Supplemental material

NEW STRUCTURAL SCAFFOLDS FOR CENTRALLY ACTING OXIME REACTIVATORS OF PHOSPHYLATED CHOLINESTERASES

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Running Title: Centrally acting ChE reactivators

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Synthetic procedures and analysis

All reactions were performed with commercially available ACS grade reagents and solvents. Anhydrous *N*,*N*-dimethylfomamide (DMF), 1,4-dioxane, toluene, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and dichloromethane (DCM) were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. All chemical shifts were reported in ppm relative to solvent resonances, as indicated (DMSO-d_6 δ 2.49, ^{1}H; δ 39.49, ^{13}C), ($CDCl_3$ δ 7.26, ^{1}H; δ 77.0, ^{13}C). ^{1}H NMR coupling constants (J) are given in Hz. The following compounds were synthesized by known literature methods; 3-(3,4-Dihydroisoquinolin-2(1H)-yl)propanamine (Vooturi et al., 2010), 1-azido-4-(methylsulfonyl)propane (Conrad et al., 1987), **9** (Beccalli et al., 2008), **10** (Stefely et al., 2010), **12** (Wang et al., 2008), **14** (Kalisiak et al., 2008), 1-azido-4-(methylsulfonyl)butane (Dorfler et al., 2008), and **RS186B** (Sato et al., 1988). All primary amines and imidazole alkyne **11** were obtained commercially.

A. General method for preparation of imidazole oximes RS113A, RS113B, RS115A, RS115B and RS115C. To a heterogenous solution of 2-formylimidazole **1** and K_2CO_3 in DMF (13 mL), the corresponding bromoalkane was added and warmed overnight at 50 °C under nitrogen. The resulting suspension was cooled to rt and filtered. Water was added to the filtrate and subsequently extracted with Et_2O (3 x 60 mL). The organic layer was dried with $MgSO_4$ and evaporated to give the corresponding alkylimidazole-2-carbaldehyde.

Hydroxylamine hydrochloride was dissolved in water and neutralized with Na_2CO_3. Alkylimidazole-2-carbaldehyde was added, and the solution was stirred at 70 °C for 1 h. The corresponding oxime was filtered out, rinsed with water and dried over P_2O_5 under vacuum.

1-Hexylimidazole-2-carbaldehyde oxime (RS113A). Prepared according to the general method A. 2-Formylimidazole **1** (1 g, 10.4 mmol), K_2CO_3 (1.7 g, 12.3 mmol), bromohexane (1.9 g, 11.5 mmol) DMF (13 mL). Yellow oil **1a** (1 g, 53 %).

Hexylimidazole-2-carbaldehyde 0.25 g (1.4 mmol), $NH_2OH·HCl$, 0.12 g (1.7 mmol), water (2 mL), Na_2CO_3 0.15 g (1.4 mmol). White solid, yield (0.24 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.04 (s, 1H), 7.30 (s, 1H), 6.99 (s, 1H), 4.22 (app s, 2H), 1.65 (app s, 2H), 1.23 (app s, 6H), 0.83 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.4, 139.5, 128.7, 123.6, 46.6, 30.8, 30.3, 25.5, 22.0, 13.9; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{10}H_{17}N_3O$, 196.3; found, 196.4.

1-Pentylimidazole-2-carbaldehyde oxime (RS113B). Prepared according to the general method A. 2-Formylimidazole **1** (1 g, 10.4 mmol), K_2CO_3 (1.7 g, 12.3 mmol), bromopentane (1.7 g, 11.4 mmol) DMF (13 mL). Yellow oil **1b** (0.86 g, 50 %).

Pentylimidazole-2-carbaldehyde 0.23 g (1.4 mmol), $NH_2OH·HCl$, 0.12 g (1.7 mmol), water (2 mL), Na_2CO_3 0.15 g (1.4 mmol). White solid, yield (0.23 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.05 (s, 1H), 7.30 (s, 1H), 6.99 (s, 1H), 4.21 (app s, 2H), 1.66 (app s, 2H), 1.29-1.17 (m, 4H), 0.87-0.80 (app m, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.4, 139.5, 128.7, 123.6, 46.6, 30.1, 28.0, 21.7, 13.9; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_9H_{15}N_3O$, 182.2; found, 182.4.

1-Butylimidazole-2-carbaldehyde oxime (RS115A). Prepared according to the general method A. 2-Formylimidazole **1** (0.75 g, 7.8 mmol), K_2CO_3 (1.3 g, 9.4 mmol), bromobutane (1.3 g, 9.4 mmol) DMF (10 mL). Yellow oil **1c** (0.69 g, 58 %).

Butylimidazole-2-carbaldehyde 0.18 g (1.2 mmol), $NH_2OH{\cdot}HCl$, 0.17 g (2.4 mmol), water (2 mL), Na_2CO_3 0.14 g (1.3 mmol). White solid, yield (0.16 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.04 (s, 1H), 7.30 (s, 1H), 6.99 (s, 1H), 4.22 (t, J = 7.2 Hz 2H), 1.65 (quint, J = 7.2 Hz, 2H), 1.23 (sext, J = 7.2 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.4, 139.5, 128.7, 123.6, 46.4, 32.4, 19.1, 13.5; LCMS (ESI) (m/z): $[M+H]^+$ calculated for $C_8H_{13}N_3O$, 168.2; found, 168.4.

1-Propylimidazole-2-carbaldehyde oxime (RS115B). Prepared according to the general method A. 2-Formylimidazole **1** (0.75 g, 7.8 mmol), K_2CO_3 (1.3 g, 9.4 mmol), bromopropane (1.1 g, 9.4 mmol) DMF (10 mL). Yellow oil **1d**, yield (0.55 g, 51 %).

Propylimidazole-2-carbaldehyde 0.17 g (1.2 mmol), $NH_2OH{\cdot}HCl$, 0.17 g (2.4 mmol), water (2 mL), Na_2CO_3 0.14 g (1.3 mmol). White solid, yield (0.16 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.04 (s, 1H), 7.31 (s, 1H), 6.99 (s, 1H), 4.19 (t, J = 7.2 Hz, 2H), 1.68 (sext, J = 7.6 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.4, 139.5, 128.7, 123.7, 48.1, 23.6, 10.7; LCMS (ESI) (m/z): $[M+H]^+$ calculated for $C_7H_{11}N_3O$, 154.2; found, 154.3.

1-Ethylimidazole-2-carbaldehyde oxime (RS115C). Prepared according to the general method A. 2-Formylimidazole **1** (0.75 g, 7.8 mmol), K_2CO_3 (1.3 g, 9.4 mmol), bromoethane (1.0 g, 9.4 mmol) DMF (10 mL). Yellow oil **1e**, yield (0.53 g, 55 %).

Ethylimidazole-2-carbaldehyde 0.15 g (1.2 mmol), $NH_2OH·HCl$, 0.17 g (2.4 mmol), water (2 mL), Na_2CO_3 0.14 g (1.3 mmol). White solid, yield (0.15 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.04 (s, 1H), 7.32 (s, 1H), 6.99 (s, 1H), 4.26 (q, J = 6.8 Hz, 2H), 1.27 (t, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.4, 139.3, 128.9, 123.0, 41.8, 16.2; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_6H_9N_3O$, 140.2; found, 140.3.

B. General method for the preparation of acetamide oximes RS41A, RS191D, RS191C, RS69A, and RS69F. The desired amine was added to solution of ethyl glyoxylate oxime **3** in ethanol with stirring. The solution was stirred at 50 °C overnight and cooled to room temperature. The resulting precipitate was filtered, washed with cold ethanol and dried under vacuum.

2-(Hydroxyimino)-*N*-(2-(pyrrolidinyl)ethyl)acetamide (RS41A). Prepared according to the general method B. Ethyl glyoxylate oxime **3** (0.75 g, 6.41 mmol), 2-(pyrrolidinyl) ethanamine (0.80 g, 7.0 mmol), ethanol (7 mL). White solid, yield (0.90 g, 76 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.03 (s, 1H), 7.46 (s, 1H), 3.28 (q, J = 4.0 Hz 2H), 2.52 (d, J = 4.0 Hz, 2H), 2.47 (app s, 4H), 1.70 (app s, 4H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.6, 143.7, 54.6, 53.5, 37.7, 23.1; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_8H_{15}N_3O_2$, 186.2; found, 186.4.

2-(Hydroxyimino)-*N*-(3-(3,4-dihydroisoquinolin-2-propyl)acetamide (RS191D). Prepared according to the general method B. Ethyl glyoxylate oxime **3** (0.15 g, 1.3 mmol), 3-(3,4-dihydroisoquinolin-2(1H)-yl)propanamine (0.29 g, 1.5 mmol), ethanol (1.3 mL). White yellowish solid, yield (0.25 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.18 (s, 1H), 7.44 (s, 1H), 7.08 (app s, 3H), 7.03 (app s, 1H), 3.52 (s, 2H), 3.21 (app d, J = 6.0 Hz, 2H), 2.78 (app s, 2H), 2.62 (app s, 2H), 2.44 (app s, 2H), 1.71 (t, J = 6.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.8, 143.8, 134.9, 134.2, 128.4, 126.4, 125.9, 125.4, 55.6, 55.3, 50.5, 37.0, 28.7, 26.5; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{19}N_3O_2$, 262.3; found, 262.3.

2-(Hydroxyimino)-*N*-(4-aminobenzyl)acetamide (RS191C). Prepared according to the general method B. Ethyl glyoxylate oxime **3** (0.15 g, 1.3 mmol), 4-(aminomethyl) benzenamine (0.19 g, 1.5 mmol), ethanol (1.3 mL). White solid, yield (0.21 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.45 (s, 1H), 7.48 (s, 1H), 6.92 (app s, 2H), 6.50 (app s, 2H), 4.96 (s, 2H), 4.16 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.5, 147.6, 143.8, 128.4, 126.0, 113.7, 41.7; LCMS (ESI) (*m/z*): $[M+Na]^+$ calculated for $C_9H_{11}N_3O_2$, 216.2; found, 216.3.

2-(Hydroxyimino)-*N*-(pyridin-3-ylmethyl)acetamide (RS69A). Prepared according to the general method B. Ethyl glyoxylate oxime **3** (0.50 g, 4.3 mmol), pyridin-3-ylmethanamine (0.60 g, 5.5 mmol), ethanol (5 mL). White solid, yield (0.46 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 8.77 (s, 1H), 8.49 (s, 1H), 8.45 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.35-7.32 (m, 1H), 4.37 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 162.1, 148.8, 148.1, 143.6, 135.1, 134.8, 123.5; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_8H_9N_3O_2$, 180.2; found, 180.3.

2-(Hydroxyimino)-*N*-(2-(indol-3-yl)ethyl)acetamide (RS69F). Prepared according to the general method B. Ethyl glyoxylate oxime **3** (0.50 g, 4.3 mmol), 2-(indol-3-yl)ethanamine (0.60

g, 5.5 mmol), ethanol (5 mL). White solid, yield (0.63 g, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 10.82 (s, 1H), 8.22 (s, 1H), 7.55 (d, J = 7.6, 1H), 7.45 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.07 (t, J = 8.0, 1H), 6.98 (t, J = 7.6 Hz, 1H), 3.43 (q, J = 6.4 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.7, 143.8, 136.2, 127.2, 122.6, 121.0, 118.3, 118.2, 111.6, 111.4, 25.1; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{13}N_3O_2$, 232.2; found, 232.3.

2-(Hydroxyimino)-2-(methyl(phenyl)amino)-*N*-(3-(pyrrolidin-1-yl)propyl)acetamide (RS166C). To a stirred solution of ethyl 2-(hydroxyimino)-2-(methyl(phenyl)amino) acetate **6** (0.10 g, 0.48 mmol) in ethanol (1 mL), 3-(pyrrolidinyl)propanamine (0.06 g, 0.50 mmol) was added. The solution was stirred at 50 °C for 2 days and then cooled to room temperature. The resulting precipitate was filtered, washed with cold ethanol and dried under vacuum. White solid, yield (0.07 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.35 (s, 1H), 7.18 (app s, 2H), 6.80 (s, 1H), 6.66 (d, J = 7.2 Hz, 2H), 3.13 (app s, 2H), 3.08 (s, 3H), 2.37 (app s, 6H), 1.65 (app s, 4H), 1.57 (app s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.5, 146.8, 145.4, 128.5, 119.2, 114.7, 53.6, 53.5, 37.7, 35.9, 28.1, 23.1; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{24}N_4O_2$, 305.4; found, 305.3.

C. General method for preparation of 1,4-triazole oximes RS185B, RS150D, RS210B, RS46A, RS182A and RS48B. To a solution of alkyne and azide in *t*-BuOH:H_2O (2:1), 0.1 M sodium ascorbate and 0.1 M $CuSO_4$ were added. The reaction mixture was warmed to 50 °C overnight, cooled to room temperature and the solvent was removed by rotary evaporation. To the crude reaction mixture, 2M NH_4OH (5 mL) was added and extracted with EtOAc (3 x 25 mL). The organic layer was dried with $MgSO_4$ and evaporated to give the corresponding 1,4-triazole oxime.

***N*-((1-(3-(2-((Hydroxyimino)methyl)-1-*H*-imidazol-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)furan-2-carboxamide (RS185B).** Prepared according to the general method C. 1-(3-Azidopropyl)-1*H*-imidazole-2-carbaldehyde oxime **7** (0.10 g, 0.51 mmol), *N*-(prop-2-yn-1-yl)furan-2-carboxamide **9** (0.08 g, 0.51 mmol), 0.1 M sodium ascorbate (1.3 mL), 0.1 M $CuSO_4$ (0.40 mL), *t*-BuOH:H_2O (2:1) (2.2 mL). White solid, yield (0.11 g, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.89 (app t, J = 5.6 Hz, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.83 (s, 1H), 7.32 (s, 1H), 7.12 (d, J = 3.2 Hz, 1H), 7.02 (s, 1H), 6.61 (s, 1H), 4.46 (d, J = 6.0 Hz, 2H), 4.31 (t, J = 7.2 Hz, 2H), 4.25 (t, J = 7.2 Hz, 1H), 2.25 (quint, J = 7.2 Hz 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 157.8, 147.7, 145.1, 145.0, 141.3, 139.6, 128.9, 123.7, 123.0, 113.6, 111.9, 46.6, 44.1, 34.2, 30.8; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}N_7O_3$, 344.3; found, 344.3.

***N*-((1-(3-(2-((Hydroxyimino)methyl)-1-*H*-imidazol-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)picolinamide (RS150D).** Prepared according to the general method C. 1-(3-Azidopropyl)-1*H*-imidazole-2-carbaldehyde oxime **7** (0.07 g, 0.36 mmol), *N*-(prop-2-yn-1-yl)picolinamide **10** (0.06 g, 0.36 mmol), 0.1 M sodium ascorbate (0.80 mL), 0.1 M $CuSO_4$ (0.22 mL), *t*-BuOH:H_2O (2:1) (1.7 mL). White solid, yield (0.09 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 9.22 (s, 1H), 8.64 (s, 1H), 8.05 (s, 2H), 7.99 (s, 2H), 7.60 (s, 1H), 7.32 (s, 1H), 7.01 (s, 1H), 4.56 (s, 2H), 4.31 (app s, 2H), 4.24 (app s, 1H), 2.25 (app s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 163.9, 149.8, 148.5, 144.9, 141.3, 139.6, 137.8, 128.9, 126.6, 123.7, 122.9, 122.0, 46.6, 44.1, 34.7, 30.8; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{18}N_8O_2$, 355.4; found, 355.3.

1-(3-(4-(1-Methyl-1*H*-imidazol-5-yl)-1*H*-1,2,3-triazol-1-yl)propyl)-1*H*-imidazole-2-carbaldehyde oxime (RS210B). Prepared according to the general method C. 1-(3-Azidopropyl)-1*H*-imidazole-2-carbaldehyde oxime **7** (0.11 g, 0.57 mmol), 5-ethynyl-1-methyl-1H-imidazole **11** (0.06 g, 0.57 mmol), 0.1 M sodium ascorbate (1.4 mL), 0.1 M $CuSO_4$ (0.50 mL), *t*-BuOH:H_2O (2:1) (2.3 mL). White solid, yield (0.09 g, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.43 (s, 1H), 8.07 (s, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 7.21 (s, 1H), 7.04 (s, 1H), 4.40 (app s, 2H), 4.32 (app s, 2H), 3.80 (s, 1H) 2.34 (app s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.3, 139.7, 139.6, 137.5, 128.9, 127.6, 123.7, 121.9, 46.9, 44.1, 32.9, 30.6; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{16}N_8O$, 301.3; found, 301.3.

2-(Hydroxyimino)-N-((1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl) acetamide (RS46A). Prepared according to the general method C. 2-(Hydroxyimino)-*N*-(prop-2-yn-1-yl)acetamide **13** (0.10 g, 0.79 mmol), 1-(2-azidoethyl)pyrrolidine **12** (0.11 g, 0.79 mmol), 0.1 M sodium ascorbate (1.8 mL), 0.1 M $CuSO_4$ (0.50 mL), *t*-BuOH:H_2O (2:1) (3.7 mL). White solid, yield (0.11 g, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.65 (s, 1H), 7.93 (s, 1H), 7.48 (s, 1H), 4.44-4.38 (m, 4H), 2.83 (t, 2H), 2.45 (app s, 4H), 1.65 (app s, 4H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.8, 144.4, 143.6, 123.1, 55.1, 53.4, 48.5, 34.2, 23.2; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{11}H_{18}N_6O_2$, 267.3; found, 267.3.

2-(Hydroxyimino)-N-((1-(4-(2-((hydroxyimino)methyl)-1*H*-imidazol-1-yl)butyl)-1*H*-1,2,3-triazol-4-yl)methyl)acetamide (RS182A). Prepared according to the general method C. 2-(Hydroxyimino)-*N*-(prop-2-yn-1-yl)acetamide **13** (0.06 g, 0.48 mmol), 1-(4-azidobutyl)-1H-imidazole-2-carbaldehyde oxime **8** (0.10 g, 0.48 mmol), 0.1 M sodium ascorbate (2 mL), 0.1 M $CuSO_4$ (0.60 mL), *t*-BuOH:H_2O (2:1) (3 mL). White solid, yield (0.07 g, 43%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 11.47 (s, 1H), 8.64 (s, 1H), 8.04 (s, 1H), 7.91 (s, 1H), 7.48 (s, 1H), 7.30 (s, 1H), 7.00 (s, 1H), 4.39-4.29 (m, 4H), 4.25 (app s, 2H), 1.77-1.63 (m, 4H); ^{13}C NMR (400 MHz, DMSO) δ 161.8, 144.5, 143.5, 141.4, 139.5, 128.8, 123.7, 122.9, 48.8, 45.9, 34.2, 27.4, 26.8; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{18}N_8O_3$, 335.3; found, 335.3.

2-(Hydroxyimino)-N-(3-(4-((2-((hydroxyimino)methyl)-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)acetamide (RS48B). Prepared according to the general method C. *N*-(3-Azidopropyl)-2-(hydroxyimino)acetamide **17** (0.12 g, 0.67 mmol), 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde oxime **15** (0.10 g, 0.67 mmol), 0.1 M sodium ascorbate (1.5 mL), 0.1 M $CuSO_4$ (0.40 mL), *t*-BuOH:H_2O (2:1) (3 mL). White solid, yield (0.12 g, 56%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 11.46 (s, 1H), 8.64 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.48 (s, 1H), 7.32 (s, 1H), 7.02 (s, 1H), 4.38 (s, 2H), 4.30 (app s, 2H), 4.24 (app s, 2H) 2.25 (app s, 2H); ^{13}C NMR (400 MHz, DMSO) δ 163.9, 149.8, 148.5, 144.9, 137.8, 126.6, 122.9, 122.0, 46.6, 34.7, 31.3, 30.7; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{16}N_8O_3$, 321.3; found, 321.3.

1-(3-(1-((4-Phenyl-2*H*-1,2,3-triazol-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)propyl)-1*H*-imidazole-2-carbaldehyde oxime (RS161B) To a solution of 2-(azidomethyl)-4-phenyl-2H-1,2,3-triazole **14** (0.12 g, 0.61 mmol) and 1-(but-3-yn-1-yl)-1*H*-imidazole-2-carbaldehyde oxime **16** (0.10 g, 0.61 mmol) in MeOH:THF (5:1) (3 mL), CuI (12 mg, 0.06 mmol) and diisopropyl amine (62 mg, 0.61 mmol) were added. The reaction mixture was stirred overnight at room temperature, and the solvent was removed by rotary evaporation. To the crude reaction mixture, 2M NH_4OH (5 mL) was added and subsequently extracted with EtOAC (3 x 25 mL). The organic layer was dried with $MgSO_4$ and evaporated to give the imidazole-2-carbaldehyde oxime **RS161B**. White solid, yield (0.15 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.43 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 7.86 (d, J = 7.2 Hz, 2H), 7.49 (app t, J = 7.6 Hz, 2H) 7.42 (d, J = 7.2 Hz, 1H), 7.17 (s, 1H), 7.04 (s, 2H), 6.90 (s, 1H), 4.51 (t, J = 7.2 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H); ^{13}C NMR (400 MHz, DMSO) δ 148.6, 144.0, 141.5, 133.5, 129.2, 129.1, 125.9, 123.3, 64.5, 46.0, 26.6; LCMS (ESI) (*m/z*): $[M+H]^+$ calculated for $C_{17}H_{17}N_9O$, 364.4; found, 364.3.

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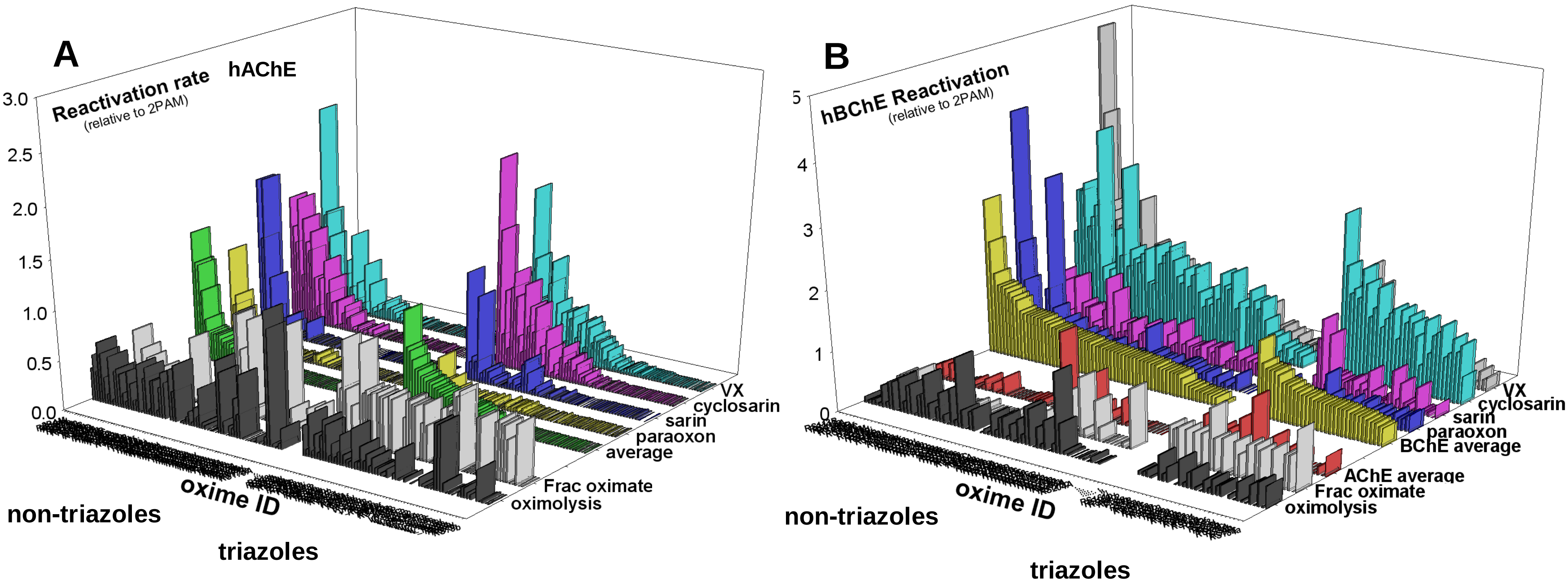
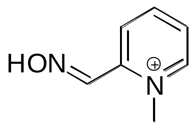
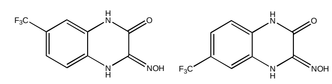
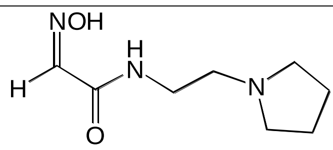
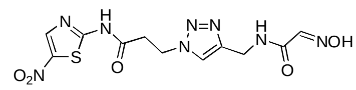
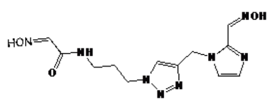
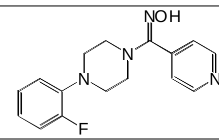
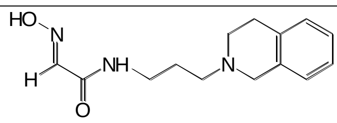
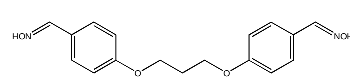
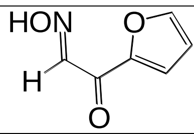
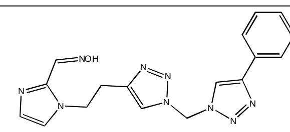
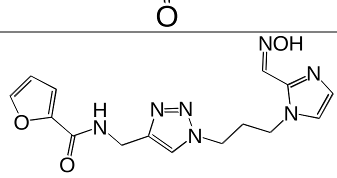
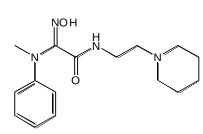
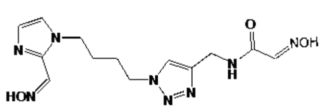
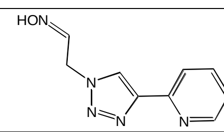
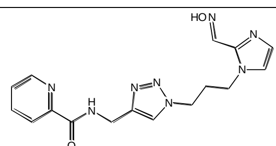
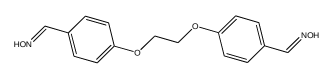
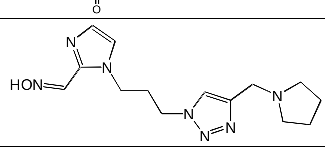
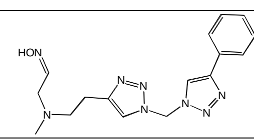
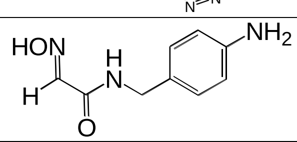
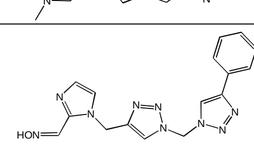
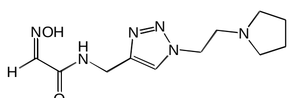
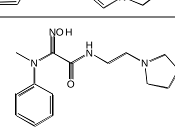
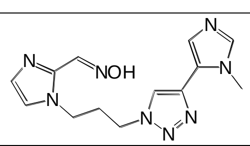
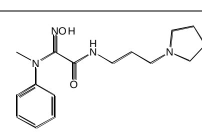
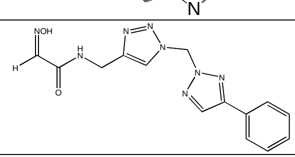
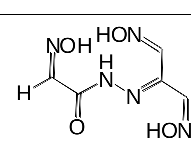
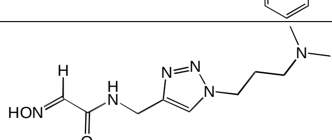
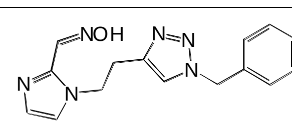
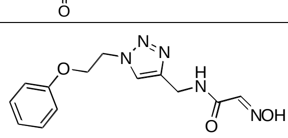
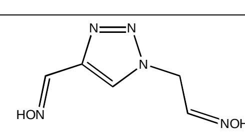
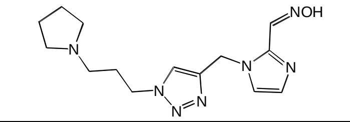
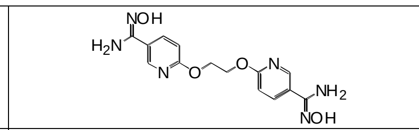
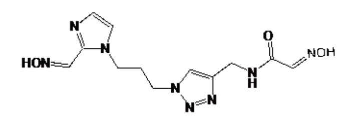
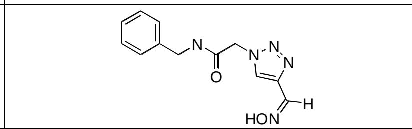
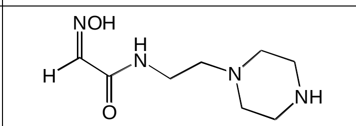
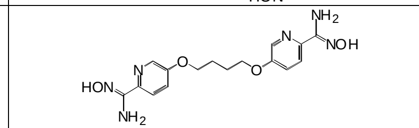
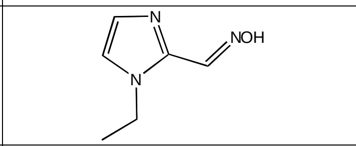
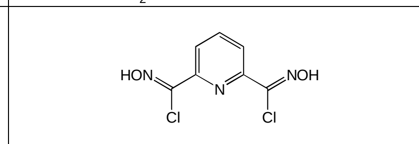
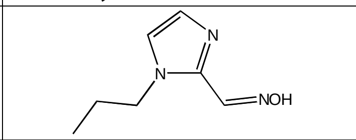
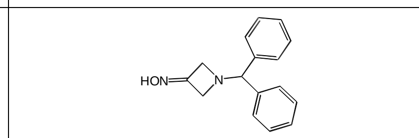
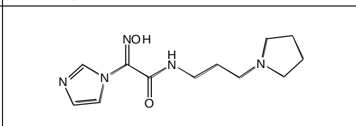
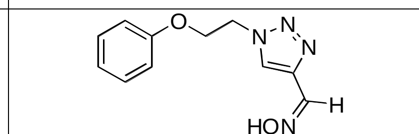
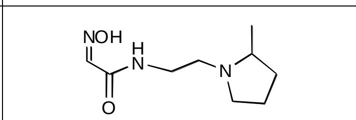
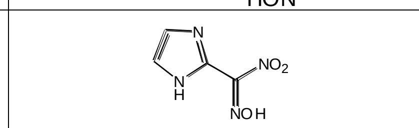
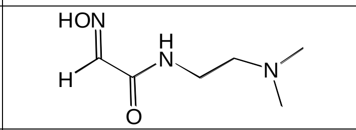
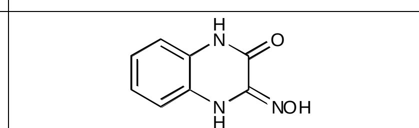
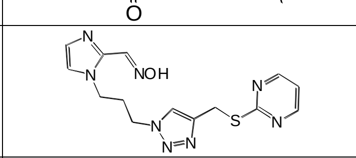
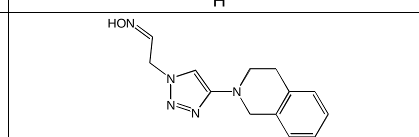
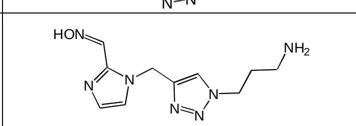
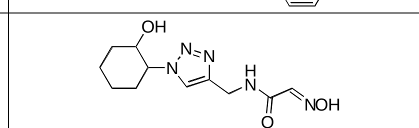
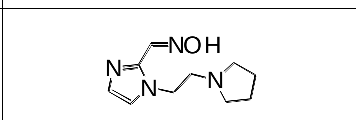
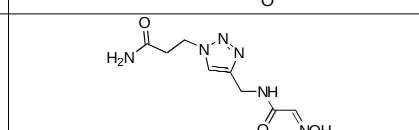
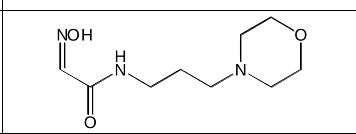
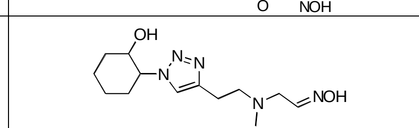
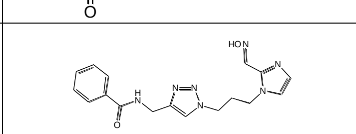
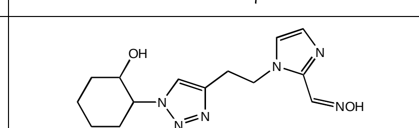
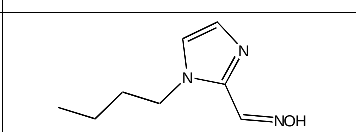
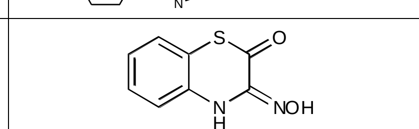
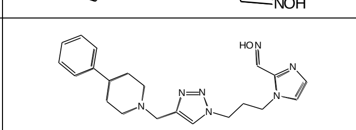
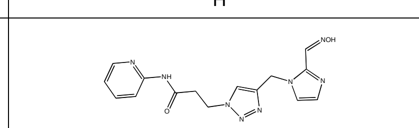
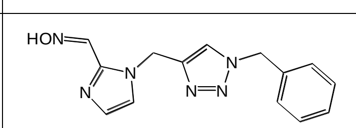
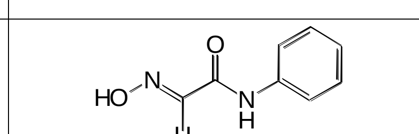
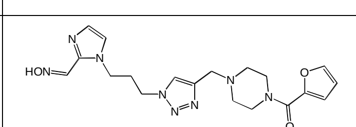
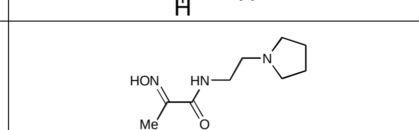
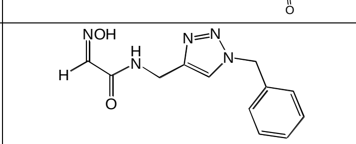
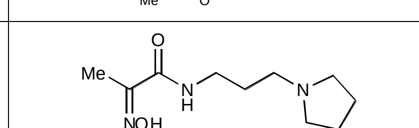
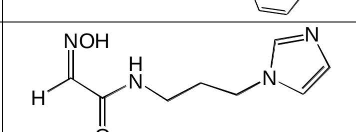
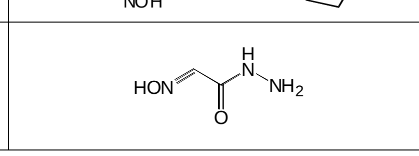
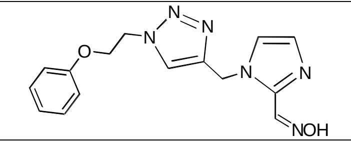
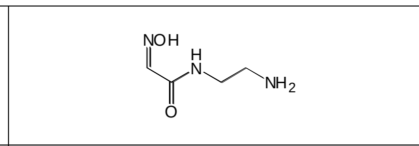
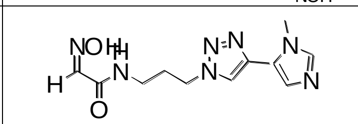
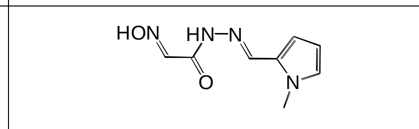
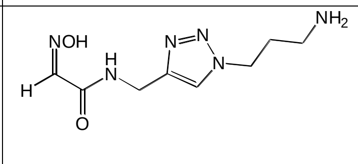
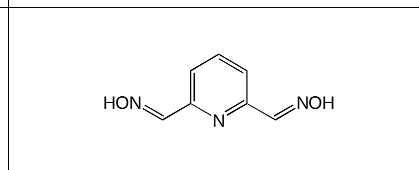
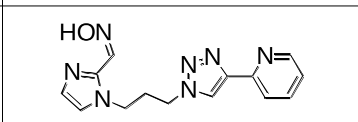
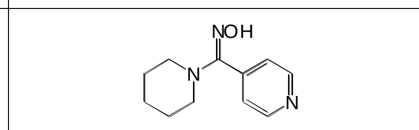
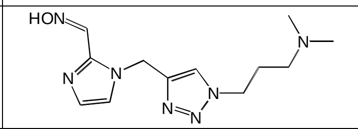
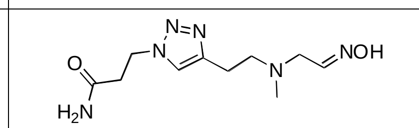
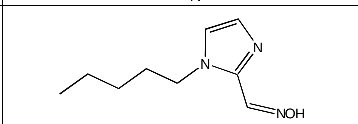
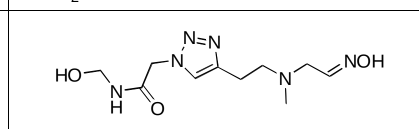
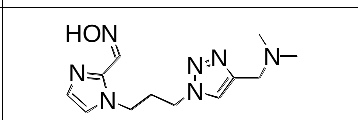
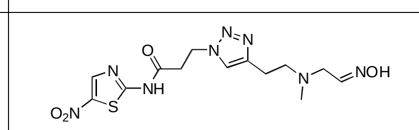
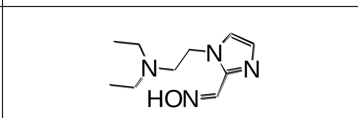
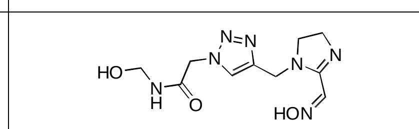
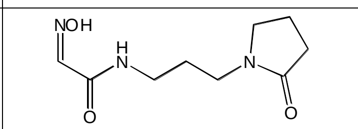
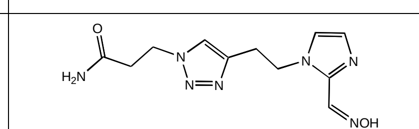
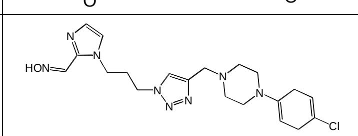
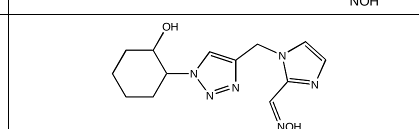
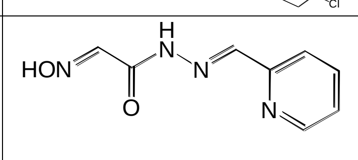
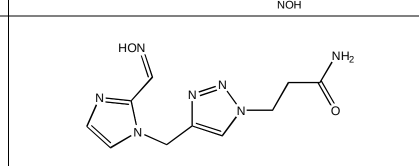
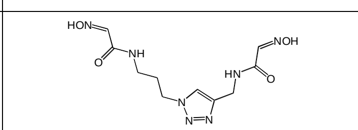
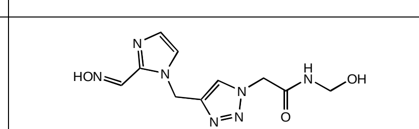
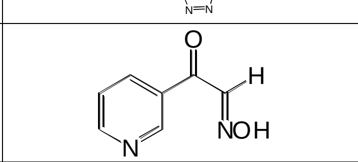
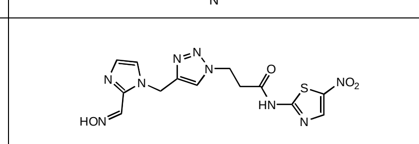
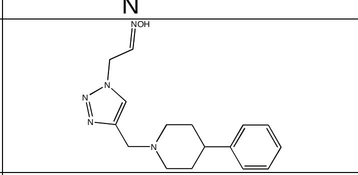
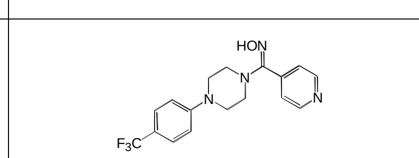
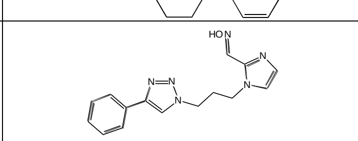
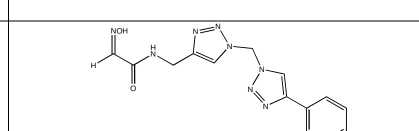
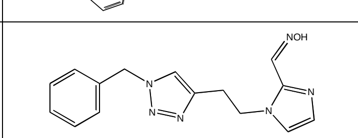
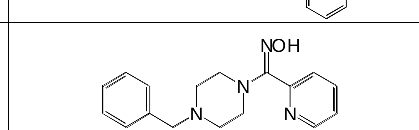
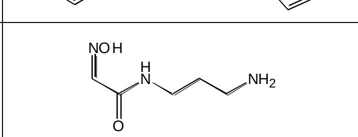
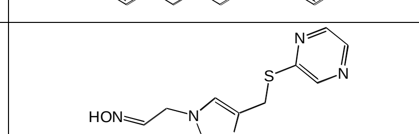
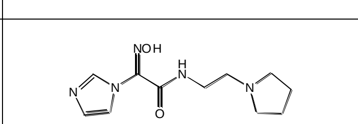
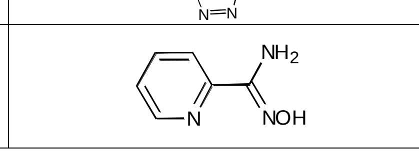


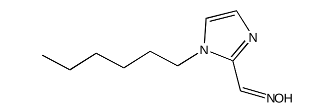
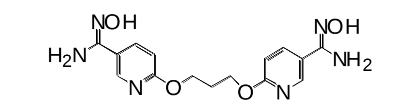
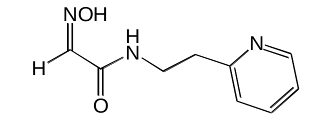
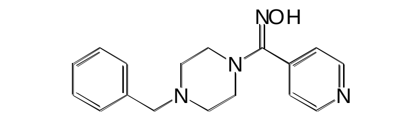
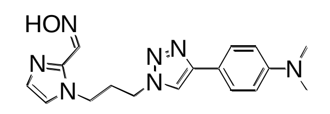
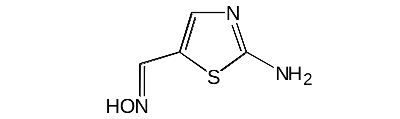
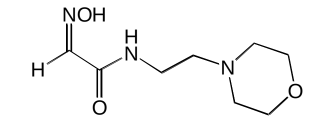
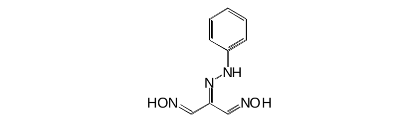
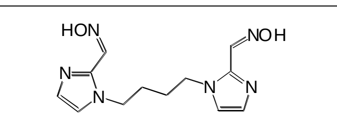
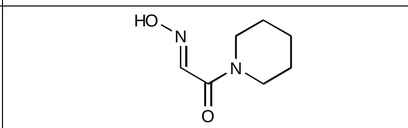
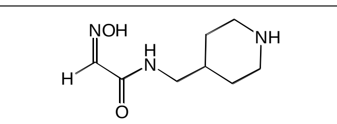
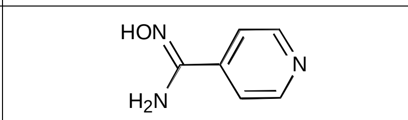
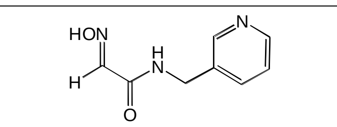
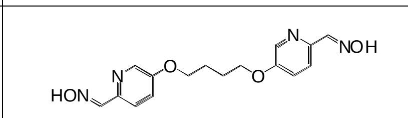
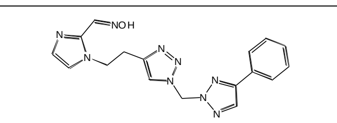
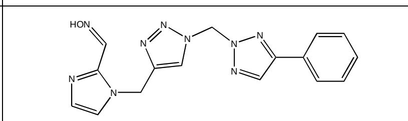
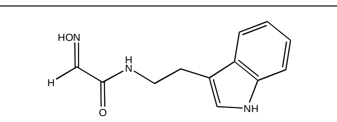
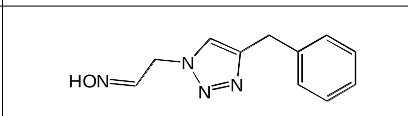
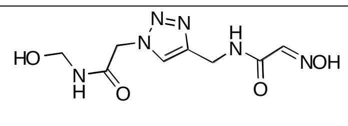
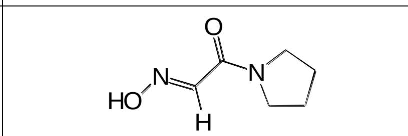
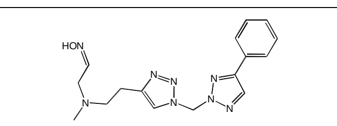
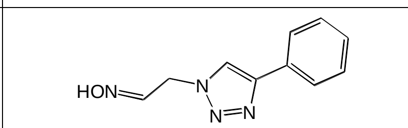
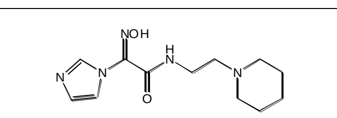
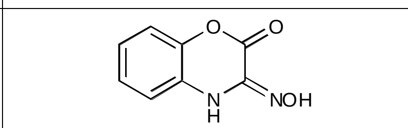
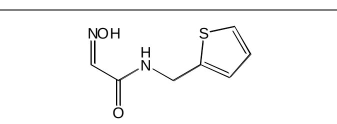
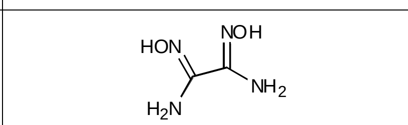
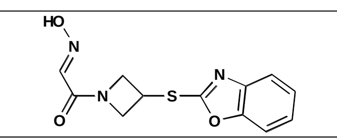
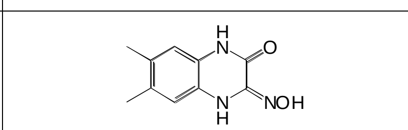
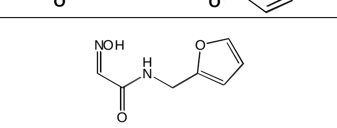
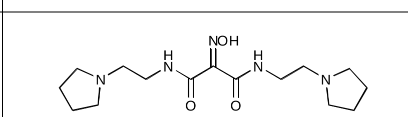
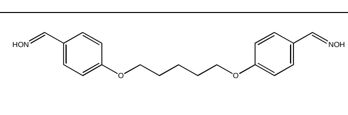
Figure S1. The effect of triazole ring in oxime structure on reactivation of VX, cyclosarin, sarin and paraoxon inhibited hAChE **(A)** and hBChE **(B)** by library of 134 or 100 (hBChE) uncharged oxime reactivators. Reactivation rates of 0.67 mM oximes are given relative to 2PAM. Average reactivation potency of oximes for all four organophosphates is given as green bars. Measured rates of oximolysis (3 x ΔA/min) and calculated fractions of oximate anion for pH 7.4 are also given as black and grey bars, respectively. Structures and reactivation potencies of all 134 oximes are given in the Table S1.

Table S1. Average oxime reactivation potency (k_{obs}^{POX}+ k_{obs}^{sarin}+ k_{obs}^{CS}+ k_{obs}^{VX})/4 relative to 2PAM.

no	oxime	oxime structure	average k_{obs}	no	oxime	oxime structure	average k_{obs}
1	**2PAM**		**1**	69	**RS172b**		**0.030**
2	**RS41A**		**0.88**	70	**V33_e2**		**0.030**
3	**RS48b**		**0.82**	71	**RS178a**		**0.028**
4	**RS191d**		**0.81**	72	**RS107b**		**0.026**
5	**RS186b**		**0.72**	73	**RS161c**		**0.026**
6	**RS185b**		**0.63**	74	**RS166d**		**0.026**
7	**RS182a**		**0.60**	75	**RS98a**		**0.026**
8	**RS150d**		**0.526**	76	**RS116A**		**0.025**
9	**RS185d**		**0.51**	77	**RS82f**		**0.025**
10	**RS191c**		**0.43**	78	**RS82b**		**0.024**
11	**RS46a**		**0.43**	79	**RS166b**		**0.023**
12	**RS210b**		**0.42**	80	**RS166c**		**0.022**
13	**RS82a**		**0.37**	81	**RS212b**		**0.02**
14	**RS45_2**		**0.37**	82	**RS212c**		**0.02**
15	**V7B**		**0.36**	83	**RS112A**		**0.019**

16	**RS46b**		**0.35**	84	**RS205c**		**0.019**
17	**RS184a**		**0.33**	85	**V20C**		**0.0181**
18	**RS69g**		**0.31**	86	**RS206c**		**0.018**
19	**RS115C**		**0.30**	87	**RS160a**		**0.017**
20	**RS115B**		**0.29**	88	**RS36b**		**0.017**
21	**RS165b**		**0.29**	89	**V18B**		**0.0155**
22	**RS69m**		**0.288**	90	**RS163c**		**0.015**
23	**RS41b**		**0.26**	91	**RS170c**		**0.015**
24	**RS185i**		**0.24**	92	**RS98c**		**0.015**
25	**RS44_2**		**0.24**	93	**V32_a2**		**0.015**
26	**RS203A**		**0.23**	94	**V32_c2**		**0.015**
27	**RS69D**		**0.23**	95	**V34_a3**		**0.015**
28	**RS150c**		**0.22**	96	**V42_4a**		**0.015**
29	**RS115A**		**0.22**	97	**RS170e**		**0.014**
30	**RS150b**		**0.216**	98	**RS119A**		**0.013**
31	**RS55a**		**0.21**	99	**RS174a**		**0.011**
32	**RS185a**		**0.21**	100	**RS143b**		**0.010**
33	**RS67a**		**0.20**	101	**RS143c**		**0.010**
34	**RS65a**		**0.19**	102	**RS157a**		**0.010**

35	**V7A**		**0.19**	103	**RS157b**		**0.010**
36	**RS210a**		**0.18**	104	**RS158b**		**0.010**
37	**RS44_1**		**0.18**	105	**RS159a**		**0.010**
38	**RS185g**		**0.17**	106	**RS178d**		**0.010**
39	**RS42a**		**0.17**	107	**V34_c3**		**0.010**
40	**RS113B**		**0.15**	108	**V35_d3**		**0.010**
41	**RS185f**		**0.15**	109	**V35_e3**		**0.010**
42	**RS204C**		**0.15**	110	**V40_d5**		**0.010**
43	**RS69k**		**0.15**	111	**V43_4c**		**0.010**
44	**RS185e**		**0.14**	112	**V46_5a**		**0.010**
45	**RS157c**		**0.133**	113	**V47_5c**		**0.010**
46	**RS13**		**0.13**	114	**V48_5d**		**0.010**
47	**RS173a**		**0.10**	115	**V49_5e**		**0.010**
48	**RS95d**		**0.10**	116	**RS178b**		**0.0090**
49	**RS150a**		**0.098**	117	**RS82c**		**0.0081**
50	**V54b**		**0.094**	118	**RS179a**		**0.0079**
51	**RS160c**		**0.091**	119	**RS72b**		**0.0079**
52	**RS165a**		**0.090**	120	**RS176b**		**0.0065**

53	**RS113a**		**0.089**	121	**RS204A**		**0.0063**
54	**RS69b**		**0.074**	122	**RS178c**		**0.0056**
55	**RS185h**		**0.062**	123	**RS99b**		**0.0054**
56	**RS69c**		**0.061**	124	**RS213b**		**0.0053**
57	**RS203B**		**0.060**	125	**RS174c**		**0.0052**
58	**RS69h**		**0.058**	126	**RS177a**		**0.0052**
59	**RS69a**		**0.056**	127	**RS205A**		**0.0052**
60	**RS161b**		**0.054**	128	**RS82d**		**0.0050**
61	**RS69f**		**0.052**	129	**RS73a**		**0.0045**
62	**V39_d2**		**0.048**	130	**RS174b**		**0.0034**
63	**RS82e**		**0.040**	131	**RS73b**		**0.0034**
64	**RS165c**		**0.037**	132	**RS170d**		**0.0033**
65	**RS69i**		**0.036**	133	**RS171a**		**0.0033**
66	**RS176a**		**0.033**	134	**RS172a**		**0.0028**
67	**RS69j**		**0.032**	135	**RS170A**		**0**
68	**RS105A**		**0.030**				