ar-H), 7.12 (d, *J*=7.6 Hz, 2H, Ar-H), 7.03 (d, *J*=6.8 Hz, 2H, Ar-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.30 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.09 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.95 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.25 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 145.23 (C-1'), 117.14 (C-2', C-6'), 116.22 (C-3', C-5'), 153.35 (C-4'); δ_P (DMSO-d_6): 18.9 ppm; IR (KBr) (ν_{max} cm^{-1}): 3264, 3132 (NH), 1729 (C=O), 1214 (P=O), 1008 (P-O-C_{alip}); LCMS (m/z, %):

465 ($M+H^+$, 100); Anal. Calcd. for $C_{21}H_{22}FN_2O_5PS$: C, 54.31; H, 4.77; N, 6.03%; found: C, 54.40; H, 4.66; N, 6.13%.



Compound **8d**

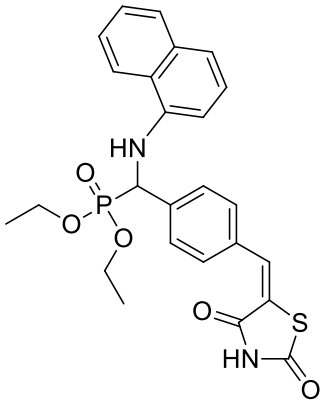
(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)((2-methylbenzo[d]oxazol-5-yl)amino)methyl)phosphonate ***(8d)****:* solid. M.P. 184-186 °C. Yield: 95%. δ_H (DMSO-d_6): 11.65 (s, 1H, Imide-H), 7.66 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.25 (d, *J*=7.2 Hz, 2H, Ar-H), 7.64 (d, *J*=7.6 Hz, 1H, Ar-H), 6.86 (d, *J*=7.2 Hz, 1H, Ar-H), 6.52 (s, 1H, Ar-H), 2.52 (s, 3H, -CH_3), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.27 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.93 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.25 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 141.62 (C-1'), 104.21 (C-2'), 142.93 (C-3'), 140.32 (C-4'), 110.32 (C-5'), 100.21 (C-6'), 163.63 (C-7'), 14.32 (C-8'); δ_P (DMSO-d_6): 21.5 ppm; IR (KBr) (ν_{max} cm^{-1}): 3271, 3141 (NH), 1738 (C=O), 1220 (P=O), 1009 (P-O-C_{alip}); LCMS (m/z, %): 502 ($M+H^+$, 100); Anal. Calcd. for $C_{23}H_{24}N_3O_6PS$: C, 55.08; H, 4.82; N, 8.38%; found: C, 55.20; H, 4.71; N, 8.48%.



Compound **8e**

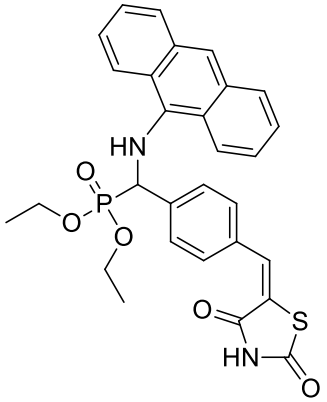
(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)((2-oxo-2H-chromen-6-yl)amino)methyl)phosphonate ***(8e)****:* solid. M.P. 194-196 °C. Yield: 94%. δ_H (DMSO-d_6): 11.64 (s, 1H, Imide-H), 7.67 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.27 (d, *J*=7.2 Hz, 2H, Ar-H), 7.88 (d, *J*=7.6 Hz, 1H, Coumarin-H), 7.27 (d, *J*=6.8 Hz, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 6.78 (d, *J*=7.6 Hz, 1H, Ar-H), 6.33 (d, *J*=6.8 Hz, 1H, Coumarin-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.30 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.95 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.25 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12

(t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 145.41 (C-1'), 114.64 (C-2'), 116.25 (C-3'), 144.66 (C-4'), 118.47 (C-5'), 109.25 (C-6'), 161.21 (C-7'), 114.63 (C-8'), 147.13 (C-9'); δ_P (DMSO-d_6): 22.7 ppm; IR (KBr) (ν_{max} cm^{-1}): 3278, 3145 (NH), 1740 (C=O), 1223 (P=O), 1012 (P-O-C_{alip}); LCMS (m/z, %): 515 ($M+H^+$, 100); Anal. Calcd. for $C_{24}H_{23}N_2O_7PS$: C, 56.03; H, 4.51; N, 5.44 %; found: C, 56.11; H, 4.59; N, 5.34 %.



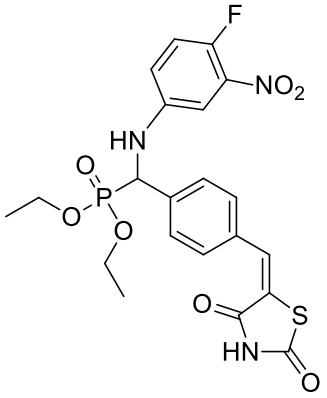
Compound **8f**

(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(naphthalen-1-ylamino)methyl)phosphonate ***(8f)****:* solid. M.P. 178-180 °C. Yield: 96%. δ_H (DMSO-d_6): 11.62 (s, 1H, Imide-H), 7.66 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.26 (d, *J*=7.2 Hz, 2H, Ar-H), 8.15 (d, *J*=7.6 Hz, 1H, Ar-H), 8.03 (d, *J*=6.8 Hz, 1H, Ar-H), 7.75 (d, *J*=7.2 Hz, 1H, Ar-H), 7.68 (t, *J*=7.6 Hz, 1H, Ar-H), 7.52 (t, *J*=6.8 Hz, 1H, Ar-H), 7.47 (t, *J*=7.2 Hz, 1H, Ar-H), 6.89 (d, *J*=7.2 Hz, 1H, Ar-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.27 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.07 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.93 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.24 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 145.41 (C-1'), 123.64 (C-2'), 136.21 (C-3'), 118.26 (C-4'), 128.07 (C-5'), 109.25 (C-6'), 125.42 (C-7'), 126.64 (C-8'), 127.13 (C-9'), 129.24 (C-10'); δ_P (DMSO-d_6): 16.8 ppm; IR (KBr) (ν_{max} cm^{-1}): 3278, 3146 (NH), 1730 (C=O), 1214 (P=O), 1005 (P-O-C_{alip}); LCMS (m/z, %): 497 ($M+H^+$, 100); Anal. Calcd. for $C_{25}H_{25}N_2O_5PS$: C, 60.47; H, 5.08; N, 5.64%; found: C, 60.58; H, 5.00; N, 5.73%.



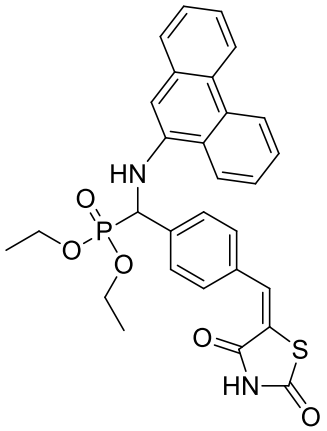
Compound **8g**

(E)-diethyl ((anthracen-9-ylamino)(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)methyl)phosphonate ***(8g)****:* solid. M.P. 201-203 °C. Yield: 97%. δ_H (DMSO-d_6): 11.63 (s, 1H, Imide-H), 7.66 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.27 (d, *J*=7.2 Hz, 2H, Ar-H), 7.83 (d, *J*=7.6 Hz, 2H, Ar-H), 7.75 (d, *J*=6.8 Hz, 2H, Ar-H), 6.63 (s, 1H, Ar-H), 7.45 (m, *J*=6.8 Hz, 4H, Ar-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.29 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.07 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.95 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.24 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 141.23 (C-1'), 117.41 (C-2' & C-14'), 123.21 (C-3' & C-13'), 126.16 (C-4' & C-12'), 125.43 (C-5' & C-11'), 129.21 (C-6' & C-10'), 133.64 (C-7' & C-9'), 116.04 (C-8'); δ_P (DMSO-d_6): 18.2 ppm; IR (KBr) (ν_{max} cm^{-1}): 3292, 3155 (NH), 1744 (C=O), 1217 (P=O), 1009 (P-O-C_{alip}); LCMS (m/z, %): 547 ($M+H^+$, 100); Anal. Calcd. for $C_{29}H_{27}N_2O_5PS$: C, 63.73; H, 4.98; N, 5.13%; found: C, 63.80; H, 4.91; N, 5.19%.



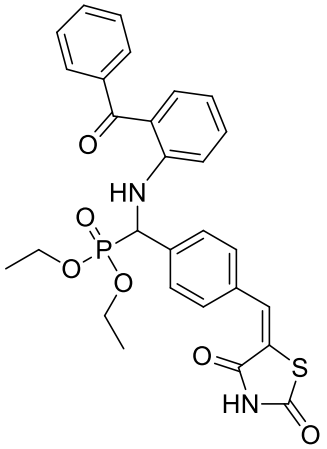
Compound **8h**

(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)((4-fluoro-3-nitrophenyl)amino)methyl)phosphonate ***(8h)****:* solid. M.P. 190-192 °C. Yield: 93%. δ_H (DMSO-d_6): 11.67 (s, 1H, Imide-H), 7.68 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.28 (d, *J*=7.2 Hz, 2H, Ar-H), 7.62 (s, 1H, Ar-H), 7.51 (d, *J*=6.8 Hz, 1H, Ar-H), 7.44 (d, *J*=7.2 Hz, 1H, Ar-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.30 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.09 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.97 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.26 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 145.41 (C-1'), 123.44 (C-2'), 116.24 (C-3'), 145.27 (C-4'), 137.05 (C-5'), 109.12 (C-6'); δ_P (DMSO-d_6): 20.4 ppm; IR (KBr) (ν_{max} cm^{-1}): 3290, 3144 (NH), 1736 (C=O), 1220 (P=O), 1011 (P-O-C_{alip}); LCMS (m/z, %): 510 ($M+H^+$, 100); Anal. Calcd. for $C_{21}H_{21}FN_3O_7PS$: C, 49.51; H, 4.15; N, 8.25%; found: C, 49.51; H, 4.15; N, 8.25%.



Compound **8i**

*(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenanthren-9-ylamino)methyl)phosphonate (**8i**):* solid. M.P. 210-212 °C. Yield: 95%. δ_H (DMSO-d_6): 11.65 (s, 1H, Imide-H), 7.65 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.27 (d, *J*=7.2 Hz, 2H, Ar-H), 8.84 (d, *J*=7.6 Hz, 2H, Ar-H), 8.07 (d, *J*=6.8 Hz, 2H, Ar-H), 7.91 (t, *J*=7.6 Hz, 2H, Ar-H), 7.75 (t, *J*=6.8 Hz, 2H, Ar-H), 6.94 (s, 1H, Ar-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.28 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.07 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.95 (m, 1H, -O-$\underline{CH_2}CH_3$), 1.23 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 142.35 (C-1'), 103.66 (C-2'), 135.23 (C-3'), 128.26 (C-4' & C-13'), 127.25 (C-5', C-6', C-11', C-12'), 124.21 (C-7' & C-10'), 118.43 (C-8'), 133.36 (C-9'), 123.15 (C-14'); δ_P (DMSO-d_6): 21.9 ppm; IR (KBr) (ν_{max} cm^{-1}): 3310, 3150 (NH), 1747 (C=O), 1223 (P=O), 1014 (P-O-C_{alip}); LCMS (m/z, %): 547 ($M+H^+$, 100); Anal. Calcd. for $C_{29}H_{27}N_2O_5PS$: C, 63.73; H, 4.98; N, 5.13%; found: C, 63.85; H, 4.89; N, 5.24%.



Compound **8j**

*(E)-diethyl (((2-benzoylphenyl)amino)(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)methyl)phosphonate (**8j**):* solid. M.P. 224-226 °C. Yield: 97%. δ_H (DMSO-d_6): 11.66 (s, 1H, Imide-H), 7.67 (s, 1H, =C-H), 7.61 (d, *J*=7.2 Hz, 2H, Ar-H), 7.26 (d, *J*=7.2 Hz, 2H, Ar-H), 7.83 (d, *J*=7.6 Hz, 2H, Ar-H), 7.73 (t, *J*=6.8 Hz, 1H, Ar-H), 7.69 (t, *J*=7.2 Hz, 2H, Ar-H), 7.58 (d, *J*=7.6 Hz, 1H, Ar-H), 7.49 (t, *J*=6.8 Hz, 1H, Ar-H), 6.88 (d, *J*=7.2 Hz, 1H, Ar-H), 6.81 (t, *J*=7.2 Hz, 1H, Ar-H), 5.25 (s, 1H, -NH), 4.79 (d, *J*= 20.0 Hz, 1H, P-CH), 4.30 (m, 2H, -O-$\underline{CH_2}CH_3$), 4.07 (m, 1H, -O-$\underline{CH_2}CH_3$), 3.96 (m,

1H, -O-$\underline{CH_2}CH_3$), 1.26 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$), 1.12 (t, *J*= 6.8 Hz, 3H, -O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 136.75 (C-1), 127.54 (C-2, C-6), 128.91 (C-3, C-5), 135.17 (C-4), 144.35 (C-7), 115.41 (C-8), 168.73 (C-9), 167.05 (C-10), 67.45 (d, *J* = 101 Hz, C-11), 63.12 (d, *J* = 5.3 Hz, C-12), 62.35 (d, *J* = 5.0 Hz, C-13), 13.64 (d, *J* = 5.0 Hz, C-14), 12.65 (d, *J* = 10.5 Hz, C-15), 149.43 (C-1'), 115.24 (C-2'), 126.28 (C-3'), 119.85 (C-4'), 134.36 (C-5'), 115.24 (C-6'), 195.45 (C-7'), 139.14 (C-8'), 129.37 (C-9' & C-13'), 128.94 (C-10' & C-12'), 133.63 (C-11'); δ_P (DMSO-d_6): 20.9 ppm; IR (KBr) (ν_{max} cm^{-1}): 3266, 3138 (NH), 1731 (C=O), 1214 (P=O), 1007 (P-O-C_{alip}); LCMS (m/z, %): 551 ($M+H^+$, 100); Anal. Calcd. for $C_{28}H_{27}N_2O_6PS$: C, 61.08; H, 4.94; N, 5.09%; found: C, 61.17; H, 4.86; N, 5.18%.

α-Amylase inhibitory activity[1,2]

Using acarbose as the reference chemical, a previously published method based on the spectrophotometric assay was slightly modified to perform the in vitro α-amylase inhibition assay of all extracts. Acarbose was used as a positive reference sample, and stock solutions of the freshly made compounds were made in distilled water. A 500 µL α-amylase solution (0.5 mg/mL in 0.02M sodium phosphate buffer, pH 6.9) was mixed with 500 µL of each sample at several concentrations (25, 50, 100, 150, and 200 µg/mL) and incubated for 10 minutes.

The reaction mixture was then heated in a boiling water bath for five minutes before being cooled to room temperature. Next, 500 µL of 1% (w/v) starch solution was added, followed by the coloring reagent, 0.5 mL of DNS reagent (12.0 g of sodium potassium tartrate tetrahydrate in 8 mL of 2M NaOH, and 96 mM 3,5-dinitrosalicylic acid solution). A UV-VIS spectrophotometer was used to measure the absorbance at 540 nm after it had been diluted with 10 mL of distilled water. By substituting 500µl of buffer for the enzyme solution, the absorbance of the blank was created. Acarbose was used in a similar manner, but without the plant extract indicated above, to provide a positive control that represented 100% enzyme activity.

Using the same methodology, the experiments were conducted three times.

% inhibition = [(AC-AS) / AC] x 100, Where AC is the absorbance of the control and AS is the absorbance of the sample

α-Glucosidase inhibitory activity[3]

Inhibition of *α*-glucosidase activity was determined using *p*-nitrophenyl-α-D-glucopyranoside (p-NPG) using previously reported method with slight modifications.[3] 100µL of plant extract or acarbose (25, 50, 100, 150, 200 and 250µg/mL) was added to 50µL of α-glucosidase (effective concentration 3.2.1.20; 1 U/mL) prepared in 0.1 M phosphate buffer (pH 6.9). Then, add 250 µL of 0.1 M phosphate buffer was added to get the final concentrations. The mixture was pre-incubated at 37 °C for 20 min. After pre-incubation, 10 µL of 10 mM p-NPG prepared in 0.1M phosphate buffer (pH 6.9) was added, and incubated at 37°C for 30 min. The reactions were stopped by adding 650 µL of 1M sodium carbonate, and the absorbance was measured in a spectrophotometer at 405 nm. The absorbance of blank with 100% enzyme activity (only the solvent with the enzyme) was measured. Acarbose was used as positive control. Repeat the experiments thrice using the same protocol. Method for calculation of α-amylase and α-glucosidase inhibitory concentration (IC_{50}). The percentage enzyme inhibition of the title compounds **4a-j** /standard was calculated using the following formula shown below, and the values were presented as mean±standard error mean of three replicates.

% inhibition = (A control – A sample / A control) x 100

Where “A control” is the absorbance of the control and “A sample” is the absorbance of the sample.

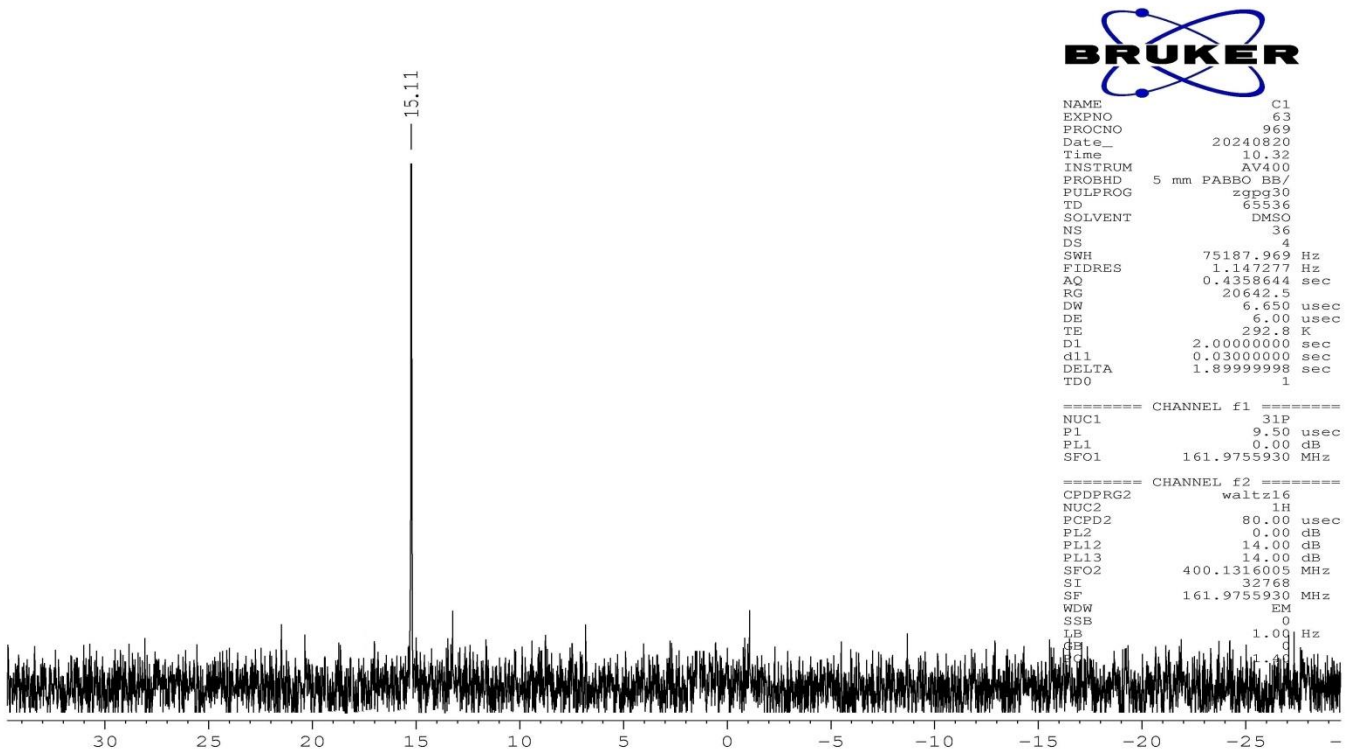


Figure S2: ^{31}P Spectrum of *(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenylamino)methyl)phosphonate* ***(8a)***

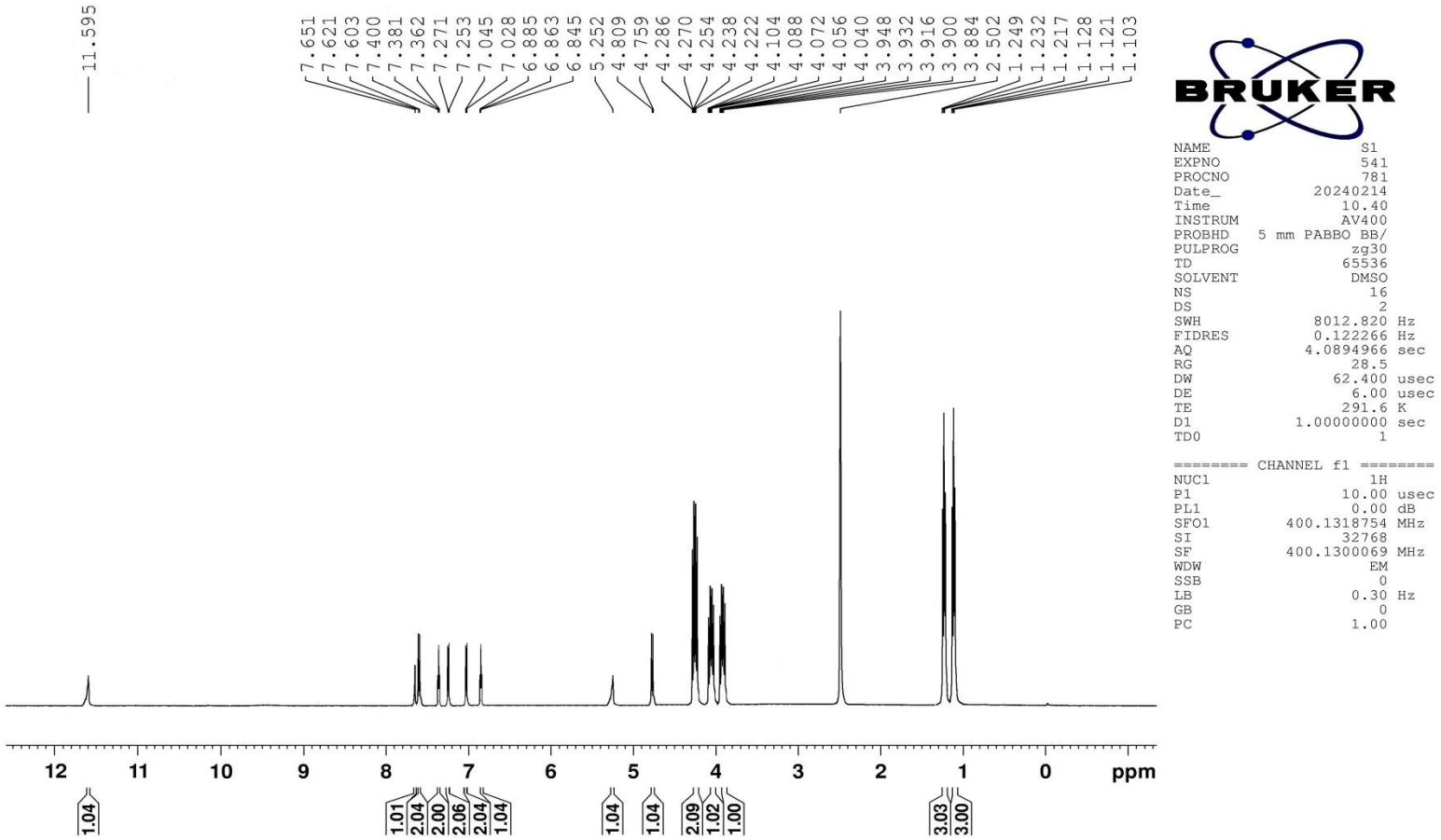


Figure S3: ^{1}H Spectrum of *(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenylamino)methyl)phosphonate* ***(8a)***

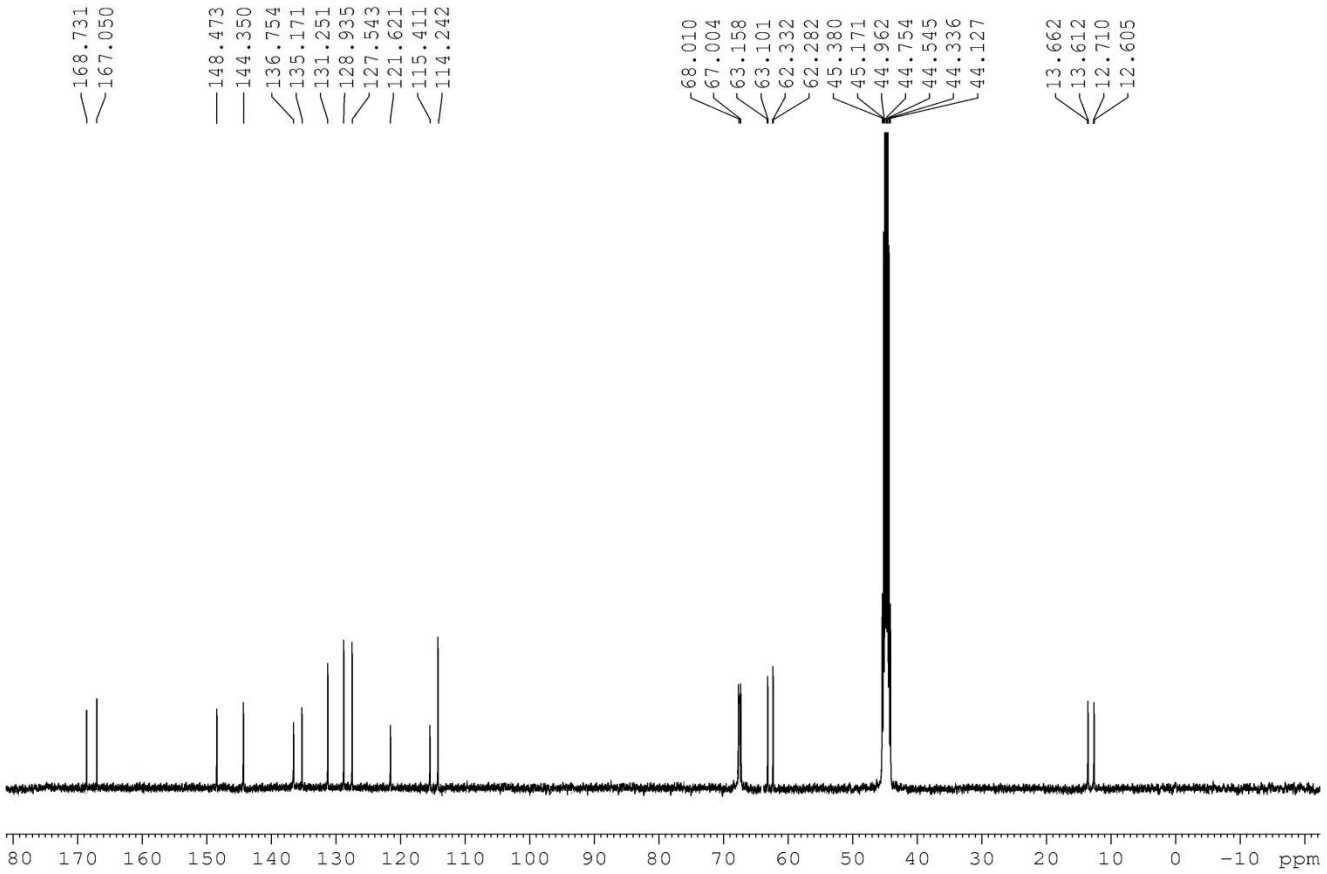


Figure S4: ^{13}C NMR Spectrum of *(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenylamino)methyl)phosphonate* ***(8a)***

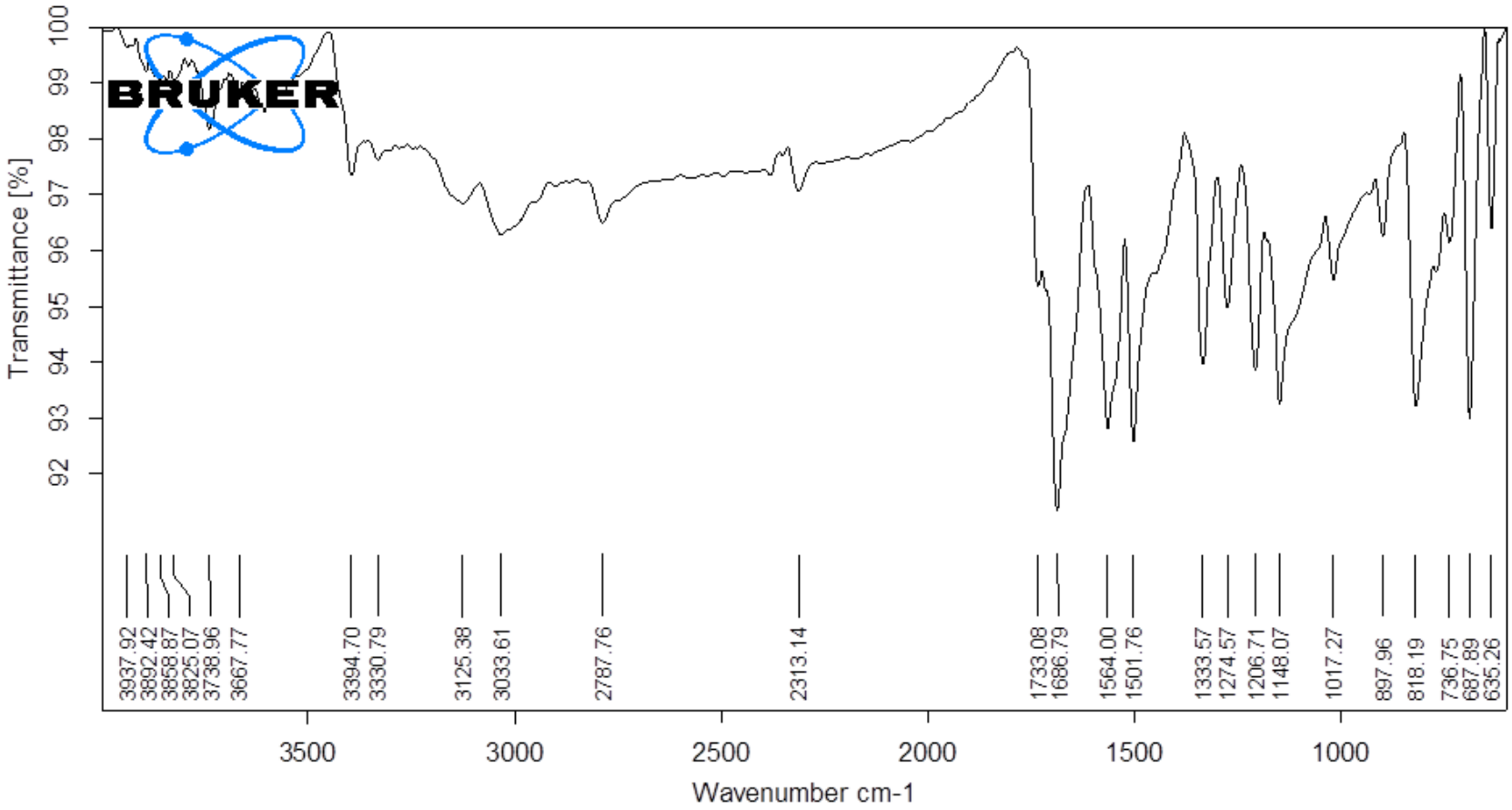


Figure S5: IR Spectrum of *(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenylamino)methyl)phosphonate* ***(8a)***

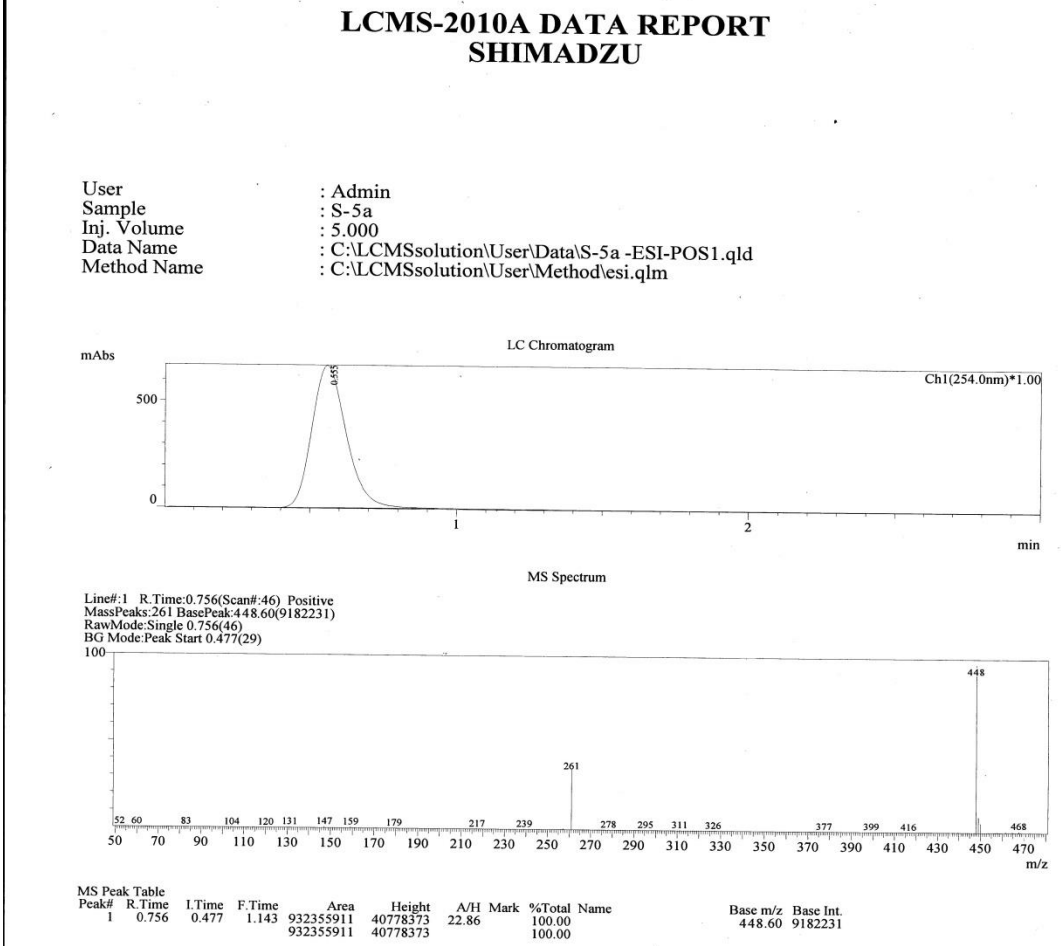
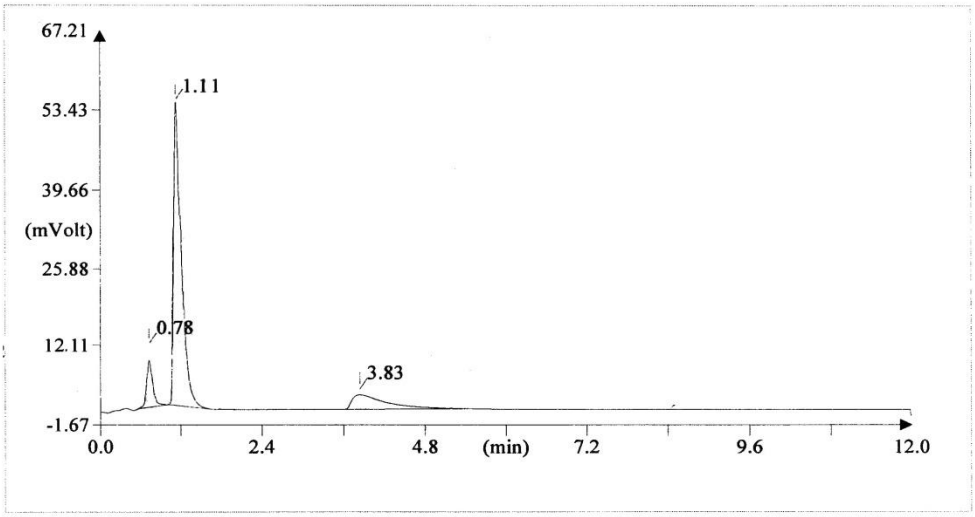


Figure S6: Mass Spectrum of *(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenylamino)methyl)phosphonate* ***(8a)***

FLASH EA 1112 SERIES CHN REPORT
THERMO FINNIGAN

Method filename:	C:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID:	SAMPLE-1
Analysis type:	UnkNown
Chromatogram filename:	UNK-01082024-1.dat
Sample weight:	1.261



Element Name	Element %	Ret. Time
Nitrogen	6. 36	0. 78
Carbon	56. 60	1. 11
Hydrogen	5. 10	3. 83

Figure S 7: CHN analysis of *(E)-diethyl ((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)(phenylamino)methyl)phosphonate* ***(8a)***

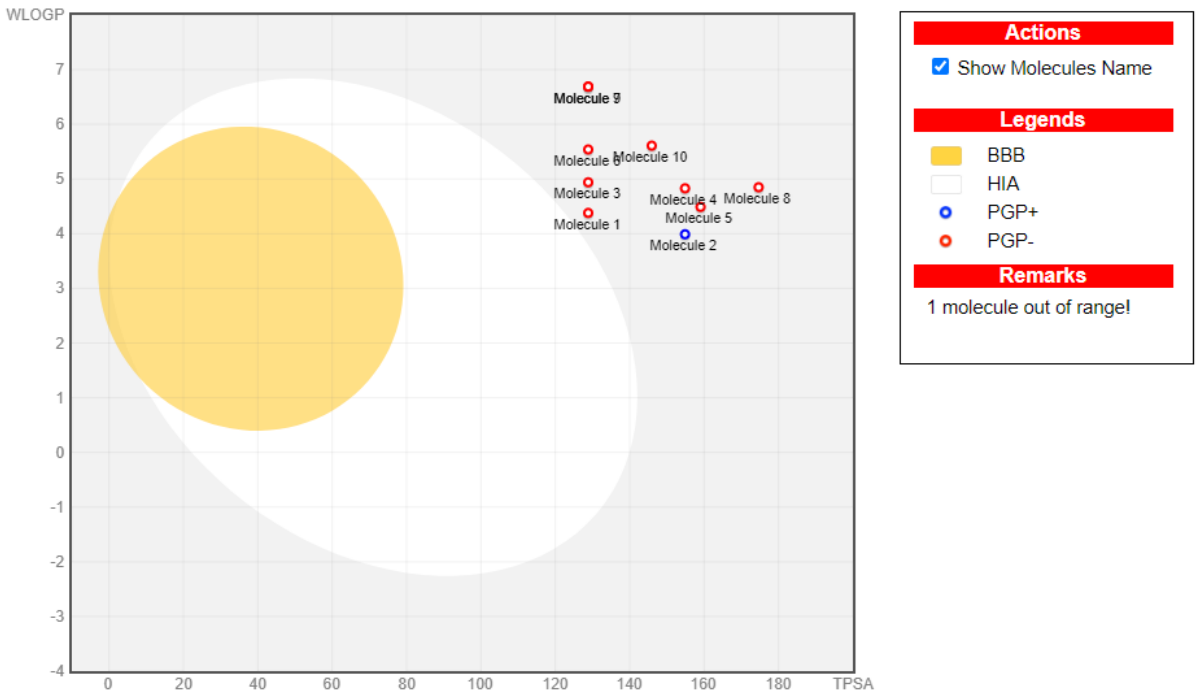
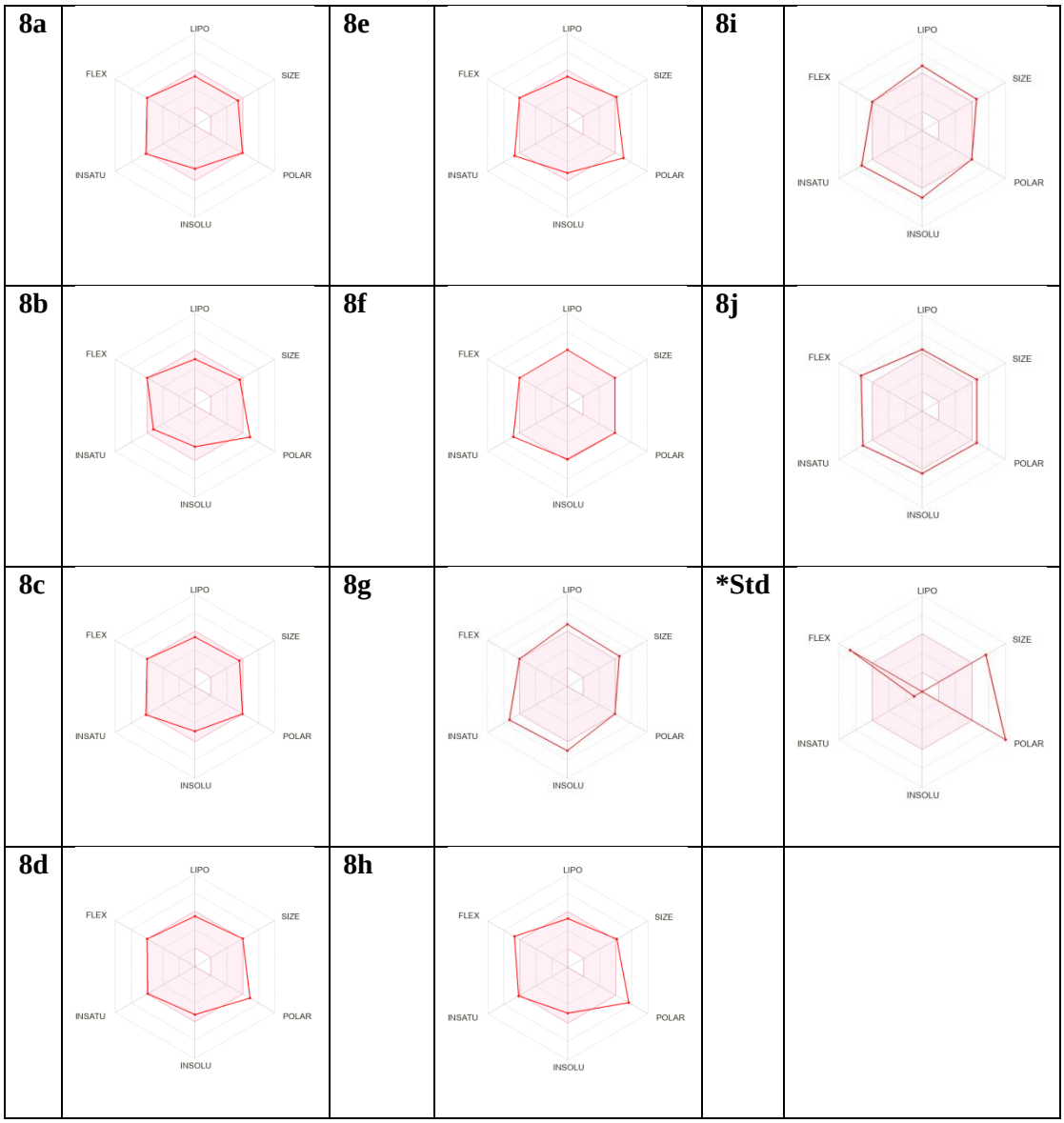


Figure S8: The BOILED-Egg diagram of the tested molecules 1-10 (**8a-j**)



*Std.-Acarbose

Figure S9: The bio radar map of the tested molecules (**8a-j**)

Table S1: Physicochemical properties of compounds **8a-j**

Compd	[a]MW	Heavy atoms	Aromatic heavy atoms	[b]Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	[c]MR	[d]TPSA	[e]iLOGP	[f]Silicos-IT class
8a	446.46	30	12	0.24	9	5	2	122.98	128.84	2.85	Poorly soluble
8b	465.46	31	11	0.35	9	7	2	122.98	154.87	3.2	Poorly soluble
8c	464.45	31	12	0.24	9	6	2	122.94	128.84	3.35	Poorly soluble
8d	501.49	34	15	0.26	9	7	2	135.52	154.87	3.04	Poorly soluble
8e	514.49	35	16	0.21	9	7	2	139.03	159.05	3.1	Poorly soluble
8f	496.52	34	16	0.2	9	5	2	140.49	128.84	3.29	Poorly soluble
8g	546.57	38	20	0.17	9	5	2	158	128.84	3.45	Insoluble
8h	509.44	34	12	0.24	10	8	2	131.76	174.66	2.45	Poorly soluble
8i	546.57	38	20	0.17	9	5	2	158	128.84	3.75	Insoluble
8j	550.56	38	18	0.18	11	6	2	152.86	145.91	3.09	Poorly soluble
Acarbose	645.6	44	0	0.92	9	19	14	136.69	321.17	1.43	Soluble

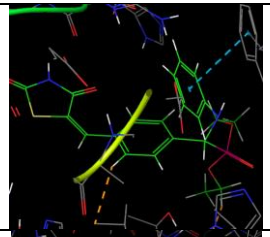
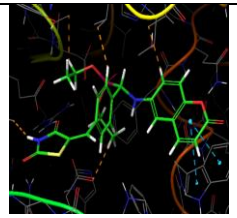
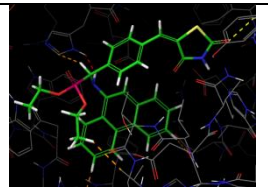
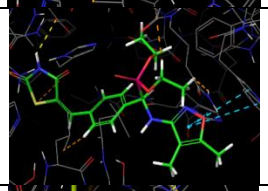
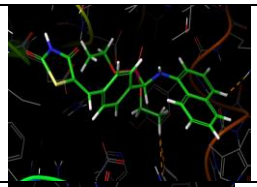
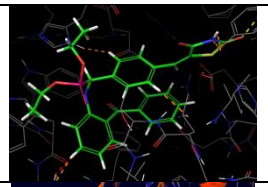
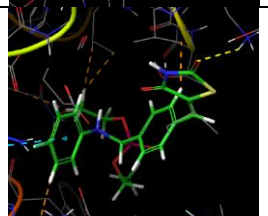
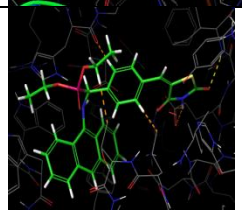
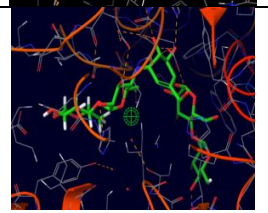
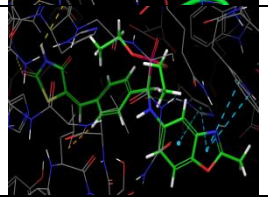
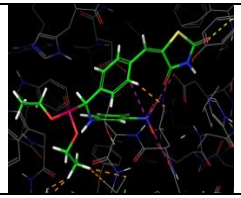
[a] Molecular weight; [b] The ratio of sp3 hybridized carbons over the total carbon count of the molecule; [c] Molar refractivity; [d] topological polar surface area (Å2); [e] lipophilicity; [f] water solubility (SILICOS-IT)

Table S2: Pharmacokinetic/ADME properties of compounds **8a-j**

Compd	[a]GI absorption	[b]BBB permeant	[c]Pgp substrate	[d]CYP1A2 inhibitor	[e]CYP2C19 inhibitor	[f]CYP2C9 inhibitor	[g]CYP2D6 inhibitor	[h]CYP3A4 inhibitor	[i]log Kp (cm/s)
8a	Low	No	No	No	Yes	Yes	No	Yes	-6.33
8b	Low	No	Yes	No	Yes	Yes	Yes	Yes	-6.78
8c	Low	No	No	No	Yes	Yes	Yes	Yes	-6.37
8d	Low	No	No	No	Yes	Yes	No	Yes	-6.5
8e	Low	No	No	No	No	Yes	No	Yes	-6.76
8f	Low	No	No	No	Yes	Yes	No	Yes	-5.75
8g	Low	No	No	No	No	Yes	No	Yes	-5.17
8h	Low	No	No	No	Yes	Yes	Yes	Yes	-6.77
8i	Low	No	No	No	No	Yes	No	Yes	-5.17
8j	Low	No	No	No	No	Yes	No	Yes	-5.63
Acarbose	Low	No	Yes	No	No	No	No	No	-16.29

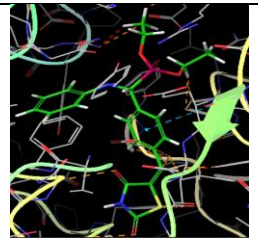
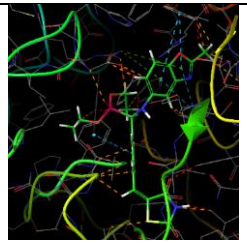
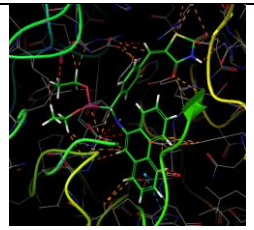
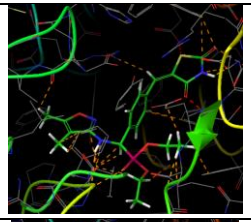
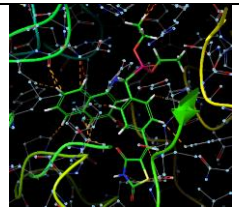
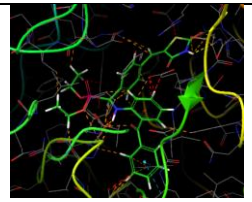
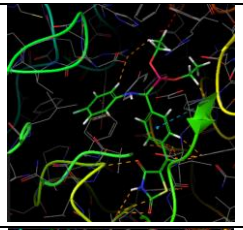
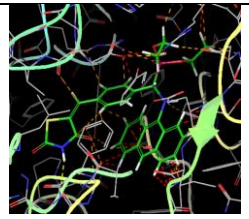
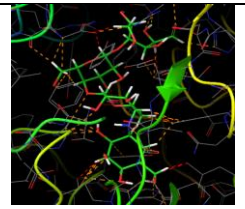
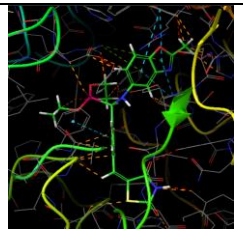
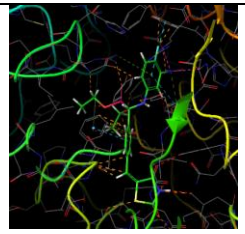
[a]Gastro intestinal absorption; [b]blood brain barrier permeant; [c]p-glycoprotein substrate; [d]CYP1A2: Cytochrome P450 family 1 subfamily A member 2; [e]CYP2C19: Cytochrome P450 family 2 subfamily C member 19; [f]CYP2C9: Cytochrome P450 family 2 subfamily C member 9; [g]CYP2D6: Cytochrome P450 family 2 subfamily D member 6; [h]CYP3A4: Cytochrome P450 family 3 subfamily A member 4; [i]skin permeation in cm/s.

Table S3: Binding energies of the title compounds (**8a-j**) and standard with α-amylase enzyme in molecular docking study

Compd	Image	B.E. (kcal /mol)	Compd	Image	B.E. (kcal/mol)	Compd	Image	B.E. (kcal/mol)
8a		-8.1	8e		-8.5	**8i**		-8.9
8b		-8.1	8f		-8.3	**8j**		-8.6
8c		-8.0	8g		-8.8	**Std***		-8.2
8d		-8.2	8h		-8.0			

Std*: Acarbose

Table S4 : Binding energies of the title compounds (**8a-j**) and standard with *α*-glucosidase enzyme in molecular docking study

Compd	Image	B.E. (kcal /mol)	Compd	Image	B.E. (kcal/mol)	Compd	Image	B.E. (kcal/mol)
8a		-6.4	8e		-5.5	**8i**		-1.1
8b		-3.1	8f		-4.2	**8j**		-0.6
8c		-5.8	8g		1.7	**Std***		-2.0
8d		-5.0	8h		-3.2			

Std*: Acarbose

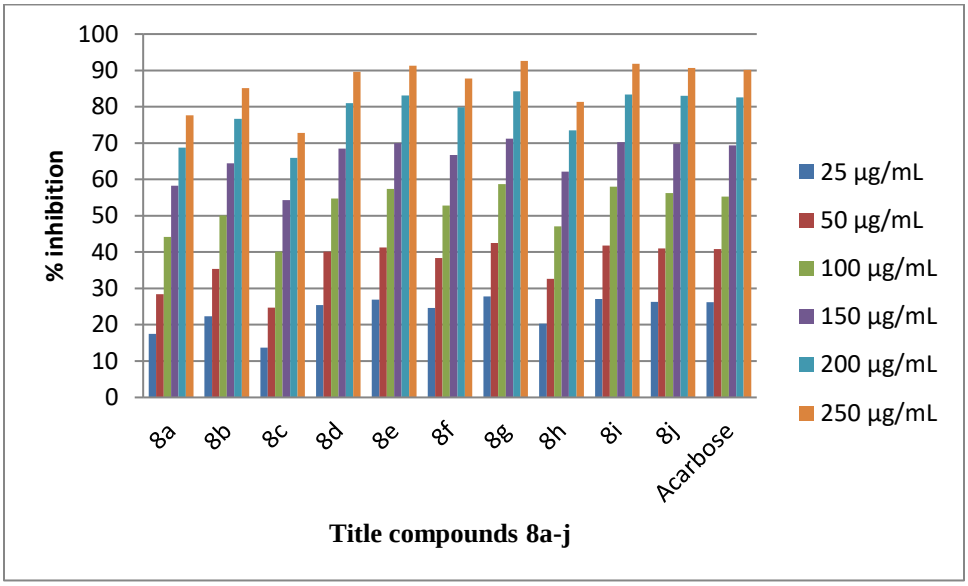


Figure S10 : α-Amylase inhibition activity results of compounds **8a-j**

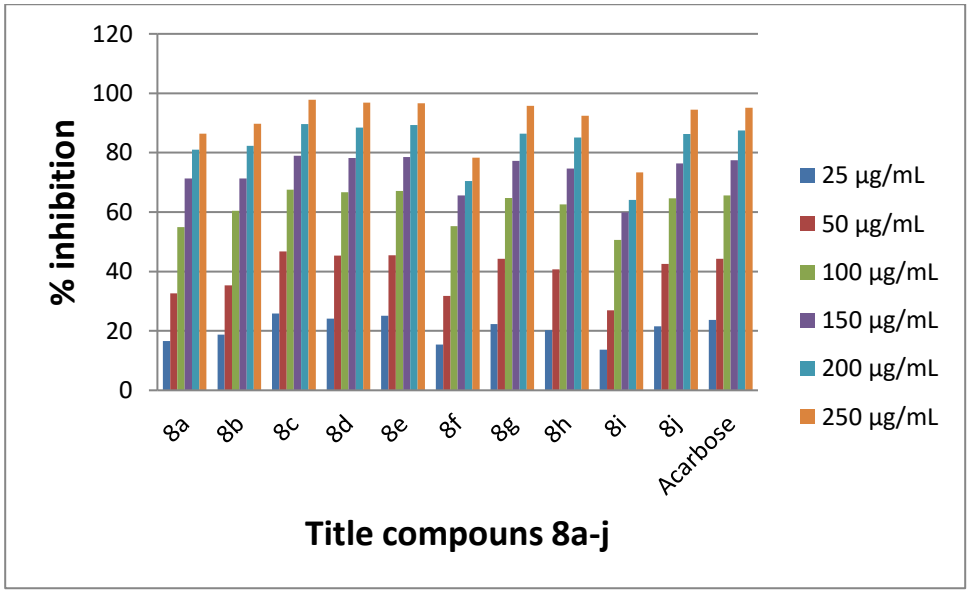


Figure S11 : α-Glucosidase inhibition activity results of compounds **8a-j**

References

[1] Nickavar, B.; Amin, G. Enzyme assay guided isolation of an alpha-amylase inhibitor flavonoid from vaccinium arctostaphylos leaves. *Iran J. Pharm. Res.* **2011**, *10*, 849-853. PMCID: PMC3813050.

[2] Patil, V. S.; Nandre, K. P.; Ghosh, S.; Rao, V. J.; Chopade, B. A.; Sridhar, B.; Bhosale, S. V.; Bhosale, S. V. Synthesis, crystal structure and anti-diabetic activity of substituted (E)-3-(benzo[d]thiazol-2-ylamino)phenylprop-2-en-1-one. *Eur. J. Med. Chem.* **2013**, *59*, 304-309. DOI: 10.1016/j.ejmech.2012.11.020.

[3] Kim, J.S.; Hyun, T.K.; Kim, M.J. The inhibitory effects of ethanol extracts from sorghum, foxtail millet and proso millet on α-glucosidase and α-amylase activities. *Food Chem.* **2011**, *124*, 1647-1651. DOI:10.1016/j.foodchem.2010.08.020