SYNTHESIS OF EVODIAMINE AND IT'S ANALOGUES

A MSC Dissertation report by:

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April ,2022

SYNTHESIS OF EVODIAMINE AND IT'S ANALOGUES

A DISSERTATION REPORT

Submitted in Partial fulfillment

Of

The Degree of M.S.C (Organic Chemistry)

By

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To the

School Of Chemical Sciences

Goa University

Goa 403206

APRIL 2022

SYNTHESIS OF EVODIAMINE AND IT'S ANALOGUES

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ACKNOWLEDGEMENT

The accomplishment and eventual outcome of this dissertation report entitle "Literature Survey on Synthesis of Evodiamine and it's analogues" required a lot of guidance and backing and I am very fortunate to get this till completion of my dissertation.

First and foremost, I would like to respect and thank my dissertation guide, Prof. Dr. Bidhan A. Shinkre, who encouraged and directed me in doing lot of research and gain knowledge and also providing me his valuable time for progress and success of dissertation.

I would like to thank Dr. Vidhyadatta M. Shet Verkar, Dean of School of Chemical Sciences who always motivated and enthusiastically supported. I would also like to thank faculty of School of Chemical Sciences for their constant cooperation.

Last but not least, I thank the almighty for hid blessing and my parents for their support and guidance during dissertation work.

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INTRODUCTION

Evodiamine, the Indoloquinazoline alkaloids isolated from ripe fruits of Evodia rutecarpine has been utilized in traditional Chinese medicine. Chinese herbal medicine represents a major source of natural compounds and is an integral part of eastern medicine. Evodiamine has diverse biological activities including anti-inflammatory, anti-obesity, antitumor effects. Evodiamine has been shown to reduce fat uptake in animal studies and has been included in dietary preparations, particularly in the Chinese herbal weight loss supplement, Wu-Chu-Yu. Evodiamine has evolved a superior ability to bind various proteins, so we also argue that it is good starting point for multi target drugs. Evodiamine has shown strong cytotoxic effects against human cancer cells in addition to apoptosis induction, suppression of invasion and metastasis. The antitumor activity of evodiamine and its derivatives has aroused substantial interest among medical chemistry researches. Evodiamine possess good inhibitory effects against lung cancer A549. Evodiamine sensitized chemoresistant breast cancer cells to Adriamycin without obvious cytotoxicity against normal human peripheral blood cells which indicated the potential of evodiamine for clinical application. Evodiamine decreased testosterone production partly by inhibition of the activity of CAMP-related pathways and 17 β-HSD in rat TICs. Two sets of carbamates based on the natural alkaloid evodiamine were designed, synthesized and evaluated at potential butyrylcholinesterase for the treatment of Alzheimer's disease. The activity of evodiamine as useful starting point for development of new agoinst of the transient receptor vanilloid type-I (TRP1) cation channel. From the chemical point of view, the indole NH of evodiamine is an excellent functional group synthesizing various derivatives plays positive roles in curing chronic diseases, such as cardiovascular disease by intervening on the risk factors and underlying determinants linked with chronic diseases.

Physiochemical Properties of Evodiamine are

Molecular formula of Evodiamine is: $C_{19}H_{17}N_3O$

IUPAC name: 21-methyl-3,13,21-triazapentacyclo [11.8.0.0^{2,10}.0^{49}.0^{15,20}] henicosa – 2(10),4,6,8,15,17,19-heptaen-14-one

Evodiamine is a fine powder of a pale-yellow crystals with no perceptible odor or taste.

Evodiamine is insoluble in water

Melting point of Evodiamine is 263-265^{0}c

Boiling point of Evodiamine is 575.1^{0}c

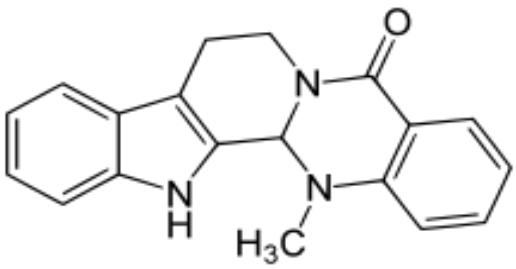
Density is 1.39 gm/cm^3

Refractive index is 1.764

It is stored at temperature 2-8^{0}c

Evodiamine can be assayed using an ultraviolet spectrophotometer at 225 nm or by high-performance liquid chromatography system using an internal standard method.

Structure



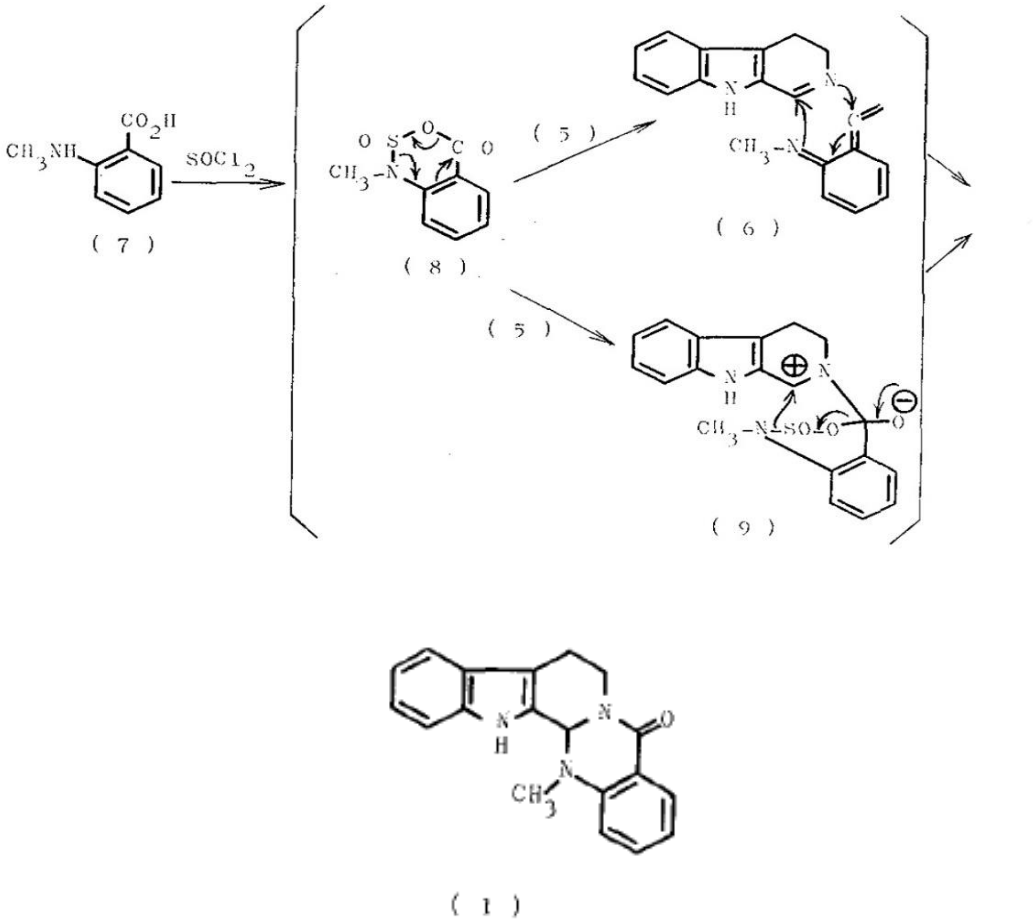
Evodiamine

LITERATURE REVIEW

2.1 Synthesis of Evodiamine through Retro Diels Alder – Reaction

Testsuji Kamet ani et al, synthesized Evodiamine by condensation of 3,4–dihydro-β-carboline. At first substrate N-methylantranilic acid (7) was heated with thionyl chloride in dry benzene to give an unstable sulfinamide anhydride (8) which was then treated with 3,4-dihydro-dihydro-β-carboline (5) in dry benzene. Sulphur dioxide evolved at room temperature and Evodiamine (1) was formed (Evodiamine 1976).

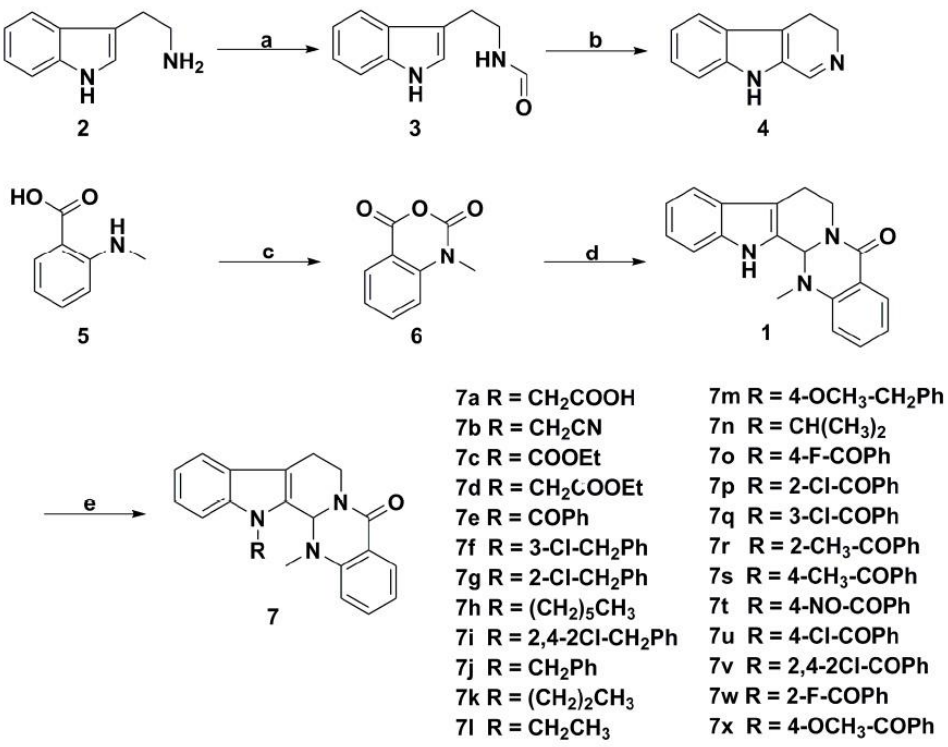
Scheme 1



2.3 Synthesis of Evodiamine (1) and evodiamine derivatives by Topo I inhibitors

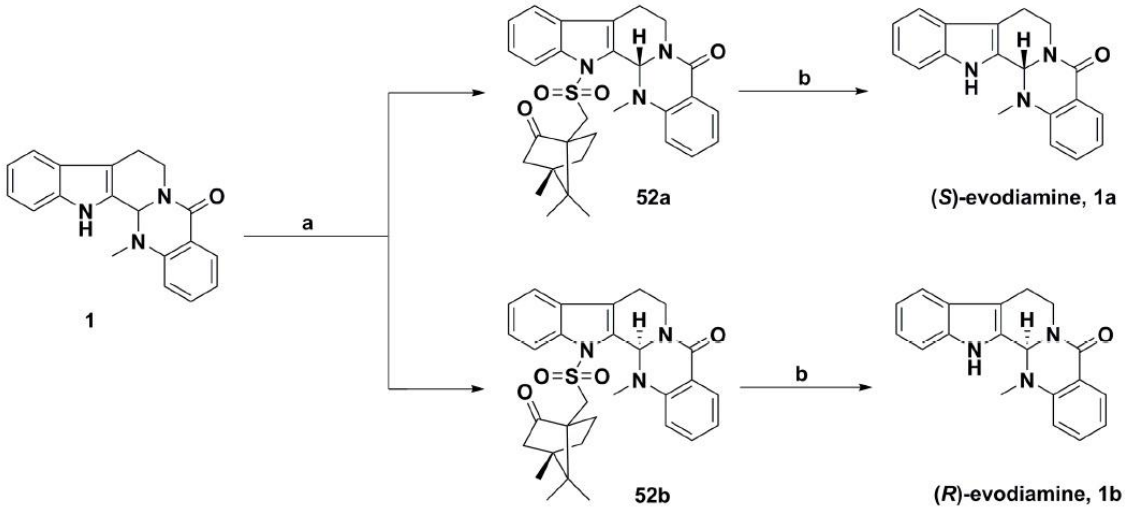
Dong et al. found that evodiamine as human Topo I inhibitor by structure – based virtual screening and lead optimization. By introducing alkyl, benzoyl, and benzyl groups and esters at N-13, evodiamine derivatives were synthesized as Topo I inhibitors. The substituted benzoyl groups were favorable for the antiproliferative effects against A549, HCT-116 AND MDA-MB-435 human cancer cell lines with IC_{50} values of 0.86,2.6 and 0.0049 μM. Through chiral high performance liquid chromatographic method Nguyen's group isolated evodiamine enantiomers from 13 Evodia rutaecarpa samples. It showed that S- (+)-evodiamine is present in higher concentration than R- (-)-evodiamine. The human sitrtuins SIRT1, SIRT2 and SIRT3 assays indicated that S configuration was favorable than R. [19](Hu et al., n.d.)

Scheme 2



Synthetic route of evodiamine **1** and evodiamine derivatives **7a–x**. Reagents and conditions: (**a**) HCOOEt, reflux, 12 h; (**b**) $POCl_3$, 0 °C 2 h, then rt, 2 h; (**c**) ClCOOEt, reflux, 12 h; (**d**) **4**, 30–60 °C, 6 h; (**e**) RX, NaH, 80 °C, 24 h.

Scheme 3

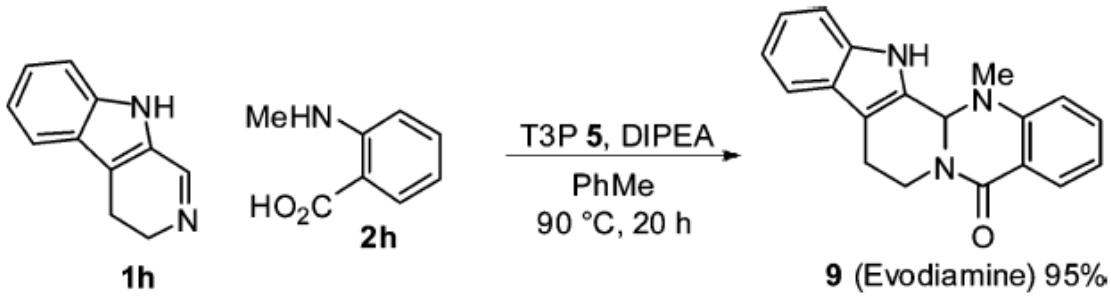


Synthetic route of evodiamine enantiomers **1a** and **1b**. Reagents and conditions: (**a**) (1*S*)-10-camphorsulfonyl chloride, NaH, 60 °C, 10 h; (**b**) NaOH, MeOH/THF 1:1, rt, 18 h.

2.4 Synthesis of Evodiamine via Direct imine Acylation

William P. Unsworth et al, proposed synthesis of Evodiamine through application of Direct imine acylation. The synthesis started from dihydrocarboline (1h) reacted with N-methyl anthranilic acid (2h) under mild nature of reagents used such as Propylphosphoric acid anhydride (T3P5) and DIPEA along with PhMe at 90^{0}c for 20 hours. Under Direct imine acylation condition 95% of Evodiamine was synthesized (Unsworth, Kitsiou, and Taylor 2013).

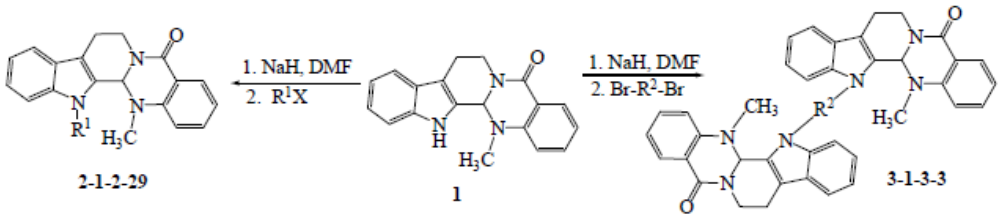
Scheme 4



2.5 Synthesis of N-13 Substituted Evodiamine derivative

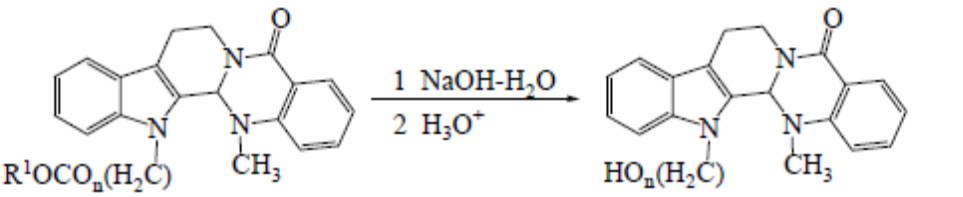
Senchuan Song et al, proposed a substitution reaction of Evodiamine with alkyl halide or p-toluene sulfonic acid ester at the N-13 position of evodiamine were completed smoothly and derived N, N – dimethylformamide (DMF). The synthetic pathways to the target compound are outlined from Scheme 1-4 (Song et al. 2013).

Scheme 5: Synthesis of N-13 substituted evodiamine derivative 2-1-2-29 and 3-1-3-3



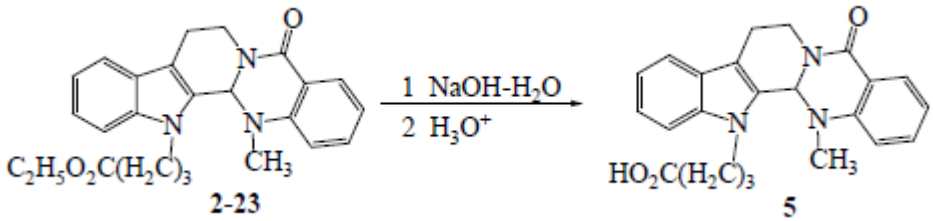
R^1 = **2-1**, -$CH_2CH{=}CH_2$; **2-2**, -$(CH_2)_3CH_3$; **2-3**, -$(CH_2)_4CH_3$; **2-4**, -$CH_2CH{=}C(CH_3)_2$; **2-5**, -$(CH_2)_7CH_3$; **2-6**, -$(CH_2)_3C_6H_5$; **2-7**, -$CH_2CH(CH_3)_2$; **2-8**, -$(CH_2)_2CH(CH_3)_2$; **2-9**, -$(CH_2)_3Cl$; **2-10**, -$(CH_2)_3Br$; **2-11**, -$(CH_2)_4Cl$; **2-12**, -$(CH_2)_2O(CH_2)_2O(CH_2)_2Cl$; **2-13**, -$CH_2COC_6H_5$; **2-14**, -$(CH_2)_2OCH_3$; **2-15**, -$(CH_2)_2O(CH_2)_3CH_3$; **2-16**, -$(CH_2)_4OCH_3$; **2-17**, -$(CH_2)_2O(CH_2)_2OCH_3$; **2-18**, -$CH_2CH(OC_2H_5)_2$; **2-19**, -$(CH_2)_2OCOCH_3$; **2-20**, -$(CH_2)_3OCOCH_3$; **2-21**, -$(CH_2)_2OCOC_2H_5$; **2-22**, -$(CH_2)_2CO_2C_2H_5$; **2-23**, -$(CH_2)_3CO_2C_2H_5$; **2-24**, (oxiran-2-yl)methyl; **2-25**, -$(CH_2)_2OCOCH(CH_3)_2$; **2-26**, -$(CH_2)_5Br$; **2-27**, -$CH_2CO_2CH_2C_2H_5$; **2-28**, -$(CH_2)_4CO_2C_2H_5$; **2-29**, -$(CH_2)_5CO_2C_2H_5$. R^2 = **3-1**, -$(CH_2)_5$-; **3-2**, -$(CH_2)_6$-; **3-3**, -$(CH_2)_2O(CH_2)_2O(CH_2)_2$-.

Scheme 6: Synthesis of N13-(hydroxyalkyl) evodiamine derivatives 4-1 and 4-2

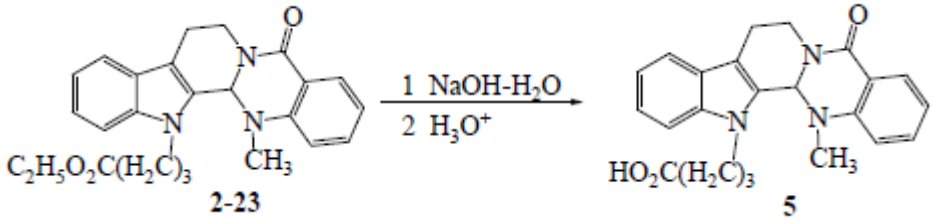


$R^1 = CH_3$, **2-19**, n = 2; **2-20**, n = 3 $R^1 = CH_3$, **4-1**, n = 2; **4-2**, n = 3

Scheme 7: Synthesis of 4-(evodiamine-N13-yl) butyric acid 5.



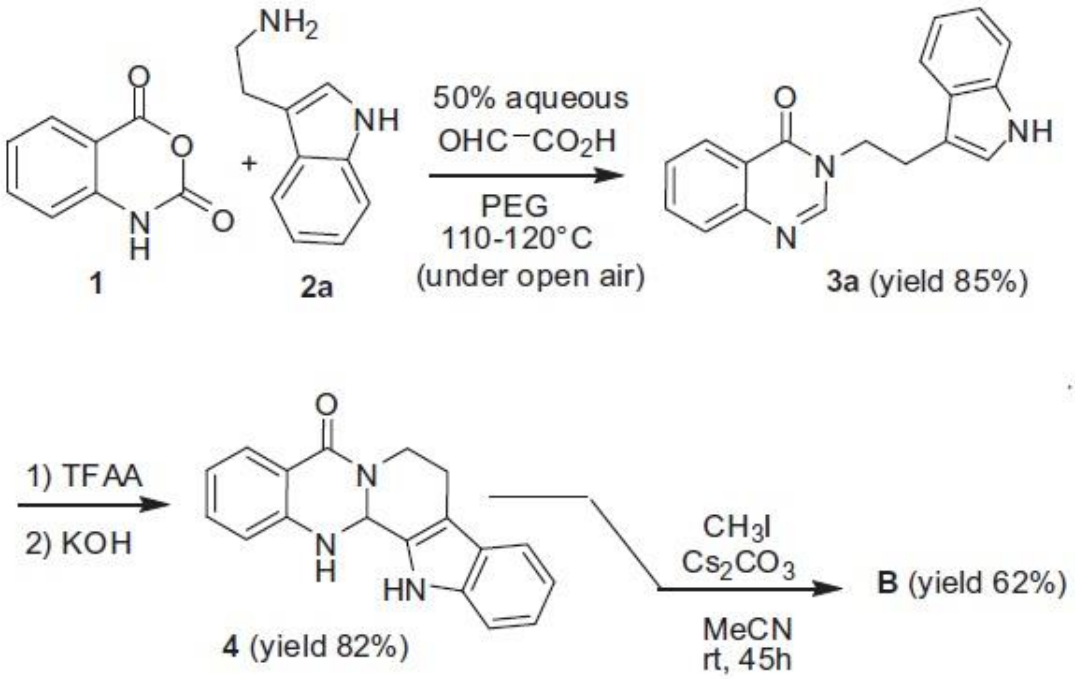
Scheme 8: Synthesis of 6,6-1-6-2.



2.6 Synthesis of Evodiamine via. Glyoxic acid in the Isatoic anhydride with amines

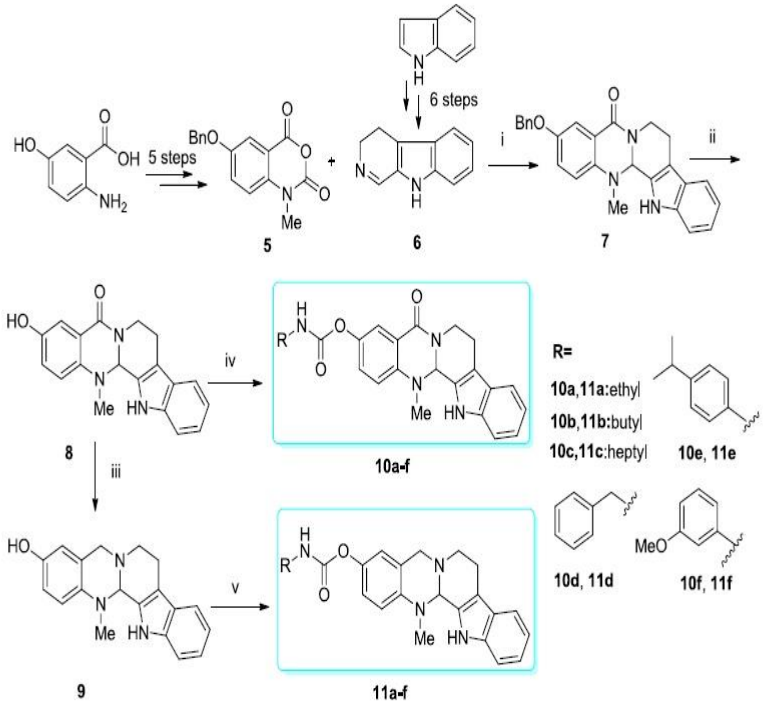
K. Raghavendra Rao et al proposed that, A dual reactant/catalyst role of glyoxylic acid in the reaction of Isatoic anhydride with various amines synthesis of 3-(un) substituted quinazoline–4(3H)–one. This metal catalyst free reaction proceeds via an unusual and unexpected cleavage of C-C bond. Synthesis of Evodiamine was carried out such that the Isatoic anhydride (1) reacted with tryptamine (2a) and glyoxylic acid in PEG-400 at 110-120°c for 15 min under open air to give the product (3a). Then the compound (3a) reacted with TFFA followed by KOH to form 13 b, 14 – dihydrorutacarpine (4). Lastly the (4) compound reacted with MeI in the presence of Cs_2CO_3 to afford Evodiamine (B) in 62% yield (Rao et al. 2014).

Scheme 9



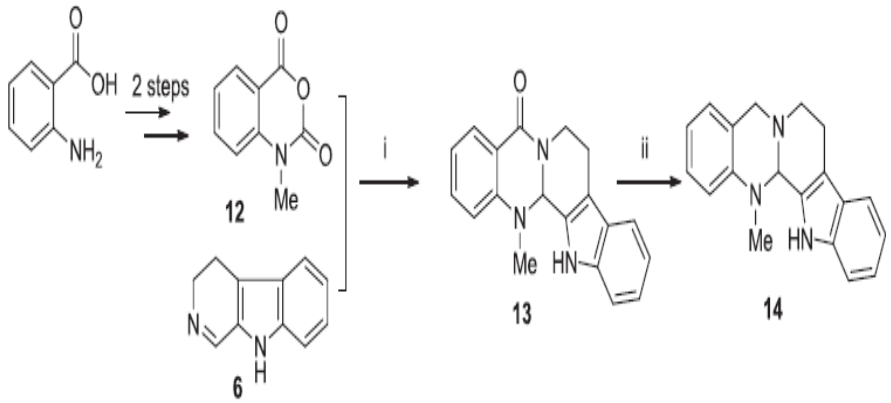
2.7 Guozheng Huang et al, proposed that two sets of carbamates based on the natural alkaloid evodiamine synthesized as potential butryrylcholinesterase inhibitor. Condensation of 4,9-dihydro-3H-pyrido[3,4-b] indole (6) and 6-(benzyloxy)-1-methyl-1-H-benzo [d] [1,3] oxazine 2,4-dione (5) was refluxed in DCM which produced 97% yield of benzyloxyevodiamine (7). Further (7) was benzylated by hydrogenation to convert it into 3-hyroxyevodiamine (8). In the presence of Hunig's base carbamoylation of 3-hydroxyevodiamine generated carbamates 10 a-f. For the production of 5-deoxo-3hydroxyevodiamine (9). (8) was reduced using lithium aluminum anhydride. Then (9) was also carbamoylated in the presence of triethylamine to afford 2nd type of carbamate (11 a-f) (Huang et al. 2014)

Scheme 10



Synthetic protocol for target carbamates **10a–f** and **11a–f**. Reagents and conditions: (i) CH_2Cl_2, reflux, 20 h; (ii) 1 atm H_2, THF, r.t., 20 h; (iii) $LiAlH_4$, THF, r.t., 8 h; (iv) isocyanate, Hünig's base, THF, 2–4 days; (v) isocyanate, triethylamine, CH_2Cl_2, 2–4 h.

Scheme11



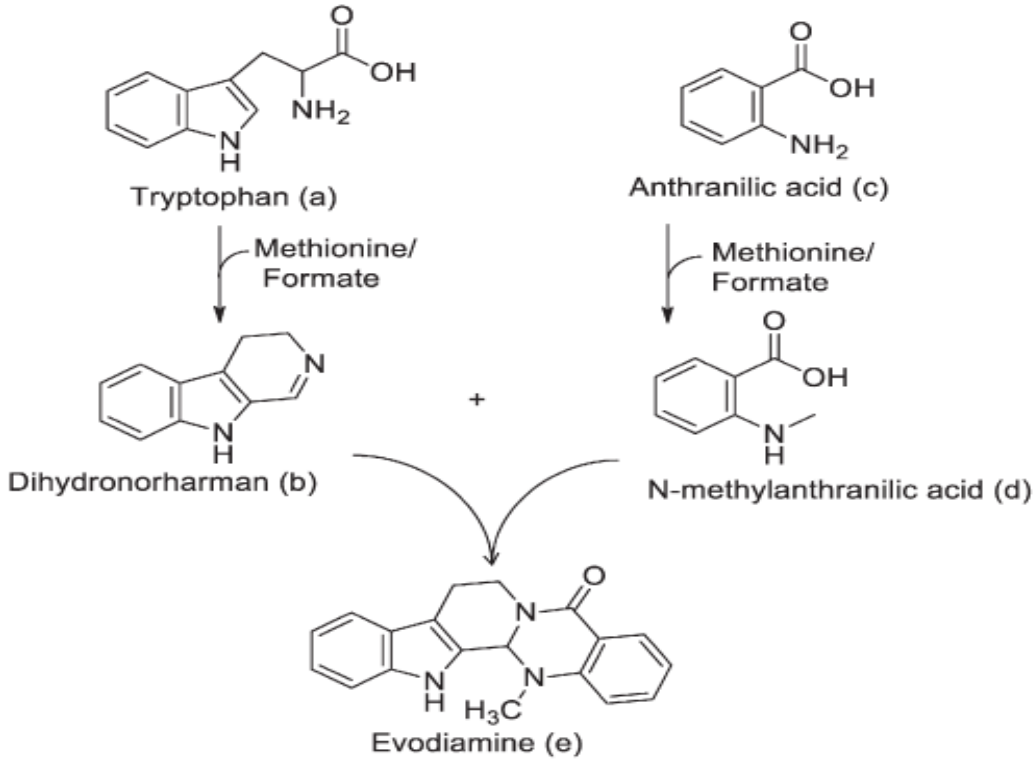
Synthetic protocol for evodiamine (**13**) and 5-deoxoevodiamine (**14**) synthesis. Reagents and conditions: (i) CH_2Cl_2, reflux, 20 h; (ii) $LiAlH_4$, THF, r.t., 8 h.

2.8 Synthesis of Evodiamine by Biogenisis

Kriti Gavaraskar reports in that Indoloquinazoline alkaloids of the E. rutaecarpa plant were biosynthesized through tryptophan -anthranilic acid metabolism path – way [9]. Early precursors for the formation of Evodiamine include formic acid, tryptophan, anthranilic acid. Biogenesis of evodiamine is carried out by precursores Tryptophan (a)and Anthranilic acid (c). During the biosynthesis tryptophan is converted to intermediate dihydronorharman (b) by using C1-unit from methionine/formate as a reagent. Similarlary anthranilic acid is converted to N-methylantranilic acid (d) using the same reagent methionine. By condensation of both dihdyronorharman (b) and N-methylantranilic acid together gave formation of Evodiamine (e). This method focuses mainly on the therapeutic or cosmeceutical application [18](Gavaraskar, Dhulap, and Hirwani 2015).

Biogenesis of Evodiamine

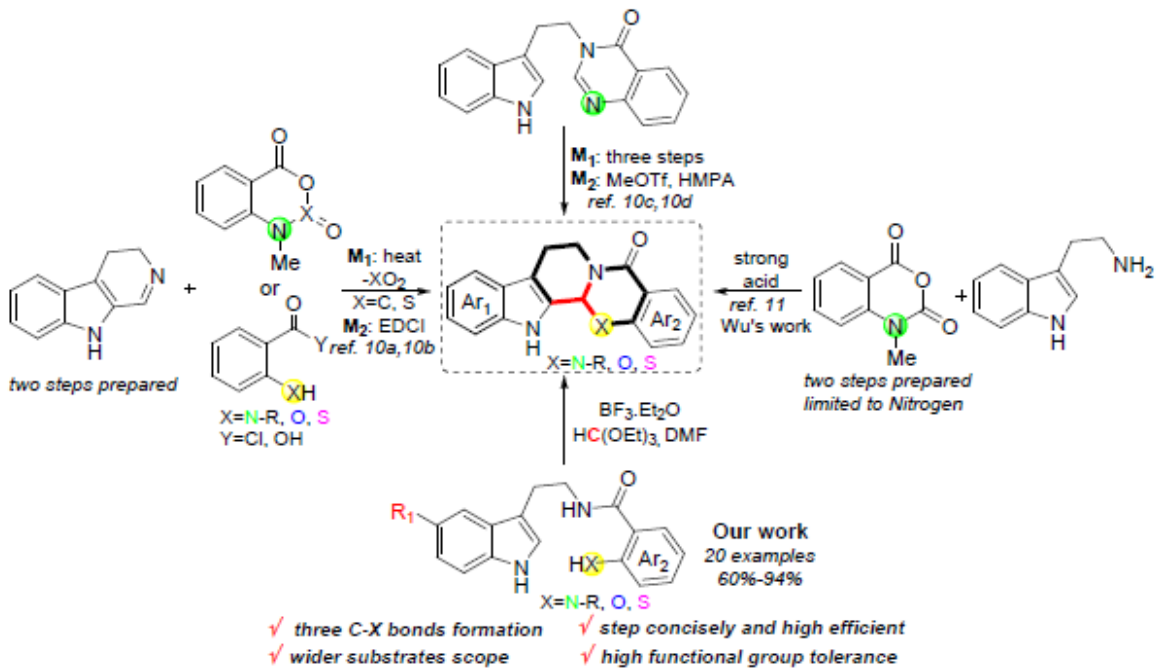
Scheme 12



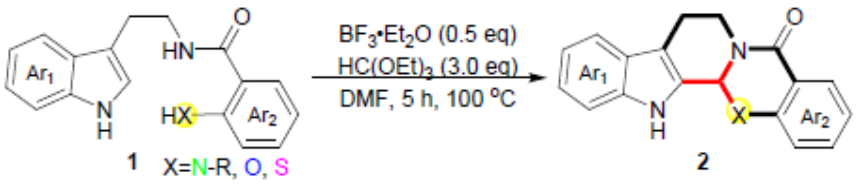
2.9 Synthesis of Evodiamine and it's Analogues via Lewis acid catalysis

Jie-Dan Deng et al, developed an efficient route to Evodiamine and various heteroatom containing analogues. In this, three chemical bonds and two fused rings were constructed within the one step. HC $(OEt)_3$ was used as carbon source along with lewis acid $AlCl_3$ as the catalyst. $BF_3.Et_2O$ in 0.5 equivalent was used as reagent and Dimethylformamide (DMF) solvent was also used for formation Evodiamine (Deng et al. 2019)

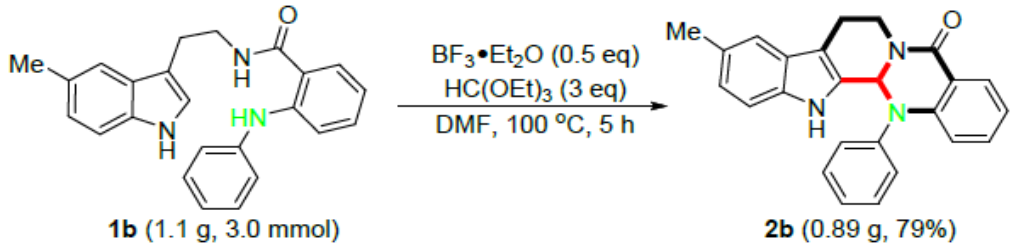
Scheme 13



Scheme 14



Scheme 15

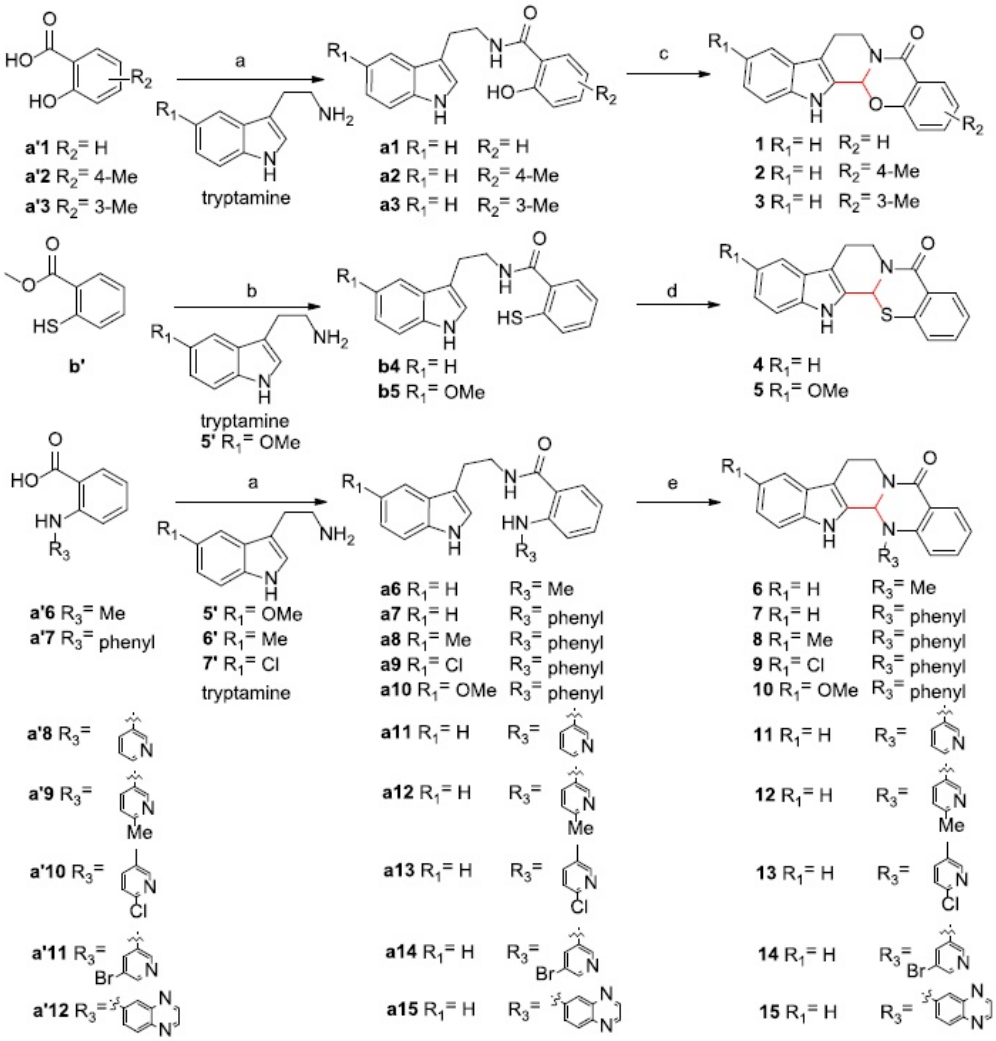


1b (1.1 g, 3.0 mmol)

2b (0.89 g, 79%)

3.0 Xiaohang Fan [b,1] et al. synthesized and designed 15 evodiamine derivatives for hepatocellular carcinoma (HCC) treatment by simultaneously targeting Topo I and Cancer -associated fibroblasts (CAFs). Previously reported synthetic processes where methyl group is replaced by N14 position. Now this N14 position is inhibiting by Topo I and reducing CAFs activation to show excellent anti liver cancer efficiency in vitro and in vivo was proven by subsequent structure-activity relationships study (SARs) and biological evaluation. 15 compounds were synthesized by one step construction of three chemical bonds and two heterocyclic-fused rings (Fan et al. 2021).

Scheme 14

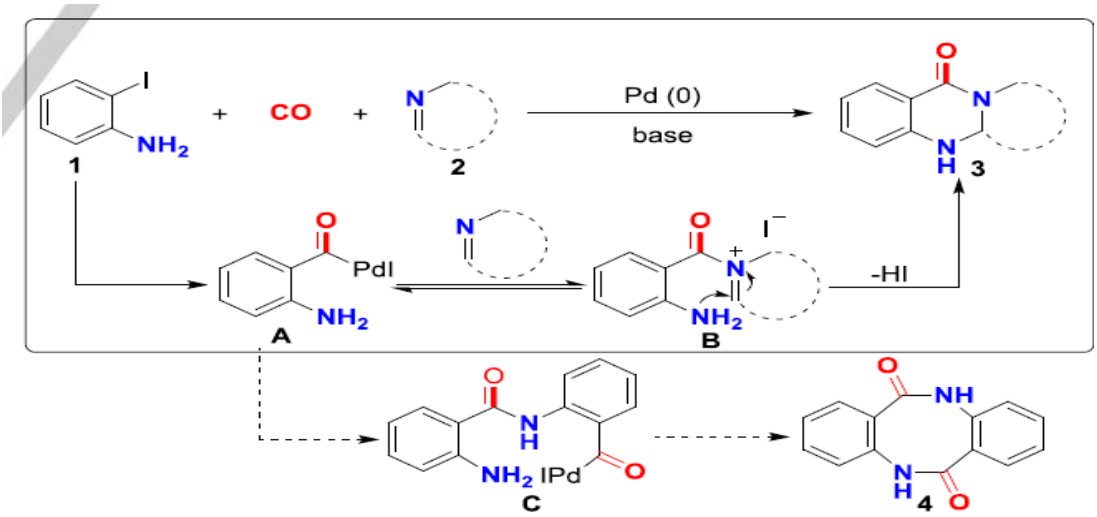


Synthetic route to evodiamine derivatives. (a) EDCI, HOBt, TEA, DCM, r.t., 16 h; (b) $AlMe_3$, DCM, r.t., 8 h; (c) $HC(OEt)_3$, $BF_3{\cdot}Et_2O$, DMF, 135 °C; (d) $HC(OEt)_3$, $BF_3{\cdot}Et_2O$, DCM, r.t; (e) $HC(OEt)_3$, $BF_3{\cdot}Et_2O$, DMF, 100 °C.

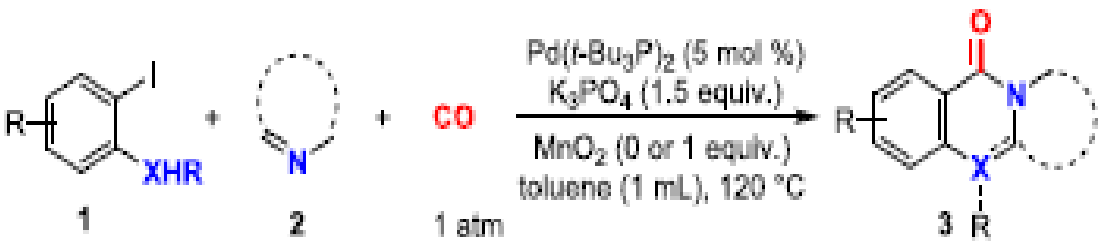
3.1 Palladium-Catalyzed Carbonylative Difunctionalization of C=N bond of Azaarenes or imines to Evodiamine

By intercepting the acylpalladium species with C=N bond of azaarenes or imines other than free amines or alcohols, the difunctionalization of C=N bond established via palladium-catalyzed carbonylation/nucleophilic addition sequence. In this method first the optical reaction condition conditions identified, investigation into the substrate scope for the present carbonylative cyclization of 2-iodoaniline with a variety of pyridines, imines and other C=N bond containing molecules was pursued. In scheme 3 ,2-iodophenol to react with 4,9-dihydro-3-H-pyrido[3,4-b] indole 2q to give evodiamine analogue 3jq in 47% yield. In scheme 4,4,9-dihydro-3-H-pyrido[3,4-b] indole 2q reacted with 2-iodo-N-methylaniline to give corresponding analogue evodiamine (3iq) (Journal, n.d.)

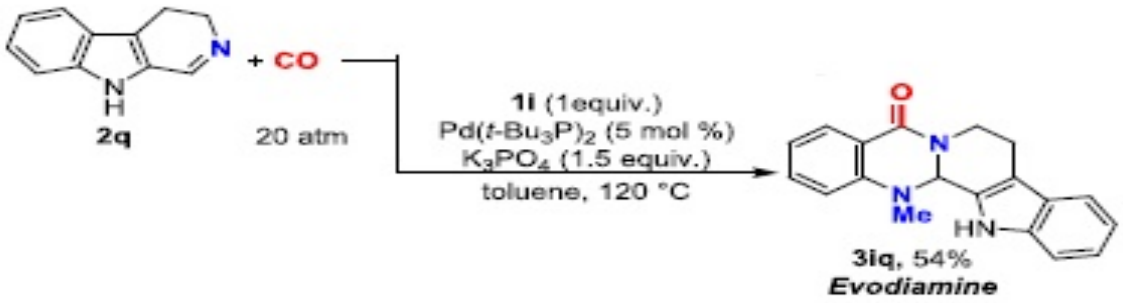
Scheme 15



Scheme 16



Scheme 17


+ CO
20 atm
1i (1equiv.)
Pd(t-Bu3P)2 (5 mol %)
K3PO4 (1.5 equiv.)
toluene, 120 °C
2q
3iq, 54%
Evodiamine

CONCLUSION

It was found that there are many low cost, high efficiency, and lesser side effect methods for synthesizing Evodiamine**.** There were many approaches reviewed for synthesis of the synthesis of Evodiamine and it's analogues like Retro Diels - Alder reaction, glyoxic acid in Isatoic anhydride with amines, Palladium-catalyzed Carbonylative of C=N bond, Direct Imine Acylation, lewis acid catalysis. The derivatives Evodiamine, N1-butyryleevodiamine showed good stability and bioavailability. As it is a natural product in ecofriendly way biogenesis was also carried out, and also by inhibition of Topo I inhibitors, by continuous bicyclization was also carried out. The N-substituted Evodiamine derivatives were also synthesized. Evodiamine and enantiomer based enhanced efficacy can be helpful to evaluate Evodiamine and its derivatives as promising scaffold for the development of novel class of multi-target-directed compounds, which can be beneficial mainly for treating cancer and inflammation.

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