SUPPLEMENTARY INFORMATION

Design and mechanistic investigation of oxime-conjugated PAMAM dendrimers as the catalytic scavenger of reactive organophosphate

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Experimental section

Materials. Unless noted otherwise, all reagents and solvents were purchased from commercial suppliers and used as received. Paraoxon (purity ≥90 % oil), pralidoxime chloride (pyridine-2-aldoxime methochloride, 99 %), obidoxime chloride (purity ≥95 %), 4-pyridinealdoxime and deuterium oxide (99.9 atom % D, containing 0.05 wt % 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt) were purchased from Sigma-Aldrich. Phosphate buffer powder was purchased from Sigma-Aldrich, and reconstituted with deuterium oxide to prepare 1 × phosphate buffered saline (PBS: 0.01 M phosphate, NaCl 0.138 M, KCl 0.0027 M, pH 7.4). Generation 5 (G5) PAMAM dendrimer was purchased as a solution in methanol (17.5 % wt/wt; Dendritech, Inc., Midland, MI). The PAMAM dendrimer solution was concentrated by a rotary evaporator *in vacuo* and dialyzed in a membrane tubing (MWCO 10000) to remove lower trailing generations of dendrimer as described elsewhere.[1-3] The polydispersity index value (PDI = weight-average MW/number-average MW = M_w/M_n = 1.010) measured for this purified dendrimer G5-$(NH_2)_n$ **1** was 1.010. The mean number of primary amines per dendrimer (n) was 114 as determined by potentiometric titration.[1, 2] G5-(glutaric acid) **2** was prepared by treating **1** G5-$(NH_2)_{114}$ with an excess amount of glutaric anhydride ([glutaric anhydride]/[NH_2] = 2) in MeOH as described elsewhere.[2, 4-6]

Analytical Methods. Structural characterization of small antidote molecules and dendrimer conjugates was performed by standard analytical methods based on ultrahigh performance liquid chromatography (UPLC), mass spectrometry (ESI; matrix assisted laser desorption ionization-time of flight (MALDI TOF)) and ^{1}H NMR spectroscopy as described earlier.[1-3, 7] ^{1}H NMR spectra were acquired with a Varian nuclear magnetic resonance spectrometer at 500 or 400 MHz under standard observation conditions.[1, 2] MALDI TOF mass spectrometry was performed on a Waters TOfsPec-2E spectrometer to determine the molecular weights of PAMAM dendrimer conjugates. UV-vis absorption spectra were acquired on a Perkin Elmer Lambda 20 spectrophotometer. UPLC was performed to assess the purity of the dendrimer conjugate on a Waters Acquity System equipped with a photodiode array detector. Samples were run through a C4 BEH column (150 × 2.1 mm, 300 Å), and eluted with a linear gradient beginning with 98:2 (v/v) water/acetonitrile (with trifluoroacetic acid (TFA) at 0.14 wt %) at a flow rate of 1 mL/min. Gel permeation chromatography (GPC) experiments were performed on an Alliance Waters

2695 separation module equipped with a 2487 dual wavelength UV absorbance detector (Waters Corporation), a Wyatt HELEOS Multi Angle Laser Light Scattering (MALLS) detector, and an Optilab rEX differential refractometer (Wyatt Technology Corporation) as described fully elsewhere.[1-3]

Synthesis of G5-(GHA)$_{n = 66}$ 4 (Scheme 1). *N*-Hydroxysuccinimide (97 mg; 0.84 mmol) and 4-dimethylaminopyridine (103 mg; 0.84 mmol) were added to **2** G5-GA dendrimer (MW = 40,200 g/mol: 157 mg; 3.9 μmol)[4] suspended in anhydrous DMF (35 mL), followed by addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (105 mg; 0.55 mmol). The reaction mixture was stirred as a suspension at room temperature for 36 hr when it became a homogenous solution. To this solution, *O*-(t-butyldimethylsilyl) protected hydroxylamine (124 mg; 0.84 mmol) was added at a ratio of [H_2NO(TBDMS)]/[G5-GA] = 216. The final reaction mixture was stirred for an additional 48 hr prior to quenching the reaction by adding water (5 mL). The reaction mixture was concentrated by a rotary evaporator *in vacuo*, yielding a colorless residue, which was then dissolved in 10 mL of PBS (without Ca^{2+} and Mg^{2+}). The solution was loaded into a dialysis membrane tubing (Spectrum® Labs, Inc.; MWCO 10 kDa), and dialyzed against PBS (1 × 2L), and deionized water (3 × 2L) over 2 days. The solution inside the tubing was collected and lyophilized to afford the G5-(GHA)$_n$ **4** as a white solid (125 mg). The purity of the dendrimer was assessed by UPLC (Figure S1 of the Supporting Information): t_r = 7.85 min; purity ≥99%. The number of hydroxamate-terminated branches per dendrimer was estimated on a mean basis by integration of the ^{1}H NMR signals for glutaryl hydroxamate (Figure S1 of the Supporting Information). The signals selected for the analysis include CH_2 protons located in the middle of the glutaric spacer (assigned as protons a). The relative ratio of the two integration values for the CH_2 peaks between glutaryl hydroxamate (GHA) and the unmodified glutaric acid (GA) was used to determine the number (n = 66) of GHA molecules: $\sum CH_2$ (GHA)/$\sum CH_2$ (GA) = n/(108-n). ^{1}H NMR (500 MHz, D_2O): δ 3.35 (s), 2.85 (s), 2.70 (s), 2.45 (s), 2.25 (m), 22.0 (m), 1.85 (m), 1.80 (m) ppm. MALDI-TOF mass spectrometry: *m/z* = 41,200 gmol^{-1}.

G5-(GHA)$_{n = 19}$ **3** was prepared and characterized in a similar manner as described above but with a lower ratio of hydroxylamine to dendrimer ([H_2NOTBDMS]/[G5-GA] = 32). G5-(GHA)$_{n = 19}$ (135 mg) was obtained as a white fluffy solid starting from G5-GA (123 mg; 3.1 μmol). ^{1}H

NMR (500 MHz, D_2O): δ 3.35 (s), 2.85 (s), 2.70 (s), 2.45 (s), 2.25 (m), 22.0 (m), 1.85 (m), 1.80 (m) ppm. MALDI TOF mass spectrometry: *m/z* = 39,600 $gmol^{-1}$.

Synthesis of 7. *t*-Butyl bromoacetate (2.4 g, 12.3 mmol) was added to a solution of **5** 4-pyridinealdoxime (1.0 g, 8.2 mmol) dissolved in acetonitrile (70 mL). The mixture was refluxed under a nitrogen atmosphere for 24 hr, and evaporated to dryness *in vacuo*, yielding a pale brown residue. After resuspension in acetone (50 mL), the solid material was collected and rinsed with acetone (50 mL). Product **6** was obtained as a pale brown solid (2.49 g, 96%). HRMS (ESI): *m/z* calcd for $C_{11}H_{17}N_4O_2$ [M^+] 237.1234, found 237.1237. The *O*-*tert*-butyl protecting group of the product **6** was removed by treatment with TFA as follows. TFA (15 mL) was added to a suspension of **6** (1.5 g, 4.7 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 30 min, and concentrated *in vacuo*, yielding a brown residue. It was suspended in acetone (50 mL), and the solid residue was collected by filtration through a Bűchner funnel and rinsed with acetone (50 mL). Product **7** was obtained as a pale brown powder. HRMS (ESI): *m/z* calcd for $C_8H_9N_2O_3$ [M^+] 181.0608, found 181.0607. ^{1}H NMR (500 MHz, D_2O): δ 8.73 (d, 2H), 8.40 (s, 1H), 8.22 (d, 2H), 5.21 (s, 2H) ppm.

Synthesis of 8. *tert*-Butyl (3-(2-bromoacetamido)propyl)carbamate was prepared as previously described elsewhere.[5, 8] A cold solution of *tert*-butyl (3-aminopropyl)carbamate (1.1 g, 6.31 mmol) was prepared in $CHCl_3$ (50 mL) cooled with an ice bath. *N*,*N*-Diisopropylethylamine (1.1 mL, 2.03 mmol) was added, followed by addition of bromoacetyl chloride (526 μL, 6.32 mmol) as a neat liquid. The reaction mixture was stirred at 5°C for 3 hr under a nitrogen atmosphere. After the reaction, the mixture was diluted with dichloromethane (200 mL), and washed with 1.0 M H_3PO_4 (50 mL) solution and a saturated sodium bicarbonate solution (50 mL). The organic layer was dried over Na_2SO_4, and evaporated to dryness *in vacuo*, yielding the product *tert*-butyl (3-(2-bromoacetamido)propyl)carbamate as a colorless syrup which was slowly solidified into white crystals (1.9 g). It was used immediately for the next step without further purification. R_f (50% EtOAc/hexane) = 0.40. Compound **5,** 4-pyridinealdoxime (0.848 g, 6.9 mmol) was added to a solution of freshly prepared *tert*-butyl (3-(2-bromoacetamido)propyl)carbamate (~6.3 mmol) in acetonitrile (70 mL). The mixture was refluxed under a nitrogen atmosphere for 24 hr, and concentrated to dryness *in vacuo*, yielding a pale brown residue. It was rinsed with a copious volume of ethyl acetate (50 mL), and product **8** was obtained as a pale brown solid (1.25 g,

48%). It was characterized by standard analytiucal methods (Figure S2 of the Supporting Information). HRMS (ESI): *m/z* calcd for $C_{16}H_{25}N_4O_4$ [M^+] 337.1870, found 337.1871. ^{1}H NMR (500 MHz, CD_3OD): δ 8.84 (d), 8.54 (d), 8.35 (s), 8.26 (d), 8.11 (s), 7.63 (d), 5.41 (s, 2H), 3.36 (m, 2H), 3.13 (m, 2H), 1.72 (m), 1.45 (s, 9H) ppm.

Synthesis of 9. TFA (10 mL) was added to compound **8** (1.15 g, 2.76 mmol) suspended in dichloromethane (10 mL). The solid material was solubilized immediately. The reaction mixture was stirred at room temperature for 30 min, and concentrated to approximately 5 mL *in vacuo*. This solution was slolwy titrated into a stirred solution of diethylether (100 mL), resulting in precipitation of the product. The product was collected by decanting the supernatant and rinsed with ether (50 mL). This solid material was dissolved in water (20 mL) and freeze-dried to yield compound **9** as a pale brown solid. ^{1}H NMR (500 MHz, CD_3OD): δ 8.84 (d, 2H), 8.23 (d, 2H), 5.44 (s, 2H), 3.36 (m, 2H), 3.00 (m, 2H), 1.99 (m, 2H) ppm.

Synthesis of G5-(4PAM)$_{n = 25}$ 11 (Scheme 1). *N*-Hydroxybenzotriazole (HOBt; 31 mg, 0.20 mmol), diisopropylethylamine (DIPEA; 0.07 mL, 0.40 mmol), and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP; 104 mg, 0.20 mmol) were added to G5-GA-EO dendrimer[9] **10** (mean of (M_n and M_w) = 76,000 gmol^{-1}; 100 mg, 1.3 μmol; Figure S3 of the Supporting Information) suspended in anhydrous DMF (10 mL). The reaction mixture was stirred at room temperature for 14 hr, after which compound **9** (TFA salt; 99 mg, 0.28 mmol) dissolved in DMF (1 mL) containing DIPEA (0.2 mL, 1.2 mmol) was added to give a ratio of [**9**]/[**10**] ≈ 214. The final reaction mixture was stirred at room temperature for an additional 24 hr, and the reaction was terminated by adding water (2 mL). The mixture was concentrated *in vacuo*, yielding a colorless residue. The product was dissolved in 5 mL of PBS (pH 7.4), loaded into a membrane dialysis tubing (MWCO 10 kDa) and dialyzed against PBS (2 × 2L) and deionized water (3 × 2L) over 2 days. The aqueous solution was collected and freeze-dried to afford G5-(4PAM)$_{n = 25}$ **11** as a white solid (87 mg). The purity of **11** was determined by UPLC (Figure S4 of the Supporting Information): t_r = 8.34 min; purity ≥99%. ^{1}H NMR (500 MHz, D_2O): δ 8.65 (broad s), 8.32 (broad s), 8.16 (broad s), 8.10 (s), 3.7-3.6 (m), 3.4-3.3 (m), 2.8 (broad s), 2.65 (broad s), 2.5 (broad s), 2.3 (broad s), 1.9 (m) ppm. The number (n = 25) of 4-PAM molecules attached to the dendrimer was estimated on a mean basis from analysis of the UV-vis absorption (280 nm).

Figure S1. (a) ^{1}H NMR spectra of G5-GA **2** and G5-$(GHA)_{66}$ **4**. Each NMR spectrum was acquired in D_2O (5 mg/mL); (b) UPLC traces of G5-$(NH_2)_{114}$ **1,** G5-GA[2, 4, 5] **2** and G5-$(GHA)_{66}$ **4**, each recorded at 1 mg/mL.

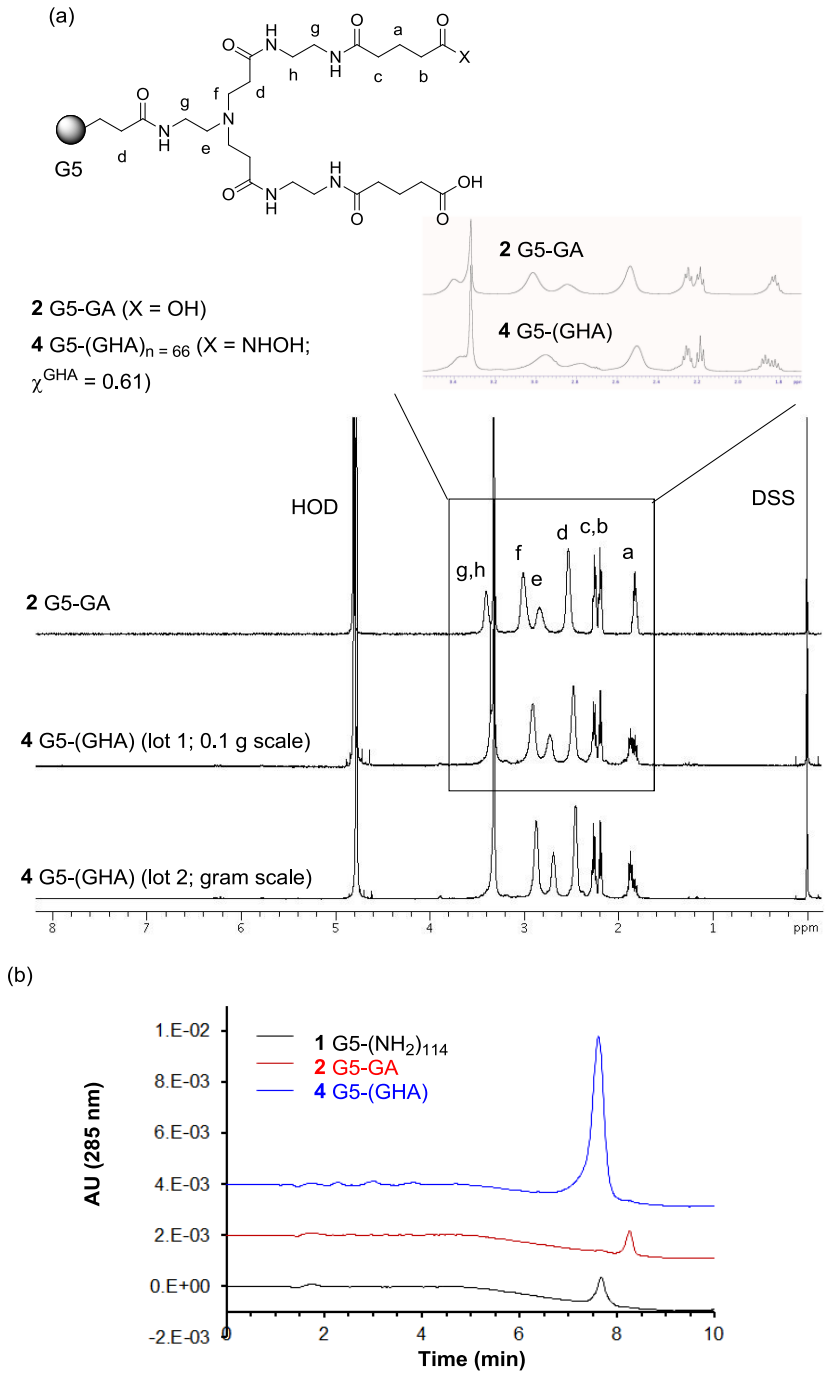


Figure S2. Copies of selected spectral data for **8** (4PAM-NHBoc) and **9** (4PAM-NH_2): a) ESI mass spectrum of **8**; b) UV-vis spectra of **9** measured in PBS (pH 7.4) at the serially diluted concentrations as indicated; a) ^{1}H NMR spectrum of **9** (CD_3OD).

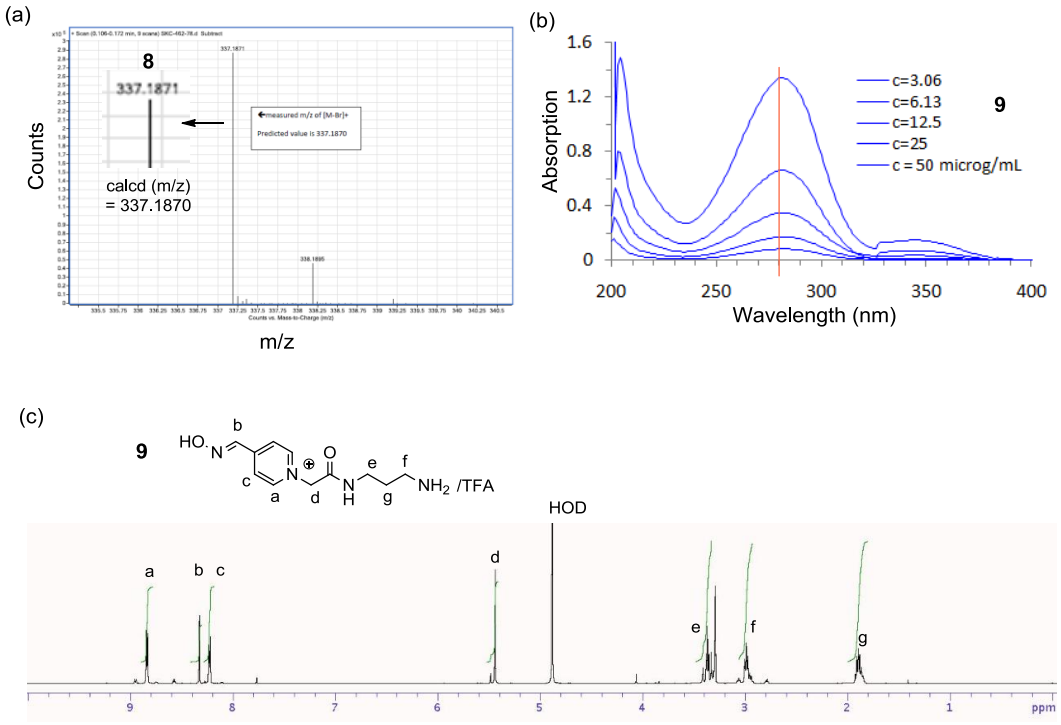


Figure S3. (a) GPC of G5-GA-EO^{9} **10**; (b, c) UPLC traces and ^{1}H NMR spectra (D_2O) for G5-GA-EO^{9} **10** and G5-GA$^{2, 4, 5}$ **2**.

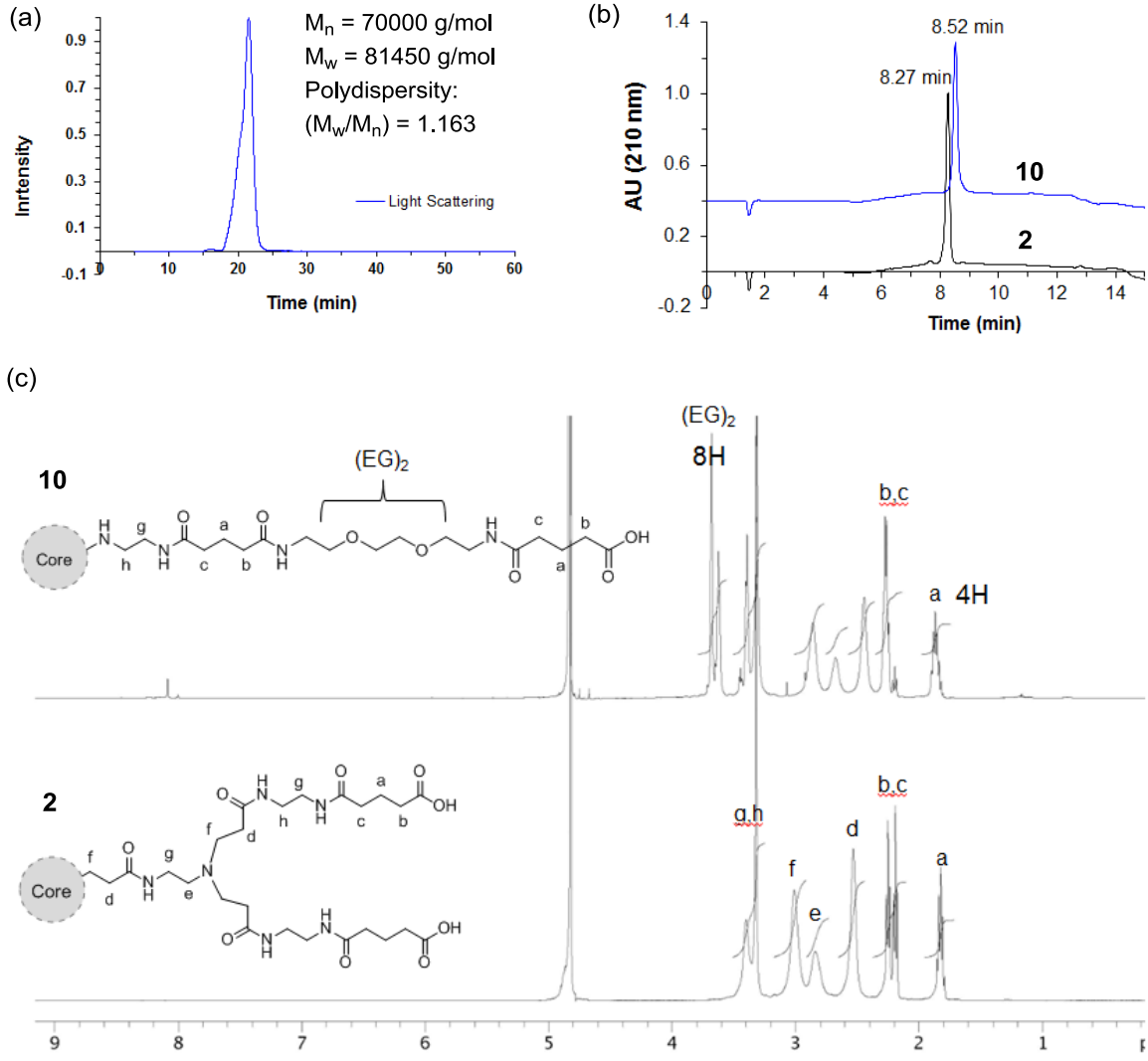


Figure S4. (a) ^{1}H NMR spectra (D_2O) for G5-GA-EO[9] **10**, G5-(4PAM)$_{25}$ **11** (χ^{4PAM} = 0.23) and 4PAM-NH_2 **9**; (b) UPLC traces of **10** and **11**; c) UV-vis spectra measured in PBS (pH 7.4).

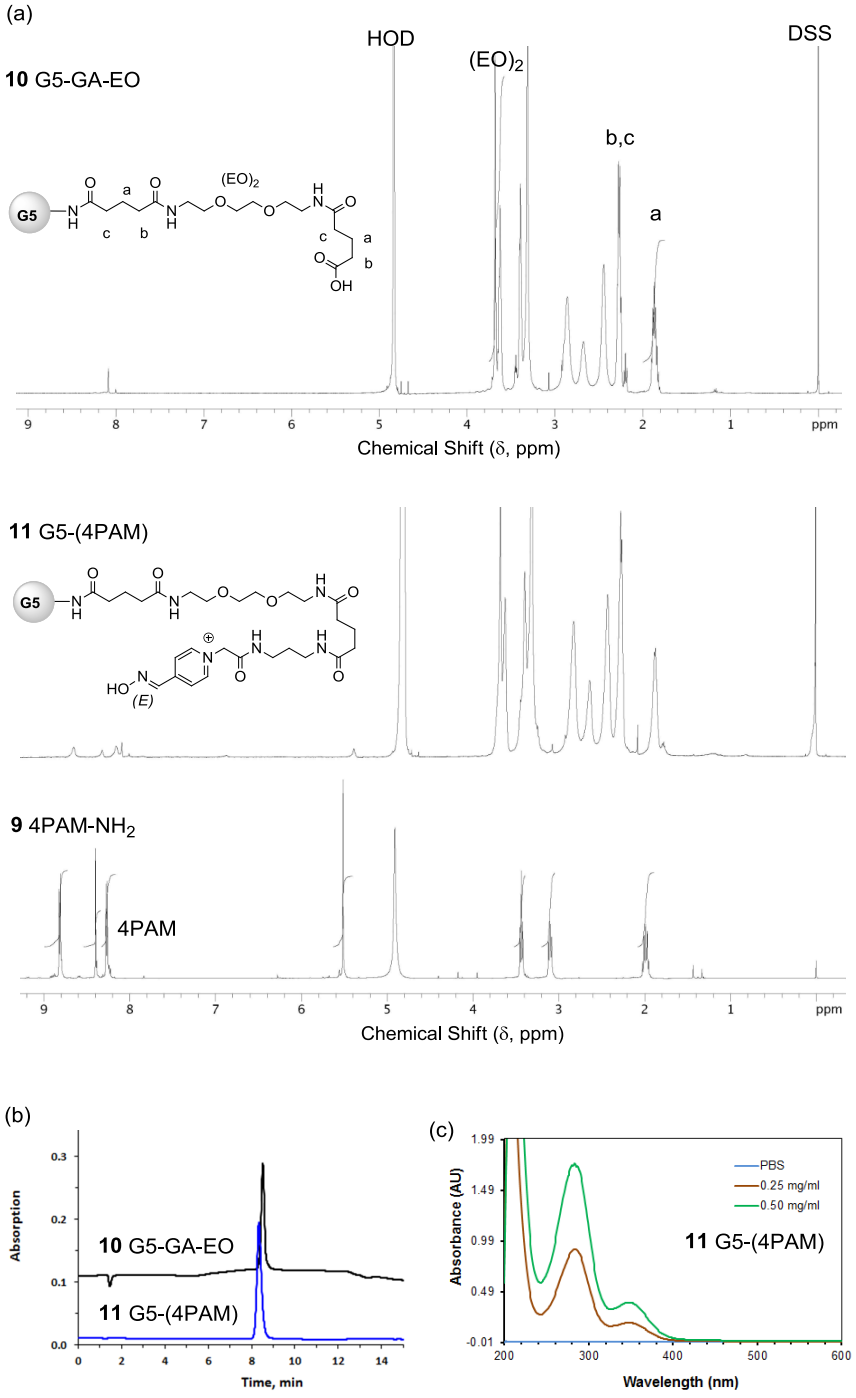
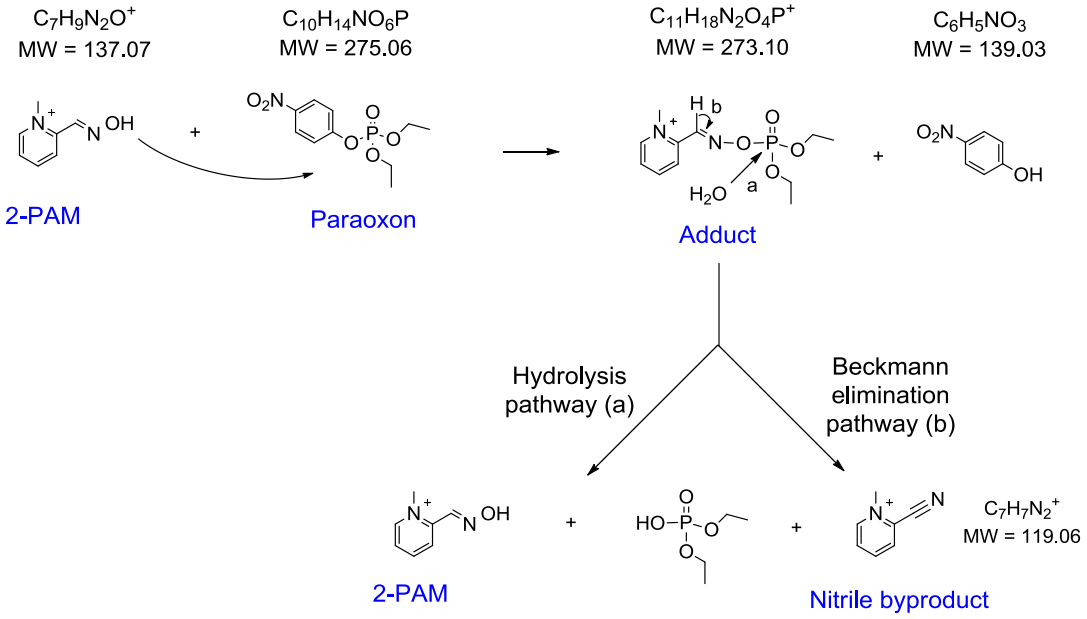


Figure S5. ESI mass spectrometric detection of a transient adduct formed from the reaction between pralidoxime (2-PAM; 14.5 mM) and paraoxon (POX; 13.1 mM) in DMF containing Et_3N (13.1 mM) at room temperature. The mass spec experiment was performed in a negative ion mode. Please note that that this adduct undergoes degradation via two pathways: (a) hydrolysis to 2-PAM; (b) Beckmann elimination to a nitrile byproduct (2-cyano-1-methylpyridinium).



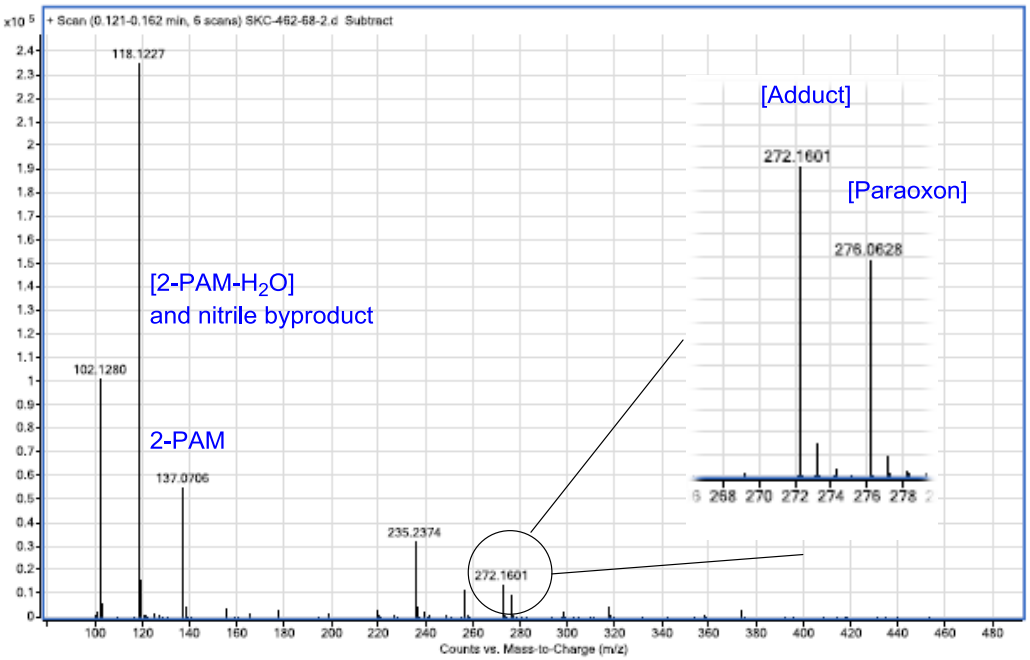


Figure S6. Full traces of ^{1}H NMR spectra acquired for the hydrolysis of POX (0.48 mM) catalyzed by G5-$(GHA)_{66}$ **4** (χ^{GHA} = 0.61; 48 μM) in deuterated PBS (pH 7.4) at room temperature.

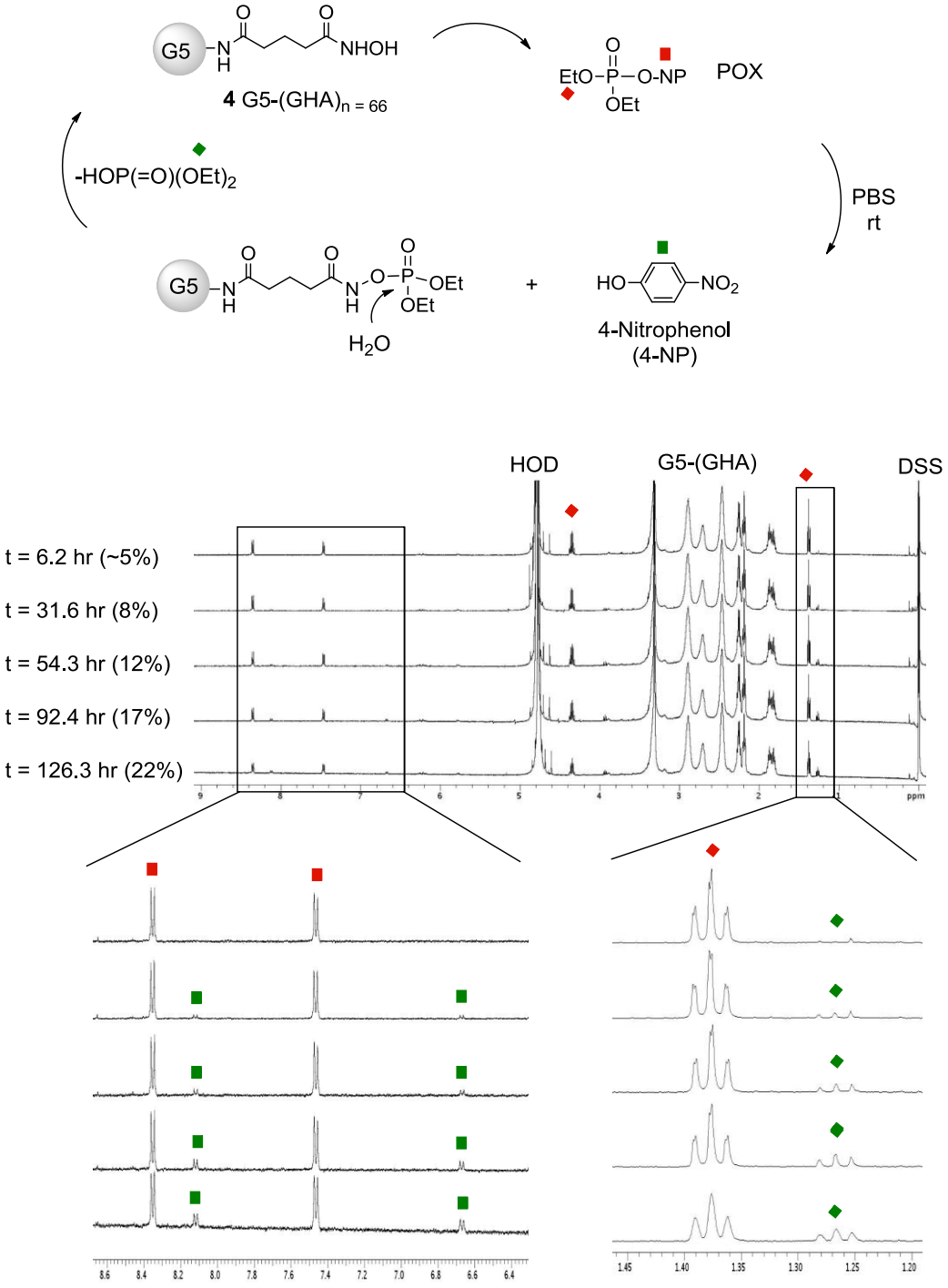
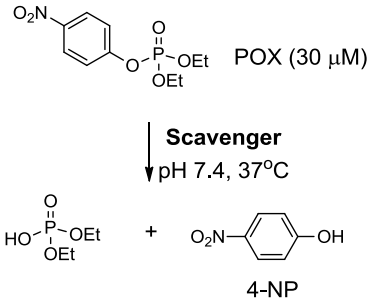
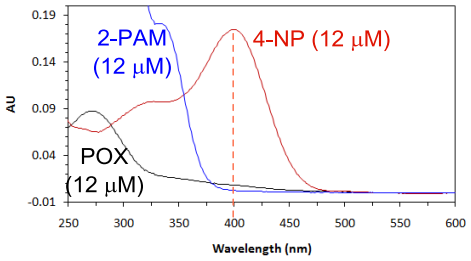
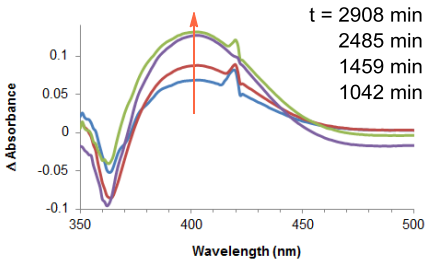


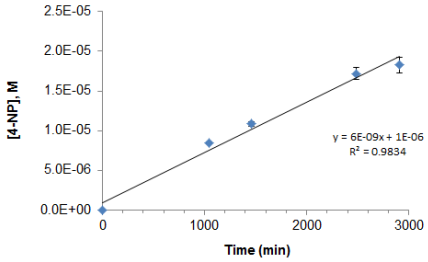
Figure S7. UV-vis colorimetric assay for determining the progress of paraoxon (POX) hydrolysis at a physiological condition: pH 7.4; temperature = 37 ± 2 ^{o}C. The hydrolysis was catalyzed by scavenger molecules as illustrated with 2-PAM (a), G5-(GHA)$_{66}$ **4** (b) or G5-(4PAM)$_{25}$ **11** (c). A figure showing overlaid UV-vis spectra, each measured separately for 2-PAM, POX or 4-nitrophhenol (4-NP), is given in the upper right corner.



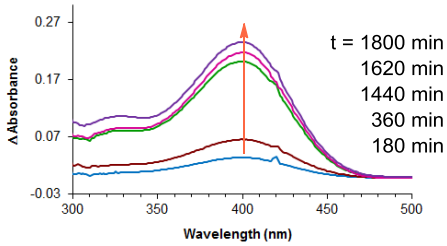


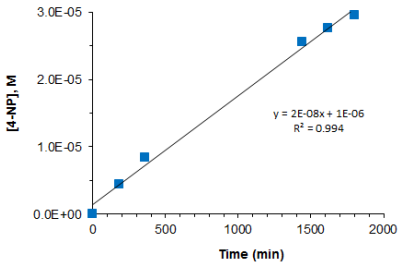
(a) Scavenger = 2-PAM: [2-PAM] = 1.5 mM



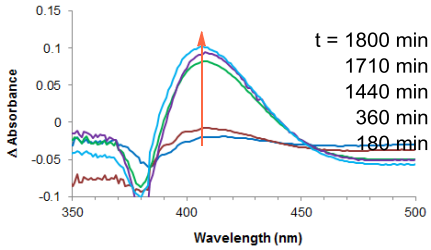


(b) Scavenger = **4** G5-(GHA)$_{66}$: [**4**] = 0.12 mM





(c) Scavenger = **11** G5-(4PAM)$_{25}$: [**11**] = 74 μM



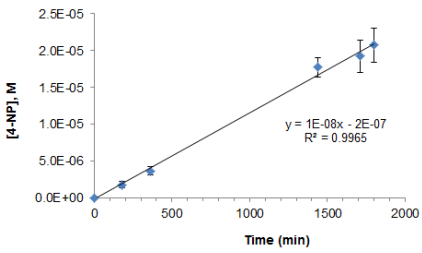


Figure S8. Kinetic parameters determined for hydrolysis of paraoxon ([POX] = 3.0×10^{-5} M) at pH 7.4 and 37 ± 2 °C. Plots of observed rate constants (k_{obsd}) as a function of scavenger concentration for dendrimer conjugates G5-$(GHA)_{66}$ **4** and G5-$(4PAM)_{25}$ **11** (a). Plots of half-life ($t_{1/2}$) as a function of scavenger concentration for dendrimer conjugates G5-$(GHA)_{66}$ **4** and G5-$(4PAM)_{25}$ **11** (b).

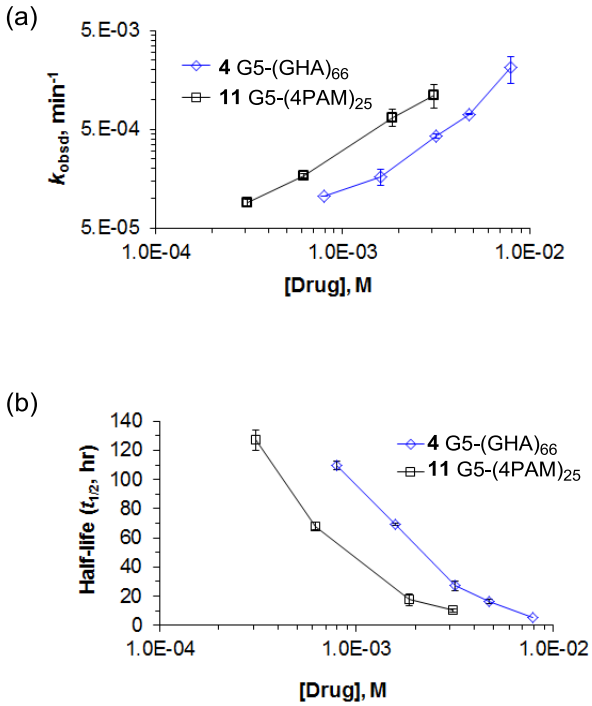


Table S1. Kinetic rate constants determined for the hydrolytic decomposition of paraoxon (POX) catalyzed by oxime antidote molecules and G5 dendrimers. Each measurement was performed at an identical condition: [POX] = 3.0×10^{-5} M; PBS (pH 7.4); temperature = 37 ± 2 ^{o}C. Each value for k_{obsd} or $t_{1/2}$ was calculated as a mean from n ≥ 3 runs, and its uncertainties are given as standard deviations (SD).

[POX], M	Drug or Dendrimer	[Drug or Dendrimer] (M)	k_{obsd} (min^{-1})[a] mean (±SD)	$t_{1/2}$ (hr)[b] mean (±SD)	Catalytic Efficiency[c]
3.0×10^{-5}	2-PAM	5.0×10^{-4}	1.4×10^{-4} (±0.055)	81 (±3.2)	11.7
		1.0×10^{-3}	2.6×10^{-4} (±0.040)	45 (±0.71)	21.7
		1.5×10^{-3}	3.3×10^{-4} (±0.29)	35 (±3.0)	27.5
		3.0×10^{-3}	**5.9×10^{-4} (±0.37)**	**20 (±1.2)**	**49.2**
	Obidoxime	1.0×10^{-3}	2.8×10^{-4} (±0.50)	41 (±7.1)	23.3
		2.0×10^{-3}	5.2×10^{-4} (±0.63)	22 (±2.7)	43.3
		3.0×10^{-3}	**6.7×10^{-4} (±1.7)**	**17 (±4.4)**	**55.8**
		6.0×10^{-3}	1.2×10^{-3} (±0.14)	9.7 (±1.1)	100
	Trimedoxime	1.0×10^{-3}	2.6×10^{-4} (±0.21)	44 (±3.5)	21.7
		2.0×10^{-3}	4.5×10^{-4} (±0.098)	26 (±0.60)	37.5
		3.0×10^{-3}	**1.1×10^{-3} (±0.33)**	**10 (±2.9)**	**91.7**
		6.0×10^{-3}	1.4×10^{-3} (±0.19)	8.4 (±1.1)	116.7
	G5-$(GHA)_{66}$ **4** (χ^{GHA} = 0.61)	1.2×10^{-5}	1.1×10^{-4} (±0.012)	110 (±1.2)	9.2
		2.4×10^{-5}	1.7×10^{-4} (±0.30)	69 (±12)	14.2
		4.9×10^{-5}	4.3×10^{-4} (±0.24)	27 (±1.5)	35.8
		7.3×10^{-5}	7.1×10^{-4} (±0.055)	16 (±0.10)	59.2
		1.2×10^{-4}	**2.1×10^{-3} (±0.63)**	**5.5 (±1.6)**	**175.0**
	G5-$(4PAM)_{25}$ **11** (χ^{4PAM} = 0.23)	1.2×10^{-5}	9.1×10^{-5} (±0.79)	127 (±11)	7.6
		2.5×10^{-5}	1.7×10^{-4} (±0.084)	68 (±3.4)	14.2
		7.4×10^{-5}	6.6×10^{-4} (±1.3)	18 (±3.4)	55.0
		1.2×10^{-4}	**1.1×10^{-3} (±0.30)**	**10 (±2.8)**	**91.7**
	Buffer alone	0	$<1.2 \times 10^{-5}$ (±0.62)	996 (±530)	1

[a] k_{obsd} refers to observed pseudo first-order rate constant.

[b] $t_{1/2}$, half-life, refers to the time required for half of the original amount (30 μM) of POX to be consumed.

[c] Catalytic Efficiency = $k_{obsd\ (drug\ or\ dendrimer\ catalyst)} \div k_{obsd\ (buffer)}$

Table S2. Kinetic rate constants determined for the hydrolytic decomposition of paraoxon (POX) catalyzed by oxime antidote molecules and G5 dendrimers at two different pH values. Each measurement was otherwise performed under an identical condition: [POX] = 1.0×10^{-5} M; temperature = 23 ± 2 °C. Each value for k_{obsd} or $t_{1/2}$ was calculated as a mean from n ≥ 3 runs, and its uncertainties are given as standard deviations (SD).

[POX], M	Drug or Dendrimer	pH	[Drug or Dendrimer] (M)	k_{obsd} (min^{-1})[a] mean (±SD)	$t_{1/2}$ (hr)[a] mean (±SD)	Catalytic Efficiency[b]
1.0×10^{-5}	2-PAM	9.0[c]	2.5×10^{-4}	1.9×10^{-4} (±0.28)	64 (±11)	6.1
			5.0×10^{-4}	**2.9×10^{-4} (±0.44)**	**41 (±7.8)**	**9.4**
			7.5×10^{-4}	4.6×10^{-4} (±0.23)	25 (±1.2)	14.8
			1.0×10^{-3}	8.6×10^{-4} (±2.5)	14 (±4.9)	27.7
			2.0×10^{-3}	2.1×10^{-4} (±0.46)	5.7 (±1.4)	6.8
		7.4[d]	**5.0×10^{-4}**	**1.0×10^{-4} (±0.71)**	**116 (±4.8)**	**37.0**
	Obidoxime	9.0	2.5×10^{-4}	2.6×10^{-4} (±0.58)	46 (±12)	8.4
			5.0×10^{-4}	**5.5×10^{-4} (±1.7)**	**19 (±4.8)**	**17.7**
			7.5×10^{-4}	7.2×10^{-4} (±1.2)	17 (±3.1)	23.2
			1.0×10^{-3}	1.4×10^{-3} (±0.31)	8.4 (±2.0)	45.2
		7.4	**5.0×10^{-4}**	**1.2×10^{-4} (±0.54)**	**96 (±4.0)**	**44.4**
	G5-$(GHA)_{19}$ **3** (χ^{GHA} = 0.18)	9.0	1.4×10^{-5}	3.6×10^{-5} (±0.20)	322 (±18)	1.2
			2.8×10^{-5}	6.8×10^{-5} (±0.21)	171	2.2
			4.9×10^{-5}	6.9×10^{-5} (±0.79)	170 (±21)	2.2
			5.6×10^{-5}	8.4×10^{-5} (±2.0)	142 (±31)	2.7
		7.4	2.3×10^{-5}	2.6×10^{-5} (±1.9)	257 (±11)	9.6
	G5-$(GHA)_{66}$ **4** (χ^{GHA} = 0.61)	9.0	7.7×10^{-6}	6.8×10^{-5} (±0.47)	170 (±12)	2.2
			1.5×10^{-5}	9.1×10^{-5} (±1.6)	130 (±22)	2.9
			3.1×10^{-5}	9.6×10^{-5} (±0.44)	121 (±5.7)	3.1
			6.2×10^{-5}	1.4×10^{-4} (±0.18)	86 (±11)	4.5
			1.2×10^{-4}	1.5×10^{-4} (±0.25)	79 (±13)	4.8
		7.4	2.4×10^{-5}	7.2×10^{-5} (±3.9)	161 (±6.7)	26.7
	Buffer alone	9.0	0	3.1×10^{-5} (±0.13)	383 (±16)	1
		7.4	0	2.7×10^{-6} (±1.1)	4316 (±1761)	1

[a] k_{obsd} and $t_{1/2}$ as defined earlier; [b] Catalytic Efficiency = $k_{obsd\ (drug\ or\ dendrimer\ catalyst)} \div k_{obsd\ (buffer)}$

[c] pH 9.0 (borate-potassium carbonate); [d] pH 7.4 (PBS)

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