Review

Progress in the Studies on Rutaecarpine

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Abstract: Rutaecarpine is an indolopyridoquinazolinone alkaloid isolated from *Evodia rutaecarpa* and related herbs, which has shown a variety of intriguing biological properties such as anti-thrombotic, anticancer, anti-inflammatory and analgesic, anti-obesity and thermoregulatory, vasorelaxing activity, as well as effects on the cardiovascular and endocrine systems. Recent progress in the studies on the isolation, synthesis, structure-activity relationship studies, biological activities and metabolism of rutaecarpine are reviewed.

**Keywords:** Alkaloid, Rutaceae, rutaecarpine.

1. Introduction

Herbs have been widely employed as important remedies all over the world [1]. Progress in science and technology in recent decades has made possible not only to isolate and characterize the biologically active constituents of herbs, but also to evaluate their biological activities. Rutaceous plants, especially *Evodia rutaecarpa* (whose dried fruit is named 'Wu-Chu-Yu' in China), have long been used for the treatment of gastrointestinal disorders, headache, amenorrhea, and postpartum hemorrhage in traditional oriental medicine [2]. Rutaecarpine (8,13-dihydroindolo-[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(7*H*)-one, **1a**), first isolated by Asahina and Kashiwaki from

acetone extracts of *Evodia rutaecarpa* after basic treatment [3] in 1915 and later from 'Wu-Chu-Yu' [4] is one of the intriguing indolopyridoquinazoline alkaloids of the Rutaceae plants.

The structure of rutaecarpine was determined by degradation methods [3]. Hydrolysis of rutaecarpine with KOH in amyl alcohol afforded anthranilic acid, while fusion with KOH yielded aniline, CO_2, NH_3 and indole-2-carboxylic acid [3]. Later infrared [5], ultraviolet spectroscopy [6], mass spectrometry [7], ^{1}H-NMR [8] and ^{13}C-NMR [8] spectroscopy were employed to confirm the structure. Finally, the molecular structure was confirmed by X-ray analysis by Fujii, Kobayashi and Hirayama [9], who reported that rutaecarpine ($C_{18}H_{13}N_3O$) gave monoclinic crystals, $P2_{1/a}$, $a = 26.909(1)$ Å, $b = 7.398(1)$ Å, $c = 14.468(1)$ Å, $\beta = 98.672(5)^o$, V = 2847.3(4) Å^3, Z = 8. It should be noted that rutaecarpine exists in two forms. The X-ray crystallographic structure of rutaecarpine is an essentially planar structure in which rings A and B as well as rings D and E are coplanar and ring C has a half-chair conformation, which can undergo a ring flip, thus having dihedral angles between the two coplanar rings (co-plane A-B *vs* D-E) of 6.20° and 6.45°, for forms A and B, respectively (Figure 1).

Figure 1. Structure and two forms of rutaecarpine molecules with numbering [9].

1a (Rutaecarpine)

molecule A   molecule B
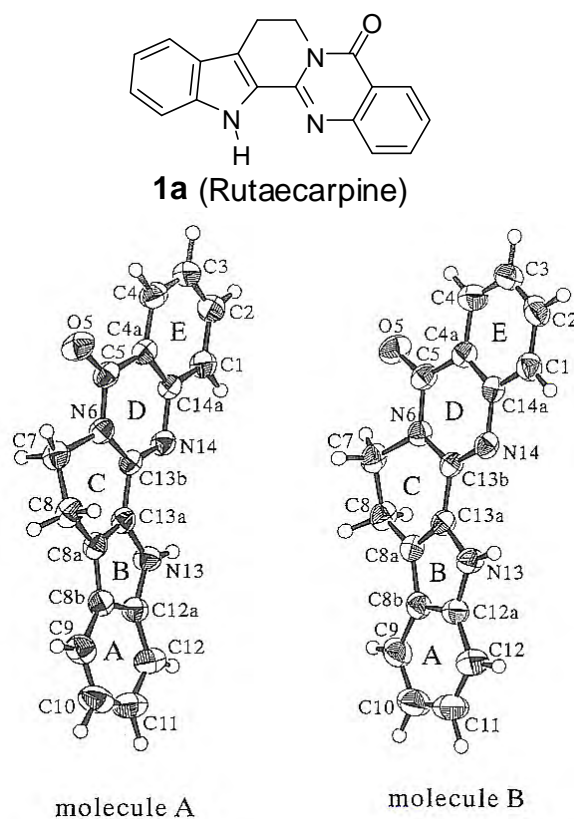
A search if the SCIFinder database (provided by the American Chemical Society) afforded 320 references, including 22 patents, covered isolation, biological activity, synthesis, metabolism, toxicology, etc, since the first report in 1915 (Table 2). Examination of these references provided three noticeable trends: references covering pharmacological properties, the annual numbers of references and number of references originating from China, are increasing (data not shown) (Table 1).

Table 1. Numbers of references published recent years.

Period	1915-2002	2003	2004	2005	2006	2007	Total
Numbers	192	18	24	31	31	24	320

Among the 10 review papers written so far, five were focused on synthesis [10], three on pharmacology [11], one on the modulation of cytochrome P450 [12], and one on detection methods [13]. A review written in 1983 by Bergman [10e] is a well organized one covering nomenclature, structure, synthesis and pharmacological properties of rutaecarpine, as well as related quinazolinone alkaloids. In addition, a review [11c], written in 1999 by Sheu, covered *in vitro* as well as *vivo* pharmacology of rutaecarpine. Although a recent review [10a], written in Chinese in 2006, provided good coverage of the syntheses of rutaecarpine based on the construction patterns for the five-ring system, since the present work will emphasize the progress in the isolation, synthesis, studies on additional pharmacological properties and the metabolism of rutaecarpine, some overlap between parts of this review and prior publications is inevitable.

Table 2. Classification of rutaecarpine references by CA Section.

| Topic	Number	Topic	Number
Pharmacology	81	Biochemical Methods	5
Alkaloid	67	Agrochemical Bioregulators	2
Plant Biochemistry	47	Analytical Chemistry	2
Pharmaceuticals & Cosmetics	39	Radiation Biochemistry	2
Pharmaceutical analysis	29	Toxicology	2
Organic Chemistry	19	Biological Chemistry	2
Heterocyclic Compounds (more than one heteroatom)	9	Miscellaneous	14
		Total	320

2. Sources of Rutaecarpine – their Distribution and Systematic Significance

As the name of the compound implies, the major sources of the quinazoline alkaloid rutaecarpine are the Rutaceae. The Rutaceae is a predominantly tropical family of trees and shrubs containing genera of importance in horticulure (*Citrus*), silviculture (*Chloroxylon*, *Flindersia*, *Zanthoxylum*) and medicine (*Pilocarpus*, *Agathosma*) [14]. It is considered to consist of about sixteen hundred species, distributed between approximately one hundred and fifty genera [15]. Among the genera of the Rutaceae, *Evodia*, *Hortia*, *Zanthoxylum*, *Phellodendron*, *Tetradium, Spiranthera, Vepris*, *Metrodorea*, *Bouchardatia,* and *Fagara* are a few species so far reported to produce rutaecarpine (Table 3).

**Table 3.** Plant Sources of Rutaecarpine

Family	Name	Ref.	Family	Name	Ref.
Rutaceae	*Evodia rutaecarpa*	[3,16-18]	Rutaceae	*Z. pistaciiflorum*	[32]
	E. ailanthifolia	[19]		*Metrodorea flavida*	[33]
	E. prerparata	[20]		*Bouchardatia neurococca*	[34]
	E. officinalis	[21]		*Phellodendron amurense*	[35-37]
	Hortia arborea	[22a]		*P. japonicum*	[38]
	H. regia	[23]		*Spiranthera odoratissima*	[39]
	H. colombiana	[24]		*Tetradium sambucinum*	[40]
	H. badinii	[22b]		*T .glabrifolium*	[41,42]
	Zanthoxylum rhetsa	[25]		*T. trichotomum*	[43]
	Z. pluviatile	[26]		*Fagara rhetza*	[44]
	Z. intergrifoliolum	[27-30]	Texaceae	*Taxus chinensis*	[45]
	Z. budrunga	[31]	Apocynaceae	*Winchia calophylla*	[46]

From the 10 rutaecarpine-generated genera of the Rutaceae listed above, *Zanthoxylum* is the only genus that has produced rutaecarpine and its derivatives such as 1-methoxyrutaecarpine (**1f**), 1-hydroxyrutaecarpine (**1h**) and 1-methoxy-7,8-dehydrorutaecarpine (**2e**) [27,28] together. Although such distribution of rutaecarpine and its possible metabolites implies something in the oxidative metabolism of rutaecarpine in the Rutaceae, the distribution of rutaecarpine in the Rutaceae does not appear to agree with presently accepted classification as Watermann pointed out [47]. In deed, three genera of the Rutaceae such as *Euxylophora* [48], *Vepris* [49], and *Leptothyrsa* [50] produced substituted rutaecarpines. *Euxylophora* produced 6 substituted rutaecarpines such as euxylophoricine A-F (**1c-e** and **2b-d**), *Vepris* two derivatives, 1-hydroxyrutaecarpine (**1h**) and 1-hydroxy-7,8-dehydro-rutaecarpine (**2f**), and *Leptothyrsa* 3-hydroxyrutaecarpine (**1j**) without any trace of rutaecarpine.
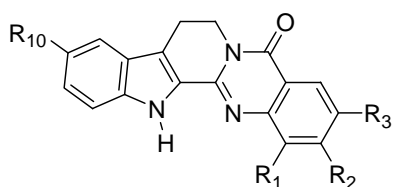
1b $R_1 = R_2 = R_3 = H$, $R_{10} = OCH_3$
(hortiacine)
c $R_1 = H$, $R_2 = R_3 = OCH_3$, $R_{10} = H$
(euxylophoricine A)
d $R_1 = H$, $R_2 = R_3 = OCH_2O$, $R_{10} = H$
(euxylophoricine C)
e $R_1 = H$, $R_2 = R_3 = R_{10} = OCH_3$
(euxylophoricine D)
f $R_1 = OCH_3$, $R_2 = R_3 = R_{10} = H$
g $R_1 = H$, $R_2 = OCH_3$, $R_3 = R_{10} = H$
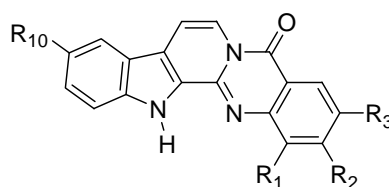
2a $R_1 = R_2 = R_3 = R_{10} = H$
b $R_1 = H$, $R_2 = R_3 = OCH_3$, $R_{10} = H$
(euxylophoricine B)
c $R_1 = H$, $R_2 = R_3 = R_{10} = OCH_3$
(euxylophoricine E)
d $R_1 = H$, $R_2 = OH$, $R_3 = OCH_3$, $R_{10} = H$
(euxylophoricine F)
e $R_1 = OCH_3$, $R_2 = R_3 = R_{10} = H$

Recently, rutaecarpine was also isolated from two new families: *Taxus chinensis* (the Texaceae) [45] and *Winchia calophylla* (the Apocynaceae) [46].

3. Studies on the Derivatives of Rutaecarpine

In this review, we only focused on the compounds with the 8,13-dihydroindolo[2',3':3,4]pyrido-[2,1-*b*]quinazolin-5(7*H*)-one rutaecarpine skeleton. The first derivative of rutaecarpine was isolated from *Hortia aborea* and named as hortiacine (**1b**), is known to be 10-methoxyrutaecarpine [22]. Additional methoxyrutaecarpines were isolated from *Euxylphora paraënsis* and named as euxylophoricine A-F (**1c**-**e** and **2b**-**d**) [48]. Among them, euxylophoricine B, E, and F are derivatives of 7,8-dehydrorutaecarpine (**2a**), which were isolated from *Phellodendron amurense* [35,36,37] three decades after the first isolation of the corresponding methoxy derivative, euxylophoricine B (**2b**) in 1968. Additionally, 1-methoxyrutaecarpine (**1f**) [27] and 1-methoxy-7,8-dehydrorutaecarpine (**2e**) [28] were isolated from *Zanthoxylum integrifoliolum* in 1996 and 2005, respectively, and 2-methoxy-rutaecarpine (**1g**) [51] was isolated from *Araliopsis tabouensis* (Rutaceae).

Table 4. Structure and Sources of Hydoxylated-Rutaecarpines.

1h R_1 = OH, R_2 = R_3 = R_4 = H
  i R_1 = R_2 = OH, R_3 = R_4 = H
  j R_1 = R_2 = H, R_3 = OH, R_4 = H
  k R_1 = R_2 = R_3 = H, R_4 = CHO

1l R_7 = OH, R_8 = H
  m R_7 = R_8 = OH

2f R_1 = OH
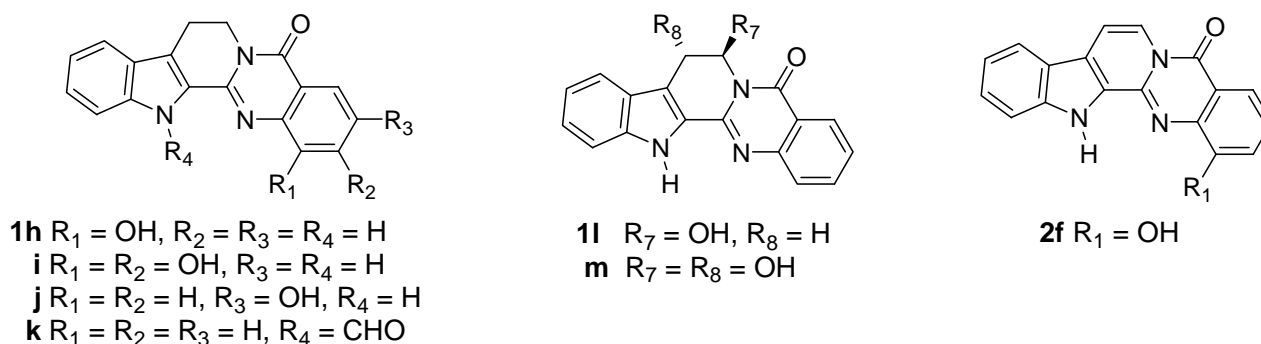
Compound	Plant	Reference(s)
1-Hydroxyrutaecarpine (**1h**)	*Euxylophora paraënsis*	[52]
	Vepris louisii	[49]
	Bouchardatia neurococca	[34]
	Tetradium glabrifolium	[41,42]
	Zanthoxylum integrifoliolum	[27-29]
	Zanthoxylum pistaciiflorum	[32]
	Spiranthera odoratissima	[39]
1,2-Dihydroxyrutaecarpine (**1i**)	*Bouchardatia neurococca*	[34]
3-Hydroxyrutaecarpine (**1j**)	*Leptothyrsa sprucei*	[50]
14-*N*-Formyrutaecarpine (**1k**)	*Zanthoxylum intergrifoliolum*	[29]

Table 4. Cont.

7-Hydroxyrutaecarpine (**1l**)	*Tetradium glabrifolium*	[53]
	T. ruticarpum	[53]
	Phellodendron amurense	[36,37]
	Evodia rutaecarpa	[54]
	Evodia officinalis	[55]
7,8-Dihydroxyrutaecarpine (**1m**)	*Phellodendron amurense*	[36,42]
7,8-Dehydrorutaecarpine (**2a**)	*Phellodendron amurense*	[35,36,41]
1-Hydroxy-7,8-dehydrorutaecarpine (**2f**)	*Vepris louisii*	[49]

A series of hydroxylated derivatives of rutaecarpine have also been isolated from the Rutaceae family, which are summarized in Table 4. Danieli, *et al*. isolated 1-hydroxyrutaecarpine (**1h**) from *Euxylophora paraënsis* in 1974 [52] as a first hydroxyrutaecarpine. The aromatic region of the ^{1}H-NMR spectrum of **1h** was too complex either to assign all the seven proton resonances or to determine the position where the OH group was attached. The structure was therefore confirmed by comparing the data of 1-hydroxyrutaecarpine that was prepared from 1,2,3,4-tetrahydronorharman-1-one and 3-hydroxyanthanilic acid. Although assignment of H4 of the E ring was possible in the 100 MHz ^{1}H-NMR spectrum, the other six aromatic proton resonances were not [49], until the HMBC experiment as well as studies on [3]J correlations with the carbons allowed the assignment of all the protons and confirmed the present structure [34]. Since then, nine additional hydroxyrutaecarpines have been isolated from various genera of Rutaceae plants and the ^{1}H- and ^{13}C-NMR data of selected rutaecarpine derivatives are summarized in Table 5.

**Table 5**. ^{1}H- and ^{13}C-NMR assignments for rutaecarpine derivatives.

Position	1a		1h	1i	1j		1l	1m	2a		2f
	δ_H	δ_C	δ_H	δ_H	δ_H	$\delta_{C(N)}$	δ_H	δ_H	δ_H	δ_C	δ_H
1	7.64	125.3	8.60[a]		7.56	128.2	7.58	7.74	7.81	126.0	
1a		146.8				140.5				147.5	
2	7.77	133.7	7.20		7.27	123.9	7.69	7.80	7.81	134.9	7.2-7.8
3	7.46	125.9	7.31[b]	7.00		155.0	7.35	7.48	7.46	124.8	7.2-7.8
4	8.22	125.9	7.53	7.59	7.48	109.7	8.21	8.24	8.50	127.7	8.18
4a		120.2				121.7				116.7	
5 (C=O)		159.9				160.3				159.2	
6(N)						155.0					
7	4.56	40.5	4.55	4.51	4.41	40.9	6.88	6.70	8.75	118.8	8.55
8	3.28	18.8	3.30	3.27	3.14	19.0	3.42 (ax) 3.59 (eq)	5.24	7.55	107.7	7.85
8a		117.3				116.6				120.9	

Table 4. Cont.

9	7.70	124.1	7.70	7.69	7.59	119.7	7.60	7.76	8.02	120.9	7.2-7.8
9a		119.3				125.0				122.5	
10	7.15	119.3	7.15	7.14	7.05	119.6	7.15	7.16	7.33	121.3	7.2-7.8
11	7.32	124.1	7.31[b]	7.31	7.22	124.3	7.31	7.29	7.48	127.4	7.2-7.8
12	7.62	112.1	7.65	7.54	7.46	112.3	7.42	7.51	7.52	112.3	7.2-7.8
12a		138.1				138.4				139.5	
13(N)						124.8					
13a		126.4				127.3				134.6	
14(N)						224.9					
14a		143.6				142.6				140.1	
OH			8.60		10.1						9.36
NH-13	11.05		11.07	11.10	11.7		10.15				12.36
solvent	Acetone-d_6				CDCl$_3$		CDCl$_3$	CD$_3$OD	CDCl$_3$		DMSO-d_6
Ref.	[34]	[8b]	[34]		[50]		[53]	[37]	[35]		[49]
NMR	100 MHz				500	125	500	100	500	125	100

[a] OH resonance. [b] Overlapped.

Recently, two indolopyridoquinazoline alkaloidal glycosides, 11-*O*-β-D-glucopyranosyl rutaecarpine (ternatoside C) and 11-*O*-α-L-rhamnosyl-(1-6)-β-D-glucopyranosyl rutaecarpine (ternatoside D) were isolated from the roots of *Ranunculus ternatus* (Ranunculaceae) [56]. However, to our surprise, the corresponding hydrolyzed product of ternatoside C and/or D, 11-hydroxyrutaecarpine, has never been isolated as yet from the natural sources even though it is an isolated metabolite of cytochrome P450-catalyzed oxidative metabolism of rutaecarpine (*vide infra*).
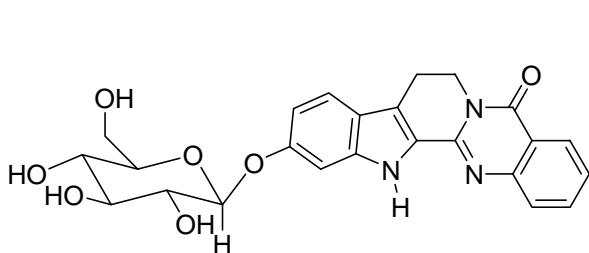
Ternatoside C
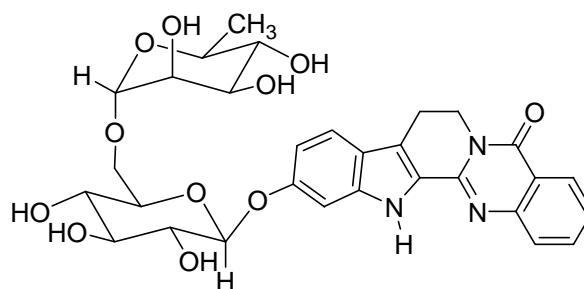
Ternatoside D

4. Synthesis

Asahina *et al*. reported two papers for the synthesis of rutaecarpine in 1927: one covered three-step synthesis from 3-(2-aminoethyl)indole-2-carboxylic acid (yield not given) (**3**) [57] and the other one-pot synthesis (24%) from ketotetrahydrocarboline (**5**), methyl anthranilate (**6b**), and PCl$_3$ [58] (Scheme 1). Later, Patcher *et al*. claimed that PCl$_3$ was inefficient and POCl$_3$ should be preferred reagent [22a].
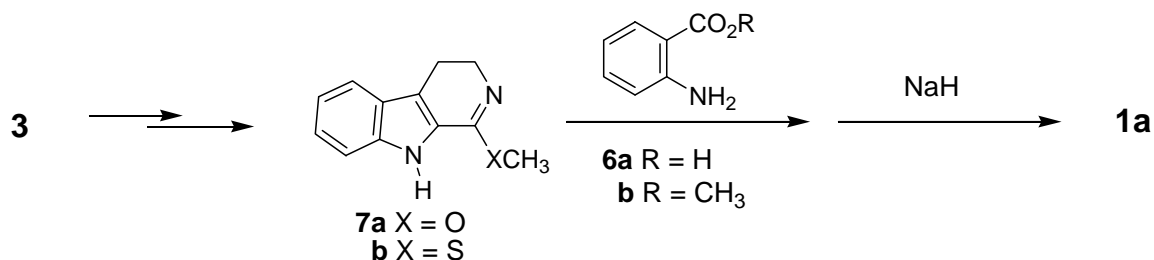
Scheme 1.
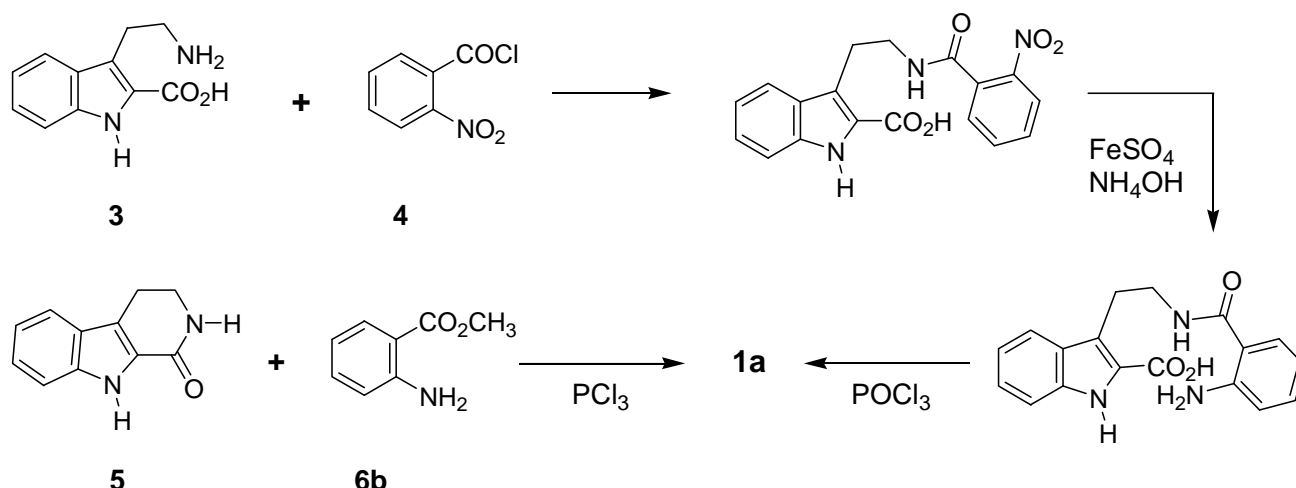
These two papers provided a good starting point for the future syntheses of rutaecarpine as these two sets of starting materials, 3-(2-aminoethyl)indole-2-carboxylic acid (**3**) and 2-nitrobenzoyl chloride (**4**) as well as 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (**5**) and methyl anthranilate (**6b**), have been employed as starting materials for the most of consequent rutaecarpine synthesis.

1) 2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-one - Derived Synthesis.

Since the first synthesis [57], several attempts to synthesize rutaecarpine and its derivatives used **5** as a starting material [59]; some of them employed structurally modified derivatives of **5** which required consturction of the D-ring at the final stage. It should be noted that compound **5**, a degradation product of rutaecarpine and related quinazolinone alkaloids, was isolated from the extract of *E. rutaecarpa* [60] as an alkaloid.

When the corresponding *O*-methyllactim **7a**, prepared from **5** by reacting with trialkyloxonium ion, was employed, the yield was improved up to 66% [61]. Recently, methylthiolactim (**7b**) was replaced for **7a**, which somewhat improved the yield (89%) [62]. The starting **7b** could be readily prepared in two steps from compound **5** [63] (Scheme 2).

Scheme 2.

Eguchi *et al*. used an aza-Wittig reaction in the presence of tributylphosphine for the construction of ring D from 2-(2-azidobenzoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (**8**) [64] (Scheme 3).

Scheme 3.
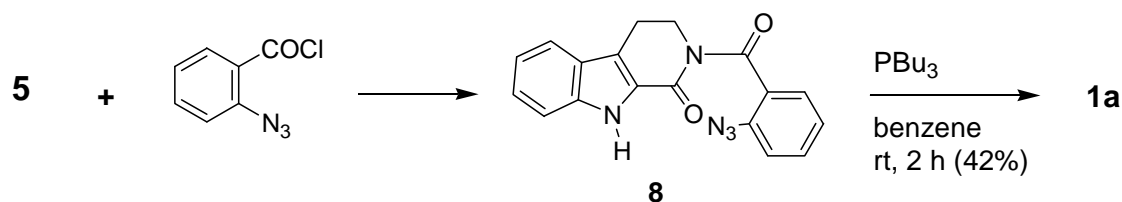
The imino chloride **9**, generated from the HCl salt of **5** and POCl$_3$, was condensed with methyl anthranilate to afford rutaecarpine in excellent yield [65a]. In addition, a one-pot synthesis of rutaecarpine from **5**, anthranilic acid (**6a**), and SOCl$_2$ in refluxing pyridine has also been established [65b] (Scheme 4).

Scheme 4.
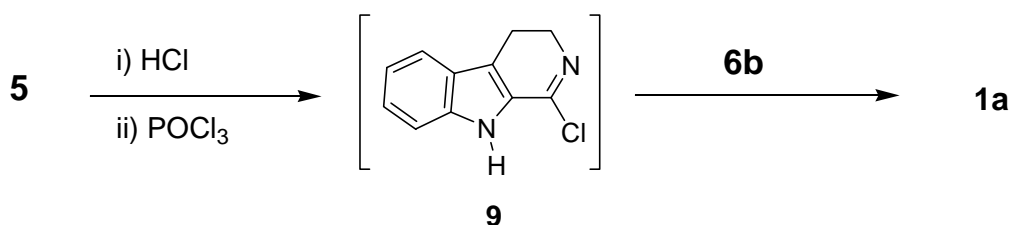
Although the procedures described above have advantages for introducing substituent(s) on the 4(3*H*)-quinazolinone skeleton, the relative unavailability of **5** and its derivatives limits the general utility of this procedure.

2) Tryptamine-Derived Synthesis

Tryptamine-derive syntheses of rutaecarpine are basically one step or stepwise constructions of the C- and D-rings of rutaecarpine (Scheme 5).

Scheme 5.

C-1 unit is formic acid, ethyl formate, etc.
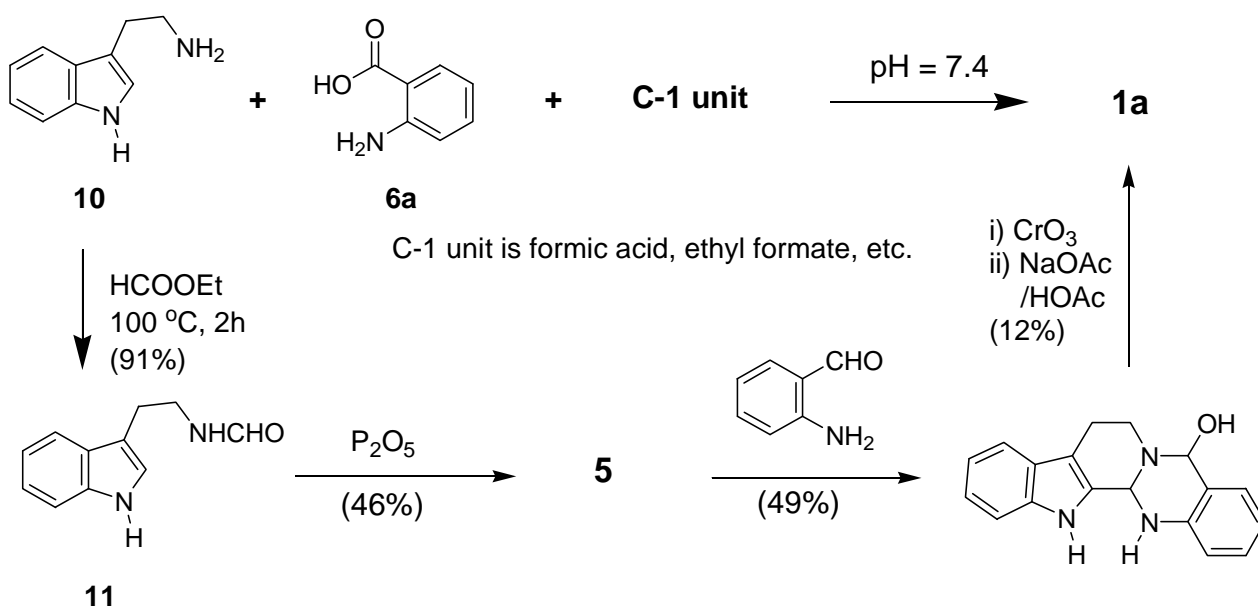
A decade after its discovery, Schöf and Steuer reported a synthesis of rutaecarpine under so-called physiological conditions by condensing anthranilic acid with 5,6-dihydro-4-carboline [66], which suggested the possible utility of tryptamine (**10**). They supported their biochemical studies by a chemical synthesis of rutaecarpine from **10** *via* **5** [67]. The carbon added to the *N* of tryptamine that would be the C2 of the quinazolinone ring, is generally afforded by formic acid, alkyl formate, triethyl orthformate, alkyloxycarbonyl halide, etc. Tryptamine (**10**) and/or its equivalents (i.e. **11**) can thus be readily available starting materials for the synthesis of rutaecarpine. First, *N*-formyltryptamine (**11**) was used as a starting material, which was reacted with sulfonamide anhydride **12** or iminoketene **13**, generated from anthranilic acid and $SOCl_2$, to afford *N*-[2-(indol-2-yl)ethyl]-4(3*H*)-quinazolinone, which was then cyclized by HCl in HOAc to afford rutaecarpine in 45% yield [68] (Scheme 6). The harsh reaction temperature (110 ^{o}C) and long time (166 h) as well as the relatively low yield may be the drawbacks to be overcome.

Scheme 6.
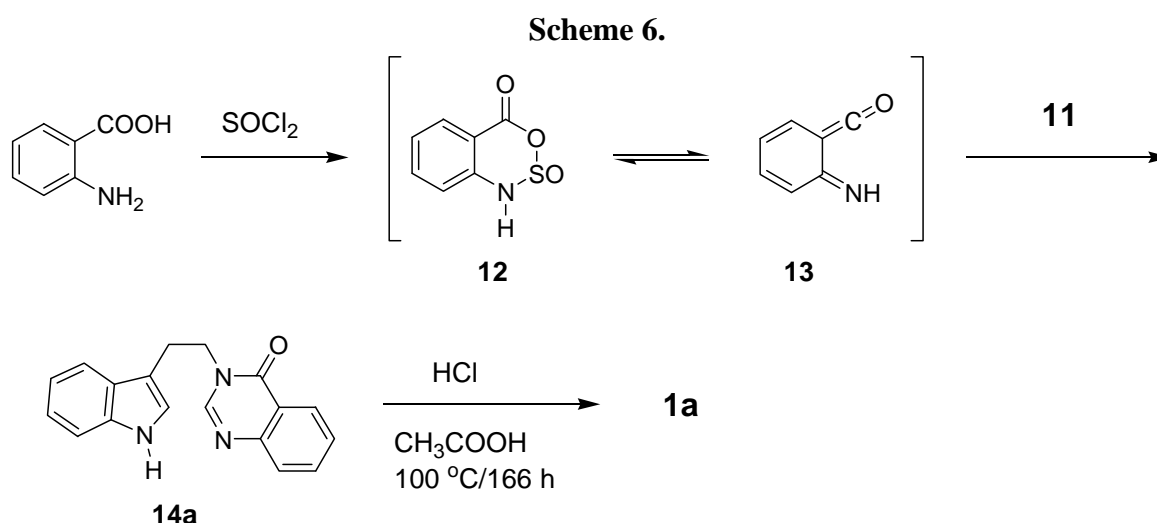
Condensation of tryptamine with isatoic anhydride (**15**) led to *N*-(2-aminobenzoyl)tryptamine (**16**). Although Horvath-Dora and Clauder claimed that reaction of **16** with triethyl orthoformate afforded 13b,14-dihydrorutaecarpine (**17**) [69b], the real structure of the product was corrected by Bergman and Bergman [8b,70] to be **14a** (Scheme 7). The structure of **17** was further confirmed by isolation from *Zanthoxylum flavum* [71] and *Evodia rutaecarpa* [72], as well as chemical synthesis [72].

Scheme 7.
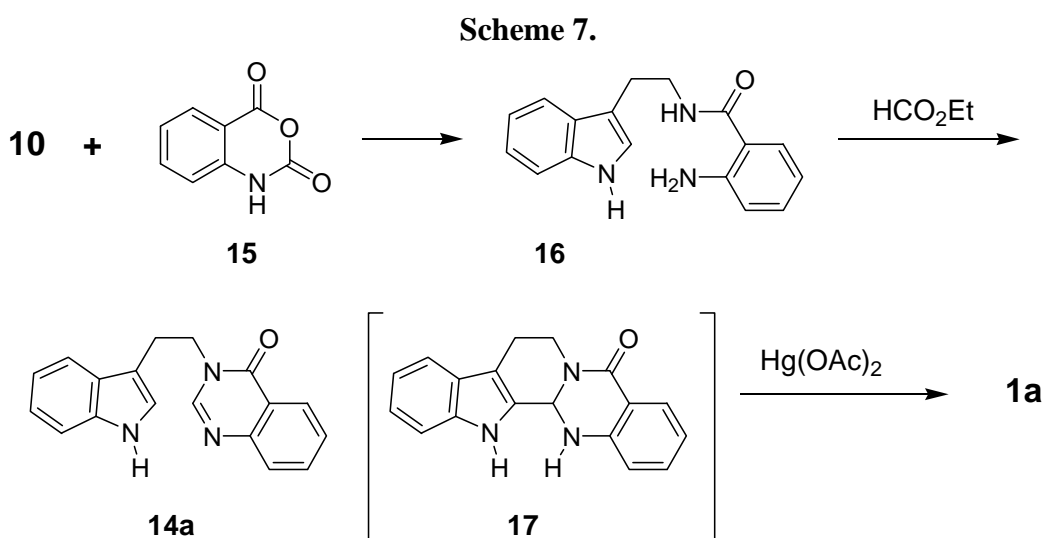
Bergman and Bergman additionally introduced a modified procedure for the preparation of **14a** by reacting *N*-(2-aminobenzoyl)tryptamine (**16**) with triethyl orthoformate in 89% yield [8b]. Attempts to convert **17** directly to rutaecarpine (**1a**) using oxidative coupling reagents such as Hg(OAc)$_2$, FeCl$_3$, and Pb(OAc)$_2$ were rather indiscriminate and resulted complex reaction mixtures (Scheme 8).

Scheme 8.
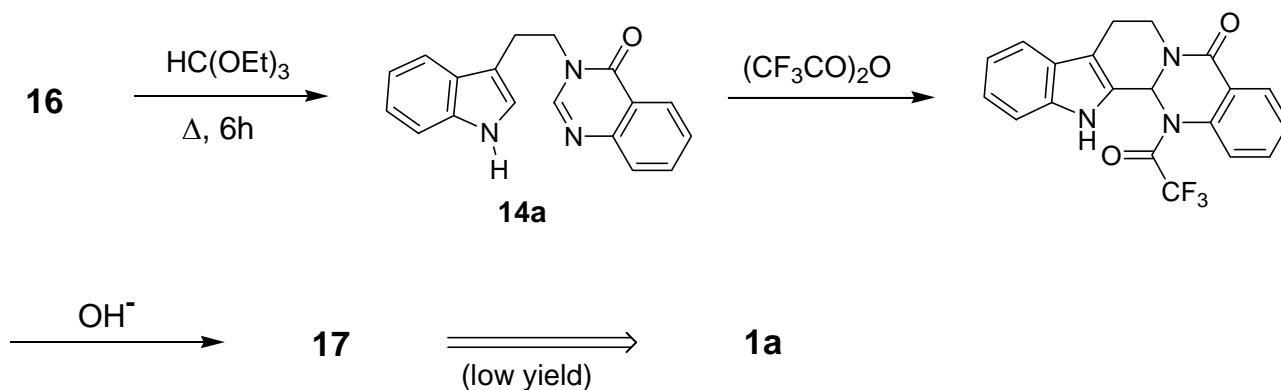
A rationale to improve the conversion of **14a** to rutaecarpine could be to introduce a good leaving group at C2 of either the 4(3*H*)-quinazolinone or the indole ring. The introduction of a good leaving group such as CF$_3$ at C2 of quinazolinone ring would not only facilitate the acid-catalyzed ring closure of **14b** to the pentacyclic intermediate **19**, but would also act as a leaving group in the final step [70]. Reaction may proceed by protonation of the 4(3*H*)-quinazolinone moiety of **14b,** followed by electrophilic attack on the indole ring leads to **19**, which has an angular CF$_3$ group in the 13b-position. The reaction time required for the three steps is less than 1 h, the reaction temperature is approximately 150 $^{\circ}$C, and the yield for each step is over 95%. This procedure has been applied for the introduction of various substituent(s) on ring A to pursue structure-activity relationship [73]. Prerequisite compound **18** could be readily prepared by reacting isatoic anhydride (**15**) with trifluoroacetic anhydride [70].

Scheme 9.
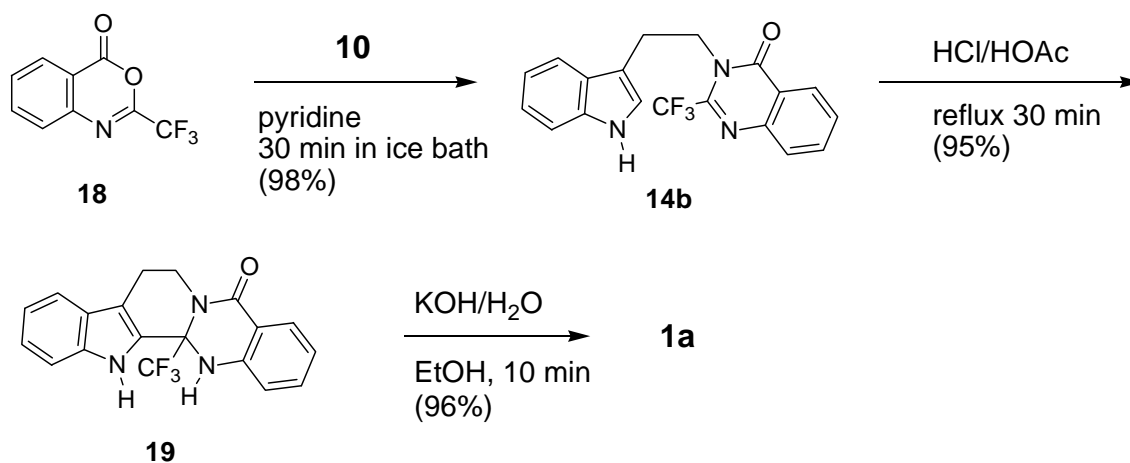
It should be noted that the reactions attempted with a relatively poor leaving Cl moiety at C2 of the quinazolinone ring afforded a mixture of products [74]. The distributions of the products **1a**, **22**, **23**, and **24** were highly dependent on the reaction conditions (Table 6). Such information and additional experimentation gave enough information to explore the mechanism of this-type of reaction as shown below (Scheme 10).

Scheme 10.
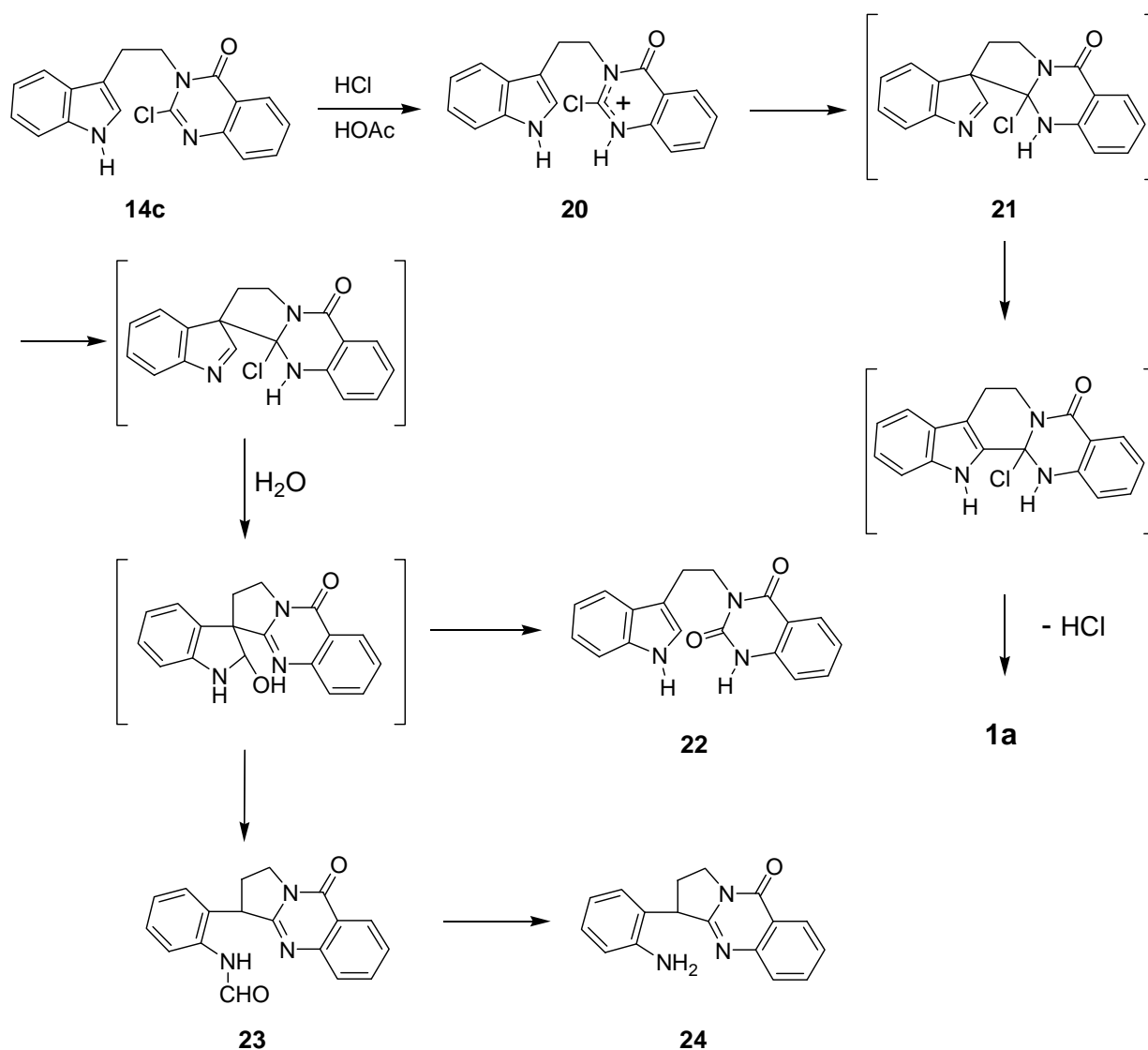
Table 6. Cyclization reaction of **14c** under various acidic conditions.

| Entry	Reaction Conditions			Product (yield in %)			
	Solvent	Time	Temp.	1a	22	23	24
1	CHCl₃ containing a small amount of HCl	1 h	Reflux	44	-	26	-
2	CHCl₃ saturated with HCl (g)	1 h	r.t.	42	-	40	-
3	Conc. HCl-H₂O-MeOH (1:20:180)	17 h	r.t.	9	20	-	70

Tryptamine was further condensed with methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate, prepared from methyl anthranilate and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt, **25**), to give a cyano compound **26**, which then underwent cyclization on heating with TFAA/HCl(g) to afford rutaecarpine in 37% overall yields [75] (Scheme 11).

Scheme 11.
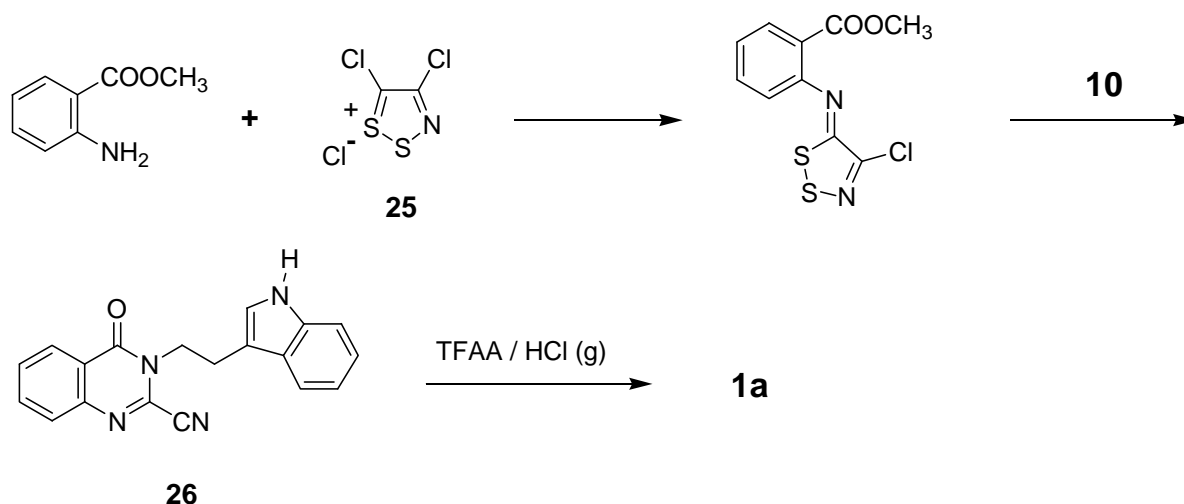
A second modification was pursued by introducing a good leaving group at C2 of the indole moiety, which then subjected to Pd-catalyzed coupling. Only the N1-acetyl derivative **28** of 3-[2-(2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (**27**), smoothly underwent a coupling reaction, while direct conversion gave poor yield [76] (Scheme 12).
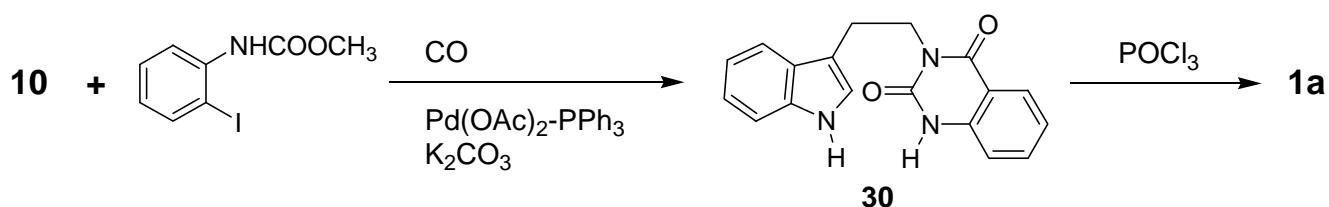
Scheme 12.
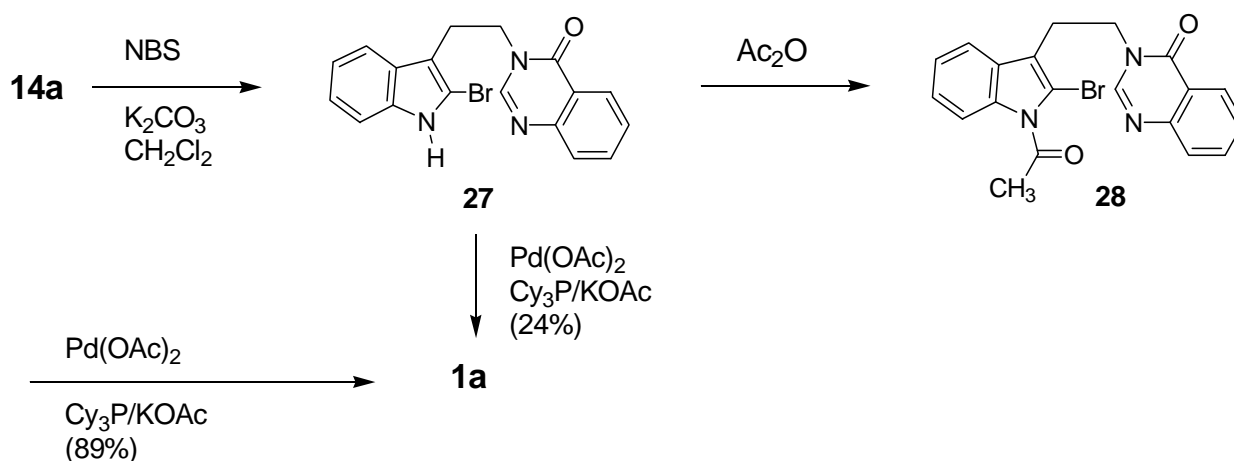
Recently a radical reaction was employed for the preparation of rutaecarpine. Bowman *et al.* used indol-2-yl radical cyclization onto the quinazolinone motif. Previously reported **27** [76] was treated with (Me₃Sn)₂ to afford an indole radical **29** which would undergo 6-*exo* cyclization to lead to rutaecarpine in 55% yield [77] (Scheme 13).

Scheme 13.

27 $\xrightarrow[\text{(55\%)}]{\text{Me}_3\text{SnSnMe}_3}$ **29** $\longrightarrow$ **1a**
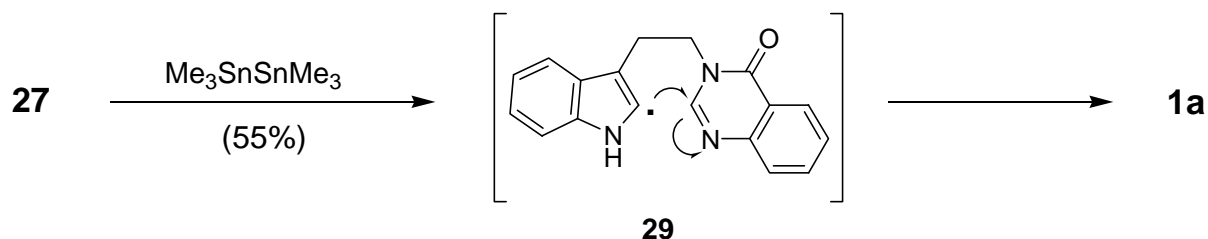
Tryptamine-derived palladium-catalyzed carbonylation of *N*-carbomethoxy-2-iodoaniline under carbon monoxide (1 atm) afforded 3-[2-(1*H*-indol-3-yl)ethyl]-(1*H*,3*H*)-quinazoline-2,4-dione (**30**), which could be readily cyclized with POCl$_3$ to lead rutaecarpine [78].
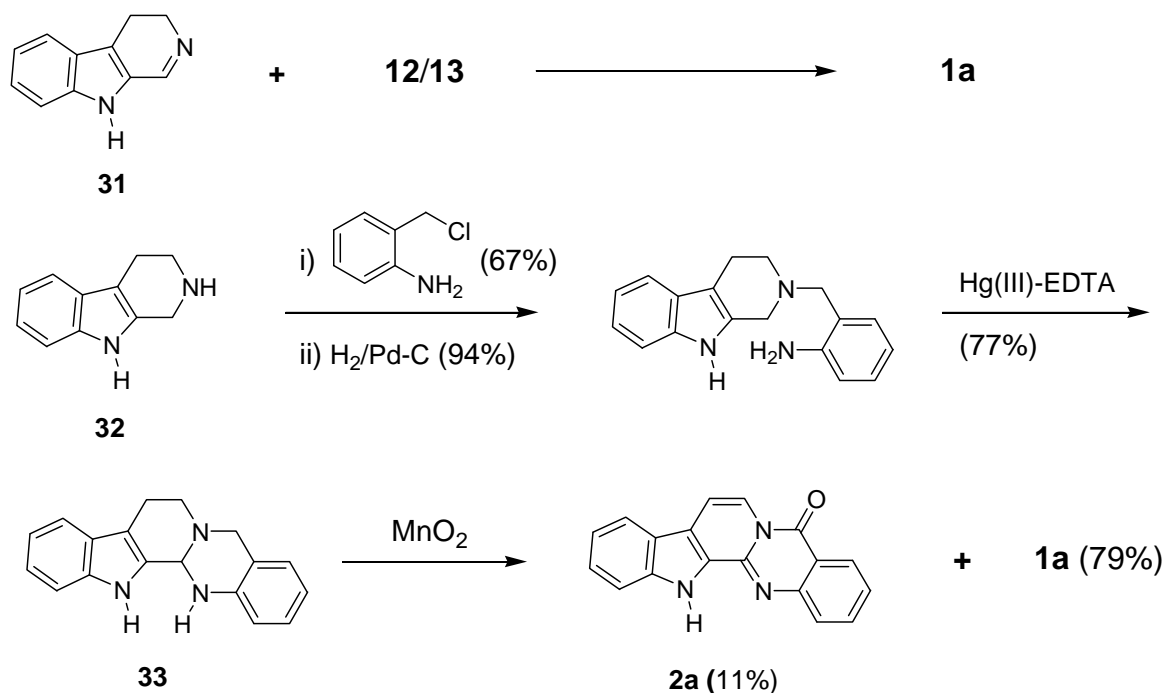
Scheme 14.

10 + NHCOOCH$_3$ / I $\xrightarrow[\substack{\text{Pd(OAc)}_2\text{-PPh}_3 \\ \text{K}_2\text{CO}_3}]{\text{CO}}$ **30** $\xrightarrow{\text{POCl}_3}$ **1a**

3) 3,4-Dihydro-β-carboline-Derived Synthesis

Several synthetic methods, reported later, employed 3,4-dihydro-β-carboline (5,6-dihydro-4-carboline, **31**) or its hydrogenated analog 1,2,3-tetrahydro-β-carboline (**32**) as key starting materials. Cycloaddition reaction of **31** to anthranilic acid-derived iminoketene **12** or **13** would lead **1a** in 85% yield [79] (Scheme 15).

Scheme 15.

31 + **12/13** $\longrightarrow$ **1a**

32 $\xrightarrow[\text{ii) H}_2\text{/Pd-C (94\%)}]{\text{i) (67\%)}}$ $\xrightarrow[\text{(77\%)}]{\text{Hg(III)-EDTA}}$

**33** $\xrightarrow{\text{MnO}_2}$ **2a (**11%) + **1a** (79%)

A four-step synthesis of rutaecarpine from **32** was additionally reported. Although the keto group at C5 and dehydrogenation at C15a and N16 position onto **33** could be accomplished with MnO$_2$, over-dehydrogenation of **1a** led 7,8-dehydrorutaecarpine (**2a**) in 11% yield [80]. This method has, however, somewhat limited general applicability due to the unavailability of the staring carboline and/or its precursor.

4) *Mackinazolinone-Derived Synthesis*

The construction of B ring of rutaecarpine at the final stage was also achieved by employing 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]-quinazolin-4-one (mackinazolinone, **34**) as a starting material. (Scheme 16). In fact, mackinazolinone was chemically prepared [81] some 30 years before its first isolation as an alkaloid from *Mackinlaya* species [82]. The Fischer indole synthesis was applied to the key intermediate 9-phenylhyrazono-9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazolin-4-one (**36**), which could be prepared by three different routes: a condensation of the corresponding 9,9-dibromo compound **35** with phenylhydrazine [83a], a direct condensation of **34** with phenyldiazonium chloride [83b,c], and three-step conversion *via* **37** [84]. The intermediate diketone **37** could also be prepared 5 steps from isatoic anhydride in 32-49% overall yields [85].

Scheme 16.
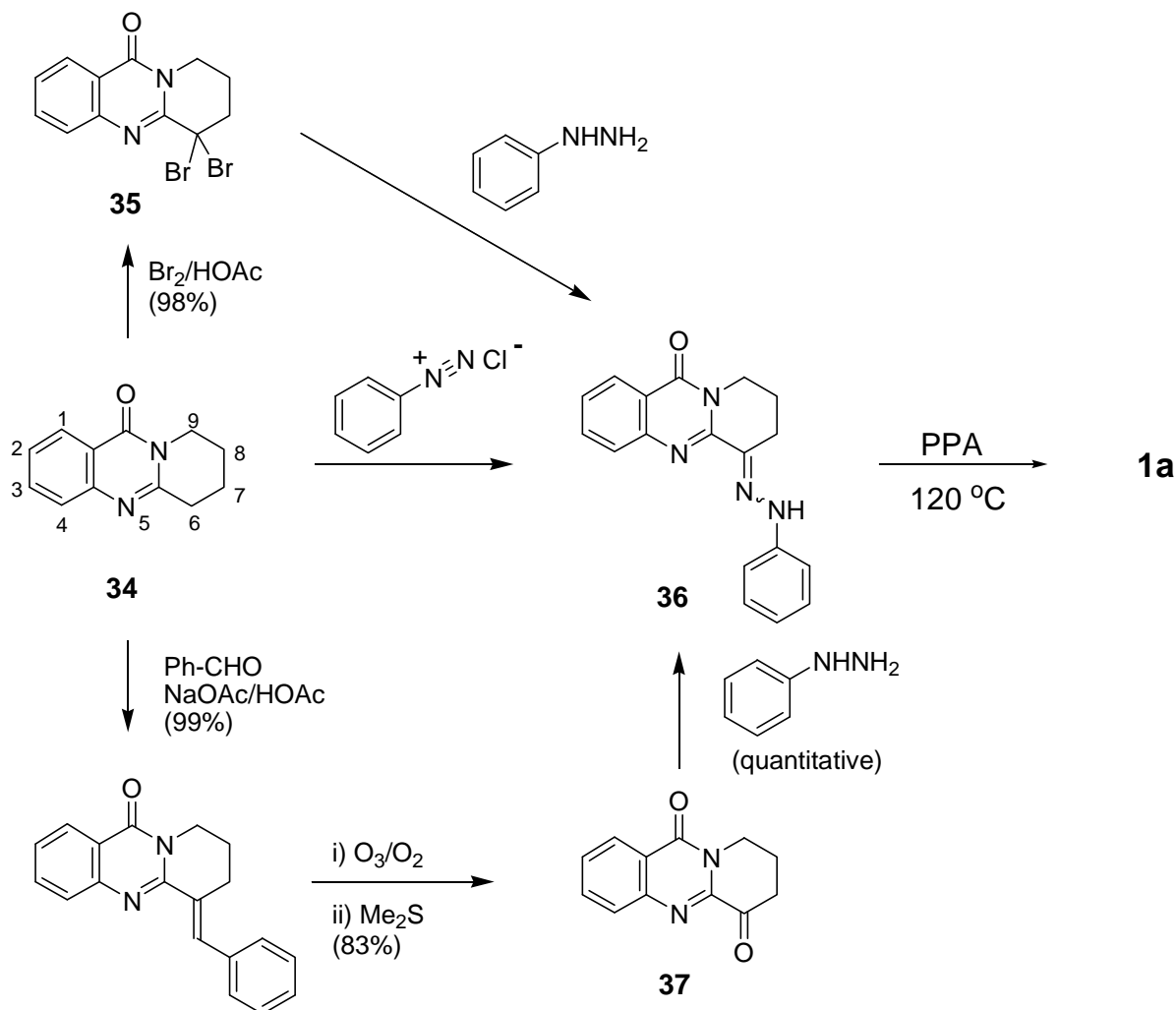
A series of synthetic procedures for **34** have been reported in the literature [86] since the first chemical synthesis [81] and isolation from natural sources [82], some of which are directly extended to the synthesis of rutaecarpine [72,84,85].

5) *Miscellaneous*

Use of 2,3-polymethylene-4(3*H*)-quinazolinone was further pursued by Kökösi *et al.* by employing deoxyvasicinone (**38**) as a starting material [87]. The Vilsmeier-Haack reaction on **38** yielded corresponding *N*,*N*-dimethylmethylidene compound **39**, which was treated with aniline in refluxing EtOH to give hydrazone **40** in 87% yield. Fischer indole synthesis was then applied to **40** to yield rutaecarpine in 40% over three-step yields *via* spiro compound **41** (Scheme 17) [74].

Scheme 17.
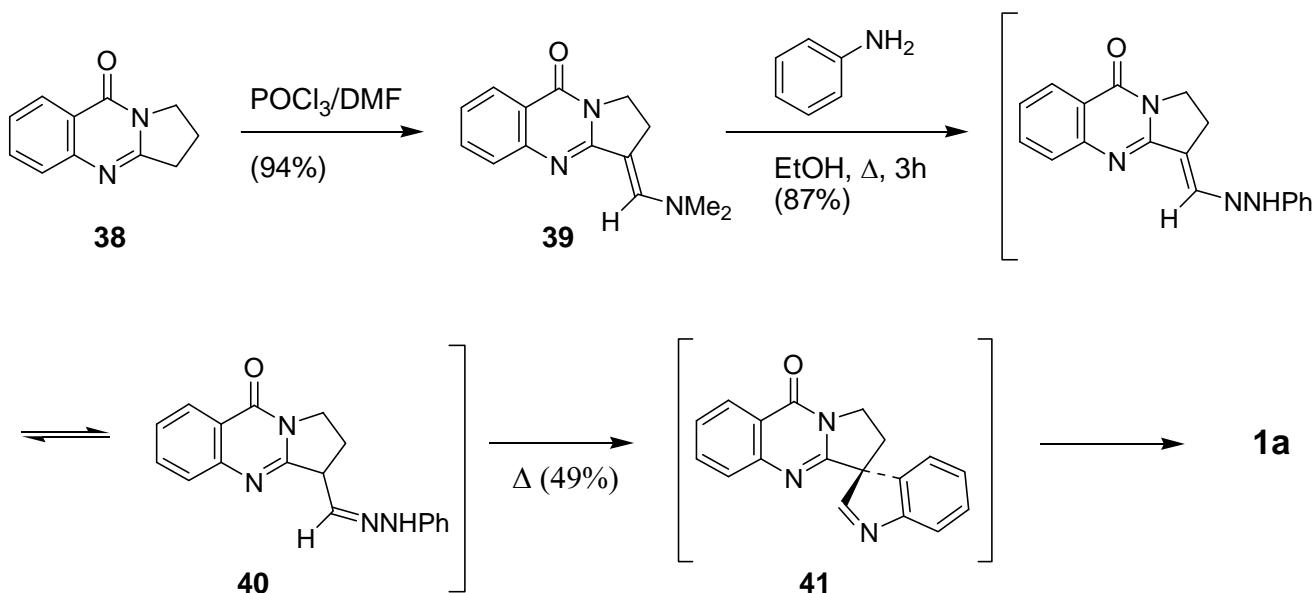
Although a lot of synthetic procedures have been reported for the synthesis of rutaecarpine, many of them were limited to for the introduction of substituent(s) only on a part of the 5 rings in the molecules. For the further pursuing the structure-activity relationship study on rutaecarpine derivatives, it definitely needs either to develop more practical methods to introduce substituents all over the 5 rings or to design (a) new procedure(s) combining methods reported so far.

5. Biological Properties

A comprehensive review written in 1999 by Sheu [11c], covered very well the *in vitro* as well as the *in vivo* pharmacology of rutaecarpine, whose pharmacological actions were reviewed under several subheadings: (1) cardiovascular effects, (2) antithrombotic activity, (3) anticancer effects, (4) antiinflammatory and analgesic effects, (5) effects on endocrine system, (6) antiobesity and thermoregulatory effects, (7) effects on smooth muscle except cardiovascular, and (8) others. Herein we cover only studies on the cytotoxicity and inhibitory activity on COX. Studies on the cytotoxicity of rutaecarpine and its derivatives are summarized in Table 7. In general, a substitution on the ring

resulted in selectivity towards specific cell lines. 11-Methoxyrutaecarpine showed selective cytotoxicity against the lung and renal cancer subpanel at 1.38 and 0.31 μM level, respectively, while the 10,11-methylenedioxy analogue showed selective cytotoxicity for the ovarian cancer subpanel [73a]. 10-Bromo- and 10-methylthiorutaecarpine showed high selectivity on a renal carcinoma cell line and strong cytotoxicity at 0.3 and 0.08 μM level, respectively [73b, 88] while 12-fluororutaecarpine showed strong cytotoxicity with selectivity on the HT-29 human cell line [89]. Introduction of substitutions on ring E affected the cytotoxicity more significantly. 2-Chlororutaecarpine showed strong inhibitory activity against topoisomerase I and II, with potency comparable to camptothecin [89]. It should be noted that the inhibitory activities on topo I and II seemed to be affected by a substitution on the E-ring but not by substitutions on ring A and C [55, 89]. In addition, rutaecarpine inhibited tumor cell migration approximately 30-40% level compared to control at 100 *μ*g/mL [90], which would be a new vista of the further studies on rutaecarpine.

Table 7. *In vitro* cytotoxicity of rutaecarpine analogues (GI$_{50}$ values in μM)[a]

	CNS U251	HT-29	A549/ ATCC	NCI-H460	OVCAR-4	786-0	Renal ACHN	HS-578T
Rutaecarpine	0.02 [73b]	31.6 [31]	14.5 [73a]	-	18.9 [73a]	-	-	22.6
11-OCH$_3$ [73a]	-	-	0.75	1.38	>25.0	0.31	-	1.59
10,11-OCH$_2$O-	-	-	>25.0	1.55	1.50	1.08	-	5.05
10-Br [88, 73b]	5	33[b]	59[c]	-	3[d]	-	>100	-
2-CH$_3$,10-Br	0.3	14[b]	18[c]	-	3[d]	-	0.3	-
10-SCH$_3$ [73b]	3	-	-	-	13[d]	-	0.08	-
1-OH [31]	-	7.39	10.43	-	-	-	-	-
2-Cl [89]	-	5.62	22.4	-	-	-	-	21.6[e]
12-F [89]	-	1.26	8.4	-	-	-	-	3.18[e]

Tumor subpanels: human lung adenocarcinoma (A549), human colon carcinoma (HT-29), leukemia (CCRF-CEM), nonsmall cell lung cancer (A549/ATCC and NCI-11460), renal cancer (786-0), ovarian cancer (OVCAR-4), and breast cancer (HS-578T).
[a]The cytotoxicity GI$_{50}$ values are the concentrations corresponding to 50% growth inhibition, and they are the averages of at least two determinations. [b]for colon SW620 cell line. [c]for lung H522 cell line. [d]for ovarian SKOV3 cell line. [e]for human breast cancer carcinoma MCF-7.

Strong and selective inhibitory activity on COX-2 has been claimed as the origin of the anti-inflammatory activity of rutaecarpine [91]. A series of substituted rutaecarpines were therefore prepared by employing Fischer indole synthesis as the key step and their inhibitory activities on COX-1 and 2 as well as selectivity on COX-2 were evaluated. The compounds 10-methanesulfonyl-rutaecarpine and 10-bromorutaecarpine showed promising inhibitory activity (IC$_{50}$ = 0.27 and 0.35 μM, respectively) with selectivity (39 and 62, respectively) [92].

It should be noted that more compounds with various substituents on each ring as well as both A- and E-ring together are definitely required to lead better and more decisive conclusion for the

structure-activity relationship and to pursue further studies in the process of drug development for specified biological activity.

6. Metabolism

Understanding of metabolic profiles of biologically active compounds in human body would be a critical step in the process of developing new candidates of drugs. In this regard, systematic studies on the metabolic biotransformations of a plant-derived biologically active rutaecarpine have been pursued. We have summarized herein the *in vitro* (rat and human liver microsomes) and *in vivo* (rat) studies done to identify the phase I and phase II metabolites of rutaecarpine.

1) Phase I Studies

In vitro phase I metabolites of rutaecarpine were determined by collision-induced dissociation (CID) fragmentation spectra of MS^2, MS^3 and retention times by LC/ESI-MS [93]. Incubation of rutaecarpine with rat liver microsomes in the presence of NADPH afforded five mono-hydroxylated rutaecarpines (M1-M5), of which three isomers were hydroxylated on ring E, and one on ring C, and one on ring A, as well as 4 di-hydroxylated rutaecarpines (Figure 2). Ueng *et al*. confirmed the structures of four mono-hydroxylated metabolites as 3-, 10-, 11-, and 12-hydroxyrutaecarpines, by synthesis and comparison of their spectral data such as mass, UV absorbance and ^{1}H-NMR spectra with those of authentic synthetic standards [94]. A later *in vitro* study with human liver microsomes afforded six mono-hydroxylated rutaecarpines of which an additional mono-hydroxylated one (M6) was found to be 9-hydroxyrutaecarpine [95]. In addition, four dihydroxylated rutaecarpines could be divided to three di-hydroxylated metabolites on the A- and C-rings and one on C- and D-rings [95]. By using combinations of chemical inhibition, immunoinhibition and metabolism by cDNA expressed cytochrome P450 (CYP) enzymes, CYP isozyme responsible for each rutaecarpine metabolite was specified as shown (Figure 1) [94,95,96].

Table 8. *In vitro* and *in vivo* Phase I metabolites of rutaecarpine.

| Metabolites	In vitro	In vivo	
	Microsomes	Urine	Faeces
7/8-Hydroxyrutaecrpine[a]	47.0 ± 1.3	N.D.[b]	N.D.[b]
3-Hydroxyrutaecarpine	4.9 ± 0.1	10.1 ± 0.9	9.9 ± 1.4
9-Hydroxyrutaecarpine	2.9 ± 0.1	7.2 ± 0.5	26.9 ± 4.2
10-Hydroxyrutaecarpine	9.5 ± 0.2	24.6 ± 2.5	15.6 ± 0.8
11-Hydroxyrutaecarpine	33.9 ± 0.7	58.1 ± 2.2	47.6 ± 2.6

[a] Not determined exact position where the OH is substituted. [b] N.D.: Not detected. For experimental details see refs [93b] and [97].

Figure 2. Metabolites of rutaecarpine.

1) Monohydroxylated metabolites (Major, in Urine, Faeces, and Bile)
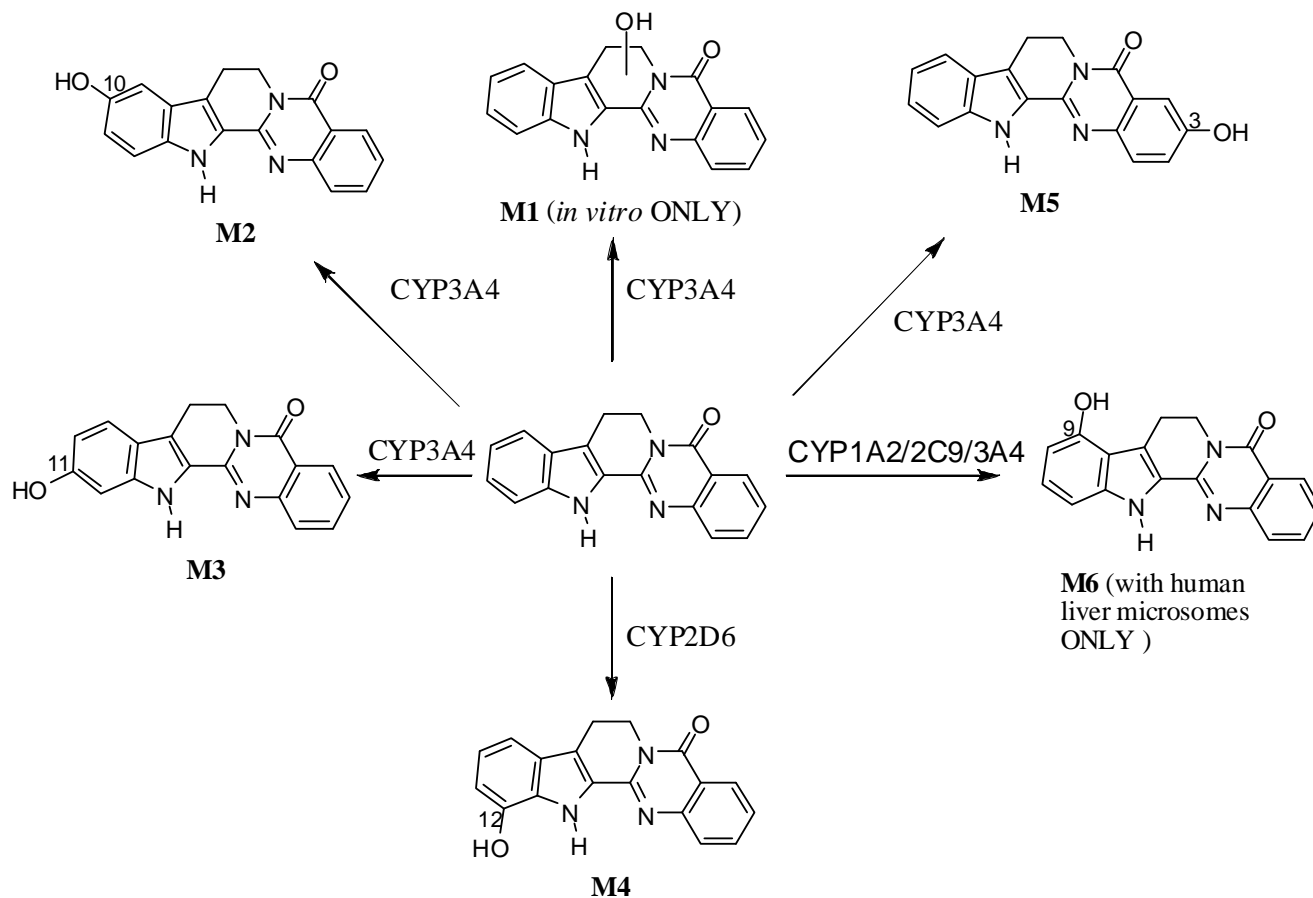
2) Dihydroxylated metabolites (Minor, in Urine and Faeces)
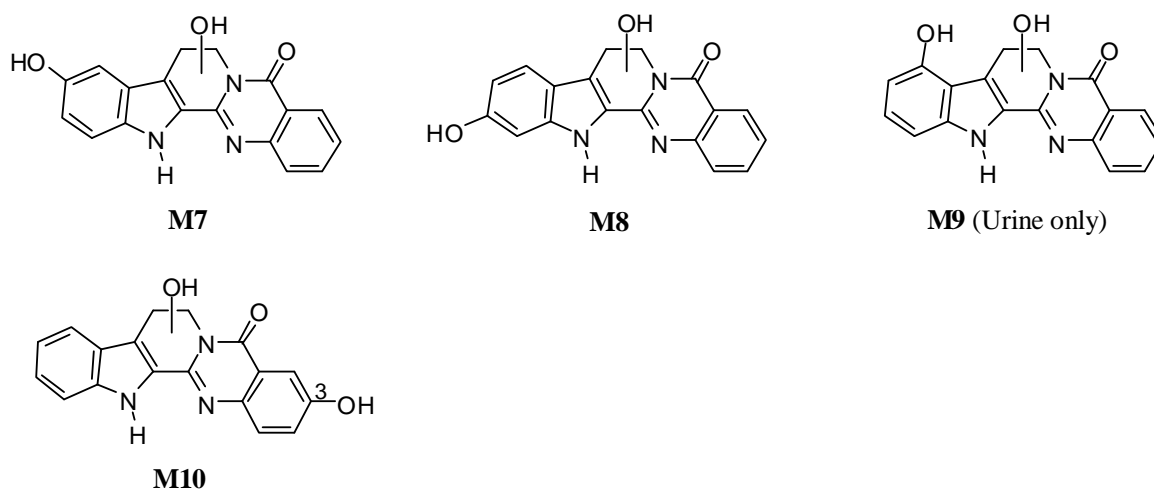
In vivo phase I studies on male Sprague-Dawley rats were also pursued to give four mono-hydroxylated metabolites such as 3-hydroxyrutaecarpine (M5, 10.1%), 9-hydroxyrutaecarpine (M4, 7.2%), 10-hydroxyrutaecarpine (M2, 24.6%) and 11-hydroxyrutaecarpine (M3, 58.1%) and 4 isobaric di-hydroxylated metabolites (M7-M10) (Figure 1) in urine [97], which were identical to the *in vitro* metabolites except one (M1) that was hydroxylated in the aliphatic moiety. On the other hand, in

faeces, the distribution of monohydroxylated metabolites were somewhat different from those in urine. Additionally, M9 was not detected in faeces. It should be noted that the formation of M1 in the rat liver microsomes accounted for 47% the total metabolites, which was not detected in the *in vivo* system. Such result could be explained by the relative amount of CYP2B enzymes in control liver *vs* in rat in which amount of CYP2B is usually very low or does not exist [98].

2) Phase II Studies

From the urine of male Sprague-Dawley rats, pretreated intravenously with rutaecarpine, 16 different phase I and II metabolites were identified including four sulfate and four glucuronide conjugates (Figure 3) [97]. Phase I metabolites of rutaecarpine were identified as four mono-hydroxylated rutaecarpines and four isobaric di-hydroxylated rutaecarpines as metabolites (*vide ante*). In addition, eight phase II metabolites were identified as conjugated with 4-sulfate (S1-S4) and 4-glucuronide (G1-G4). On the other hand, in faeces, 11 different metabolites were identified, in which the di-hydroxylated metabolite M9 and 4 glucuronides G1-G4 were not detected.

Figure 3. *In vivo* Phase II metabolites of rutaecarpine.

1) Sulfates (Urine and Faeces)
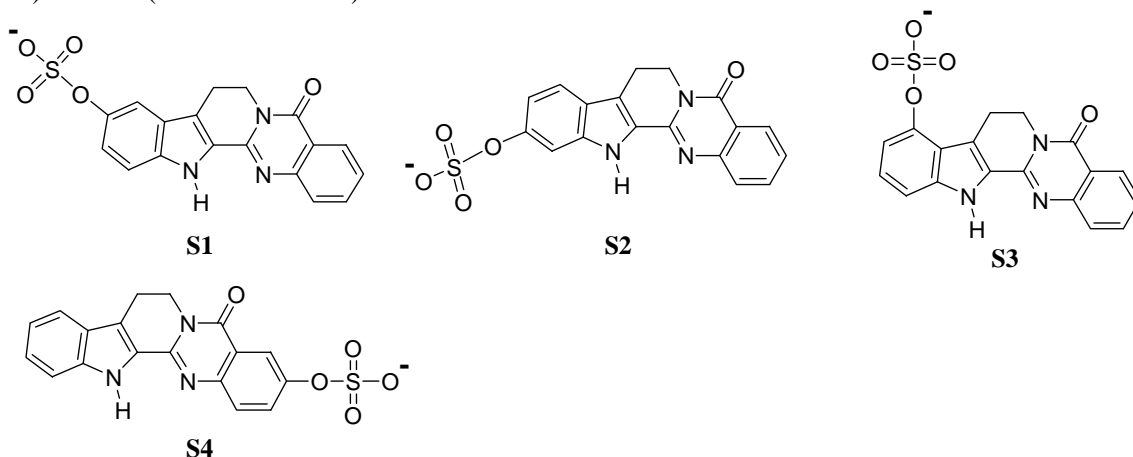
2) Glucuronides (Urine)
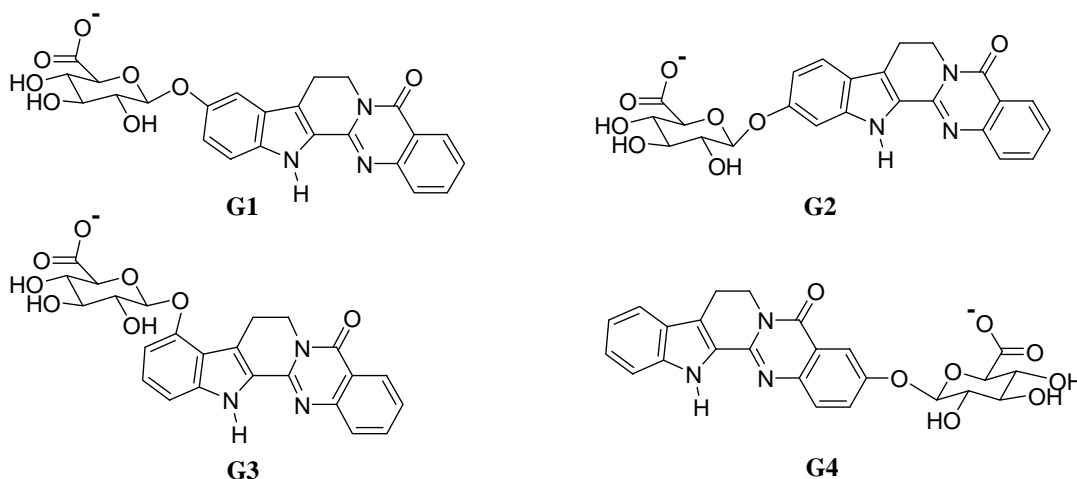
7. Conclusions

Herbal medicines have been employed as the main source for the development of new agents for treating diseases as well as disorders. Although many of them are still used as mixtures and/or extracts, without identification of active ingredient(s), or with unknown biological action mechanisms, many drugs of the currently used in clinics as a single identity are originally derived from herbs and other plants. Rutaecarpine is one of the important alkaloids isolated from the Rutaceae, exhibits a variety of interesting biological properties, thus continuously attract the scientists in academy as well as industry. Recent years have witnessed the steady progress in the chemistry and biology of rutaecarpine. In the present review, we focused only at the area of natural sources, derivatives, synthesis, biological activities and metabolism of rutaecarpine.

We anticipate that recent progress in science and technology will permit the isolation and identification of new minor rutaecarpine-related components, as well as their biological activities. In addition, more efficient and/or practical methods for the synthesis of rutaecarpine derivatives are still required to pursue structure-activity relationship study and to find more potent compounds for drug development.

Acknowledgements

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