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Synthesis of lipophilic sila derivatives of *N*-acetylcysteineamide, a cell permeating thiol

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***N*-acetyl-L-cysteine (L-NAC) is a potent antioxidant that can reduce levels of reactive oxygen species. *N*-acetyl-cysteine-amide, the amide form of L-NAC, has recently been reported to be more lipophilic and permeable through cell membranes than NAC, and to be able to traverse the blood–brain barrier. In this communication we report the synthesis and characterization of highly lipophilic sila-amide derivatives of L-NAC that may show enhanced cell penetration and bioavailability.**

Supporting information may be found in the online version of this article.

Keywords: antioxidant; *N*-acetyl-L-cysteine; lipophilic; blood–brain barrier; sila drugs

Introduction

N-acetyl L-cysteine[1,2] (L-NAC, **2**) the acetylated form of the simple amino acid L-cysteine (**1**), is a more efficiently bio-absorbed and used form of L-cysteine,[3] while its stereoisomer, D-NAC (**3**) usually does not display activity under similar conditions (Scheme 1).[4]

L-NAC is a powerful antioxidant,[2,5] a premier antitoxin,[6] an immune support substance,[7,8] and a precursor to glutathione (**4**),[9] an antioxidant critical in protecting against oxidative stress. L-NAC is able to decrease reactive oxygen species (ROS) levels through two separate mechanisms.[1] It can directly reduce compounds with its sulfhydryl group,[1,10] and it can also boost cellular levels of glutathione through conversion into metabolites that can stimulate glutathione synthesis.[1,11,12]

These antioxidants are intrinsically connected to the regulation of the cellular physiological redox state,[1,3,13] disruption of which can lead to oxidative injury via processes such as inflammation,[14] and mutagenesis.[15] L-NAC can also enhance hypoxia-induced apoptosis in human cancer cell lines. Hence, it is not surprising that L-NAC displays anticarcinogenic and antimutagenic properties and has been proposed for cancer treatment.[13,16–18]

However, the administration of L-NAC is usually employed only to target tissues outside of the central nervous system. *N*-acetylcysteine amide (NACA, AD4, **5**) is a more lipophilic derivative[19] which is a better radical scavenger[20,21] and is able to cross the blood–brain barrier (Scheme 2).[22–24] AD4 has been shown to increase cellular levels of glutathione[23] and to attenuate oxidative stress[20,21,23] related to disorders such Alzheimer's disease, Parkinson's disease and multiple sclerosis.[24–27]

ROS also play an important role in the pathogenesis of airway inflammation and hyperresponsiveness.[28–30] Studies have demonstrated that antioxidants such as L-NAC are able to reduce airway inflammation and hyperreativity in animal models of allergic disease.[31,32] AD4 is able to attenuate this response by regulating the activation of key transcription factors such as NF-kβ and HIF-1α.[29]

Sila-amidation of certain pharmacological agents has shown to increase potency and selectivity.[33,34] Silicon substitution onto the L-NAC molecule should lead to more lipophilic compounds of type **6**,[34–36] better able to penetrate across the gut wall and cell membranes.[36] This may result in improved pharmacological properties,[37,38] including bioavailability, metabolism and/or pharmacokinetics. Towards this goal, we report the synthesis and characterization of silicon derivatives **6a–c**. These compounds can be prepared from *N*-acetyl-L-cysteine (**2**) as shown in Scheme 3.

Protection of the thiol group was obtained by conversion of **2** into thiazolidine **7** using Montmorilline K 10 clay in an acetone/2,2-dimethoxypropane solvent mixture.[39,40] Although conversion of **7** into an acyl chloride derivative fails, direct amidation to **8** can be achieved by first forming a mixed anhydride which can be reacted with the respective sila amine to give amido derivatives of type **8a–c**. A final deprotection step using HCl in methanolic solution[41] affords the desired compounds **6a–c**.

Experimental

General Methods

Manipulation of air and moisture sensitive compounds was performed in a nitrogen atmosphere glove box or using standard

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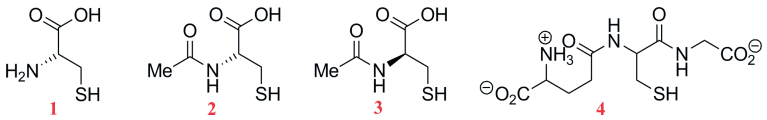
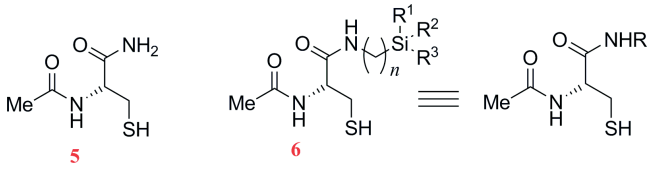


Scheme 1. L-cysteine (1), *N*-acetyl L-cysteine (2), *N*-acetyl D-cysteine (3) and glutathione (4).



Scheme 2. AD4 (5) and silicon derivatives (6).

high-vacuum line techniques. Hexane and CH_2Cl_2 were distilled from CaH_2. All other solvents and reagents were used as received. *N*-acetyl-L-cysteine, ethyl chloroformate and triethylamine were received from Sigma–Aldrich. 3-Aminopropyltrimethylsilane, aminomethyltrimethylsilane, chloromethyldimethylphenylsilane and 3-chloropropyltrimethylsilane were purchased from Gelest. Aminomethyldimethylphenylsilane was synthesized as previously reported.[33]

^{1}H NMR spectra were obtained on a Varian Unity 500 spectrometer, ^{13}C {H} NMR spectra were obtained on a Varian Unity 500 spectrometer operating at 125 MHz, ^{29}Si {H} NMR spectra were obtained on a Varian Unity 500 spectrometer operating at 99 MHz. ESI mass spectra were determined on a VG AutoSpec M mass spectrometer. Chemisar Laboratories Inc. of Ontario, Canada performed elemental analysis. Melting points were determined on Mel-Temp Laboratory Device.

*(R)-4-carboxy-3-acetyl-2,2-dimethylthiazolidine (**7**)*[39,40]

A suspension of *N*-acetyl-*S*-cysteine (1.0 g, 6 mmol) and montmorillonite K10 (0.2 g, 20 wt%) in 40 ml of anhydrous acetone–2,2-dimethoxypropane (1 : 3) mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered, and solvent was evaporated to give (*R*)-4-carboxy-3-acetyl-2,2-dimethylthiazolidine (1.12 g, 95% yield) as white solid (90% pure) which was later purified by recrystallization from acetone–hexane (1.03 g, 84% yield). ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.48 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.95 (s, 3 H, NAc), 2.86 (dd, J = 13.3, 7.1, 1 H, CH*H*), 3.00 (dd, J = 13.3, 5.1, 1 H, C*H*H), 4.67 (ddd, J = 8.0, 7.1, 5.1, 1 H, CH), 12.80 (br. s, 1 H, OH).

General Synthesis of 6a–c

A solution of **7** (1 equiv) and triethylamine (1 equiv) in dichloromethane (4 ml for 1 mmol **7**) was cooled to −5 °C and a solution of ethyl chloroformate (1 equiv) in dichloromethane (1 ml for 1 mmol **7**) was added dropwise. After 15 min of stirring at −5 °C, the respective sila amine (1 equiv) was slowly added to the reaction mixture. Stirring was continued for 25 min at −5 °C and 15 h at room temperature. The reaction mixture was then diluted with dichloromethane (6 ml for 1 mmol **7**) and washed thoroughly with portions of 5% hydrochloric acid, sodium bicarbonate and water (6 ml for 1 mmol **7**). The dichloromethane solution was then dried over magnesium sulfate and evaporated to give intermediates of type **8**.

A solution of **8** in 2 M HCl methanolic solution (15 ml for 1 mmol **7**) was stirred at room temperature for 24 h. The methanol was removed under reduced pressure and the reaction worked up with dichloromethane–brine. The dichloromethane solution was then dried with $MgSO_4$, filtered and evaporated to give the respective derivatives of type **6**.

*Synthesis of (R)-2-acetamido-3-mercapto-N-(3-(trimethylsilyl) propyl)propanamide (**6a**)*

The title compound was prepared using **7** (1.03 g, 5 mmol) to give (*R*)-4-(trimethylsilyl)propyl)propanamide-3-acetyl-2,2-dimethylthiazolidine (**8a**, 1.2 g, 59% yield) as a pale yellow oil (85% pure) by ^{1}H NMR spectroscopy, which was used for the next step without further purification.

From **8a** (0.8 g, 2 mmol) **6a** (0.5 g, 67% yield) was obtained as pale yellow oil (85% pure) by ^{1}H NMR spectroscopy. Recrystallization from dichloromethane–hexane mixture at −20 °C gave pure product (0.4 g, 57% yield) as a white solid; m.p. = 97–100 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ −0.02 (s, 9 H, TMS), 0.49 (m, 2 H, CH_2), 1.50 (ddd, J = 14.8, 12.2, 7.3 Hz, 2 H, CH_2), 1.62 (dd, J = 9.7 Hz; 8.0 Hz, 1 H, SH), 2.04 (s, 3 H, NAc), 2.75 (ddd, J = 13.7, 9.7, 7.1 Hz, 1 H, C*H*H), 2.93 (ddd, J = 13.0, 7.9, 4.9 Hz, 1 H, CH*H*), 3.23 (m, 1 H, C*H*H), 3.27 (m, 1 H, CH*H*), 4.60 (dt, J = 7.5, 7.5, 5.0 Hz, 1 H, CH), 6.84 (dd, J = 16.0, 6.2 Hz, 2 H, 2 NH). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz) δ −1.8 (3 C, TMS), 13.8, 23.1, 24.0, 26.7, 42.8, 54.5, 169.7 (CO), 170.3 (CO). ^{29}Si {^{1}H} NMR ($CDCl_3$, 99 MHz) δ 0.58 (s, TMS). MS (electrospray ionization, MeOH) m/z $(M + Na)^+$ calcd for $C_{11}H_{24}N_2O_2SSiNa$, 299.1225; found, 299.1214. Anal. calcd for $C_{11}H_{24}N_2O_2SSi$: C, 47.79; H, 8.75; N, 10.13. Found: C, 48.00; H, 9.16; N, 9.83.

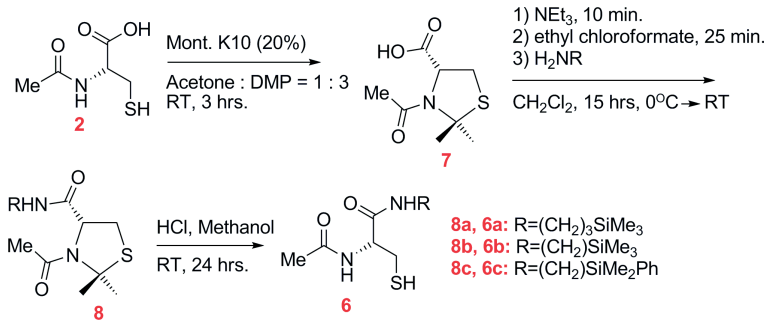
*Synthesis of (R)-2-acetamido-3-mercapto-N-[3-(trimethylsilyl) methyl]propanamide (**6b**)*

From **7** (3.09 g, 15 mmol) (*R*)-[4-(trimethylsilyl)methyl] propanamide-3-acetyl-2,2-dimethylthiazolidine (**8b**, 3.64 g, 83% yield) was attained as a pale yellow oil (85% pure) by ^{1}H NMR spectroscopy, which was used in the next step without further purification.

Using **8b** (3.7 g, 13 mmol) **6b** (1.97 g, 61% yield) was afforded as a pale yellow oil, 85% pure by ^{1}H NMR spectroscopy. Recrystallization from dichloromethane–hexane mixture at −20 °C gave pure product (1.6 g, 51% yield) as a white solid; m.p. = 103–106 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 9 H, TMS), 1.61 (td, J = 14.1 Hz, 7.1 Hz, 7.1 Hz, 1 H, SH), 2.03 (s, 3 H, NAc), 2.66–2.94 (m, 4 H, $2CH_2$), 4.62 (dt, J = 7.6, 7.6, 5.1, 1 H, CH), 6.82 (br. s, 1 H, NH), 6.99 (d, J = 8.0 Hz, 1 H, NH). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz) δ −2.7 (3 C, TMS), 23.1, 26.7, 29.9, 54.6, 169.8 (CO), 170.3 (CO). ^{29}Si {^{1}H} NMR ($CDCl_3$, 99 MHz) δ 0.19 (s, TMS). MS (electrospray ionization, MeOH) m/z $(M + Na)^+$ calcd for $C_9H_{20}N_2O_2SSiNa$, 271.0912; found, 271.0902. Anal. calcd for $C_9H_{20}N_2O_2SSi$: C, 43.51; H, 8.11; N, 11.28. Found: C, 43.40; H, 8.37; N, 11.34.

*Synthesis of (R)-2-acetamido-3-mercapto-N-[3-(dimethylphenylsilyl) methyl]propanamide (**6c**)*

Starting with **7** (1.23 g, 6 mmol) gave (*R*)-[4-(dimethylphenylsilyl) methyl]propanamide-3-acetyl-2,2-dimethylthiazolidine (**8c**, 1.2 g,



Scheme 3. Synthesis of sila-amide derivatives of L-NAC.

57% yield) as a pale yellow oil (90% pure) by ^{1}H NMR spectroscopy, which was used for the next step without further purification.

Subsequently **8c** (1.2 g, 3 mmol) was converted to **6c** (0.63 g, 67% yield) as a pale yellow oil (90% pure) by ^{1}H NMR spectroscopy. Recrystallization from dichloromethane–hexane mixture at −20 °C gave pure product (0.56 g, 60% yield) as a white solid; m.p. = 93–96 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.37 (s, 6 H, $SiMe_2$), 1.48 (v. t, J = 8.8 Hz, 1 H, SH), 1.95 (s, 3 H, NAc), 2.64 (ddd, J = 13.7, 9.8, 7.4 Hz, 1 H, C*H*H), 2.82–2.93 (m, 2 H, 2 CH*H*), 3.07 (dd, J = 15.4, 6.1 Hz, 1 H, C*H*H), 4.53 (dd, J = 12.2, 7.4 Hz, 1 H, CH), 6.59 (br. s, 1 H, NH), 6.80 (d, J = 7.6 Hz, 1 H, NH), 7.38 (d, J = 6.9 Hz, 3 H, Ph), 7.52 (m, 2 H, Ph). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz) δ −4.1 (2 C, SiMe), 23.0, 26.6, 29.0, 54.5, 128.0, 129.6, 133.7, 136.1, 169.7 (CO), 170.2 (CO). ^{29}Si {^{1}H} NMR ($CDCl_3$, 99 MHz) δ −5.01 (s, $SiMe_2$). MS (electrospray ionization, MeOH) m/z $(M + Na)^+$ calcd for $C_{14}H_{22}N_2O_2SSiNa$, 333.1069; Found, 333.1082. Anal. calcd for $C_{14}H_{22}N_2O_2SSi$: C, 54.16; H, 7.14; N, 9.02. Found: C, 54.21; H, 7.56; N, 8.85.

Conclusions

The synthesis of novel lipophilic, silicon-containing derivatives of AD4 can be performed by protection of *N*-acetyl-L-cysteine and subsequent amidation and deprotection. The resulting compounds are more lipophilic than **5** and hence should be useful towards optimizing pharmacological properties of this antioxidant derivative.

Supporting information

Supporting information may be found in the online version of this article.

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