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STUDIES ON THE SYNTHESIS OF β-CARBOLINE AND ITS DERIVATIVES AS POTENTIAL ANTIMALARIAL DRUG COMPONENTS

(Kajian Mengenai Sintesis β-Karbolina dan Terbitannya sebagai Komponen Ubat Anti Malaria yang Berpotensi)

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Abstract

β-Carboline constitutes a tricyclic pyrido[3,4-b] indole ring structure and is widely recognized for its prevalent biological activities. In recent years, numerous studies have reported on its excellent biological activities, particularly anti-cancer, anti-fungal, anti-malarial agents and many more. Thus, a collective of β-carboline derivatives were synthesized to explore its pharmacological properties. The synthetic approach towards β-carboline derivatives has been constructed in a two-step reaction, including Pictet-Spengler condensation reaction and the iodine-mediated oxidative dehydrogenation reaction. Pictet-Spengler was carried out by treating aldehydes bearing different substituents with tryptamine in the presence of trifluoroacetic acid. The synthesized intermediates were then aromatized to give the desired β-carboline derivatives. All these synthesized intermediates and β-carboline derivatives were analyzed and confirmed by NMR and ATR-FTIR spectroscopy. The working foundation established in this study will be applied in future research and development of new broad-spectrum β-carboline based anti-malarial drugs. Compounds **6**, **9** and **12** synthesized in this work could be promising anti-malaria candidates in this future user.

Keywords: β-carboline, oxidative dehydrogenation reaction, pictet-spengler condensation, tetrahydro-β-carboline, trifluoroacetic acid

Abstrak

β-Karbolina membentuk struktur cincin indol pyrido trisiklik [3,4-b] dan diiktiraf secara meluas untuk aktiviti biologinya yang lazim. Dalam beberapa tahun kebelakangan ini, banyak kajian telah dilaporkan mengenai aktiviti biologinya yang sangat baik terutamanya sebagai agen anti-kanser, anti-kulat, anti-malaria dan banyak lagi. Oleh itu, satu kolektif terbitan β-karbolina telah disintesis untuk meneroka lebih lanjut sifat farmakologinya. Pendekatan sintetik terhadap terbitan β-karbolina telah dibina dalam tindak balas dua langkah yang merangkumi tindak balas pemeluwapan Pictet-Spengler dan tindak balas dehidrogenasi oksidatif pengantara iodin. Pictet-Spengler telah dijalankan dengan merawat aldehid yang mengandungi substituen berbeza dengan triptamina dengan kehadiran trifluoroasetik asid. Perantaraan yang disintesis kemudiannya diaromatis untuk memberikan terbitan β-karbolina yang dikehendaki. Semua perantaraan yang disintesis dan terbitan β-karbolina ini dianalisis dan disahkan oleh spektroskopi NMR dan ATR-FTIR. Asas kerja yang ditubuhkan dalam kajian ini akan digunakan dalam penyelidikan dan pembangunan masa depan ubat antimalaria berasaskan β-karbolina spektrum luas baharu. Kompaun **6**, **9** dan **12** yang disintesis dalam kerja ini boleh menjanjikan calon anti-malaria pada pengguna masa hadapan ini.

Kata kunci: terbitan β-karbolina, tindak balas pendehidrogenan oksidatif, pemeluwapan picter-spengler, tetrahydro-β-karbolina, trifluoroasetik asid

Introduction

In the year 2020, WHO estimated 241 million malaria cases leading to 627 000 deaths, globally [1] whilst based on the annual Commonwealth Malaria Report 2022, the increment of malaria incidences and mortality rates has been reported and ever since the outbreaks of COVID-19. This pandemic disrupted all malaria services and progressed.

Malaria is a global disease induced by apicomplexan parasites derived from plasmodium species [2] where plasmodium falciparum and plasmodium vivax were found to be the most dominant genus contributed to the accession of mortality and morbidity rates [3]. These parasites are carried by female *Anopheles* mosquitoes and infect the human bloodstream upon bloodmeals.

Over the years, multiple treatments and approaches like vector control, vaccines and chemotherapy have been used to combat this infectious disease [4]. The most popular malaria treatments are the common artemisinin-based combination (Fig.1) therapies (ACTs). These first-line treatments comprise artemisinin derivatives such as artesunate-mefloquine (AS-MQ), artesunate-sulfadoxine-pyrimethamine (AS+SP) and artesunate-pyronaridine [5]. The absence of a vaccine and the complexity of these plasmodium species lifecycle triggers the resistance of these strains towards the ACTs [6] and other available drugs [7]. Thus, studies on such artemisinin-based molecules will lead to the potential discovery of new and effective anti-malarial drugs.

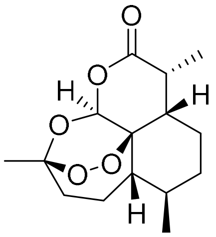
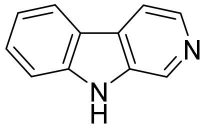


Figure 1. Parent structure of artemisinin

Natural β-carboline alkaloid **1** was found to hold the essential moiety in the exploration of various kinds of drugs due to its excellent biological and pharmacological activities which include anti-plasmodial [8], anti-fungal [9], anti-microbial [10], anti-cancer [11] and more. The scaffolds of β-carboline are extensively distributed in natural products such as plants, insects, marine invertebrates and plant-derived foods [12]. β-Carboline is a part of the indole alkaloid family [13] with a deviating degree of aromaticity [14] of the N-containing six-membered rings. Unsaturated members of β-carboline are known as fully aromatic-β-carbolines (FAβCs). In contrast, the partially saturated and completely saturated rings are known as dihydro-β-carbolines (DHβCs) and tetrahydro-β-carboline (THβCs), respectively (Fig.2).



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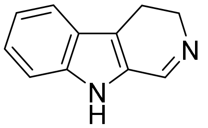

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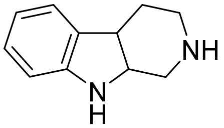

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Figure 2. Aromaticity of β-carbolines: (**1**) FAβCs, (**2**) DHβCs, (**3**) THβCs

Yeung et al. (2010) discovered that β-carboline derivatives, spiroindolones or spirotetrahydro β-carbolines possess good anti-malarial activity with in vitro IC_{50} of 90nM. The racemic mixture of spiroazepineindole has been identified to exhibit good efficacy against NF54 and chloroquine-resistant (KI) parasite strains [8]. Additionally, azepineindole (Fig.3) and tetrahydro-β-carboline derivative also (Fig.4) showed a moderate potency towards anti-malarial activity. Tetrahydro-β-carboline (THβCs) and fully aromatic-β-carboline (FAβCs) derivatives such as 5-chloro-tetrahydro-β-carboline [6] exhibit satisfaction activities with low toxicity towards human cells. As for [15], they had reported two guanidine conjugated β-carboline compounds composing excellent activities against malaria strains with IC_{50} values of 0.6 to 1.0 μM.

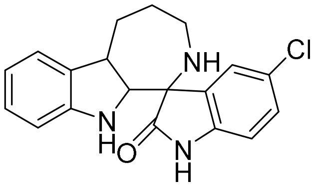


Figure 3. Azepineindole

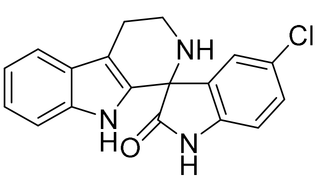


Figure 4. Tetrahydro-*β*-carboline derivative

In line with our interest in finding and developing novel anti-plasmodial agents, we are intrigued to synthesize β-carboline derivatives using tryptamine with various benzaldehyde substituents by applying two facile synthesis reactions. The application of the Pictet-Spengler condensation reaction was the most reported method to synthesize THβCs with the aid of strong Brønsted acids to promote the ring closure of imine. In order to synthesize FAβCs, an oxidative dehydrogenation reaction with iodine was found to be more feasible and convenient [16]. Herein, we report a collection of synthesis results upon applying the Pictet-Spengler reaction catalyzed by trifluoroacetic acid (TFA) and oxidative dehydrogenation reaction.

Materials and Methods

Procedure for the synthesis of compounds 6a-g:

Benzaldehyde (1.0 equiv.) was added to a stirred suspension of tryptamine (1.0 equiv.) and TFA (1.5 equiv.) in DCM. The resulting solution was stirred for 24 hours. The reaction mixture was extracted with EtOAc and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated and purified by silica gel column chromatography with n-hexane, EtOAc (4:1) gradient and 3% triethylamine.

Procedure for the synthesis of compounds 7a-g:

Compound **6(a-g)** (1.0 equiv.) was added to DMSO, iodine, I_2 (0.5 equiv.) and followed by H_2O_2 (1.0 equiv.) and the resulting mixture was stirred at 100˚C for 12 hours. The reaction mixture was poured over cold water extracted with EtOAc and dried over anhydrous Na_2SO_4. The organic layer was evaporated and purified by silica gel column chromatography eluting with a gradient of n-hexane and EtOAc (9:1).

Results and Discussion

4-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)benzonitrile (6a). Yield: 82%, yellow solid. IR ν cm^{-1}: 3344, 2491, 1659,1449,641cm^{-1}. 1H-NMR (400 MHz, METHANOL-D4) δ 7.86 (dt, J = 8.4, 1.8 Hz, 2H), 7.59-7.54 (m, 3H), 7.29-7.27 (m, 1H), 7.17-7.06 (m, 2H), 6.01 (s, 1H), 3.65-3.53 (m, 2H), 3.23-3.12 (m, 1H). 13C-NMR (101 MHz, METHANOL-D4) δ 139.2, 137.3, 132.9, 130.6, 126.1, 125.8, 122.7, 119.5, 118.0, 117.6, 114.0, 111.2, 108.1, 56.1, 40.8, 18.1.

1-(4-bromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (6b). Yield: 60%, brown oil. IR ν cm^{-1}: 3067,2174, 1670, 1455, 722 cm^{-1}. 1H-NMR (400 MHz, METHANOL-D4) δ 7.67-7.65 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.32-7.26 (m, 3H), 7.14-7.07 (m, 2H), 5.89 (s, 1H), 3.28-3.15 (m, 4H). 13C-NMR (101 MHz, METHANOL-D4) δ 137.2, 133.4, 132.3, 131.4, 126.6, 125.9, 124.4, 122.5, 119.4, 117.9, 111.1, 107.9, 56.2, 40.7, 18.2.

1-(3-bromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (6c). Yield: 66%, yellow oil. IR ν cm^{-1}: 3239, 2179, 1675, 1432, 744 cm^{-1}. 1H-NMR (400 MHz, METHANOL-D4) δ 7.61 (dt, J = 7.6, 1.7 Hz, 1H), 7.55-7.50 (m, 2H), 7.39-7.32 (m, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.14-7.03 (m, 2H), 5.68 (s, 1H), 3.51-3.38 (m, 2H), 3.12-3.05 (m, 2H). 13C-NMR (101 MHz, METHANOL-D4) δ 138.7, 137.1, 132.6, 132.3, 130.7, 128.2, 128.1, 126.1, 122.7, 122.2, 119.2, 117.8, 111.0, 108.3, 56.3, 41.0, 19.1.

1-(3-nitrophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (6d). Yield: 92%, yellow oil. IR ν cm^{-1}: 3258, 2180,1667, 1135, 667 cm^{-1}. 1H-NMR (400 MHz, METHANOL-D4) δ 8.40-8.37 (m, 1H), 8.32 (t, J = 2.1 Hz, 1H), 7.80-7.73 (m, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.19-7.07 (m, 2H), 6.10 (s, 1H), 3.67-3.58 (m, 2H), 3.24-3.18 (m, 2H). 13C-NMR (101 MHz, METHANOL-D4) δ 148.7, 137.3, 136.2, 135.7, 130.5, 126.1, 125.9, 125.0, 124.5, 122.7, 119.6, 118.1, 111.2, 108.3, 56.0, 41.0, 18.2.

1-(4-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (6e). Yield: 90%, yellow solid. IR ν cm^{-1}: 3055, 1617, 1415, 1321, 742 cm^{-1}. 1H-NMR (400 MHz, METHANOL-D4) δ 7.63 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 3H), 7.20-7.18 (m, 1H), 7.00 (tdd, J = 14.9, 7.0, 1.2 Hz, 2H), 5.23 (s, 1H), 4.07 (q, J = 7.2 Hz, 1H), 3.21 (dt, J = 12.5, 5.4 Hz, 1H), 3.07-3.01 (m, 1H), 2.92-2.78 (m, 2H). 13C-NMR (101 MHz, METHANOL-D4) δ 146.1, 136.7, 132.7, 129.3, 127.0, 125.1, 125.1, 121.1, 118.5, 117.5, 110.7, 109.2, 56.8, 41.2, 21.5.

1-(naphthalen-1-yl)-2,3,4,9-tetrahydro-1*H*-pyridol[3,4-*b*]indole (6f). Yield: 76%, brown oil. IR ν cm^{-1}: 3055, 1617, 1415, 1321, 742 $cm^{-1.}$ 1H-NMR (400 MHz, CHLOROFORM-D) δ 8.22-8.29 (1H), 7.86-7.93 (1H), 7.80-7.84 (1H), 7.55-7.61 (2H), 7.47-7.53 (1H), 7.33-7.40 (1H), 7.21-7.30 (1H), 7.10-7.18 (2H), 5.85-5.95 (1H), 3.29-3.39 (1H), 3.13-3.22 (1H), 2.84-3.03 (2H). 13C-NMR (101 MHz, METHANOL-D4) δ 147.2, 146.1, 145.7, 138.8, 136.7, 136.7, 132.7, 129.3, 128.3, 127.0, 125.1, 125.1, 121.1, 118.5, 117.5, 110.7, 109.2, 56.8, 41.2, 21.5.

1-(4-isopropylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (6g). Yield: 53%, yellow oil. IR ν cm^{-1}: 3136, 3057, 1453, 1359, 1710, 744 cm^{-1}. 1H-NMR (400 MHz, CHLOROFORM-D) δ 7.59-7.63 (1H), 7.52-7.55 (1H), 7.18-7.21 (4H), 7.09-7.13 (2H), 5.10-5.15 (1H), 4.08-4.14 (1H), 3.32-3.40 (1H), 3.07-3.15 (1H), 2.86-2.96 (2H), 2.80-2.84 (1H), 1.24-1.25 (3H), 1.22-1.23 (3H). 13C-NMR (101 MHz, CHLOROFORM-D) δ 149.0, 148.7, 141.3, 139.1, 135.9, 134.7, 128.5, 127.5, 126.9, 121.7, 119.4, 118.3, 110.9, 110.2, 57.9, 43.0, 34.0, 24.1, 24.1, 22.6.

4-(9H-pyrido[3,4-b]indol-1-yl)benzonitrile (7a). Yield: 33%, yellow oil. IR ν cm^{-1}: 3240, 2922, 1670, 1136, 746 cm^{-1}. 1H-NMR (400 MHz, METHANOL-D4) δ 8.42 (dd, J = 5.5, 1.8 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 8.15-8.09 (m, 3H), 7.97-7.93 (m, 2H), 7.61-7.54 (m, 2H), 7.29 (dd, J = 8.2, 6.9 Hz, 1H). 13C-NMR (101 MHz, METHANOL-D4) δ 139.2, 137.3, 132.9, 130.6, 126.1, 125.8, 122.7, 119.5, 118.0, 117.6, 114.0, 111.2, 108.1, 56.1, 40.8, 18.1.

1-(4-bromophenyl)-9H-pyrido[3,4-b]indole (7b). Yield: 71%, yellow solid. IR ν cm^{-1}: 2983, 1736, 1372, 1233, 1043, 607 cm^{-1}. 1H-NMR (400 MHz, CHLOROFORM-D) δ 8.54-8.57 (1H), 8.13-8.18 (1H), 7.93-7.97 (1H), 7.81-7.87 (2H), 7.68-7.73 (2H), 7.48-7.59 (2H), 7.29-7.35 (1H). 13C-NMR (101 MHz, METHANOL-D4) δ 137.2, 133.4, 132.3, 131.4, 126.6, 125.9, 124.4, 122.5, 119.4, 117.9, 111.1, 107.9, 56.2, 40.7, 18.2

1-(3-bromophenyl)-9H-pyrido[3,4-b]indole (7c). Yield: 41%, yellow solid. IR *v* cm^{-1}: 3061, 2925, 1231, 742, 673 cm^{-1}. 1H-NMR (400 MHz, ACETONE-D6) δ 8.48 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 7.3 Hz, 1H), 8.20 (t, J = 1.8 Hz, 1H), 8.10-8.05 (m, 2H), 7.64-7.61 (m, 2H), 7.55-7.46 (m, 2H), 7.27 (td, J = 7.5, 0.9 Hz, 1H). 13C-NMR (101 MHz, METHANOL-D4) δ 138.6, 133.1, 132.7, 132.4, 131.6, 126.9, 124.4, 122.5, 117.4, 117.9, 111.3, 104.1, 56.2, 46.7, 19.2

1-(3-nitrophenyl)-9H-pyrido[3,4-b]indole (7d). Yield: 33%, yellow solid. IR *v* cm^{-1}: 3403, 2922, 1348, 729 cm^{-1}. 1H-NMR (400 MHz, ACETONE-D6) δ 8.57-8.47 (m, 3H), 8.41-8.15 (m, 4H), 7.62 (dd, J = 8.2, 0.9 Hz, 1H), 7.57-7.53 (m, 1H), 7.49 (d, J = 8.7 Hz, 0H), 7.29 (td, J = 7.5, 0.9 Hz, 1H). 13C-NMR (101 MHz, METHANOL-D4) δ 148.7, 137.3, 136.2, 135.7, 130.5, 126.1, 125.9, 125.0, 124.5, 122.7, 119.6, 118.1, 111.2, 108.3, 56.0, 41.0, 18.2

1-(4-(trifluoromethyl)phenyl)-9H-pyrido[3,4-b]indole (7e). Yield: 48%, yellow oil. IR *v* cm^{-1}: 3018, 1214, 743, 668 cm^{-1}. 1H-NMR (400 MHz, CHLOROFORM-D) δ 8.58 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 5.0 Hz, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.59-7.50 (m, 2H), 7.35-7.31 (m, 1H). 13C-NMR (101 MHz, CHLOROFORM-D) δ 139.8, 136.8, 128.9, 128.6, 128.4, 126.2, 126.2, 125.9, 125.9, 125.6, 125.1, 122.0, 120.8, 120.7, 120.2, 114.6, 112.2, 111.7.

1-(naphthalen-1-yl)-9H-pyrido[3,4-b]indole (7f). Yield: 56%, brown oil. IR *v* cm^{-1}: 3345, 2921, 1625, 741 cm^{-1}. 1H-NMR (400 MHz, CHLOROFORM-D) δ 8.65 (d, J = 5.0 Hz, 1H), 8.20 (t, J = 8.2 Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 7.98 (dd, J = 12.8, 8.2 Hz, 2H), 7.77 (dd, J = 7.1, 1.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 8.0, 7.1 Hz, 1H), 7.54-7.49 (m, 2H), 7.42-7.36 (m, 2H), 7.33-7.29 (m, 1H). 13C-NMR (101 MHz, CHLOROFORM-D) δ 142.4, 140.5, 138.8, 134.7, 134.1, 129.6, 128.9, 128.7, 128.0, 126.9, 126.4, 125.8, 125.5, 122.0, 121.7, 120.4, 114.2, 111.8.

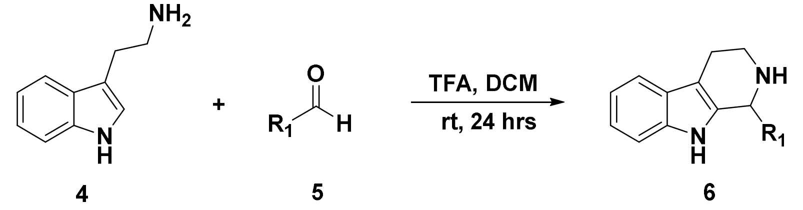
1-(4-isopropylphenyl)-9H-pyrido[3,4-b]indole (7g). Yield: 46%, yellow solid. IR *v* cm^{-1}: 3382, 2956, 1456, 743 cm^{-1}. 1H-NMR (400 MHz, CHLOROFORM-D) δ 8.54 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 5.5 Hz, 1H), 7.87 (dd, J = 6.4, 1.8 Hz, 2H), 7.54 (t, J = 1.1 Hz, 1H), 7.49 (s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.32-7.28 (m, 1H), 2.99 (t, J = 6.9 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H). 13C-NMR (101 MHz, METHANOL-D4) δ 139.1, 137.2, 134.4, 132.3, 132.1, 128.6, 125.9, 124.4, 122.5, 120.8, 119.4, 117.9, 116.1, 111.1, 107.9, 74.3, 56.2, 40.7, 17.2.

Tryptamine was designated as the model substrate due to its readily synthetic availability. The utilization of benzaldehyde derivatives as the electrophile to undergo condensation with tryptamine commanded most of the initial attention. The Pictet-Spengler reaction was applied to induce the formation of the cyclic ring via C-C bond by the usage of tryptamine as the starting material.

Technically, the Pictet-Spengler reaction expressed the formation of iminium salt upon acid-catalyzed condensation of tryptamine with benzaldehyde derivatives followed by *endo* cyclization between the nucleophilic carbon at the C-2 position and resulting in the intermediate product of N-heterocyclic ring with new C-C bond. Looking at the structure of tryptamine, both carbon-2 and carbon-3 can act as a nucleophile. Spiroindolenine intermediate is produced if the reaction proceeds to attack at carbon-3 before undergoing the 1,2-alkyl shift to yield the tetrahydro-β-carboline (THβCs) intermediates.

In this study, a collective of benzaldehyde derivatives and tryptamine were used to develop a series of tetrahydro-β-carboline (THβCs) and fully aromatic-β-carbolines (FAβCs). Generally, benzaldehyde (**5**) bearing electron-withdrawing group (EWG) provided a higher yield of intermediate THβCs (**6**) compared to those with an electron-donating group (EDG) (Table 1). This can be explained by the inductive and resonance effects of the substituents. Benzaldehyde with electron-donating groups (EDG) in **6f-g** activated the ring and reduced the electrophilicity of the carbonyl carbon, resulting in weaker reactivity and lower product yields. On the contrary, benzaldehydes bearing electron-withdrawing groups (EWG) in **6a-e** contributed substantially greater yields.

Table 1. Scope of reactions of tryptamine with different substituted benzaldehydes

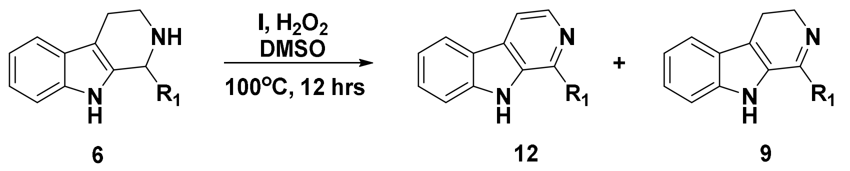


Entry	**R1**	**Yield (%)**
6a	*p*-cyanophenyl	82
6b	*p*-bromophenyl	60
6c	*m*-bromophenyl	66
6d	*m*-nitrophenyl	92
6e	*p*-(trifluoromethyl)phenyl	90
6f	*o*-napthaldehyde	76
6g	*p*-isopropylphenyl	53

Each of the intermediate products, THβCs (**6**) proceeded for aromatization by utilizing the oxidative dehydrogenation reaction with iodine. There are various ways to promote the aromatization and construction of these β-carboline structures. However, a few drawbacks were highlighted. Some procedures such as applying heat with palladium, Pd on carbon, C [17] or sulphur, S [18] or boiling the intermediate THβCs with organic solvents over high temperature with oxidizing agents are not favorable because they require raucous condition. Method utilizing reagents such as chloranil [19], DDQ [20], trichloroisocyanuric acid [21], $PhI(OAc)_2$ [22], N-chlorosuccinimide [23] and IBX [24] could promote aromatization. However, they were reported to suffer from disadvantages of using excess reagents, having massive waste production and affording low yield of target compounds.

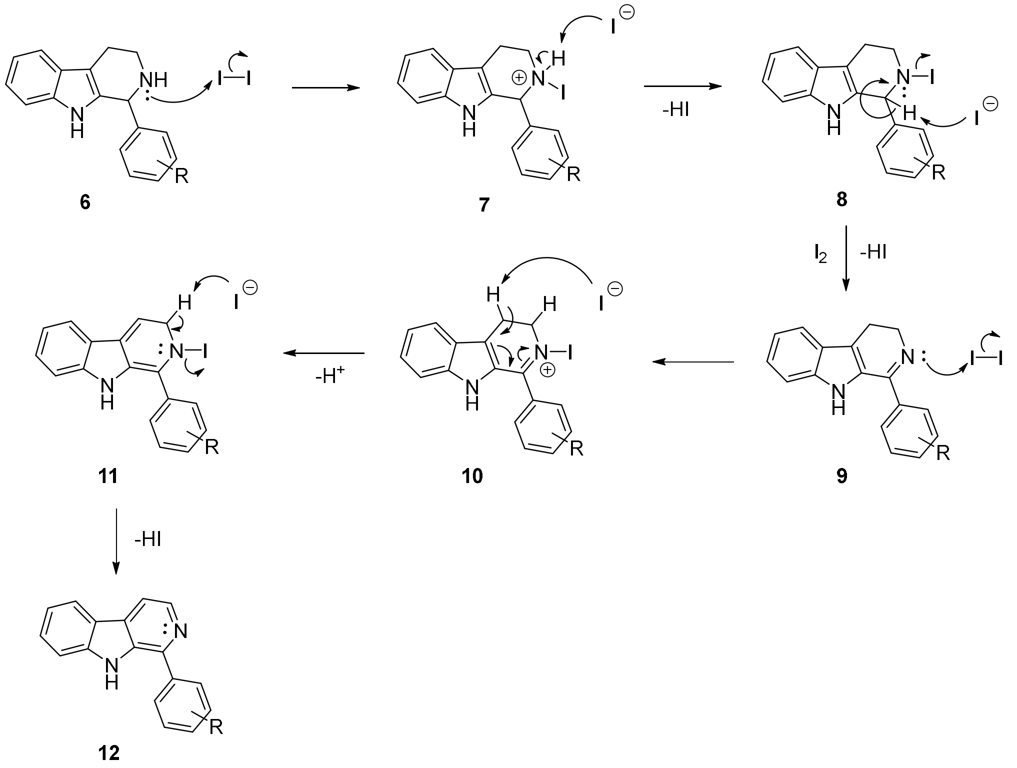
According to Table 2, THβCs with both the electron-withdrawing group (EWG) and electron-donating group (EDG) provided moderate product yields since the electronic effect and activation profile of each of the benzaldehyde substituent does not affect the aromatization of the N-heterocyclic ring. The moderate yields of the target products, FAβCs (**12**) can be explained by the formation of DHβCs (**9**) as the minor products. Alternately, complete aromatization of THβCs could also be achieved by increasing the equivalent amount of H_2O_2 [16],[25].

Table 2. Aromatization of tetrahydro-β-carboline (THβCs) intermediates



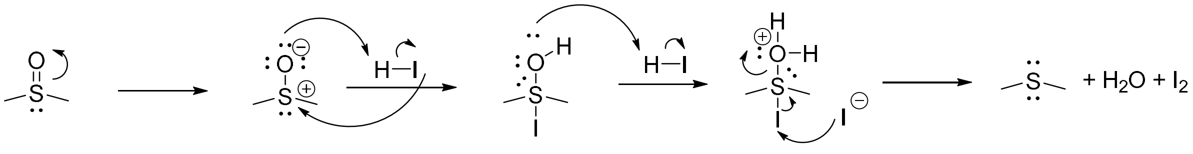
Entry	R1	Yield (%)
7a	*p*-cyanophenyl	33
7b	*p*-bromophenyl	71
7c	*m*-bromophenyl	41
7d	*m*-nitrophenyl	33
7e	*p*-(trifluoromethyl)phenyl	48
7f	*o*-napthaldehyde	56
7g	*p*-isopropylphenyl	46

The mechanism of oxidative dehydrogenation reaction can be explained by the initial N-iodination of THβCs intermediate (**6**) where the lone pair of the nitrogen attacks the iodine, followed by the formation of imine intermediate, DHβCs (**9**) *via* dehydroiodination process. Next, DHβCs undergo another N-iodination reaction to yield an ammonium intermediate (**10**). Subsequent deprotonation and dehydroiodination upon this intermediate promote aromatization and give our final target product of FaβCs (Scheme 1).



Scheme 1. Mechanism of iodine-mediated oxidative dehydrogenation

The regeneration of iodine, I_2 is crucial to maintain a continuous cycle for this reaction. Dehydroiodination reaction took at least twice to produce HI where its acidic proton will promote the removal of water, reduction of DMSO to dimethyl sulfate (DSM) and regeneration of iodine, I_2 (Scheme 2). H_2O_2 promotes an atmospheric environment to control the reduction activity by oxidizing the DMS to DMSO and catalyzed the reaction activity [26].



Scheme 2. Mechanism on regeneration of iodine, I_2

Conclusion

In conclusion, a series of tetrahydro-β-carboline intermediates were synthesized via Pictet-Spengler reaction from tryptamine and benzaldehydes with different substituents. Benzaldehydes bearing the electron-withdrawing groups (EWG) provided higher yields compared to those with electron-donating groups (EDG). Application of iodine-mediated oxidative dehydrogenation method promoted the aromatization of N-heterocyclic ring of THβCs intermediates into fully aromatized-β-carbolines (FAβCs) as the major products and dihydro-β-carbolines (DHβCs) as the minor products. Further study on the biological properties of the synthesized products toward anti-malaria activities are currently in progress.

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