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Diversity oriented total synthesis (DOTS) of pyridoquinazolinone alkaloids and their analogues

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Abstract

A short diversity oriented total synthesis (DOTS) of substituted rutaecarpines, homo-luotonins, homo-vasicinone, homo-isaindigotones and homo-vasnetine has been achieved from the key tricyclic intermediate. The [*6,6,6*] tricyclic ketone, the mackinazolindione, was accessed from simple substrates *i.e.,* quinazolinone diester obtained from the disubstituted anthranilamide which in turn was prepared from the coupling of amino acid ester and ethyl oxalyl chloride with isatoic anhydride and Dieckmann condensation chemistry.

Keywords

Homo-vasicinone; Homo-luotonin; Aza-rutaecarpine; Pyridoquinazolinone; Diversity oriented total synthesis

1. Introduction

Quinazolinone, a ubiquitous nitrogen-containing heterocyclic structural motif that occurs in natural products (NPs) and pharmaceutically active molecules is a privileged scaffold for drug discovery[1]. It is found in approximately 200 natural products isolated from various natural sources including plants, microorganisms, and animals, and nearly 70 of them harbor pyridoquinazolinone core (Fig. 1; highlighted in red). The majority of

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Author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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the pyridoquinazolinones belong to the rutaecarpine class. Rutaecarpine (**1)** is a major indolopyridoquinazolinone alkaloid first isolated by Asahina from *Evodia rutaecarpa* [2a,b] (the dried fruit of it is called '*Wu-Chu-Yu*' in traditional Chinese medicine). Interest in this class of rather old natural products has been growing lately, presumably due to their characteristic structures and intriguing biological properties. This late surge of interest is evident by the 1300 references that cite rutaecarpine in the *SciFinder* database provided by the American Chemical Society of which about 150 are patents, and nearly 1200 of them are from with in the last two decades. The biomedicinal potential of this parent alkaloid of the quinazolinone class is immense, especially for cardiovascular diseases [3]. It is a COX inhibitor and is also shown to possess anti-inflammatory [4], vasorelaxing [5], antiplatelet [6], antianoxic [7], anti-diabetic [8], and antitumor [9] activities, among others. Some of the naturally occurring substituted rutaecarpines that have been listed in Fig. 1 are known to have similar or better activities while quite a few of them have not been fully explored or tested yet. Other major metabolites of *Wu-Chu-Yu*, evodiamine (**3a**), and dehydroevodiamine (DHEA) (**27**), are also well documented for their biomedicinal potential attested by the 1600 citations of which 275 are patents in *SciFinder*, and 1500 of those are within the last two decades, again indicating the late surge of interest [10]. The other notable members of the pyridoquinazolinone class, beside the various hydroxy, alkoxy *etc.* substituted versions of rutaecarpine and evodiamine, include euxylophorecins A-F (**15a-e**) [11], orisuaveolines A-B (**16a-b**) [12], hortiamines (**22a-b**) [13], fantanesines A-C (**24a-c**) [14], euxilophorines A-D (**30a-d**) [15,16], the glycosylated sugars such as ternatosides (**31a-b**) [16], and the conchacarpines A-B (**35a-b**) [17]. More recent and complex pyridoquinazolinones such as scedapins A-E (**36a-e**) [18], neosartoryadins A-B (**37a-b**) [19], and spiroquinazolines (**38–46**) [19e] harbor further linear and spiro fusions along with chiral carbon framework, and are shown to be anti-viral based on their screening and docking results. For example, scedapins and their analogues such as quinadoline are projected to have a potential for inhibition of COVID-19 type coronaviruses. They exhibited impressive binding affinity with human ACE-2 or SARS-CoV-2 main protease [20a-e]. Dievodiamine **47b** is the only dimer known in the pyridoquinazolinone class however, its biomedicinal potential has not been explored yet [20f,g]. In general, the intriguing chemical architectures with vast and unique structural diversity of this class coupled with the promising biomedicinal potential attracted the attention of synthetic and medicinal chemists which led to the development of a plethora of impressive total synthetic routes to rutaecarpine and its natural congeners [21], and the methodologies for pyridoquinazolinone cores in general [22]. Yet, there is no universal diversity oriented total synthesis route or strategy that could be broadly adapted for the various members of this class. Motivated by the opportunity and intrigued by the structural similarity among these pyridoquinazolinone alkaloids, we were involved in developing a divergent synthetic strategy *via* the key mackinazolindione intermediate (Scheme 1) amenable for DOTS and completed the synthesis of rutaecarpine successfully [23]. However, the synthetic potential of the route remained to be explored for the synthesis of other natural and unnatural pyridoquinazolinone analogues listed in Fig. 1.

The building blocks utilized for the synthesis of mackinazolinedione *i.e.,* various substituted isatoic anhydrides and amino acids are easily available, and the route has inbuilt diversity.

Hence it is suitable for the diversity-oriented total synthesis of various pyrido quinazolinone NPs in conjunction with the variations in the late-stage annulations of the AB cores onto the substituted mackinazolindione **48** by utilizing the substituted hydrazines or amines, or through the functionalization of the piperidone ring *via* the carbonyl chemistry as shown in Scheme 1. Attesting to this untapped potential of the route, Abe et al., have adopted our chemistry and the mackinazolindione intermediate to access fontanesines and their analogues [24]. As part of our recent initiation of a quinazolinone based medchem approach [25] for the development of novel anti-microbial and anthelminthic agents we revisited the chemistry of the mackinazolindione and decided to utilize its further potential to synthesize a more diverse set of natural and unnatural analogues and the efforts and results towards that direction have been delineated herein.

2. Results & discussion

Our large-scale synthesis of tricyclic quinazolinone core mainly relied on adapting our earlier method [23] (Scheme 2). It commenced with the synthesis of γ-amino butyrate hydrochloride **56** from γ-amino butyricacid **55**, alcohol, and thionyl chloride. The resulting γ-amino butyrate hydrochloride **56** was treated with isatoic anhydride and Et_3N in the presence of a catalytic amount of DMAP in DMF to furnish the amine **57**, which was further condensed with ethyl oxalyl chloride to obtain the bisamide **58** in large scale (>100g). The cyclodehydration of the amide was achieved with PCl_3 in refluxing xylene to form the quinazolinone. Having obtained the diester **59** with suitable functionalities needed, it was subjected to Dieckmann condensation in the presence of NaH. Gratifyingly, the β-ketoester **60** was produced in decent yields even on a large scale and did not need any further purification. The decarboxylation of **60** in the presence of refluxing 6 N HCl produced dione **61** in good yield. Having accessed the mackinazolindione **61** in large quantity (>10g in 6 steps from GABA; some of the steps could be coaxed into one pot, however, the optimization studies were not undertaken), we undertook the efforts to showcase its utility in total and diverted total synthesis of quinazolinone alkaloids. First, we wanted to obtain the homo-vasicinone *via* the reduction of dione **61**, however, it proved not as straightforward as we initially had hoped. The tricyclic benzylic ketone **61** was easily over reduced by BH_3 (Scheme 3, Path A) or $NaBH_4$ (Scheme 3, Path B). Even under Luche reduction condition ($CeCl_3/NaBH_4$, Scheme 3, Path C), which is used for the selective reduction of α,β-unsaturated ketones to allylic alcohols, the over reduction ensued to produce the compound **62**, where both the C=O and C=N bonds were reduced. The weaker reducing agents that we turned to either failed or resulted in unidentified products. Notably, the $NaBH_3CN$ promoted the formation of a dimer whose structure could not be completely deduced, while the attempted $NaBH(OAc)_3$ reduction led to hydration of the ketone resulting in geminal diol **63** (Scheme 3, Path D). After continuous experimentation, we were delighted to find that the L-selectride produced the desired homo-vasicinone **64** in a decent yield (Scheme 3, Path E).

We then decided to proceed with the annulation of indole core onto the pyridoquinazolinone **61** (Scheme 4). Thus, the dione **61** was subjected to Fischer indolization [26] with various hydrazines in H_3PO_4 at 180 °C. We successfully obtained rutaecarpine **1** as

reported earlier and its analogues **65**, and **66** *i.e.,* substituted indolopyridoquinazolinones. However, the reaction of dione **61** with 4-methoxyphenylhydrazine hydrochloride to obtain hortiacine **18** was not as straightforward as others were. It failed under the H_3PO_4 conditions. After careful experimentation with various reaction conditions, we found out that it could be obtained from dione **61** in the presence of $ZnCl_2$/AcOH at 150 °C in 18h. We then proceeded to prepare the ring heteroatom substituted rutaecarpines, *e.g.,* aza-rutaecarpines. Towards that direction, we brominated the dione **61** successfully to obtain the bromo compound **67**. It was subjected to condensations with bis-nucleophiles, such as 2-aminopyridine and thiourea, thus generating hitherto unreported compounds **68** and **70** (Scheme 5) in moderate yields. However, disappointingly the attempts to access diaza-rutaecarpine **69** were not successful as was the condensation with urea derivative (Scheme 5).

Next, we focused on the annulation of quinoline core onto the pyridoquinazolinone **61** to obtain the homo-luotonin analogues [27]. Towards that direction, we subjected the dione **61** for the Friedlander condensation [28] with various *o*-aminophenyl systems to access the pyridoquinazolinoquinolines. To obtain the homo-luotonin A **71** we have employed 2-nitrobenzaldehyde as the surrogate for 2-aminobenzaldehyde since the latter is unstable in the classical Friedlander condensation conditions. The amenability of this chemistry to prepare the analogues of homo-luotonin A is showcased with Friedlander condensation of dione **61** with *o*-amino aceto-/propio-/benzo-phenones, and 2-aminobenzonitrile to obtain the methyl, ethyl, benzyl, and amino substituted homo-luotonins **72–76**, respectively. Noteworthy, in our initial attempts cyanoenamine intermediate **75** was isolated in condensation of dione **61** with 2-aminobenzonitrile, which was reluctant to further cyclize to form the quinoline core. In our persistent efforts, compound **75** was found to undergo further cyclization in the presence of TfOH to give **78**, and this new reagent also effected the one-step synthesis of **78** from **61** directly (Scheme 6).

In our further synthetic efforts, the dione **61** was subjected to Wittig olefination with various phosphonium salts to access the analogues of homo-isaindigotone [29]. A small collection of pyridoquinazolinonyl olefins has been built (Scheme 7). Interestingly, only the stable Wittig reagents reacted with dione **61** to generate the olefins **77**–**81** reliably. NOESY was used to assign the configuration of these olefins. Though Nepali et al. [30] reported that (*E*)-olefins of type **77** did not have the correlation between H_1 and H_2, the weak signal of $H_1 - H_2$ was still observed in our case. As we cannot find more support for the existence of the (*Z*)-isomer, such as the correlation between the H of the quinazolinone core and the H of the arylidene group, we assigned (*E*)-configuration to these olefins. Our assignment was further affirmed by the crystal structure of olefin **77** confirming the (*E*)-configuration. This selectivity for the formation (*E*)-isomers can be attributed to the steric hindrance between the nitrogen lone pair of quinazolinone core and the benzene ring of the arylidene group [34] (See supplementary material, S84).

Finally, we have subjected the dione **61** to various aniline substrates hoping to access the homologues of 3-hydroxyanisitone, desmethoxyaniflorine, and vasnetine *etc.* [31] Disappointingly, our efforts with most of these nucleophilic additions did not proceed as

hoped. Only homo-vasnetine **83** was obtained *via* the reductive amination of the enamine-imine tautomeric mixture resulting from the condensation of **61** with *o*-aminobenzoate in the presence of TsOH. The lack of reactivity of the carbonyl towards the pi- or substituted N-nucleophiles can either be attributed to the keto-enol tautomerism that **61** can engage under strong acidic or basic conditions, or it could be just that the substituted anilines are not nucleophilic enough to react with **61** as nucleophiles (Scheme 8).

3. Conclusions

In summary, we have utilized the mackinazolindione **61** as a key intermediate and gained a diversity oriented total synthesis access to various pyridoquinazolinone, indolopyridoquinazolinone, and pyridoquinazolinoquinoline natural products and their analogues. Our route involves readily available starting materials and inexpensive reagents and is amenable to large scale synthesis. It is also amenable to access analogues through the inbuilt diversity points and late-stage annulations of the AB or DE cores with suitably substituted synthons. Furthermore, it is flexible for the solid phase synthesis of the title compounds as it employs amino acid coupling chemistry which is well established on polymeric resins (peptide chemistry). This work attests to the power of DOTS to access focused libraries of natural product analogues for NP-based med chem approach. We found out that the column purification over a Et_3N pre-washed SiO_2 produced better yields than the regular SiO_2 columns. However, it is pertinent to mention that the yields have not been optimized at this time. We believe that the key mackinazolindione is a versatile synthon and the chemistry disclosed herein is simple and reliable that would find applications in the total synthesis of other pyridoquinazolinone natural products reported (Fig. 1) and yet to be reported, some of which is underway in our lab as is screening studies of the library generated herein and the results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data has been submitted as Supporting Information with the submission of this article.

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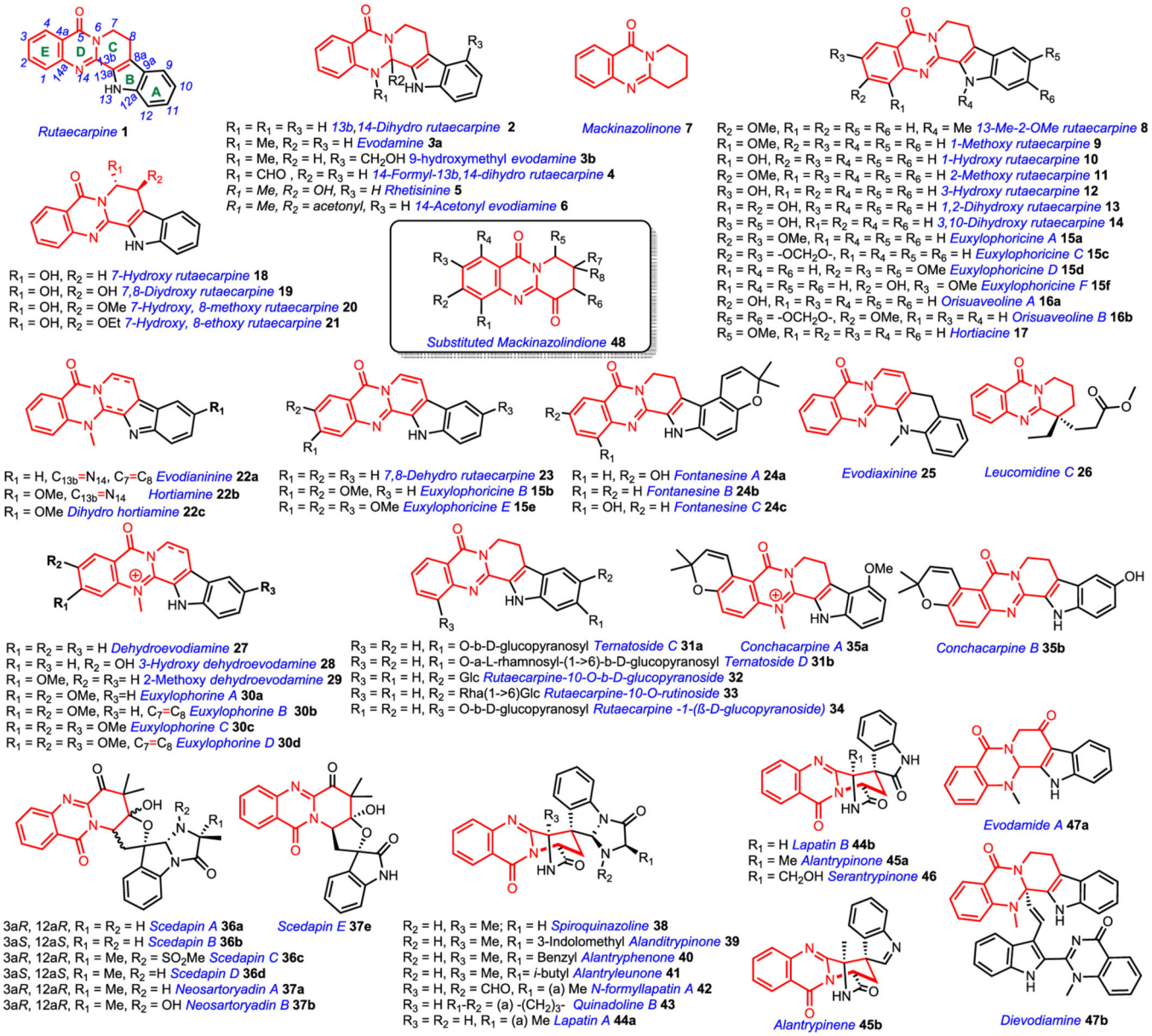
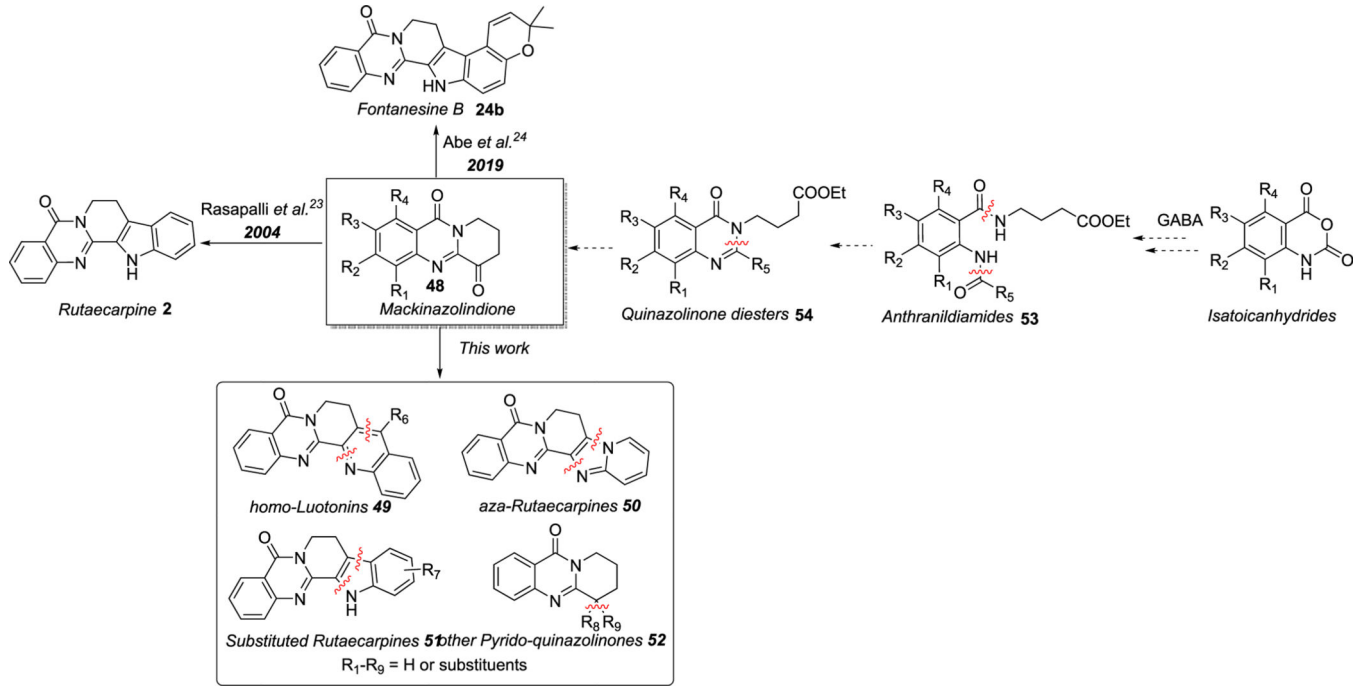


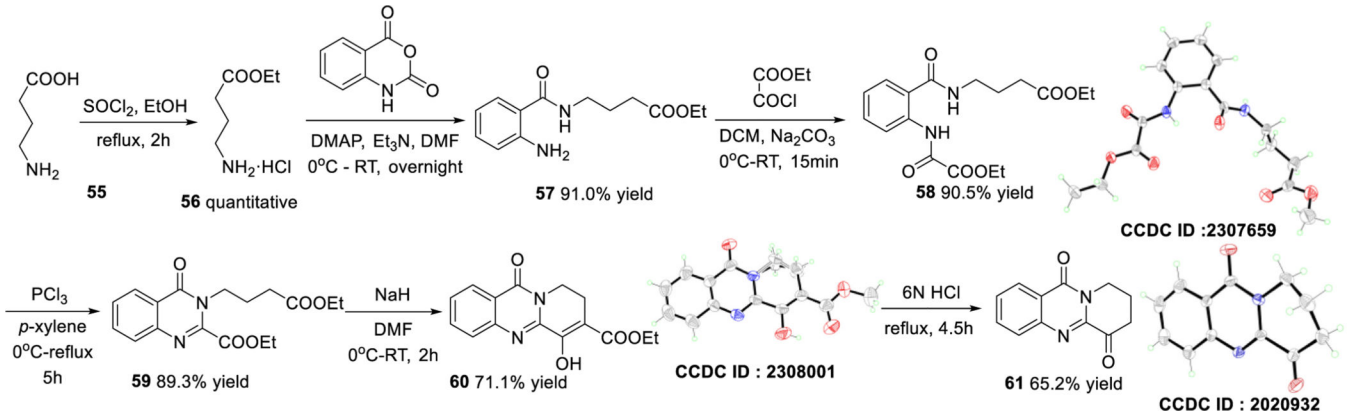
Fig. 1.

Structures of known pyridoquinazolinone natural products and mackinazolinedione.



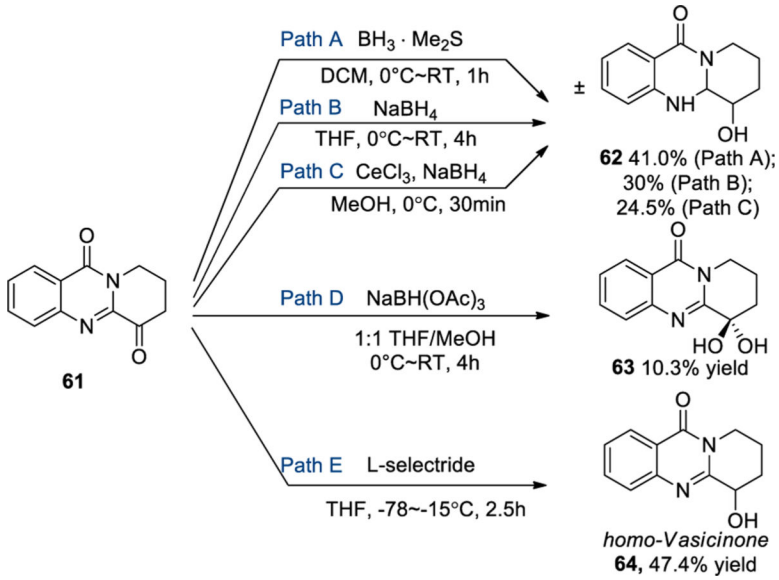
Scheme 1.

The retrosynthetic analysis of substituted pyridoquinazolinones to the substituted mackinazolindione.



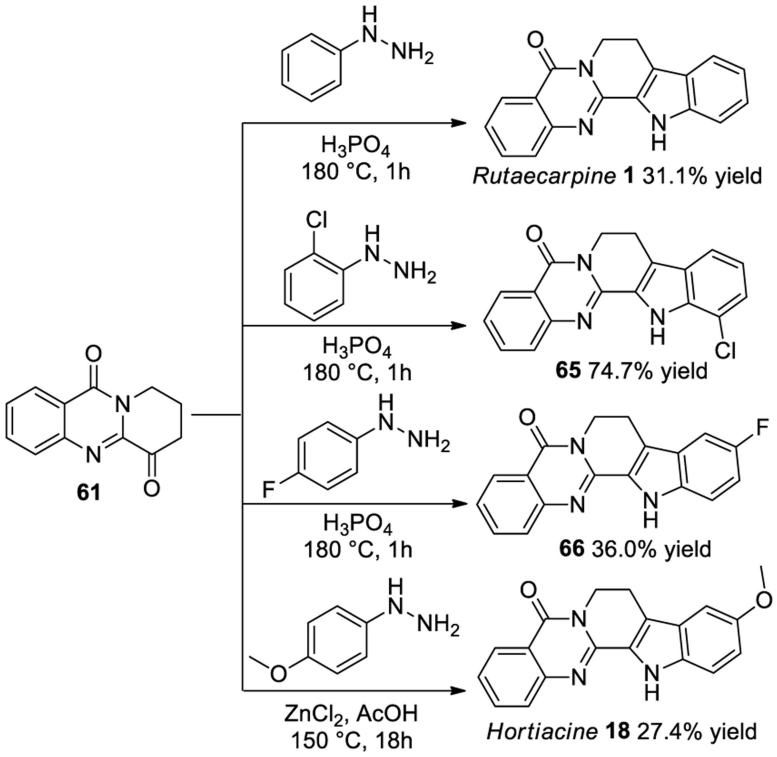
Scheme 2.

Synthesis of unsubstituted mackinazolindione **61**.

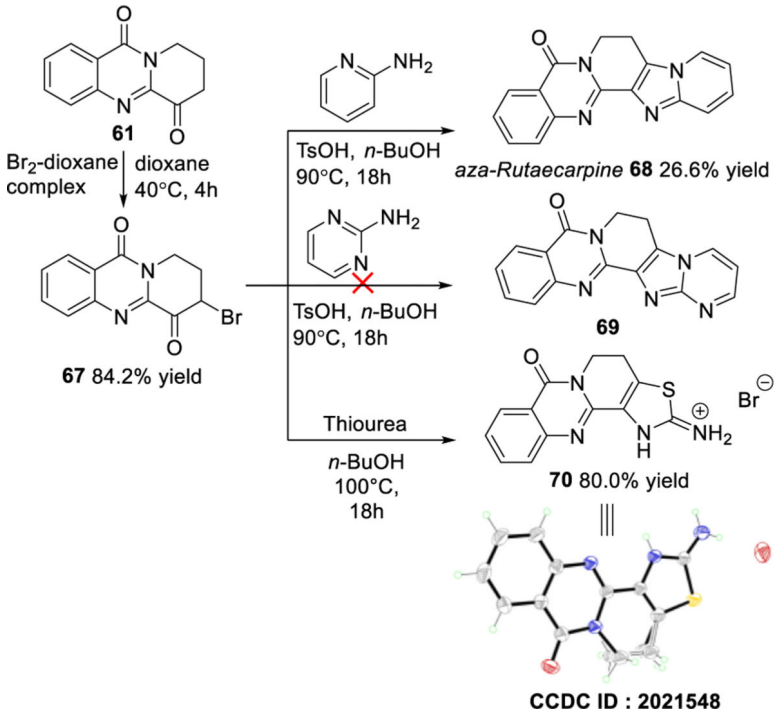


Scheme 3.

Synthesis of homo-vasicinone *via* reduction of 61.

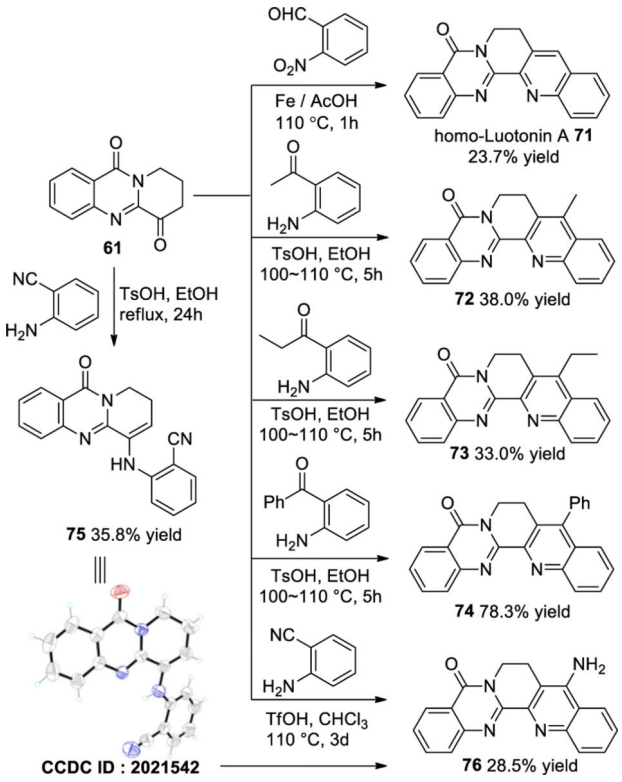


Scheme 4.
Synthesis of indolopyridoquinazolinones.



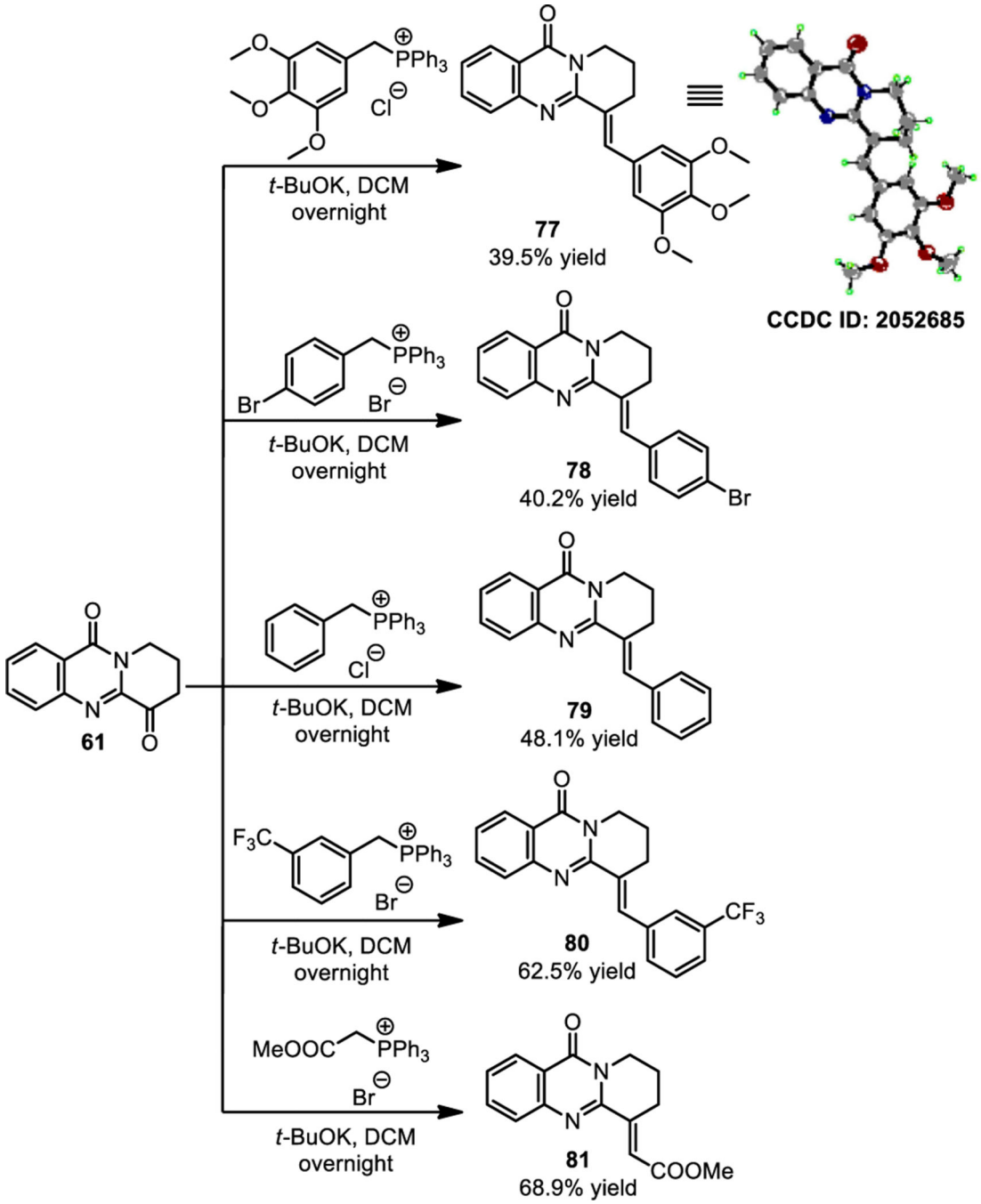
Scheme 5.

Synthesis of aza-rutaecarpines *via* bromide **67**.

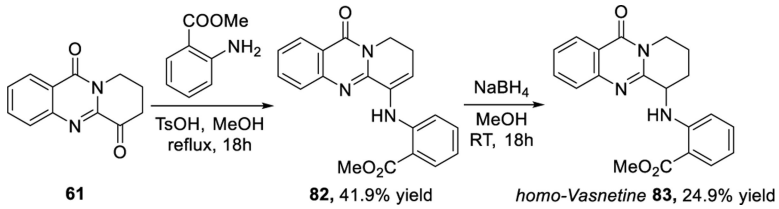


Scheme 6.

Synthesis of homo-luotonins *via* Friedlander condensation.



Scheme 7.
Synthesis of homo-isaindigotones *via* Wittig Olefination of **61**.



Scheme 8.

Synthesis of homo-vasnetine *via* reductive amination.