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A Simple Heterocyclic Fusion Reaction and its Application for Expeditious Syntheses of Rutaecarpine and its Analogs

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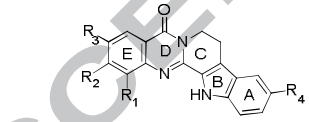
ABSTRACT

Abstract—In the search for new inhibitors of cholinesterases, a simple heterocyclic fusion reaction of isatoic anhydride **8** and 3,4-dihydroisoquinoline **22** was discovered which involves a spontaneous dehydrogenation upon heating. Applying the reaction, the bioactive natural alkaloid rutaecarpine and several substituted derivatives out of tryptamines and anthranilic acids or isatoic anhydrides, respectively, can be synthesized without tedious chromatographic purification. This provides simple and fast access to larger amounts of compounds with this privileged structure in medicinal chemistry.

Quinazolinones are among the so-called privileged molecules for drug discovery. Natural and synthetic quinazolinones have been described to possess diverse biological activities including anticancer, antiinflammatory, antimalarial, antiviral, antioxidant, CNS depressant and several other activities.[1]



1a $R_1 = R_2 = R_3 = R_4 = H$ (rutaecarpine)
1b $R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$ (hortiacine)
1c $R_1 = H$, $R_2 = R_3 = OCH_2O$, $R_4 = H$ (euxylophoricine C)
1d $R_1 = H$, $R_2 = R_3 = R_4 = OCH_3$ (euxylophoricine D)
1e $R_1 = OH$, $R_2 = R_3 = R_4 = H$ (1-hydroxyrutaecaprine)
1f $R_1 = H$, $R_2 = OCH_3$, $R_3 = R_4 = H$ (2-methoxyrutaecaprine)
1g $R_1 = R_2 = OH$, $R_3 = R_4 = H$ (1,2-dihydroxyrutaecaprine)
1h $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$ (1-methoxyrutaecaprine)
1i $R_1 = R_2 = H$, $R_3 = OH$, $R_4 = H$ (3-hydroxyrutaecaprine)
1j $R_1 = H$, $R_2 = R_3 = OCH_3$, $R_4 = H$ (euxylophoricine A)

Figure **1**. Structures of rutaecarpine and its naturally occurring derivatives

Rutaecarpine (**1a**, Figure **1**) is a natural quinazolino carboline-type alkaloid first isolated in 1915 from *Evodia rutaecarpa*[2] which is used in Traditional Chinese Medicine as a herbal remedy for the treatment of inflammation-related disorders.[3,4] Later, it was also separated from other plant families such as *Horita, Zanthoxylum, Euxylophorea,* and several others. A couple of natural derivatives of rutaecarpine (**1b**-**1j**) bearing hydroxy and methoxy groups at ring A or E also have also been isolated from various plants.[1a, 3, 5]

Accumulating research has proven useful biological properties of rutaecarpine **1a** and its natural and synthetic analogs, such as anti-platelet aggregation,[6] vasorelaxing,[7] antiobesity,[8] cytotoxity,[9] and cyclooxygenase-2 inhibitory activitiy.[10]

Its multiple biological activities intrigued many efforts on the syntheses of **1a** and its analogs, which are – despite the simplicity of the pentacyclic structure - in most cases far from being effortless.[11] Briefly, these syntheses can be divided into four distinct types: (1) using derivatives of

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anthranilic acid (**2**-**9**, Figure 2) and tryptamine (**10**-**17**, Figure **3**) to build the D ring or C, D rings simultaneously at the final stage; [12] (2) first synthesis of the tricyclic intermediate 8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazoline-6,11(7*H*)-dione via different schemes, then applying Fischer indole synthesis as the final step; [13] (3) pre-obtaining the reduced structure of rutaecarpine, then oxidation to achieve the target structure;[14] (4) metal catalyzed or radical cyclization to form C ring as the key step.[15] Also methods outside these categories have been described.[16]

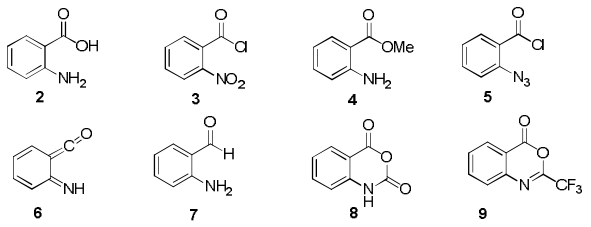


Figure **2**. Structures of anthranilic acid and its derivatives applied as synthones of rutaecarpine

Usually, activated derivatives of anthranilic acid and tryptamine represent the reactive forms of the two starting materials. For example, compounds **3** and **15** were utilized by Asahina *et al.* in 1927 for the first synthesis of rutaecarpine **1a**.[12a]

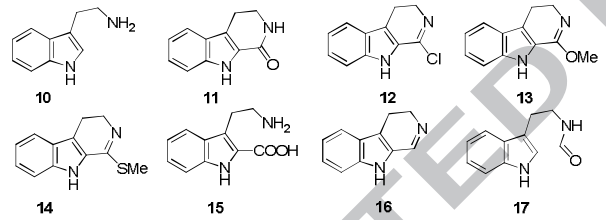
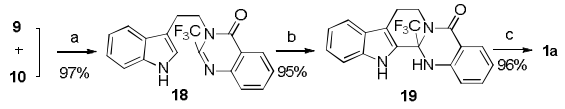


Figure **3**. Structures of tryptamine and its derivatives applied as synthones of rutaecarpine

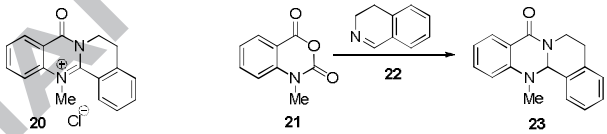
Generally, all these methods are multi-step synthetic procedure, require special reagents and/or starting materials and therefore lead to small quantities of the target structures, often not enough for further pharmacological evaluations. Up to now, probably one of the most effective methods (Scheme **1**) is Bergman's synthesis, which uses compound **9** and tryptamine **10** to form the intermediate **18**. Treatment of intermediate **18** under acidic condition achieves the closure of ring C and formation of **19**, which loses CHF_3 to yield compound **1a**. In this method, rutaecarpine could be obtained from compounds **9** and **10** in less than 1 hr via 3 steps in almost quantative yield.[12g]



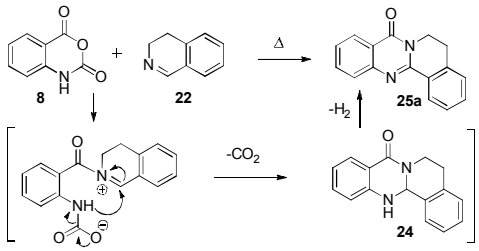
Scheme **1**. Bergman's synthesis of **1a.**[12g] Reagents and conditions: a) pyridine; b) HCl, AcOH; c) KOH, EtOH

Our group has developed several novel inhibitors of both acetyl- and butyrylcholinesterase derived from dehydroevodiamine and rutaecarpine **1a**.[17] A structure like compound **20** represents a selective inhibitor of acetylcholinesterase for putative treatment of Alzheimers' disease.[17a] During our search for new inhibitors of cholinesterases, compound **23** (the benzo-analog of the alkaloid evodiamine) was synthesized by condensation of *N*-methyl isatoic anhydride **21** and 3,4-dihydroisoquinoline **22** in toluene under reflux in moderate yield (Scheme **2**).[17d] Reacting the related unsubstituted isatoic anhydride **8** with **22**, the expected molecule would be compound **24**.[18] Surprisingly, compound **25a** formed as confirmed by its spectral data (Scheme 3).[15b, 17a, 19]

We assumed compound **24** occurs as the intermediate during the reaction, which dehydrogenates spontaneously upon heating to be converted into **25a**. The same spontaneous dehydrogenation also occurred in the so-called retro mass-spectral synthesis of **1a** in Kametani's group.[12e] Che *et al*. used aryl azides **5** as nitrogen source for C–N bond formation, compounds **24** and **25a** were obtained in the same reaction with yield of 73% and 9%, respectively.[19]

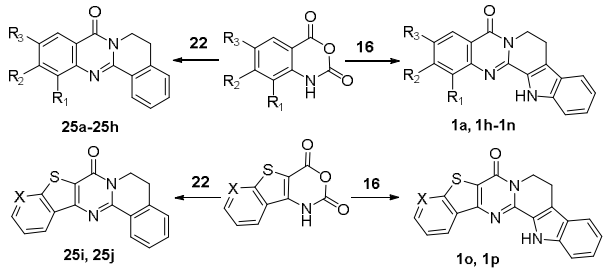


Scheme **2**. The structure of acetylcholinesterase inhibitor **20** and synthesis of the benzo-evodiamine **23**



Scheme **3**. Synthesis of the benzo-rutaecarpine **25a**

Our pilot reaction achieved the unexpected benzo-rutaecarpine **25a** in moderate yield (50%). We assumed that the relatively low yield resulted from incomplete conversion of compound **24** to **25a** in toluene and we monitored the reaction progress by HPLC. Running the reaction in THF also encountered the same problem while in DMF conversion was completed with concomitant increased yield.



Scheme **4**. Syntheses of **1a** and its analogs

Since **25a** bears a closely related quinazolinone structure to rutaecarpine, it is reasonable to apply this method to synthesize **1a** and its analogs. A mixture of isatoic anhydride **8** and 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole **16** (which can be synthesized from tryptamine via a 2-step scheme in quantitative yield without chromatographic purification[20]), was stirred in DMF at 95 °C for 20 hrs to afford **1a** in 93% yield.

It is noticeable that both simple isatoic anhydride **8** and **16** were utilized in the synthesis of **1a**. Bergman *et al.* converted **8** into **9** for their effective synthesis.[12g] Chavan *et al*. used **8** as starting material via 6-step synthesis to give 8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazoline-6,11(7*H*)-dione, which was subjected to the Fischer indole synthesis to yield **1a**.[13f] Also **16** (together with **6**) appeared in Kametani group's synthesis.[12e] Nevertheless, to our knowledge, both **8** and **16** are not applied in the same reaction.

R or X	Compounds	Yield
$R_1 = R_2 = R_3 = H$	**1a** (rutaecarpine)	93%
	25a	72%
$R_1 = OCH_3$, $R_2 = R_3 = H$	**1h** (1-methoxyrutaecarpine)	89%
	25b	75%
$R_1 = R_2 = H$, $R_3 = OH$	**1i** (3-hydroxyrutaecarpine)	85%
	25c	83%
$R_1 = H$, $R_2 = R_3 = OCH_3$	**1j** (euxylophoricine A)	75%
	25d	78%
$R_1 = R_2 = H$, $R_3 = OBn$	**1k** (3-benzyloxyrutercarpine)	96%
	25e	79%
$R_1 = R_2 = H$, $R_3 = Cl$	**1l** (3-chlororutaecarpine)	83%
	25f	77%
$R_1 = Br$, $R_2 = H$, $R_3 = CH_3$	**1m** (1-bromo-3-methylrutaecarpine)	91%
	25g	86%
$R_1 = R_2 = H$, $R_3 = NO_2$	**1n** (3-nitrorutaecarpine)	81%
	25h	69%
X=CH	**1o**	94%
	25i	89%
X=N	**1p**	76%
	25j	79%

Table **1**. Overall yield for the synthesis of rutaecarpine and its analogs (for assignment of structures cf. Scheme **4**)

After succeeding in the preparation of rutaecarpine, the new method was utilized in the syntheses of analogs of rutaecarpine (**1h**–**1p**), and its benzo homologs (**25a-25**j) (Scheme **4**). Firstly, the respective isatoic anhydrides were prepared from appropriate 2-aminobenzoic acid and triphosgene in theoretical yield. The isatoic anhydrides were then mixed with **16** or **22** in DMF and heated at 95 °C overnight. Water was added to the cooled reaction mixture, and then the desired products precipitated and collected by filtration with good to excellent yield (69 - 96%, Table **1**). Normally the substituted group on ring E did not influence the reaction. Without protection of the hydroxy group, compound **1i** and **25c** could be obtained smoothly, which proved free OH groups do not trouble the reaction process. Electron donating or withdrawing groups also did not deteriorate the yield: 3-Nitrorutaecarpine **1n** was obtained in similar yield as 3-benzoxyrutaecarpine **1k**.

Compound **1p** had previously been synthesized by Daïch *et al*., but only in 39% yield.[12i] Our method drastically improves the yield and even avoids any chromatographic purification. 1-Methoxyrutaecarpine (**1h**) was separated from *Zanthoxylum integrifoliolum* and showed anti-platelet aggregation activity, but had never been synthesized in a lab.[6] Our method therefore completed the first total synthesis of **1h**. This method can also be easily applied in the total synthesis of **1b**-**1g** when appropriate 2-aminobenzoic acids are available.

In conclusion, here we described a novel, short and versatile method for expeditious syntheses of rutaecarpine and its analogs giving high yields and devoid of tedious purification procedures. Unlike previously described procedures, neither multi-step syntheses nor special reagents are necessary, and no special starting materials have to be prepared prior to the synthesis. Applying this fusion reaction, 20 compounds were obtained. Elucidation of putative cytotoxicity[9] of the compounds obtained is ongoing and will be reported soon.

Acknowledgments

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Supplementary Data

Supplementary data (experimental procedures and spectral data for the intermediate isatoic anhydrides, **1a**, **1i–1q**, **25a-25j)** associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet

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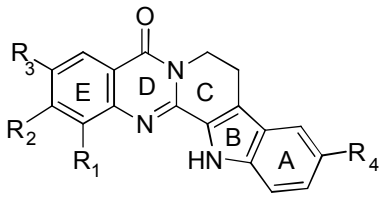

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1d $R_1 = H$, $R_2 = R_3 = R_4 = OCH_3$ (euxylophoricine D)
1e $R_1 = OH$, $R_2 = R_3 = R_4 = H$ (1-hydroxyrutaecaprine)
1f $R_1 = H$, $R_2 = OCH_3$, $R_3 = R_4 = H$ (2-methoxyrutaecaprine)
1g $R_1 = R_2 = OH$, $R_3 = R_4 = H$ (1,2-dihydroxyrutaecaprine)
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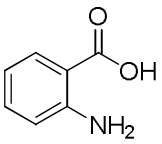
1i $R_1 = R_2 = H$, $R_3 = OH$, $R_4 = H$ (3-hydroxyrutaecaprine)
1j $R_1 = H$, $R_2 = R_3 = OCH_3$, $R_4 = H$ (euxylophoricine A)



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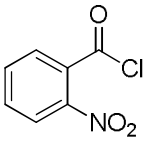

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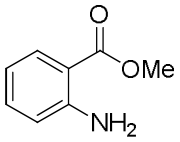

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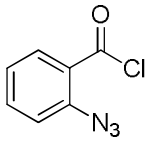

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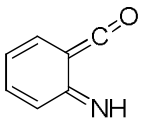

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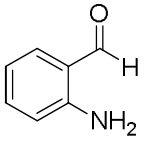

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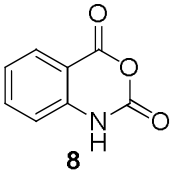

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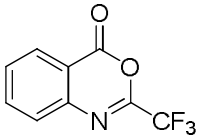

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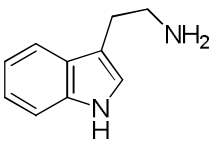

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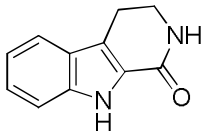

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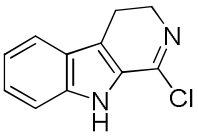

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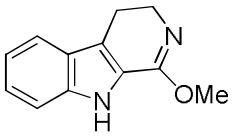

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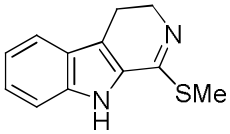

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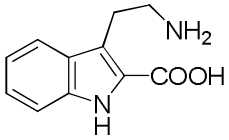

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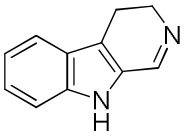

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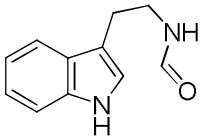

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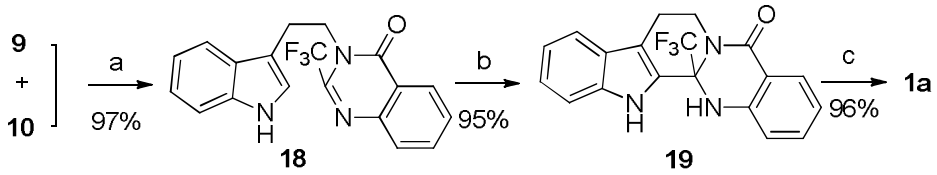

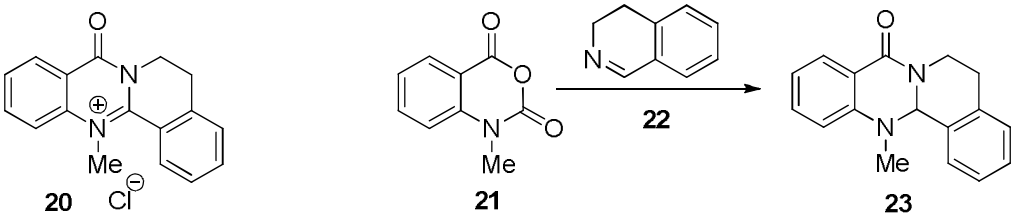

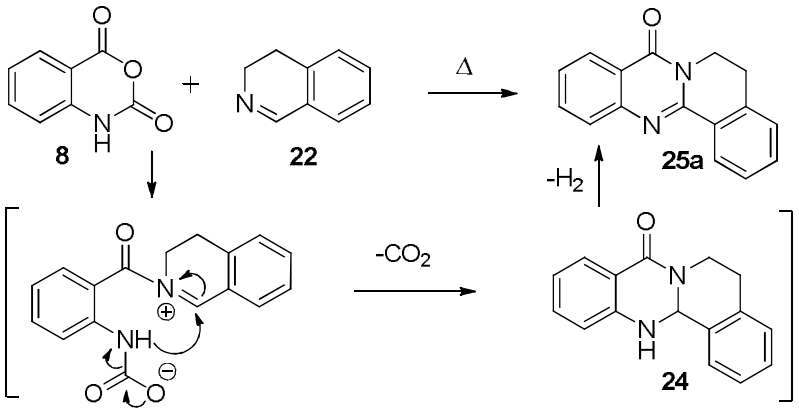

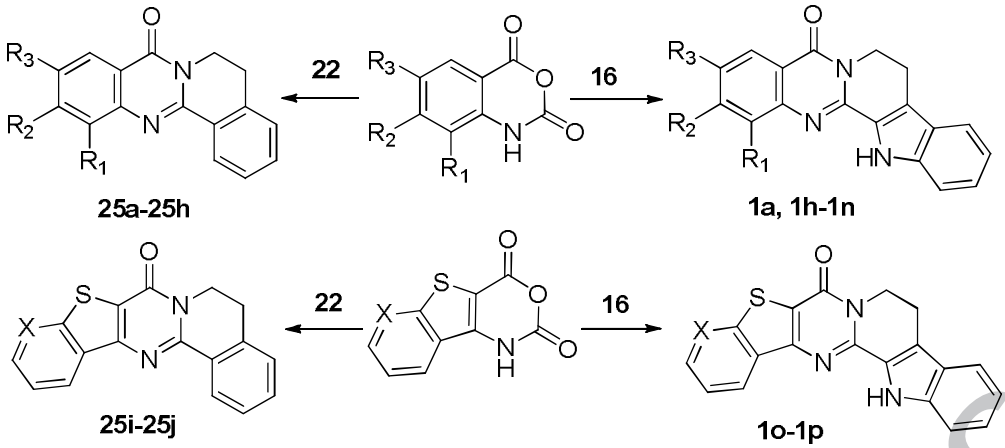

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