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COMMUNICATION

Design and synthesis of benzylpyrazolyl coumarin derivatives *via* a four-component reaction in water: investigation of the weak interactions accumulating in the crystal structure of a signified compound†

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A combinatorial library of benzylpyrazolyl coumarin derivatives have been synthesized by a green one-pot four-component reaction between aryl hydrazine/hydrazine hydrate (1), ethyl acetoacetate (2), aromatic aldehydes (3) and 4-hydroxycoumarin (4). Molecular scaffolds which assimilate bio-active 3-benzylsubstituted 4-hydroxycoumarins as well as a pyrazolone ring in a single nucleus may be worthwhile molecules from a biological point of view. The reactions were performed in water and employed glacial acetic acid as the right choice of catalyst, and was demonstrated to be the key for rendering the reaction possible and obtained good to excellent yields under reflux conditions within a short period of time. The crystal structures of (*R*/*S*)-benzylpyrazolyl coumarin, easily produced by a chromatography-free highly product-selective reaction, were explored by means of single crystal X-ray diffraction analysis and the main intra- and intermolecular interactions perceivable through crystal structure analysis. The presence of a strong intramolecular hydrogen bond was confirmed. In addition, the whole crystal structure consists of other intermolecular hydrogen bonds, such as CH···O and aromatic CH···π interactions between *R*- and *S*-molecules and CH···O, NH···O and aromatic CH···π interactions among only *R*-molecules and *S*-molecules in the asymmetric unit.

Introduction

The task of achieving efficacy in all features of chemical construction in the medicinal field is the design and synthesis of biologically active molecules. Green chemistry can be recognized as pioneering research, which widely reports intrinsic atom economy, energy savings, waste reduction, easy work ups and the avoidance of hazardous chemicals.[1] The development of a simple, eco-friendly reaction protocol for the synthesis of highly functionalized compound libraries of medicinal motifs is an attractive area of research in both academia and the pharmaceutical industry.[2] Multi-component reactions (MCRs) in water have been shown to be powerful tools in the search for developing libraries of medicinal scaffolds as well as for the requirements of green chemistry because of the cheap, easy availability and relevant character.[3]

3-Substituted 4-hydroxycoumarin particularly 3-benzylsubstituted 4-hydroxycoumarin derivatives are of much importance because they exist in many natural products. It is also established that these compounds also exhibit a wide range of biological activities due to its abundance in medicinal scaffolds namely warfarin, phenprocoumon, coumatetralyl, carbochromen, bromadialone (Fig. 1a) offering antibacterial, anti-HIV,[4] antiviral,[5] anticoagulant,[6] antioxidant[7] and anticancer activities.[8]

Pyrazolones are also important structural cores in many drug substances of medicinal fields. Heterocyclic nucleus containing pyrazolones (*viz.* phenazone, propyphenazone, ampyrone and metamizole) (Fig. 1b) are useful antipyretic and analgesic drugs,[9] whilst edaravone (MCI-186) has been used for treating brain[10] and myocardial ischemia.[11] In addition, pyrazolones possess kinase inhibitory properties, particularly of enzymes which catalyze the phosphorylation of serine and threonine in proteins, and is also used for treating diseases related to these enzymes, such as rheumatoid arthritis, psoriasis, bone loss, cancer and other proliferative diseases like antimicrobial, antifungal,[12] antimycobacterial,[13] antibacterial,[14] anti-inflammatory,[15] antitumor,[16] gastric secretion stimulatory,[17] antidepressant,[18] antifilarial activities[19] and anti-tubercular activities.[20]

A molecular scaffold which assimilates 3-benzylsubstituted coumarin as well as pyrazolone moieties might integrate properties of both, and the synergism of both the heterocyclic moieties in a single nucleus may result in the formation of some worthwhile molecules from a biological point of view. It is surprising that there is no compound possessing such a molecular skeleton reported in the literature to date. We herein wish to report, for the first time, a glacial acetic acid catalyzed four-component reaction for the combinatorial synthesis of highly functionalized benzylpyrazolyl coumarin frameworks in water medium under reflux conditions (Scheme 1). The present work materializes as a part of our ongoing research programme recently published on the synthesis of various biologically active coumarin moieties.[21]

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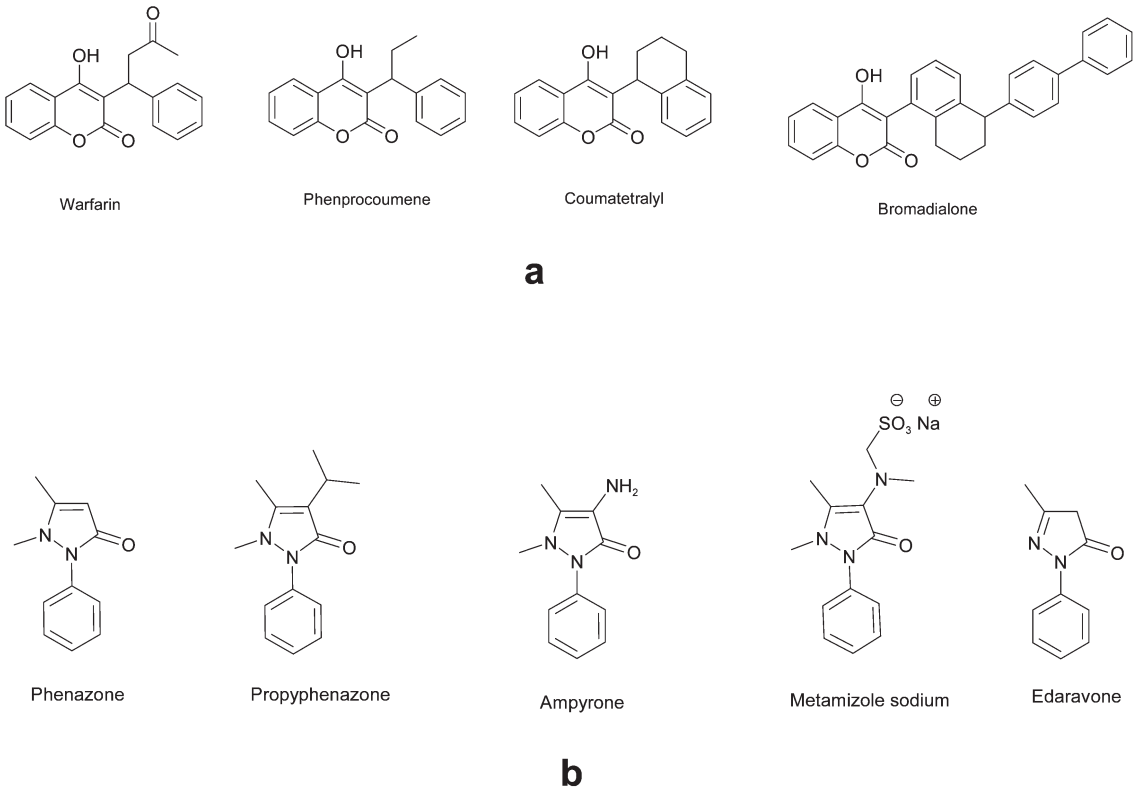
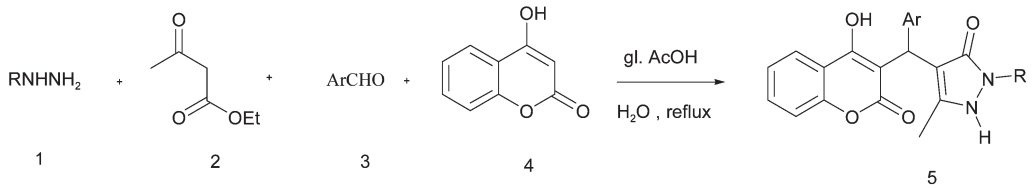


Fig. 1 (a) Some biologically active 3-substituted coumarin; (b) bio-active pyrazolone moieties.



Scheme 1 Green synthesis of benzylpyrazolyl coumarins.

Result and discussion

To recognize the optimization of the reaction conditions, the reaction was studied by employing a series of catalysts and solvents as well as under solvent-free conditions with the hope to maximize the product yield in short reaction times (Table 1). Initially, phenyl hydrazine (1.0 mmol), ethyl acetoacetate (1.0 mmol), 3-nitrobenzaldehyde (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol) were refluxed in the presence of H_2O and ethanol as the solvent without any catalyst, however, the reaction, even after 24 h, failed to afford any product (Table 1, entries 1 and 2). Then the reaction was carried out in water in the presence of *p*-toluenesulphonic acid (PTSA) under reflux conditions and the product was isolated in 26% yield (Table 1, entry 3). The reactions were also restrained by using trifluoroacetic acid (TFA), trifluoro methanesulphonic acid (TfOH) and formic acid as the catalyst (Table 1, entries 4, 5 and 6). Lewis acid catalysts, such as $Cu(OAc)_2$ and $InCl_3$ were tested but did not promote the reaction (Table 1, entries 7 and 8), while the use of nano crystalline ZnO as a catalyst in aqueous media provided a trace amount of the desired product (Table 1, entry 9). We then applied glacial acetic acid (AcOH) (10 mol%) as catalyst in water, eventually we achieved satisfaction because the reaction proceeded well, affording the desired product in 94% yield within 40 min (Table 1, entry 10). AcOH played a key and amazing catalytic role in this particular MCR in comparison to other organic acids applied, which can be attributed to its low acidity, marked solvent character (towards polar organic substrates and reagents), high tunability of solvent (water) polarity and the created ambient conditions which optimized the reaction purity, yield and speed for the reaction to proceed.

Taking glacial acetic acid (AcOH) as the right catalyst for the experiment, we then concentrated our attention on designing and also generalizing the favorable conditions for the reaction. We firstly attempted some screening tests with glacial AcOH. The quantity of the catalyst had a large effect on the formation of the desired product. The use of 5 mol% glacial AcOH diminished the quantity of the yield, whereas the yield of the product also decreased when we used 15 mol% glacial AcOH (Table 1, entries 11 and 12). Water (Table 1, entry 10) showed superiority

Table 1 Screening of catalyst and solvents and reaction conditions

Entry	Catalysts	Solvent	Condition	Time (h)	Yield[a,b] (%)
1	—	H_2O	Reflux	24	—[c]
2	—	EtOH	Reflux	24	—[c]
3	PTSA (10 mol%)	H_2O	Reflux	24	26
4	TFA (10 mol%)	H_2O	Reflux	24	23
5	TfOH (10 mol%)	H_2O	Reflux	24	22
6	HCOOH (10 mol%)	H_2O	Reflux	24	41
7	$Cu(OAc)_2$ (10 mol%)	H_2O	Reflux	24	—[c]
8	$InCl_3$ (10 mol%)	H_2O	Reflux	24	—[c]
9	Nano ZnO	H_2O	Reflux	24	Trace
10	**Gl. AcOH (10 mol%)**	**H_2O**	**Reflux**	**40 min**	**94**
11	Gl. AcOH (5 mol%)	H_2O	Reflux	40 min	77
12	Gl. AcOH (15 mol%)	H_2O	Reflux	40 min	84
13	Gl. AcOH (10 mol%)	EtOH	Reflux	40 min	68
14	Gl. AcOH (10 mol%)	CH_3CN	Reflux	40 min	32
15	Gl. AcOH (10 mol%)	$CHCl_3$	Reflux	40 min	37
16	Gl. AcOH (10 mol%)	—	110 °C	40 min	46

[a] All reactions were carried out with phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol), 3-nitrobenzaldehyde (1 mmol) and 4-hydroxycoumarin (1 mmol). [b] Yield of isolated product. [c] Reaction failed to provide any product.

to the other solvents tested [ethanol (Table 1, entry 13), acetonitrile (Table 1, entry 14) and chloroform (Table 1, entry 15)], while under the solvent-free conditions (Table 1, entry 16) at 110 °C, AcOH failed to provide satisfactory outputs. Therefore water was chosen as the solvent for this reaction as the maximum yield (94%) was obtained under aqueous conditions. Hence, these optimized conditions were applied for all experiments: taking equimolar amounts of substituted hydrazine (**1**), ethyl acetoacetate (**2**), aromatic aldehydes (**3**) and 4-hydroxy coumarin (**4**) under reflux conditions in the presence of 10 mol% glacial acetic acid in aqueous media (Scheme 1). Typically, a mixture of substituted hydrazine (1.0 mmol), ethyl acetoacetate (1.0 mmol), aromatic aldehydes (1.0 mmol), 4-hydroxycoumarin (1.0 mmol) and 10 mol% glacial acetic acid in 3 ml water was refluxed for 30–55 min, which afforded a library of benzylpyrazolyl coumarin (**5**) derivatives in good to excellent yields (80–94%) (Table 2).

To study the scope and limitations of this protocol, we employed a wide range of aromatic aldehydes. Phenyl hydrazine, hydrazine hydrate and *p*-nitrophenylhydrazine are also applied for developing the pyrazolone ring with ethyl acetoacetate to access the corresponding benzylpyrazolyl coumarin derivatives. The reaction proceeded smoothly and provided excellent yields and tolerated unsubstituted benzaldehydes, and also electron-withdrawing and electron-donating *para*-substituted benzaldehydes. The reactions were consistently carried out at the 1 mmol scale and no change of product yield was observed when scaled up to the 10 mmol scale. From the context of green chemistry, it was positive to find that the final products could be isolated by filtration due to their lower solubility in the glacial acetic acid–water mixture. Furthermore, their purity was too high to require their preparation in an analytically pure form by single recrystallization, thus avoiding extraction steps and chromatographic separations. Therefore, we preferred water as the reaction medium over unsafe organic solvents which decrease the chemical impurity, easy work-up procedure and produce large volumes of waste from the discarded chromatographic static phases. The structure of the final products were well characterized by using spectral (IR, ^1H, ^{13}C NMR and HRMS) and elemental analysis data (ESI†). The structural motif was fully established by single X-ray crystallographic analysis of one signified compound **5d** (Fig. 2).[22] Compound **5d** (CCDC 886519†) crystallized in the monoclinic *P*2(1)/*n* space group with two molecules in the asymmetric unit, and formed a heterochiral dimer synthon by intermolecular H-bonding, such as CH···O and aromatic CH···π interactions between *R*- and *S*-molecules in the solid state (Fig. 3). Weak interactions (such as CH···O, NH ···O and aromatic CH···π interactions) were also observed, extending the structure into an infinite chain along the *b*-direction by *R*-molecules (Fig. 4) only and for *S*-molecules (Fig. 5) in the unit cell.

Presumably, the four-component reaction seems to proceed following the mechanistic pathway presented in Scheme 2. Initially, aryl hydrazine/hydrazine hydrate is reacted with ethyl acetoacetate to generate the pyrazolone ring (**I**). Additionally, glacial acetic acid catalyzed the Knoevenagel reaction between 4-hydroxycoumarin and aromatic aldehyde to form the Knoevenagel product (**II**). Subsequently, during the Michael addition step, nucleophilic attack on (**II**) by the tautomeric form of pyrazolone (**I**) afforded the desired product (**5**) *via* intermediate (**III**). Alternatively, there is another possible reaction pathway for the reaction, *via* the formation of intermediate (**IV**) followed by reaction with 4-hydroxycoumarin to afford **5**. We tried to isolate intermediate (**IV**) from the two-component reaction between pyrazolone (**I**) and *m*-nitrobenzaldehyde and the three-component reaction of phenyl hydrazine, ethyl acetoacetate and *m*-nitrobenzaldehyde in presence of glacial acetic acid in water, and found that bis-pyrazolone (Fig. 7(ii))was formed. We also attempted a reaction between 4-hydroxycoumarin and *m*-nitrobenzaldehyde, where bis-coumarin (Fig. 7(i)) was formed instead of intermediate (**II**). These results revealed that intermediates (**II**) and (**IV**) were both very reactive towards the subsequent reaction with pyrazolone and 4-hydroxycoumarin respectively. Hence information on the relative rates of formation, as well as further reactions of (**II**) and (**III**) with pyrazolone or 4-hydroxycoumarin respectively, could not be obtained and evaluated. Therefore, information on whether the multicomponent reactions proceeded

Table 2 Substrates scope for the synthesis of benzylpyrazolyl coumarins (**5**)

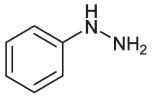
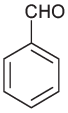
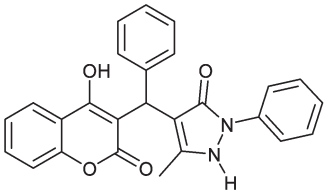
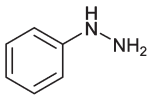
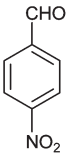
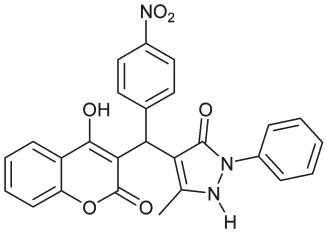
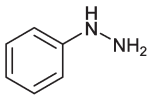
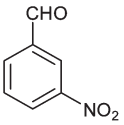
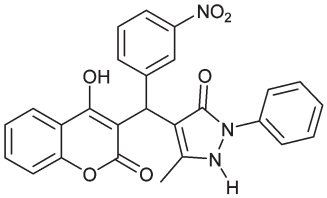
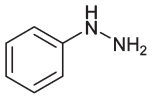
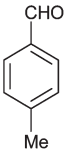
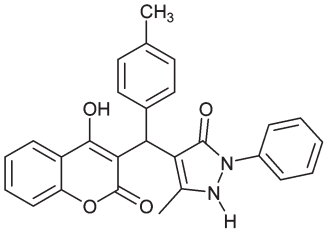
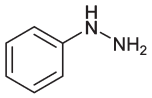
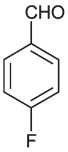
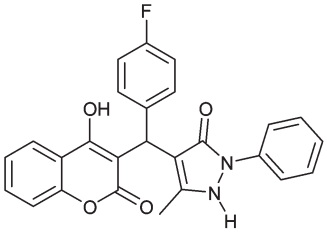
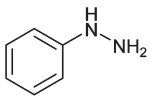
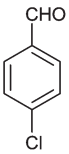
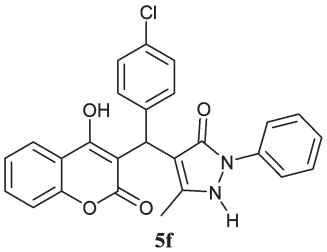
Entry	Hydrazines	Aldehydes	Product	Time (min)	Yield[a] (%)
1			 **5a**	30	93
2			 **5b**	35	92
3			 **5c**	40	94
4			 **5d**	45	92
5			 **5e**	40	93
6			 **5f**	45	93

Table 2 *(Contd.)*

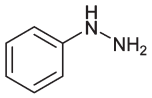
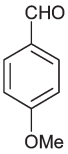
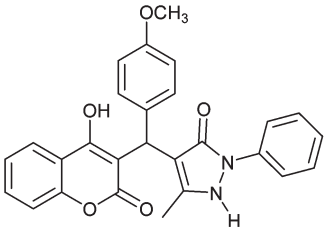
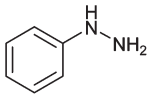
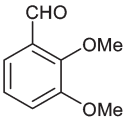
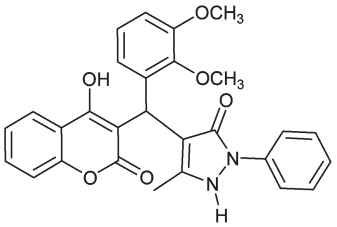
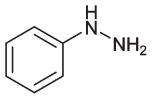
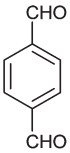
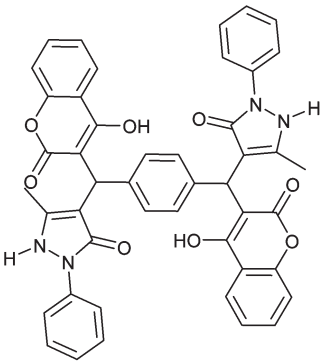
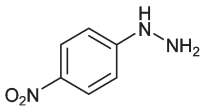
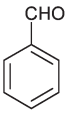
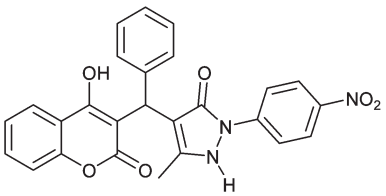
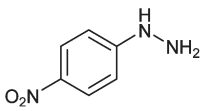
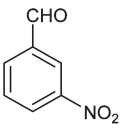
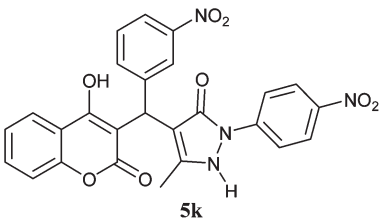
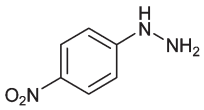
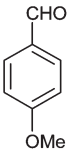
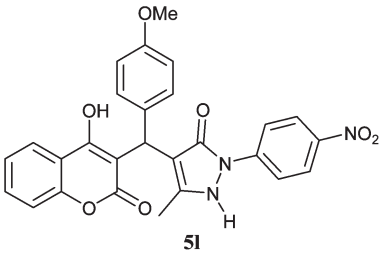
Entry	Hydrazines	Aldehydes	Product	Time (min)	Yield[a] (%)
7			 **5g**	45	90
8			 **5h**	50	89
9			 **5i**	55	88
10			 **5j**	45	86
11			 **5k**	50	83
12			 **5l**	55	80

Table 2 *(Contd.)*

Entry	Hydrazines	Aldehydes	Product	Time (min)	Yield[a] (%)
13	$H_2N^{NH_2}$	CHO	**5m**	35	91
14	$H_2N^{NH_2}$	CHO, NO_2	**5n**	30	90
15	$H_2N^{NH_2}$	CHO, OMe	**5o**	40	90

[a] Yield of the isolated product.

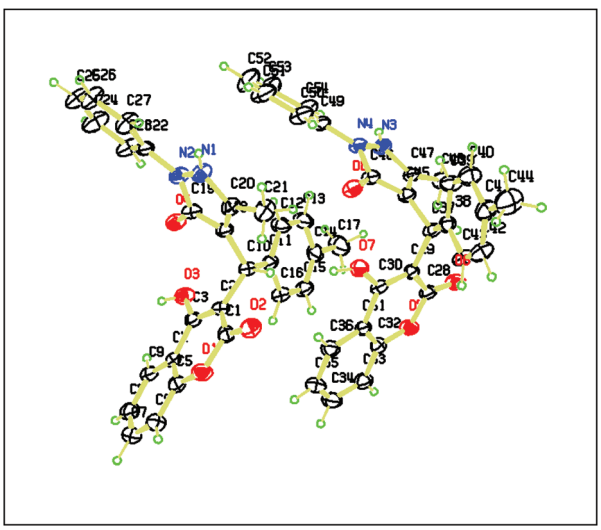


Fig. 2 ORTEP diagram of the single crystal of compound **5d**: CCDC 886519.†

through intermediate (**II**) or (**IV**) could not be ascertained in the current study.

It is pertinent to mention here that after completion of the reaction, tautomerisation occurred in the pyrazolone ring of **5**, and it may exist in three tautomeric forms, *viz.* the CH, OH and NH forms (Fig. 6) as reported[23] previously, but we observed that tautomerisation occurred only in the NH form, which was established through ^{1}H NMR and the X-ray crystallographic study.

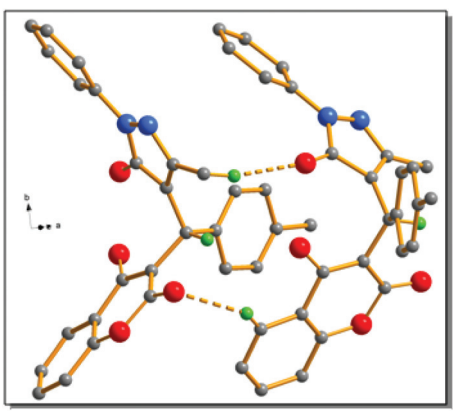


Fig. 3 The intermolecular H-bonds in the asymmetric unit between *R*- and *S*-molecules. All hydrogens, except those participating in H-bonding have been omitted for clarity.

We can conclude that the reaction is very product-selective, affording only benzylpyrazolyl coumarins (**5**), bis-coumarin, bis-pyrazolone and their annulated products (Fig. 7) were not observed at all in this reaction.

Conclusion

In conclusion, a highly product-selective and chromatography-free four-component reaction protocol was developed in the presence of glacial acetic acid in water under mild reaction conditions which afforded highly potent benzylpyrazolyl coumarin

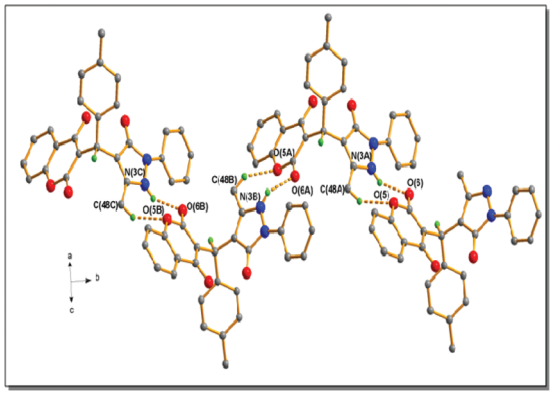


Fig. 4 The intermolecular H-bonds among the *R*-molecules. All hydrogens, except those participating in the H-bonding have been omitted for clarity. Symmetry codes: A 1.5 − *x*, −0.5 + *y*, 1.5 − *z*. B *x*, −1 + *y*, *z*. C 1.5 + *x*, −1.5 + *y*, 1.5 − *z*.

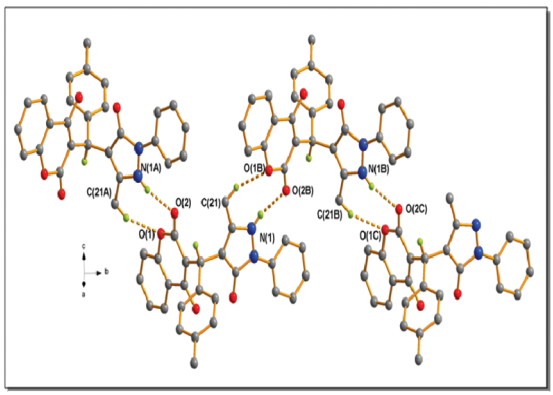
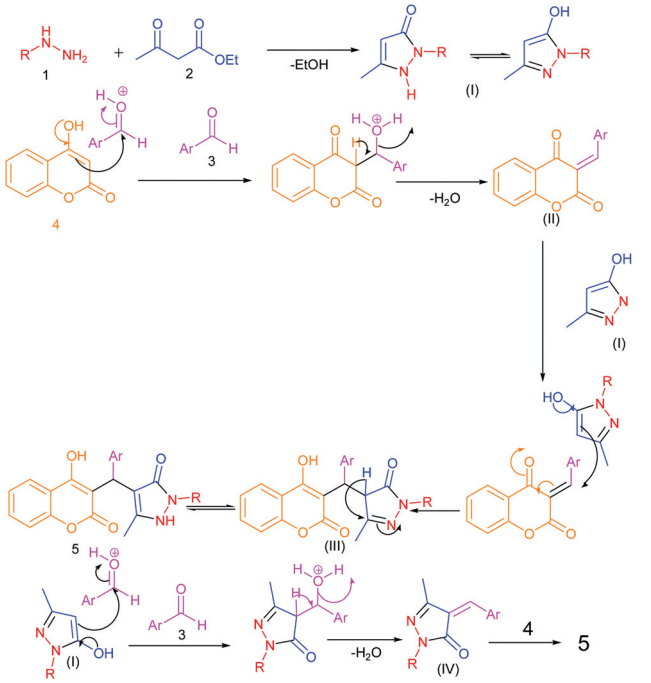


Fig. 5 The intermolecular H-bonds among the *S*-molecules. All hydrogens, except those participating in the hydrogen bonds have been omitted for clarity. Symmetry codes: A 0.5 − *x*, −0.5 + *y*, 1.5 − *z* B *x*, 1 + *y*, *z*, C 0.5 − *x*, 0.5 + *y*, 1.5 − *z*.

scaffolds in good to excellent yields. Several green chemistry principles were included for the development of the combinatorial libraries: it is a one-pot multicomponent reaction offering only ethanol and water as the byproducts. The one representative molecular structure was investigated by means of X-ray diffraction analysis.

Experimental procedure

To a mixture of 10 mol% glacial acetic acid and 5 ml water, hydrazine **1** (1 mmol), ethyl acetoacetate **2** (1 mmol), aromatic aldehyde **3** (1 mmol) and 4-hydroxycoumarin **4** (1 mmol) were added and heated to reflux. The resulting clear solution, that gradually became turbid, was stirred for the stipulated time mentioned in Table 2. After completion of the reaction (indicated by TLC), the free flowing solid was filtered and washed with water (10 ml) to afford the desired products as pale yellow solids. The product thus obtained was recrystallized from ethanol to get pure compounds as white or pale yellow crystals. The isolated compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS, elemental analysis and an X-ray crystallographic study.



Scheme 2 Plausible mechanism for the formation of benzylpyrazolyl coumarins.

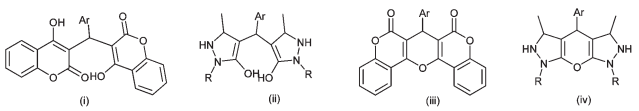


Fig. 7 Bis-coumarin (i), bis-pyrazolone (ii) and their annulated products (iii and iv)

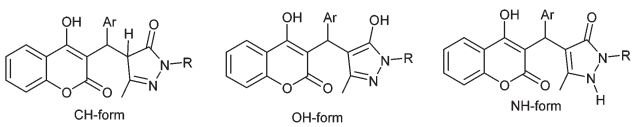


Fig. 6 Three tautomeric forms of benzylpyrazolyl coumarin.

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