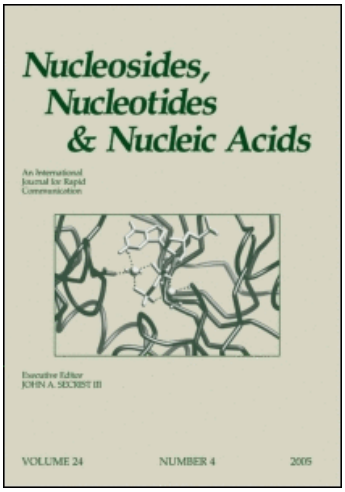

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Open-Chain Carbocyclic Analogs of Adenosine with Dihalovinyl Unit as Potential Inhibitors of *S*-Adenosyl-L-homocysteine Hydrolase

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ABSTRACT

Vinylogously extended deoxyeritadenine derivatives were synthesized as acyclic/carbocyclic analogues of the 6′-halo(homovinyl)adenosines, which are known to be potent inhibitors of *S*-adenosyl-L-homocysteine hydrolase. Swern oxidation of 9-[3-(*t*-butyldimethylsilyloxy)-4-hydroxybutyl]adenine (**4**) followed by Wittig olefination and desilylation gave access to ethyl 6-(adenin-9-yl)-4-hydroxy-2(*E*)-hexenoate (**7**) and 5-(adenin-9-yl)-1,1-dibromo-1-penten-3-ol (**9**). No inhibition of AdoHcy Hydrolase was observed with **7** and **9**.

Key Words: *S*-Adenosyl-L-homocysteine hydrolase; Carbocyclic nucleosides; Acyclic nucleosides; Enzyme inhibition.

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INTRODUCTION

The enzyme *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase (EC 3.3.1.1) effects hydrolytic cleavage of AdoHcy to adenosine (Ado) and L-homocysteine (Hcy).[1] The cellular levels of AdoHcy and Hcy are critical since AdoHcy is a potent feedback inhibitor of crucial transmethylation enzymes,[1,2] and elevated plasma levels of Hcy in humans have been shown to be a risk factor in coronary artery diseases.[3] A number of inhibitors which function as substrates for the "3′-oxidative activity" of AdoHcy hydrolase and convert the enzyme from its active form (NAD^+) to its inactive form (NADH, type I inhibition) have been prepared.[1a,2]

Inhibitors which function as substrates for the "5′/6′-hydrolytic activity" include the vinyl fluoride **A,**[4] homovinyl halides **B** and **C,**[5,6] and 4′-acetylene derivatives,[7] among others (Fig. 1).[1b] Addition of an enzyme-sequestered water molecule across the 5′,6′-double bond (e.g., in **C**; Y = F) was proposed to generate the homoAdo 6′-carboxyl fluoride at the active site of the enzyme which caused type II (covalent binding) inhibition.[6] The doubly homologated vinyl halides **D** with greater conformational flexibility at C5′ were not substrate for the "hydrolytic activity" of the AdoHcy hydrolase.[8] Also diene derivatives **E** and **F** were type I inhibitors.[9] Guillerm et al., reported that 5′-thioadenosine analogs substituted at sulfur with difluoromethyl[10a] and allenyl and propynyl groups[10b] were processed by "hydrolytic activity" of the enzyme causing its irreversible inactivation. The X-ray crystal structures of AdoHcy hydrolase revealed dual role for a catalytic water molecule at the active site.[11]

Carbocyclic and acyclic analogs of adenosine were identified as the most potent inhibitors of AdoHcy hydrolase with potent antiviral activities.[1a] Among them, the 2,3-dihydroxypropyl adenine [(*S*)-DHPA], and carboxylic analog D-eritadenine [**G**; 2(*R*),3(*R*)-dihydroxy-4-(adenin-9-yl) butanoic acid] were found to be most active (Fig. 2). Holy and co-workers showed that eritadenine analogs with α-hydroxy carboxylate function present are more potent inhibitors than their β-hydroxy counterparts.[12] Moreover, aristeromycin and neplanocin A are very potent inhibitors of AdoHcy hydrolase[1a,13] and halovinyl analogs of aristeromycin **H** were processed by the "hydrolytic activity" of the enzyme.[14] Kitade et al., reported that aldehyde **I** caused irreversible inactivation of the AdoHcy hydrolase and employed this inhibitor as an affinity labeling probe.[15] They also reported synthesis of acyclic adenosines with an unsaturated side chain **J** (vinylogs of L-eritadenine).[16] We now describe syntheses of vinylogously extended β-deoxyeritadenine derivatives as

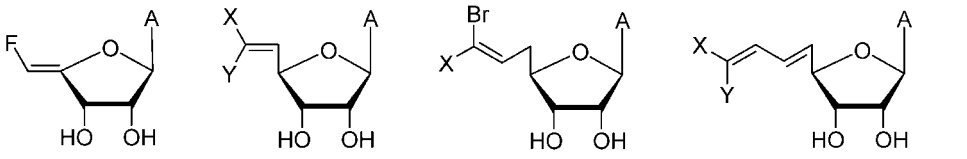

Figure 1.

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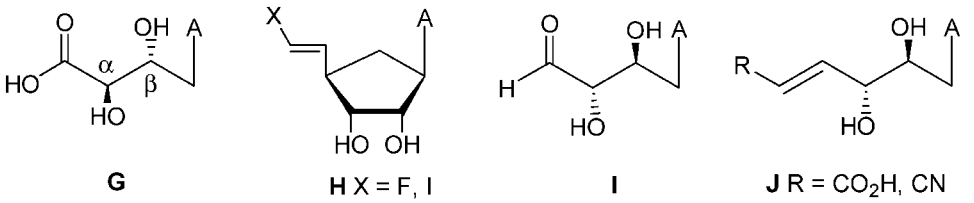


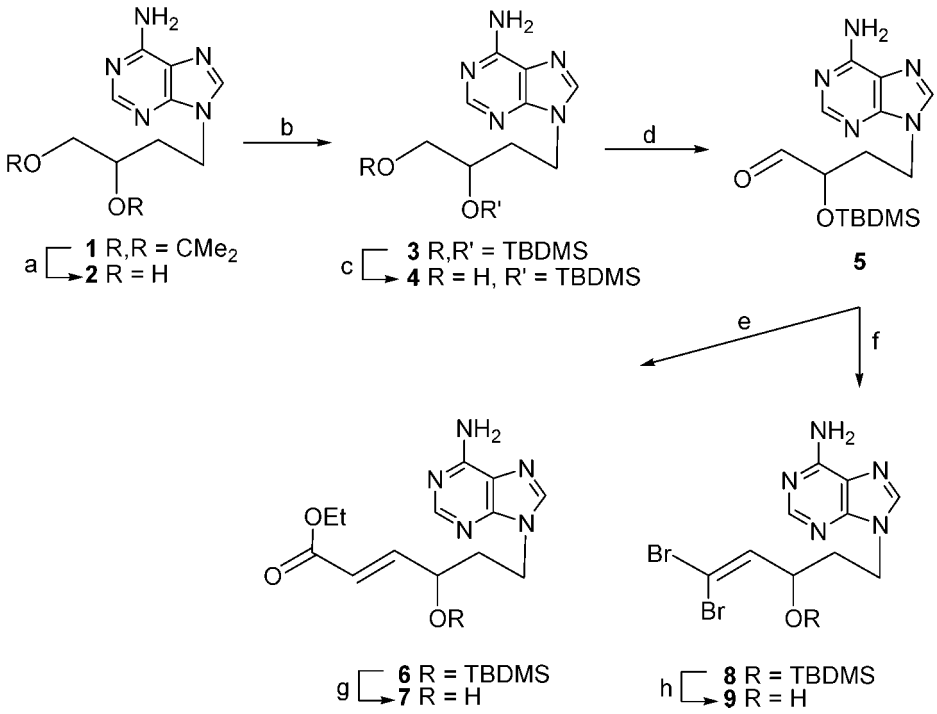
Figure 2.

acyclic/carbocyclic analogs of the halo(homovinyl) adenosine inhibitors and their interaction with AdoHcy hydrolase.

RESULTS AND DISCUSSION

Chemistry

Silylation of 9-(3,4-dihydroxybutyl) adenine **2**[17] with tert-butyldimethylsilyl (TBDMS) chloride/imidazole/*N*,N-dimethylformamide (DMF) gave disilylated **3**. Selective deprotection of the primary hydroxyl[18] with $AcOH/H_2O/THF$ gave **4** (Sch. 1). Moffatt oxidation [dicylohexylcarbodiimide (DCC) $/Me_2SO/Cl_2CHCO_2H$]



Scheme 1.

of **4** gave the corresponding α-hydroxy aldehyde **5** in low yield. However Swern oxidation of **4** followed by treatment of the aldehyde **5** with ethoxycarbonylmethylene-stabilized Wittig reagent gave **6** as a single product 65% yield. Deprotection with *tetra*-butylammonium fluoride (TBAF) yielded vinylogously extended ester **7**. The ^{1}H NMR coupling constants for **7** ($J_{4'\text{-}5'} = 15.3$ Hz) are indicative of *trans* geometry. Swern oxidation of **4** and treatment of the aldehyde **5** with generated in situ (dibromomethylene)phosphorane (Ph_3P/CBr_4)[19] gave **8**. Desilylation ($NH_4/MeOH$)[20] yielded open-chain (dibromo)vinyl nucleoside **9** as β-deoxyeritadenine analogue.

Inactivation of *S*-Adenosyl-L-homocysteine Hydrolase

Both compounds **7** and **9** showed no inhibitory activity against human placental *S*-adenosyl-L-homocysteine hydrolase at concentrations up to 200 μM. This may indicate that removal of one of the hydroxy group of eritadenine (from carbon β) diminished the binding affinity of the compounds towards the enzyme in comparison with their parent compound D-eritadenine which is a strong inhibitor of the enzyme with K_i value of 3 nM.[21]

In summary, novel dibromovinyl **9** and unsaturated ester **7** were prepared from 9-(3,4-dihydroxybutyl)adenine **2** as vinylogously extended β-deoxyeritadenine analogs. These open-chain carbocyclic adenosine derivatives showed no activities against AdoHcy hydrolase.

EXPERIMENTAL

^{1}H (Me_4Si) NMR spectra were determined with solution in $CDCl_3$ at 400 MHz and ^{13}C (Me_4Si) at 100.6 MHz unless otherwise noted. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) technique. Reagent grade chemicals were used and solvents were dried by reflux over and distillation from CaH_2 under an argon atmosphere except THF (K/benzophenone). TLC was performed on Merck kieselgel 60-F_{254} with MeOH/$CHCl_3$ (1 : 9) and EtOAc/MeOH (95 : 5) as developing systems, and products were detected with 254 nm light. Merck kieselgel 60 (230–400 mesh) was used for column chromatography. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN.

9-(3,4-*O*-Isopropylidene-3,4-dihydroxybutyl)adenine (1). Compound **1** was prepared (71%) by condensation of the sodium salt of adenine with 4-*O*-(*p*-toluenesulfonyl)-1,2-*O*-isopropylidene-1,2,4-butanetriol.[17] The latter was prepared (81%) by treatment of 1,2-*O*-isopropylidene-1,2,4-butanetriol[22] with TsCl/pyridine/24 h/∼0°C → ambient temperature: ^{1}H NMR δ 1.36 (s, 3, CH_3), 1.45 (s, 3, CH_3), 2.00–2.05 (m, 1, H2′), 2.22–2.24 (m, 1, H2″), 3.57–3.59 (m, 1, H3′), 4.03–4.06 (m, 2, H4′,4″), 4.34–4.43 (m, 2, H1′,1″), 5.76 (br s, 2, NH_2), 7.86 (s, 1, H8), 8.38 (s, 1, H2); MS *m*/*z* 264 (100, MH^+).

9-(3,4-Dihydroxybutyl)adenine (2). A solution of **1** (110 mg, 0.42 mmol) in CF_3COOH/H_2O (9 : 1) (5 ml) was stirred for 30 min at ∼0°C, evaporated, and

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coevaporated [toluene (3×) and EtOH (2×)], and the residue was crystallized (EtOH) to give **2** (73 mg, 78%) with physical and spectroscopic data as reported.[17]

9-[3,4-(Di-*t*-butyldimethylsilyloxy)butyl]adenine (3). TBDMS-Cl (593 mg, 3.92 mmol) and imidazole (534 mg, 7.85 mmol) were added to a stirred solution of **2** (350 mg, 1.57 mmol) in dried DMF (8 mL), and the mixture was stirred at ambient temperature overnight. The reaction mixture was partitioned between EtOAc//NH_4Cl/H_2O and the water layer was extracted with EtOAc. The combined organic phase was washed (brine), dried (Na_2SO_4), and evaporated. Column chromatography ($CHCl_3 \rightarrow 3\%$ MeOH/$CHCl_3$) gave **3** (610 mg, 86%): ^{1}H NMR δ 0.04 (s, 6, $2 \times CH_3$), 0.09 (s, 6, $2 \times CH_3$), 0.88 (s, 9, *t*-Bu), 0.92 (s, 9, *t*-Bu), 2.02–2.07 (m, 1, H2′), 2.21–2.26 (m, 1, H2″), 3.46 (dd, $J = 6.8$, 10.0 Hz, 1, H4′), 3.59 (dd, $J = 5.2$, 10.0 Hz, 1, H4″), 3.78–3.81 (m, 1, H3′), 4.32–4.45 (m, 2, H1′,1″), 5.96 (br s, 2, NH_2), 7.84 (s, 1, H8), 8.42 (s, 1, H2); MS m/z 452 (100, MH^+). Anal. Calcd for $C_{21}H_{41}N_5O_2Si_2$ (451.76): C, 55.83; H, 9.15; N, 15.50. Found: C, 55.59; H, 9.25; N, 15.28.

9-[3-(*t*-Butyldimethylsilyloxy)-4-hydroxybutyl]adenine (4). Compound **3** (400 mg, 0.887 mmol) was added to a solution of CH_3CO_2H/H_2O/THF (13 : 7 : 3; 8 mL) and the mixture was stirred at ambient temperature until the spot from fully desilylated byproduct **2** starting to appear on TLC. Then reaction mixture was partitioned (EtOAc//$NaHCO_3/H_2O$) and the aqueous layer was extracted with next portion of EtOAc. The combined organic phase was washed ($NaHCO_3$, brine), dried (Na_2SO_4), evaporated and column chromatographed ($CHCl_3 \rightarrow 4\%$MeOH/$CHCl_3$) to give recovered **3** (140 mg, 35%) and **4** (155 mg, 52%). Compound **4** had: ^{1}H NMR δ 0.04 (s, 6, $2 \times CH_3$), 0.88 (s, 9, *t*-Bu), 2.16–2.19 (m, 2, H2′, 2″), 3.61 (dd, $J = 4.5$, 11.4 Hz, 1, H4′), 3.65 (dd, $J = 5.2$, 11.4 Hz, 1, H4″), 3.88 (“quint.”, $J = 5.2$ Hz, 1, H3′), 4.26–4.36 (m, 2, H1′,1″), 6.17 (br s, 2, NH_2), 7.80 (s, 1, H8), 8.29 (s, 1, H2); ^{13}C NMR δ −4.4 & −4.1 (CH_3), 18.5 (*t*-Bu), 26.2 (*t*-Bu), 34.5 (C2′), 40.8 (C1′), 65.5 (C4′), 70.6 (C3′), 119.8 (C5), 140.7 (C8), 150.4 (C4), 153.0 (C2), 155.5 (C6); MS m/z 338 (100, MH^+).

Ethyl 6-(Adenin-9-yl)-4-(*t*-butyldimethylsilyloxy)-2(*E*)-hexenoate (6). Anhydrous DMSO (46.2 mg, 0.042 mL, 0.59 mmol) was added to a stirred solution of freshly distilled oxalyl chloride (37.7 mg, 0.029 mL, 0.04 mmol) in dried CH_2Cl_2 (4.0 mL) at −60°C. After 15 min, a solution of **4** (50 mg, 0.148 mmol) in dried CH_2Cl_2 (6 mL, containing 3 drops of DMSO) was added and stirring was continued for another 1.5 h at −60°C and then Et_3N (90 mg, 0.12 mL, 0.89 mmol) was added and the mixture was allowed to warm to ambient temperature. After 5 min. ethyl (triphenylphoshoranylidene)acetate (62 mg, 0.178 mmol) was added to the crude aldehyde **5**. After 18 h, the reaction mixture was washed [water (3×), brine] and the organic layer was dried (Na_2SO_4) and was evaporated. Column chromatography ($CHCl_3 \rightarrow 4\%$ MeOH/$CHCl_3$) gave **6** (39 mg, 65%) and recovered **4** (10 mg, 20%). Compound **6** had: ^{1}H NMR δ 0.04 & 0.06 ($2 \times$ s, 2×3, $2 \times CH_3$), 0.92 (s, 9, *t*-Bu), 1.28 (t, $J = 7.1$ Hz, 3, CH_3), 2.19–2.23 (m, 2, H5′,5″), 4.18 (dq, $J = 2.0$, 7.1 Hz, 2, CH_2), 4.26–4.29 (m, 2, H6′,6″), 4.46–4.52 (m, 1, H4′), 5.92 (dd, $J = 1.6$, 15.5 Hz, 1, H2′), 6.13 (br s, 2, NH_2), 6.83 (dd, $J = 4.5$, 15.5 Hz, 1, H3′) 7.76 (s, 1, H8), 8.35 (s, 1, H2);

^{13}C NMR δ −4.6 & −4.1 (CH_3), 14.6 (CH_3), 18.6 (*t*-Bu), 26.2 (*t*-Bu), 36.8 (C5′), 40.4 (C6′), 60.9 (CH_2), 69.5 (C4′), 119.2 (C5), 121.3 (C2′) 140.9 (C8), 149.1 (C3′), 150.4 (C4), 153.1 (C2), 155.8 (C6), 166.5 (CO); MS *m/z* 406 (100, MH^+).

Ethyl 6-(Adenin-9-yl)-4-hydroxy-2(*E*)-hexenoate (7). TBAF/THF (0.24 mL; 1 M) was added to a solution of **6** (48 mg, 0.118 mmol) in dried THF (3 mL) and the mixture was stirred at ambient temperature for 30 min. Volatiles were evaporated and the residue was column chromatographed ($CHCl_3 \rightarrow 5\%$ MeOH/$CHCl_3$) to give **7** (25 mg, 73%) as white crystals (EtOH): mp 161–162°C; UV max 262 nm (ε 13 200), min 234 nm (ε 4700); ^{1}H NMR (MeOH-d_4) δ 1.19 (t, $J = 7.1$ Hz, 3, CH_3), 1.91–1.99 (m, 1, H5′), 2.13–2.20 (m, 1, H5″), 4.06 (q, $J = 7.1$ Hz, 2, CH_2), 4.18–4.21 (m, 1, H4′), 4.29–4.33 (m, 2, H6′,6″), 5.90 (dd, $J = 2.2$, 15.5 Hz, 1, H2′), 6.76 (dd, $J = 4.5$, 15.5 Hz, 1, H3′) 8.04 (s, 1, H8), 8.14 (s, 1, H2); ^{13}C NMR (MeOH-d_4) δ 11.9 (CH_3), 34.2 (C5′), 38.9 (C6′), 58.9 (CH_2), 66.1 (C4′), 117.5 (C5), 118.4 (C2′) 140.3 (C8), 148.1 (C4), 148.7 (C3′), 151.0 (C2), 154.7 (C6), 165.3 (CO); MS *m/z* 292 (100, MH^+). Anal. Calcd for $C_{13}H_{17}N_5O_3$ (291.31): C, 53.60; H, 5.88; N, 24.04. Found: C, 53.72; H, 6.01; N, 24.21.

5-(Adenin-9-yl)-1,1-dibromo-3-(*t*-butyldimethylsilyloxy)-1-penten (8). Oxidation of **4** (168 mg, 0.5 mmol) as described for **6** gave crude 4-(adenin-9-yl)-2-(*t*-butyldimethylsilyloxy)butanal (**5**). This material was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$) and organic layer was washed (H_2O, brine) and was evaporated. Flash column chromatography ($CHCl_3 \rightarrow 3\%$ MeOH/$CHCl_3$) gave **5** [83 mg, ∼50%; ^{1}H NMR δ 9.45 (s, 1, CHO); purity ∼85%]. The solution of the above material in CH_2Cl_2 (5 mL) was added via syringe into a mixture containing (dibromomethylene)triphenylphoshorane [generated in situ by stirring of CBr_4 (249 mg, 0.75 mmol) and PPh_3 (293 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0°C under Ar for 5 min]. After 2 h, the reaction mixture was partitioned (H_2O/CH_2Cl_2) and the organic layer was washed with water and brine. The water layer was back extracted with CH_2Cl_2 (4×). The combined organic phase was dried (Na_2SO_4) and evaporated. Column chromatography ($CHCl_3 \rightarrow 3\%$MeOH/$CHCl_3$) gave **8** (74 mg, 30% overall from **4**): ^{1}H NMR δ 0.05 & 0.06 (2 × s, 2 × 3, 2 × CH_3), 0.90 (s, 9, *t*-Bu), 2.19 (“q”, $J = 7.2$ Hz, Hz, 2, H4′,4″), 4.31 (t, $J = 7.2$ Hz, 2, H5′,5″), 4.40 (“q”, $J = 6.4$ Hz, 1, H3′), 5.75 (br s, 2, NH_2), 6.37 (d, $J = 8.0$ Hz, 1, H2′), 7.92 (s, 1, H2), 8.39 (s, 1, H8); MS *m/z* 494 (50, MH^+ [$^{81}Br_2$]), 492 (100, MH^+ [$^{81/79}Br_2$]), 490 (49, MH^+ [$^{79}Br_2$]).

5-(Adenin-9-yl)-1,1-dibromo-1-penten-3-ol (9). Compound **8** (35 mg, 0.07 mmol) and NH_4F (39 mg, 1.05 mmol) in MeOH (3 mL) were refluxed for 1 h. Evaporation and column chromatography ($CHCl_3 \rightarrow 6\%$ MeOH/$CHCl_3$) followed by RP-HPLC purification (preparative LC-18S column, $10 \rightarrow 60\%$ CH_3CN/H_2O for 90 min at 2.5 mL/min) gave **9** (12 mg, 46%; t_R 65 min): ^{1}H NMR (MeOH-d_4) δ 2.07–2.21 (m, 2, H4′,4″), 4.21 (dt, $J = 4.8$, 8.2 Hz, 1, H3′), 4.39 (t, $J = 6.8$ Hz, 2, H5′,5″), 6.48 (d, $J = 8.0$ Hz, 1, H2′), 8.15 (s, 1, H2), 8.24 (s, 1, H8); ^{13}C NMR δ 35.2 (C4′), 40.3 (C5′), 69.4 (C3′), 89.8 (C1′), 119.1 (C5), 141.0 (C2′), 141.9 (C8), 148.1 (C4), 152.7 (C2), 155.7 (C6); MS (APCI) *m/z* 380 (51, MH^+ [$^{81}Br_2$]), 378 (100, MH^+ [$^{81/79}Br_2$]), 376 (50, MH^+ [$^{79}Br_2$]). Anal. Calcd. For $C_{10}H_{11}Br_2N_5O$ (377.04): C, 31.86; H, 2.94; N, 18.57. Found: C, 32.11; H, 3.12; N, 18.34.

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Inactivation of AdoHcy Hydrolase. Various concentrations of compounds **7** and **9** (0.4–200 μM) were incubated with human AdoHcy hydrolase (0.17 μM) in wells of a 96-well microtiter plate containing 120 μL of 50 mM potassium phosphate buffer (pH 7.2), 1.0 μg of AdoHcy hydrolase, 10 μL of adenosine deaminase (40 U/mL), and 40 μL of the substrate AdoHcy (1 mM). The reaction mixture was incubated at 37°C for 7 min, and the reaction was terminated by addition of 10 μL of 9-(2′,3′-dihydroxycyclopentanyl) adenine (DHCaA; 100 mM), a potent AdoHcy hydrolase inhibitor. After 5 min, 10 μL of 5′,5′-dithiobis(2-nitrobenzoic acid) (DTNB; 2 mM) was added to each well to develop the color for 5 min and the absorbance at 405 nm was read with a plate reader (Molecular Devices). Negative control (blank) was included by replacing the substrate AdoHcy with water. The average enzyme activities from duplicated assays were used to calculate the percentage of the enzyme inhibition by inhibitors against the enzyme activity measured at zero inhibitor concentration.

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