Green Chemistry, 2015, 17(7), 3766-3770

Molecular Iodine Catalysed One-Pot Synthesis of Chromeno[4,3-b]quinolin-6-ones under Microwave Irradiation*

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ABSTRACT

We demonstrate a facile one pot approach for the regioselective synthesis of chromeno[4,3-*b*] quinoline derivatives in excellent yields under microwave (MW) irradiation. This transformation presumably proceeds *via* a three-component tandem annulation of 4-hydroxycoumarin with aromatic aldehydes and aromatic anilines, involving a Hofmann-Martius type rearrangement.

Keyword: Microwave Irradiation; Molecular Iodine

Introduction

An emerging strategy in the design and synthesis of new drugs is the combination of two distinct pharmacophores into a single molecule, well documented as pharmacophore hybridization.[1,2] Since natural products have been the most consistent source of drug leads, they have become attractive pharmacophoric components in hybrid molecules.[3] The hybrid approach is a promising path to drug molecules that are able to modulate multiple targets.[4]

Coumarin bearing hybrids, both of natural and synthetic origins, are of great importance in medicinal chemistry. For example, our previous work clearly underscores the importance of these privileged scaffold, as coumarin-chalcone (**1**)[5] and coumarin-monastrol (**2**)[13c] hybrids displayed potent and selective anticancer activities. In addition, many natural products including neo-tanshinlactone (anticancer) (**3**) and satiagonamine (wound healing) (**4**) are representative examples of coumarin fused frame works (Figure 1).[6]

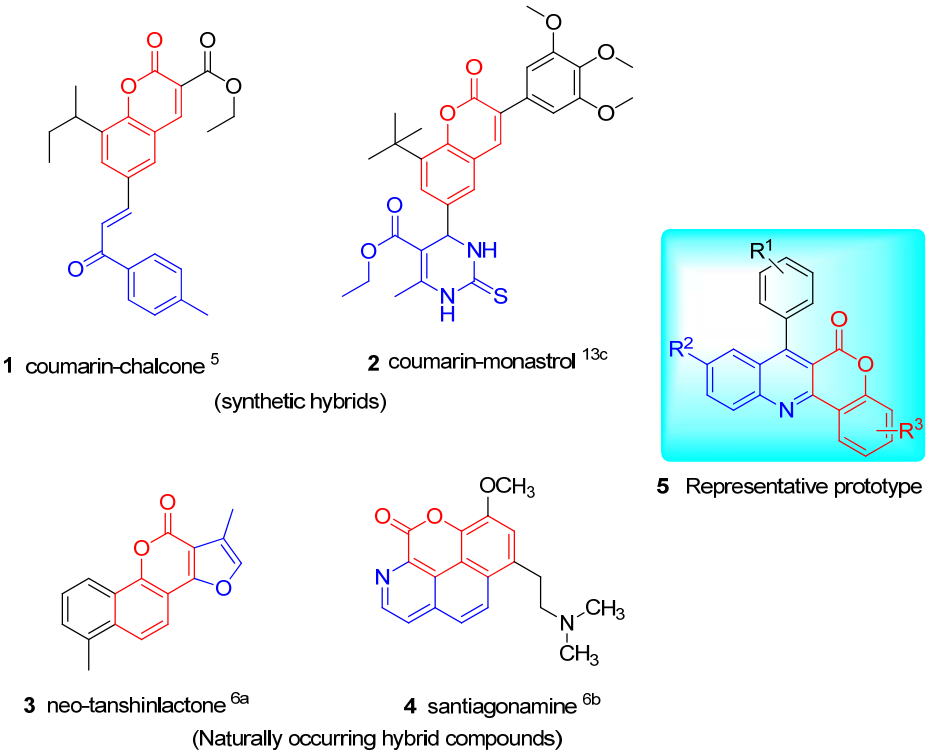


Figure 1. Coumarin containing biologically active hybrids.

A major challenge often encountered in the synthesis of these enticing hybrids is the design of highly efficient chemical reaction sequences in a minimum number of synthetic steps. One such protocol to realize these goals involves the use of multi-component reactions, that enable the creation of several bonds in a single operation and offers remarkable advantages such as convergence, operational simplicity, facile automation, reduction in the number of work-ups, thus rendering the transformations more environmentally friendly.[8]

General strategies for the synthesis of coumarin-quinoline hybrids rely on lengthy multistep protocols consisting of unfriendly procedures, resulting in very low overall yields.[5,6] Recently, Iaroshenka et al. used 4-chloro-3-(trifloroacetyl) coumarin as a novel building block for the synthesis of 7-(trifluoromethyl)-6H-chromeno[4,3-b]quinolin-6-ones in a two step method.[9a] While, Jie Wu et al.[9b] and Tabakovic et al.[9c] synthesized 6H-chromeno-[4,3-b]quinolines by using 4-chloro-2-oxo-2H-chromene-3-carbaldehyde and reacting with anilines. Martinez *et al.*,[10a] Weike Su *et al.*[10b] and Khan *et al.* [10c] described the synthesis of fused coumarin-quinoline hybrids in a two step sequence. However, some of these are typically associated with low to no yields with electron withdrawing groups (26%) [10], multiple step reaction sequences, use of toxic reagents, and complicated by-products. In terms of one pot synthesis protocol, Khan *et al*. have reported a one pot synthesis of chromeno[3,4-b] quinoline derivatives through Michael initiated ring closure by employing three-component condensation of aromatic aldehydes, 3-aminocoumarins and cyclic 1,3 diketones.[11] So there is great scope to develop a convenient and general approach towards the synthesis of coumarin- fused quinoline hybrids (Figure 1, **5**) from inexpensive, non-toxic and readily available reagents with improved yields in an eco-friendly fashion. As a part of

our ongoing efforts to develop cost effective and simpler new methodologies for the synthesis of hybrid pharmacophores,[12,13] we wish to report herein a simple and convenient synthesis of coumarin- fused quinoline hybrids *via* a one-pot three-component tandem annulation of 4-hydroxycoumarin with aromatic aldehydes and aromatic anilines using molecular iodine as an efficient catalyst (Scheme 1). To the best of our knowledge, this is the first one pot report for the synthesis of chromeno[4,3-b]quinolin-6-ones.

Molecular iodine has recently received much attention due to its low-cost, nontoxic, ready availability, easy handling, and affording the corresponding products in excellent yields with high selectivity.[14] In an attempt to carry out the union of *p*-toluidine (**5b**), 4-hydroxycoumarin (**6a**) and 4-chlorobenzaldehyde (**7h**), molecular iodine in acetic acid under microwave irradiation was investigated (scheme 1).

Scheme 1 Synthesis of Chromeno[4,3-b]quinolin-6-one

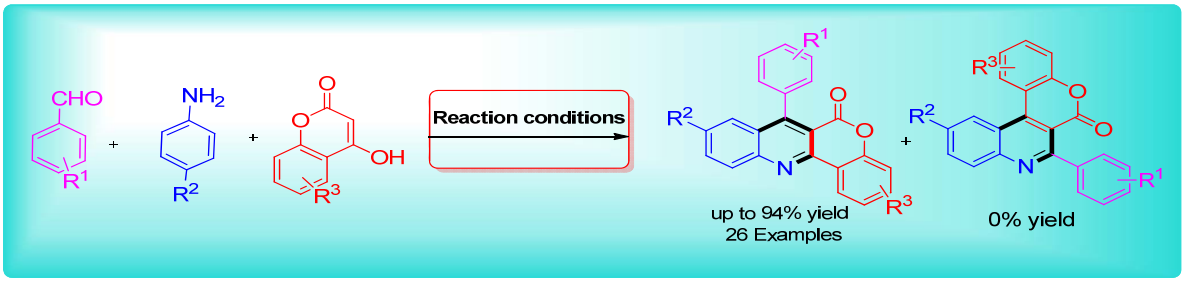


Table 1 Optimization of reaction conditions[a]

S.No	Solvent	Catalyst (eq)[a]	Time (hrs)	Yield (%)[b]
1	CH_3COOH	I_2 (0.5)	10	75
2	CH_3COOH	$BF_3.OEt_2$(0.5)	10	0
3	CH_3COOH	$SnCl_2$(0.5)	10	10
4	CH_3COOH	$Bi(NO_2)_3$(0.5)	10	12
5	CH_3COOH	$AlCl_3$(0.5)	10	10
6	CH_3COOH	CuI(0.5)	10	10
7	CH_3COOH	I_2(20mol%)	10	79
8	CH_3COOH	$AuCl_3$(0.5)	10	18
9	CH_3COOH	Ag(OTf)(0.5)	10	20
10	DMF	I_2 (0.5)	10	0
11	Dioxane	I_2 (0.5)	10	10
12	TFA	I_2 (0.5)	10	0
13	CH_3COOH	I_2 (10mol%)	10	85
14	CH_3COOH	I_2 (5mol%)	10	62

[a]Reaction conditions: *p*-toluidine (**5b**) (1 mmol), 4-hydroxycoumarin (**6a**) (1 mmol), 4-chlorobenzaldehyde (**7h**) (1 mmol), catalyst in 5mL solvent at 100-110 °C. [b]Yield of product isolated after column chromatography.

The compound **8abh** having a skeleton of 7-(4-chlorophenyl)-9-methyl-6H-chromeno[4,3-b]quinolin-6-one, was formed as the sole product in albeit moderate yield. This interesting result prompted us to further investigate the reaction. To find the optimal reaction conditions, we screened a large number of Lewis acid catalysts (Table 1, entry 1-9) but left out without much success. Much to our delight, we observed that only iodine can efficiently catalyse the reaction to furnish 7-(4-chlorophenyl)-9-methyl-6H-chromeno[4,3-b]quinolin-6-one **8abh**. In an attempt to evaluate the catalytic efficiency of iodine, we carried out the reaction with *p*-toluidine **5b**, 4-hydroxycoumarin **6a** and 4-chlorobenzaldehyde **7h** in acetic acid in the presence of various equivalents of iodine. The reaction occurred most efficiently with 10mol% iodine under MW conditions at 165 °C (Table 2, entry 16). However, in the absence of iodine (Table 2, entry 18), poor yields were observed even after prolonged heating, clearly indicating that molecular iodine is essential to facilitate the reaction (Scheme 2c).

Table 2 Optimization of MW reaction conditions [a]

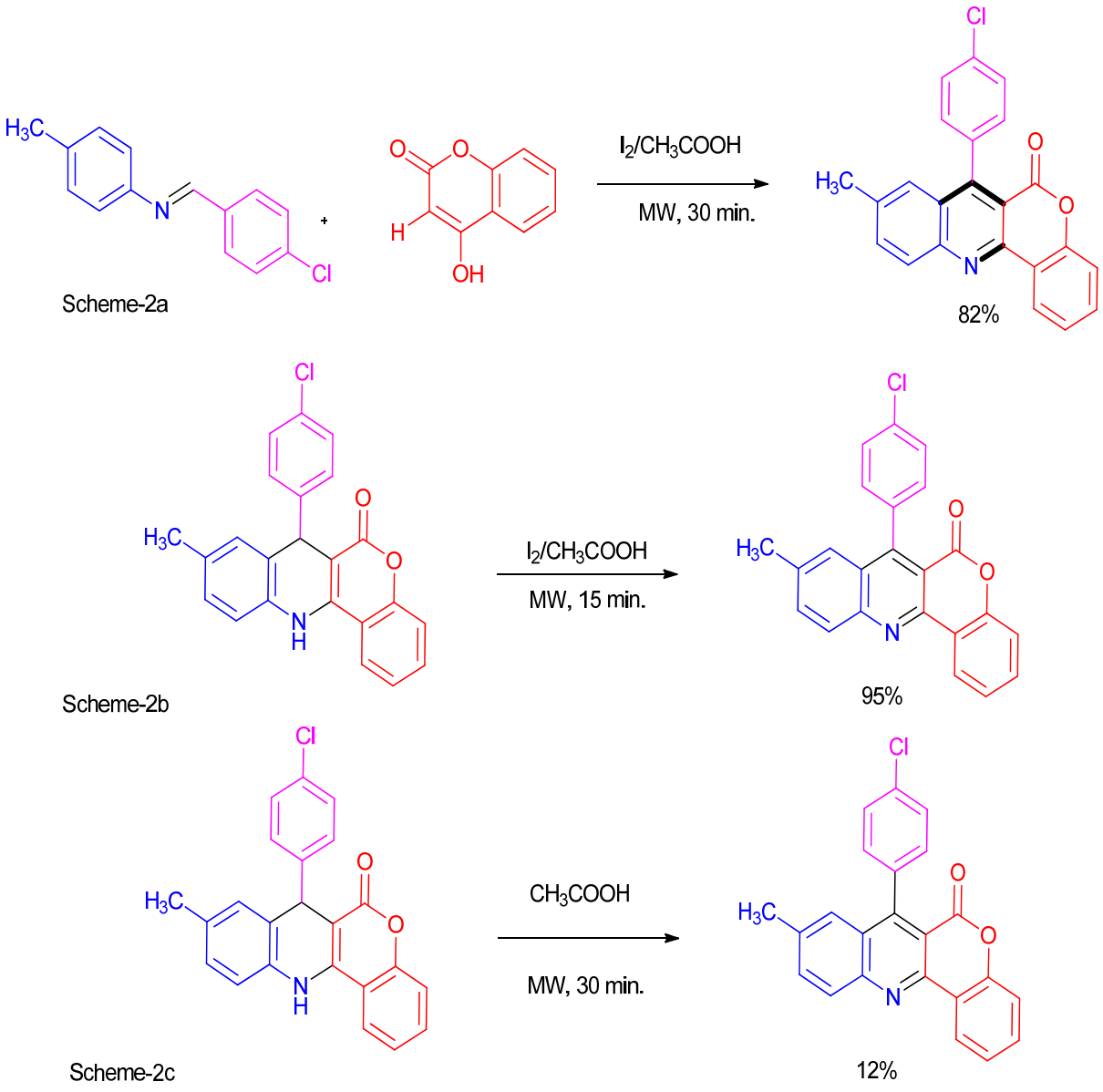
S.No	Solvent	Catalyst (eq)[a]	Time (mins)	Yield (%)[b]
15	CH_3COOH	I_2 (5mol%)	30	65
16	**CH_3COOH**	**I_2 (10mol%)**	**30**	**85**
17	CH_3COOH	I_2 (10mol%)	15	45
18	CH_3COOH	No catalyst	15	18
19	CH_3COOH	I_2 (20mol%)	15	55
20	CH_3COOH	I_2 (20mol%)	30	85
21	CH_3COOH	I_2 (0.5)	30	78

[a]Reaction conditions: *p*-toluidine (**5b**) (1 mmol), 4-hydroxycoumarin (**6a**) (1 mmol), 4-chlorobenzaldehyde (**7h**) (1 mmol), catalyst, in 1mL solvent, MW irradiation, 165 °C. [b]Yield of product isolated after column chromatography.

After determining the amount of catalyst, we further evaluated the reaction with various solvents (Table 1, entry 10-12) but the yields were found to be better in acetic acid only. With a set of optimized conditions in hand, we next examined the scope of this cyclization process (Scheme 1). The effect of substituents on the arene of aldehyde undergoing the cyclization reaction was first examined. This aromatic ring was found to be tolerant to both electron-rich groups, such as methyl (**8abe**), isopropyl (**8abd**), methoxy (**8ahc**), dimethoxy (**8abb**) and trimetoxy (**8aba**) and electron deficient groups, such as cyano (**8abj**), nitro (**8abk**) and trifluoromethyl (**8abl**) (scheme 3). Notably, the halogen containing motifs, such as fluro (**8abg**), Chloro (**8abh**), and Bromo (**8abi**) work well in this transformation. It is noteworthy that even heteroaromatic aldehyde, such as 3-thiophene (scheme 5, **8abm**), could also be employed to give the chromeno[4,3-b]quinolin-6-one product in good yield. Also, the presence or absence of the methyl substituent on the coumarin moiety had no effect on the yield and reaction time (scheme 5, **8bbe** and **8cbe**). Similarly, a variety of aromatic amines (scheme 4) were also successfully reacted under the same reaction conditions. However, aliphatic amines and aldehydes failed to undergo the rearrangement. The structure of chromeno[4,3-b]quinolin-6-ones was assigned on the basis of 1D (1H, 13C), 2D NMR, IR spectroscopy and mass spectrometry analysis. In addition, the structure was unambiguously

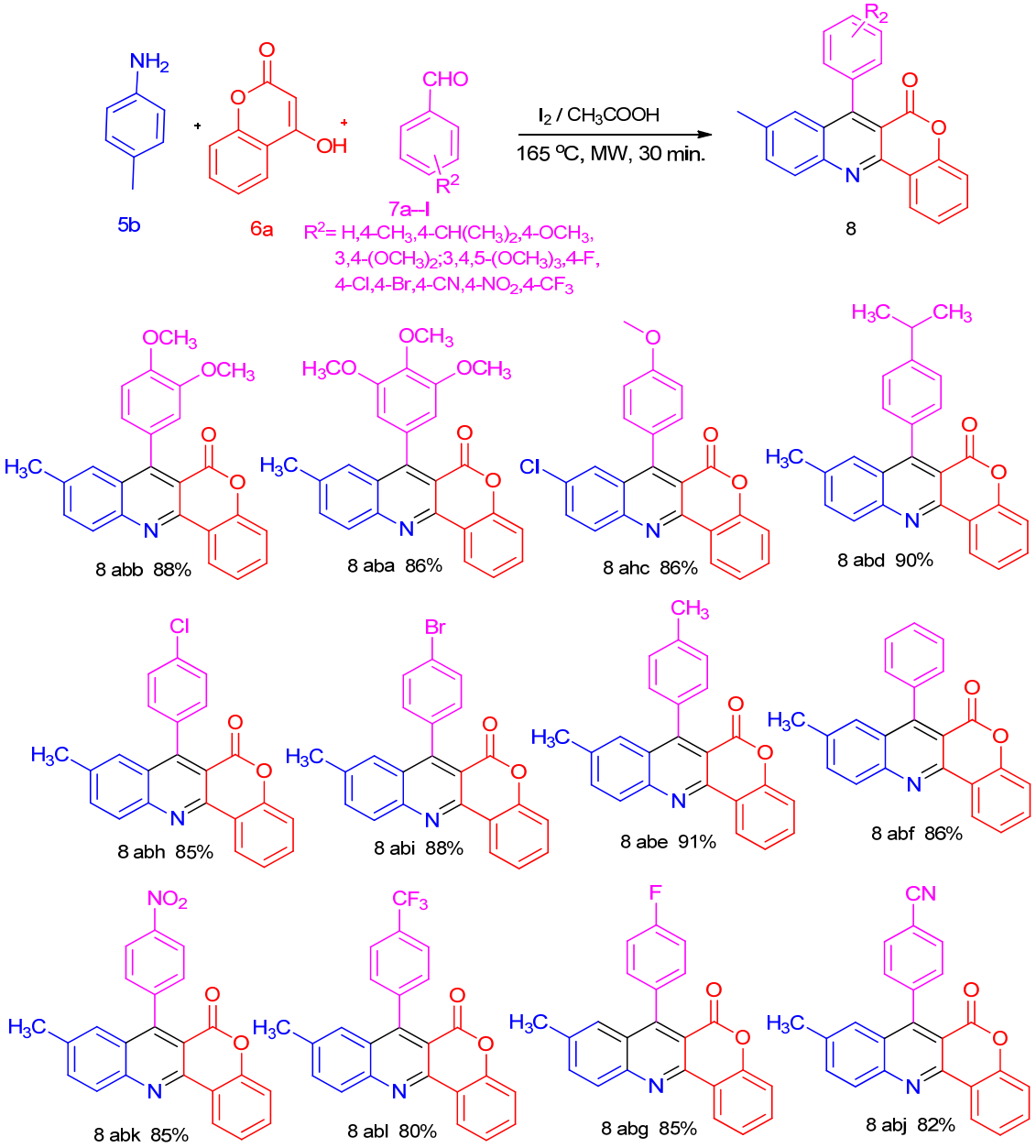
confirmed by X-ray diffraction analysis of compound **8abh** (Figure 2). The most plausible mechanism pathway for coumarin-fused quinolines is depicted in Scheme 6. The first step is the condensation of aldehyde **7h** and aromatic amine **5b** which gave Schiff base **a**. The nucleophilic attack (Mannich reaction) of coumarin **6a** on imine **a** resulted in unstable adduct **b**. The adduct **b** then underwent

Scheme 2 Controlled experiments:



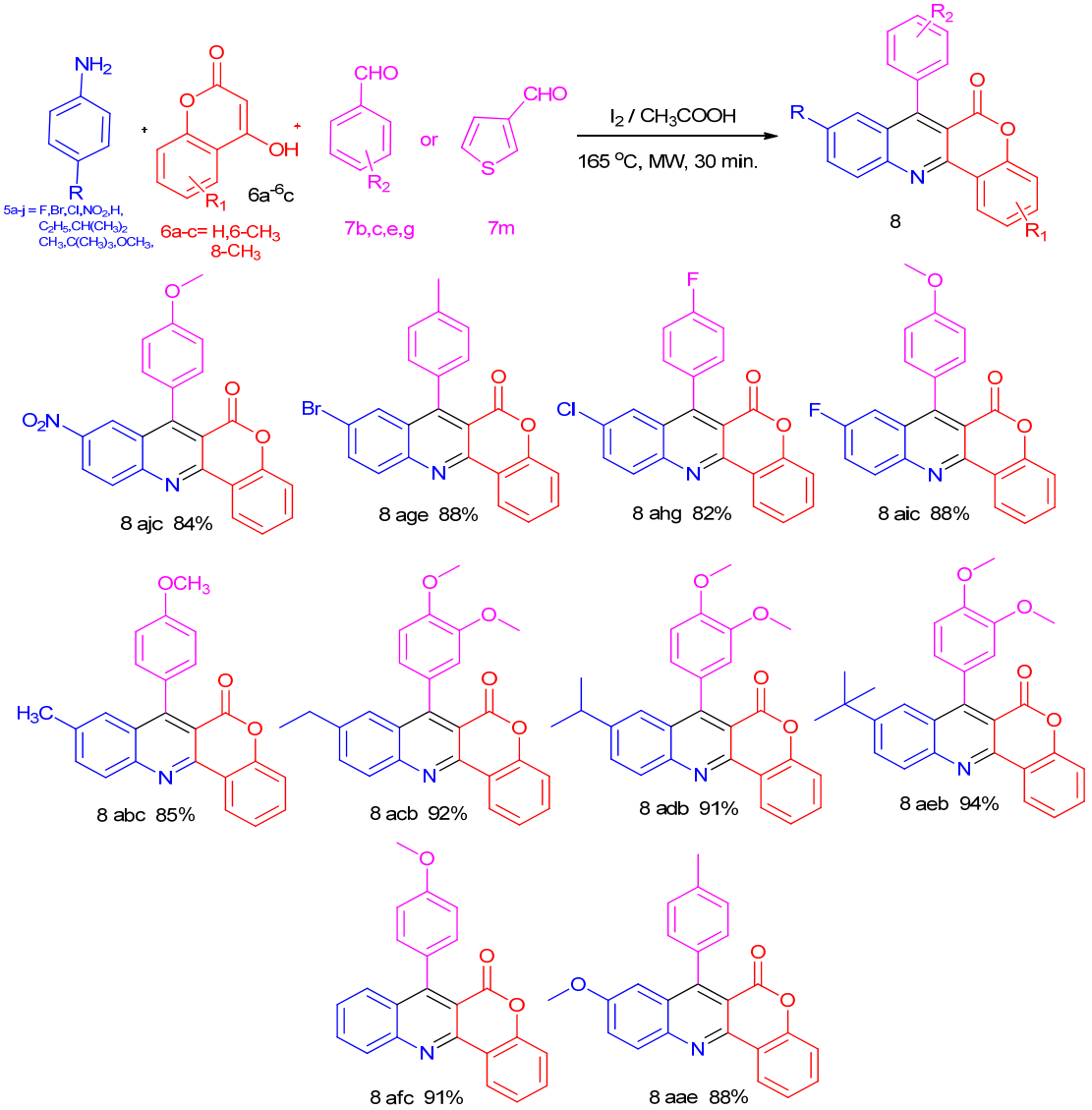
Reaction conditions: *p*-toluidine (**5b**) (1 mmol), 4-hydroxycoumarin (**6a**) (1 mmol), 4-chlorobenzaldehyde (**7h**) (1 mmol), catalyst, in 1mL solvent, MW irradiation, 165 °C.

Scheme 3 Scope of different aldehydes under Optimized Reaction conditions



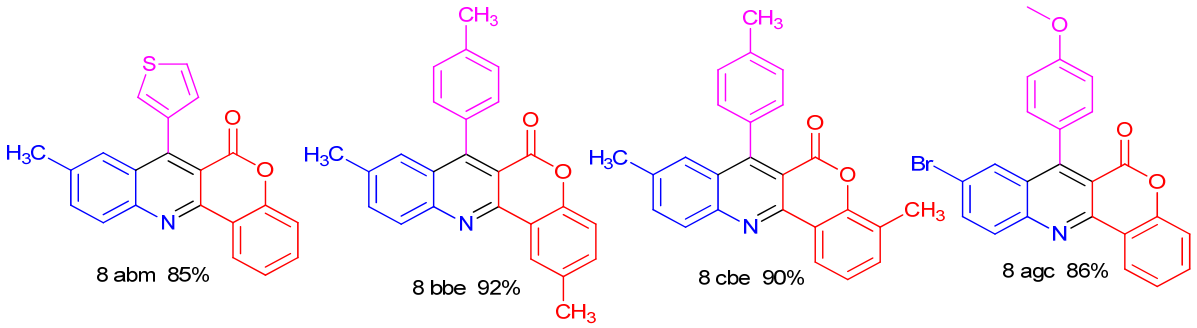
Reaction conditions: *p*-toluidine (**5b**) (1 mmol), 4-hydroxycoumarin (**6a**) (1 mmol), 4-chlorobenzaldehyde (**7h**) (1 mmol), catalyst, in 1mL solvent, MW irradiation, 165 °C.

Scheme 4 Scope of different amines under optimized reaction conditions



Reaction conditions: *p*-toluidine (**5b**) (1 mmol), 4-hydroxycoumarin (**6a**) (1 mmol), 4-chlorobenzaldehyde (**7h**) (1 mmol), catalyst, in 1mL solvent, MW irradiation, 165 °C.

Scheme 5: Diversified Chromeno[4,3-b]quinolin-6-one



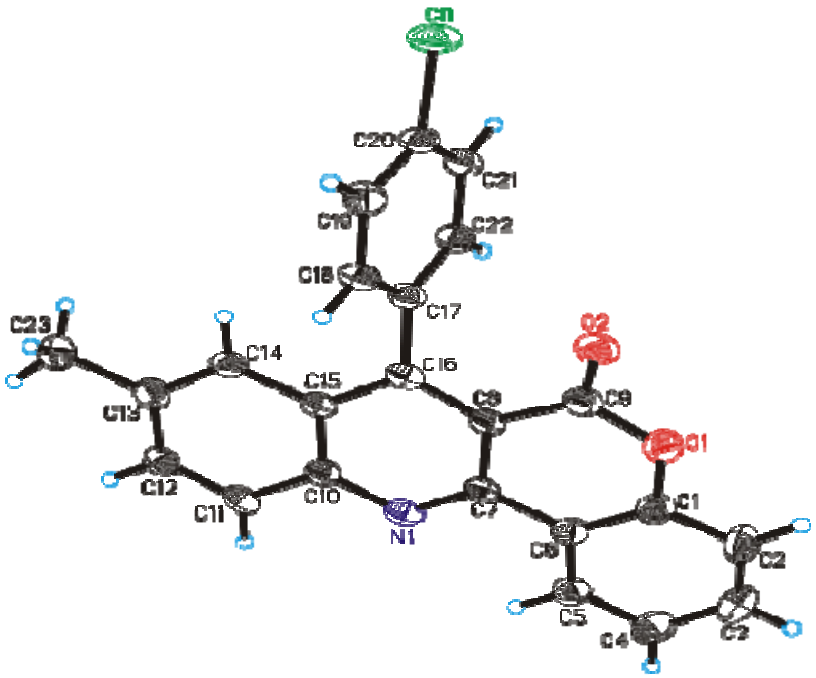
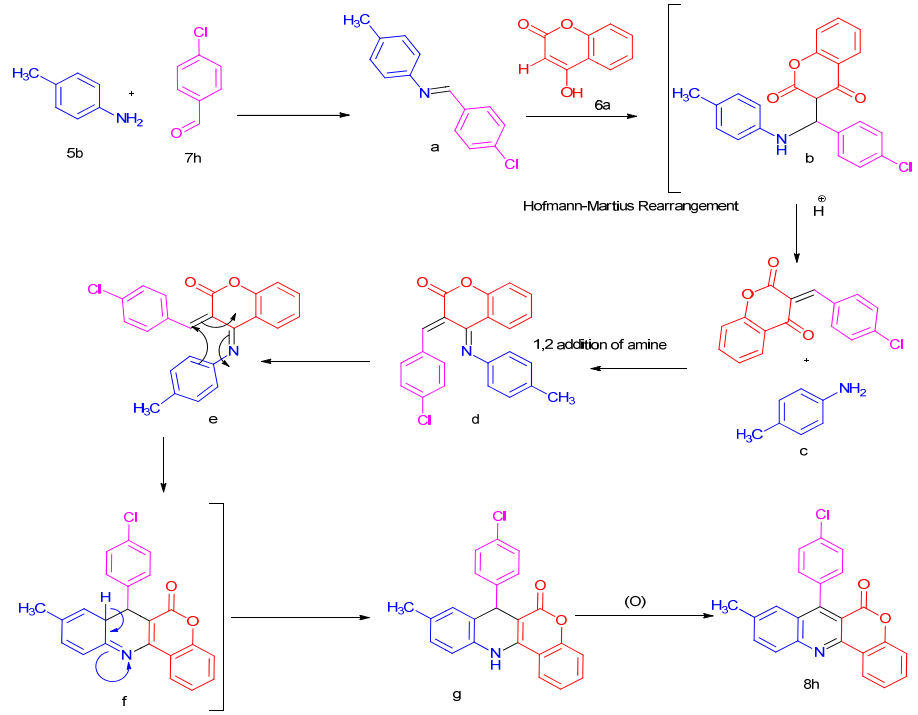


Figure 2. ORTEP diagram of compound **8abh.**

rearrangement *via* transition states (**c**, **d,** **e** and **f**) to give thermodynamically stable intermediate **g**[10c]**,** which undergoes oxidation to furnish the desired final product **8abh**. This hypothesis was supported by controlled experiments (scheme 2): as it was found that the isolated Schiff base **a** was readily converted into the desired final product **8abh** with 4-hydroxy coumarin under the stabilised reaction conditions (Scheme-2a), further intermediate **g** also furnished thedesired product **8abh** under same conditions (Scheme-2b).

Scheme 6: Mechanistic proposal for the formation of Chromeno[4,3-b]quinolin-6-one **8abh**



In conclusion, we have established a novel protocol for the construction of a series of coumarin-fused quinolines from aryl amines, aldehydes, and 4-hydroxy coumarin under MW conditions by using molecular iodine as the sole catalyst. The developed process may find application in the synthesis of diverse libraries of hybrid drug like scaffolds. This strategy is an effective method to construct a complex core in a single operation from simple starting materials and environmentally benign oxidant in an eco-friendly fashion.

Acknowledgement
Authors are grateful to Director, CSIR-CDRI for his constant support and encouragement, Dr. S. P. Singh for technical support, SAIF for NMR, IR, and Mass spectral data. The CSIR, New Delhi, is thanked for the award of Senior Research Fellowship to G.R.P, L.R.S and A.S.R. We thank Dr. Tejender S. Thakur of Molecular and Structural Biology Division, CSIR-Central Drug Research Institute for supervising the X-ray Data collection and structure determination of our compound reported in this paper.This is **CSIR-CDRI Communication No. 8989**.

Notes and references

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