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Efficient synthesis of deuterium labeled hydroxyzine and aripiprazole

Mohit Vohra,* Mahendra Sandbhor, and Andrew Wozniak

Hydroxyzine and aripiprazole are active pharmaceutical ingredients that have been largely acknowledged for their antipsychotic properties. Deuterium labeled isotopes of hydroxyzine and aripiprazole are internal standards that can aid in the further research of non-isotopic forms via quantification analysis using HPLC-MS/MS.

The synthesis of hydroxyzine-d_8 was accomplished by coupling piperazine-d_8 with 4-chlorobenzhydryl chloride followed by the reaction of the first intermediate with 2-(2-chloroethoxy) ethanol to afford 11.7% of hydroxyzine-d_8 with 99.5% purity. The synthesis of aripiprazole-d_8 was also achieved in two steps. 1,4-Dibromobutane-d_8 reacted with 7-hydroxy-3,4-dihydro-2(1H)-quinolinone. The first intermediate was then coupled with 1-(2, 3-dichlorophenyl)piperazine hydrochloride to produce 33.4% of aripiprazole-d_8 with 99.93% purity.

Keywords: hydroxyzine; aripiprazole; internal standard; deuterium label; synthesis

Introduction

2-[2-[4-[(4-Chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]ethanol (hydroxyzine) and 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one (aripiprazole) are active pharmaceutical ingredients that have been widely recognized for their efficacy in managing various psychotic disorders. Despite their similar antipsychotic properties, both drugs differ substantially in their mechanism of action.

Hydroxyzine, which is marketed under the commercial name Vistaril™ (Toronto Research Chemicals, Toronto, ON), primarily acts as a receptor antagonist. Hydroxyzine's ability to inhibit the activity of cholinergic, adrenergic, and serotonergic receptors underlies its success in reducing the physical and psychological manifestations of anxiety and depression.[1,2] Aripiprazole, commercially known as Abilify™ (Toronto Research Chemicals, Toronto, ON), is a second generation antipsychotic drug that is commonly prescribed to patients suffering from schizophrenia, bipolar disorder, and major depression.[3] The widespread effectiveness of this drug is due to its action as a partial dopamine and serotonin receptor agonist, and also as an adrenergic and muscarinic antagonist.[4,5]

Although a significant amount of information is known about the action of hydroxyzine and aripiprazole, further research is being conducted to evaluate the suitability of both active pharmaceutical ingredients in treating a broader range of medical conditions.[6–8] As part of these studies, it is important to have an internal standard that will help to measure the metabolism and elimination of hydroxyzine and aripiprazole. Labeled isotopes are ideal internal standards because they allow for accurate quantification of drug metabolites via liquid chromatography-tandem mass spectrometry (LC-MS/MS).[9] Aripiprazole-d8 and hydroxyzine-d8 are available commercially from CDN isotopes and AlsaChim (Illkirch Graffenstaden, France), respectively. While previous research has successfully demonstrated the synthesis of ^{14}C-labeled aripiprazole[10] and deuterated aripiprazole,[11] no studies have been reported regarding the synthesis of deuterium labeled hydroxyzine. The following paper describes an efficient and economically feasible method of synthesizing hydroxyzine-d_8 and aripiprazole-d_8.

Experimental

Deuterated materials were purchased from CDN Isotopes Inc (Leacock Pointe-Claire, QC). All other chemicals and solvents were obtained from commercial sources without further purification. Mass spectra were recorded using Waters (Micromass ZQ, Milford, MA) equipped with a Thermo Betasil C18 (Thermo Hypersil-Keystone, Bellefonte, PA) (150 × 2.1 mm, 3 μ). ^{1}H NMR spectra were recorded on a Varian AS500 instrument (Varian Medical Systems, Inc., Hansen Way Palo Alto, CA). Liquid chromatography–mass spectrometry (LC-MS) was recorded using column: Thermo Betasil C18 (150 × 2.1 mm, 3 μ) and gradient solvents [mobile phase A (100:0.1, water/trifluoroacetic acid); mobile phase B (100:0.1, acetonitrile/trifluoroacetic acid).

Chromatography on silica gel columns was performed using Merck silica gel 60 (Merck KGaA, Darmstadt, Germany) (230–400 meshes), and analytical thin layer chromatography (TLC) was conducted on a glass plate coated with a 0.25 cm thin layer of silica gel 60F_{254} Whatman (Whatman PLC, Maidstone Kent, United Kingdom).

1-[(4-Chlorophenyl)phenylmethyl]piperazine-d_8 (3)

Piperazine-d_8 (**2**) (1.0 g, 10.6 mmol, 98% D enrichment) was dissolved in acetonitrile (15 ml), followed by the addition of potassium carbonate (0.58 g, 4.2 mmol) and 4-chlorobenzhydryl chloride (**1**) (1.0 g, 4.2 mmol). The resulting reaction mixture was heated at 85°C and stirred overnight. The reaction was monitored via MS and TLC in methanol and dichloromethane (1:9) and showed almost complete conversion to the desired product **3** (*Rf* = 0.2). The reaction was optimized using unlabeled

Sussex Research Laboratories Inc., Ottawa, Ontario, Canada

**Correspondence to: Mohit Vohra, Sussex Research Laboratories Inc., Chemistry, Ottawa, Ontario, Canada.*
E-mail: mvohra@ucalgary.ca

material and monitored by LC-MS (UV detection). The unlabeled product (**3'**) showed retention time (R_t) of 18.12 min and dimer (**11**) showed R_t = 18.52 min. It was then brought at room temperature and diluted with acetonitrile (50 ml) and filtered. The filtrate was concentrated *in vacuo* and chromatographed on silica to furnish the desired product **3** as yellowish thick oil (1.0 g, 32.1% based on **2**).

^{1}H NMR ($CDCl_3$) ς 7.34–7.42 (4H, Ar), 7.18–7.32 (5H, Ar), 4.22 (1H, CH), 2.05 (1H, NH).

Electrospray ionization (ESI) for $C_{17}H_{11}D_8ClN_2$: 294 (M), 295 (M + 1).

2-(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy) ethanoldihydrochloride-d_8 (5)

About 1.0 g (3.4 mmol) of **3** was dissolved in acetonitrile (50 ml), followed by the addition of potassium carbonate (0.93 g, 6.73 mmol) and 2-(2-chloroethoxy)ethanol (**4**) (0.72 g, 5.78 mmol). The resulting reaction mixture was heated at 85°C and stirred overnight. TLC in methanol and dichloromethane (1:9) showed the desired product (*Rf* = 0.55). The reaction was also monitored by LC-MS (UV detection). The desired product (**5**) showed R_t of 11.90 min. The reaction was brought at room temperature and filtered. The filtrate was concentrated *in vacuo* and was chromatographed using 1–5% methanol in ethyl acetate. The pure oily compound obtained after concentration was dissolved in ether (150 ml) and then treated with 2N ethereal HCl (20 ml). The resulting white suspension was stirred for 20 min and filtered. The cake was washed with hexane and dried to furnish **5** (dihydrochloride salt) as white solid (0.61 g, 39%, 98% D enrichment).

^{1}H NMR (CD_3OD):ς 7.60–7.50 (4H, m, Ar), 7.40–7.32 (4H, m, Ar), 7.32–7.27(1H, m, Ar), 4.89 (1H, bs, CH), 3.81 (2H, t, *J* = 10 Hz), 3.69 (2H, t, *J* = 8 Hz), 3.59 (2H, t, *J* = 8 Hz), 3.41 (2H, t, *J* = 10 Hz).

ESI for $C_{21}H_{19}D_8ClN_2O_2$: 382 (M), 383(M + 1).

LC-MS UV detector purity: 99.5%.

7-(4-Bromobutoxy)-3,4-dihydro-2-(1*H*)-quinolinone-d_8 (8)

A mixture of 7-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**6**) (0.65 g, 3.98 mmol), potassium carbonate (1.1 g, 7.98 mmol), and 1,4-dibromobutane-d_8 (**7**) (5 g, 22.32 mmol, 99% D enrichment) in methyl ethyl ketone (MEK) (20 ml) was heated at 75°C in a 50-ml sealed flask overnight. TLC in ethyl acetate/hexanes (1:1) showed complete conversion to desired product (*Rf* = 0.75). The reaction was optimized using unlabeled material and monitored by LC-MS (UV detection). The product (**8'**) showed R_t = 8.21 min and dimer (**12**) showed R_t = 14.34 min. Potassium carbonate was removed by filtration and concentrated to produce a crude oil (7 g), which was subsequently purified by silica gel column chromatography. The non-polar fractions from hexanes recovered pure 1,4-dibromobutane-d_8 (**7**) (3.53 g). In the reaction, only 1.47 g (1.7 equivalents) of **7** was consumed. The desired product **8** was obtained as a white solid (0.97 g, 46.6%, calculated on the basis of **7** consumed) with ethyl acetate/hexanes (1:4).

^{1}H NMR ($CDCl_3$): ς 8.32 (1H, bs, NH), 7.05 (1H, d, *J* = 8 Hz), 6.53 (1H, dd, *J* = 8.5, 2 Hz), 6.35 (1H, d, *J* = 2.5 Hz), 2.91 (2H, t, *J* = 8 Hz), 2.63 (2H, t, *J* = 7 Hz).

ESI for $C_{13}H_8D_8BrNO_2$: 306 (M), 308 (M + 2), 613 (2M + 1).

7-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolinone-2(1*H*)-one-d_8 (10)

A mixture of 7-(4-bromobutoxy)-3,4-dihydro-2-(1*H*)-quinolinone-d_8 **8** (0.96 g, 3.13 mmol), 1-(2,3-dichlorophenyl)piperazine hydrochloride (**9**) (1 g, 3.76 mmol), and powdered sodium carbonate (797 mg, 7.52 mmol) in ethanol (15 ml) was heated at 80°C in a sealed reaction flask overnight. The reaction was monitored by LC-MS (UV detection). The desired product (**10**) showed R_t = 15.21 min. Ethanol was evaporated, and the solid mass was partitioned between ethyl acetate and water. The ethyl acetate layer was separated and washed with water and brine, dried over sodium sulfate and chromatographed. The final crude product was eluted with 1–5% methanol in ethyl acetate to afford the desired compound (1.02 g, 72%, 99% D enrichment) as a white solid.

^{1}H NMR ($CDCl_3$) ς 8.02 (1H, bs, NH), 7.17–7.13 (2H, m), 7.05 (1H, d, *J* = 8.5 Hz), 6.97 (1H, dd, *J* = 7.0, 2.0 Hz), 6.54 (1H, dd, *J* = 8.0, 2.5 Hz), 6.33 (1H, d, *J* = 2.5 Hz), 3.08 (4H, bs), 2.90 (2H, t, *J* = 8.0 Hz), 2.66 (4H, bs), 2.62 (2H, t, *J* = 8.0 Hz).

ESI for $C_{23}H_{19}D_8Cl_2N_3O_2$: 456.3 (M + 1), 458.3 (M + 3), 459.3 (M + 4).

LC-MS UV detector purity: 99.93%.

Results and discussion

Large-scale synthesis of non-deuterated hydroxyzine and its intermediates[12,13] and Aripiprazole[4] has been reported previously. However, we developed an efficient and economically feasible method of synthesizing hydroxyzine-d_8 and aripiprazole-d_8 to act as an internal standard.

For the purposes of preparing an effective standard, several deuterium atoms were introduced to prevent any discrepancies during mass spectrophotometry analysis. In the case of halogen containing compounds similar to hydroxyzine and aripiprazole, a minimum of five and six deuterium atoms are necessary. Mass increases below the M + 5 and M + 6 ranges may result in interference from the natural form of the compound and make it significantly more difficult to quantify drug levels.[9]

The synthesis of hydroxyzine-d_8 (**5**) was accomplished in two steps using piperazine-d_8 **2**. The use of any other deuterated materials was avoided because the addition of deuterium atoms to any alternative location on hydroxyzine would entail a greater number of steps and introduce a higher cost to the production process. In the first step, piperazine-d_8 (2.5 equivalents) was directly reacted with **1** in a sealed reaction flask capable of accommodating the vapor pressure of acetonitrile at 85°C. Intermediate **3** was purified via column chromatography and afforded a 32.1% yield based on the labeled piperazine. Hydroxyzine-d_8 was synthesized after coupling **3** with 2-(2-chloroethoxy) ethanol to account for an overall yield of 11.7% yield based on **2** following purification.

In a previous report,[12] the synthesis of non-isotopic hydroxyzine was accomplished using multiple equivalents of piperazine in

Table 1. Optimization of intermediate **3**

Equivalents of piperazine-d_8	Equivalents of 4-chlorobenzehydryl chloride	Equivalents of potassium carbonate	Percent dimer (11) formation[a] (%)
1.1	1	1	38.3
2.5	1	1	15.9
5	1	1	7.6

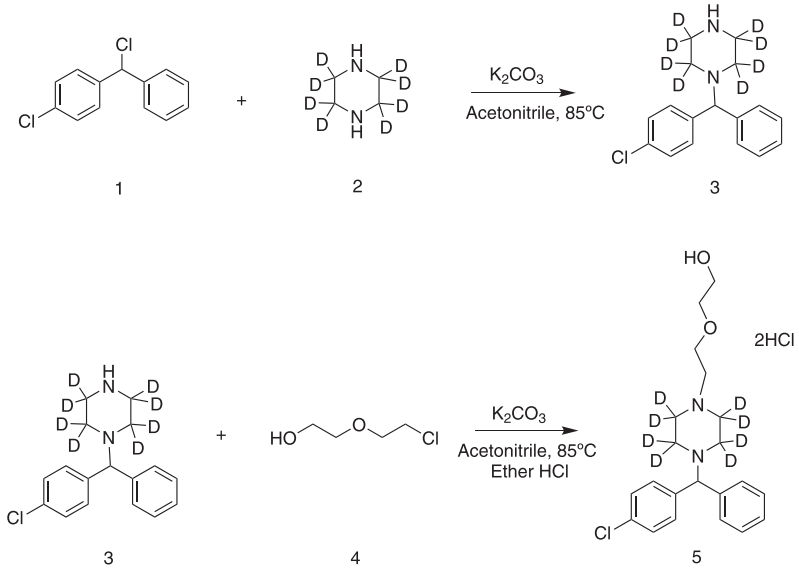
[a]Percent dimer formation was determined via LC-MS.

Table 2. Optimization of intermediate **8**

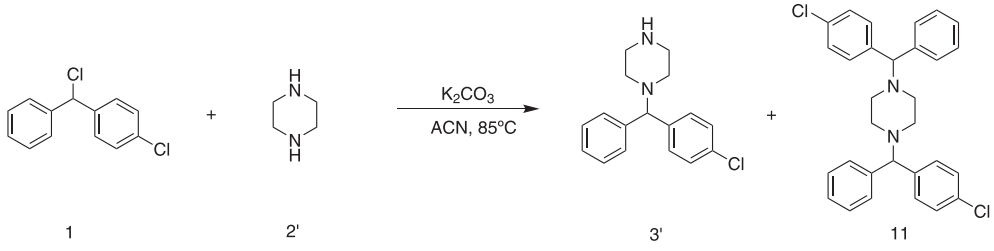
Equivalents of 1,4-dibromobutane-d_8	Equivalents of 7-hydrxy-3,4-dihydro-2(1H)-quinolinone	Equivalents of potassium carbonate	Percent dimer (12) formation[a] (%)
1	1	2	23
3	1	2	18
5.6	1	2	0

[a]Percent dimer formation was determined via LC-MS.

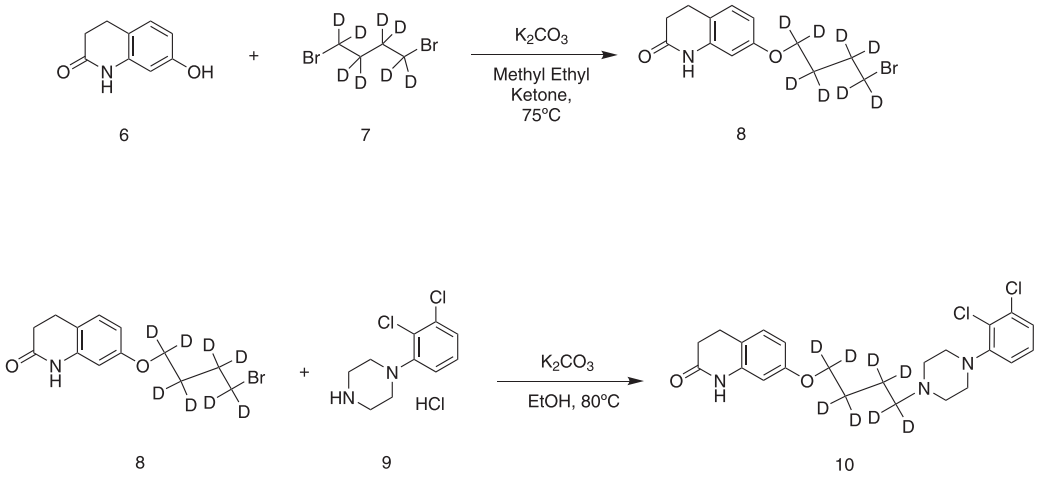
order to minimize dimer formation between piperazine and **1**. The approach taken in this patent[12] was attempted with piperazine-d_8 in modified conditions (shown in experimental section). In order to maximize the yield of **3**, the reaction conditions for step 1 were optimized using non-labeled piperazine. Three trial reactions were performed by reacting 1.1, 2.5, and 5 equivalents of piperazine **2′** with a single equivalent of **1** as shown in Table 1. As expected, it was found that an increase in the number of equivalents of **2′** was accompanied with lower dimer formation **11** and a higher yield of the desired compound **3′**. LC-MS analysis showed that the reaction with 1.1 and 2.5 equivalents of **2′** resulted in 38.3% and 15.9% of **11,** respectively. The least amount of dimer product,



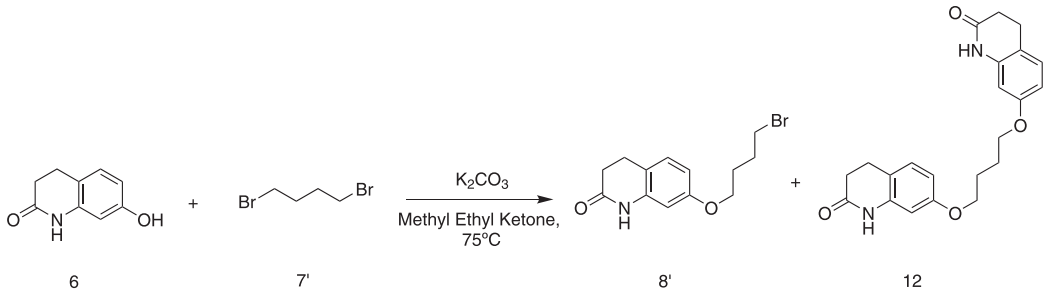
Scheme 1. Synthesis of hydroxyzine-d_8.



Scheme 2. Reaction optimization of step 1 in Scheme 1.



Scheme 3. Synthesis of aripiprazole-d_8.



Scheme 4. Reaction optimization of step 1 in Scheme 3.

7.6%, was noted when using 5 equivalents of **2′**. During our synthesis, 2.5 equivalents of piperazine-d_8 was used due to economic feasibility.

The synthesis of aripiprazole-d_8 (**10**) was completed in two convenient steps. 1,4-Dibromobutane-d_8 **7** (5.6 equivalents) was coupled with quinolinone **6** in a sealed reaction flask to furnish **8** in 46.6% yield. After column chromatography, further coupling was performed between **8** and **9** to produce the final compound **10**, accounting for an overall yield of 33.4% based on **7**.

Our major concern involved the formation of large amounts of dimer between 1,4-dibromobutane (**7′**) and **6**. In a previous paper[4] describing the synthesis of non-deuterated aripiprazole, 3 equivalents of **7′** was reacted with **6** in dimethylformamide, resulting in major dimer **12** formation. We performed a brief optimization study with varying equivalents of **7′** in order to improve the yield of **8′**. The reactions were performed in a sealed reaction flask at 75°C in MEK and potassium carbonate (2 equivalents). Under the same conditions, three trials were performed using 1, 3, and 5.6 equivalents of **7′**. It was observed by LC-MS analysis that the use of 1 and 3 equivalents of 1,4-dibromobutane did not result in reaction completion and lead to the formation of 23% and 18% of dimer **12** impurity, respectively, as shown in Table 2. However, the trial reaction with 5.6 equivalents of **7′** successfully went to completion after 12 h with minimal dimer formation.

In a previous patent,[11] the synthesis of aripiprazole-d_8 was reported using a two-step approach similar to ours but involved the use of potassium hydroxide and isopropanol.[13] The first step described in this patent resulted in a yield of 21.3% based on **7**, which is significantly less than the 46.6% yield obtained in our synthetic method. Moreover, in our approach, 85% of the unreacted 1,4-dibromobutane-d_8 (3.53 g) was conveniently recovered in pure form by column chromatography. This recovered material was subsequently reused in the same reaction with **6**, and resulted in an identical percentage yield as the original reaction. Therefore, the method described by us appears to be more efficient because a higher percent yield was obtained by consuming only 1.7 equivalents of **7** as opposed to the 3 equivalents used in the patent.[11] It is likely that our use of potassium carbonate rather than potassium hydroxide minimized halohydrin formation from 1,4-dibromobutane-d_8, which might have occurred in the patented method. Potassium carbonate and MEK are also a more convenient combination of base and solvent for this reaction compared with potassium hydroxide and isopropanol because excess potassium carbonate can be filtered off due to its insolubility in MEK. In addition, the use of potassium hydroxide at elevated temperatures may result in deprotonation of the isopropanol to form a weak base capable of causing further by-product formation; see Schemes 1–4.

Conclusion

The synthesis of hydroxyzine-d_8 and aripiprazole-d_8 was successfully accomplished in an economically feasible manner. Both molecules were produced by using multiple equivalents of either piperazine-d_8 or 1,4-dibromobutane-d_8 in the first step to avoid dimer formation. In order to improve the efficiency of these reactions, two brief optimization experiments were performed. Using the scheme described in this paper, hydroxyzine-d_8 and aripiprazole-d_8 can be synthesized and used as internal standards to aid in further research of the commercially marketed non-deuterated forms.

Conflict of Interest

The authors did not report any conflict of interest.

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