Metal-Catalyst-Free Green and efficient synthesis of five and six membered fused *N*-heterocyclic quinazoline derivatives

M.V. Madhubabu, R. Shankar, G. Rajeshwar Reddy, T. Srinivasa Rao, Mandava V. Basaveswara Rao, Ragunadh Akula

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Tetrahedron Letters

Graphical Abstract:

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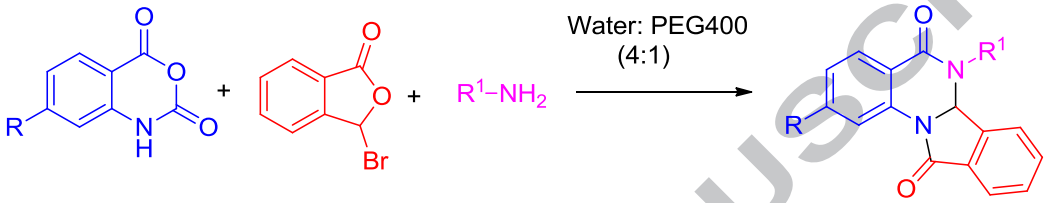

R= H, Cl, Br

R^1 = aliphatic, aromatic

20 examples
66-92%Yields

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ABSTRACT

An efficient and green approach has been developed for the construction of Tetracyclic nitrogen-bridgehead compounds were designed and synthesized in good yields. The reaction of easily prepared 3-bromoisobenzofuran-1(3*H*)-one with isatoic anhydride and amines gave the desired Isoindoloquinazolinone derivatives in moderate to good yields. It is also amenable for scale-up.

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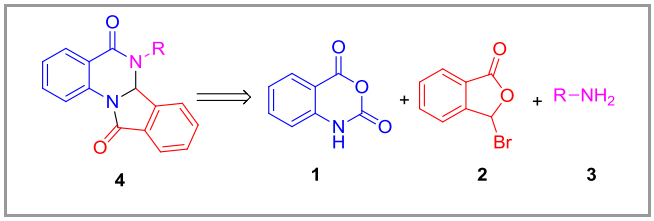
The controlled synthesis of different *N*-heterocycles is essential in both the agrochemical and pharmaceutical industries.[1] Over the last few decades compounds containing a quinazoline structure have been in the focus of different research areas first due to their existence as a common core structure in several drugs and natural products.[2] In addition many unnatural quinazolinones show significant biological activities acting as anticancer,[3] antibacterial,[4] anti-inflammatory,[5] antihypertensive,[6] antidiabetic,[7] anticonvulsant,[8] and antianxietic agents.[9] Because of varied biological properties of quinazolinone derivatives, it is essential to develop efficient and convenient methods to prepare these derivatives.

Therefore, many groups used this nitrogen bridgehead core structure as a vital component in the development of numerous experimental therapeutics and prospective drug candidates.[10] Dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione is an important five and six membered fused *N*-heterocyclic quinazoline derivative. Pal *et al.* synthesized 6,6*a*-dihydroisoindolo[2,1-a]quinazoline-5,11-dione derivatives by employing a three component reaction of isatoic anhydride, an amine and 2-formyl benzoic acid, using montmorillonite K10 as the catalyst. [11] Bunce *et al.* reported the synthesis of substituted quinazolinones using a dissolving metal reduction–condensative cyclization strategy [12] and Sashidhara team also reported the synthesis of Dihydroisoindolo[2,1-a]quinazoline-5,11-dione by using acetic acid.[13] However, such syntheses are still suboptimal because of the use of catalysts, forcing reaction conditions and long reaction times. Methodologies often address the growing concern about environmental safety and hazard. Since performing chemical reactions in water in the presence of a catalyst derived from biomass enhances the greenness of the process, the development of such economic and eco-friendly methodologies therefore is the central focus in the area of green and sustainable chemistry. Our group previously reported numerous protocols for the synthesis of quinazolinone based biologically active natural products and their derivatives.[14] In this communication we wish to report a Metal and Catalyst-Free Green and straight forward synthesis of dihydroisoindolo [2,1-a]quinazoline-5,11-dione [15] derivatives by using isatoic anhydride,[16] an

amine and 3-bromoisobenzofuran-1(3*H*)-one [17] in water and PEG as a co solvent. The retro synthetic strategy employed for the synthesis of dihydroisoindolo [2,1-*a*]quinazoline-5,11-dione is depicted in **Scheme 1**.



Scheme 1: Retrosynthesis of **11**.

Initially when isatoic anhydride **1**, amine **3** and 3-bromoisobenzofuran-1(3*H*)-one **2** were treated under the conditions applied for construction of dihydroisoindolo quinazoline in water gives 46% of the desired product **4a**. The compound **4a** was characterized by ^{1}H NMR, ^{13}C NMR, HRMS and IR. Substituted dihydroisoindolo [2,1-*a*]quinazoline-5,11-dione. In an effort to develop optimal conditions, various solvents were studied for the preparation of **4**. Initially, isatoic anhydride **1**, propargyl amine **3**, 3-bromoisobenzofuran-1(3*H*)-one **2**, were chosen as model substrates to optimize reaction conditions.

Table 1: Screening of solvents.

S.No.	Solvent	Temp °C	Time (h)	Yield[a] (%)
1	Ethanol	75	24	52
2	1,4-dioxane	90	24	45
3	DMF	90	24	35
4	DMSO	90	24	38
5	PEG 400	25	24	0
6	PEG 400	65	24	52
7	PEG 400	75	24	58
8	PEG 400	95	12	72
9	PEG 200	90	24	63
10	Ethylene Glycol	95	24	62
11	H_2O	25	24	0
12	H_2O	80	24	46
13	H_2O	95	18	68
14	H_2O/Ethanol (1:1)	85	18	74
15	H_2O /MeCN (1:1)	80	24	51
16	H_2O/ Ethylene Glycol (1:1)	90	24	42
17	H_2O/PEG-400 (1:1)	30	12	40
18	H_2O /PEG-400 (1:1)	60	16	70
19	H_2O /PEG-400 (1:1)	95	12	90
20	H_2O /PEG-400 (2:1)	95	12	86
23	H_2O /PEG-400 (3:1)	95	12	88
24	H_2O /PEG-400 (4:1)	95	12	92

[a] Isolated yield.
Reaction and conditions: Isatoic anhydride **1** (1.0 mmol), propargyl amine **3** (1.1 mmol), 3-bromoisobenzo-furan-1(3*H*)-one **2** (1.0 mmol), and water: PEG 400 (4:1) at 95 °C.

The solvents have a strong effect on these reactions with respect to yield. The solvents namely Ethanol, 1,4-dioxane, DMSO, DMF, PEG-400, PEG-200, Ethylene Glycol and Water (Table 1, entries 1-13) were screened. Further we have screened various combinations of other solvents like H_2O/Ethanol (1:1), H_2O /MeCN (1:1), H_2O/ Ethylene Glycol (1:1), H_2O/PEG-400 (1:1), H_2O /PEG-400 (2:1), H_2O /PEG-400 (3:1) and H_2O /PEG-400 (4:1) Table 1, entries 14-24). Combination of water and PEG-400 (4:1) had proven to be the best condition for this reaction (Table 1, entry 24).

The recovery solvent was examined in the reaction of isatoic anhydride **1**, propargyl amine **3** and 3-bromoisobenzofuran-1(3*H*)-one **2** at 95 °C. When the reaction was completed, filter the product and the recovered solvent was reused in place of fresh solvent for this reaction and several times without significant loss of activity. It was found that the activities of recovered solvent and fresh solvent were almost same and it was not impacting the reaction time and yield over four runs (Table 3, entries 1–5).

Table 2: Recover and Recyclability of PEG: water (1:4) mixture.

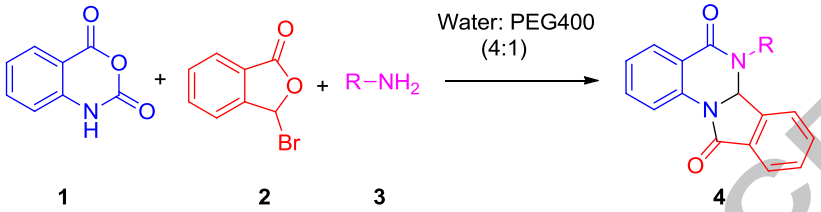
S.No.	Cycle	Time (h)	Yield[a] (%)
1	Fresh	12	92
2	1	12	92
3	2	12	91
4	3	12	91
5	4	12	91

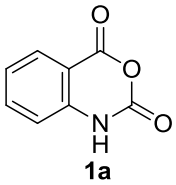
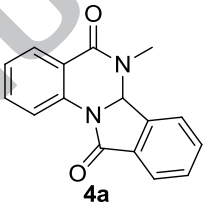
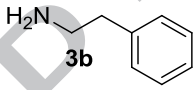
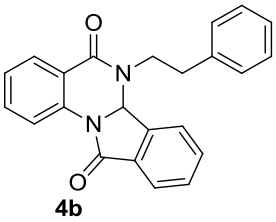
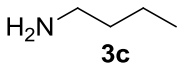
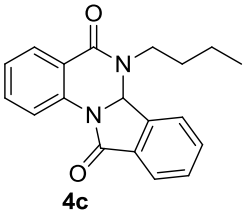
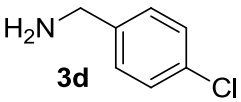
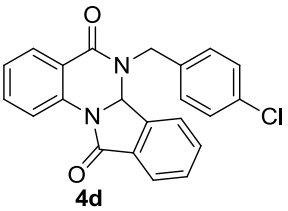
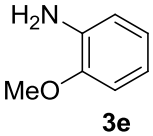
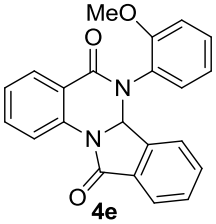
[a] Isolated yield.
Reaction and conditions: Isatoic anhydride **1** (1.0 mmol), propargyl amine **3** (1.1 mmol), 3-bromoisobenzo-furan-1(3*H*)-one **2** (1.0 mmol), and water: PEG 400 (4:1) at 95 °C.

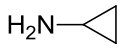
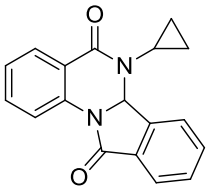
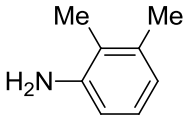
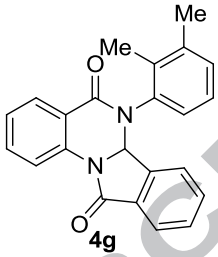
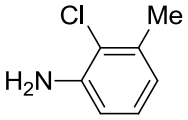
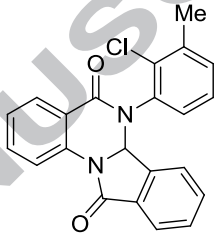
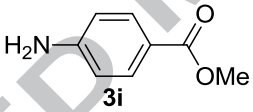
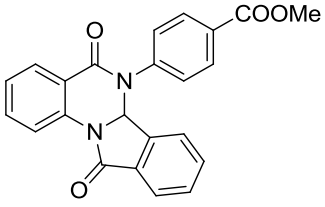
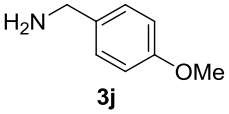
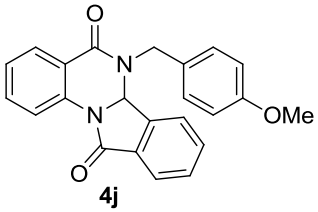
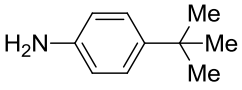
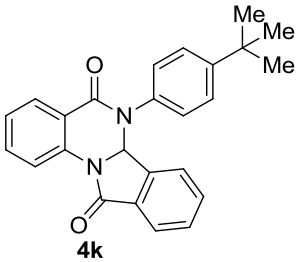
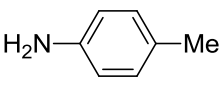
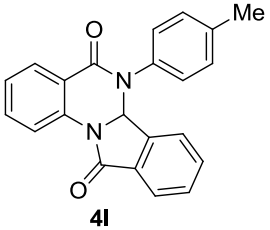
With the optimized conditions in hand, we explored the applicability of our reaction. We employed a variety of substituted amines **and** substituted isatoic anhydrides the results are summarized in **Table 3,** good yields were

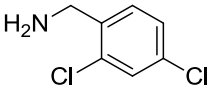
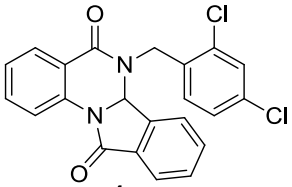
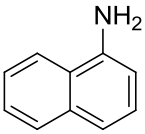
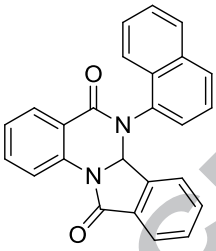
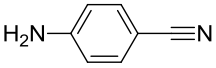
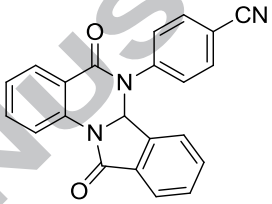
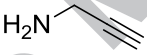
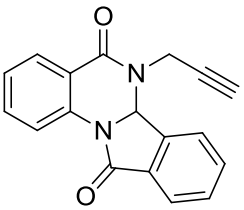
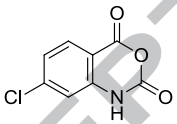
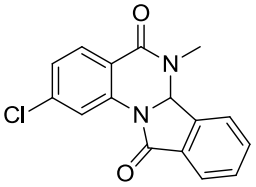
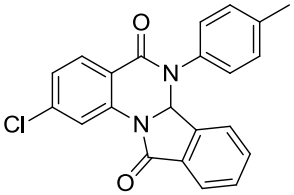
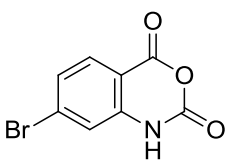
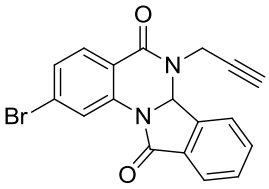
observed when the reaction was conducted with aliphatic amines when compared to the aromatic amines due to the more reactivity of aliphatic amine and substitution on isatoic anhydrides not having any impact on yield when compared to the simple isatoic anhydrides

Table 3: Synthesis of various dihydroisoindolo [2,1-a]quinazoline-5,11-dione derivatives.



S.No.	Isotoic anhydride	Amine	Product	Yield (%)[a]
1	 1a	H_2N-CH_3 3a (in water)	 4a	91
2	1a	 3b	 4b	87
3	1a	 3c	 4c	92
4	1a	 3d	 4d	81
5	1a	 3e	 4e	71

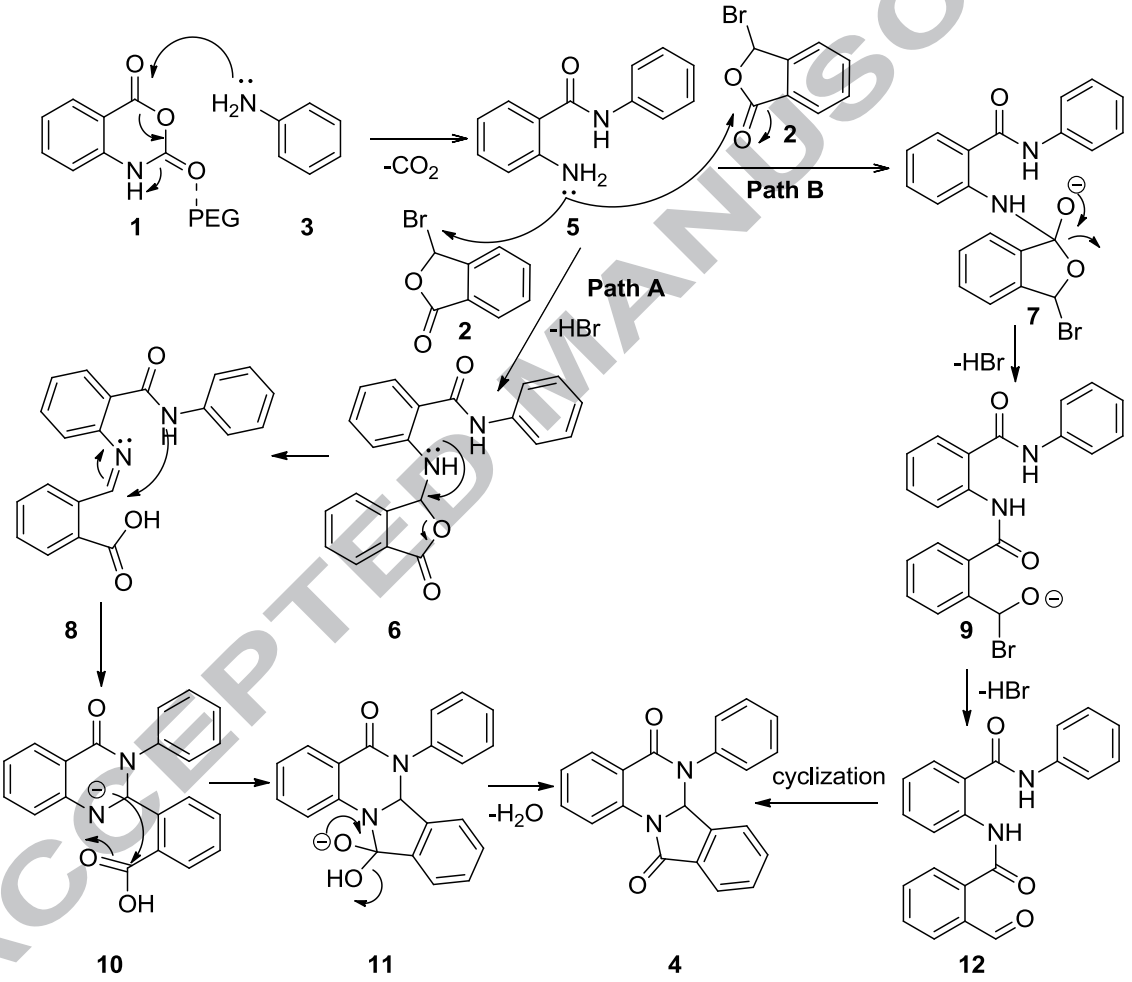
6	**1a**	 **3f**	 **4f**	**88**
7	**1a**	 **3g**	 **4g**	**68**
8	**1a**	 **3h**	 **4h**	**71**
9	**1a**	 **3i**	 **4i**	**73**
10	**1a**	 **3j**	 **4j**	**82**
11	**1a**	 **3k**	 **4k**	**69**
12	**1a**	 **3l**	 **4l**	**76**

13	**1a**	 **3m**	 **4m**	**68**
14	**1a**	 **3n**	 **4n**	**71**
15	**1a**	 **3o**	 **4o**	**66**
16	**1a**	 **3p**	 **4p**	**92**
17	 **1b**	**3a**	 **4q**	**90**
18	**1b**	**3l**	 **4r**	**78**
19	 **1c**	**3p**	 **4s**	**88**

Reaction and conditions: Isatoic anhydride **1** (1.0 mmol), amine **3** (1.1 mmol), 3-bromoisobenzo-furan-1(3*H*)-one **2** (1.0 mmol), and water: PEG 400 (4:1) at 95 °C.

The **Scheme 2** represents a plausible mechanism for the three component reaction leading to the compound **4**. The nucleophilic attack of primary amine on carbonyl group of isatoic anhydride **1** followed by ring opening and subsequent decarboxylation provided the compound **5**. **Path A**: Nitrogen nucleophile of **5** can readily displaces the bromine of 3-bromoisobenzofuran-1(3*H*)-one **2** will yield the **6** which on deprotanation provides emine **8**. This could then undergo subsequent cyclization will yield **10** and further cyclization of intermediate **10** with carboxylic acid will yield **4.** **Path B:** nitrogen nucleophile of **5** can attack on carbonyl group of 3-bromoisobenzofuran-1(3*H*)-one **2** will yield the **7**. Intermediate **7** rearranges to give diamide intermediate **9**; This could then undergo the HBr elimination to give aldehyde intermediate **12** and subsequent cyclization of **12** would give the product **4,.**

Scheme 2: The proposed reaction mechanism for the formation of **4**.



Conclusion:

In conclusion, we have developed a short and efficient, Metal free, Catalyst-Free, greener approach for the synthesis of dihydroisoindolo [2,1-*a*]quinazoline-5,11-dione derivatives in Water. This synthetic approach involves construction of two new rings *via* sequential C–N bond formation. Prominent advantages of this method are broad scope, operational simplicity, economic viability, good yield of the products in shorter reaction time, easy work-up, and reusability of the solvent.

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Highlights of the work

- An efficient and green approach for the synthesis of Tetracyclic nitrogen-bridgehead compounds.
- Synthetic approach involves construction of two new rings via sequential C–N bond formation.
- Recover and Recyclability of solvent was established.