# “Review On Synthesis Of Rutaecarpine”

A Dissertation Report

Submitted in Partial Fulfilment

Of

The Degree of M.Sc.(Organic Chemistry)

By

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Goa University

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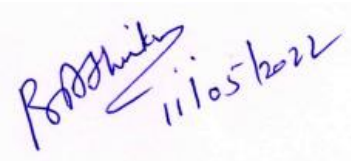
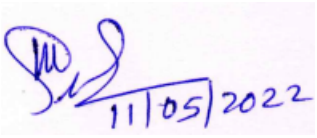
# CERTIFICATE

This is to certify that the dissertation entitled “ Review on Synthesis of Rutaecarpine” is bonafide work carried out by Ms. Prachi Lalitkumar Parab under my supervision in partial fulfilment of the requirement for the award of degree of Master of Science in Chemistry at the school of Chemical Sciences, Goa University.

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# STATEMENT

I hereby declare that the matter presented in this dissertation entitled, REVIEW ON SYNTHESIS OF RUTAECARPINE is based on literature review carried out by me in the School of Chemical Sciences, Goa University, Goa under the supervision of Dr. Bidhan Shinkre and same has not been submitted elsewhere for the award of degree or diploma.

Prachi L. Parab

(M.Sc. Student)

# INDEX

**1.Introduction:** Many studies indicate that traditional chinese herbs are beneficial in the prevention and treatment of cardiovascular diseases. Rutaecarpine is an indolopyridoquinazolinone[1] alkaloid was first isolated[2] from a chinese herbal drug, Wu-Chu-Yu(asahina and Kashiwaki,1915),which is the dried, unripe fruit of Evodia rutaecarpa. Rutaceous plants, mainly Evodia rutaecarpa[3] have been used for the treatment of gastrointestinal disorders, headache, amenorrhea, and postpartum hemorrhage in traditional oriental medicine. Many studies indicate that traditional chinese herbs are beneficial in the prevention and treatment of cardiovascular diseases[4].

Representatively, rutaecarpine(1a) and its derivatives attracted considerable attention of pharmaceutical scientists due to their broad biological activities including anti-thrombiotic, anticancer[5][6], anti-inflammatory[7] and analgesic, anti-obesity[8] and thermoregulatory, vasorelaxing[9] activity, as well as effects on cardiovascular[4] and endocrine system. Therefore, synthesis of rutaecarpine becomes utmost important. Over the last few decades, hundreds of quinazolinone alkaloids[10] with a polycyclic structural motifications(analogues of rutaecarpine)[11] have been discovered and studied for various purposes. Recently, biologically active hybrid analogues,8-norrutaecarpine and 7-hydroxy-8-norutaecarpine, have been isolated and synthesised[12] also rutaecatpine analogues have been tested against CNS cancer[13]. A review written in 2015 by Joung-Keun Son, Hyeun Wook Chang and Yurngdong Jahng[14]. mentioned 733 references found in the SciFinder database provided by the American Chemical Society. In addition, 55 patents have been reported based on isolation, biological activity, synthesis, metabolism, and toxicology in the year 2015. Numbers of papers till 2015 covering rutaecarpine are summarized in Table 1 and few of which listed below.

**Table 1.** Numbers of references listed for recent years.

| Period | 1915–2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Numbers | 339 | 42 | 46 | 43 | 59 | 69 | 64 | 52 | 19 | 733 |

The characterization of chemical constituents in Evodia Rutacarpa extract was carried out by high speed counter chromatography with two phase solvent system[2] and the structure of rutaecarpine was determined by degradation method, Rutaecarpine on fusion with KOH gave aniline, CO2, NH3 and indole-2-carboxylic acid[15]. Although hydrolysis of rutaecarpine with KOH in amyl alcohol yielded anthranilic acid. Following infrared, ultraviolet spectroscopy, mass spectrometry, 1H-NMR and 13C-NMR spectroscopy were used to confirm the structure of rutaecarpine. Later, the molecular structure was confirmed by X-ray analysis by Fujii, Kobayashi and Hirayama [9], who reported that rutaecarpine (C18H13N3O) gave monoclinic crystals.

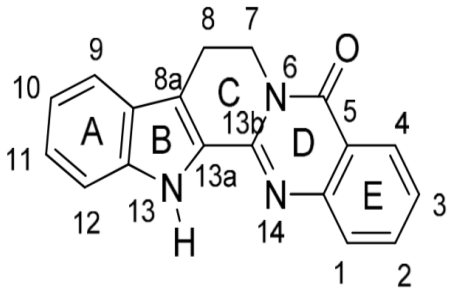


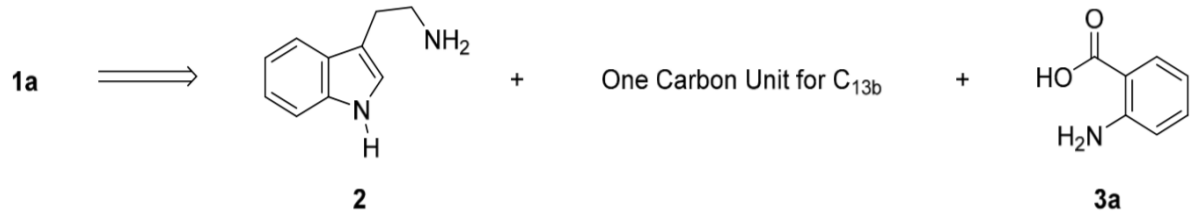

**Figure 1.** Structure of rutaecarpine (**1a**).

## 2.Literature Review:

This review summarizes data on the synthesis, and biological activities of rutaecarpine published over the recent years, aiming to provide more evidence supporting the same.

## I.Synthesis of Rutaecarpine

A comprehensive review written in 2008 by Seung Ho Lee, Jong-Keun Son, Byeong Seon Jeong, Tae-Cheon Jeong, Hyeon Wook Chang, Eung-Seok Lee and Yurngdong Jahng[15] covered very well the series of synthetic procedures for rutaecarpine which have been reported in the literature over the years, this report complements the riview written in 2015. A simple retrosynthetic analysis of rutaecarpine gives tryptamine (2) which is equivalents for the indole moiety, and anthranilic acid (3a) which is equivalents for the quinazolinone moiety, which now leaves an additional one-carbon unit needed for the C13b atom in rutaecarpine (Scheme 1).




**Scheme 1:** Retrosynthesis analysis for rutaecarpine synthesis.

Tryptamine (2) has been one of most popular starting materials and the compounds 4, 5, and 6 (Figure 2) have been used as alternative starting materials which provide the A,B,C-ring system(figure 1) and the one-carbon unit at C13b(scheme 1).

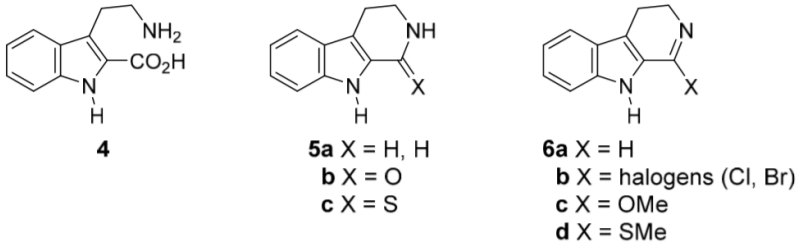



**Figure 2.** Structures of tryptamine (**2**) equivalents for rutaecarpine synthesis.

However, sequence benzoic acid derivatives **3b-I** with nitrogen at *ortho*-position (Figure 3) were used as an equivalents for quinazolinone moiety.

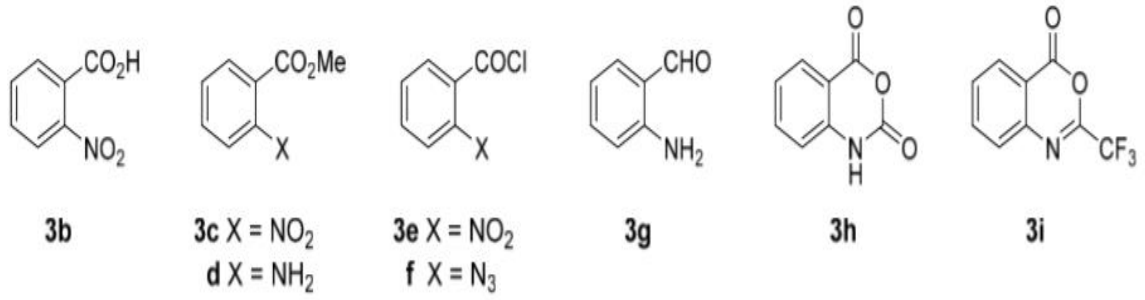
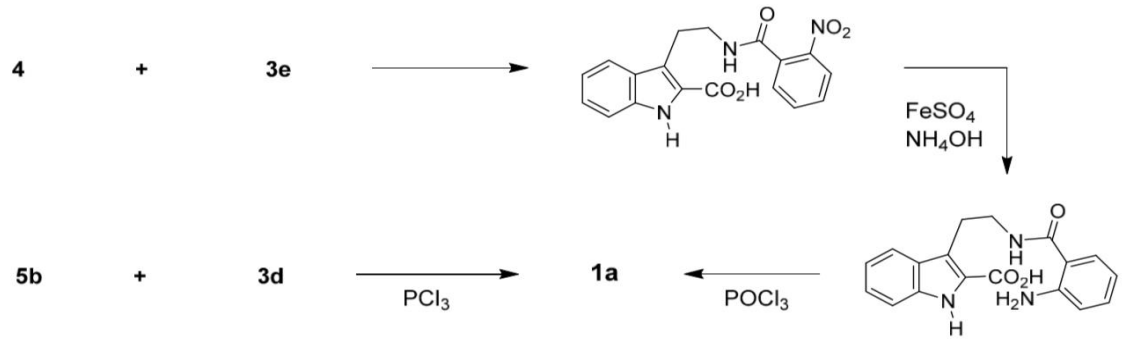



**Figure 3.** Stuctures of equivalents for quinazolinone moiety.

In fact, in 1927 Asahina et al. reported two papers for the synthesis of rutaecarpine, using above synthetic equivalents, one involved three-step synthesis from 3-(2-aminoethyl)indole-2-carboxylic acid (4) and 2-nitrobenzyol chloride(3e) and the other one pot synthesis (24%) from ketotetrahydrocarboline (5b), methyl anthranilate (3d), and PCl3 [58] (Scheme 2). Later, Patcher et al. claimed that PCl3 was inefficient and POCl3 should be preferred.

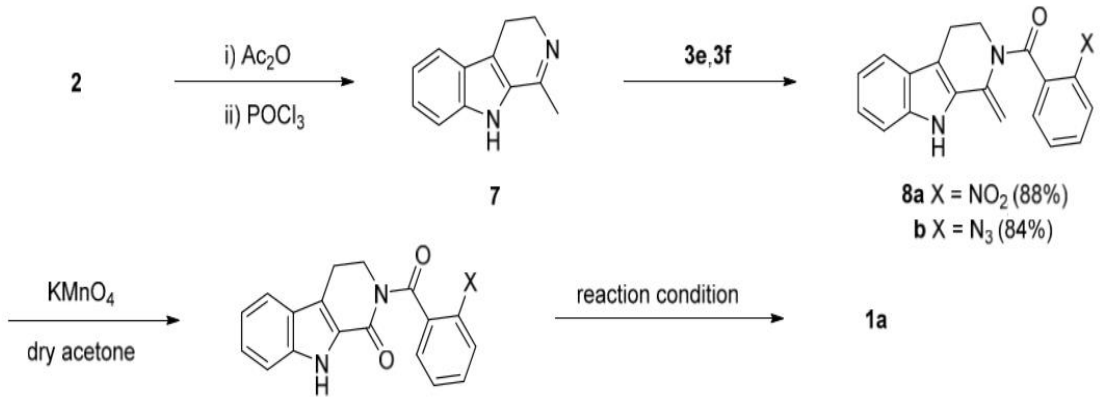



**Scheme:** Synthesis of rutaecarpine by Asahina et al.

These two papers provided a good starting point for the future syntheses of rutaecarpine as these two sets of starting materials, 3-(2-

aminoethyl)indole-2-carboxylic acid (3) and 2-nitrobenzoyl chloride (4) as well as 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (5) and methyl anthranilate (6b), have been employed as starting materials for the most of consequent rutaecarpine synthesis.

Lee et al. and Kamal et al[14]. designed the quinazolinone skeleton using one-pot cyclization. Tryptamine was exposed to a Bischler-Napieralsky reaction to five starting material(7), which was then condensed with 3e and 2-azidobenzoyl chloride (3f) to give 8a and 8b, respectively. Cleavage of the exocyclic double bond led to the corresponding ketone 9. It is worth noting that cleavage of the exocyclic double bond on 8 by ozonolysis failed, whereas oxidative cleavage with KMnO4 lead to ketones 9a and 9b in 32% and 67% yield, respectively (Scheme 3).

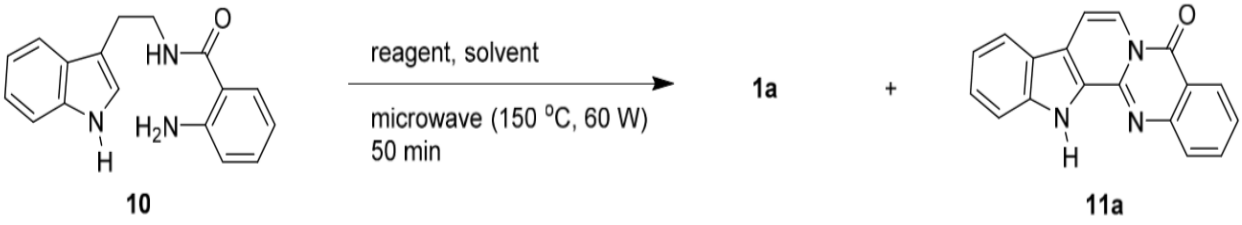


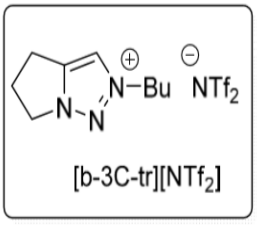

| X | reaction condition | yield |
|---|---|---|
| $NO_2$ | i) Sn/HCl; ii) NaOH, $Et_3N$ | 94% |
| $N_3$ | i) $Ph_3$; ii) aq. $NH_3$ | 62% |
| $N_3$ | $Ni_2B$, HCl, microwave (70 W) | 90% |

**Scheme 3:** Synthesis of rutaecarpine by Lee et al. and Kamal et al[14].

The reduction of the nitro group in 9a by tin chloride resulted in subsequent cyclization giving 1a in 94% yield. However, in the presence

of Ph3P and NH4OH or Ni2B in HCl-MeOH under microwave irradiation 2-azobenzamide (9b) undergoes an aza-Wittig reductive cyclization.For preparation of rutaecarpine from one-carbon unit reagent and (10) (The starting material 10 was prepared from tryptamine and isatoic anhydride (3h) in over 90% yield.) Tseng et al. considered the possible use of bicyclic 1,2,3-triazolium ionic liquids using Microwave-assisted cyclization resulted in 1a and 7,8-dehydrorutaecarpine (11a) in ratios dependent on the reaction conditions (Scheme 4).



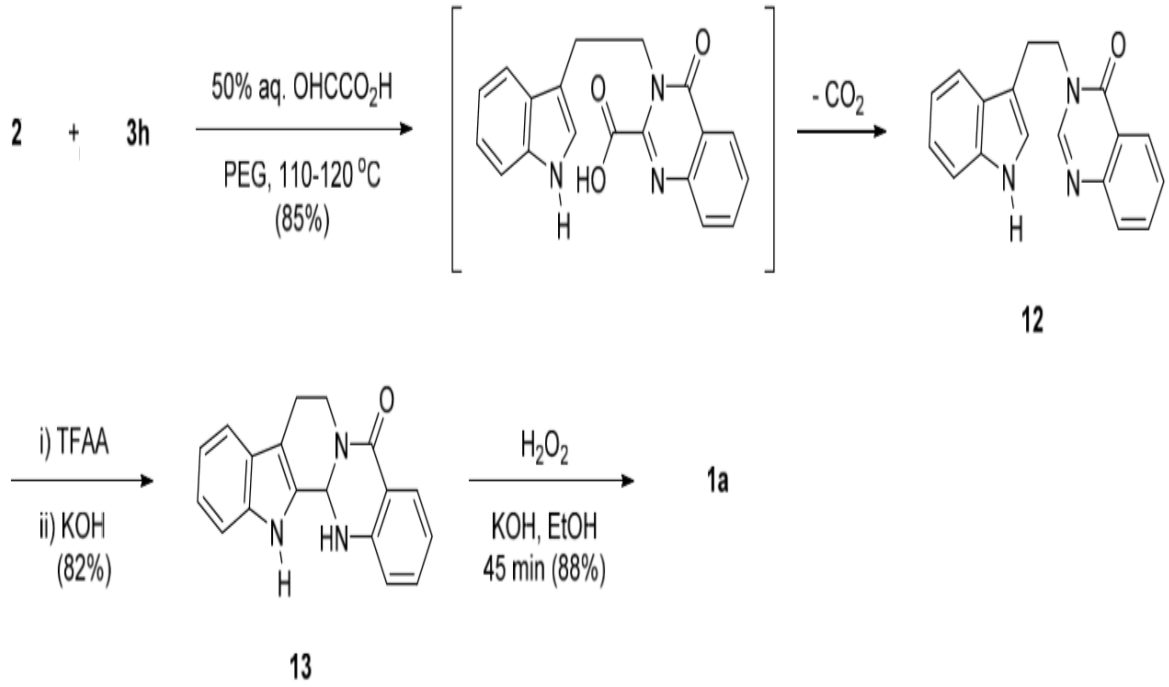




| entry | reagent | solvent | isolated yield (**1a** + **11a**) | **1a**:**11a**(ratio) |
|---|---|---|---|---|
| 1 | Vilsmeier reagent | [b-3C-tr][$NTf_2$] | 68% | 100:0 |
| 2 | DMF | [b-3C-tr][$NTf_2$] | 13% | 77:23 |
| 3 | Vilsmeier reagent | DMF | 58% | 66:34 |
| 4 | DMF | DMF | no reaction | |

**Scheme 4:** Synthesis of rutaecarpine by Tseng et al.

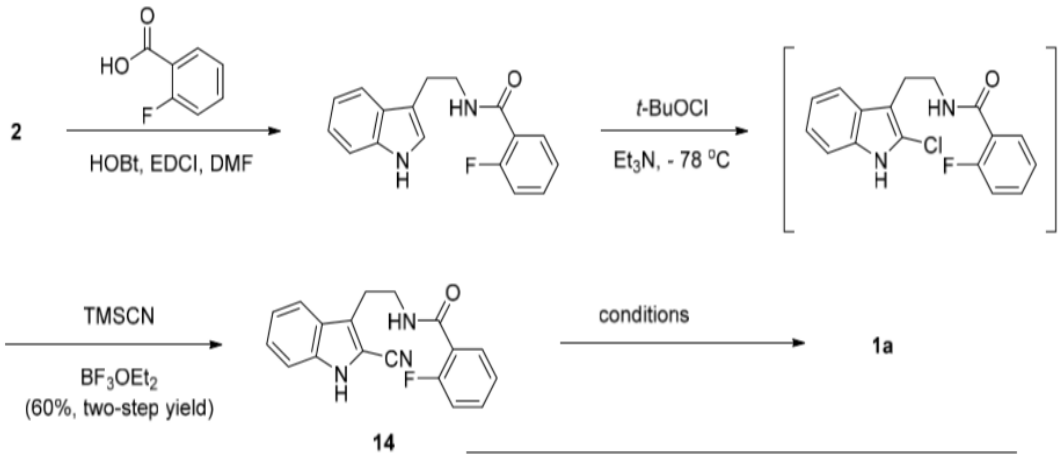
Rao et al. used the same stratergy as above but instead of Vilsmeier-Haack reagent or DMF, he used 50% aqueous glyoxylic acid. Reaction of (2) and isatoic anhydrid in the presence of 50% aqueous glyoxylic acid gave 12 in 3h, which was later subjected to acid-catalyzed cyclization followed by H2O2/KOH-catalyzed dehydrogenation to produce rutaecarpine (1a) (Scheme 5). Although the authors did not mention a possible reaction mechanism, the high reaction temperature would lead to decarboxylation of the possible intermediate 3-[2-(1H-

indol-3-yl)ethyl]-4-oxo-3,4-dihydroquinazoline-2carboxylic acid, to produce 12.




**Scheme 5:** Synthesis of rutaecarpine by Rao et al[14].

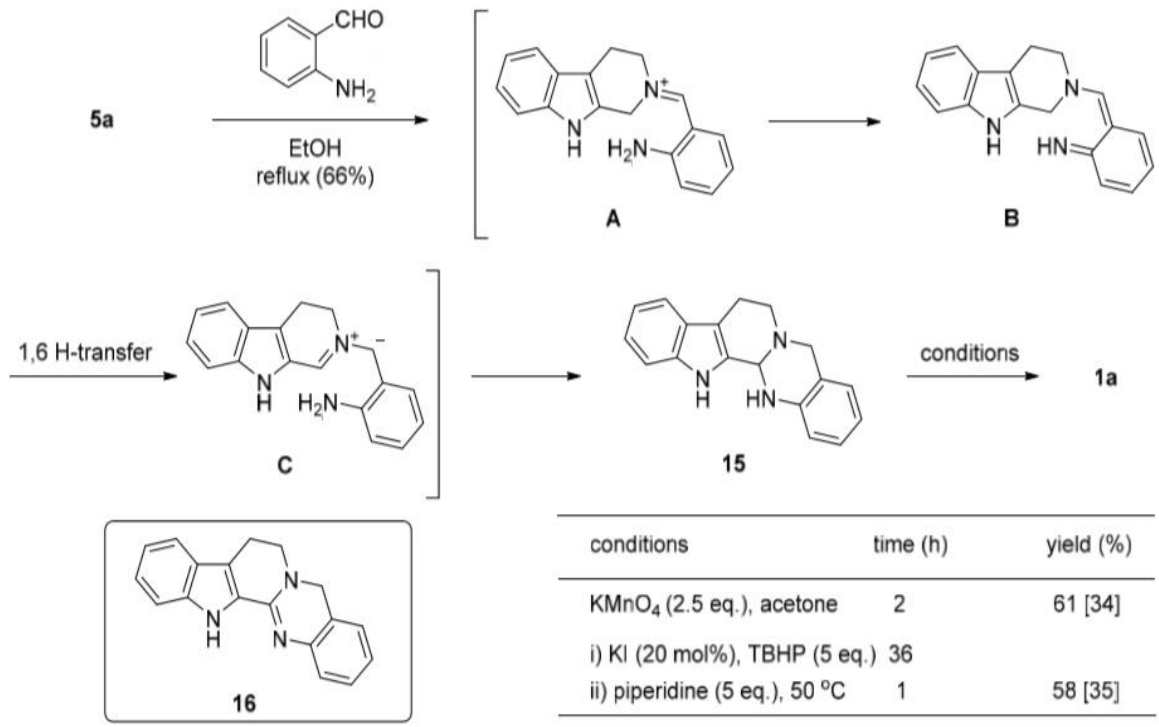
The authors Liang, et al. optimized the reaction conditions and worked on base initiated intramolecular anionic cyclization of the 2-cyno compound (14) and found DBU was the reagent of choice for the synthesis of rutaecarpine. The 2-cyanoindole compound 14 was prepared in two-steps from tryptamine and 2-fluorobenzoic acid via a 2-chloroindolenine, generated by an electrophilic aromatic substitution reaction at the C2 position in the indole moiety by t-butyl hypochlorite, followed by nucleophilic substitution of the 2-chloro group by cyanide anion in the presence of BF3 (Scheme 6).




| conditions | time (h) | yield (%) |
|---|---|---|
| 20 eq. KO*t*-Bu/THF, 200 °C | 0.5 | 19 |
| 3 eq. DBU/DMF, 150 °C | 24 | 91 |
| 3 eq. DBU/DMF, 150 °C | 36 | 93 |
| DBU neat, 150 °C | 5 | 68 |

**Scheme 6:** Synthesis of rutecarpine by Liang, et al.

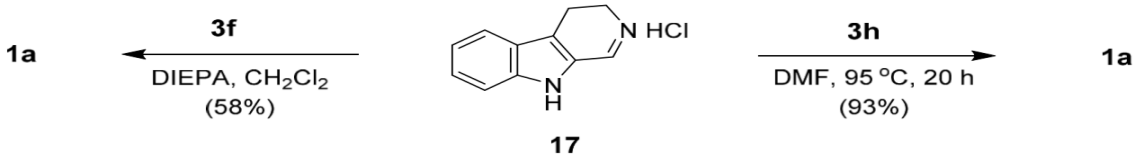
Zheng et al. worked on the oxidation of s ring-fused aminal to rutaecarpine via an alpha-amination of an N-heterocycle as the key reaction (Scheme 7). The alpha-position of 1,2,3,4-tetrahydro-βcarboline (5a) was activated by reacting with 2-aminobenzaldehyde to form an iminium ion (A), which was converted to the quinonoidal intermediate (B) by rearrangement of adjacent systems and a proton loss. 1,6-Hydrogen atom transfer in B led to the dipolar intermediate C, which ultimately afforded the cyclized aminal product (15). Oxidation of 15 by KMnO4 afforded rutaecarpine (1a) in 61% yield (Scheme 7). It should be noted that the MnO2 oxidation of dehydroaminal such as 16 yielded 1a and fully dehydrogenated product (11a) in an 8:1 ratio [37].




| conditions | time (h) | yield (%) |
|---|---|---|
| $KMnO_4$ (2.5 eq.), acetone | 2 | 61 [34] |
| i) KI (20 mol%), TBHP (5 eq.) | 36 | |
| ii) piperidine (5 eq.), 50 °C | 1 | 58 [35] |

**Scheme 7:** Synthesis of rutaecarpine via aminal[14]

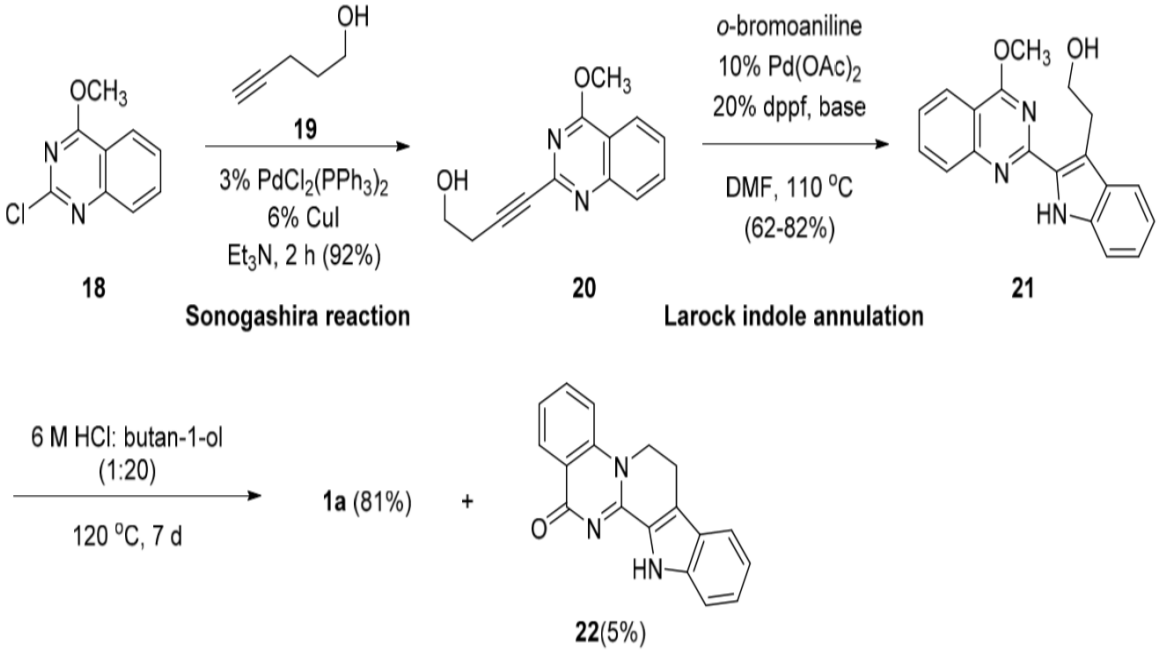
On the other hand, reaction between 3,4-dihydro-β-carboline (17) and o-azidobenzoyl chloride (3f) in the presence of Hunigs base delivered 1a in 58% yield [38], while reaction with 3h afforded 1a in 93% yield [39] (Scheme 8).




**Scheme 8:** Synthesis of rutaecarpine[14].

In 1991 Pan and Bannister worked on construction of the C-ring to synthesise rutacarpine via N6-C7 bond formation using Sonogashira reaction and Larock indole synthesis, by which Sonogashiras Pd(0)-catalyzed ethynylation of 19 to 18 led to 20, followed by intramolecular Pd(0)-catalyzed indole formation to construct 21. The acid-catalyzed

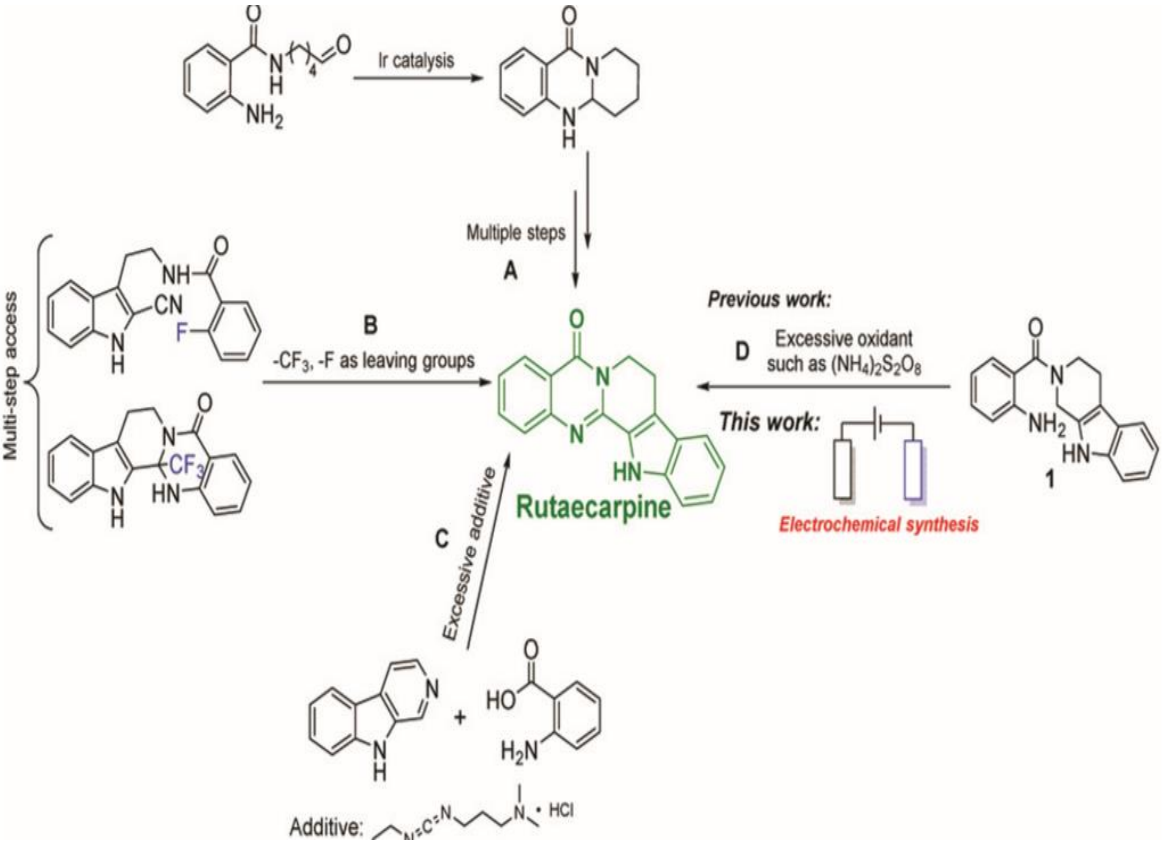
cyclization of 21 resulted in 1a in 81% yield with a by product 22 (Scheme 9).



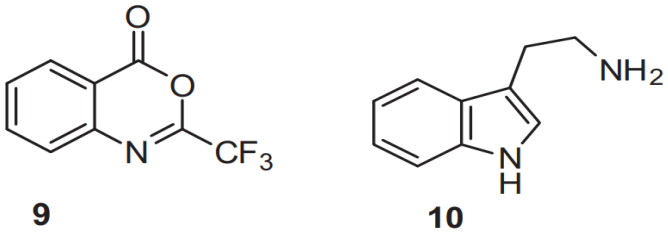

**Scheme 9:** Synthesis of rutaecarpine by Pan and Bannister[14].

Generally, all these methods are traditional multi-step synthetic procedures, requires special reagents, which suffered from tedious steps, harsh conditions, limited scope and poor yields which often not enough for further pharmacological evaluation(scheme 10, Paths A and B). In past decades, with speedy development of synthetic methodology, chemist have designed simple and diversed ways to synthesise rutaecarpine. Sus group has accomplished synthesis of rutaecarpine under the action of excess EDCI (Scheme 10, Path C). In literature there are numbers of synthetic protocols available for synthesis of rutaecarpine, however, newer methodologies are always desirable. For example, Bergmans synthesis[16], which uses compound (9) and tryptamine (10) to form intermediate (18). Treatment of intermediate (18) under acidic conditions achieves the closure of ring and formation

of (19), which loses CHF3 to yield compound (1a). In this method, rutaecarpine could be obtained in less than 1 h via 3 steps in almost quantitative yield. (scheme11)

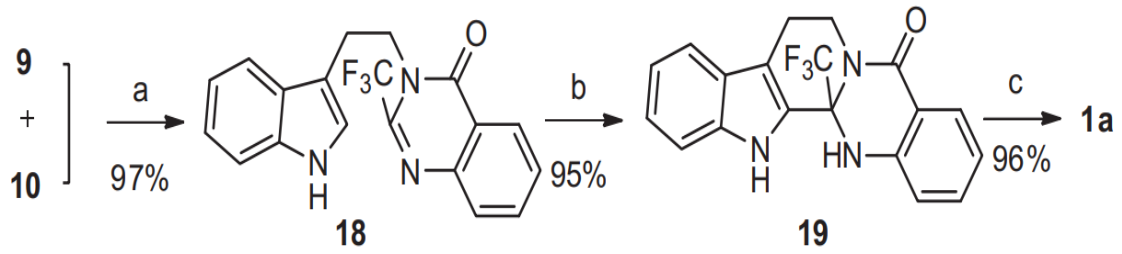



**Scheme 10:** Synthesis of rutaecarpine by Sus Group.



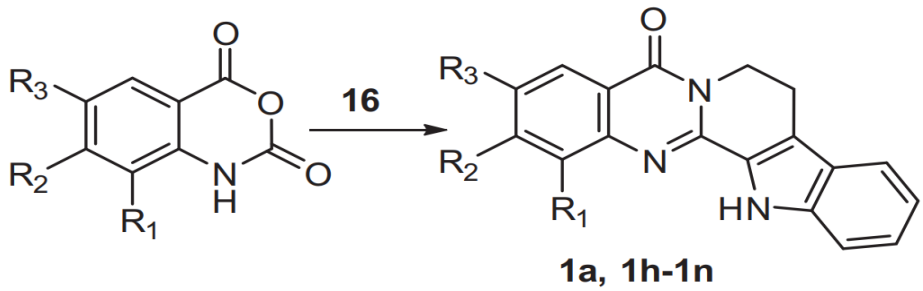
**9** **10**

**Figure:** 9,10.




**Scheme 11 :** Bergmans synthesis of rutaecarpine. Reagents and conditions: (a) pyridine; (b) HCl, AcOH; (c) KOH, EtOH; (1a) Rutaecarpine[16].

G. Huang et al. in 2014[16], described a novel, short and vesatile method for expenditious syntheses of rutaecarpine. In this method mixture of isatoic anhydride 8 and 4,9-dihydro-3H-pyrido[3,4-b]indole 16 (which can be synthesized from tryptamine via a 2-step scheme), was stirred in DMF at 95 C for 20 h to afford rutaecarpine in 93% yield.




1a R1=R2=R3=R4=H(rutaecarpine)

**Scheme 12:** Synthesis of rutaecarpine by G. Huang et al[16].

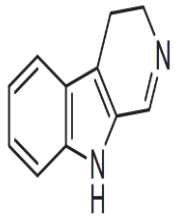
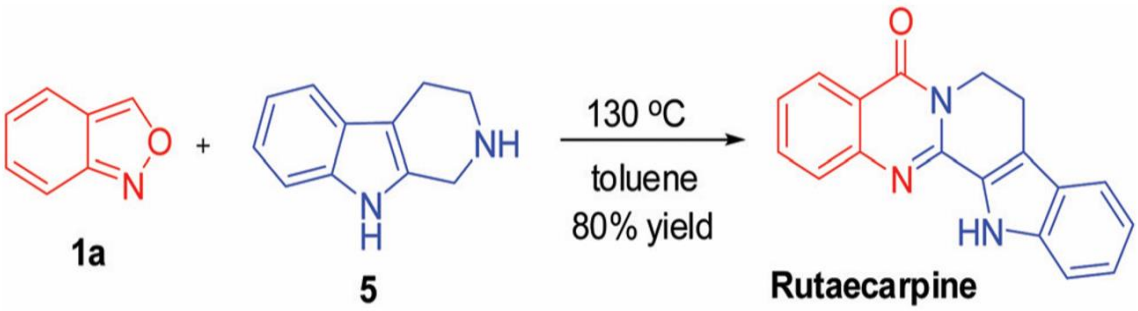



**Figure:** 16

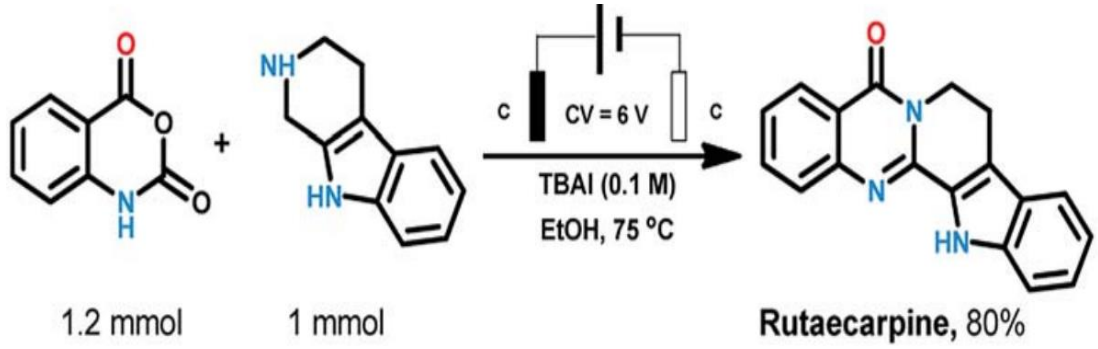
Recently(2019) Qian-Yu Li, Shi-Yan Cheng, Hai-Tao Tang and Ying-Ming Pan[17]. designed a synthetic route for synthesises of rutaecarpine alkaloid via an electrochemical cross dehydrogenation coupling (CDC)reaction, in which 2-Aminophenyl ketone derivatives and (2-aminophenyl)(pyrrolidin-1-yl)methanone were subjected to CDC reactions under the optimized reaction conditions(RVC anode (100 PPI, 1 cm × 1 cm × 1.2 cm), Pt plate cathode (1 cm × 1 cm), undivided cell, constant current = 10 mA, 3 (0.3 mmol), n-Bu4NPF6 (20 mol%), and CH3CN (5 mL), under air atmosphere at 70 °C for 4 h.) to obtain rutaecarpine in satisfactory yield.

Jian Li, Zheng-Bing Wang, Yue Xu, Xue-Chen Lu, Shang-Rong Zhu and Li Liu[18]. (2019) designed a one step cyclization approach to rutaecarpine synthesis by using readily available substrates including anthranils(1a) and 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (5) in toluene at 130◦C(Scheme 13) and the desired product rutaecarpine obtained in 80% yield. Thus, this method provided a convenient approach to these quinazolinone containing compounds, the synthesis of which otherwise required several steps from known starting materials. The developed transformation proceeds with the merits of high step-and atom-efficiency, a broad substrate scope, and good to excellent yields, without additional catalyst, and offers a practical way for the preparation of rutaecarpine and its derivatives.




**Scheme 13:** Synthesis of rutaecarpine using one step cyclization approach[18].

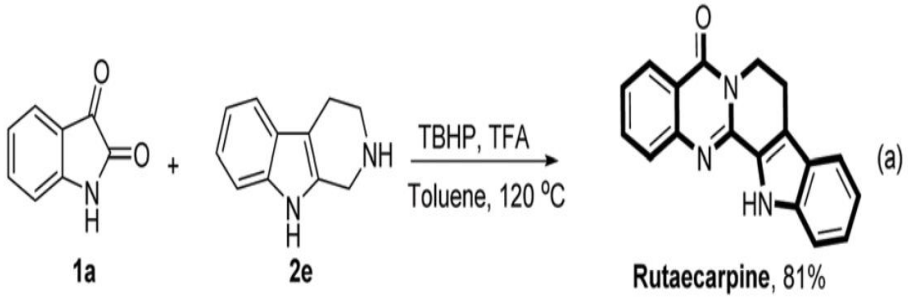
Xingyu Chen,Xing Zhang, Sixian Lu and Peng Sun[19]. established a direct decarboxylative cyclization between readily available isatoic anhydrides and cyclic amines to construct polycyclic fused quinazolinones employing electrochemical methods(scheme14). This was performed in an undivided cell without the use of a transition-metal-catalyst and external oxidant. Rutaecarpine was obtained in 80% yield.




**Scheme 14:** Synthesis of rutaecarpine by direct cyclization using electrochemical methods[19].

Feng-Cheng Jia, Tian-Zhi Chena and Xiao-Qiang Hu[20]. In 2020 demonstrated an efficient, one step TFA/TBHP-promoted oxidative cyclisation with the use of commercially available isatin(1a) and 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2e) as the substrate under optimal conditions, delivering the biologically important Rutaecarpine in 81%

yield (Scheme15). This protocol involes simple operation, mild and metal-free condition, as well as high yield, which provides an alternative for the straightforward synthesis of Rutaecarpine in high efficiency.




**Scheme 15:** Synthesis of rutaecarpine via one step TFA/TBHP [20]

**II.Biological Activities:** Many drugs were originally derived from herbs and many natural resources. In many regions of the world, herbal medicines has been used for treating diseases and disorders for thousands of years. Many herbal preparations are claimed to be effective in treating diseases, but in most cases the active ingredient in these herbal mixtures are unknown. For this reason, many researchers enthusiastically work in the field of the identification of new constituents with biological activities, and the total or semi synthesis of new constituents. Rutaecarpine is an excellent example of a biologically active constituent from natural resources due to its pharmacological actions such as, cardiovascular effects, antiplatelet activity, antithrombotic activity, anticancer activity, anti-inflammatory and analgesic effects, effects on the endocrine system, anti-obesity and thermoregulatory effects, effects on smooth muscle, and others. It has also been found out that Rutaecarpine Significantly Enhances the Sensitivity of ABCB1-Overexpressing Cancer Cells to Anticancer Drugs[6]. In addition, rutaecarpine has preventive potential against

hepatotoxicant-induced liver damage. Rutaecarpine pretreatment ameliorates APAP-induced hepatic damage by inhibiting oxidative pathways[21].

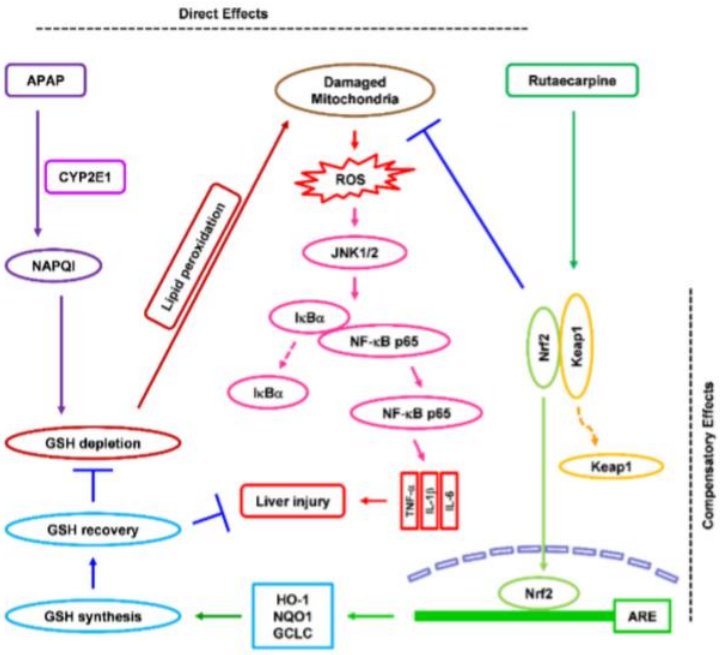



**Figure3:** Protective effect of Rutaecarpine in APAP-induced liver damage in mice.

It has been shown that the dissolubility of rutaecarpinr is very low, which affects its absorption efficiency. It has been suggested that the solid dispersion of rutaecarpine ptoduces anti-hypertensive effect inSHR, while crude rutaecarpine has very poor effects at the same doses. This kind of attempts will increase the druggability of rutaecarpine[4].

**3.Conclusion:** In summery**,** we have discussed different methods for synthesis of rutaecarpine, from multistep processes to one step protocol. In past decades, chemist have developed various simple ways to synthesise rutaecarpine. One of such method is CDC reactions. Electro-organic chemistry is an important part of organic synthesis. It has been considered to achieve reaction under mind condition, and replaces the use of oxidizing and reducing agents. Therefore, electro-organic chemistry provides a new route to achieve CDC reactions and have successfully synthesised rutaecarpine[17]. As one of the most representative alkaloids of Evodiarutaecarpa, rutaecarpine has shown a variety of pharmacological properties, thus continuously attract the scientists in academy as well as industry. In recent years, modification of rutaecarpine structures have been investigated for long time and potential structure activity relationship have been studying.

With rapid development in methodologies, will permit more progress in development of green, environment-friendly synthesis method, isolation and identification of rutaecarpine as well as the understanding of the precise pharmacological properties of rutaecarpine will definitely help the development of this new drug.

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