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การสังเคราะห์อนุพันธ์ทริปตามีนสามขั้นตอนจากอินโดล-3-คาร์บอกซาลดีไฮด์

Three-Steps Synthesis of Tryptamine Derivatives from Indole-3-Carboxaldehyde

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บทคัดย่อ

วัตถุประสงค์และที่มา : วิธีการทั่วไปในการสังเคราะห์อนุพันธ์ทริปทามีนเกี่ยวข้องกับการรีดักชัน 3-(2-ไนโตรไวนิล)อินโดล โดยใช้ลิเทียมอะลูมิเนียมไฮไดรด์เป็นตัวรีดิวซ์ในตัวทำละลายเตตระไฮโดรฟูแรนที่ปราศจากความชื้น อย่างไรก็ตามวิธีนี้นำไปสู่การกำจัดฮาโลเจนบางส่วนของ 3-(2-ไนโตรไวนิล)อินโดล ที่มีอะตอมฮาโลเจนบนวงอินโดลส่งผลให้เกิดผลิตภัณฑ์ผสมระหว่างทริปทามีนและฮาโลทริปทามีน นอกจากนี้ ข้อจำกัดของการใช้วิธีการที่เคยรายงานไว้ประกอบด้วยสภาวะการทดลองที่รุนแรง ลิเทียมอะลูมิเนียมไฮไดรด์เป็นตัวรีดิวซ์ที่ไวต่ออากาศ ความชื้น และมีราคาแพง ในการศึกษานี้ได้พัฒนาการสังเคราะห์อนุพันธ์ทริปทามีน สาม ขั้นตอน จากอินโดล-3-คาร์บอกซาลดีไฮด์ที่หาได้ง่ายในท้องตลาดด้วยปฏิกิริยาเฮนรี และปฏิกิริยารีดักชันหมู่ไวนิลไนโตรให้ได้เป็นเอทิลเอมีนโดยใช้โซเดียมโบโรไฮไดรด์ และนิกเกิลอะซิเตตเตตระไฮเดรต เป็นตัวรีดิวซ์

วิธีดำเนินการวิจัย : ศึกษาการสังเคราะห์อนุพันธ์ทริปทามีน ผ่านสามขั้นตอนจากอินโดล-3-คาร์บอกซาลดีไฮด์ที่หาได้ง่ายในท้องตลาด ด้วยปฏิกิริยาเฮนรี และปฏิกิริยารีดักชันของหมู่ไวนิลไนโตรให้ได้เป็นเอทิลเอมีน โดยใช้โซเดียมโบโรไฮไดรด์ และนิกเกิลอะซิเตตเตตระไฮเดรต เป็นตัวรีดิวซ์ วิธีการนี้ได้ศึกษาการสังเคราะห์อนุพันธ์ทริปทามีนโดยใช้สารตั้งต้น 3-(2-ไนโตรไวนิล)อินโดลที่หลากหลาย

ผลการวิจัย : ในขั้นตอนแรกอนุพันธ์ 3-(2-ไนโตรไวนิล)อินโดลถูกสังเคราะห์ได้ในร้อยละที่สูงจากอินโดล-3-คาร์บาลดีไฮด์ด้วยปฏิกิริยาเฮนรี จากนั้นรีดิวซ์อนุพันธ์ 3-(2-ไนโตรไวนิล)อินโดลที่ได้ด้วยโซเดียมโบโรไฮไดรด์ได้เป็น 3-(2-ไนโตรเอทิล)อินโดล ในขั้นตอนสุดท้าย 3-(2-ไนโตรเอทิล)อินโดลถูกเปลี่ยนเป็นอนุพันธ์ของทริปทามีนโดยใช้โซเดียมโบโรไฮไดรด์ (4 เท่า) เป็นตัวรีดิวซ์และนิกเกิลอะซิเตตเตตระไฮเดรต (1 เท่า) เป็นตัวเร่งปฏิกิริยาในตัวทำละลายผสมของอะซิโตไนไตรล์และน้ำ (60:1) ที่อุณหภูมิห้องเป็นเวลา 20 นาที ส่งผลให้เกิดผลิตภัณฑ์อนุพันธ์ทริปทามีนร้อยละ 35-80

สรุปผลการวิจัย : วิธีการสังเคราะห์นี้แสดงให้เห็นถึงแนวทางการสังเคราะห์ทริปทามีนรวมถึงทริปทามีนที่มีฮาโลเจนเป็นองค์ประกอบโดยผ่านสามขั้นตอนจากสารตั้งต้นอินโดล-3-คาร์บาลดีไฮด์ที่หาซื้อได้ง่าย ขั้นตอนสำคัญของการศึกษาได้แก่การใช้สารผสมระหว่างโซเดียมโบโรไฮไดรด์และนิกเกิลอะซิเตตเตตระไฮเดรตในการรีดิวซ์สาร 3-(2-ไนโตรเอทิล)อินโดลให้เป็นอนุพันธ์ทริปทามีน

คำสำคัญ : ทริปทามีน ; อะลิฟาติกเอมีน ; นิกเกิล(II) อะซิเตตเตตระไฮเดรต ; โซเดียมโบโรไฮไดรด์ ; รีดักชัน

Abstract

Background and Objectives : The conventional approach to synthesizing tryptamine derivatives typically involves reducing 3-(2-nitrovinyl)indoles using $LiAlH_4$ as a reducing reagent in a dry THF solvent. However, the method often leads to partial dehalogenation of the 3-(2-nitrovinyl)indole bearing halogen atom on the indole ring, resulting in a mixture of tryptamine and halotryptamine products. Furthermore, limitations of this method include harsh reaction conditions, sensitivity to air and moisture, and the requirement for an expensive reducing agent $LiAlH_4$. In this study, a three-step synthesis of tryptamine derivatives from commercially available indole-3-carboxaldehyde was developed utilizing the Henry reaction and reduction of the resulting vinyl nitro moiety to ethyl amine, employing a combination of $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ as the reducing agent.

Methodology : To study the synthesis of tryptamine derivatives via a three-step process from commercially available indole-3-carboxaldehyde involves the Henry reaction and reduction of the resulting vinyl nitro group to ethyl amine, using $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ as the reducing agent. The synthesis of tryptamine derivatives using various starting materials of 3-(2-nitrovinyl)indole was demonstrated.

Main Results : Initially, 3-(2-nitrovinyl)indole derivatives were synthesized in good to excellent yields from indole-3-carboxaldehyde via Henry reaction. The resulting 3-(2-nitrovinyl)indole derivatives were then reduced using $NaBH_4$, leading to the formation of 3-(2-nitroethyl)indoles. In the final steps, the conversion 3-(2-nitroethyl)indoles to the desired tryptamine derivative was accomplished by employing a combination of $NaBH_4$ (4 equiv) as a reducing agent and $Ni(OAc)_2 \cdot 4H_2O$ (1 equiv) as a catalyst in a mixed solvent of acetonitrile and water (60:1) at room temperature for 20 minutes.

Conclusions : Tryptamine derivatives, including halogenated tryptamines, were synthesized in moderate to good yield via a three-step process from commercially available indole-3-carbladehydes. The key approach involves the use of a combination between $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ for reducing 3-(2-nitroethyl)indoles to tryptamine derivatives.

Keywords : tryptamine ; aliphatic amine ; $Ni(OAc)_2 \cdot 4H_2O$; $NaBH_4$; reduction reaction

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Introduction

Tryptamine and its derivatives, an important alkaloid, have been isolated from various marine and terrestrial natural sources (Fahy *et al.*, 1991; Karamyan *et al.*, 2010). These compounds feature an indole ring linked to an alkylamino side chain at the C-3 position, thereby enhancing water solubility and providing acid resistance (Fahy *et al.*, 1991; Karamyan *et al.*, 2010; Chantana *et al.*, 2021). Naturally occurring tryptamine derivatives demonstrate diverse biological activities, including anti-serotonin (Bifulco *et al.*, 1995), antibacterial (Karamyan *et al.*, 2010), antimicrobial (Campana *et al.*, 2019), anticancer (Chantana *et al.*, 2021), anti-Alzheimer (Asghar *et al.*, 2024), and inhibition of human bradykinin B2 effects (Bifulco *et al.*, 1995) (Figure 1). Consequently, the development of efficient methods for the construction of tryptamine derivatives is highly relevant to medicinal chemistry and drug development.

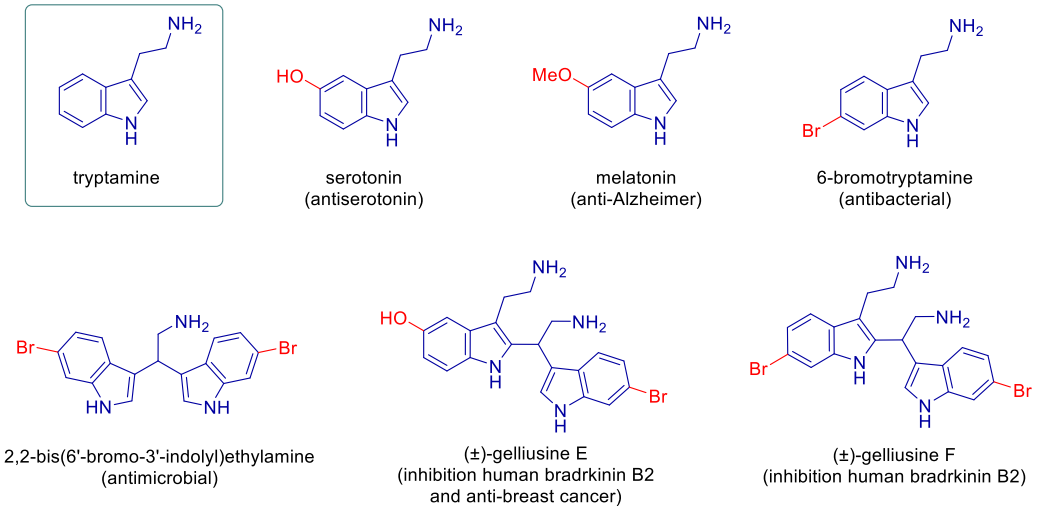
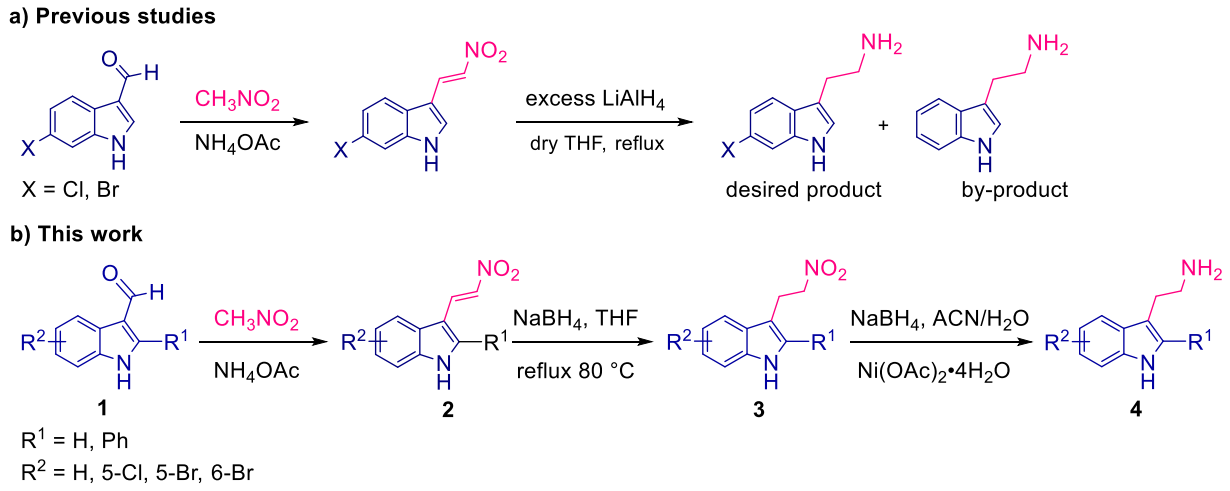


Figure 1 Representative natural tryptamine alkaloids

In recent years, significant attention has been focused on the synthesis of tryptamine derivatives, particularly tryptamine and 6-bromotryptamine (Schumachert *et al.*, 1999; Ye *et al.*, 2018; Scott *et al.*, 2021; Brogan *et al.*, 2011). Many of these synthetic methods involve the reduction of 3-(2-nitrovinyl)indole (**2**) using a strong reducing agent, lithium aluminum hydride ($LiAlH_4$), in dry tetrahydrofuran (THF) under reflux conditions. However, when dealing with 3-(2-nitrovinyl)indole (**2**) containing halogen atom on the indole ring, dehalogenation of the halogen atom can lead to the formation of dehalogenated tryptamine adduct as a by-product (Scheme 1a) (Scott *et al.*, 2021; Brogan *et al.*, 2011). Furthermore, this process is sensitive to both moisture and air, requiring

specifically dried THF as a solvent. Removing trace amounts of water from THF typically involves using flammable sodium metal under reflux conditions before distillation, making the method somewhat cumbersome. While dry THF is commercially available, its cost is relatively high.

Previously, Setamdideh *et al.* successfully developed an efficient and expedient approach for the novel synthesis of aromatic amines from aromatic nitro compounds. The method utilized $NaBH_4$ as a reducing agent and nickel(II) acetate tetrahydrate [$Ni(OAc)_2{\cdot}4H_2O$] as a catalyst in a mixed solvent of acetonitrile (ACN) and water at room temperature, achieving high to excellent yields of aromatic amine products (Setamdideh *et al.*, 2011). However, this methodology has not yet been applied to the synthesis of tryptamine derivatives (**4**). In this paper, we have developed a simple and practical method for synthesizing tryptamine derivatives (**4**), including halogenated tryptamines, from indole-3-carboxaldehyde (**1**) via the Henry reaction and reduction of the resulting vinyl nitro moiety (**2**) to ethyl amine (**4**), This synthesis employs a combination of $NaBH_4$ and $Ni(OAc)_2{\cdot}4H_2O$ as the reducing agent (Scheme 1b).



Scheme 1 Representative procedures for the synthesis of tryptamine derivatives

Methods

General methods: All chemicals were purchased from commercial sources and used without further purification. High-resolution 400 MHz ^{1}H NMR, along with 100 MHz ^{13}C NMR spectra, were performed using Bruker DPX-400 spectrometers at the Chemistry Department, Faculty of Science, Burapha University. All spectra were measured in $CDCl_3$ or DMSO-d_6 as solvent. Infrared (IR) spectra were recorded on a Perkin Elmer System 2000 FT-

IR spectrometer. Radial chromatography was conducted on a chromatotron using Merck silica gel 60 PF_{254}. Thin layer chromatography (TLC) was performed with Merck silica gel 60 PF_{254} aluminium plate.

Synthesis of the 3-(2-nitrovinyl)indole derivatives **2**: A mixture of indole-3-carboxaldehyde derivatives **1** (1 mmol), NH_4OAc (0.0617 g, 0.8 mmol), and CH_3NO_2 (3 mL, 55.9 mmol) was refluxed in a round-bottom flask. The reaction was allowed to proceed until completion, as monitored by TLC analysis. Subsequently, the reaction mixture was stirred and cooled to room temperature. Water (10 mL) was added to the reaction mixture, followed by successive extractions with EtOAc (2 x 10 mL), water (10 mL), and NaCl (10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated to obtain a crude product. The product was subsequently purified by column chromatography (30-50% EtOAc/Hexane) to yield compounds **2a-2e**.

*3-(2-Nitrovinyl)indole (**2a**)*; yellow solid (95%); R_f = 0.50 (mobile phase = 40% EtOAc-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (brs, 1H), 8.42 (d, *J* = 12.0 Hz, 1H), 8.24 (s, 1H), 8.00 (d, *J* = 12.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.30-7.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.8, 136.4, 134.8, 131.2, 124.7, 123.4, 122.0, 120.6, 112.9, 108.3

*2-Phenyl-3-(2-nitrovinyl)indole (**2b**)*; yellow solid (80%); R_f = 0.42 (mobile phase = 30% EtOAc-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.64 (brs, 1H), 8.22 (d, *J* = 16.0 Hz, 1H), 8.09 (d, *J* = 16.0 Hz, 1H), 8.02 (d, *J* = 4.0 Hz, 1H), 7.68-7.59 (m, 5H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.36-7.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 147.9, 137.0, 134.1, 131.7, 130.0, 129.9, 129.9, 129.8, 129.2, 129.0, 125.2, 124.0, 122.4, 121.1, 112.6, 105.0

*5-Chloro-3-(2-nitrovinyl)indole (**2c**)*; orange solid (62%); R_f = 0.38 (mobile phase = 30% EtOAc-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.60 (brs, 1H), 8.38 (d, *J* = 12.0 Hz, 1H), 8.29 (s, 1H), 8.10 (d, *J* = 1.8 Hz, 1H), 8.09 (d, *J* = 12.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.1, 136.3, 134.2, 132.2, 126.9, 123.6, 122.7, 120.0, 114.5, 108.0

*5-Bromo-3-(2-nitrovinyl)indole (**2d**)*; yellow solid (99%); R_f = 0.80 (mobile phase = 40% EtOAc-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (brs, 1H), 8.39 (d, *J* = 13.5 Hz, 1H), 8.28 (s, 1H), 8.22 (d, *J* = 1.7 Hz, 1H), 8.10 (d, *J* = 13.5 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.5, 136.8, 134.0, 132.0, 124.6, 123.7, 122.3, 115.9, 115.4, 108.2

*6-Bromo-3-(2-nitrovinyl)indole (**2e**)*; yellow solid (99%); R_f = 0.84 (mobile phase = 40% EtOAc-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.29 (brs, 1H), 8.37 (d, *J* = 13.5 Hz, 1H), 8.23 (s, 1H), 8.00 (d, *J* = 13.9 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.6, 136.8, 134.1, 132.0, 124.6, 123.7, 122.3, 116.0, 115.5, 108.3

Synthesis of the 3-(2-nitroethyl)indole derivatives ***3***: A solution of $NaBH_4$ (0.0454 g, 6 mmol) in THF (5 mL) was stirred at room temperature for 15 min. Subsequently, a solution of **2** in THF (5 mL) was added to the reaction mixture and refluxed for 1 h. The reaction was allowed to proceed until completion, as monitored by TLC analysis. Subsequently, the reaction mixture was stirred and cooled to room temperature. The solution was cooled to 0 °C in an ice bath, and the excess $NaBH_4$ was removed by successive additions of water (10 mL), followed by successive extractions with EtOAc (2 x 10 mL), water (10 mL), and NaCl (10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated to obtain a crude product. The product was subsequently purified by radial chromatography (hexane to 30% EtOAc/Hexane) to yield compounds **3a-3e**.

*3-(2-Nitroethyl)indole (**3a**)*; light yellow solid (41%); R_f = 0.62 (mobile phase = 30% EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (brs, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.15-7.04 (m, 2H), 6.90 (d, *J* = 2.0 Hz, 1H), 4.54 (t, *J* = 8.0 Hz, 2H), 3.36 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 126.7, 122.7, 122.5, 119.9, 118.2, 111.6, 109.9, 75.8, 23.6

*2-Phenyl-3-(2-nitroethyl)indole (**3b**)*; yellow solid (25%); R_f = 0.77 (mobile phase = 30% EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (brs, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.45-7.44 (m, 5H), 7.34-7.32 (m, 1H), 7.20 (m, 2H), 4.56-4.52 (m, 2H), 3.60-3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 135.9, 132.4, 129.4, 128.6, 128.4, 128.2, 123.0, 120.5, 118.4, 111.3, 106.4, 75.2, 23.4

*5-Chloro-3-(2-nitroethyl)indole (**3c**)*; light yellow solid (70%); R_f = 0.43 (mobile phase = 30% EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (brs, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 4.65 (t, *J* = 7.2 Hz, 2H), 4.45 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 127.9, 125.9, 124.1, 123.0, 117.8, 112.6, 110.2, 75.7, 23.5

*5-Bromo-3-(2-nitroethyl)indole (**3d**)*; light yellow solid (90%); R_f = 0.53 (mobile phase = 40% EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (brs, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 4.65 (t, *J* = 7.2 Hz, 2H), 3.44 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 128.6, 125.6, 124.0, 121.0, 113.4, 113.0, 109.9, 75.7, 23.5

*6-Bromo-3-(2-nitroethyl)indole (**3e**)*; light yellow solid (70%); R_f = 0.85 (mobile phase = 40% EtOAc-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (brs, 1H), 7.36 (d, *J* = 1.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.87 (brs, 1H), 4.53 (t, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 125.6, 123.4, 123.2, 119.4, 116.0, 114.5, 110.2, 75.8, 23.5

Synthesis of the tryptamine derivatives ***4****:* A solution of **3** (0.5 mmol) in ACN/H_2O (1.5:0.05 mL) was added $Ni(OAc)_2{\cdot}4H_2O$ (0.5 mmol) and the mixture was stirred for 5 min. Subsequently, $NaBH_4$ (0.1816 g, 4 mmol) was

gradually introduced into the reaction mixture, and a fine black precipitate was immediately deposited. The reaction mixture was stirred for 20 min, during which the progress of the reaction was monitored through TLC analysis. Following this, the mixture was quenched by adding aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and evaporated to obtain a crude product. Purification of the crude product was carried out using radial chromatography (Hexane to 20:80:0.2 mL MeOH/ CH_2Cl_2) to yield compounds **4a-4e**.

*Tryptamine (**4a**)*; pale orange solid (80%); R_f = 0.25 (mobile phase = 20% MeOH-CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (brs, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 3.04 (t, *J* = 4.0 Hz, 2H), 2.92 (t, *J* = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 127.6, 122.3, 122.2, 122.1, 119.4, 119.0, 114.0, 111.3, 42.5

*2-Phenyltryptamine (**4b**)*; pale yellow solid (35%); R_f = 0.60 (mobile phase = 20% MeOH-CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (brs, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.40-7.32 (m, 2H), 7.19 (m, 1H), 7.12 (m, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 7.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 133.0, 129.2, 129.1, 128.2, 128.1, 128.0, 122.7, 120.1, 120.0, 119.2, 119.1, 111.1, 111.0, 58.4, 29.8

*5-Chlorotryptamine (**4c**)*; yellow solid (35%); R_f = 0.20 (mobile phase = 20% MeOH-CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.29 (brs, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1 H), 7.07 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.01 (d, *J* = 2.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8, 128.0, 125.4, 123.2, 121.1, 117.5, 113.1, 109.6, 39.3, 22.8

*5-Bromotryptamine (**4d**)*; brown solid (38%); R_f = 0.10 (mobile phase = 20% MeOH-CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.18 (brs, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.23 (s, 1 H), 7.17 (dd, *J* = 8.6, 1.9 Hz, 1H), 2.91-2.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 129.2, 124.4, 123.2, 120.7, 113.4, 123.4, 110.8, 42.5, 28.8

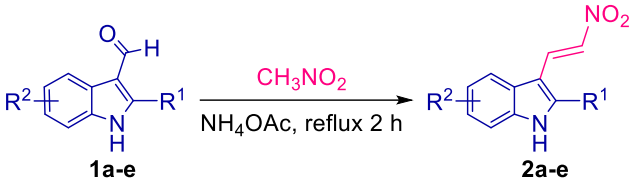
*6-Bromotryptamine (**4e**)*; white solid (37%); R_f = 0.13 (mobile phase = 20% MeOH-CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (brs, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.02 (s, 1H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 126.6, 122.7, 120.3, 115.7, 114.2, 114.1, 42.3, 29.3

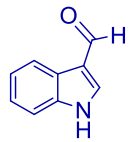
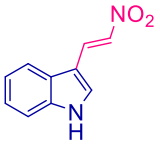
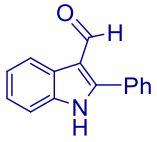
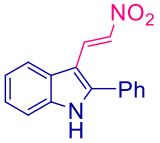
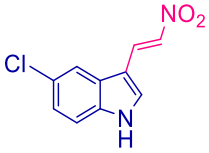
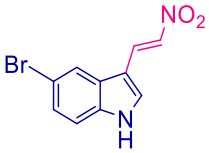
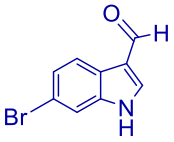
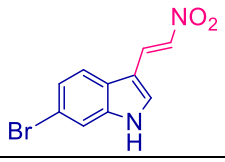
Results

The synthesis of tryptamine derivatives (**4**) commenced with the preparation of 3-(2-nitrovinyl)indole (**2a-2e**) through the Henry reaction of indole-3-carboxaldehyde (**1a-1e**) with nitromethane and NH_4OAc under reflux

conditions. The synthesis proceeded smoothly, and the desired products **2a-2e** were obtained in moderate to excellent yields (Table 1).

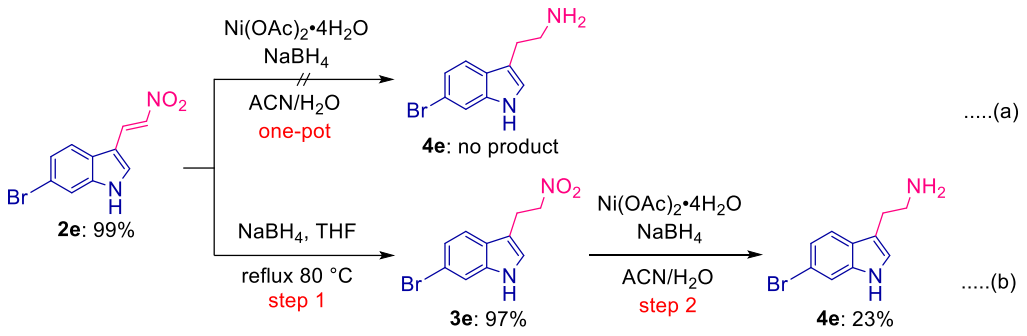
Table 1 Conversion of indole-3-carboxaldehyde (**1a-e**) to 3-(2-nitrovinyl)indole (**2a-2e**)



Entry	Indole-3-carboxaldehyde (**1**)	Product (**2**)	Yield of **2** (%)
1			95
2			55
3			62
4			99
5			99

Initially, the synthesis of tryptamine derivatives (**4**) was employed via a one-pot approach, involving the reduction of 6-bromo-3-(2-nitrovinyl)indole (**2e**) with $NaBH_4$ in the presence of $Ni(OAc)_2{\cdot}4H_2O$ in a mixture of acetonitrile (ACN) and water solvent [14]. Unfortunately, a complex mixture of unidentified products was observed (Scheme 2a). Consequently, the synthesis of tryptamine derivatives (**4**) was re-evaluated through a two-step process (Scheme 2b). Initially, the reduction of 6-bromo-3-(2-nitrovinyl)indole (**2e**) using $NaBH_4$ yielded a 97% yield

of **3e**. Subsequently, the direct reduction of 6-bromo-3-(2-nitroethyl)indole (**3e**) was performed with $NaBH_4$ and $Ni(OAc)_2{\cdot}4H_2O$ in a mixture of acetonitrile and water at room temperature, resulting in a 23% yield of 6-bromo-tryptamine (**4e**) (Scheme 2b)

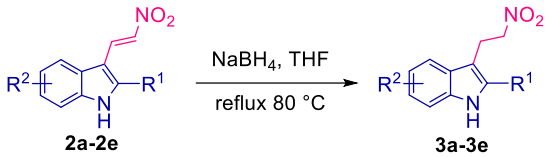


Scheme 2 Synthesis of 6-bromotryptamine (**4e**) via one-pot and two steps approach

Later, the synthesis of 3-(2-nitroethyl)indole (**3a-3e**) was achieved through the reduction of 3-(2-nitrovinyl)indole (**2**) using $NaBH_4$ as the reducing agent in THF under reflux conditions. The synthesis proceeded smoothly, and the desired products **3** were obtained with yields ranging from lower to excellent (Table 2).

Systematic studies were conducted to optimized the conditions for reducing 6-bromo-3-(2-nitroethyl)indole (**3e**) using $NaBH_4$ and $Ni(OAc)_2{\cdot}4H_2O$ as a crucial step in the synthesis of 6-bromotryptamine (**4e**) (Table 3). This investigation involved assessing the reducing agent, catalyst, and solvent. In the experiment shown in Table 3, it was found that when using 1 equivalent of $Ni(OAc)_2{\cdot}4H_2O$ catalyst and 4 equivalents of $NaBH_4$ in a mixture of acetonitrile and water (60:1) (Table 3, entry 3), significant results were observed.

Table 2 Conversion of 3-(2-nitrovinyl)indole (**2a-2e**) to 3-(2-nitroethyl)indole (**3a-3e**)



2a-2e **3a-3e**

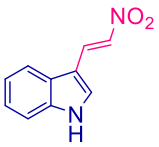
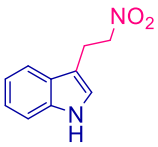
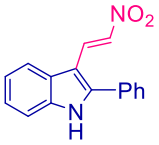
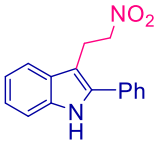
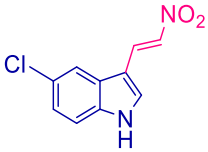
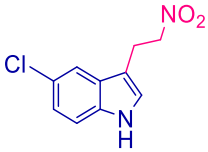
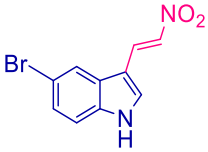
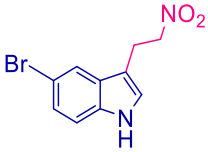
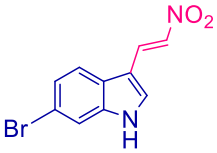
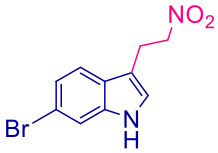
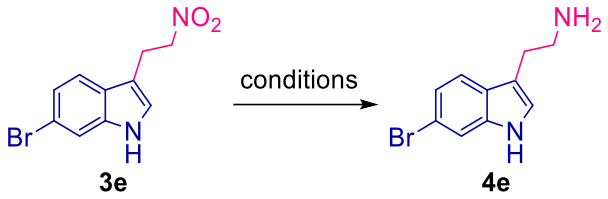
Entry	3-(2-nitrovinyl)indole (**2**)	Product (**3**)	Yield of **3** (%)
1			90
2			25
3			70
4			90
5			97

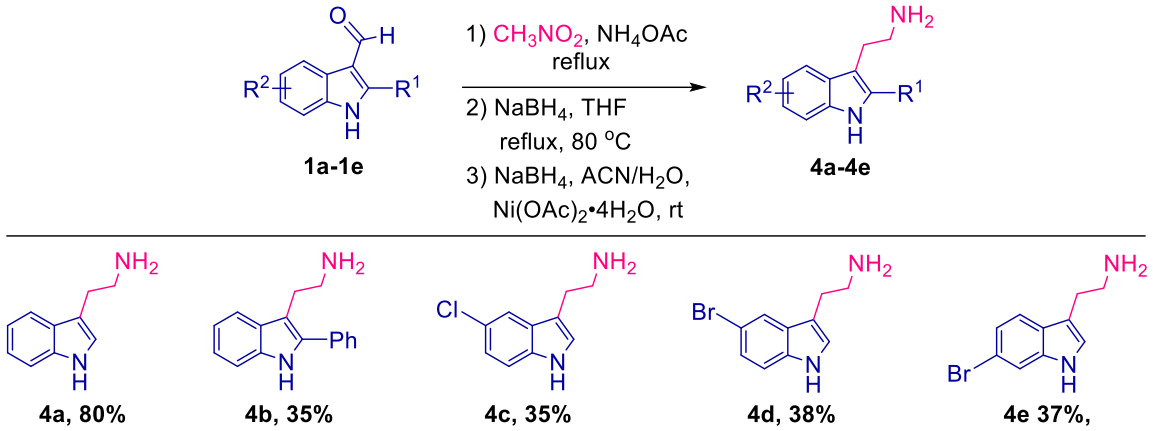
Table 3 Optimization studies for synthesis of 6-bromotryptamine (**4e**)



Entry	Step 2					
	$Ni(OAc)_2 \cdot 4H_2O$ (equiv)	$NaBH_4$ (equiv)	ACN : H_2O (mL)	Temp (°C)	Time (min)	Yield of **4e** (%) [a]
1	-	4.0	3.00 : 0.05	rt	20	-
2	0.2	4.0	3.00 : 0.05	rt	20	23
3	1.0	4.0	3.00 : 0.05	rt	20	37
4	1.0	-	3.00 : 0.05	rt	20	-
5	-	-	3.00 : 0.05	rt	1,440	-

[a] Reaction conditions: **3e** (1.0 mmol)

Although the yield of the desired product, 6-bromotryptamine (**4e**) under optimal conditions is modest, this method presents a novel approach to synthesizing tryptamine derivatives via reduction with $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ as a catalyst. These methods are simple and practical for synthesizing tryptamine derivatives. Furthermore, employing the same route as that used for **4e**, various starting materials from 3-(2-nitrovinyl)indole **2a-2e** underwent smoothly conversion. This process yielded **4a-4e** in yields ranging from trace to 80% under optimal conditions (Scheme 3).



Scheme 3 Tryptamine and its derivatives were synthesized under optimized conditions.

Discussion

The synthesis of tryptamine derivatives (**4a-4e**) is initiated by synthesizing 3-(2-nitrovinyl)indole (**2**) through the Henry reaction, involving the variation of indole-3-carboxaldehyde (**1**) with nitromethane and NH_4OAc. This process yields 3-(2-nitrovinyl)indole (**2a-2e**) in moderate to excellent yields. In the case of indole-3-carboxaldehyde (**1a**) without substituents on the indole ring, product **2a** is obtained with a yield of 95% (Table 1, entry 1). However, using 2-phenyl-3-carboxaldehyde (**1b**) as the starting material leads to the formation of product **2b** with a yield of 55% (Table 1, entry 2), attributed to the steric effects of phenyl at C2 position resulting in moderate product formation. The type of substituent on the indole ring at position 5 of Indole-3-carboxaldehyde (**1c-1d**), whether chlorine (5-Cl) or bromine (5-Br), influences the product yield (Table 1, entries 3-4). This variation is attributed to the higher electronegativity of chlorine compared to bromine, which leads to a lower electrophilicity of the aldehyde when the indole ring is substituted with 5-chlorine. Consequently, in the presence of substituents with high electronegativity, the product yield tends to be reduced. However, bromine substituents on the indole ring at position 5 (5-Br) and position 6 (6-Br) found that the positions of the substituents on the indole ring had no significant difference in product formation, with both yielding 99% of products **2d** and **2e**, consistent with Scott *et al.*, 2021 (Table 1, entries 4-5). This indicates that the positions of substituents on the indole ring do not significantly affect product formation when the substituents are identical.

The reduction of the vinyl and nitro group of 6-bromo-3-(2-nitrovinyl)indole (**2e**) was carried out using $NaBH_4$ as the reducing reagent, with $Ni(OAc)_2{\cdot}4H_2O$ serving as the catalyst in a mixture of ACN and water at room temperature. For the synthesis, 6-bromotryptamine (**4e**) via a one-pot synthesis approach. The experimental results

revealed the formation of several complex mixtures. This could be attributed to an incomplete reaction, involving only vinyl reduction, and possibly stemming from the coordination of $Ni(OAc)_2 \cdot 4H_2O$ with the nitro group, resulting in vinyl amine (Scheme 2a), but the desired product **4e** was not detected. 6-Bromotryptamine (**4e**) underwent an unsuccessful one-pot synthesis. Consequently, the synthesis of tryptamine derivatives (**4**) was re-evaluated through a two-step process (Scheme 2b) approach. The reduction of the vinyl group of 6-bromo-3-(2-nitrovinyl)indole (**2e**) was initially carried out using $NaBH_4$ at 80°C for 1 h, resulting in the production of 6-bromo-3-(2-nitroethyl)indole (**3e**) in an 97% yield. Subsequently, the direct reduction of 6-bromo-3-(2-nitroethyl)indole (**3e**) was performed with $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ in a mixture of acetonitrile and water at room temperature. This process entailed a selective reaction, employing $NaBH_4$ as a reducing reagent that specifically targeted the nitro group of **3e**. The presence of the bromine atom on the indole ring facilitates the formation of 6-bromotryptamine (**4e**) as the main product, yielding 23%, without undergoing dehalogenation. Notably, no tryptamine was produced as a by-product (Scheme 2b).

The synthesis of 3-(2-nitroethyl)indole derivatives (**3a-3e**) was conducted through the reduction of 3-(2-nitrovinyl)indole (**2a-2e**) using $NaBH_4$ as the reducing agent in THF under reflux conditions for 1 h. Under these conditions, products ranging from low to excellent yields can be synthesized, encompassing a variety scope of derivatives. When 3-(2-nitrovinyl)indole (**2a**) was used as the starting material, no substituent on the indole ring was utilized (Table 2, entry 1), leading to the formation of product **3a** in 90% yield. However, when the substituent on the indole ring was changed to 2-phenyl (**3b**), the yield of the product decreased to 25% (Table 2, entry 2). This results may be attributed to the electron-releasing group and steric effects of phenyl, resulting in only a small amount of product being obtained. Furthermore, when substituents such as chlorine (5-Cl) and bromine (5-Br) were introduced at position 5 of 3-(2-nitrovinyl)indole (**2**), the product yields of **3c** and **3d** were obtained in 70% and 90%, respectively (Table 2, entries 3-4). This significant difference in product yield may be due to the electronic properties of the electron-withdrawing group of chlorine. However, when comparing the yields of the bromine substituent at position 5 (**3d**) and position 6 (**3e**) on the indole ring, it was found that they were similar (Table 2, entries 4-5). This observation suggests that the position of the substituent did not affect the product yield in the reduction step of the vinyl nitro moiety (**2**) to ethyl nitro group (**3**).

From the results of the study, the optimization conditions for reducing 6-bromo-3-(2-nitroethyl)indole (**3e**) to 6-bromotryptamine (**4e**) are presented in Table 3. Initially, when utilizing $NaBH_4$ (4 equiv) without $Ni(OAc)_2 \cdot 4H_2O$ at room temperature in a mixture of acetonitrile and water (60:1), no reaction was observed for the conversion of **3e** (Table 2, entry 1). However, upon the addition of $Ni(OAc)_2 \cdot 4H_2O$ (0.2 equiv) to $NaBH_4$ (4 equiv) at room temperature

in acetonitrile and water (10:1), the reduction of nitro compounds **3e** was occurred. During this reduction, the decomposition of $NaBH_4$ took place, leading to the formation of a black precipitate. This precipitate may be a boride, zerovalent metal, or a mixture of these compounds. The result was the obtainment of **4e** with a yield of 23% (Table 2, entry 2) (Setamdideh *et al.,* 2011). Increasing the catalyst loading of $Ni(OAc)_2.4H_2O$ to 1 equiv under the same conditions, while maintaining the solvent ratio of acetonitrile and water (60:1), resulted in the desired **4e** with a yield of 37% (Table 2, entry 3). In the absence of the reducing reagent $NaBH_4$ at room temperature in acetonitrile and water (60:1), no reaction was observed for the conversion of **3e** (Table 2, entry 4). Additionally, a control experiment conducted without $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ at room temperature for 24 h led to the recovery of both starting materials in near-quantitative yields (Table 2, entry 5). From the results in entry 3 and 4, by the combination of $NaBH_4$ with catalytic amounts of $Ni(OAc)_2 \cdot 4H_2O$ in ACN and water, a reduction of nitro compound avoiding dehalogenation was detected, and importantly, no tryptamine by-product was observed.

The strategy for the construction of 6-bromotryptamine (**4e**) involves the ability to access structurally diverse tryptamine derivative simply by varying the readily available indole-3-carboxaldehyde (**1**) as the starting material. By an identical route to that used for synthesis 6-bromotryptamine (**4e**) from the 3-(2-nitrovinyl)indole (**2**) such as 3-(2-nitrovinyl)indole (**2a**), 2-phenyl-3-(2-nitrovinyl)indole (**2b**), 5-chloro-3-(2- nitrovinyl)indole (**2c**), 5-bromo-3-(2-nitrovinyl)indole (**2d**) (Scheme 3). The reduction of the vinyl nitro compound (**2**) is followed by the direct reduction of 3-(2-nitroethyl)indole (**3**), leading to the formation of product **4a** (80%), and products **4b-4e**, which are obtained in yields ranging from 35% to 38%. The percentage of output obtained is similar, indicating that product formation in the reduction of the nitro group to the amine group is not affected by the type and position of the substituent group on the indole ring.

Conclusions

In conclusion, this study presents a straightforward and practical approach for synthesizing tryptamine derivatives, including halogenated tryptamines. The reactions proceeded smoothly, avoiding dehalogenation, and importantly, no tryptamine by-product was observed. The desired products were obtained in moderate to good yields through a three-step process starting from indole-3-carboxaldehyde (**1**), involving the Henry reaction and reduction of the resulting vinyl nitro compound (**2**) to ethylamine (**4**). This method utilizes a combination of $NaBH_4$ and $Ni(OAc)_2 \cdot 4H_2O$ as the reducing agent.

Acknowledgements

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