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Synthesis of deuterium-labeled zaleplon-d_5 as an internal standard

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Zaleplon is licensed for the short-term treatment of insomnia. Excessive usage causes side effects; hence, the drug is controlled. Identifying zaleplon in a drug abuser requires an isotope-labeled internal standard. This work presents a synthesis of stable isotope-labeled internal standard for zaleplon, zaleplon-d_5, by a five-step synthetic sequence.

Keywords: insomnia; abused drug; zaleplon; zaleplon-d_5; internal standard

Introduction

Drugs of abuse are typically detected and identified by gas chromatography-mass spectrometry (GC-MS) because of the high sensitivity of this method and its ability to separate complex mixtures of organic compounds.[1–4] Standard samples used for analyzing controlled drugs in Taiwan are very difficult to obtain. The use of deuterium-labeled controlled drugs as internal standards for use in GC-MS analysis is well documented.[5–9] This work describes a synthesis of zaleplon-d_5, which can serve as an internal standard for the identification of zaleplon by GC-MS analysis.

Zaleplon is a pyrazolopyrimidine sedative–hypnotic[10,11] agent for the treatment of insomnia.[11] Other members of this class include zopiclone, zolpidem and eszopiclone.[12] Zaleplon is a short acting benzodiazepine-like hypnotic drug, which is licensed for the short-term treatment of patients with insomnia who experience early morning awakening. It does not increase sleep duration, unlike other hypnotics.[13]

Investigations into the action of zaleplon have demonstrated that it selectively binds to the benzodiazepine type 1 site on the γ-aminobutyric acid subtype A ($GABA_A$) receptor/chloride-ion channel complex.[14,15] It has a short action onset time, peak plasma concentration time and elimination half-life of approximately 1 h each.[16] Zaleplon is effective in treating insomnia with fewer residual central nervous system or 'hangover' effects than are observed in patients on other drugs of the benzodiazepine group.[17–19] These advantages have resulted in an enormous increase in the use of zaleplon worldwide.

Zaleplon is reportedly a habit-forming drug, meaning that addiction may occur. Stopping this medication abruptly after prolonged or frequent use may cause major withdrawal effects, such as mood change, anxiety and restlessness.[20] Accompanying side-effects include hallucination,[10] severe confusion,[21] daytime drowsiness,[22] dizziness,[23] headache,[24,25] vomiting[20] and others.

Zaleplon is regulated as a controlled drug in some countries such as the United States,[26] because an increasing number of investigations have reported abuse and intoxication.[10,27,28] High-purity standards, including isotopically labeled analogs, are required to ensure accurate analyses of controlled substance and related compounds. To our knowledge synthesis of stable-labeled standard for analyzing zaleplon has not been published. Accordingly, an approach for synthesizing such a standard is described herein.

Results and discussion

Our first route to zaleplon-d_5 is shown in Scheme 1. Initially, 3′-nitroacetophenone **1** was treated with *N*,*N*-dimethylformamide dimethylacetal under reflux to yield the intermediate, enamide **2**.[29,30] Another key intermediate, 5-amino-1*H*-pyrazole-4-carbonitrile (**4**) was obtained by refluxing ethoxymethylenemalononitrile (**3**) and hydrazine hydrate in ethanol.[31] In the following step, compounds **4** and **2** underwent cyclization under mild acidic condition at reflux to yield 7-(3-nitro-phenyl)-pyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (**5**).[29] An efficient reduction of **5** using 10% Pd/C catalyst at an H_2 pressure of 60 psi gave 7-(3-amino-phenyl)-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**6**). The 3-amino phenyl pyrazolopyrimidine **6** was treated with an acetic anhydride and pyridine to produce acetamide **7**.[32]

Introduction of the isotopic label was attempted by treating acetamide **7** with ethyl iodide-d_5 in the presence of sodium hydride, under an inert atmosphere at 50°C. Unfortunately, the yield of zaleplon-d_5 so obtained was insignificant. Various alternative conditions were tried but the maximum yield obtained was only 20%.[33] The purification of zaleplon-d_5 was also problematical as zaleplon-d_5 could not be successfully crystallized and elution from a silica column was difficult. Therefore, this route was abandoned.

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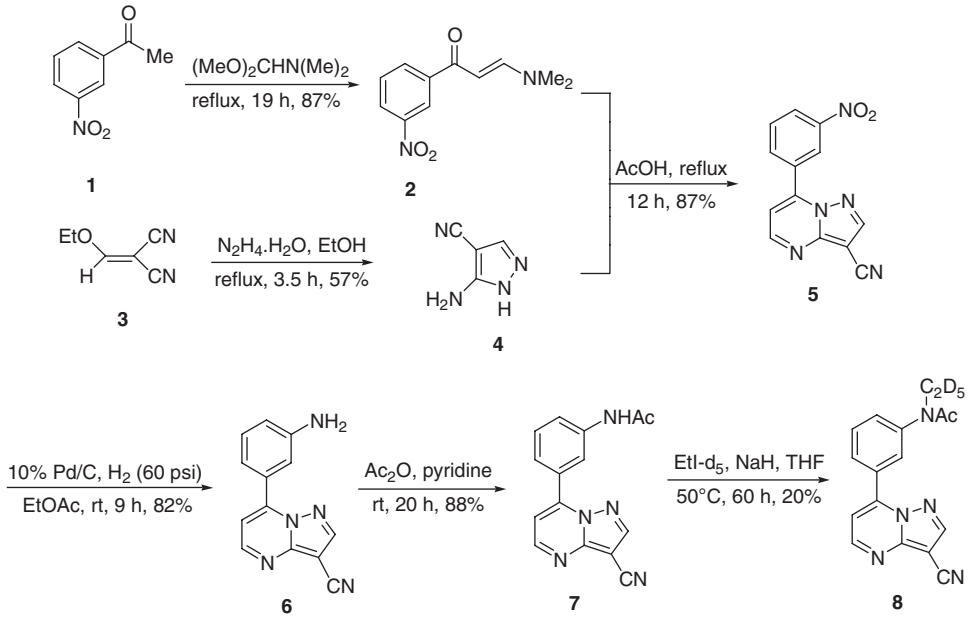
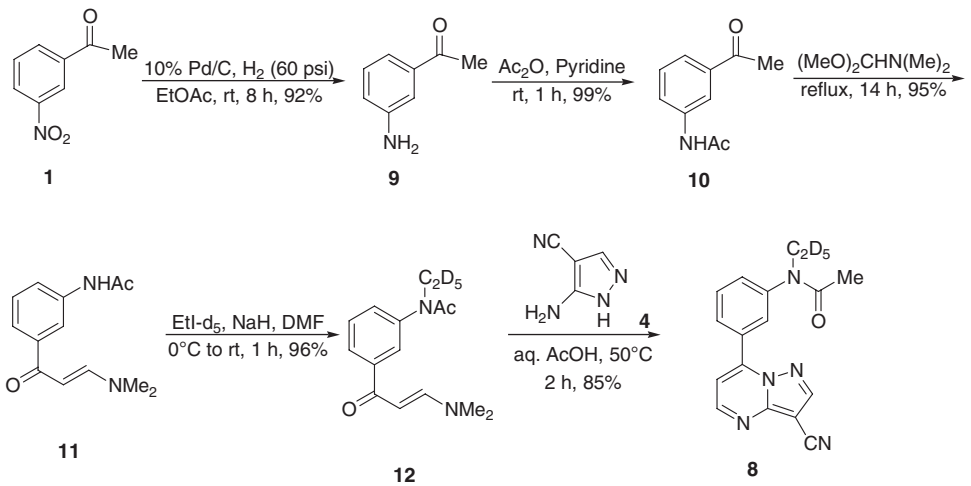


Scheme 1



Scheme 2

Dusza *et al.* described another route that satisfied our yield requirements, shown in Scheme 2.[34] Their synthesis started from compound **10**, which is not commercially available. Therefore, the route was modified to start with compound **1**, which is readily available and inexpensive. 3′-Nitroacetophenone **1** was reduced to 3′-aminoacetophenone **9**[35] and subsequent acylation yielded the acetamide **10**, which in turn was treated with *N*,*N*-dimethylformamide dimethylacetal to produce enamide **11**. Enamide **11** was alkylated using ethyl iodide-d_5 and sodium hydride as base at room temperature to yield the *N*-ethylated enamide **12**.[34] In the final step, *N*-ethylenamide **12** was coupled with 5-aminopyrazole **4** in aqueous acid at 50°C to produce zaleplon-d_5 **8** in 85% yield.[36] Further purification by recrystallization of the crude product from 30% aqueous acetic acid yielded colorless crystals of zaleplon-d_5 **8**.[37]

In summary, this work presents an elegant route to zaleplon-d_5, an internal standard for zaleplon analysis. This synthesis makes way for the quantitative detection of zaleplon in drug abusers.

Experimental

General

^{1}H NMR spectra were acquired at 300 and 400 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 $CHCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using a JASCO FT/IR 410 spectrometer. All reactions were performed in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone in argon. Benzene and *N*,*N*-dimethylformamide 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) or basic Al_2O_3, which were purchased from Macherey-Nagel.

All reactions were initially optimized using unlabeled compounds.

*Synthesis of 3-dimethylamino-1-(3-nitro-phenyl)-2-propen-1-one (**2**)*: A mixture of 3′-nitroacetophenone (**1**) (5.00 g, 30.2 mmol) and *N,N*-dimethylformamide dimethylacetal (4.00 mL, 30.2 mmol) was heated at reflux for 19 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue suspended in *n*-heptane (30 mL). The solid obtained was isolated by filtration to give **2** (5.82 g, 26.4 mmol). Yield: 88%. Compound **2** was used in the subsequent reaction without further purification.

*Synthesis of 5-amino-1H-pyrazole-4-carbonitrile (**4**)*: A mixture of **3** (4.00 g, 32.7 mmol) and 80% hydrazine hydrate (1.49 mL, 30.7 mmol) was refluxed in EtOH (20 mL) for 3.5 h. The solvent was removed *in vacuo*. The resulted solid was purified by column chromatography using silica gel as the stationary phase and 45% ethyl acetate–hexane as the mobile phase, yielding **4** as a yellow solid (2.04 g, 18.9 mmol). Yield: 58%. M.p.: 168–169°C, [lit. 167–169°C].[31] ^{1}H NMR (300 MHz, DMSO-d_6, δ): 11.98 (br s, 1 H), 7.57 (br s, 1 H), 6.26 (br s, 2 H). ^{13}C NMR (75.5 MHz, dimethyl sulfoxide (DMSO)-d_6, δ): 154.9, 138.9, 115.8, 73.8. IR (KBr, thin film): 3416, 3342, 3147, 2958, 1570, 1221, 1034, 716 cm^{-1}. MS-EI (*m/z*): 108 (M^+, 100), 79 (10), 54 (15), 53 (26), 52 (22). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_4H_4N_4$, 108.0436; found 108.0427.

*Synthesis of 7-(3-nitro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**5**)*: A mixture of **2** (3.42 g, 15.5 mmol) and **4** (1.50 g, 13.8 mmol) in glacial acetic acid (24 mL) was refluxed for 12 h. The reaction mixture was poured into ice water (50 mL) and extracted with chloroform (3 × 50 mL). The organic phase was washed using 1 M NaOH (2 × 50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to give a residue, which was purified by column chromatography using silica gel as the stationary phase and 35% ethyl acetate–hexane as the mobile phase, furnished **5** as brown crystals (2.62 g, 9.9 mmol). Yield: 70%. M.p.: 213–214°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.95 (d, J = 4.2 Hz, 2H), 8.88 (d, J = 2.1 Hz, 1 H), 8.47 (m, 2 H), 7.94 (t, J = 8.2 Hz, 1 H), 7.72 (t, J = 3.0 Hz, 1 H). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ): 154.3, 151.3, 148.0, 147.8, 145.7, 136.5, 131.3, 130.8, 126.5, 125.2, 113.7, 111.7, 82.1. IR (KBr, thin film): 3069, 2227, 1608, 1530, 1357, 1272, 839, 741, 728 cm^{-1}. MS-EI (*m/z*): 265 (M^+, 100), 264 (74), 220 (23), 219 (87), 218 (89), 165 (25), 140 (10). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{13}H_7N_5O_2$, 265.0600; found 265.0609.

*Synthesis of 7-(3-amino-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**6**)*: *7-(3-Nitro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**5**)* (0.20 g, 0.75 mmol) was dissolved in ethyl acetate (100 mL) in a pressure vessel and 10% Pd/C (40 mg) was added to it. The vessel was connected to a shaker-type hydrogenation apparatus and a hydrogen atmosphere of 60 psi was maintained inside the reaction vessel at room temperature for 9 h. The reaction mixture was then filtered by vacuum through celite pad. Solvent was evaporated under vacuum. The resulted product was purified by column chromatography using silica gel as the stationary phase and 40% ethyl acetate–hexane as the mobile phase produced **6** as pale yellow crystals (0.14 g, 0.59 mmol). Yield: 86%. M.p.: 227–228°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.83 (d, J = 4.5 Hz, 1H), 8.82 (s, 1H), 7.42 (d, J = 4.6 Hz, 1 H), 7.25 (s, 1 H), 7.23 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 5.43 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ): 154.0, 151.6, 149.2, 149.0, 147.6, 130.4, 129.6, 117.5, 117.451, 114.8, 113.9, 110.7, 81.6. IR (KBr, thin film): 2916, 2221, 1447, 846, 783 cm^{-1}. MS-EI (*m/z*): 235 (M^+, 100), 234 (55), 208 (5), 117 (6), 91 (4), 65 (5). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{13}H_9N_5$, 235.0858; found 235.0862.

*Synthesis of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-acetamide (**7**)*: To compound (**6**) (0.22 g, 0.97 mmol) acetic anhydride (2.28 mL, 24.1 mmol) and pyridine (2.28 mL) were successively added. The reaction mixture was stirred at room temperature for 20 h. The mixture was then poured into stirred water (35 mL). The solid formed was collected by filtration and purified by column chromatography using silica gel as the stationary phase and 50% ethyl acetate–hexane as the mobile phase yielding **7** as colourless crystals (0.24 g, 0.85 mmol). Yield: 88%. M.p.: 254–255°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 10.22 (s, 1H), 8.82 (d, J = 4.5 Hz, 1H), 8.59 (s, 1H), 8.36 (s, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d_6, δ): 169.2, 154.2, 151.5, 148.0, 147.7, 139.9, 130.3, 129.6, 124.8, 122.5, 120.4, 113.9, 111.1, 81.8, 24.4. IR (KBr, thin film): 3432, 2916, 2232, 1542, 440 cm^{-1}. MS-EI (*m/z*): 277 (M^+, 4), 265 (100), 264 (23), 219 (44), 218 (50), 174 (18), 135 (15), 57 (21). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{15}H_{11}N_5O$, 277.0964; found 277.0965.

*Synthesis of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N–[$^2H_5$]-ethyl-acetamide (**8**)*: (Scheme 1) A mixture of **7** (0.50 g, 1.8 mmol) and ethyl iodide-d_5 (2.12 mL, 26.5 mmol; isotopic abundance 99%, Cambridge Isotope Laboratories Inc.) in dry THF (75 mL) was added under an inert atmosphere to the reaction flask that contained sodium hydride (0.81 g, 33.7 mmol). This reaction mixture was then stirred at 50°C for 60 h. Excess sodium hydride was then destroyed by adding water (10 mL) and the aqueous phase finally extracted with ethyl acetate. Collected ethyl acetate fractions were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a residue, which was further purified by recrystallization of the product using 30% aqueous acetic acid, yielding **8** as colorless crystals (0.11 g, 0.35 mmol). Yield: 20%. M.p.: 185–186°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.79 (d, J = 4.2 Hz, 1 H), 8.42 (s, 1 H), 7.97 (d, J = 8.1 Hz, 1 H), 7.93 (s, 1 H), 7.67 (t, J = 7.8 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.20 (d, J = 4.2 Hz, 1 H), 1.9 (s, 3 H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 169.9, 152.7, 151.4, 147.1, 147.0, 143.4, 131.5, 130.9, 130.4, 130.0, 129.6, 112.7, 110.0, 83.7, 43.6 (m), 23.0, 12.1 (m). IR (KBr, thin film): 3055, 2359, 2229, 1615, 1548, 1484, 1392, 1223, 698 cm^{-1}. MS-EI (*m/z*): 310 (M^+, 55), 268 (50), 251 (18), 250 (100), 234 (4), 219 (5), 132 (5). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{17}H_{10}D_5N_5O$, 310.1585; found 310.1588.

*Synthesis of 1-(3-amino-phenyl)-ethanone (**9**)*: 3′-Nitroacetophenone (**1**) (5.00 g, 30.2 mmol) was dissolved in ethyl acetate (50 mL) in a pressure vessel and 10% Pd/C (150 mg) was added to it. The vessel was connected to shaker-type hydrogenation apparatus and hydrogen atmosphere of 60 psi was maintained inside the reaction vessel at room temperature for 8 h. The reaction mixture was then filtered through celite pad. The solvent was evaporated under vacuum and the resulted product was purified by column chromatography using basic silica gel as the stationary phase and 20% ethyl acetate–hexane as the mobile phase, producing **9** as colorless crystals (3.77 g, 27.9 mmol). Yield: 92%. M.p.: 108–110°C [lit.100–101°C].[38] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.30 (d, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 3.80 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 198.4, 146.8, 138.2, 129.4, 119.6, 118.7, 114.0, 26.6. IR (KBr, thin film): 3467, 3370, 1668, 1627, 1599, 1491, 1458, 1321, 870, 778, 685 cm^{-1}. MS-EI (*m/z*): 135 (M^+, 94), 120 (93), 92 (100), 66 (25), 65 (89), 63 (27). HRMS-EI (*m/z*): $[M]^+$ calcd. for C_8H_9NO, 135.0684; found 135.0689.

Synthesis of N-(3-acetyl-phenyl)-acetamide (**10**): Acetic anhydride (9.58 mL, 101.4 mmol) and pyridine (9.58 mL, 118.5 mmol) were successively added to the 1-(3-amino-phenyl)-ethanone (**9**) (2.74 g, 20.3 mmol). This reaction mixture was stirred at room temperature for 1 h under argon. The mixture was then slowly poured into stirring water; the temperature was increased suddenly. This aqueous layer was extracted by ethyl acetate and collected organic layer was dried over anhydrous Na_2SO_4 and concentrated to give **10** as white solid (3.56 g, 20.1 mmol). Yield: 99%. M.p.: 140–141°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.66 (br s, 1H), 8.05 (d, J = 1.5 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.36 (t, J = 9.0 Hz, 1H), 2.55 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 198.4, 169.3, 138.8, 137.5, 129.2, 124.7, 124.0, 119.3, 26.7, 24.4. IR (KBr, thin film): 3355, 2359, 1702, 1672, 1591, 1482, 1278, 1213, 905, 797, 695, 545 cm^{-1}. MS-EI (*m/z*): 177 (M^+, 89), 135 (91), 120 (100), 105 (35), 92 (52), 65 (24). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{10}H_{11}NO_2$, 177.0790; found 177.0781.

Synthesis of N-[3-(3-dimethylamino-acryloyl)-phenyl]-acetamide (**11**): A mixture of *N*-(3-acetyl-phenyl)-acetamide (**10**) (2.26 g, 12.8 mmol) and *N,N*-dimethylformamide dimethylacetal (6.1 mL, 45.9 mmol) was refluxed for 14 h. The reaction mixture was cooled to room temperature and the excess solvent was evaporated *in vacuo* to afford **11** (2.79 g, 12.0 mmol). Yield: 95%. M.p.: 184–186°C. ^{1}H NMR (300 MHz, CD_3OD, δ): 8.00 (s, 1H), 7.80 (d, J = 12.0 Hz, 1H), 7.68 (d, J = 6.0 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 5.75 (d, J = 12.2 Hz, 1H), 3.17 (s, 3H), 2.97 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (75.5 MHz, CD_3OD, δ): 189.3, 170.3, 155.7, 140.9, 138.6, 128.3, 122.7, 122.3, 118.7, 91.8, 44.1, 36.2, 22.4. IR (KBr, thin film): 3264, 2356, 1687, 1637, 1414, 1317, 1281, 1116, 791 cm^{-1}. MS-EI (*m/z*): 232 (M^+, 94), 216 (25), 215 (98), 189 (22), 147 (31), 98 (100), 70 (39), 55 (35). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{13}H_{16}N_2O_2$, 232.1212; found 232.1204.

Synthesis of N-[3-(3-dimethylamino-acryloyl)-phenyl]-N-ethyl-acetamide-d_5 (**12**): A mixture of *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-acetamide (**11**) (2.28 g, 9.8 mmol) and sodium hydride (0.45 g, 19.6 mmol) in dimethylformamide (20 mL) was stirred for 30 min under argon, then cooled in an ice bath, and a solution of ethyl iodide-d_5 (0.98 ml, 12.3 mmol) in dimethylformamide (10 mL) was added in small portions. The mixture was then stirred at room temperature for 30 min and extracted three times with hexane. The extracts were discarded, water was added and this aqueous solution was again extracted with dichloromethane. The collected organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield **12** (2.22 g, 8.36 mmol). Yield: 84%. M.p.: 113.5–114.5°C. ^{1}H NMR (400 MHz, CD_3OD, δ): 7.90 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 12.0 Hz, 1H), 7.71 (s, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 5.82 (d, J = 12.0 Hz, 1H), 3.15 (s, 3H), 2.95 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (75.5 MHz, CD_3OD, δ): 187.5, 170.8, 155.9, 142.6, 142.1, 130.5, 129.5, 126.9, 126.7, 91.4, 44.3, 43.8 (m, very weak), 36.4, 21.5, 11.9 (m, very weak). IR (KBr, thin film): 3042, 2360, 1632, 1550, 1481, 1424, 1286, 1190, 1172, 910, 762, 619 cm^{-1}. MS-EI (*m/z*): 265 (M^+, 44), 248 (36), 222 (17), 205 (25), 173 (13), 144 (13), 98 (100), 70 (12). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{15}H_{15}D_5N_2O_2$, 265.1834; found 265.1835.

Synthesis of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-[$^2H_5$]-ethyl-acetamide (**8**): (Scheme 2) A mixture of *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-ethyl-acetamide-d_5 (**12**) (2.22 g, 8.4 mmol), 3-aminopyrazol-4-carbonitrile (**4**) (0.90 g, 8.37 mmol), acetic acid (6.2 mL) and water (19.2 mL) was heated to 50°C. After about 2 h, the reaction was stopped and the mixture was cooled to 10°C. The resulted crystalline product was collected by filtration, washed with water and dried *in vacuo* to afford **8** as colourless crystals (2.2 g, 7.0 mmol). Yield: 84%. All spectral data are identical to the previously synthesized compound **8**.

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