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Efficient Synthesis of Impurity-C of Antimigraine Agent Rizatriptan Benzoate

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Supporting Information

ABSTRACT: During the commercial manufacturing of antimigraine drug Rizatriptan benzoate, several impurities are reported to be formed. This present work demonstrates a convergent and short synthesis of the most critical impurity (C) of Rizatriptan, [2-(5-((1H-1,2,4-triazol-1-yl)methyl)-1H-indole-2-yl)-*N*,*N*-dimethylethanamine (**1**)], recently reported in U.S. Pharmacopeia.

INTRODUCTION

Rizatriptan benzoate [Figure 1; brand name: MAXALT, Merck and Co. Inc., USA; a selective 5-hydroxytryptamine$_{1B/1D}$ (5-

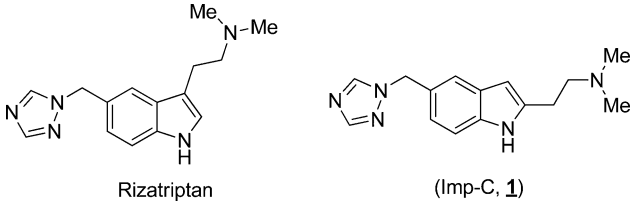

Figure 1.

$HT_{1B/1D}$) receptor antagonist], chemically known as *N*,*N*-dimethyl-5-(*1H*-1,2,4-triazol-1-yl-methyl)-1*H*-indole-3-ethanamine monobenzoate, is used for the treatment of migraine and severe headaches. By binding with serotonium receptors in the brain, rizatriptan benzoate makes the blood vessels in the brain narrower, which results in relieving the pain.[1,2]

Impurity profiling (i.e., identification as well as quantification of impurities) of an active pharmaceutical ingredient is of fundamental significance for medical safety reasons and also for the drug effectiveness and is now receiving vital attention from regulatory authorities. The International Conference of Harmonization (ICH) has published guidelines on impurities in new drug substances, products, and residual solvents.[3] The level of total impurities must be reduced typically to less than 1.0%, and each individual impurity of 0.1% or above must be identified. Hence, there is a good demand for considerable quantity of the impurity reference standards for both regulatory authorities and pharmaceutical companies, as each impurity needs to be quantified in the drug substances. A literature survey on Rizatriptan benzoate revealed that nine process related impurities have been identified, and few of them have been synthesized.[4] Recently, the U.S. Pharmacopeia reported a new process related impurity (**1**) for Rizatriptan benzoate which is basically a regio-isomer of the parent API. To the best of our knowledge, there is no commercial vendor for this new impurity and also there is no literature reported synthesis of **1**. For the impurity profile study for our bulk API Rizatriptan benzoate, we planned to investigate the synthesis of **1**. Herein we wish to report a short synthesis which we believe will be of immense help to organic chemists from pharmaceutical companies from all over the world. Moreover, our approach would provide an easy access to the synthesis of 2-substituted indole derivatives.

After extensive literature study on the synthesis of 2-substituted indole derivatives, we decided to approach the indole formation by using the well-known Sonogashira coupling[5] (iodo-aniline **5** with homopropargyl alcohol (**4**) followed by in situ indocyclization[6] as key steps which would provide the critical indole moiety **2**[7] (Scheme 1)). Then onwards the synthesis of the target compound **1** can be easily accomplished from the critical alcohol intermediate **2** by using a couple of straightforward conversions. **5** can be obtained from commercially available nitro-compound **7**, following literature procedures.[8]

RESULTS AND DISCUSSION

As per our strategy, 4-nitrobenzyl bromide (**7**) was reacted with the sodium salt of triazole to afford the nitro derivative (**8**). Reduction of the nitro group of **8** followed by controlled iodination[9] of the resulting aniline **6** using I_2 and aqueous $NaHCO_3$ furnished the desired iodo-aniline **5** in good yield (Scheme 2).

The critical Sonogashira coupling of iodo compound **5** with homopropargyl alcohol followed by in situ indole formation was attempted under various reported conditions, but it failed to give us the desired indole moiety **2**, instead the uncyclized condensed intermediate **3**[10] was isolated in most of the cases (Scheme 3). Our efforts to cyclize **3** under various conditions (using various metal alkoxides, fluorides, and Lewis acids even at elevated temperature)[11] proved to be ineffectual.

At this stage we decided to examine the endocyclization by protecting the alcohol group of **3**. Accordingly, THP-protected **9** was prepared by the coupling of iodo compound **5** with the THP-protected alcohol **10**[12] under Sonogashira conditions. Intermediate **9** was subjected to endocyclization under various conditions, but again all our efforts were in vain in arriving at the desired indole moiety (Scheme 4).

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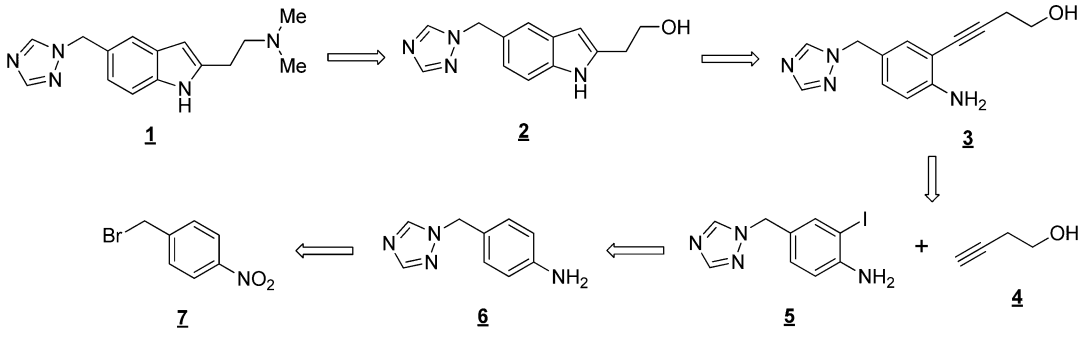
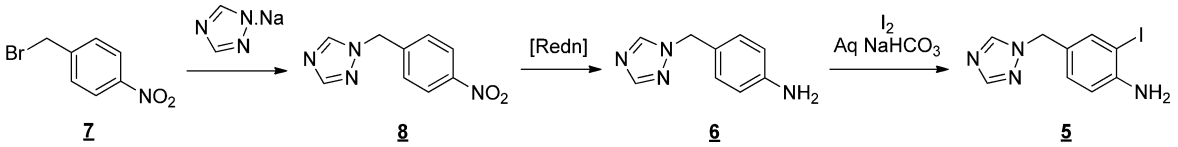
Scheme 1.



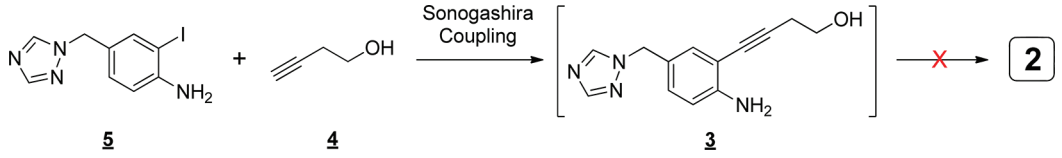
1 2 3 7 6 5 4

Scheme 2.



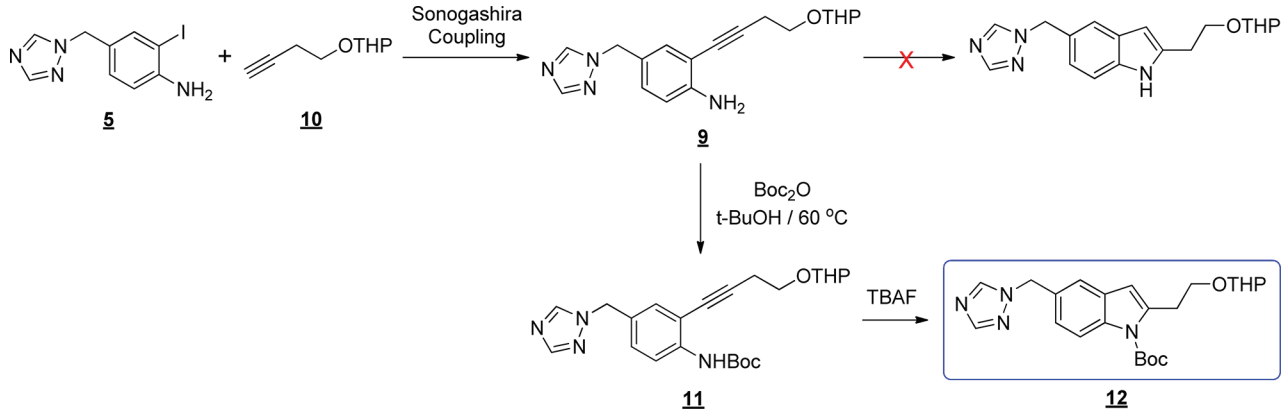
7 8 6 5

Scheme 3.



5 4 3

Scheme 4.



5 10 9 11 12

Since intermediate **9** failed to give us the desired indole derivative, we decided to investigate the endocyclization using a protected amino-intermediate (such an example is reported in ref 13). Accordingly, Boc protection of **9** was effected with Boc anhydride in *tert*-butanol at elevated temperature to provide Boc protected intermediate **11**[14] in reasonable yield. Subsequent cyclization of completely protected **11** was attempted under various conditions (K_2CO_3, DMF, 120 °C: ^{t}BuOK in methanol under heating; catalytic $Pd(PPh_3)_4$ under heating; DBU in methanol and water under heating), wherein a very small amount of product **12** was observed (as shown in Table 1).

Fortunately, when the cyclization was done using TBAF in THF under reflux conditions, the substrate smoothly underwent cyclization to provide the indole derivative **12** with reasonable yield. Once we had the critical indole derivative **12** in hand, the only thing left was to manipulate this advanced intermediate to the target compound **1.**

Table 1. Optimization of Cyclization Conditions

reagents	conditions	time	yield (isolated yield)
$Pd(PPh_3)_4$	DMF, 120 °C	15 h	
^{t}BuOK	MeOH, 80 °C	12 h	20%
K_2CO_3	DMF, 120 °C	15 h	43%
DBU	MeOH, water, 100 °C, sealed tube	48 h	28%
TBAF	THF, reflux	4 h	78%

This was successfully accomplished (Scheme 5) starting with acid-catalyzed removal of the THP in **12**, followed by mesylation of the resulting alcohol **13**, and subsequent amination with anhydrous dimethyl amine solution in THF

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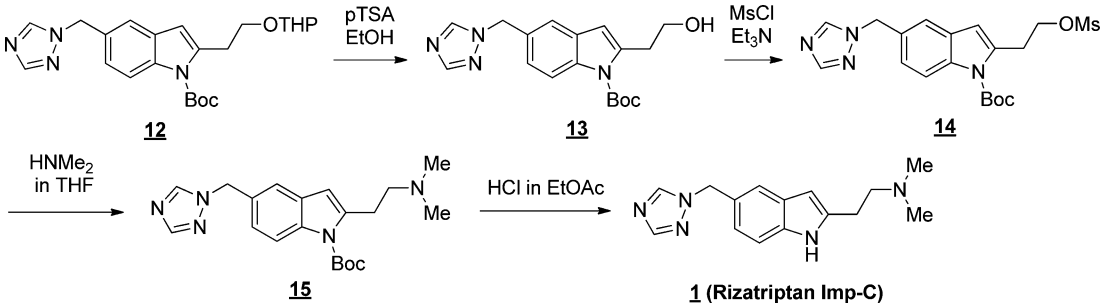
Scheme 5.



(prepared by bubbling of $HNMe_2$ in THF) and finally Boc deprotection with dilute HCl provided **1** in workable yield.

CONCLUSION

A short and efficient synthesis of Impurity-C (**1**) of antimigraine drug Rizatriptan benzoate has been described; this study will provide an access to the reference standard of this impurity for regulatory authorities and also help immensely organic chemists from pharmaceutical companies currently developing the drug.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian 400 MR spectrometer in $CDCl_3$ and DMSO-d_6, and mass spectra were determined on an API-2000LCMS mass spectrometer, Applied Biosystems. Elemental Analysis was done in a VarioEL III instrument.

EXPERIMENTAL DETAILS

Preparation of 4-((*1H*-1,2,4-Triazol-1-yl)methyl)-2-iodobenzenamine (5). To a solution of **6** (10 g, 0.06 mol) in water (1.0 lit.) were added sodium bicarbonate (7.3 g, 0.09 mol) and iodine (14.7 g, 0.06 mol) under vigorous stirring. The reaction mixture was stirred for 30 h. After complete conversion of the starting material (as indicated by TLC), the reaction was quenched by the addition of solid sodium thiosulfate (3.0 g) followed by extraction with ethyl acetate (2 × 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered; solvent was evaporated to obtain a crude residue. The crude product was purified via silica gel column chromatography using methanol and dichloromethane (1:99) as eluent to yield 15.5 g of **5** (90%) as a light brown solid.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.0 (s, 1H), 8.0 (s, 1H), 7.6 (d, 1H, J = 1.8 Hz), 7.1 (dd, 1H, J = 1.8, 8.2 Hz), 6.7 (d, 1H, J = 8.2 Hz), 5.2 (s, 2H), 4.2 (bs, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 152.0, 147.2, 142.7, 138.8, 129.5, 125.4, 114.6, 83.7, 52.4. ESI-Mass: For $C_9H_9N_4I$ (M+H)/z: 301.1, Found: (M+H)/z: 301.0, (M+23)/z: 322.9. Anal. for $C_9H_9N_4I$, calcd C, 36.02; H, 3.02; N, 18.67. Found: C, 35.93; H, 3.11; N,18.76.

Preparation of 2-(But-3-ynyloxy)tetrahydro-2*H*-pyran (10). To a solution of homopropargyl alcohol (5.0 g, 71 mmol), in dichloromethane (75 mL) were added dihydropyrane (9.7 mL, 107 mmol) and *p*-TSA (1.4 g, 7 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at rt for 6 h. After complete consumption of the starting material, the reaction mixture was diluted with dichloromethane and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to get a crude residue. The product was purified via silica gel (neutralized with triethyl amine) column chromatography using hexane as eluent to yield 7.7 g (70%) of **10** as colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 4.6 (m, 1H), 3.9−3.8 (m, 2H), 3.6−3.5 (m, 2H), 2.5 (m, 2H), 2.0 (t, 1H, J = 2.7 Hz), 1.9−1.8 (m, 1H), 1.8−1.7 (m, 1H), 1.6−1.5 (m, 4H).

Preparation of 4-((*1H*-1,2,4-Triazol-1-yl)methyl)-2-(4-(tetrahydro-*2H*-pyran-2-yloxy)but-1-ynyl)benzenamine (9). To a solution of **5** (5.0 g, 17 mmol) and **10** (3.9 g, 25 mmol) in DMF (50.0 mL, LR grade) were added CuI (0.32 g, 2.0 mmol, anhydrous, purchased from Aldrich) and diisopropylethylamine (1.0 mL, 7.4 mmol). The reaction mixture was degassed with nitrogen, followed by the addition of $PdCl_2(PPh_3)_2$ (0.59 g, 0.8 mmol). The reaction mixture was allowed to stir for 6 h at rt. After complete consumption of the starting material, the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The product was purified via silica gel (neutralized with triethyl amine) column chromatography using ethyl acetate and hexane (7:3) as eluent to yield 4.9 g (92%) of **9** as a gummy liquid.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.0 (s, 1H), 7.9 (s, 1H), 7.2 (d, 1H, J = 2.0 Hz), 7.0 (dd, 1H, J = 2.0, 8.3 Hz), 6.7 (d, 1H, J = 8.3 Hz), 5.2 (s, 2H), 4.7 (m, 1H), 4.3 (bs, 2H), 3.9 (m, 2H), 3.6 (m, 1H), 3.5 (m, 1H), 2.7 (t, 2H, J = 6.8 Hz), 1.8−1.7 (m, 2H), 1.6−1.5 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 152.1, 148.3, 132.1, 129.3, 123.1, 114.4, 108.8, 98.8, 93.4, 77.3, 65.7, 62.3, 53.2, 30.6, 25.4, 21.1, 19.4. ESI-Mass: For $C_{18}H_{22}N_4O_2$ (M+H)/z: 327.4, Found: (M+H)/z: 327.1, (M+Na)/z: 349.0. Anal. for $C_{18}H_{22}N_4O_2$, calcd: C, 66.24; H, 6.79; N, 17.16; Found: C, 66.19; H, 7.10; N, 17.41.

Preparation of *tert*-Butyl 4-((1*H*-1,2,4-Triazol-1-yl)-methyl)-2-(4-(tetrahydro-*2H*-pyran-2-yloxy)but-1-ynyl)-phenylcarbamate (11). To a solution of **9** (4.8 g, 15.0 mmol) in *tert*-butanol (58 mL) was added Boc anhydride (6.8 mL, 30 mmol), and the reaction mixture was heated to 60 °C for 15 h. After complete consumption of the starting material (checked by TLC), *tert*-butanol was distilled off, diluted with water, and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The product was purified via silica gel (neutralized with triethyl amine) column chromatography using ethyl acetate and hexane (3:2) as eluent to yield 5.2 g (83%) of **11** as a gummy liquid.

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^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.1 (d, 1H, J = 8.6 Hz), 8.0 (s, 1H), 8.0 (s, 1H), 7.2 (d, 1H, J = 1.8 Hz), 7.2 (dd, 1H, J = 1.8, 8.6 Hz), 5.2 (s, 2H), 4.7 (m, 1H), 3.9 (m, 2H), 3.7 (m, 1H), 3.5 (m, 1H), 2.8 (t, 2H, J = 6.8 Hz), 1.8−1.3 (m, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 152.2, 151.9, 139.8, 131.3, 128.7, 127.8, 117.7, 112.1, 98.7, 95.1, 80.9, 76.0, 65.3, 62.1, 52.7, 30.4, 28.1, 25.2, 21.0, 19.3. ESI-Mass: For $C_{23}H_{30}N_4O_4$ (M+H)/z: 427.52; Found: (M+H)/z: 427.1; (M+Na)/z: 449.0. Anal. for $C_{23}H_{30}N_4O_4$: Calcd. C, 64.77; H, 7.09; N, 13.14. Found: C, 64.90; H, 7.23; N, 12.73.

Preparation of *tert*-Butyl 5-((*1H*-1,2,4-Triazol-1-yl)-methyl)-2-(2-tetrahydro-*2H*-pyran-2-yloxy)ethyl)-1H-indole-1-carboxylate (12). To a solution of **11** (3.5 g, 8.3 mmol) in THF (18.0 mL) was added TBAF (16.4 mL, 16.0 mmol, 1. 0 M solution in THF), and the reaction mixture was heated to reflux for 4 h. After complete cyclization, the reaction mixture was cooled to room temperature, the reaction was quenched with saturated ammonium chloride solution (5 mL), THF was distilled off, and the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The product was purified via silica gel (neutralized with triethyl amine) column chromatography using ethyl acetate and hexane (4:1) as eluent to yield 2.73 g (78%) of **12** as a gummy liquid.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.1 (d, 1H, J = 8.6 Hz), 8.0 (s, 1H), 7.9 (s, 1H), 7.4 (s, 1H), 7.1 (dd, 1H, J = 1.5, 8.6 Hz), 6.4 (s, 1H), 5.4 (s, 2H), 4.6 (m, 1H), 4.1 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 3.5 (m, 1H), 3.3 (t, 2H, J = 6.6 Hz), 1.8−1.7 (m, 2H), 1.7 (s, 9H), 1.6−1.5 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 152.0, 150.2, 142.8, 140.0, 136.5, 129.8, 128.4, 123.4, 119.7, 116.1, 107.9, 98.9, 84.2, 66.0, 62.4, 53.8, 30.7, 30.6, 28.2, 25.4, 19.5. ESI-Mass: For $C_{23}H_{30}N_4O_4$ (M+H)/z: 427.52, Found: (M+H)/z: 427.0; (M+Na)/z: 449.1. Anal. for $C_{23}H_{30}N_4O_4$: Calcd. C, 64.77; H, 7.09; N, 13.14. Found: C, 64.32; H, 6.93; N, 13.40.

Preparation of *tert*-Butyl 5-((*1H*-1,2,4-Triazol-1-yl)-methyl)-2-(2-hydroxyethyl)-1H-indole-1-carboxylate (13). To a solution of **12** (0.7 g, 1.6 mmol) in ethanol (10.0 mL) was added *p*-TSA (0.16 g, 0.8 mmol), and the reaction mixture was stirred for 15 h. After complete THP deprotection (checked by TLC), the reaction was quenched by the addition of 2 mL of saturated sodium bicarbonate, THF was distilled off, and the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The product was purified via silica gel column chromatography using methanol and dichloromethane (1:49) as eluent to yield 0.5 g (89%) of **13** as a gummy liquid.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.0 (d, 1H, J = 8.6 Hz), 8.0 (s, 1H), 8.0 (s, 1H), 7.4 (d, 1H, J = 1.3 Hz), 7.2 (dd, 1H, J = 1.7, 8.6 Hz), 6.4 (s, 1H), 5.4 (s, 2H), 3.9 (t, 2H, J = 6.2 Hz), 3.3 (t, 2H, J = 6.2 Hz), 1.7 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 152.0, 150.4, 142.8, 139.5, 136.6, 129.6, 128.8, 123.7, 119.8, 116.3, 108.7, 84.6, 61.6, 53.9, 33.3, 30.9, 28.2. ESI-Mass: For $C_{18}H_{22}N_4O_3$ (M+H)/z: 343.40, obtained: (M+H)/z: 343.0; (M+Na)/z: 365.0. Anal. for $C_{18}H_{22}N_4O_3$, Calcd. C, 63.14; H, 6.48; N, 16.36; Found: C, 62.73; H, 7.27; N, 17.02.

Preparation of 2-(1-(*tert*-Butoxycarbonyl)-5-((*1H*-1,2,4-triazol-1-yl)methyl)-*1H*-indol-2-yl)ethyl Methanesulfonate (14). To a solution of **13** (0.36 g, 1.1 mmol) in dichloromethane (5.0 mL) were added diisopropyl ethylamine (0.28 mL, 1.6 mmol) and mesyl chloride (0.1 mL, 1.2 mmol) at 0 °C. The reaction mixture was allowed to stir at rt for 2 h. After completion of the reaction (checked by TLC), the reaction mixture was diluted with water and dichloromethane, and it was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The crude product (**14**) was used for the next reaction without any further purification.

Preparation of *tert*-Butyl-5-((*1H*-1,2,4-triazol-1-yl)-methyl)-2-(2-(dimethylamino)ethyl)-1H-indole-1-carboxylate (15). A THF solution of dimethylamine (10 mL) was added to the crude product (obtained from the previous step) at room temperature. The reaction mixture was heated to 60 °C in a sealed tube for 5 h. After complete consumption of the starting material (checked by TLC), excess reagent was evaporated, the reaction mixture was diluted with water, and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The product was purified via silica gel column chromatography using ethyl acetate as eluent to yield 0.28 g (72% for two steps) of **15** as a gummy liquid.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.1 (d, 1H, J = 8.6 Hz), 8.0 (s, 1H), 8.0 (s, 1H), 7.4 (s, 1H), 7.2 (dd, 1H, J = 1.3, 8.6 Hz), 6.4 (s, 1H), 5.4 (s, 2H), 3.2 (t, 2H, J = 7.3 Hz), 2.7 (t, 2H, J = 7.3 Hz), 2.4 (s, 6H), 1.7 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 152, 150.2, 142.8, 141.0, 136.4, 129.8, 128.6, 123.5, 119.8, 116.2, 107.5, 84.3, 58.5, 53.9, 45.2, 29.7, 28.2. ESI-Mass: For $C_{20}H_{27}N_5O_2$ (M+H)/z: 369.47, Found: (M+H)/z: 370.1. Anal. for $C_{20}H_{27}N_5O_2$, Calcd. C, 65.02; H, 7.37; N, 18.96. Found: C, 65.44; H, 6.78; N, 18.76.

Preparation of 2-(5-((*1H*-1,2,4-Triazol-1-yl)methyl)-*1H*-indole-2-yl)-*N*,*N*-dimethylethanamine (1). To a THF solution of compound (**15**) (0.2 g, 0.54 mmol) was added 3 N HCl in EtOAc (3.0 mL) at room temperature, and the reaction mixture was allowed to stir for 30 min at rt. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a crude residue. The product was purified via silica gel column chromatography using methanol and dichloromethane (3:97) as eluent to yield 120 mg (82%) of Impurity C (**1**) as a gummy liquid.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 10.0 (s, 1H), 7.9 (s, 2H), 7.5 (s, 1H), 7.3 (d, 1H, J = 8.3 Hz), 7.0 (dd, 1H, J = 1.6, 8.3 Hz), 6.2 (s, 1H), 5.4 (s, 2H), 3.0 (t, 2H, J = 6.1 Hz), 2.7 (t, 2H, J = 6.1 Hz), 2.4 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 151.8, 142.7, 140.4, 135.8, 128.7, 125.0, 121.3, 120.1, 111.4, 99.3, 58.7, 54.7, 45.1, 24.9. ESI-Mass: For $C_{15}H_{19}N_5$, (M+H)/z: 269.35, found: (M+1)/z: 269.9; (M+Na)/z: 292.0. Anal. for $C_{15}H_{19}N_5$, C, 66.89; H, 7.11; N, 20.00; Found: C, 66.80; H, 6.85; N, 20.40.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data of selected intermediates and the final compound. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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