Supporting Information

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Ultrasound-assisted synthesis of α-aminophosphonates using nano ZnO catalyst: evaluation of their anti-diabetic activity

Meson Haji Basha [1,2], Chennamsetty Subramanyam [1],

C. Gladis Raja Malar [3], Katare Kiran Kumar [4],

Mohan Seelam [1], Vedula Naga Lakshmi [5] and Kammela Prasada Rao[1]

[1]Department of Chemistry (recognized as research centre by A.N. University), Bapatla Engineering College (Autonomous), Bapatla, Andhra Pradesh, India -522101

[2]Department of Chemistry, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India -522510

[3] Department of Chemistry, Vel Tech Multi Tech Dr.Rangarajan Dr.Sakunthala Engineering College, Avadi, Chennai, Tamil Nadu, India-600062

[4] Department of Chemistry, K. B. N. College (A), kotha pet, Vijayawada -520001 Andhra Pradesh, India - 534007

[5]Department of Chemistry, Ch.S.D.St.Theresa's College for Women (A), Eluru, Andhra Pradesh, India-534003

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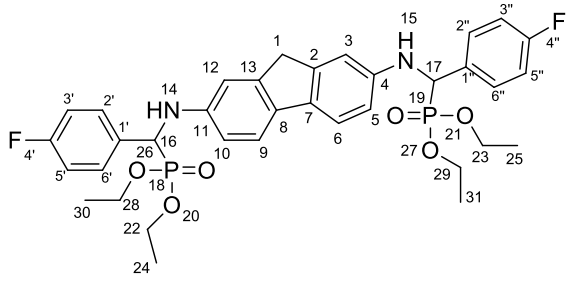
S1 :Materials and Characterization Techniques

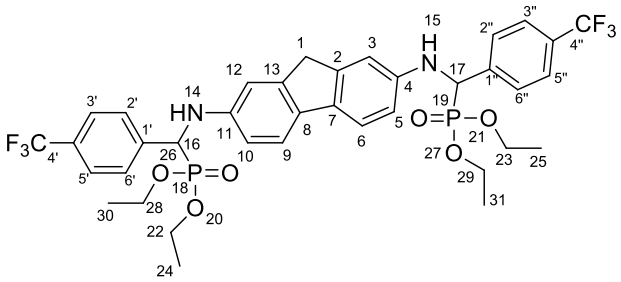
The molecular docking investigation was carried out with 1-Click docking software and the Auto Dock Vina docking technique. All compounds' structures were sketched and optimized with Marvin View software before being transferred to the appropriate format. *In silico* testing used the 1-Click docking software in conjunction with the Auto Dock Vina approach. IC_{50} values were determined, and biological activity graphs were created with Excel software. Only a small percentage of the chemicals purchased from Sd. Fine Chem. Ltd. in India went through traditional refinement operations. Reactions were carried out on a magnetic agitator that doubled as a hot plate. TLC was used to analyze the chemical purity of silica gel-coated aluminum sheets. A Bruker AMX spectrometer was used to record NMR spectra at ^{31}P (161.9 MHz), ^{1}H (400 MHz), and ^{13}C (100 MHz). The SHIMADZU 2010A was used to perform LC-MS analysis, whereas the T.F. Flash 1112 was used for CHN analysis. FTIR spectra were recorded with a Bruker IFS 55 spectrometer in KBr. Chemical shifts and coupling constants (*J* values) were represented in ppm and Hz, respectively, with 's' for singlet, 'd' for doublet, 't' for triplet, and 'm' for multiplet in NMR spectra. Sonication was carried out with a BANDELIN SONOREXR (Germany) ultrasonic bath with a frequency of 35 kHz and a nominal power of 200 W, capable of thermostatically regulating heating from 30°C to 80°C. The reaction vessel was positioned inside the ultrasonic bath containing water.

*Spectral data of compounds **4b-j***



Compound **4b**

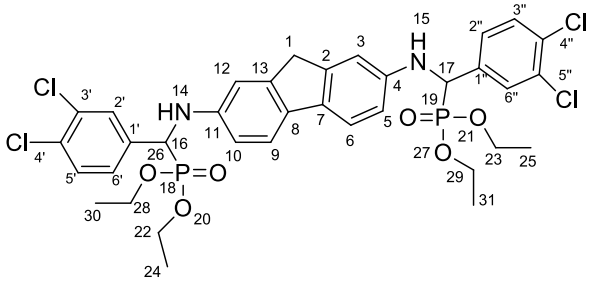
*Tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis((4-fluorophenyl)methylene))bis(phosphonate) (**4b**).* M.F.: $C_{35}H_{40}F_2N_2O_6P_2$; Yield: 94%; Solid. M.P. 201-203 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.06 (d, 4H, Ar-H), 6.77 (d, 4H, Ar-H). 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 162.1 (C-4', C-4"), 146.4 (C-4, C-11), 141.4 (C-2, C-13), 130.8 (C-1', C-1"), 128.8 (C-7, C-8), 128.1 (C-6, C-9), 126.9 (C-2', C-2", C-6', C-6"), 116.2 (C-3', C-3", C-5', C-5"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 21.4 ppm. IR (KBr) (ν_{max} cm^{-1}): 3289 (NH), 1218 (P=O), 1015 (P-O-C_{alip}); LCMS (m/z, %): 685 ($M+H^+$,100). Anal. Calcd: C, 61.40; H, 5.89; N, 4.09%. Found: C, 61.51; H, 5.80; N, 4.20%.



Compound **4c**

*Tetraethyl(((9H-fluorene-2,7-diyl)bis(azanediyl))bis((4-(trifluoromethyl)phenyl)methylene))bis-(phosphonate) (**4c**).*

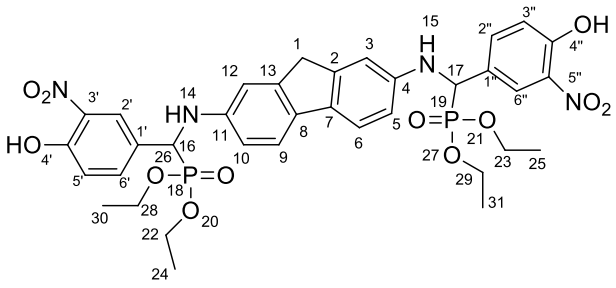
M.F.: $C_{37}H_{40}F_6N_2O_6P_2$: Yield: 96%; Solid. M.P.225-227 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.42 (d, 4H, Ar-H), 6.91 (d, 4H, Ar-H), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, J = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, J= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, J= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 146.4 (C-4, C-11), 141.4 (C-2, C-13), 138.7 (C-1', C-1"), 128.8 (C-7, C-8), 128.5 (C-4', C-4"), 128.1 (C-6, C-9), 126.5 (C-2', C-2", C-6', C-6"), 126.4 (C-3', C-3", C-5', C-5"), 123.2 (C-7', C-7"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, J = 5.2 Hz, C-22 & C-28), 62.85 (d, J = 5.0 Hz, C-23 & C-29), 56.71 (d, J = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, J = 5.1 Hz, C-24 & C-30), 13.88 (d, J = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 22.5 ppm. IR (KBr) (ν_{max} cm^{-1}): 3316 (NH), 1219 (P=O), 1017 (P-O-C_{alip}); LCMS (m/z, %): 785 (M+H$^+$,100). Anal. Calcd: C, 56.64; H, 5.14; N, 3.57%. Found: C, 56.76; H, 5.03; N, 3.67%.



Compound **4d**

*Tetraethyl(((9H-fluorene-2,7-diyl)bis(azanediyl))bis((3,4-dichlorophenyl)methylene))bis(phosphonate) (**4d**).*

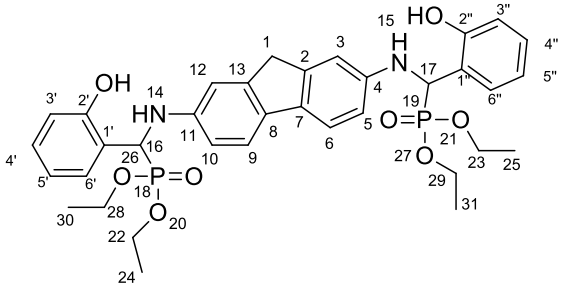
M.F.: $C_{35}H_{38}Cl_4N_2O_6P_2$; Yield: 93%; Solid. M.P.235-237 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.12 (d, 2H, Ar-H), 7.06 (s, 2H, Ar-H), 6.78 (d, 2H, Ar-H), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, J = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, J= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, J= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 146.4 (C-4, C-11), 141.4 (C-2, C-13), 134.5 (C-1', C-1"), 132.4 (C-3', C-3"), 130.5 (C-4', C-4"), 129.2 (C-5', C-5"), 128.8 (C-7, C-8), 128.1 (C-6, C-9), 127.2 (C-2', C-2"), 125.3 (C-6', C-6"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, J = 5.2 Hz, C-22 & C-28), 62.85 (d, J = 5.0 Hz, C-23 & C-29), 56.71 (d, J = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, J = 5.1 Hz, C-24 & C-30), 13.88 (d, J = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 19.8 ppm. IR (KBr) (ν_{max} cm^{-1}): 3267 (NH), 1223 (P=O), 1016 (P-O-C_{alip}); LCMS (m/z, %): 787 (M+H$^+$,100), 785 (M-2, 78%), 789 (M+2, 48%). Anal. Calcd: C, 53.45; H, 4.87; N, 3.56%. Found: C, 53.53; H, 4.80; N, 3.66%.



Compound **4e**

*Tetraethyl(((9H-fluorene-2,7-diyl)bis(azanediyl))bis((3,4-dichlorophenyl)methylene))bis(phosphonate) **(4e)***.

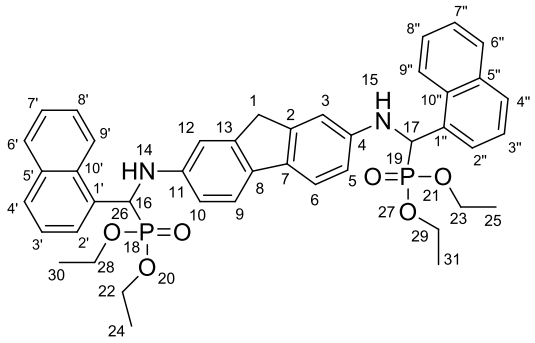
M.F.: $C_{35}H_{40}N_4O_{12}P_2$; Yield: 95%; Solid. M.P.212-214 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.76 (s, 2H, Ar-H), 7.19 (d, 2H, Ar-H), 6.93 (d, 2H, Ar-H), 5.82 (s, 2H, -OH), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 151.2 (C-4', C-4"), 146.4 (C-4, C-11), 141.4 (C-2, C-13), 134.9 (C-6', C-6"), 134.7 (C-3', C-3"), 128.8 (C-7, C-8), 128.7 (C-1', C-1"), 128.1 (C-6, C-9), 122.5 (C-2', C-2"), 117.4 (C-5', C-5"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 24.2 ppm. IR (KBr) (ν_{max} cm^{-1}): 3354 (NH), 1227 (P=O), 1018 (P-O-C_{alip}); LCMS (m/z, %): 771 (M+H$^+$,100). Anal. Calcd: C, 54.55; H, 5.23; N, 7.27%. Fund: C, 54.64; H, 5.14; N, 7.37%.



Compound **4f**

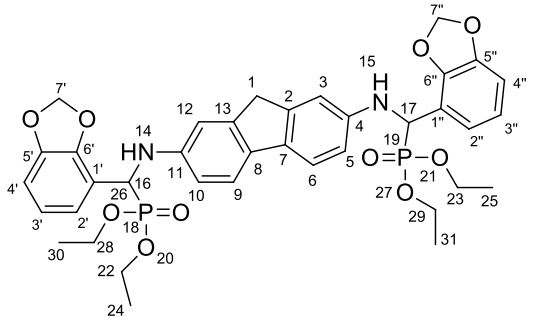
Tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis((2-hydroxyphenyl)methylene))bis(phosphonate) ***(4f)***.

M.F.: $C_{35}H_{42}N_2O_8P_2$: Yield: 93%; Solid. M.P.185-187 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 6.98 (d, 2H, Ar-H), 6.79 (d, 2H, Ar-H), 6.63 (t, 2H, Ar-H), 6.53 (d, 2H, Ar-H), 5.43 (s, 2H, -OH), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 155.4 (C-2', C-2"), 146.4 (C-4, C-11), 141.4 (C-2, C-13), 129.1 (C-6', C-6"), 128.8 (C-7, C-8), 128.1 (C-6, C-9), 127.5 (C-4', C-4"), 122.3 (C-1', C-1"), 120.5 (C-5', C-5"), 112.8 (C-3', C-3"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 23.3 ppm. IR (KBr) (ν_{max} cm^{-1}): 3326 (NH), 1224 (P=O), 1016 (P-O-C_{alip}); LCMS (m/z, %): 681 (M+H$^+$,100). Anal. Calcd: C, 61.76; H, 6.22; N, 4.12%. Found: C, 61.65; H, 6.32; N, 4.21%.



Compound **4g**

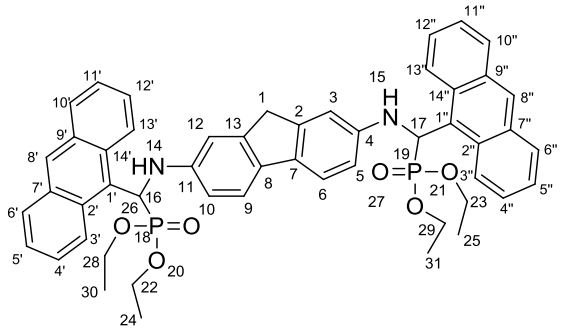
*Tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(naphthalen-1-ylmethylene))bis(phosphonate) (**4g**).*
M.F.: $C_{43}H_{46}N_2O_6P_2$: Yield: 89%; Solid. M.P.193-195 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.84 (d, 2H, Ar-H), 7.74 (d, 2H, Ar-H), 7.43 (d, 2H, Ar-H),), 7.38 (t, 2H, Ar-H), 7.23 (t, 2H, Ar-H), 7.14 (t, 2H, Ar-H), 7.05 (d, 2H, Ar-H), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 146.4 (C-4, C-11), 141.4 (C-2, C-13), 134.1 (C-7', C-7"), 133.6 (C-1', C-1"), 131.5 (C-2', C-2"), 128.8 (C-7, C-8), 128.1 (C-6, C-9), 127.3 (C-6', C-6"), 127.1 (C-9', C-9"), 126.4 (C-8', C-8"), 122.4 (C-3', C-3"), 124.7 (C-4', C-4"), 124.1 (C-5', C-5"), 123.5 (C-10', C-10"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 16.8 ppm. IR (KBr) (ν_{max} cm^{-1}): 3306 (NH), 1215 (P=O), 1011 (P-O-C_{alip}); LCMS (m/z, %): 749 (M+H$^+$,100). Anal. Calcd: C, 68.97; H, 6.19; N, 3.74%. Found: C, 68.89; H, 6.28; N, 3.65%.



Compound **4**

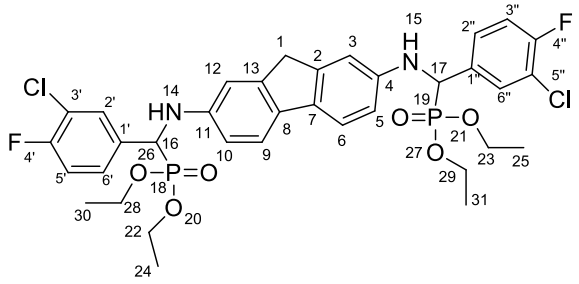
*Tetraethyl(((9H-fluorene-2,7-diyl)bis(azanediyl))bis(benzo[d][1,3]dioxol-5-ylmethylene))bis-(phosphonate) (**4h**).*
M.F.: $C_{37}H_{42}N_2O_{10}P_2$; Yield: 94%; Solid. M.P.209-211 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 6.76 (d, 2H, Ar-H), 6.69 (d, 2H, Ar-H), 6.52 (s, 2H, Ar-H), 5.73 (s, 4H, O-C**H**$_2$-O). 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 149.6 (C-5', C-5"), 146.5 (C-4', C-4"), 146.4 (C-4, C-11), 141.4 (C-2, C-13), 129.9 (C-1', C-1"), 128.8 (C-7, C-8), 128.1 (C-6, C-9), 121.5 (C-2', C-2"), 116.4 (C-3', C-3"), 113.4 (C-6', C-6"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 102.5 (C-7', C-7"), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-

31); ^{31}P NMR spectrum (DMSO-d_6): δ 18.7 ppm. IR (KBr) (ν_{max} cm^{-1}): 3295 (NH), 1214 (P=O), 1009 (P-O-C_{alip}); LCMS (m/z, %): 737 (M+H$^+$,100). Anal. Calcd: C, 60.32; H, 5.75; N, 3.80%. Found: C, 60.43; H, 5.65; N, 3.90%.



Compound **4i**

*Tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(anthracen-9-ylmethylene))bis(phosphonate) (**4i**).*
M.F.: $C_{51}H_{50}N_2O_6P_2$; Yield: 96%; Solid. M.P.218-220 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.83 (d, 4H, Ar-H), 7.71 (d, 4H, Ar-H), 7.63 (s, 2H, Ar-H), 7.38 (t, 4H, Ar-H), 7.29 (t, 4H, Ar-H), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 146.4 (C-4, C-11), 141.4 (C-2, C-13), 136.6 (C-8', C-8"), 133.7 (C-1', C-1"), 129.5 (C-7', C-7", C-9', C-9"), 129.2 (C-10', C-10"), 128.8 (C-7, C-8), 128.5 (C-4', C-4"), 128.4 (C-2', C-2", C-14', C-14"), 128.1 (C-6, C-9), 127.9 (C-6', C-6"),127.2 (C-5', C-5"), 127.1 (C-13', C-13"), 126.4 (C-3', C-3"), 126.3 (C-11', C-11"), 126.8 (C-12', C-12"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 17.1 ppm. IR (KBr) (ν_{max} cm^{-1}): 3318 (NH), 1224 (P=O), 1014 (P-O-C_{alip}); LCMS (m/z, %): 849 (M+H$^+$,100). Anal. Calcd: C, 72.16; H, 5.94; N, 3.30%. Found: C, 72.27; H, 5.84; N, 3.41%.



Compound **4j**

*Tetraethyl(((9H-fluorene-2,7-diyl)bis(azanediyl))bis((3-chloro-4-fluorophenyl)methylene))bis-(phosphonate) (**4j**).*
M.F.: $C_{35}H_{38}Cl_2F_2N_2O_6P_2$; Yield: 97%; Solid. M.P.181-183 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6)**:** δ 7.58 (d, 2H, Ar-H), 6.81 (s, 2H, Ar-H), 6.51 (d, 2H, Ar-H), 7.11 (s, 2H, Ar-H), 7.06 (d, 2H, Ar-H), 6.83 (d, 2H, Ar-H), 5.42 (s, 2H, NH), 4.39 (m, 4H, -O-$\underline{CH_2}CH_3$), 4.08 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.95 (d, *J* = 16 Hz, 2H, P-CH), 3.91 (m, 2H, -O-$\underline{CH_2}CH_3$), 3.73 (s, 2H, -CH_2), 1.27 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$), 1.13 (t, *J*= 6.8 Hz, 6H, -O-$CH_2\underline{CH_3}$); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 159.3 (C-4', C-4"), 146.4 (C-4, C-11), 141.4 (C-2, C-13), 132.5 (C-1', C-1"), 129.2 (C-6', C-6"), 128.8 (C-7, C-8), 128.1 (C-6, C-9), 127.1 (C-

2', C-2"), 121.4 (C-5', C-5"), 116.4 (C-3', C-3"), 111.6 (C-3, C-12), 110.8 (C-5, C-10), 64.07 (d, *J* = 5.2 Hz, C-22 & C-28), 62.85 (d, *J* = 5.0 Hz, C-23 & C-29), 56.71 (d, *J* = 104 Hz, C-16 & C-17), 37.3 (C-1), 14.85 (d, *J* = 5.1 Hz, C-24 & C-30), 13.88 (d, *J* = 10.2 Hz, C-25 & C-31); ^{31}P NMR spectrum (DMSO-d_6): δ 21.8 ppm. IR (KBr) (ν_{max} cm^{-1}): 3319 (NH), 1226 (P=O), 1016 (P-O-C_{alip}); LCMS (m/z, %): 753 ($M+H^+$,100), 751 (M-2,98), 755 (M+2,50). Anal. Calcd: C, 55.79; H, 5.08; N, 3.72%. Found: C, 55.88; H, 5.01; N, 3.80%.

S2 :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

S3 :α-Glucosidase Inhibitory Activity[3]

With minor adjustments, the previously described approach was used to evaluate the inhibition of α-glucosidase activity using p-nitrophenyl-α-D-glucopyranoside (p-NPG).[3] 50µL of α-glucosidase (effective concentration 3.2.1.20; 1 U/mL) produced in 0.1 M phosphate buffer (pH 6.9) was mixed with 100µL of plant extract or acarbose with concentrations of 25, 50, 100, 150, 200, and 250 µg/mL. To obtain the final concentrations, 250 µL of 0.1 M phosphate buffer was then added. For 20 minutes, the mixture was pre-incubated at 37 °C. 10 µL of 10 mM p-NPG produced in 0.1M phosphate buffer (pH 6.9) was added after pre-incubation, and the mixture was incubated for 30 minutes at 37°C. 650 µL of 1M sodium carbonate was added to halt the reactions, and the absorbance at 405 nm was measured in a spectrophotometer. The absorbance of a blank that had 100% enzyme activity—that is, just the enzyme-containing solvent—was measured. As a positive control, acarbose was employed. Using the same methodology, conduct the experiments three times. The α-amylase and α-glucosidase inhibitory concentration (IC50) calculating method. Using the formula below, the percentage enzyme inhibition of the title compounds **4a-j**/standard was determined. The results were displayed 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.

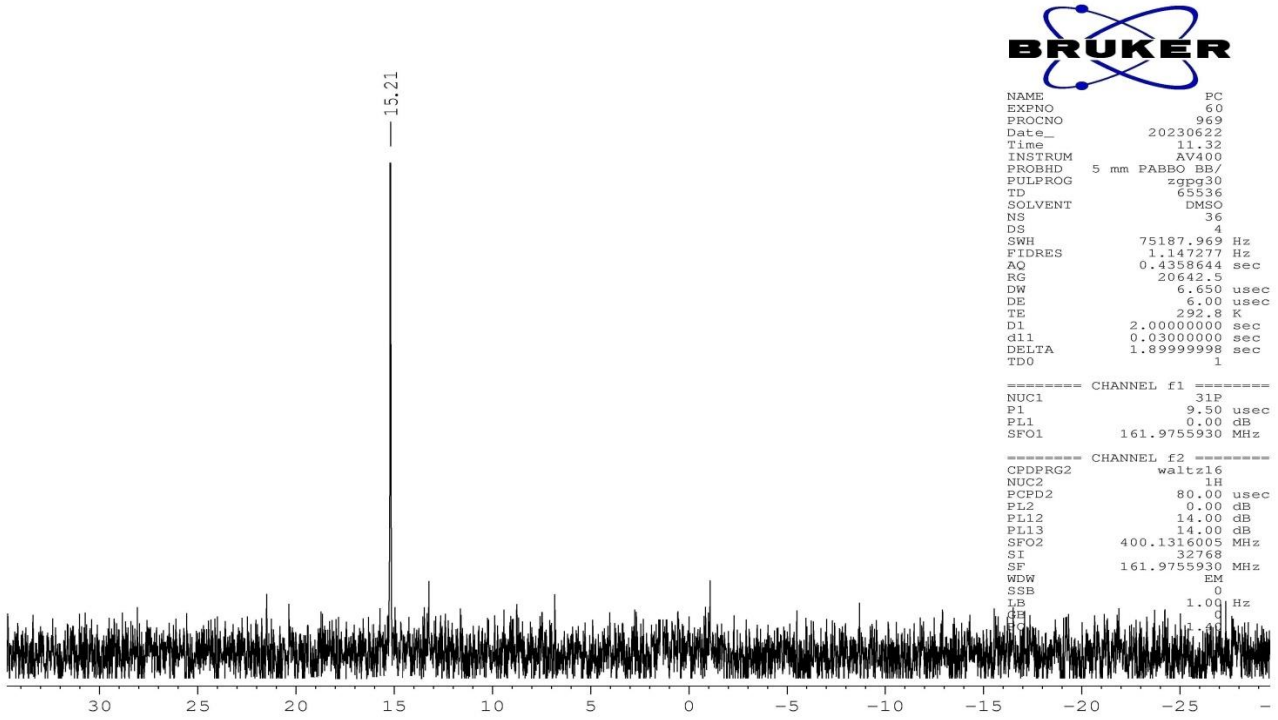


Figure S1: ^{31}P Spectrum of tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(phenylmethylene))bis(phosphonate)(**4a**)

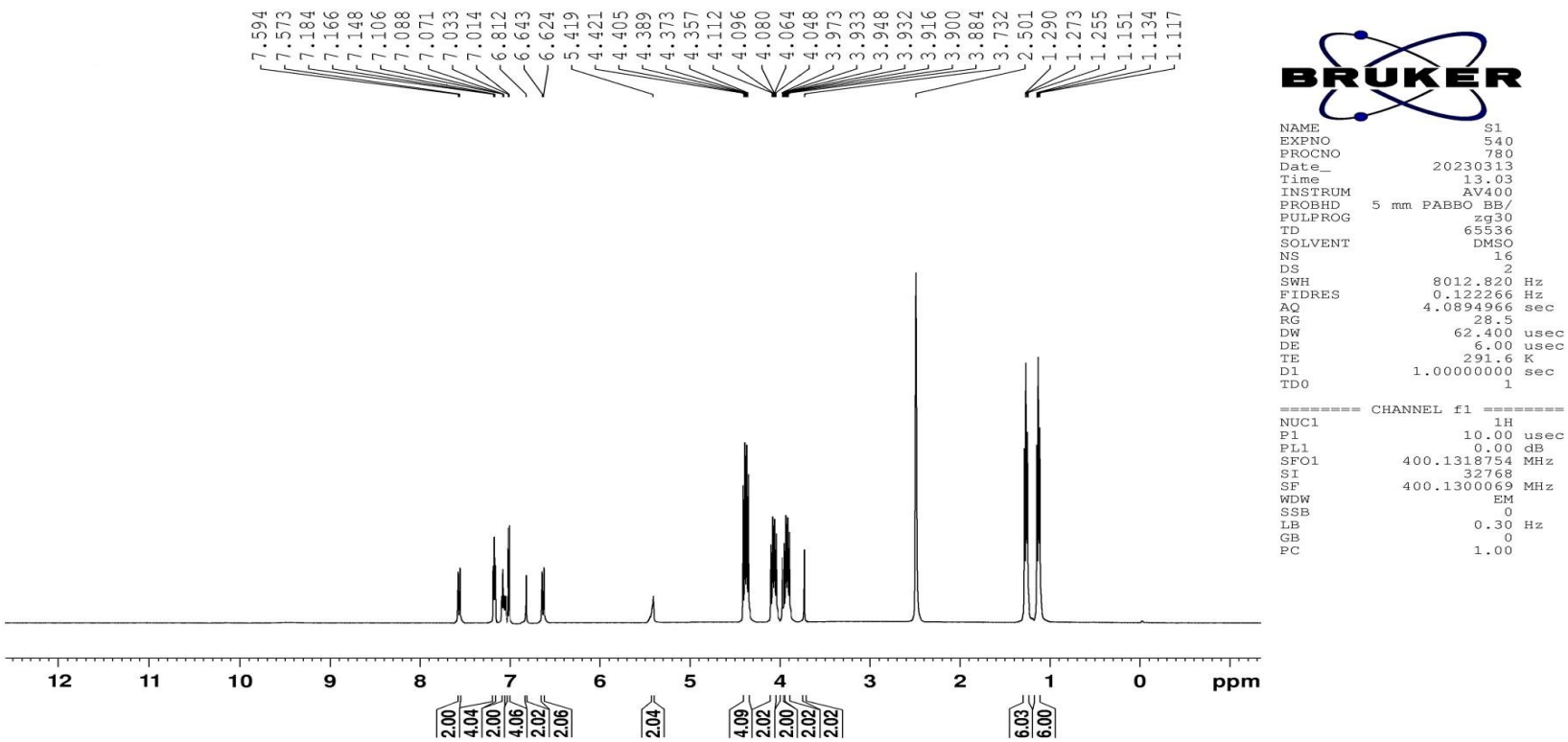


Figure S2: ^{1}H Spectrum of tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(phenylmethylene))bis(phosphonate)(**4a**)

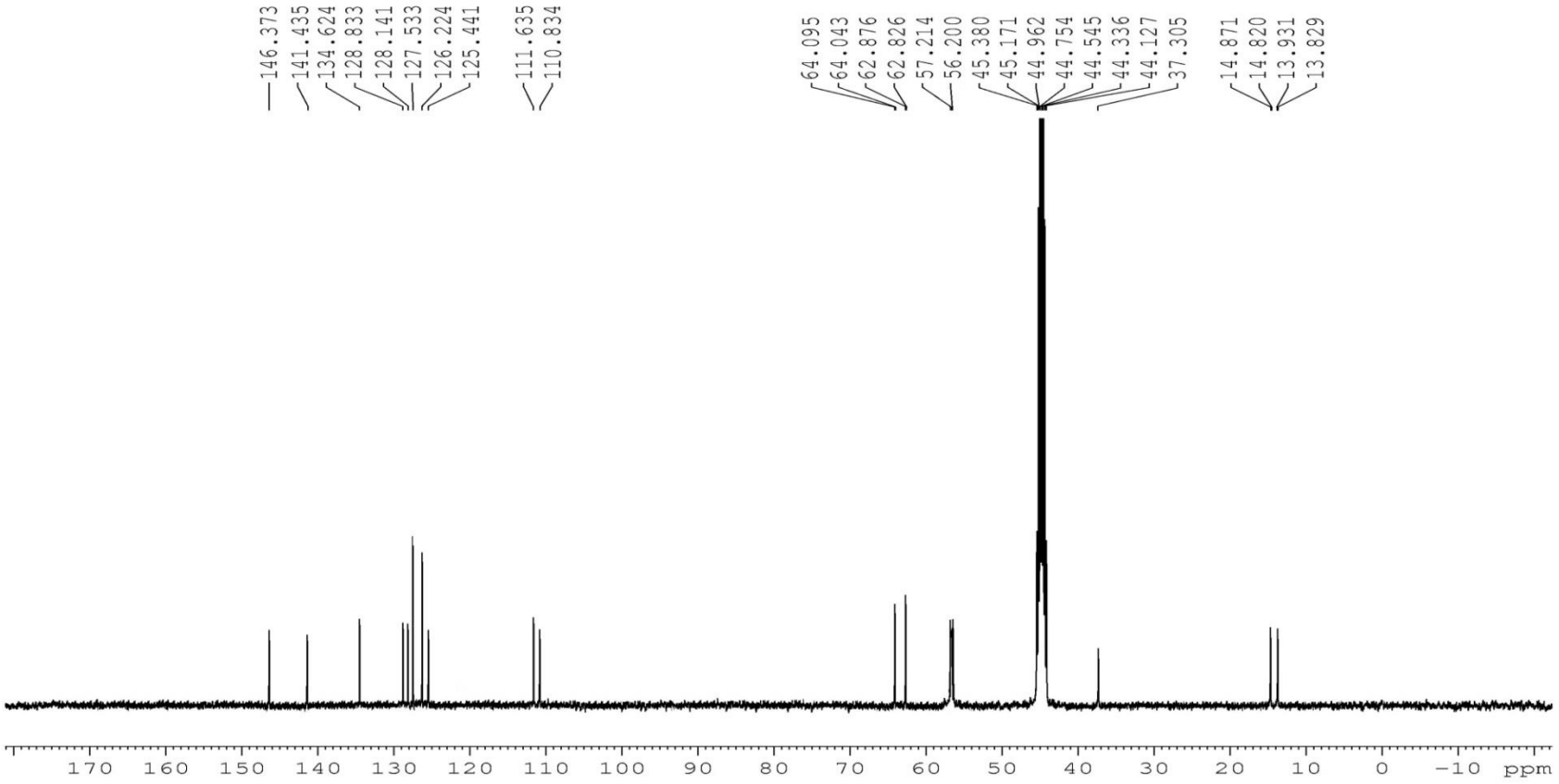


Figure S3: ^{13}C NMR Spectrum of tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(phenylmethylene))bis(phosphonate)(**4a**)

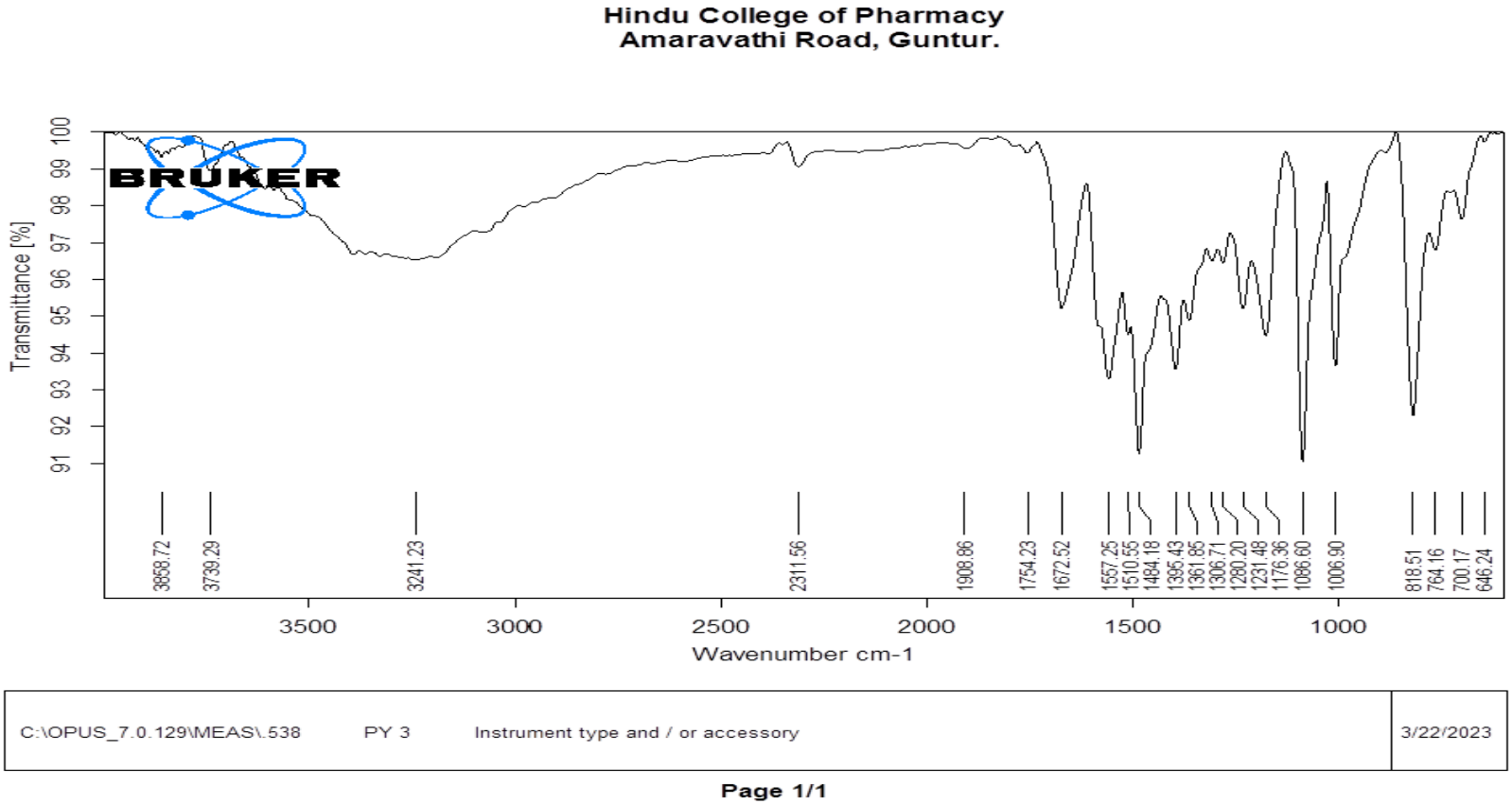


Figure S4: IR Spectrum of tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(phenylmethylene))bis(phosphonate)(**4a**)

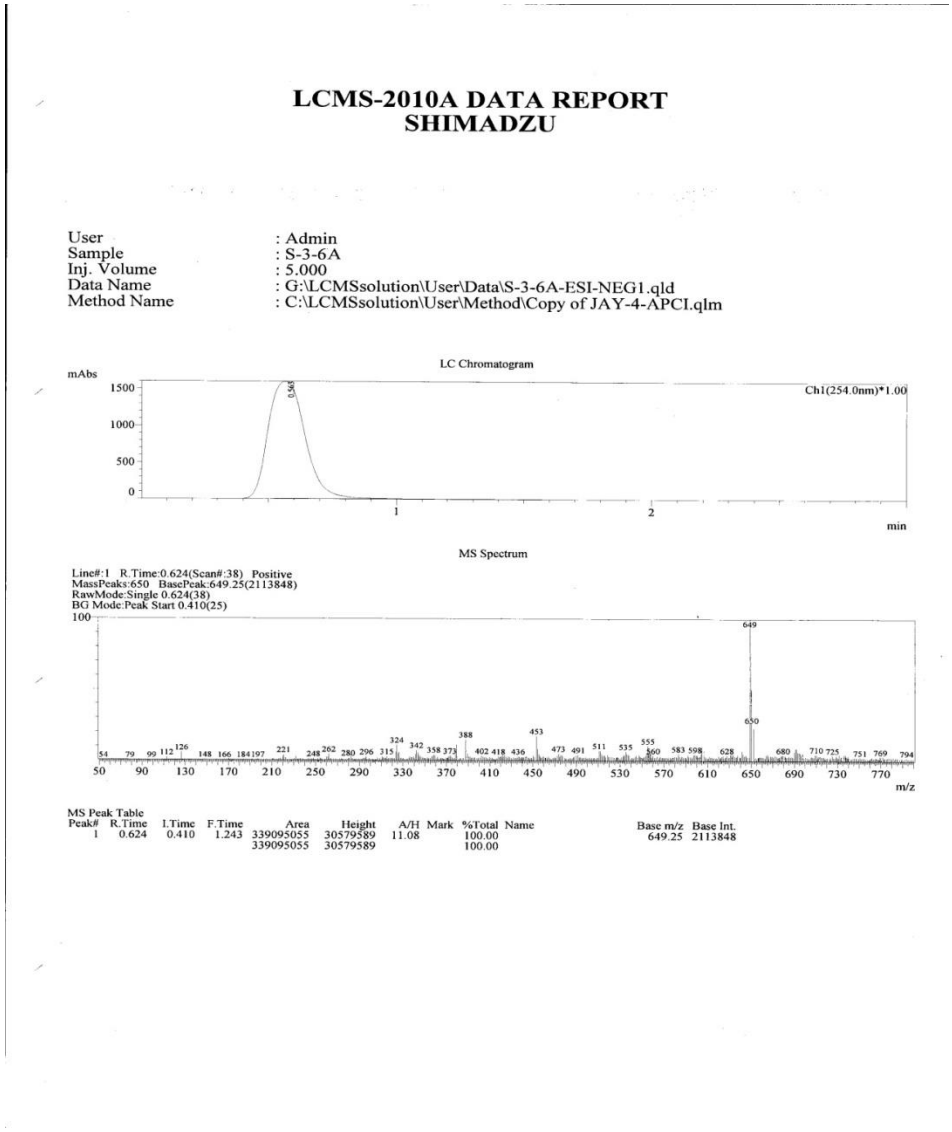
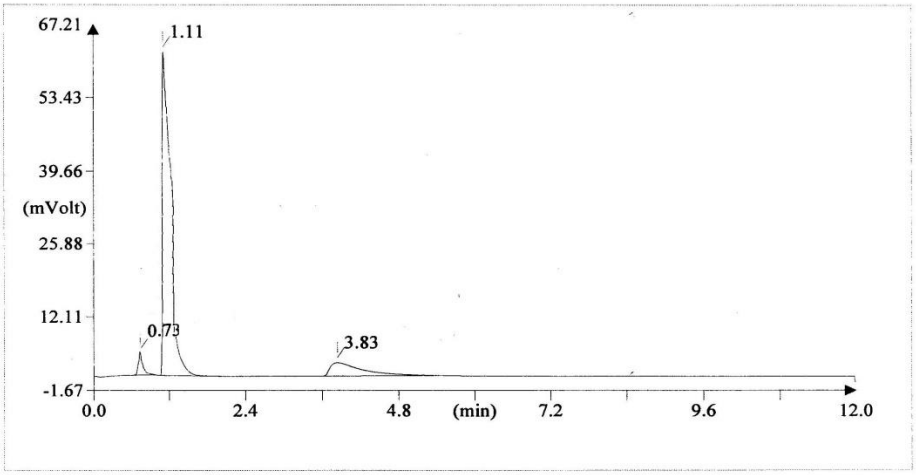


Figure S5: Mass Spectrum of tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis-(phenylmethylene))-bis(phosphonate)(**4a**)

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-6 (# 7)
Analysis type:	UnkNown
Chromatogram filename:	UNK-25062023-7.dat
Sample weight:	1.261



Element Name	Element %	Ret. Time
Nitrogen	4.43	0.73
Carbon	64.91	1.11
Hydrogen	6.42	3.83

Figure S6: CHN analysis of tetraethyl (((9H-fluorene-2,7-diyl)bis(azanediyl))bis(phenylmethylene))-bis(phosphonate)(**4a**)

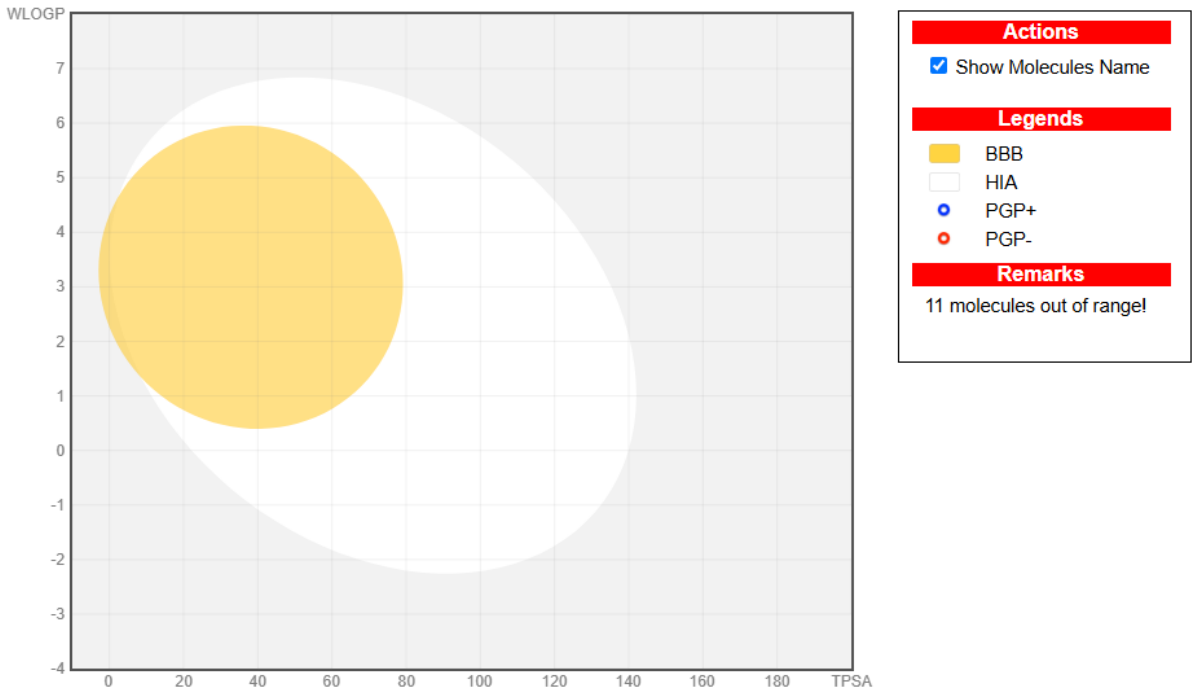


Figure S7: The BOILED-Egg diagram of the tested molecules 1-10 (**4a-j**)

Table S 1: Physicochemical properties of compounds **4a-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
4a	648.67	45	24	0.31	16	6	2	182.6	114.74	5.29	Poorly soluble
4b	684.65	47	24	0.31	16	8	2	182.51	114.74	5.15	Poorly soluble
4c	784.66	53	24	0.35	18	12	2	192.6	114.74	5.77	Insoluble
4d	786.45	49	24	0.31	16	6	2	202.64	114.74	6.42	Insoluble
4e	770.66	53	24	0.31	18	12	4	199.44	221.1	4.53	Insoluble
4f	680.66	47	24	0.31	16	8	4	186.64	155.2	4.48	Poorly soluble
4g	748.78	53	32	0.26	16	6	2	217.61	114.74	6.06	Insoluble
4h	736.68	51	24	0.35	16	10	2	194.72	151.66	6.17	Poorly soluble
4i	848.9	61	40	0.22	16	6	2	252.62	114.74	6.53	Insoluble
4j	753.54	49	24	0.31	16	8	2	192.53	114.74	6.07	Insoluble
Acarbose	645.6	44	0	0.92	9	19	14	136.69	321.17	0.63	Highly soluble

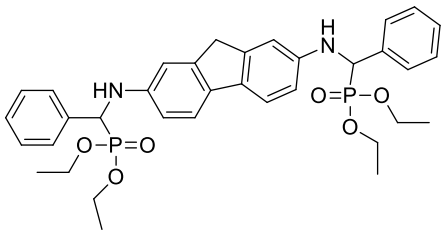
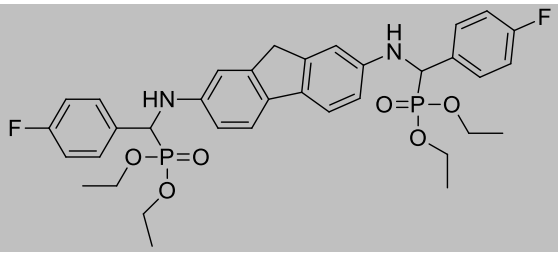
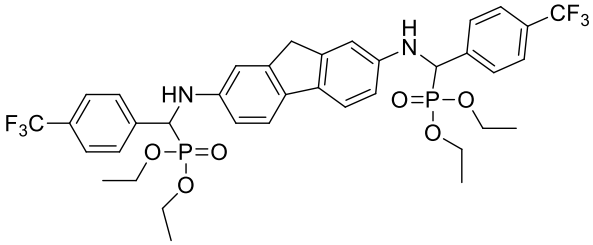
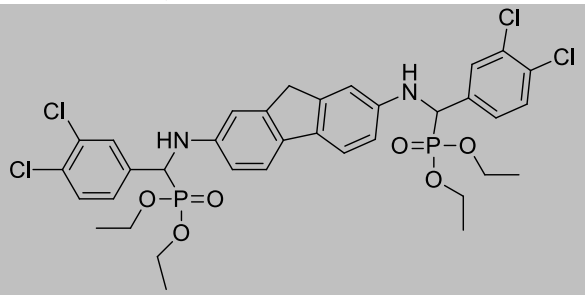
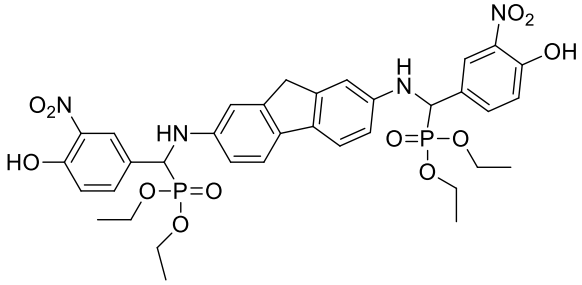
[a] Molecular weight; [b] The ratio of sp3 hybridized carbons over the total carbon count of the molecule; [c] Molar refractivity; [d] topological polar surface area (Å2); [e] lipophilicity; [f] water solubility (SILICOS-IT)

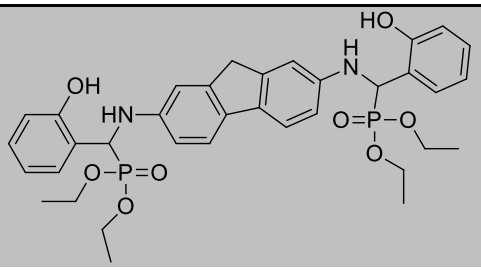
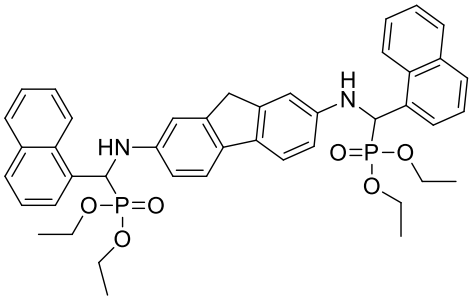
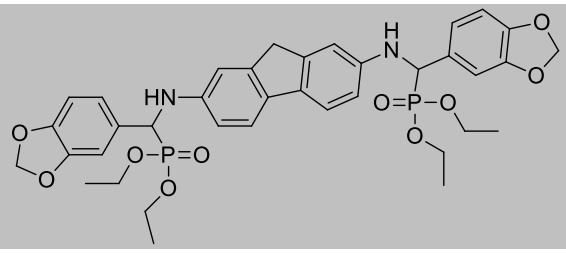
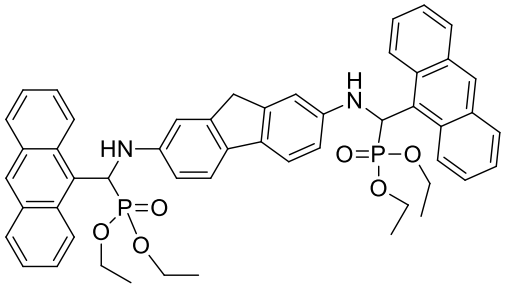
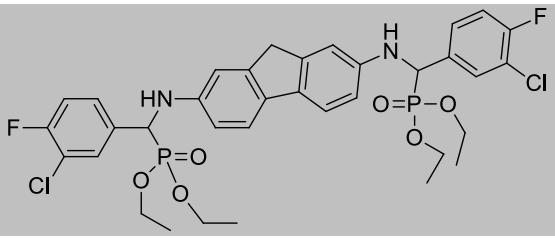
Table S2: Pharmacokinetic/ADME properties of compounds **4a-j**

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)
4a	Low	No	Yes	Yes	Yes	No	Yes	Yes	-5.48
4b	Low	No	Yes	Yes	Yes	No	Yes	Yes	-5.56
4c	Low	No	Yes	No	Yes	No	No	Yes	-5.05
4d	Low	No	Yes	Yes	No	No	No	Yes	-4.54
4e	Low	No	Yes	No	No	Yes	No	Yes	-6.19
4f	Low	No	Yes	Yes	Yes	No	No	Yes	-6.18
4g	Low	No	Yes	No	Yes	No	No	Yes	-4.31
4h	Low	No	Yes	No	Yes	No	No	Yes	-6.29
4i	Low	No	Yes	No	No	No	No	No	-3.34
4j	Low	No	Yes	Yes	No	No	No	Yes	-5.09
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 (**4a-j**) and standard with *α*-amylase and *α*-glucosidase enzymes in molecular docking study

Compd	Structure	*α*-amylase enzyme	*α*-glucosidase enzyme
		Binding energy (kcal /mol)	Binding energy (kcal/mol)
4a		-8.1	-7.2
4b		-7.7	-7.9
4c		-7.5	-8.5
4d		-8.6	-7.6
4e		-7.9	-7.7

4f		-8.0	-7.8
4g		-8.6	-8.9
4h		-8.5	-7.7
4i		-8.9	-9.2
4j		-7.8	-8.1
Std*	Acarbose	-8.2	-7.8

Std*: Acarbose

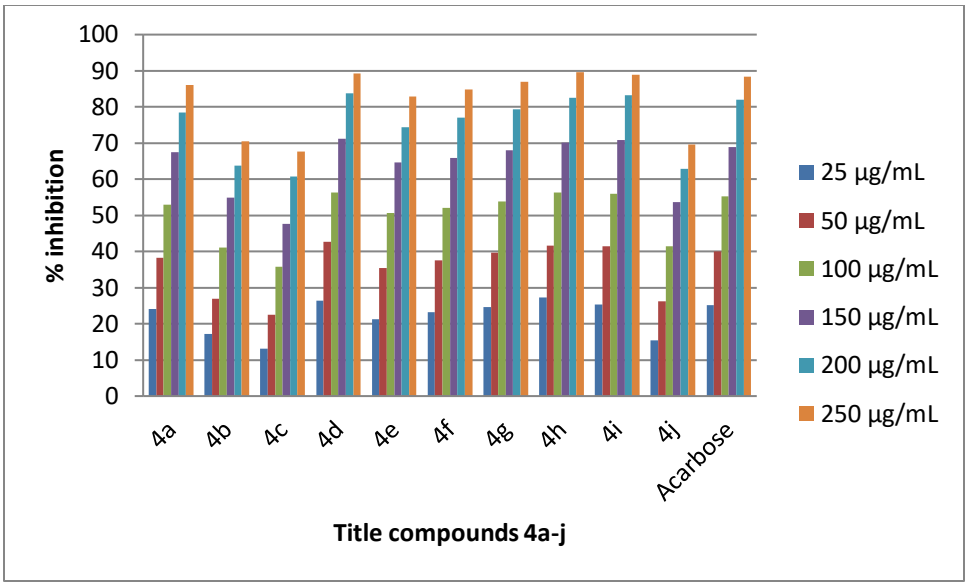


Figure S8 : α-Amylase inhibition activity results of compounds **4a-j**

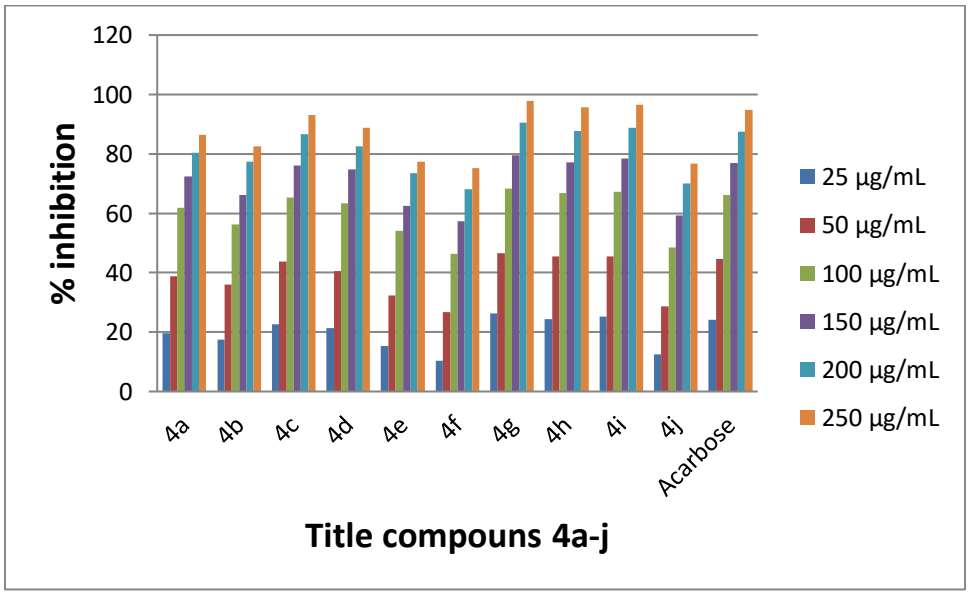


Figure S9 : α-Glucosidase inhibition activity results of compounds **4a-j**

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.