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Research Article

Synthesis of deuterium labeled phenethylamine derivatives

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Summary

The synthesis of a series of five deuterium labeled phenethylamine derivatives, 4-bromo-2,5-[$^2H_6$]-dimethoxyphenethylamine (2C-B), 4-chloro-2,5-[$^2H_6$]-dimethoxyphenethylamine (2C-C), 2,5-[$^2H_6$]-dimethoxy-4-iodophenethylamine (2C-I), 2,5-[$^2H_6$]-dimethoxy-4-ethylthiophenethylamine (2C-T-2) and 2,5-[$^2H_6$]-dimethoxy-4-*n*-propylthiophenethylamine (2C-T-7) from 1,4-[$^2H_6$]-dimethoxybenzene is described. The isotopically labeled compounds are used as internal standards in gas chromatography-mass spectrometry (GC-MS) assays. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: deuterium labeling; phenethylamine; designer drugs; 2C-C; 2C-B; 2C-I; 2C-T-2; 2C-T-7

Introduction

The increased availability of 2C-series (phenethylamine derivatives) on the illicit drug market has become a serious societal problem.[1] Shulgin *et al.* in their publication Phenethylamines I Have Known And Loved (PiHKAL), documented over 179 phenethylamine derivatives, including 3,4-methylenedioxymeth-amphetamine (NMDA), mescaline, 2C-B, 2C-C, 2C-I, 2CT-2 and 2C-T-7, and described the procedures for producing these drugs.[2] Phenethylamine derivatives are increasingly abused psychoactive drugs and well documented in literature.[3–8] The continuing designer drug exploration of

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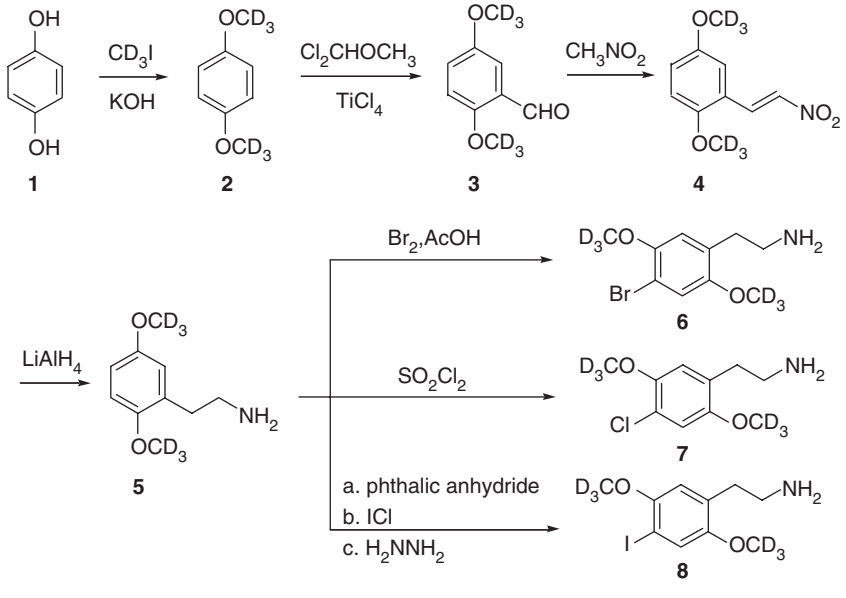
homologous series and their widespread consumption has resulted in an increasing number of reports regarding abuse and intoxication.

The abuse of psychoactive drugs derived from phenylethylamine and phenylisopropylamine groups has became a serious societal problem in Taiwan in the recent decade.[9–15] Amphetamine, its *N*-methyl homologues methylamphetamine, and ring-substituted analogues, MDMA and 3,4-methylenedioxyethylamphetamine (MDE) are among the most widely abused drugs among young individuals.

Stable isotope labeled internal standards for controlled drugs analyses in Taiwan are extremely difficult to obtain. This work describes synthetic routes to, and characterization of, [$^2H_6$]-2C-C, [$^2H_6$]-2C-B, [$^2H_6$]-2C-I; [$^2H_6$]-2C-T-2 and [$^2H_6$]-2C-T-7, and presents their characteristic analytical data for them. The synthetic method presented herein is promising for synthesizing a wide variety of other amphetamine-based drugs. According to our knowledge, these compounds have never been investigated in literature.

Results and discussion

Although 2C-B, 2C-C, 2C-I 2C-T-2 and 2C-T-7 have been readily prepared by several synthetic routes,[2] preparing [$^2H_6$]-2C-B, [$^2H_6$]-2C-Cl, [$^2H_6$]-2C-I, [$^2H_6$]-2C-T-2 and [$^2H_6$]-2C-T-7 has not been described previously. Scheme 1 presents the general synthetic scheme to prepare [$^2H_6$]-2C-B (**6**), [$^2H_6$]-2C-C (**7**) and [$^2H_6$]-2C-I (**8**). 1,4-[$^2H_6$]-Dimethoxybenzene (**2**) was prepared by reacting hydroquinone and [$^2H_3$]-methyl iodide.[16–19] Compound **2** was treated with



Scheme 1. Synthesis of compounds 6–8

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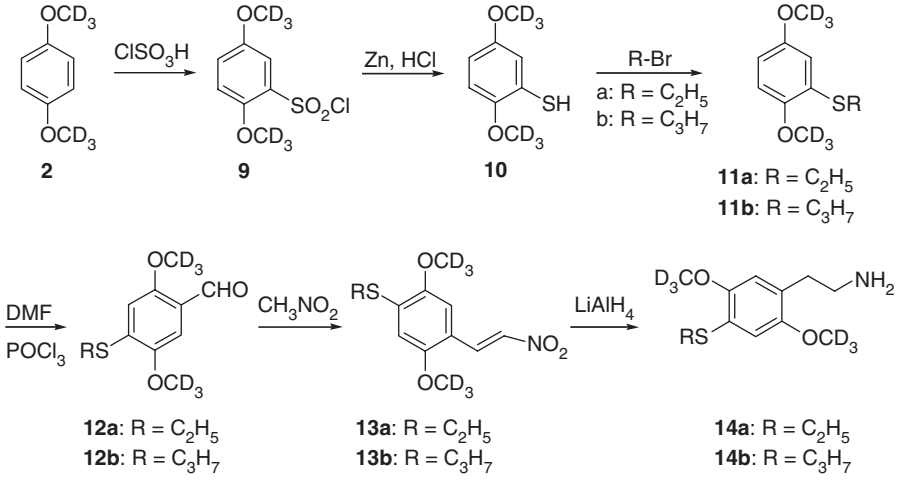
dichloromethyl methyl ether and $TiCl_4$ gave 2,5-[$^2H_6$]-dimethoxybenzaldehyde (**3**),[20–25] which was then condensed with nitromethane to yield 1,4-[$^2H_6$]-dimethoxy-2-(2-nitrovinyl)benzene (**4**). Reduction of compound **4** with $LiAlH_4$ produced 2-(2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (**5**). The bromination of **5** with bromine in acetic acid yielded 2-(4-bromo-2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (**6**), and chlorination of **5** with SO_2Cl_2 gave 2-(4-chloro-2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (**7**). Treatment of **5** with phthalic anhydride gave 2-[2-(2,5-[$^2H_6$]-dimethoxyphenyl)ethyl]isoindole-1, 3-dione, which was then reacted with iodine monochloride (ICl) and gave 2-[2-(4-iodo-2,5-[$^2H_6$]-dimethoxyphenyl)ethyl]isoindole-1,3-dione, which was treated with hydrazine to generate 2-(4-iodo-2,5-[$^2H_6$]-dimethoxyphenyl) ethylamine (**8**).

Scheme 2 presents the preparation of [$^2H_6$]-2C-T-2 (**14a**) and [$^2H_6$]-2C-T-7 (**14b**). 2,5-[$^2H_6$]-Dimethoxybenzenesulfonyl chloride (**9**) was prepared by reacting 1,4-[$^2H_6$]-dimethoxybenzene (**2**) with chlorosulfonic acid. Compound **9** was reduced to generate 2,5-[$^2H_6$]-dimethoxybenzenethiol (**10**) by zinc in hydrochloric acid. Alkylation of compound **10** by bromoethane yielded 2,5-[$^2H_6$]-dimethoxyphenyl ethyl sulfide (**11a**), and the formylation by *N,N*-dimethylformamide and phosphoryl chloride produced 4-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxybenzaldehyde (**12a**). Condensation of compound **12a** with nitromethane formed 1-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxy-4-(2-nitrovinyl) benzene (**13a**). Reduction of compound **13a** by lithium aluminum hydride gave 2,5-[$^2H_6$]-dimethoxy-4-ethylthiophenethylamine hydrochloride (**14a**). Next, compound **10** was treated with bromopropane, and the same procedures as described earlier generated the corresponding 2,5-[$^2H_6$]-dimethoxyphenyl *n*-propyl sulfide (**11b**), 2,5-[$^2H_6$]-dimethoxy-4-propylsulfanylbenzaldehyde



Scheme 2. Synthesis of compounds 14a and 14b

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(**12b**), 1,4-[$^2H_6$]-dimethoxy-2-(2-nitrovinyl)-5-propylsulfanylbenzene (**13b**) and 2,5-[$^2H_6$]-dimethoxy-4-*n*-propylthiophenethylamine hydrochloride (**14b**).

Experimental

General

^{1}H NMR spectra were acquired at 300 MHz (indicated in each case), and ^{13}C NMR were acquired at 75.5 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were obtained on a Micromass Platform II mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were obtained on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on a JASCO FT/IR 410 spectrometer. All reactions were performed in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone in argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. All air sensitive reactions were performed in dry glassware under nitrogen using a standard glovebox. Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) which was purchased from Macherey-Nagel.

All reactions were initially optimized using unlabeled compounds.

*Synthesis of 1,4-[$^2H_6$]-dimethoxybenzene (**2**).* Potassium hydroxide pellets (4.30 g, 77.0 mmol) were ground to a powder, tetrabutylammonium bromide (0.39 g, 1.2 mmol) and hydroquinone (3.40 g, 30.0 mmol) were then added, and ground under a nitrogen atmosphere at room temperature.[16–19] [$^2H_3$]-Methyl iodide (5.6 ml, 93.0 mmol; isotopic abundance 99.5%, Cambridge Isotope Laboratories Inc.) was then added and the mixture was heated in an oil bath for 3 days at 40–45°C. The crude mixture was then transferred to a separating funnel with water and diethyl ether, and aqueous phase was extracted using diethyl ether. The extracts were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue that was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase to give (**2**) as a white crystalline solid (4.22 g, 29.0 mmol). Yield: 98%. m.p.: 56–57°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.90 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.7, 114.6, 55.2–54.6 (m). IR (KBr, thin film): 3164, 3106, 3061, 3044, 2505, 2217, 2065, 1943, 1867 cm^{-1}.

*Synthesis of 2,5-[$^2H_6$]-dimethoxybenzaldehyde (**3**).* To a solution of **2** (3.50 g, 25.0 mmol) in dry dichloromethane (478 ml) cooled in an ice bath was added titanium chloride (5.0 ml, 46.0 mmol), and dichloromethyl methyl ether ($C1_2CHOCH_3$) (4.2 ml, 46.5 mmol) under an argon atmosphere.[20–25] The dark red reaction solution was stirred at room temperature for 15 min until the starting material was completely consumed as monitored by thin layer

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chromatography (TLC). The reaction was quenched by adding water (185 ml), and the dichloromethane layer was washed with water (140 ml) and then dried over anhydrous magnesium sulfate. The solution was filtered, and the filtrate was concentrated by rotary vacuum evaporation. The residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:39) as the mobile phase to give (**3**) as a white crystalline solid (3.15 g, 18.3 mmol). Yield: 73%. m.p.: 50–51°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.48 (s, 1 H), 7.33 (d, $J = 3.2$ Hz, 1 H), 7.15 (dd, $J = 9.1$, 3.3 Hz, 1 H), 6.95 (d, $J = 9.1$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 189.5, 156.7, 153.5, 124.9, 123.4, 113.3, 110.4, 55.6–54.7 (m). IR (KBr, thin film): 3098, 3052, 2873, 2231, 2070, 1674, 1616, 1495, 1432, 1401, 1293, 1221 cm^{-1}. MS-FAB (*m*/*z*): 173 ($M^+ + 1$, 100). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_9H_4D_6O_3$, 172.1000; found 172.1002.

*Synthesis of 1,4-[$^2H_6$]-dimethoxy-2-(2-nitrovinyl)benzene (**4**).* A solution of 2,5-[$^2H_6$]-dimethoxybenzaldehyde (**3**) (2.90 g, 17.0 mmol) in nitromethane (5.77 ml, 105.0 mmol) was treated with anhydrous ammonium acetate (0.29 g) and heated at 100°C for 2.5 h until the starting material was completely consumed by TLC monitoring. The solvent was removed under vacuum yielding 2,5-[$^2H_6$]-dimethoxy-β-nitrostyrene (**4**) (3.50 g, 16.0 mmol) as a yellow crystal. Yield: 73%. m.p.: 121–122°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.14 (d, $J = 13.6$ Hz, 1 H), 7.88 (d, $J = 13.7$ Hz, 1 H), 7.03-6.99 (dd, $J = 9.0$, 3.0 Hz, 1 H), 6.96 (d, $J = 2.9$ Hz, 1 H), 6.91 (d, $J = 8.9$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.9, 153.5, 138.4, 135.3, 119.4, 119.1, 116.3, 112.4. IR (KBr, thin film): 3104, 2221, 2075, 1616, 1496, 1346, 1253, 1234 cm^{-1}. MS-FAB (*m*/*z*): 216 ($M^+ + 1$, 10), 170 (19), 75 (1 0 0). HRMS-FAB (*m*/*z*): $[M + H]^+$ calculated for $C_{10}H_6D_6NO_4$, 216.1137; found 216.1145.

*Synthesis of 2-(2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (**5**).* A suspension of lithium aluminum hydride (2.70 g, 70.0 mmol) in anhydrous tetrahydrofuran (68.0 ml) under an inert atmosphere was stirred and heated to reflux. A solution of 2,5-[$^2H_6$]-dimethoxy-β-nitrostyrene (**4**) (3.50 g, 16.0 mmol) in tetrahydrofuran (15.0 ml) was added dropwise, and the reaction mixture was maintained at reflux for 24 h. After cooling in an ice bath, excess hydride was destroyed using a mixture of tetrahydrofuran and water (1:1) (20 ml), followed by adding 2 N aqueous sodium hydroxide (20 ml). The solid was removed by filtration through celite, and the filter cake was washed with additional tetrahydrofuran. The combined filtrate and washes were concentrated under vacuum, and the residue acidified by dilute hydrochloric acid. Washing with dichloromethane (2 × 30 ml) removed most color, and the aqueous phase was basified with aqueous sodium hydroxide and extracted with dichloromethane (3 × 50 ml). After removing the solvent, the residue was readily converted to

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hydrochloride salt by dissolving its in diethyl ether, neutralizing it with HCl(g), and producing a permanent turbidity. The product was reprecipitated from methanol/diethyl ether. Crystals of 2,5-[$^2H_6$]-dimethoxyphenethylamine hydrochloride (**5**) (1.55 g, 6.9 mmol) spontaneously formed and were removed by filtration and washed with Et_2O. Yield: 43%. ^{1}H NMR (300 MHz, D_2O, δ): 6.92 (d, J = 8.9 Hz, 1 H), 6.84-6.80 (dd, J = 8.9, 3.0 Hz, 1 H), 6.78 (d, J = 3.0 Hz, 1 H), 3.13 (t, J = 6.8 Hz, 2 H), 2.86 (t, J = 6.9 Hz, 2 H). ^{13}C NMR (75 MHz, CD_3OD, δ): 153.7, 151.7, 125.4, 116.5, 112.4, 111.2, 39.4, 28.6. IR (KBr, thin film): 2965, 2908, 2832, 2753, 2653, 2564, 2464, 2217, 2063, 1500, 1238 cm^{-1}. MS-FAB (*m*/*z*): 188 (M^+-Cl, 100), 185 (8), 171 (42), 158 (10), 75 (8). HRMS-FAB (*m*/*z*): [M^+-Cl] calculated for $C_{10}H_{10}D_6NO_2$, 188.1552; found 188.1553.

*Synthesis of 2-(4-bromo-2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (**6**).* Bromine (0.43 ml, 8.4 mmol) dissolved in acetic acid (2.5 ml) and added to a well-stirred solution of 2,5-[$^2H_6$]-dimethoxyphen-ethylamine (1.50 g, 8.0 mmol) in glacial acetic acid (2.5 ml). After a few minutes, a solid precipitated with the simultaneous evolution of considerable heat. The reaction mixture was allowed to return to room temperature, filtered, and the solids were washed sparingly with cold acetic acid. The entire mass of acetic acid-wet salt was dissolved in warm water, and made basic to a pH 11 with 2 M aqueous sodium hydroxide, and extracted with dichloromethane. Removal of the solvent gave **6** (0.50 g, 1.9 mmol). Yield: 24%. ^{1}H NMR (300 MHz, CD_3Cl, δ): 7.02 (s, 1 H), 6.74 (s, 1 H), 2.93 (t, J = 6.9 Hz, 2 H), 2.74 (t, J = 7.2 Hz, 2 H). ^{13}C NMR (75 MHz, CD_3Cl, δ): 151.9, 149.6, 118.3, 115.7, 115.0, 110.7, 56.3-54.8(m), 42.0, 31.9. IR (KBr, thin film): 3367, 2938, 2854, 2217, 2129, 2071, 1581, 1492, 1488, 1392, 1106 cm^{-1}. MS-EI (*m*/*z*): 267 (16), 265 (17), 250 (12), 248 (12), 238 (91), 236 (100), 157 (3). HRMS-EI (*m*/*z*): [M^+] calculated for $C_{10}H_8D_6BrNO_2$, 265.0578; found 265.0580.

*Synthesis of 2-(4-chloro-2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (**7**).* Sulfuryl chloride (0.5 ml, 6.0 mmol) was added dropwise to an ice-cold and well-stirred solution of 2,5-[$^2H_6$]-dimethoxyphenethylamine (**5**) (0.90 g, 4.0 mmol) in glacial acetic acid (8.0 ml), and the temperature kept $<30^\circ$C. The clear solution was stirred at room temperature for 3 h, and diethyl ether (10 ml) added. The mixture was stirred for further 30 min, and the solid was collected by filtration. The collected solid was purified by recrystallization from a mixture of methanol and diethyl ether, thereby producing **7d** · HCl (0.30 g, 1.2 mmol). Yield: 29%. ^{1}H NMR (300 MHz, D_2O, δ): 6.96 (s, 1 H), 6.85 (s, 1 H), 3.08 (t, J = 6.7 Hz, 2 H), 2.87 (t, J = 6.8 Hz, 2 H). ^{13}C NMR (75 MHz, CD_3OD, δ): 151.6, 149.1, 124.1, 121.1, 115.2, 112.8, 39.2, 28.2. IR (KBr, thin film): 3422, 2935, 2900, 2225, 2071, 1496, 1454, 1400, 1222, 1095 cm^{-1}. MS-EI

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(*m*/*z*): 223 (5), 221 (15), 194 (34), 192 (100), 176 (10), 174 (31), 75 (17). HRMS-EI (*m*/*z*): [M^+] calculated for $C_{10}H_8D_6ClNO_2$, 221.1084; found 221.1081.

*Synthesis of 2-(4-iodo-2,5-[$^2H_6$]-dimethoxyphenyl)ethylamine (***8***).* A mixture of phthalic anhydride (0.58 g, 3.9 mmol) and 2,5-[$^2H_6$]-dimethoxyphenethylamine (**4**) (0.49 g, 2.6 mmol) was heated to 130°C, and a clear phase was formed. After the hot melt had settled for a few moments, it was cooled to room temperature, and yielded a crude solid product. The crude product was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:9) as the mobile phase and produced a white crystal **8a** (0.59 g, 1.86 mmol). Yield: 71%. m.p.: 109–110°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.82–7.79 (m, 2 H), 7.70–7.67 (m, 2 H), 6.71–6.68 (m, 3 H), 3.96 (t, J = 6.9 Hz, 2 H), 2.99 (t, J = 7.1 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 168.2, 153.3, 152.0, 133.7, 132.2, 127.6, 123.0, 116.6, 112.6, 112.2, 111.1, 37.8, 29.7. IR (KBr, thin film): 3073, 2938, 2217, 2063, 1774, 1708, 1504, 1392, 1295 cm^{-1}. MS-EI (*m*/*z*): 317 (100), 170.2 (96), 160 (63), 157 (38), 77 (25), 75 (6). HRMS-EI (*m*/*z*): [M^+] calculated for $C_{18}H_{11}D_6NO_4$, 317.1528; found 317.1533. A solution of iodine monochloride (0.1 ml, 2.0 mmol) in acetic acid (1.0 ml) was added to to a solution of *N*-(2-(2,5-[$^2H_6$]-dimethoxyphenyl)ethyl)phthalimide (**8a**) (0.49 g, 1.5 mmol) in warm (35°C) acetic acid (5.0 ml) that was being vigorously stirred. This mixture was stirred for 1 h at about 30°C. The reaction mixture was poured into water (40 ml) and extracted with dichloromethane. The extracts were washed with a solution of sodium sulfite (0.06 g) in water (4.5 ml), and the solvent was removed under vacuum to give a crude product. The crude product was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:10) as the mobile phase and produced a white crystal **8b** (0.65 g, 1.5 mmol). Yield: 95%. m.p.: 154–155°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.82–7.79 (m, 2 H), 7.72–7.68 (m, 2 H), 7.15 (s, 1 H), 6.60 (s, 1 H), 3.96 (t, J = 6.8 Hz, 2 H), 2.99 (t, J = 7.0 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 168.2, 152.5, 152.3, 133.9, 132.0, 127.8, 123.1, 121.4, 113.6, 83.6, 37.5, 29.6. IR (KBr, thin film): 3459, 3058, 2931, 2857, 2225, 2129, 2071, 1770, 1712, 1484, 1392 cm^{-1}. A solution of *N*-(2-(2,5-[$^2H_6$]-dimethoxy-4-iodophenyl)ethyl)phthalimide **(8b)** (0.65 g, 1.5 mmol) in hot 2-propanol (8 ml) was treated with hydrazine hydrate (0.2 ml, 53.9 mmol), and the clear solution was heated to 100°C. After a few minutes, a milky solid was generated. Heating was continued for 1.5 h, the reaction mixture was cooled, and the solids removed by filtration. These solids were washed with ethanol, and the combined filtrates and washes removed the solvent under vacuum giving a syrupy product **8**. This crude product was used for the identification without further purification. ^{1}H NMR (300 MHz, CD_3Cl, δ): 7.20 (s, 1 H), 6.66 (s, 1 H), 2.93 (t, J = 6.6 Hz, 2 H), 2.74 (t, J = 6.8 Hz, 2 H).

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^{13}C NMR (75 MHz, CD_3Cl/CD_3OD, δ): 151.9, 151.8, 128.2, 120.9, 113.2, 82.0, 40.6, 33.19. IR (KBr, thin film): 2927, 2861, 2221, 2067, 1631, 1577, 1484, 1388, 1303, 1226 cm^{-1}. MS-EI (*m*/*z*): 313 (26), 284 (1 0 0), 266 (14), 251 (9), 78 (28). HRMS-EI (*m*/*z*): [M^+] calculated for $C_{10}H_8D_6NO_2I$, 313.0440; found 331.0444.

*Synthesis of 2,5-[$^2H_6$]-dimethoxybenzenesulfonyl chloride (***9***).* Chlorosulfonic acid (22.33 ml, 336 mmol) was cautiously added to a solution of 1,4-[$^2H_6$]-dimethoxybenzene (**2**) (6.00 g, 42.0 mmol) in dichloromethane (37.8 ml) under good ventilation and stirring. With approximately half of the chlorosulfonic acid added, a vigorous evolution of hydrogen chloride gas occurred and a substantial amount of solids were generated. As the addition of chlorosulfonic acid was continued, these solids redissolved, forming a clear, dark-green solution. Toward the end of the addition, some solids again formed, and the solution turned dark red. After stirring for 20 min, the reaction solution was added to ice water. The two phases were separated, and the aqueous phase was extracted with dichloromethane. The original organic phase and the extracts were combined and dried over anhydrous magnesium sulfate. The solvent was then removed under vacuum, and the residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:9) as the mobile phase and produced a yellowish crystal of 2,5-[$^2H_6$]-dimethoxybenzene-sulfonyl chloride (**9**), (5.06 g, 21.0 mmol). Yield: 50%. m.p.: 119–120°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.46 (d, $J = 3.1$ Hz, 1 H), 7.25 (dd, $J = 9.1$, 3.1 Hz, 1 H), 7.07 (d, $J = 9.1$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 152.6, 151.5, 131.8, 123.8, 114.7, 113.4, 56.5–54.7 (m). IR (KBr, thin film): 3120, 3061, 2236, 2078, 1571, 1495, 1414, 1365, 1230, 1172, 1100 cm^{-1}.

*Synthesis of 2,5-[$^2H_6$]-dimethoxybenzenethiol (***10***).* The following reaction is also extremely vigorous and must be performed in a well-ventilated enclosure. The 2,5-[$^2H_6$]-dimethoxybenzenesulfonyl chloride (**9**) (5.00 g, 20.0 mmol) was added to a solution of 25% sulfuric acid (v/v) (22.4 ml) in a beaker, and the mixture was heated at 100°C. The acid chloride yellow crystals floated on the aqueous layer surface. Under vigorous stirring, zinc dust (6.74 g, 103.0 mmol) was added using a small amount for each addition. Following the addition of zinc dust, the mixture was heated for 1 h at 100°C. Next, the reaction mixture was cooled to room temperature, and then filtered through celite in a Buchner funnel, and the residual metal was washed with diethyl ether. The two-phase filtrate was separated, and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was then purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase, which produced a yellowish crystal

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2,5-[$^2H_6$]-dimethoxythiophenol (**10**), (2.53 g, 14.4 mmol). Yield: 72%. ^1H NMR (300 MHz, $CDCl_3$, δ): 6.84 (d, $J = 2.9$ Hz, 1 H), 6.78 (d, $J = 8.9$ Hz, 1 H), 6.65 (dd, $J = 8.9$, 2.9 Hz, 1 H), 3.88 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.2, 148.5, 121.2, 114.4, 111.1, 110.8, 52.2–53.9 (m). IR (KBr, thin film): 3160, 3066, 3034, 2572, 2249, 2222, 2128, 2070, 1598, 1585, 1485 cm^{-1}. MS-FAB (*m*/*z*): 177 ($M^+ + 1$, 35), 176 (1 0 0), 144 (73), 115 (22). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_8H_4D_6O_2S$, 176.0772; found 170.0775.

*Synthesis of 2-ethylsulfanyl-1,4-[$^2H_6$]-dimethoxybenzene (***11a***).* A solution of 2,5-[$^2H_6$]-dimethoxythiophenol (**10**) (2.53 g, 14.4 mmol) in ethanol (14.5 ml) was added to a solution of potassium hydroxide (0.89 g, 15.8 mmol) in ethanol (21.0 ml), and then ethyl bromide (2.15 ml, 28.8 mmol) was added. A white solid was immediately precipitated, and the reaction was further refluxed for 1.5 h. After the reaction mixture had cooled to room temperature, it was added to water (45 ml), acidified with hydrochloric acid, and the aqueous phase was extracted with dichloromethane. The pooled extracts were washed with 5% sodium hydroxide, dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The residue was purified, by flash column chromatography, using silica gel as the stationary phase and ethyl acetate–hexane (1:49) as the mobile phase, and produced a yellowish liquid 2,5-[$^2H_6$]-dimethoxyphenyl ethyl sulfide (**11a**), (2.81 g, 13.7 mmol). Yield: 95%. ^1H NMR (300 MHz, $CDCl_3$, δ): 6.82 (d, $J = 2.9$ Hz, 1 H), 6.77 (d, $J = 8.8$ Hz, 1 H), 6.68 (dd, $J = 8.8$, 2.9 Hz, 1 H), 2.95 (q, $J = 7.4$ Hz, 2 H), 1.35 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.8, 151.2, 126.3, 114.9, 111.1, 110.5, 56.0–54.3 (m), 25.8, 13.9. IR (KBr, thin film): 3072, 3034, 2965, 2968, 2872, 2212, 1481, 1477 cm^{-1}. MS-FAB (*m*/*z*): 205 ($M^+ + 1$, 43), 204 (1 0 0), 175 (6.5), 75 (11). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_{10}H_8D_6O_2S$, 204.1085; found 204.1085.

*Synthesis of 1,4-[$^2H_6$]-dimethoxy-2-propylsulfanylbenzene (***11b***).* A solution of 2,5-[$^2H_6$]-dimethoxythiophenol (**10**) (1.19 g, 6.8 mmol) in ethanol (6.9 ml) was added to a solution of potassium hydroxide (0.42 g, 7.4 mmol) in ethanol (9.2 ml), and then 1-bromopropane (1.23 ml, 13.5 mmol) was added. A white solid was immediately precipitated, and the reaction was further refluxed for 1.5 h. After the reaction mixture had cooled to room temperature, it was added to water (30 ml), acidified with hydrochloric acid, and the aqueous phase was extracted with dichloromethane. The pooled extracts were washed with 5% sodium hydroxide, dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The residue was purified, by flash column chromatography, using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase, and produced a yellowish liquid 2,5-[$^2H_6$]-dimethoxyphenyl *n*-propyl sulfide (**11b**), (1.43 g, 6.6 mmol). Yield: 97%.

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^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.82 (d, $J = 2.9$ Hz, 1 H), 6.77 (d, $J = 8.8$ Hz, 1 H), 6.67 (dd, $J = 8.8$ Hz, 3.0, 1 H), 2.88 (t, $J = 7.2$ Hz, 2 H), 1.73–1.66 (m, 2 H), 1.06 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.8, 151.3, 126.6, 114.9, 111.1, 110.4, 55.7–54.5 (m), 33.7, 22.2, 13.6. IR (KBr, thin film): 3070, 3033, 2958, 2927, 2869, 2246, 2215, 2069, 1589, 1481, 1280, 1222, 1106 cm^{-1}. MS-FAB (*m*/*z*): 219 ($M^+ + 1$, 56), 218 (1 0 0), 204 (6), 191 (14), 176 (15), 144 (44). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_{11}H_{10}D_6O_2S$, 218.1242; found 218.1257.

*Synthesis of 4-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxybenz-aldehyde (***12a***).* A mixture of phosphoryl chloride ($POCl_3$) (3.08 ml, 39.8 mmol) and *N,N*-dimethylformamide (3.10 ml, 33.3 mmol) was heated to 100°C. To this solution was added 2,5-[$^2H_6$]-dimethoxyphenyl ethyl sulfide (**11a**), (2.71 g, 13.3 mmol) and the mixture was heated for additional 20 min at 100°C. This mixture was then added to a well-stirred warm water (pre-heated to 55°C) and stirred for 1.5 h by which time the oily phase had completely solidified. The solid was isolated by filtration, and washed with additional water. These solids were dissolved in ethyl acetate, dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum. The residue, which was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19) as the mobile phase, produced a white solid 2,5-[$^2H_6$]-dimethoxy-4-ethylthiobenzaldehyde (**12a**), (2.90 g, 12.5 mmol). Yield: 94%. m.p.: 85–86°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.35 (s, 1 H), 7.24 (s, 1 H), 6.76 (s, 1 H), 3.03 (q, $J = 7.4$ Hz, 2 H), 1.44 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 188.8, 156.9, 150.0, 137.6, 121.2, 109.0, 107.2, 55.9–54.8 (m), 25.0, 13.3. IR (KBr, thin film): 3120, 3066, 3039, 2967, 2927, 2869, 2231, 2208, 2123, 2069, 1660, 1594, 1477 cm^{-1}. MS-FAB (*m*/*z*): 233 ($M^+ + 1$, 100), 232 (44), 204 (2), 203 (3), 75 (15). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_{11}H_8D_6O_3S$, 232.1034; found 232.1040.

*Synthesis of 2,5-[$^2H_6$]-dimethoxy-4-propylsulfanyl-benzaldehyde (***12b***).* A mixture of $POCl_3$ (1.39 ml, 14.9 mmol) and *N,N*-dimethylformamide (1.39 ml, 18.0 mmol) was heated to 100°C. To this solution was added 2,5-[$^2H_6$]-dimethoxyphenyl *n*-propyl sulfide (**11b**), (1.30 g, 6.0 mmol) and the mixture was heated for additional 20 min at 100°C. This mixture was then added to a well-stirred warm water (pre-heated to 55°C) and stirred for 1.5 h by which time the oily phase had completely solidified. The solids was isolated by filtration, and washed with additional water. These solids were dissolved in ethyl acetate, dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum. The residue, which was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19) as the mobile phase, produced a yellow solid

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2,5-[$^2H_6$]-dimethoxy-4-(n-propyl-thio)benzaldehyde (**12b**), (1.26 g, 5.1 mmol). Yield: 86%. m.p.: 82–83°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.35 (s, 1 H), 7.24 (s, 1 H), 6.76 (s, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 1.82–1.75 (m, 2 H), 1.12 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 188.6, 156.9, 150.1, 137.8, 121.3, 110.4, 107.3, 56.0–55.2 (m), 32.9, 21.7, 13.6. IR (KBr): 3037, 3035, 2964, 2927, 2859, 2221, 2069, 1670, 1589, 1481, 1405, 1267, 1226 cm^{-1}. MS-FAB (m/z): 247 ($M^+ + 1$, 100), 246 (38), 133 (10), 75 (6), 43 (4). HRMS-FAB: [M^+] calculated for $C_{12}H_{10}D_6O_2S$, 246.1191; found 246.1195.

Synthesis of 1-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxy-4-(2-nitrovinyl)benzene (**13a**). Anhydrous ammonium acetate (92 mg) was added to a solution of 2,5-[$^2H_6$]-dimethoxy-4-(ethylthio)benzaldehyde (**12a**), (2.80 g, 12.0 mmol) in nitromethane (22.9 ml, 420.0 mmol), and the mixture was heated under reflux for 80 min (the reaction progress must be monitored by thin layer chromatography (TLC), to determine the point at which the starting aldehyde has been consumed). Excess nitromethane was removed under vacuum leaving an orange–red crystal of 1-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxy-4-(2-nitrovinyl)benzene (**13a**), (3.15 g, 11.4 mmol). Yield: 95%. m.p.: 153–154°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.14 (d, J = 13.5 Hz, 1 H), 7.86 (d, J = 13.5 Hz, 1 H), 6.82 (s, 1 H), 6.76 (s, 1 H), 3.03 (q, J = 7.4 Hz, 2 H), 1.42 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 154.3, 150.2, 137.1, 135.2, 134.3, 115.4, 112.1, 109.5, 56.1–55.0 (m), 25.3, 13.5. IR (KBr, thin film): 3097, 2975, 2931, 2227, 2069, 1612, 1594, 1490, 1413, 1342, 1247, 1226 cm^{-1}. MS-FAB (m/z): 276 ($M^+ + 1$, 3), 257 (2), 247 (2), 217 (7), 215 (3), 75 (1 0 0), 74 (17). HRMS-FAB (m/z): [M^+] calculated for $C_{12}H_9D_6NO_4S$, 275.1092; found 275.1104.

Synthesis of 1,4-[$^2H_6$]-dimethoxy-2-(2-nitrovinyl)-5-propylsulfanylbenzene (**13b**). Anhydrous ammonium acetate (39 mg) was added to a solution of 2,5-[$^2H_6$]-dimethoxy-(*n*-propylthio)benzaldehyde (**12b**), (1.26 g, 5.1 mmol) in nitromethane (9.79 ml, 180.0 mmol, and the mixture was heated under reflux for 1 h (this reaction progress must be monitored by TLC, to determine the point at which the starting aldehyde has been consumed). Excess nitromethane was removed under vacuum leaving an orange–red crystal of 1,4-[$^2H_6$]-dimethoxy-2-(2-nitrovinyl)-5-propylsulfanylbenzene (**13b**), (1.41 g, 4.9 mmol). Yield: 95%. m.p.: 121–122°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.14 (d, J = 13.5 Hz, 1 H), 7.85 (d, J = 13.6 Hz, 1 H), 6.82 (s, 1 H), 6.76 (s, 1 H), 2.96 (t, J = 7.2 Hz, 1 H), 1.83–1.71 (m, 2 H), 1.11 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 154.3, 150.2, 136.9, 135.2, 134.6, 115.3, 112.0, 109.3, 56.1–54.7 (m), 33.1, 21.9, 13.6. IR (KBr, thin film): 3142, 2967, 2940, 2070, 1616, 1602, 1553, 1490, 1387, 1342, 1275, 1239, 1100 cm^{-1}. MS-FAB (m/z): 290 ($M^+ + 1$, 46), 289 (12), 274 (46), 260 (8), 246 (19), 244 (1 0 0), 218 (12), 43

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(46). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_{13}H_{11}D_6NO_4S$, 289.1249; found 289.1250.

*Synthesis of 2-(4-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxyphenyl) ethylamine (***14a***)*. A suspension of lithium aluminum hydride (2.20 g, 58.0 mmol) in anhydrous tetrahydrofuran (93.4 ml) in an ice-bath was stirred under helium and fuming sulfuric acid (1.54 ml) added to this mixture, (*Caution*: Add fuming sulfuric acid with extreme caution, as adding too fast may catch fire.) After stirring for 1 min, to this solution was added a solution of 1-ethylsulfanyl-2,5-[$^2H_6$]-dimethoxy-4-(2-nitrovinyl)benzene (**13a**), (3.15 g, 11.4 mmol) in tetrahydrofuran (44.8 ml), and the mixture was stirred for further 5 min at 0°C. After the reaction mixture had warmed to room temperature, it was stirred for 1 h and the temperature was increased to 40°C, and stirred for a further 30 min. Excess hydride was destroyed by the cautious addition of wet tetrahydrofuran (2.4 ml of water and 11.6 ml of tetrahydrofuran), followed by adding 5% aqueous sodium hydroxide to stop the reaction. The reaction mixture was filtered through celite, and the filter cake was washed with tetrahydrofuran. The solvents were removed from the combined filtrates, and the residue was acidified by adding sulfuric acid (1 M). The acidic aqueous phase was washed with dichloromethane. After making the aqueous phase basic with 25% aqueous sodium hydroxide, aqueous phase was extracted with dichloromethane. The extracts were pooled and the solvent was removed under vacuum to provide 2,5-[$^2H_6$]-dimethoxy-4-ethylthiophenethylamine (**14a**). This crude product was dissolved in diethyl ether (50 ml), and then treated with hydrogen chloride. The solid was collected by filtration, and then purified by recrystallization using ethanol and diethyl ether to give 2,5-[$^2H_6$]-dimethoxy-4-ethylthiophenethylamine.HCl (**14a**.HCl), (2.17 g, 7.64 mmol). Yield: 67%. ^{1}H NMR (300 MHz, D_2O, δ): 6.90 (s, 1 H), 6.84 (s, 1 H), 3.14–3.09 (t, J = 7.1 Hz, 2 H), 2.88–2.81 (m, 4 H), 1.16 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (75 MHz, D_2O, δ): 151.7, 151.0, 124.0, 122.8, 114.3, 113.4, 55.9–55.4 (m), 39.6, 27.8, 26.2, 13.3. IR (KBr, thin film): 2956, 2904, 2751, 2657, 2555, 2061, 2048, 1608, 1486, 1400, 1226, 1059 cm^{-1}. MS-FAB (*m*/*z*): 248 (M^+-Cl, 95), 233 (8), 231 (100), 218 (32), 217 (14), 75 (6). HRMS-FAB (*m*/*z*): [M^+-Cl] calculated for $C_{12}H_{14}D_6NO_2S$, 248.1585; found 248.1597.

*Synthesis of 2-(2,5-[$^2H_6$]-dimethoxy-4-propylsulfanyl-phenyl)ethylamine (***14b***)*. A suspension of lithium aluminum hydride (0.77 g, 20.0 mmol) in anhydrous tetrahydrofuran (20.2 ml) in an ice-bath was stirred under helium and fuming sulfuric acid (0.50 ml) added to this mixture, (*Caution*: Add fuming sulfuric acid with extreme caution, as adding too fast may catch fire.) After stirring for 1 min, to this solution was added a solution of 1,4-[$^2H_6$]-dimethoxy-2-(2-nitrovinyl)-5-propylsulfanylbenzene (**13b**), (1.30 g, 4.5 mmol) in tetrahydrofuran (7.5 ml), and the mixture was heated under reflux for 10 hr. After the reaction mixture had

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cooled to room temperature, excess hydride was destroyed by the cautious addition of 2-propanol (3.32 ml), followed by 5% aqueous sodium hydroxide to stop the reaction. The reaction mixture was filtered through celite, and the filter cake was washed with tetrahydrofuran, 2-propanol and diethyl ether. The solvents were removed from the combined filtrates, and the residue was acidified by adding sulfuric acid (1 M). The acidic aqueous phase was washed with dichloromethane. After making the aqueous phase basic with 25% aqueous sodium hydroxide, the aqueous phase was extracted with dichloromethane. The extracts were pooled and the solvent was removed under vacuum to provide 2,5-[$^2H_6$]-dimethoxy-4-*n*-propylthiophenethylamine hydrochloride (**14b**). This crude product was dissolved in diethyl ether (50 ml), and then treated with hydrogen chloride. The solid was collected by filtration, and then purified by recrystallization using ethanol and diethyl ether to give 2,5-[$^2H_6$]-dimethoxy-4-*n*-propylthiophenethylamine.HCl (**14a**.HCl), (0.47 g, 1.8 mmol). Yield: 40%. ^{1}H NMR (300 MHz, D_2O, δ): 6.92 (s, 1 H), 6.85 (s, 1 H), 3.16 (t, $J = 7.1$ Hz, 2 H), 2.90–2.82 (m, 4 H), 1.57–1.49 (m, 2 H), 0.92 (t, $J = 7.3$ Hz, 3 H). ^{13}C NMR (75 MHz, CD_3OD, δ): 151.8, 151.7, 124.4, 122.9, 113.8, 112.5, 55.1–54.0 (m), 39.4, 33.7, 28.3, 22.1, 12.3. IR (KBr, thin film): 2958, 2923, 2904, 2819, 2753, 2657, 2460, 2213, 2048, 1484, 1400, 1222 cm^{-1}. MS-FAB (*m*/*z*): 262 (M^+-Cl, 96), 247 (5), 245 (100), 232 (22), 203 (7), 189 (7). HRMS-FAB (*m*/*z*): [M^+-Cl] calculated for $C_{13}H_{16}D_6NO_4S$, 262.1742; found 262.1744.

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