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A solvent- and catalyst-free tandem reaction: synthesis, and photophysical and biological applications of isoindoloquinazolinones†

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An easy green synthetic approach for fused isoindoloquinazolinones has been developed under neat reaction (yields up to 91%) conditions. This new one-pot tandem methodology involves condensation of readily available anthranilamide with 3-(2-formylcycloalkenyl)-acrylic ester under solvent- and catalyst-free conditions. This strategy avoids the use of oxidant, and heavy metal catalysts and also is free from work-up and generation of toxic by-products. A dramatic change of photophysical properties of dihydroisoindoloquinazolinones in basic and aqueous media has also been documented in our study. Moreover, our model synthetic compound shows cytotoxic activity towards metastatic HepG2 and PC3 cancer cell lines.

Introduction

In recent years, one-pot tandem chemical transformations under metal- and solvent-free conditions have widely been used for complex organic molecule syntheses with reduced reaction time period and minimum energy requirement. A variety of chemical conversions, like oxidation, reduction, substitution, condensation, *etc.* have been developed using this principle.[1] Hence, heterocyclic ring formation using this green technique has been an active and attractive field in the recent era.[2]

Among the heterocyclic molecular architectures, *N*-fused heterocycles are ubiquitous in nature and a common structural motif for bioactive molecules and drug candidates. In particular, substituted quinazolinones have a wide range of biological and pharmacological activities, such as diuretic, anti-inflammatory, antidiabetic, anti-hepatitis C, anticonvulsant, antileshmanial, anticancer and so forth.[3] Two major types of fused quinazolinones available in nature are carbocycle fused quinazolinones, such as phaitanthrin, tryptanthrin, vasicione *etc.* (Fig. 1)[4] and heterocycle fused quinazolinones, like luotonin A and wuzhuyurutine A.[5] Quinazolinone molecular frameworks are also popular as efficient organic fluorescence materials.[6] Hence, development of a modern synthetic strategy for fused quinazolinones and their applications in *in vitro* and *in vivo* bio-systems are highly needed.[7]

Different approaches have been reported in the literature to synthesize highly condensed quinazolinone derivatives.[8] Suzuki coupling followed by Pd/Cu catalysed oxidative C–H amination,[9] and tandem Sonogashira coupling and hydroamination cyclization[10] are the two independent approaches towards fused quinazolinone, where 2-bromobenzaldeyde and anthranilamide were taken as the starting materials. Another recent report involves ruthenium(II)-catalyzed one-pot oxidative C–H/N–H functionalization of substituted dihydroquinazolinones with alkynes.[11] Radical cyclization of *N*-(2-iodobenzyl)-*N*-acylcyanamides is another reported strategy to access fused pyrroloquinazoline.[12] Li-Jiang Xuan and his group synthesized the same scaffolds *via* ruthenium-catalyzed oxidative coupling of 2-arylquinazolinones followed by an intramolecular aza-Michael reaction.[13] However, to the best of our knowledge, no attention has been devoted towards the synthesis of fused quinazolinones under metal- and solvent-free conditions. For eco-friendly reaction conditions, the chemical community always searches for green reactions under metal-free and solvent-free conditions. It is always better to perform the reaction in a non-hazardous solvent medium such as water, but it is also far better to run a reaction without any solvent, which reduces the steps in a multistep procedure *e.g.* work up and purification. As a part of our ongoing studies devoted towards the development of new heterocycles,[14] we have disclosed here an operatively simple, catalyst- and solvent-free synthesis of pyrrolo/isoindolo quinazolinone derivatives from 3-(2-formylcycloalkenyl)-acrylic ester derivatives **1** and anthranilamide **2** under heating conditions (120 °C) with moderate to good yields (Scheme 1). In addition, their photophysical properties have been studied, which are limited in the literature.

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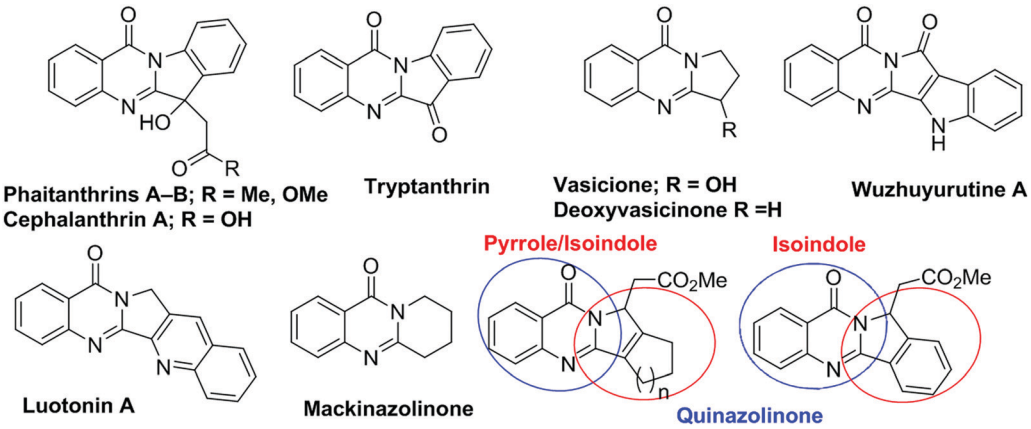
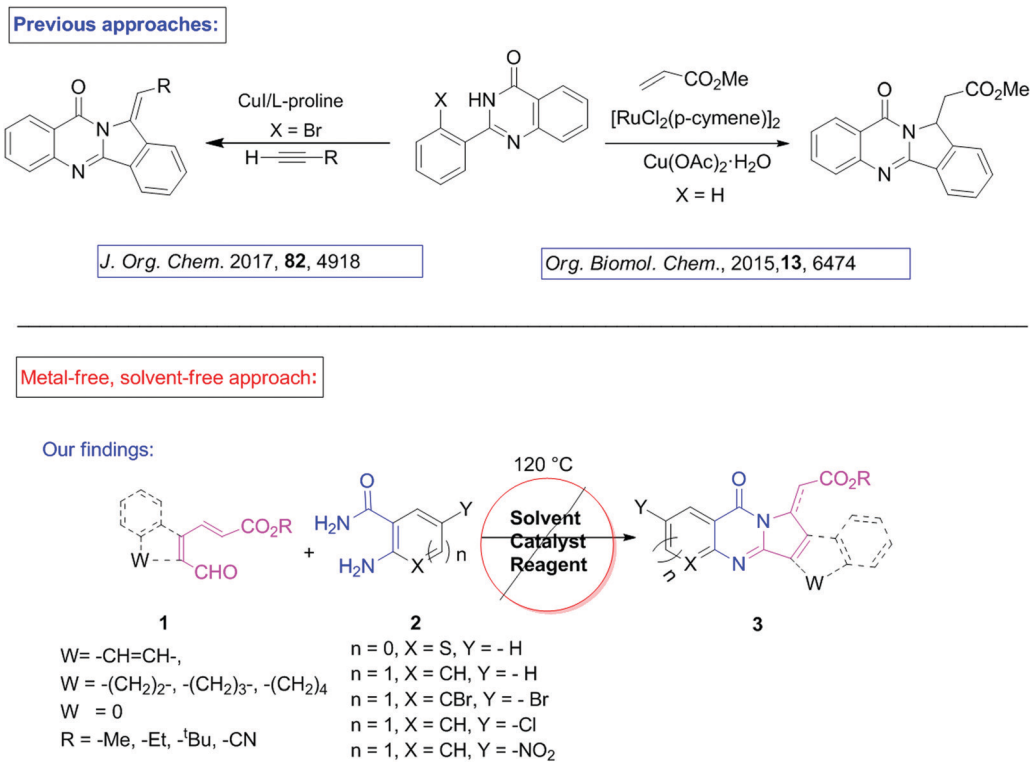


Fig. 1 Naturally occurring bioactive fused quinazolinone scaffolds.



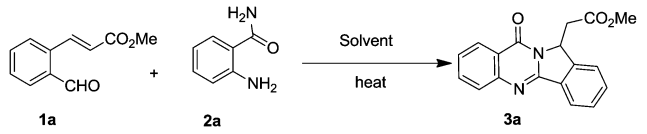
Scheme 1 Previous approaches *vs.* the present approach towards polycyclic fused quinazolinone.

Results and discussion

At the outset of this investigation to synthesize highly condensed fused quinazolinone derivatives **3**, the reaction was commenced with (*E*)-methyl 3-(2-formylphenyl)acrylate **1a** and anthranilamide **2a** in DMSO at room temperature, but no reaction occurred (Table 1; entry 1). However, the intermolecular condensation reaction followed by intramolecular aza-cyclization in one-pot succeeded by increasing the temperature up to 120 °C in DMSO (entry 4). It was found that cyclization was inefficient below 120 °C (entries 2 and 3). The two component coupling reaction proceeds satisfactorily in toluene and ethanol (entries 5 and 6). However, no fruitful product was isolated in acetonitrile, THF and dioxane (entries 7–9). In order to increase the efficacy of our developed methodology, studies without any solvent were carried out and the desired fused quinazolinone **3a** was obtained in very good yield (91%), (entry 10).

With the optimal conditions in hand, the scope of the new two-component neat reaction was evaluated with a variety of substrates as shown in Table 2. Methyl/ethyl/tertiary butyl (*E*)-3-(2-formylphenyl)acrylates were smoothly converted to the corresponding isoindoloquinazolines **3a–3c** in moderate to high yields. The cyclised product **3b** was unambiguously confirmed by X-ray crystal structure as shown in Table 2.[15] With this encouraging result in hand, the scope of the neat reaction was examined with different cycloalkenyl derivatives. Formation of

Table 1 Optimization of the reaction conditions towards a highly condensed quinazolinone[a]



1a 2a 3a

Entry	Solvent	T (°C)	Time (h)	Yield of **3a** (%)
1	DMSO	25	8	0
2	DMSO	60	8	0
3	DMSO	80	8	0
4	DMSO	120	2	82
5	Ethanol	78	2.5	73
6	Toluene	110	3	85
7	Acetonitrile	82	6	0
8	THF	66	6	0
9	Dioxane	101	6	0
10	—	**120**	**2**	**91**[b]

[a] Conditions: (*E*)-methyl 3-(2-formylphenyl)acrylate **1a** (1 mmol), anthranilamide **2a** (1 mmol), and solvent (2 ml). [b] Reaction performed without solvent.

the oxidized and reduced forms of the cyclized product depends on the nature of the ring. Aromatic moieties of ester derivatives were prone to air oxidation and lead to **3a–3f**, whereas the corresponding cycloalkenyl ester derivatives **3i–3p** (7 and 8 membered rings) are reluctant to undergo air oxidation. On the contrary, methyl/ethyl (*E*)-3-(2-formylcyclohexenyl)acrylates **3g** and **3h** smoothly transformed to their corresponding oxidized quinazolinones.

The two component coupling reactions of 2-aminothiophene-3-carboxamide **2d** with (*E*)-3-(2-formylphenyl)acrylates under neat conditions were well tolerated and deliver **3f**, **3m** and **3n**. We further extended the scope of the novel methodology to pentacyclic quinazolinones **3o** but the yield of the desired product was reduced to 55% due to the high steric constancy of the starting material. Notably, chloride and bromide substituted anthranilamides (**2b–2c**) were unable to produce cyclized products **3d** and **3e** at 120 °C under neat conditions and the condensations were performed at 140 °C under solvent-free conditions, which resulted in the formation of the desired products (**3d** and **3e**) in good yields. The neat reaction of **1a** furnished a very low yield of **3r** for an electron withdrawing substituted anthranilamide ($-NO_2$), but the same reaction gave satisfactory yield of two isomeric quinazolinones **3r** and **3s** in DMSO at 120 °C. Nevertheless, only one isomer **3p** was generated for the cycloheptenyl system under equivalent conditions. Our green protocol was equally adequate compared to another acrylonitrile-substituted aza-Michael acceptor and furnished a good yield of quinazolinone derivative **3q**. Furthermore, we have extended the scope of the reaction to the substrate (2*E*,4*E*)-methyl 6-oxo-4-phenylhexa-2,4-dienoate, which furnished cyclised product **3t** with a good yield of 72%.

The mechanism of the reaction could be ascertained *via* a four-step sequential process in one-pot (Scheme 2). The step-atom economical mechanistic pathway involves Schiff base (**A**) formation followed by intramolecular aza-cyclisation to produce intermediate **B**, which affords the quinazolinone derivative after air oxidation.[16] The quinazolinone intermediate **C** undergoes intramolecular aza-Michael reaction and provided fruitful condensed derivatives **3a–3h** and **3q–3r**.[13] The product formation of **3i–3p** could be elucidated *via* a competitive intramolecular aza-Michael reaction of more nucleophilic amide *N*-atoms.

The formation of **3s** and **3t** could be explained *via* a two-step 1,5-H shift of intermediate **I** (Scheme 3).

Interestingly, it is noticed that the substrate **3j** possesses high fluorescent properties and hence investigation of the photophysical properties has also been discussed. The tolerance of these valuable functional groups would offer an opportunity for further transformations.

Photophysical studies

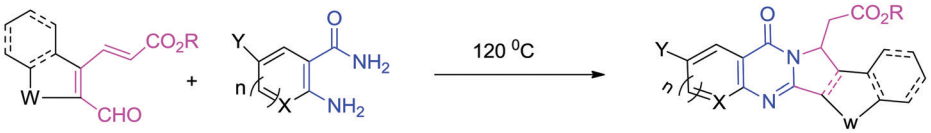
After successful synthetic studies, attention was drawn towards photophysical studies of the synthesized dihydroquinazolinone molecule **3j**. The UV/Vis absorption spectra of degassed 2×10^{-6} M solution of **3j** in different solvents have been recorded (ESI;† Fig. S1), and the results are tabulated in Table 3.

Excited state properties of quinazolinone derivative **3j** were investigated by fluorescence emission spectroscopy. Like those of other quinazolinone derivatives, the fluorescence properties of **3j** were also found to be strongly dependent on solvent polarity.[17] The heterocyclic compound **3j** showed negative solvatochromatic emission (Fig. 2) as a function of solvent polarity.[18] As the solvent polarity increases (from non-polar *e.g.* toluene to polar *e.g.* acetonitrile (MeCN)), a hypsochromic shift for **3j** was noticed and the emission maximum was found to shift from 431 to 416 nm. The above solvent effect observed is due to the close lying ($^1\pi$–π^*) and (^{1}n–π^*) singlet excited states.[19] The higher dissolving ability of a solvent with lower dielectric constant (non-polar solvent) favours the π–π^* interaction in the quinazolinone unit and produces greater emission.[20] Conversely, in polar protic solvent (*e.g.* MeOH) due to the intermolecular H-bonding effect with the quinazolinone unit, the π–π^* transition dominates, which results in shifting of the emission band towards longer wave length.

The fluorescence properties of dihydroquinazolinone derivative **3j** were also investigated in an aqueous binary solvent system to understand the effect of hydrogen bonding interaction. The emission spectra (Fig. 3) of **3j** in MeCN–H_2O binary mixtures were recorded and it was observed that with an increasing amount of water in the MeCN–H_2O mixture, there is a bit of a bathochromic shift with a gradual decrease in fluorescence intensity. The above fact can be attributed to solute–solvent interactions through the formation of hydrogen bonds between the solvent and the heterocyclic part of the quinazolinone moiety (Scheme 4).[21]

As the quinazolinone derivative contains a basic labile proton (NH), it is quite interesting to check the emission spectral behaviour with increase of pH (Fig. 4). The fluorescence maximum of **3j** in neutral MeCN is around 412 nm, which is red shifted to $\approx$437 nm by the successive addition of different concentrations of NaOH (micromolar). This is because in pure MeCN, protonated **3j** is the predominant species. Thus the fluorescence spectrum in pure MeCN is mainly due to

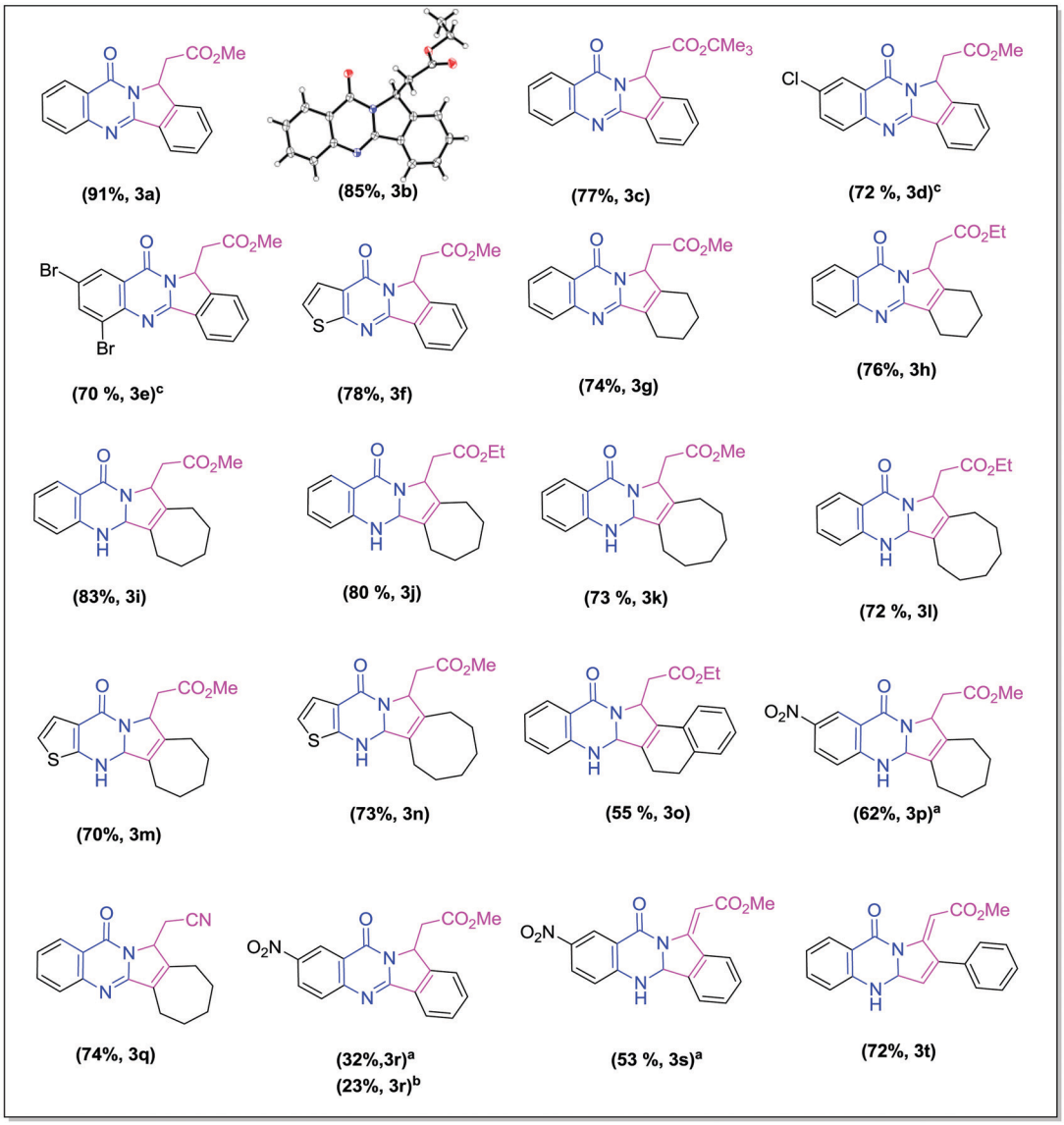
Table 2 Substrate scope for tandem one-pot neat reaction[b]



1
W = -CH=CH-
W = -(CH2)2-, -(CH2)3-, -(CH2)4-
W = 0
R = -Me, -Et, -tBu

2
n = 0, 1
X = CH, S, CBr
Y = -H, -Cl, -Br

3

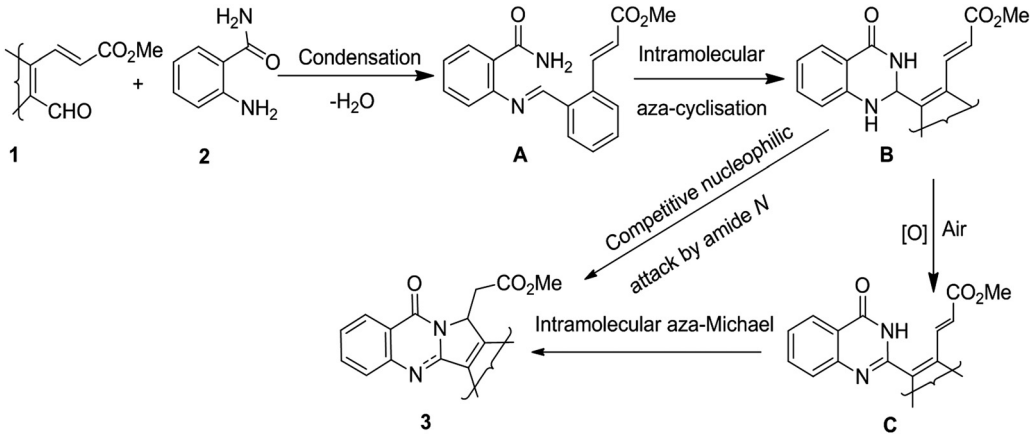


[a] Reactions were performed in DMSO. [b] Conditions: (*E*)-methyl 3-(2-formylcycloalkenyl)acrylate **1a** (1 mmol), and anthranilamide **2** (1 mmol). [c] Reactions were performed at 140 °C.

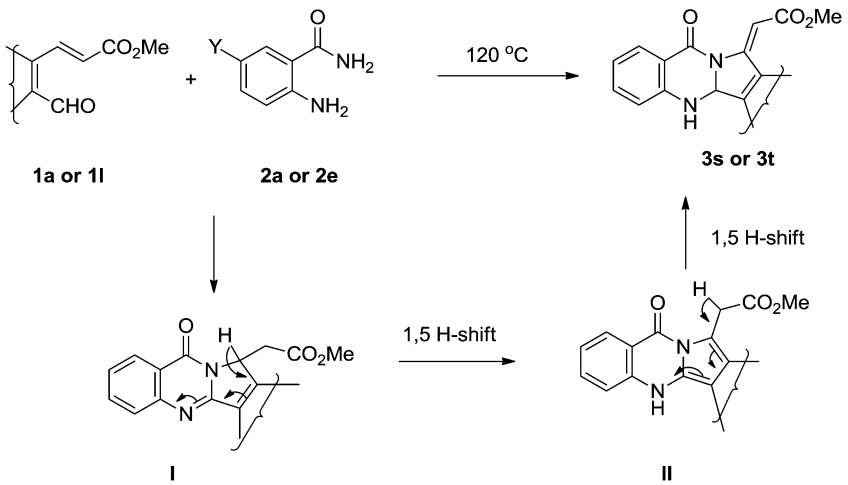
protonated **3j** in the excited state. At higher pH, a bathochromic shift was obtained due to the deprotonation of **3j** followed by extended conjugation and the decrease of fluorescence intensity may be explained by the lower solubility of the molecule in an alkaline solution (Scheme 5).

Biological study

After successful investigation of the photophysical properties, our research turned towards biological application of our model compound **3j** using two different metastatic cancer cell



Scheme 2 Plausible mechanism for the synthesis of fused quinazolinones.



Scheme 3 Synthetic route of isomerised quinazolinone.

Table 3 UV-Vis absorption and fluorescence data of **3j** in different solvents

Solvent	ε^a (25 °C)	δH hydrogen bonding^b	$\lambda_{max}{}^c$ (nm)	$\varepsilon_{max}{}^d$	$\lambda_{emi}{}^e$ (nm)	Stokes' shift^f (nm)
Toluene	2.38	2.0	330	132 000	431	101
Chloroform	4.81	7.1	329	159 000	431	101
DCM	9.10	7.1	331	133 000	429	98
MeOH	33.00	19.4	333	120 500	430	97
CAN	37.50	6.1	331	119 000	416	82
DMSO	46.70	7.8	329	87 500	416	87

[a] Dielectric constant at 25 °C. [b] Hydrogen bonding capability. [c] Maximum absorption wavelength. [d] Molar absorption coefficient at maximum absorption wavelength. [e] Maximum emission wavelength. [f] Difference between maximum absorption wavelength and maximum emission.

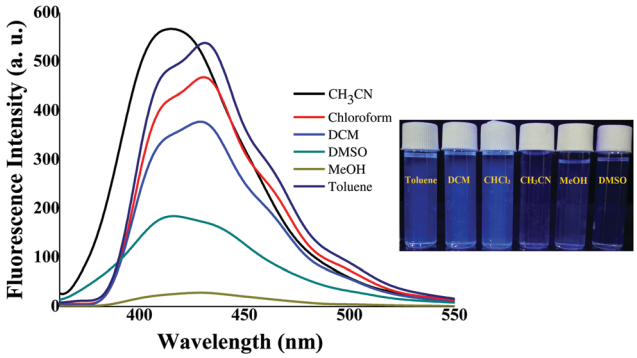


Fig. 2 Fluorescence spectra of quinazolinone derivatives **3j** in different solvents.

lines; hepatocellular carcinoma (HepG2) and prostate cancer (PC3). HepG2 is a human liver cancer cell line, obtained from the liver tissue of a 15-year-old American adolescent boy of European ancestry.[22] The human prostate cancer cell line (PC3) is derived from bone metastasis of a grade IV prostatic adenocarcinoma from a 62-year-old male Caucasian, which is used widely in research and drug development.[23] To examine the anticancer activity of the compound **3j**, HepG2 and PC3 were seeded in 48-well plates at 1×10^4 cells per well in DMEM and RPMI (10% FBS) medium, respectively, and exposed to **3j** at different concentrations for 24 h (Fig. 5). After incubation, the cells were washed twice with PBS and incubated with MTT

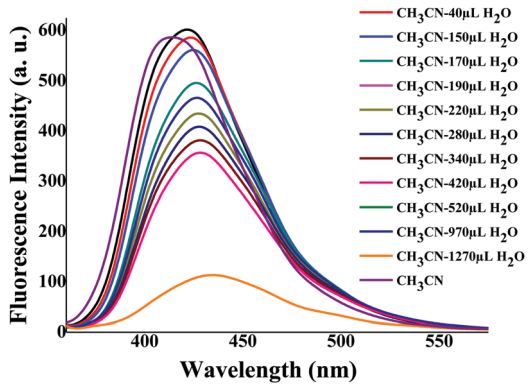


Fig. 3 Fluorescence quenching of **3j** *vs.* water % in MeCN–H_2O mixtures.

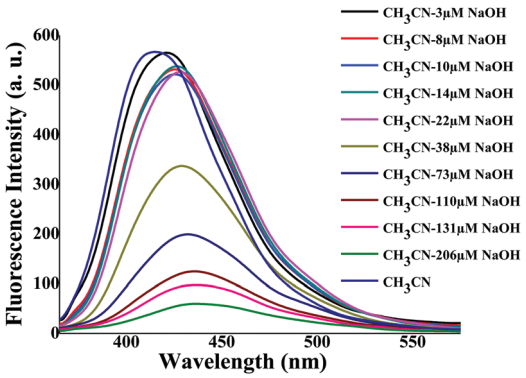
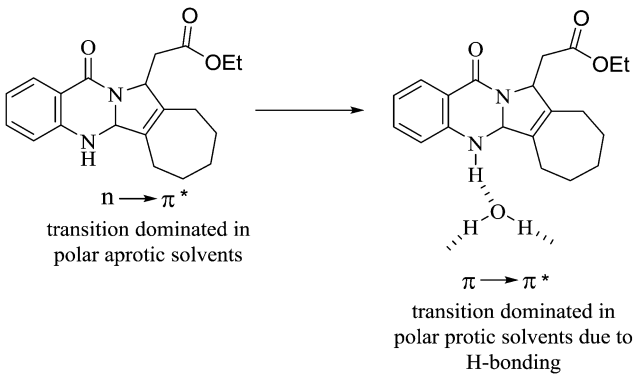


Fig. 4 Fluorescence spectral change of **3j** by stepwise addition of NaOH in MeCN (λ_{max} shifted from 408 nm in pure MeCN to 438 nm in MeCN-206 μM NaOH).



Scheme 4 Solvent–solute H-bonding interactions.

solution (450 μg ml^{-1}) for 3 h at 37 °C. The resulting formazan crystals were dissolved in an MTT solubilising buffer and the absorbances were measured at 570 nm by using a microplate reader (Biotek, USA). Each point was assessed in triplicate. Untreated cells were considered as 100% viable. We found that this compound has significant anticancer activity against both of the cell lines. The IC-50 values of this compound were found to be 134 μg ml^{-1} for HepG2 cells and 112 μg ml^{-1} for PC3 cells.

Cells were incubated with increasing concentrations of the compound for 24 h and their percentage of survivability was assessed by the MTT assay. Data represented are means ± SD of three identical experiments made in three replicates.

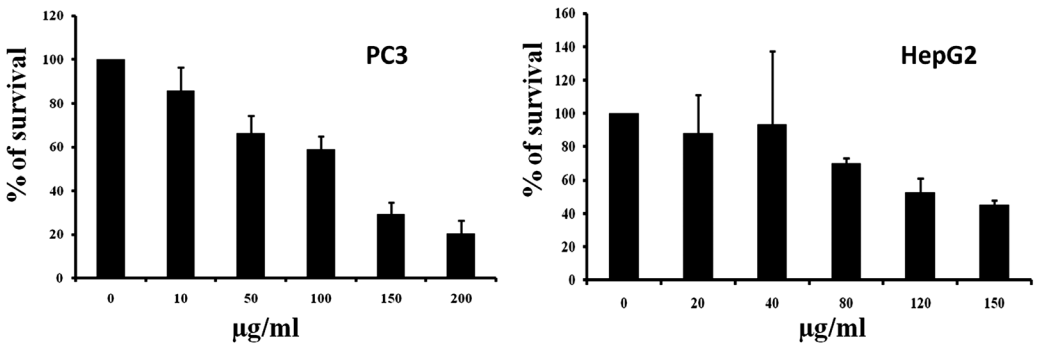
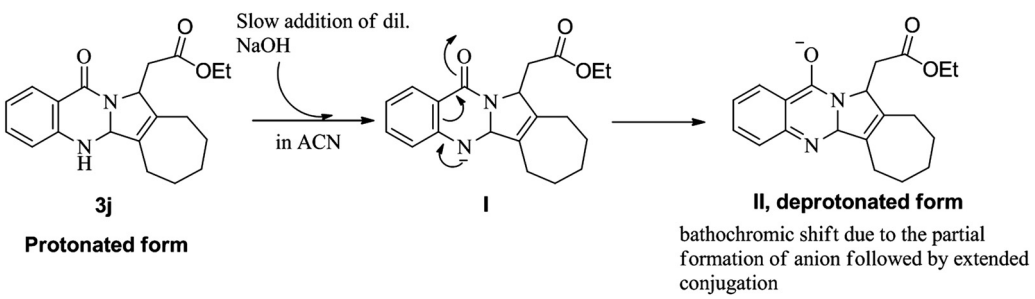


Fig. 5 Cytotoxic effects of the compound **3j** on PC3 and HepG2 cells.



Scheme 5 Solute–alkali interaction in the excited state.

Conclusion

To conclude, an environmentally benign catalyst and solvent-free tandem approach for the synthesis of highly functionalized fused quinazolinones with good to excellent yields has been demonstrated. The designed substrates, 3-(2-formylcycloalkenyl)-acrylic ester derivatives, are effective coupling partners for anthranilamide compounds to synthesize highly fused quinazolinones under neat conditions with wide substrate scope, step-atom economy and minimal work-up procedure. The synthesized compounds show good fluorescence properties and hence photophysical properties in different solvents and solvent–solute interactions in the excited state of the synthesized fluorophore are also documented. Since our study compound chemosensitized HepG2 and PC3 cell lines, we will use this compound in an *in vivo* mouse model for future research.

Conflicts of interest

There are no conflicts to declare.

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