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TBHP-Mediated Oxidative Decarboxylative Cyclization in Water: Direct and Sustainable Access to Anti-malarial Polycyclic Fused Quinazolinones and Rutaecarpine

Xingyu Chen,[a] Fei Xia,[a] Yifan Zhao,[a] Ji Ma,[a] Yue Ma,[a] Dong Zhang,[a] Lan Yang,[a] and Peng Sun[a]*

[a] *Artemisinin Research Center and Institute of Chinese Materia Medica, Academy of Chinese Medical Sciences, Beijing, 100700, P. R. China*

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Summary of main observation and conclusion Polycyclic fused quinazolinones with anti-malarial activity were synthesized through TBHP-mediated oxidative decarboxylative cyclization between commercially available isatins and cyclic amines in one step. The reaction proceeds smoothly in water without additional transition-metal catalyst, acid and base. The newly synthesized products were evaluated to exhibit moderate to good anti-malarial activity against chloroquine drug-sensitive Plasmodium falciparum 3D7 strain. Additionally, this method also provides direct approach to Rutaecarpine in good yield.

Background and Originality Content

Malaria is one of the major global health issues which account for two hundred million human infections and over half a million deaths each year according to the World Malaria Report in 2018.[1] Nitrogen heterocyclic compounds have played pivotal roles in malaria chemotherapy progressing from quinine to chloroquine, mefloquine and amodiaquine in the last century.[2] Recently, the emerging of drug-resistant parasites resulted in failures of response to the first-line drugs in the Greater Mekong Subregion including Thailand, Myanmar, Laos and China.[3] As a result, there is always an urgent need to develop novel anti-malarial nitrogen containing heterocyclic agents to overcome the resistance to clinical medications. Quinazolinones represent a class of interesting nitrogen heterocyclic compounds which are widely present in natural products and pharmaceutical materials.[4] (Fig. 1) A series of quinazolinone type alkaloids and its analogues have been prepared and evaluated to show good antimalarial activity against plasmodium malaria parasite.[5] Nevertheless, the potent of this privileged skeleton on malaria treatment remain underestimated.

The exploration of green and sustainable chemical reactions

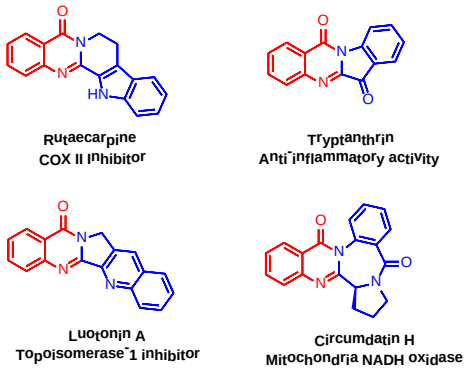


Figure 1 Bioactive polycyclic fused quinazolinones.

for drug synthesis and modification which could minimize the use or emission of hazardous materials is one of the most pressing tasks in medicinal chemistry.[6] The classical method to obtain quinazolinones are based on the condensations between 2-aminobenzamides and other one carbon source such as alcohols, aldehydes, toluene and etc. [7] While, the construction of polycyclic quinazolinones still relatively underdeveloped. Recently, C-H activation strategy were explored to prepared polycyclic quinazolinones from pre-synthesized quinazolinones. Representatively, Ma, Szostak[8] and Jana[9] developed Rh and Ru catalyzed cyclization reaction respectively. Alternatively, intramolecular oxidative cyclization were also achieved by Zheng[10] and Pan[11] through $(NH_4)_2S_2O_8$, light-diriven and electrochemistry oxidation method. Isatins is a kind of common

used bulk chemical which are plentifully supplied in low price.[12] In the last few years, a series of pioneering work have been established by Prof. Wu and coworkers to construct privilege heterocycles through TBHP-mediated decarboxylative cyclization between isatins and corresponding materias.[13] Based on these brilliant works, and as our continued interests in the development of anti-malarial agents from traditional Chinese herb and synthetic molecules since the discovery of artemisinin by professor Youyou Tu and co-workers,[14] herein, we have established an eco-friendly methodology to prepare a series of anti-malarial polycyclic fused quinazolinones from readily available isatins and cyclic amines in one step. (Fig. 2)

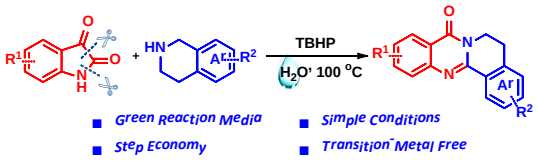


Figure 2 TBHP-mediated direct synthesis of polycyclic fused quinazolinones.

Results and Discussion

Results (Optimization of reaction conditions)

Result 1 (Optimization of reaction conditions). In this study, to provide effective and economically affordable potential therapeutic agents for patients in many underdeveloped malaria-endemic areas, we chose isatin (**1a**) and tetrahydroisoquinoline (**2a**) as the model substrates to prepare fused quinazolinones. Initially, the examination of 1a and **2a** in the presence of TBHP and potassium carbonate in DMSO at 100 °C gave the desired polycyclic quinazolinone products **3a** in the yield of 67% (Table 1, Entry 1). In order to improve the efficiency of the reaction, tripotassium phosphate and potassium hydroxide were tested to produce **3a** in the yields of 65%, and 53% respectively (Table 1, Entries 2-3). Organic bases such as triethylamine and pyridine were also investigated, while the yields were maintained at about 60%. The yield was promoted to 79% when we removed the base from the reaction system (Table 1, Entry 6). Next, a variety of solvents were screened (Table 1, Entries 7-13). The solvent DMF, THF, EtOH and HFIP gave inferior product yields from 40% and 62% (Table 1, Entries 7-10). When CH_3CN and DCE were used, over 80% yields were obtained (Table 1, Entries 11-12). To our delight, water was proved to be appropriate for this reaction in the later examination to provide a high yield of 83% (Table 1, Entry 13). Due to its safe and green specificity, water was chosen as the admirable medium of the reaction. Increased the temperature to 125 °C, 80% of **3a** was prepared (Table 1, Entry 14). The yield decreased rapidly with the reduction of temperature to 75 °C (Table 1, Entry 15). No product was observed when the reaction was carried out at 50 °C (Table 1, Entry 16). 82% yield was obtained when the amount of TBHP was reduced to 3.0 equivalents (Table 1, Entry 17). The yield was promoted to 85% with 2.5 equiv. of TBHP (Table 1, Entry 18). The high yield of 85% was maintained when the amount of TBHP was reduced to 2.0 equiv. (Table 1, Entry 19). A lower yield was obtained with a further reduction of the oxidant to 1.5 equivalents (Table 1, Entry 20). When the reaction was conducted in the absence of TBHP, no product was detected (Table 1, Entry 21).

Table 1 Optimization of reaction conditions.

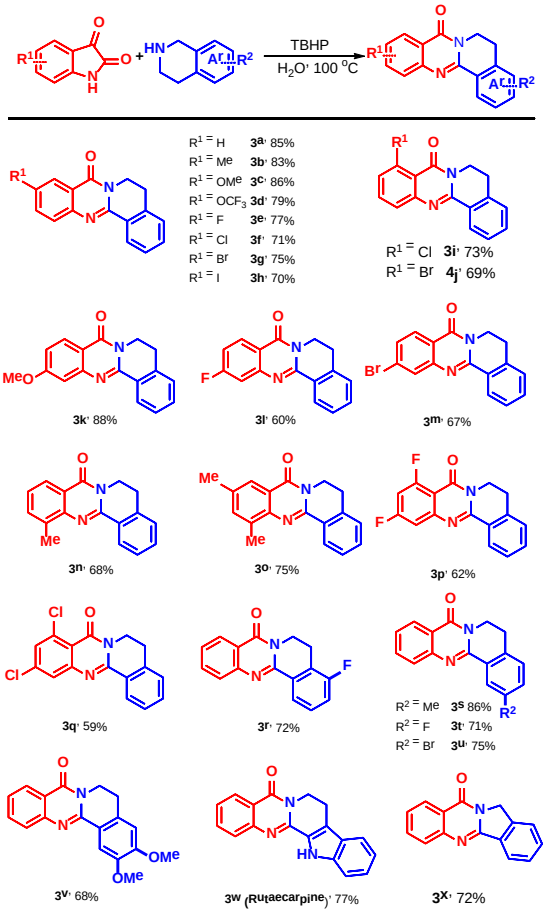
Entry [a]	Solvent	Base	Temperature (°C)	Yield [b]
1	DMSO	K_2CO_3	100	67%
2	DMSO	K_3PO_4	100	65%
3	DMSO	KOH	100	53%
4	DMSO	Et_3N	100	60%
5	DMSO	pyridine	100	63%
6	DMSO	/	100	79%
7	DMF	/	100	62%
8	THF	/	100	45%
9	EtOH	/	100	51%
10	HFIP	/	100	40%
11	CH_3CN	/	100	80%
12	DCE	/	100	81%
13	H_2O	/	100	83%
14	H_2O	/	125	80%
15	H_2O	/	75	52%
16	H_2O	/	50	0%
17 [c]	H_2O	/	100	82%
18 [d]	H_2O	/	100	85%
19 [e]	H_2O	/	100	85%
20 [f]	H_2O	/	100	68%
21 [g]	H_2O	/	100	0%

[a] Reaction conditions: **1a** (0.75 mmol, 1.5 equiv.), **2a** (0.5 mmol, 1.0 equiv.), TBHP (70% in water, 4.0 equiv.), base (1.0 mmol, 2.0 equiv.), solvent (2 mL), 12 hours under air atmosphere; [b] Isolated yields; [c] 3.0 equiv. of TBHP was used; [d] 2.5 equiv. of TBHP was used; [e] 2.0 equiv. of TBHP was used; [f] 1.5 equiv. of TBHP was used; [g] No TBHP was added.

Result 2 (Scope exploration of the substrates). After the condition optimization, we turned to examine the scope of the substrates as shown in Table 2. We are pleased to find that various isatins and cyclic amines performed smoothly under the standard conditions to give corresponding fused quinazolinones in moderate to good yields. Firstly, a series of isatins derivatives were investigated. Electron neutral and donating groups (5-Me

and 5-OMe) proved to be favorable for this transformation, affording **3b** and **3c** in excellent yields (83% and 86%, respectively). Trifluoromethoxy substituted products **3d** was also obtained in

Table 2 Scope exploration of the substrates. [a, b]

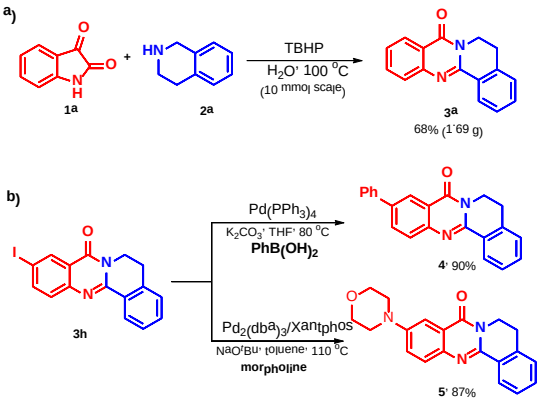


[a] Reaction conditions: **1** (0.75 mmol, 1.5 equiv.), **2** (0.5 mmol, 1.0 equiv.), TBHP (70% in water, 2.0 equiv.), solvent (2 mL), 12 hours under air atmosphere; [b] Isolated yields.

the yield of 79%. In addition, an array of halogen-substituted isatins, including fluoro-, chloro-, bromo- and iodo- at the C-5 position, were also compatible with the reaction conditions, and the corresponding products (**3e**-**3h**) were generated in the yield from 70% to 77%, which provide the possibility for further synthetic elaboration. Apart from 6-substituted quinazolones, products with substituent group at 5-, 7- and 8- position were also synthesized in over 60% yield (**3i**-**3n**). Furthermore, multi-substituted products were provided through our method in the yield from 59% to 75% (**3o**-**3q**). Next, the scope of substituted cyclic amines was also explored. Methyl and halogen substituted tetrahydroisoquinolines at 5- and 7- position were tried to prepared desired products in the yields from 71% to 86% (**3r**-**3u**). To our satisfaction, di-substituted quinazolones **3v** was also obtained in 68% yield. It was exiting that the developed approach could also be applied to the synthesis of Rutaecarpine (**3w**) from commercially available starting materials in 77% yield. This should be the first aqueous synthetic route to Rutaecarpine (**3w**) as far as we know.[15] Isoindoline with five-membered ring was also proved to be compatible with this procedure to give corresponding product **3x** in the yield of 72%.

Result 3 (Synthetic applications for this reaction). To illustrate the synthetic practicality of this reaction, scale- up experiment was performed at 10 mmol scales to obtain 68% yield (Scheme 1a). Morpholine and phenyl are common structural motif in pharmaceutical molecules. Transition-metal catalysed late-stage functionalization is efficient strategy in drug synthesis and modification. Finally, to generate structural diverse products for bio-evaluation, the generated product **3h** was further transformed through palladium-catalysed cross coupling reaction with morpholine and phenylboronic acid leading to **4** and **5** in good yields respectively (Scheme 1b).

Scheme 1 Synthetic applications for this reaction.

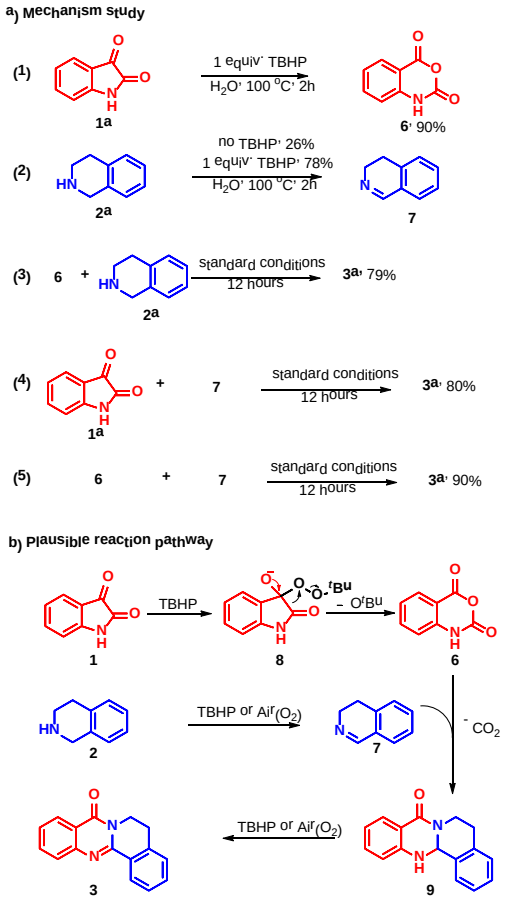


Result 4 (Anti-malarial evaluation). With the newly synthesized fused quinazolones in hand, we set out to evaluate the anti-malarial activities of selected examples against chloroquine drug-sensitive Plasmodium falciparum 3D7 strain. The inhibition of parasite growth was measured at the concentrations ranging from 0.5 nM to 400.0 μM by the SYBR Green assay (For comprehensive details of the assay, see Electronic Supplementary Information Table S1). The results indicated the selected examples exhibited moderate to good anti-malarial activity.

Result 5 (Mechanism study). Next, a series of experiments were conducted in order to figure out the mechanism of this procedure, as shown in Scheme 2. Firstly, **1a** was treated with 1.0 equivalent of TBHP at 100 °C for 2 hours individually, and 6 was generated in the yield of 90% (Scheme 2a1). Substrate **2a** could be transformed to **7** in the function of 1.0 equivalent of TBHP or air (Scheme 2a2). Compound **6** could react with **2a** under standard conditions to yield **3a** in 79% yield (Scheme 2a3). When **7** was treated with **1a** with 2 equiv. of TBHP, **3a** was obtained in the yield of 80% (Scheme 2a4). When we treated **6** and **7** in the standard conditions, 90% **3a** was generated. These results revealed that **6**, **7** could be identified as the intermediates of the

reaction. Based on these observations and literature precedent, a plausible reaction pathway is depicted for the formation of compound **3** (Scheme 2b). At first, intermediate **8** generated via the nucleophilic attack of TBHP to **1**. Next, intramolecular rearrangement occurred to offer isatin anhydride **6** with the release of tertiary butanol. The following decarboxylative cyclization between **6** and **7** which generated from **2** in the function of TBHP or air afforded intermediate **9**. Ultimately, **3** was produced via the oxidation of **8** by air or TBHP.

Scheme 2 Mechanism study and proposed reaction pathway.



Conclusions

In conclusion, a green and sustainable procedure has been developed to construct polycyclic fused quinazolinones and Rutaecarpine in water. Highly effective antimalarial agent was synthesized directly from cheap bulk chemical raw materials without the emissions of toxic contaminants, which may provide affordable alternatives for people from impoverished malaria epidemic areas. Comprehensive bio-evaluations of the products are underway in our laboratory.

Experimental

Experiment detail for the oxidative decarboxylative cyclization: A round bottom flask was charged with isatins **1** (0.75 mmol, 1.5 equiv.), tetrahydroisoquinolines **2** (0.5 mmol, 1.0 equiv.), H_2O_2 (70% in water, 1 mmol, 2.0 equiv.) and 2 mL H_2O. The reaction mixture was vigorously stirred at 100 °C (oil temperature) for 12 hours. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (10 mL). The organic phase was washed with water and brine respectively. The solvent was concentrated in vacuo and purified by flash chromatography on silica gel to afford the desired product.

Characterization of the products:

5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3a**)
Yield 85%; White solid, m.p. 193-195 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.36 – 8.28 (m, 1H), 7.81 – 7.72 (m, 2H), 7.52 – 7.40 (m, 3H), 7.29 (d, *J* = 7.4 Hz, 1H), 4.42 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 149.4, 147.8, 137.1, 134.2, 131.7, 129.6, 128.0, 127.6, 127.5, 126.9, 126.5, 120.8, 100.0, 39.6, 27.5 ppm; HRMS (ESI) calcd for $[C_{16}H_{12}N_2O+H]+$ 249.0950, found 249.1062.

10-methyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3b**)
Yield 83%; White solid, m.p. 182-183 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.7, 1.5 Hz, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 4.41 (t, *J* = 6.5 Hz, 2H), 3.09 (t, *J* = 6.5 Hz, 2H), 2.50 (s, 3H) ppm; ^{13}C NMR (150 MHz, CDCl3) δ 161.7, 148.6, 145.8, 136.9, 136.7, 135.7, 131.5, 129.7, 127.9, 127.6, 127.5, 127.4, 126.3, 120.5, 39.6, 27.5, 21.4 ppm; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O+H]+$ 263.1179, found 263.1176.

10-methoxy-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3c**)
Yield 86%; Light yellow solid, m.p. 169-170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 3.0 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.36 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 4.43 (t, J = 6.5 Hz, 2H), 3.94 (s, 3H), 3.10 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 158.3, 147.4, 142.5, 136.7, 131.3, 129.7, 129.3, 127.7, 127.6, 127.5, 124.6, 121.5, 106.2, 55.8, 39.8, 27.5 ppm; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O_2+H]+$ 279.1128, found 279.1125.

10-(trifluoromethoxy)-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3d**) Yield 79%; white solid, m.p. 194-196 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 2.9 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.58 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.47 (dt, J = 31.4, 7.5 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 4.42 (t, *J* = 6.4 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.9, 149.8, 147.1, 147.0, 146.3, 137.0, 132.0, 129.7, 129.2, 128.1, 127.7, 127.6, 127.6, 121.6, 121.3, 119.6, 118.2, 39.8, 27.4 ppm; HRMS (ESI) calcd for $[C_{17}H_{11}F_3N_2O_2+H]+$ 333.0845, found 333.0840.

10-fluoro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3e**)
Yield 77%; white solid, m.p. 206-208 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.87 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.70 (dd, *J* = 8.9, 4.9 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 4.34 (t, *J* = 6.5 Hz, 2H), 3.04 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 160.0, 158.9, 147.8, 143.5, 135.9, 130.8, 129.0, 129.0, 128.4, 126.9, 126.7, 126.5, 122.0, 121.8, 120.9, 110.7, 110.6, 38.8, 26.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}FN_2O+H]+$ 267.0928, found 267.0924.

10-chloro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3f**)

Yield 71%; white solid, m.p. 179-180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.26 (d, *J* = 2.3 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.51 – 7.41 (m, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 4.40 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 149.6, 146.3, 137.0, 134.7, 132.2, 132.0, 129.3, 129.3, 128.0, 127.7, 127.6, 126.2, 121.7, 39.8, 27.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}ClN_2O+H]^+$ 283.0633, found 283.0631.

10-bromo-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3g**) Yield 75%; light yellow solid, m.p. 190-192 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.43 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.49 (td, *J* = 7.4, 1.5 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 4.40 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 149.8, 146.6, 137.4, 137.0, 132.0, 129.4, 129.4, 129.3, 128.1, 127.7, 127.6, 122.1, 119.9, 39.8, 27.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}ClN_2O+H]^+$ 327.0126, found 327.0126.

10-iodo-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3h**) Yield 70%; white solid, m.p. 194-196 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.1 Hz, 1H), 8.44 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.98 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.39 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 3.09 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 149.9, 147.1, 142.9, 137.0, 135.7, 132.0, 129.4, 129.3, 128.1, 127.7, 127.6, 122.3, 90.8, 39.8, 27.4 ppm; HRMS (ESI) calcd for $[C_{12}H_{11}IN_2O+H]^+$ 374.9989, found 374.9986.

9-chloro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3i**) Yield 73%; light yellow solid, m.p. 200-202 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.49 (td, *J* = 7.4, 1.5 Hz, 1H), 7.44 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 4.37 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 150.2, 150.0, 137.2, 134.1, 133.5, 132.0, 129.2, 129.0, 128.0, 127.6, 127.5, 127.0, 117.9, 39. 6, 27.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}ClN_2O+H]^+$ 283.0633, found 283.0631.

9-bromo-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3j**) Yield 69%; white solid, m.p. 220-222 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.55 – 7.48 (m, 1H), 7.48 – 7.43 (m, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 150.1, 149.7, 137.2, 133.8, 133.0, 132.0, 129.0, 128.0, 127.7, 127.6, 127.5, 121.5, 118.8, 39.7, 27.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}BrN_2O+H]^+$ 327.0128, found 327.0127.

11-methoxy-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3k**) Yield 88%; light yellow solid, m.p. 177-179 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.46 (td, *J* = 7.4, 1.5 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.02 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.38 (t, *J* = 6.5 Hz, 2H), 3.93 (s, 3H), 3.08 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 161.2, 150.0, 150.0, 137.1, 131.7, 129.6, 128.4, 127.9, 127.6, 127.5, 116.8, 114.4, 108.0, 55.6, 39.4, 27.5 ppm; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O_2+H]^+$ 279.1128, found 279.1125.

11-fluoro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3l**) Yield 60%; white solid, m.p. 169-170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 – 8.43 (m, 1H), 8.32 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.50 (td, *J* = 7.4, 1.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 9.7, 2.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.17 (td, *J* = 8.5, 2.5 Hz, 1H), 4.40 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 165.7, 161.0, 150.6, 150.0, 149.9, 137.2, 132.1, 129.6, 129.5, 129.3, 128.2, 127.7, 127.6, 117.5, 117.5, 115.4, 115.2, 112.8, 112.6, 39.6, 27.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}FN_2O+H]^+$ 267.0928, found 267.0923.

11-bromo-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3m**) Yield 67%; white solid, m.p. 176-178 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 1.8 Hz, 1H), 7.53 (dd, J = 8.5, 1.9 Hz, 1H), 7.48 (td, J = 7.4, 1.4 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 4.37 (t, *J* = 6.5 Hz, 2H), 3.09 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 150.4, 148.8, 137.1, 132.0, 130.2, 129.8, 129.2, 128.8, 128.3, 128.2, 127.7, 127.5, 119.5, 39.6, 27.3 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}BrN_2O+H]^+$ 327.0128, found 327.0127.

12-methyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3n**) Yield 68%; white solid, m.p. 165-167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 4.41 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H), 2.71 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1, 148.0, 146.3, 136.9, 136.1, 134.7, 131.5, 130.0, 128.0, 127.6, 127.5, 126.1, 124.5, 120.7, 39.5, 27.5, 17.3 ppm; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O+H]^+$ 263.1179, found 263.1175.

10,12-dimethyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3o**) Yield 75%; white solid, m.p. 201-203 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.27 (d, *J* = 7.2 Hz, 1H), 4.41 (t, *J* = 6.5 Hz, 2H), 3.09 (t, *J* = 6.5 Hz, 2H), 2.68 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 147.3, 144.3, 136.8, 136.3, 136.2, 135.8, 131.3, 130.1, 127.9, 127.5, 127.4, 124.0, 120.5, 39.6, 27.5, 21.4, 17.2 ppm; HRMS (ESI) calcd for $[C_{18}H_{16}N_2O+H]^+$ 277.1335, found 277.1332.

9,11-difluoro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3p**) Yield 62%; white solid, m.p. 223-224 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.52 (td, *J* = 7.4, 1.4 Hz, 1H), 7.45 (td, *J* = 7.7, 1.3 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.23 (ddd, *J* = 9.4, 2.6, 1.4 Hz, 1H), 6.87 (ddd, *J* = 11.1, 9.0, 2.5 Hz, 1H), 4.37 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 166.5, 164.9, 163.4, 161.6, 158.2, 158.2, 151.3, 151.2, 151.1, 137.4, 132.4, 128.8, 128.3, 127.7, 127.6, 109.2, 109.2, 109.1, 109.0, 107.5, 103.0, 102.8, 102.8, 102.7, 39.2, 27.3 ppm; HRMS (ESI) calcd for $[C_{16}H_{10}F_2N2O +H]^+$ 285.0834, found 285.0829.

9,11-dichloro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3q**) Yield 59%; Light yellow solid, m.p. 230-232 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.51 (td, *J* = 7.4, 1.4 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 4.35 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.4, 159.3, 151.0, 150.7, 139.3, 137.3, 135.3, 132.4, 129.0, 128.7, 128.1, 127.7, 127.6, 126.4, 116.4, 39.6, 27.3 ppm; HRMS (ESI) calcd for $[C_{16}H_{10}Cl_2N_2O+H]^+$ 317.0243, found 317.0240.

4-fluoro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3r**) Yield 72%; Light yellow solid, m.p. 198-200 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (t, *J* = 8.2 Hz, 2H), 7.81 – 7.74 (m, 2H), 7.49 (ddd, *J* = 8.1, 5.1, 3.1 Hz, 1H), 7.41 (td, *J* = 8.0, 5.5 Hz, 1H), 7.23 (t, *J* = 8.5 Hz,

1H), 4.43 (t, *J* = 6.5 Hz, 2H), 3.15 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 159.9, 158.3, 148.4, 147.5, 134.4, 131.6, 128.4, 128.4, 127.7, 126.9, 126.9, 124.4, 124.2, 123.7, 123.6, 120.8, 118.2, 118.0, 38.9, 20.1, 20.0 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}FN_2O+H]+$ 267.0924, found 267.0924.

2-methyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3s**) Yield 86%; white solid, m.p. 165-167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.29 (s, 1H), 7.81 – 7.70 (m, 2H), 7.45 (ddd, *J* = 8.1, 6.6, 1.6 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 3.05 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 149.6, 147.8, 137.4, 134.2, 132.6, 129.3, 128.2, 127.5, 127.4, 126.9, 126.4, 120.8, 39.8, 27.1, 21.2 ppm; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O+H]+$ 263.1179, found 263.1175.

2-fluoro-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3t**) Yield 71%; light yellow solid, m.p. 211-213 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 1H), 8.19 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.77 (d, *J* = 4.0 Hz, 2H), 7.48 (dt, *J* = 8.1, 4.1 Hz, 1H), 7.27 (q, *J* = 5.2 Hz, 1H), 7.18 (td, *J* = 8.3, 2.7 Hz, 1H), 4.41 (t, *J* = 6.5 Hz, 2H), 3.08 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 161.6, 161.3, 148.4, 148.3, 147.6, 134.4, 132.7, 132.7, 131.4, 131.4, 129.2, 129.2, 127.7, 126.9, 126.9, 120.9, 119.0, 118.8, 114.6, 114.5, 39.7, 26.8 ppm; HRMS (ESI) calcd for $[C_{16}H_{14}FN_2O+H]+$ 267.0928, found 267.0924.

2-bromo-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3u**) Yield 75%; light yellow solid, m.p. 223-225 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 – 8.48 (m, 1H), 8.35 – 8.29 (m, 1H), 7.81 – 7.72 (m, 2H), 7.52 – 7.42 (m, 3H), 7.30 (d, *J* = 7.4 Hz, 1H), 4.43 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 149.4, 147.9, 137.1, 134.2, 131.7, 129.6, 128.1, 127.6, 127.5, 126.9, 126.5, 120.8, 39.6, 27.5 ppm; HRMS (ESI) calcd for $[C_{16}H_{11}BrN_2O+H]+$ 327.0128, found 327.0120.

2,3-dimethoxy-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**3v**) Yield 68%; Light yellow solid, m.p. 207-209 °C; δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.9 Hz, 1H), 7.98 (s, 1H), 7.79 – 7.70 (m, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 6.73 (s, 1H), 4.40 (t, *J* = 6.5 Hz, 2H), 4.04 (s, 3H), 3.96 (s, 3H), 3.03 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 152.2, 149.3, 148.6, 147.9, 134.1, 130.9, 127.3, 126.9, 126.1, 121.8, 120.5, 110.1, 109.7, 56.2, 56.1, 39.7, 27.0 ppm; HRMS (ESI) calcd for $[C_{18}H_{16}N_2O_3+H]+$ 309.1234, found 309.1228.

8a,13,13a-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one (**3w**) Yield 77%; Light yellow solid, m.p. 260-261 °C; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.85 (s, 1H), 8.15 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.43 (t, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-*d6*) δ 161.0, 147.8, 145.7, 139.1, 134.7, 127.5, 127.0, 126.8, 126.3, 125.4, 125.1, 121.2, 120.3, 120.1, 118.2, 113.0, 41.2, 19.4 ppm.

isoindolo[1,2-b]quinazolin-10(12H)-one (**3x**) Yield 72%; White yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 5.4 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 5.06 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 154.9, 149.5, 139.7, 134.2, 132.7, 132.3, 128.9, 127.4, 126.5, 126.4, 123.5, 120.6, 49.8 ppm.

10-phenyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**4**) A sealed tube was charged with **3h** (0.5 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (0.05 mmol, 10 mol%), K_2CO_3 (1.0 mmol, 2.0 equiv.), phenylboronic acid (1.0 mmol, 2.0 equiv.) and THF 2 mL. The reaction mixture was then vigorously stirred at 80 °C (oil temperature) for 12 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of celite. The mixture was concentrated in vacuo and purified by flash chromatography on silica gel to afford the desired product **4** in 90% yield. Yield 90%; Light yellow solid, m.p.188-189 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.2 Hz, 1H), 8.52 – 8.46 (m, 1H), 8.01 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 3H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 4.44 (t, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 6.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 149.3, 147.1, 139.8, 139.4, 137.0, 133.1, 131.7, 129.6, 129.0, 128.2, 128.0, 127.8, 127.6, 127.5, 127.2, 124.7, 121.0, 39.7, 27.5 ppm; HRMS (ESI) calcd for $[C_{22}H_{16}N_2O+H]+$ 324.1332, found 324.1330.

10-morpholino-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (**5**) A sealed tube was charged with **3h** (0.2 mmol, 1.0 equiv), $Pd_2(dba)_3$ (0.01 mmol, 5 mol%), XantPhos (0.02 mmol, 10 mol%), NaO_tBu (0.4 mmol, 2.0 equiv), morpholine (0.4 mmol, 2.0 equiv) and toluene 2 mL. The reaction mixture was then vigorously stirred at 110 °C (oil temperature) for 12 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of celite. The mixture was concentrated in vacuo and purified by flash chromatography on silica gel to afford the desired product **5** in 87% yield. Yield 87%; Light yellow solid, m.p. 193-195 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.65 (d, *J* = 2.9 Hz, 1H), 7.42 (ddt, *J* = 12.4, 8.1, 5.0 Hz, 3H), 7.27 (s, 1H), 4.41 (t, *J* = 6.4 Hz, 2H), 3.90 (t, *J* = 4.7 Hz, 4H), 3.30 (t, *J* = 4.7 Hz, 4H), 3.09 (t, *J* = 6.4 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 149.8, 147.0, 141.5, 136.6, 131.1, 129.8, 128.7, 127.6, 127.6, 127.4, 123.6, 121.4, 109.7, 66.8, 49.0, 39.7, 27.6 ppm; HRMS (ESI) calcd for $[C_{20}H_{19}N_3O_2+H]+$ 334.1547, found 334.1546.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Entry for the Table of Contents

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TBHP-Mediated Oxidative Decarboxylative Cyclization in Water: Direct and Sustainable Access to Anti-malarial Polycyclic Fused Quinazolinones and Rutaecarpine

ingyu Chen, Fei Xia, Yifan Zhao, Ji Ma, Yue Ma, Dong Zhang, Lan Yang, and Peng Sun*

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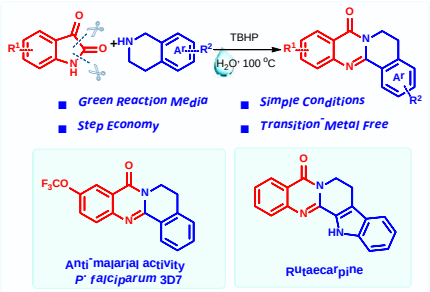

A green and sustainable decaboxylative cyclization between isatins and cyclic amines has been established to synthesize anti-malarial polycyclic fused quinazolinones and Rutaecarpine in water.

