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Synthesis of deuterium-labeled cyamemazine and monodesmethyl cyamemazine

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A novel approach is presented for the synthesis of cyamemazine maleate and *N*-desmethyl cyamemazine maleate using a 10-(amino-2-methylpropyl)phenothiazine derivative. This method was successfully applied to the synthesis of [$^2H_6$] cyamemazine maleate and *N*-desmethyl-[$^2H_3$]cyamemazine maleate. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: schizophrenia; [$^2H_6$]cyamemazine maleate; *N*-desmethyl-[$^2H_3$]cyamemazine maleate; antipsychotic; cyamepromazine; deuterium labeled

Introduction

Cyamemazine (Tercian) also known as Cyamepromazine is a phenothiazine aliphatic chain class neuroleptic low-medium potency first generation typical antipsychotic drug.[1] Cyamemazine differs from other phenothiazine neuroleptics in the nature of its pharmacological profile. It is used for the management of schizophrenia[2] but is especially useful as a treatment for psychosis-associated anxiety due to its anxiolytic properties.[3] It has also been used for the treatment of affective disorders, anxiety restlessness, and benzodiazepine withdrawal syndrome.[2]

Although cyamemazine is classed as a typical antipsychotic, several studies have shown that in addition to acting as a dopamine D_2 antagonist, it has a potent antagonistic effect on serotonin receptors (5-HT_{2A}, 5-HT_{2C}, and 5-HT_3).[4,5] These actions are thought to be responsible for its anxiolytic properties. The anxiolytic effects of cyamemazine were studied in mice, but results were inconclusive.[3] This discrepancy was attributed to the combined activity of cyamemazine on dopamine D_2 receptors and 5-HT_{2C} and 5-HT_3 receptors. This explains the activity of cyamemazine in the management of alcohol withdrawal and benzodiazepine withdrawal syndrome. Cyamemazine is metabolized in liver into two major metabolites, one of which is monodesmethyl cyamemazine.[6] Samples of both compounds labeled with stable isotopes were required as internal standards for the quantification of cyamemazine and monodesmethyl cyamemazine in biological samples.

Despite modern developments in bio-analytical techniques, compounds labeled with stable isotopes are extremely valuable as internal standards in the analysis of samples from metabolic studies. A well-designed labeled compound can provide high quality information about the identity and quantification of drug-related compounds in biological samples. This information can be very useful at key decision points in drug development.

Several synthetic approaches were known for the synthesis of cyamemazine[7–9] and monodesmethyl cyamemazine,[6] but the synthesis of labeled [$^2H_6$]cyamemazine maleate and monodesmethyl [$^2H_3$]cyamemazine maleate was not known. In this study, we developed a novel synthetic approach for the cyamemazine maleate, [$^2H_6$]cyamemazine maleate, monodesmethyl cyamemazine maleate, and [$^2H_3$]monodesmethyl cyamemazine maleate. The commercial synthesis of cyamemazine involves treating the sodium salt of 3-cyanophenothiazine with 1-dimethyl-amino-2-methyl-3-chloropropane hydrochloride.[7] It was envisaged that the synthesis of deuterium-labeled cyamemazine derivatives using the manufacturing route would be difficult. Therefore, an alternate synthesis was developed in which both cyamemazine and monodesmethyl cyamemazine could be prepared from a common intermediate, namely, 10-(amino-2-methylpropyl)phenothiazine derivative (**7**).

Scheme 1 depicts the synthetic route for the preparation of unlabeled cyamemazine maleate (**8**), and Scheme 2 represents the synthesis of [$^2H_6$]cyamemazine maleate (**9**). 2-Methyl-1, 3-propanediol (**1**) was selectively monotosylated[10] to give 1-tosyl-2-methyl-3-propanol, which was treated with potassium phthalimide in DMF at 90 °C to give phthalimido propanol derivative[11] (**3**). The phthalimido propanol derivative was halogenated[12] with iodine, triphenylphophine, and imidazole in THF at 0 °C to yield iodine compound (**4**), which reacted with the sodium salt of 3-cyanophenothiazine (**5**) in DMF at room temperature to give phthalimido phenothiazine derivative[7] (**6**). The phthalimide group in compound (**6**) was deprotected[13] with hydrazine monohydrate in ethanol at 70 °C to give the common intermediate 10-(amino-2-methylpropyl)phenothiazine derivative (**7**). The amine (**7**) was treated with dimethyl sulfate (Scheme 1) and dimethyl sulfate-d_6(Scheme 2) in THF at 60 °C to give the tertiary amines, which were treated with maleic acid in ethanol to obtain cyamemazine maleate (**8**) and [$^2H_6$]cyamemazine maleate (**9**), respectively, in separate experiments.

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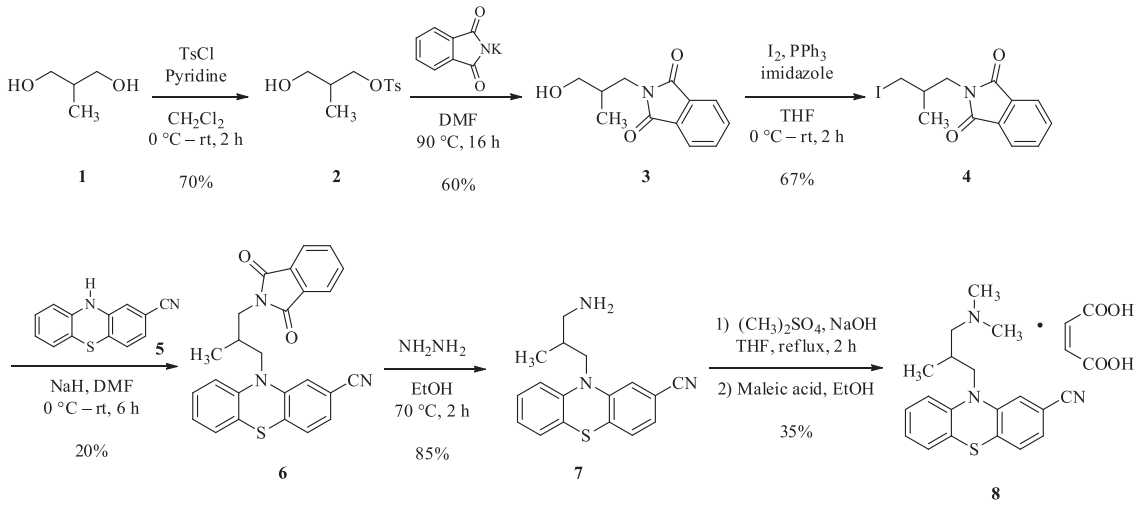
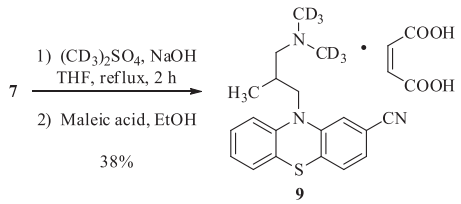


Scheme 1. Synthesis of cyamemazine maleate.



Scheme 2. Synthesis of [$^2H_6$] cyamemazine maleate.

Schemes 3 and 4 illustrate the synthesis of monodesmethyl cyamemazine maleate (**12**) and [$^2H_3$]monodesmethyl cyamemazine maleate (**14**), respectively. The common intermediate (**7**) was protected[14] with di-*tert*-butyl dicarbonate. The phenothiazine carbamate was *N*-methylated[15] with NaH/CH_3I and NaH/CD_3OTs[16], separately to give *N*-methyl phenothiazine carbamate derivatives (**11**) and (**13**), respectively. The carbamate deprotetction of *N*-methylphenothiazine carbamates (**11**) and (**13**) was carried out separately with HCl in MTBE. The secondary amines were treated with maleic acid in ethanol to afford monodesmethyl cyamemazine maleate (**12**) and [$^2H_3$]monodesmethyl cyamemazine maleate (**14**), respectively in separate experiments.

Experimental

General

All reagents were purchased from commercial sources and were used as received. ^{1}H NMR spectra were obtained on a Bruker (Methyl *tert* Butylether) AVANCE 300 spectrometer at 300 MHz or Bruker AVANCE 400 spectrometer at 400 MHz with tetramethylsilane used as an internal reference. Thin layer chromatography (TLC) was performed using Whatman No. 4500–101 (Diamond No. MK6F silica gel 60 Å) plates. Visualization of TLC plates was performed using UV light (254 nm). HPLC was obtained on an Agilent HPLC using ZORBAX Eclipse XDB-C18, 150mm × 4.6 mm, 5 μm.

*Synthesis of 3-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (**2**)*

To a stirred solution of **1** (50.0 g, 0.554 mol, 1.0 equiv) in CH_2Cl_2 (500 mL) was added pyridine (105.26 g, 1.385 mol, 2.5 equiv) and cooled at 0 °C under nitrogen atmosphere. Then, solid tosyl chloride (94.8 g, 0.499 mol, 0.9 equiv) was added portion wise slowly under nitrogen atmosphere. After completion of addition, the reaction mass was stirred at same temperature about 3 h. When TLC (4:6, EtOAc/hexanes) showed complete consumption of the starting material, the reaction mixture was diluted with water (100 mL), stirred well, separated the organic layer, washed with 2 M HCl (100 mL) then with sat. $NaHCO_3$ soln (50 mL), dried over Na_2SO_4, and evaporated to dryness to give crude, which was purified by column chromatography to afford **2** (92.0 g, 70%,) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.03–4.00 (m, 2H), 3.58–3.52 (m, 2H), 2.45 (s, 3H), 2.05–1.95 (m, 1H), 0.92 (d, J = 7.2 Hz, 3H); MS (MM) *m/z* 245 $[M+H]^+$.

*Synthesis of 2-(3-hydroxy-2-methylpropyl) isoindoline-1, 3-dione (**3**)*

To a stirred solution of **2** (50.0 g, 0.204 mol, 1.0 equiv) in DMF (250 mL) was added potassium phthalimide (45.5 g, 0.245 mol, 1.2 equiv) and stirred the reaction mixture at 90°C about 16 h under nitrogen atmosphere. When TLC (2:8, EtOAc/hexanes) showed complete consumption of the starting material, the reaction mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL), dried over Na_2SO_4, and evaporated to dryness to give crude, which was purified by column chromatography to afford **3** (27.0 g, 60%,) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.85 (m, 2H), 7.75–7.72 (m, 2H), 3.72 (d, J = 6.0 Hz, 2H), 3.54–3.50 (m, 1H), 3.39–3.35 (m, 1H), 2.77 (bs, 1H), 2.11–2.01 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H). MS (MM) *m/z* 220 $[M+H]^+$.

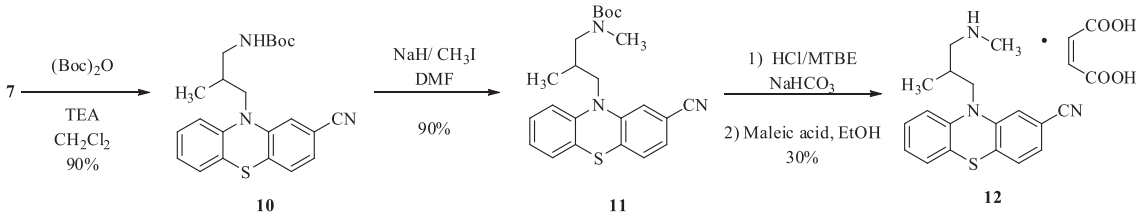
*Synthesis of 3 2-(3-iodo-2-methylpropyl) isoindoline-1, 3-dione (**4**)*

To a stirred solution of **3** (130 g, 0.593 mol, 1.0 equiv) in THF (800 mL) was added triphenylphosphine (233 g, 0.89 mol, 1.5 equiv) followed by addition of imidazole (80.0 g, 1.18 mol, 2.0 equiv) and cooled at 0 °C under nitrogen atmosphere. Then, solid iodine (180 g, 0.71 mol, 1.2 equiv) was added portion wise slowly under nitrogen atmosphere. After completion of addition, the reaction mass was stirred at room temperature about 3 h. When TLC (4:6, EtOAc/hexanes) showed complete consumption of the starting material, the reaction mixture was diluted with water (1000 mL) and extracted with EtOAc (2 × 500 mL), dried over Na_2SO_4, and evaporated to dryness to give crude, which was purified by column chromatography to afford **4** (130 g, 67%,) as a colorless solid.

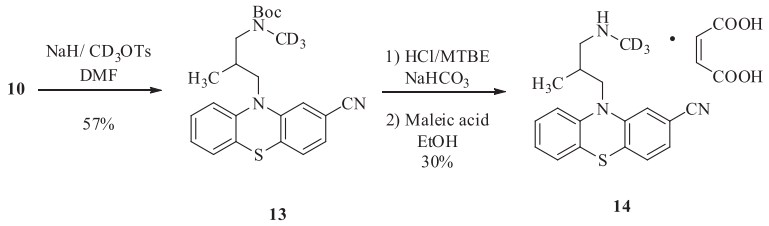
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.84 (m, 2H), 7.75–7.72 (m, 2H), 3.71–3.57 (m, 2H), 3.27–3.22 (m, 1H), 3.14–3.08 (m, 1H), 2.17–2.10 (m, 1H), 1.06 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 329 $[M+H]^+$.

*Synthesis of 10-(3-(1, 3-dioxoisoindolin-2-yl)-2-methylpropyl)-10H-phenothiazine-2-carbonitrile (**6**)*

To a stirred solution of 60% NaH (8.90 g, 0.223 mol, 2.0 equiv) in DMF (100 mL) at 0 °C was added compound **5** (25.0 g, 0.111 mol, 1.0 equiv)



Scheme 3. Synthesis of monodesmethyl cyamemazine maleate.



Scheme 4. Synthesis of [$^2H_3$]monodesmethyl cyamemazine maleate.

in DMF (100 mL), and stirred under nitrogen for 30 min. Then, compound **4** (47.5 g, 0.145 mol, 1.3 equiv) in DMF (100 mL) was added slowly by maintaining a temperature of 0 °C about 30 min. After completion of addition, the reaction mixture was brought at room temperature and stirred about 16 h. TLC (2:8, EtOAc/hexanes) showed 10% of the starting material remains in the reaction mixture; the reaction mixture was diluted with water (500 mL) and extracted with MTBE (2 × 500 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give, crude which was purified by silica gel column chromatography to afford **6** (6.5 g, 15%) as pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.63–7.61 (m, 2H), 7.11–7.04 (m, 3H), 6.99–6.75 (m, 4H), 3.90–3.83 (m, 1H), 3.76–3.69 (m, 1H), 3.66–3.52 (m, 2H), 2.56–2.47 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H); MS (MM) *m/z* 426 $[M+H]^+$.

*Synthesis of 10-(3-amino-2-methylpropyl)-10H-phenothiazine-2-carbonitrile (**7**)*

To a stirred solution **6** (6.50 g, 15.3 mmol, 1.0 equiv) in ethanol (100 mL) was added 35% hydrazine hydrate(20 mL) and stirred under nitrogen for 70 °C about 4 h. When TLC (3:7, EtOAc/hexanes) showed completion of the starting material, the reaction mixture was diluted with MTBE (100 mL), and the precipitated solids were filtered and washed with MTBE (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **7** (4.00 g, 85%) as yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48–7.33 (m, 3H), 7.27–7.17 (m, 2H), 7.11–6.97 (m, 2H), 4.00–3.93 (m, 1H), 3.68–3.61 (m, 1H), 2.64–2.58 (m, 1H), 2.46–2.44 (m, 1H), 1.97–1.86 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 296 $[M+H]^+$.

*Synthesis of 10-(3-(dimethylamino)-2-methylpropyl)-10H-phenothiazine-2-carbonitrile maleate (**8**)*

To a stirred solution of **7** (500 mg, 1.69 mmol, 1.0 equiv) in THF (50 mL) was added dimethyl sulfate (250 mg, 1.86 mmol, 1.1 equiv) refluxed at 70 °C about 2 h. Then, the reaction mixture was cooled at 0 °C and was added a solution of NaOH (200 mg, 5.08 mmol, 3.0 equiv) in water (2.0 mL) followed by dimethyl sulfate(0.250 g, 1.86 mmol, 1.1 equiv) and refluxed the contents about 2 h. When TLC (1:9, MeOH/CH_2Cl_2) showed completion of the starting material, the reaction mixture was cooled at room temperature and diluted with water (50 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude, which was purified by silica gel column chromatography to obtain the tertiary amine, which was stirred in a solution of maleic acid (200 mg, 1.69 mmol, 1.0 equiv) in ethanol (10 mL) about 30 min. The precipitated solids were filtered out and dried to afford **8** (250 mg, 35%) as pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ9.13 (bs, 1H), 7.53–7.47 (m, 1H), 7.45–7.39 (m, 2H), 7.31–7.23 (m, 2H), 7.15–7.03 (m, 2H), 6.02(s, 2H), 3.98–3.78 (m, 2H), 3.05–2.99 (m, 2H), 2.69 (s, 6H), 2.30–2.27 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 324 $[M+H]^+$; HPLC >98%; m.p. 206–208 °C.

*Synthesis of [$^2H_6$]10-(3-(dimethylamino)-2-methylpropyl)-10H-phenothiazine-2-carbonitrile maleate (**9**)*

To a stirred solution of **7** (500 mg, 1.69 mmol, 1.0 equiv) in THF (30 mL) was added dimethyl sulfate-d_6(250 mg, 1.86 mmol, 1.1 equiv) refluxed at 70 °C about 2 h. Then, the reaction mixture was cooled at 0 °C and was added a solution of NaOH (200 mg, 5.08 mol, 3.0 equiv) in water (2.0 mL) followed by dimethyl sulfate-d_6(250 mg, 1.86 mmol, 1.1 equiv) and refluxed the contents about 2 h. When TLC (1:9, MeOH/CH_2Cl_2) showed completion of the starting material, the reaction mixture was cooled at room temperature and diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude, which was purified by silica gel column chromatography to obtain the tertiary amine, which was stirred in a solution of maleic acid (200 mg, 1.69 mmol, and 1.0 equiv) in ethanol (10 mL) about 30 min. The precipitated solids were filtered out and dried to afford **9** (0.28 g, 38%) as pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.06 (bs, 1H), 7.53–7.45 (m, 1H), 7.43–7.39 (m, 2H), 7.31–7.23 (m, 2H), 7.15–7.03 (m, 2H), 6.02(s, 2H), 3.98–3.78 (m, 2H), 3.04–2.99 (m, 2H), 2.30–2.29 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 330 $[M+H]^+$; HPLC >98%; m.p. 207–209 °C; isotopic abundance >99%.

Synthesis of tert-butyl (3-(2-cyano-10H-phenothiazin-10-yl)-2-methylpropyl)carbamate (**10**)

To a stirred solution of **7** (1.50 g, 5.08 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 0 °C was added triethylamine(1.40 mL, 1.016 mmol, 2.0 equiv) followed by di-*tert*-butyl dicarbonate (1.10 g, 5.08 mmol, 1.0 equiv) and stirred under nitrogen at room temperature about 3 h. When TLC (2:8, EtOAc/hexanes) showed completion of the starting material, the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude, which was purified by silica gel column chromatography to afford **10** (1.80 g, 90%) as pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26–7.15 (m, 4H), 7.05–7.6.99 (m, 2H)7.98, 6.91–6.88 (m, 1H), 4.80 (bs, 1H), 3.84–3.64 (m, 2H), 3.20–3.05 (m, 2H), 2.30–2.22 (m, 1H), 1.38 (s, 9H), 1.00 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 396 $[M+H]^+$.

Synthesis of tert-butyl (3-(2-cyano-10H-phenothiazin-10-yl)-2-methylpropyl)(methyl)carbamate (**11**)

To a stirred solution of 60% NaH (330 mg, 8.22 mmol, 2.5 equiv) in DMF (10 mL) at 0 °C was added compound **10** (1.30 g, 3.29 mmol, 1.0 equiv) in DMF (5 mL), stirred under nitrogen for 30 min. Then, methyliodide (0.50 mL, 8.22 mmol, 2.5 equiv) in DMF (10 mL) was added slowly by maintaining a temperature of 0 °C about 30 min. After completion of addition, the reaction mixture was brought at room temperature and stirred about 5 h. When TLC (2:8, EtOAc/hexanes) showed completion of the starting material, the reaction mixture was diluted with water (50 mL) and extracted with Methyl *tert* Butylether (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude, which was purified by silica gel column chromatography to afford **11** (1.20 g, 90%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.06 (m, 4H), 6.94–6.91 (m, 2H), 6.81–6.78 (m, 1H), 3.77–3.74 (m, 1H), 3.59–3.52 (m, 1H), 3.29–3.26 (m, 1H), 3.06–3.04 (m, 1H), 2.73 (s, 3H) 2.36–2.26 (m, 1H), 1.37 (s, 9H), 0.91 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 410 $[M+H]^+$.

*Synthesis of 10-(2-methyl-3-(methylamino)propyl)-10H-phenothiazine-2-carbonitrile maleate (**12**)*

To a stirred solution of **11** (500 mg, 1.21 mmol, 1.0 equiv) in Methyl *tert* Butylether (5 mL) was added 20% solution of HCl in Methyl *tert* Butylether (20 mL) at 0 °C and stirred at room temperature about 16 h. The precipitated solids were filtered and neutralized with sat. $NaHCO_3$ solution (30 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain secondary amine residue, which was stirred in a solution of maleic acid (140 mg, 1.21 mmol, 1.0 equiv) in ethanol (10 mL) about 30 min. The precipitated solids were filtered out and dried to afford **12** (150 mg, 30%) as pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (bs, 1H), 7.49–7.39 (m, 3H), 7.30–7.23 (m, 2H), 7.13–7.02 (m, 2H), 6.01(s, 2H), 3.99–3.92 (m, 1H),3.84–3.77 (m, 1H),3.03–2.97 (m, 1H),2.86–2.79 (m, 1H), 2.54 (s, 3H), 2.30–2.29 (m, 1H), 0.99 (d, J = 6.6Hz, 3H); MS (MM) *m/z* 310 $[M+H]^+$; HPLC >98%; m.p. 203–205 °C.

Synthesis of [$^2H_3$] tert-butyl (3-(2-cyano-10H-phenothiazin-10-yl)-2-methylpropyl)(methyl)carbamate (**13**)

To a stirred solution of 60% NaOH (130 mg, 3.16 mmol, 2.5 equiv) in DMF (10 mL) at 0 °C was added compound **10** (500 mg, 1.26 mmol, 1.0 equiv) in DMF (5 mL), stirred under nitrogen for 30 min. Then, CD_3OTs (5.94 g, 3.16 mol, 2.5 equiv) in DMF (10 mL) was added slowly by maintaining a temperature of 0 °C about 30 min. After completion of addition, the reaction mixture was brought at room temperature and stirred about 5 h. When TLC (2:8, EtOAc/hexanes) showed the completion of the starting material remains in the reaction mixture, the reaction mixture was diluted with water (50 mL) and extracted with Methyl *tert* Butylether (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude, which was purified by silica gel column chromatography to afford **13** (300 mg, 57%) as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.13 (m, 4H), 7.01–6.88 (m, 3H), 3.86–3.74 (m, 1H), 3.66–3.59 (m, 1H), 3.36–3.33 (m, 1H), 3.12–3.09 (m, 1H), 2.36–2.26 (m, 1H), 1.43 (s, 9H), 0.98 (d, J = 6.6 Hz, 1H); MS (MM) *m/z* 413 $[M+H]^+$.

*Synthesis of [$^2H_3$]10-(2-methyl-3-(methylamino)propyl)-10H-phenothiazine-2-carbonitrile maleate (**14**)*

To a stirred solution of **13** (250 mg, 0.605 mmol, 1.0 equiv) in Methyl *tert* Butylether (5 mL) was added 20% solution of HCl in MTBE(10 mL) at 0 °C and stirred at room temperature about 16 h. The precipitated solids were filtered and neutralized with sat. $NaHCO_3$ solution (15 mL) and extracted with EtOAc (2 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain secondary amine residue, which was stirred in a solution of maleic acid (70 mg, 0.605 mmol, 1.0 equiv) in ethanol (5 mL) about 30 min. The precipitated solids were filtered out and dried to afford **14** (70 mg, 30%) as pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.26 (bs, 1H), 7.50–7.39 (m, 3H), 7.31–7.23 (m, 2H), 7.13–7.02 (m, 2H), 6.02(s, 2H), 3.99–3.93 (m, 1H),3.84–3.77 (m, 1H),3.03–2.97 (m, 1H), 2.86–2.79 (m, 1H), 2.30–2.29 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H); MS (MM) *m/z* 313 $[M+H]^+$; HPLC >98%; m.p. 205–206 °C; isotopic abundance >98%.

Results and discussion

The identity and purity of the cyamemazine derivatives synthesized were confirmed by ^{1}H NMR, MS, and HPLC analyses. After recrystallization from ethanol, all cyamemazine maleate derivatives were obtained as pale yellow needles with melting points in the expected range. The deuterium incorporation in [$^2H_6$]cyamemazine was >99% and in [$^2H_3$] monodesmethyl cyamemazine was >98%. This corresponds well with the reported deuterium abundance for the labeled starting material (CD_3OTs, >98% atom D) and indicates that there was no loss of deuterium by exchange during the syntheses. These compounds were considered to be of acceptable quality for use as internal standards in bio-analytical studies

Conclusion

We have reported a novel procedure for the synthesis of maleate derivatives of cyamemazine and monodesmethyl cyamemazine. This was successfully applied in the synthesis of deuterium-labeled derivatives [$^2H_6$]cyamemazine and [$^2H_3$]monodesmethyl cyamemazine maleate.

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Conflict of Interest

The authors did not report any conflict of interest.

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