

Cite this: *RSC Adv.*, 2019, 9, 3755

# An efficient, mild and metal free L-proline catalyzed construction of fused pyrimidines under microwave conditions in water†

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One-pot condensation of 4-hydroxy coumarins, aldehydes and urea/thiourea to build C–C and C–N bonds is described. Fused pyrimidines have been synthesized under mild reaction conditions using L-proline. The protocol has been performed rapidly and efficiently in water under metal free conditions. Heterocyclic derivatives have been synthesized using the present methodology and avoid the use of hazardous solvents over conventional organic solvents. A proposed mechanism could be established for three component reactions. The present study reveals the first case in which L-proline has been explored as a homogeneous catalyst in the synthesis of fused pyrimidines in water under microwave irradiation. This synthesis involves simple workup and acceptable efficiency. The most notable feature of this protocol is the ability of the catalyst to influence asymmetric induction in the reaction.

Received 9th September 2018

Accepted 10th January 2019

DOI: 10.1039/c8ra07517d

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## 1. Introduction

Multicomponent reactions (MCRs) have high efficiency and are a tool for development of different scaffolds for synthesis of many active drugs.<sup>1,2</sup> In modern organic chemistry, the development of environmentally benign procedures in chemical and pharmaceutical industries has become a crucial and demanding research area. MCRs offer several advantages such as one-pot rather than multi-step synthesis of target compounds, and avoiding unnecessary expensive purification, toxic reagents and solvents.<sup>3</sup> Proline is a chiral organo-catalyst having advantages over other catalyst such as being inexpensive, efficient and readily available.<sup>4</sup> Proline act as an acid or a base which catalyzes chemical transformations similar to enzymatic catalysis.<sup>5</sup> L-Proline has been effectively used in various organic transformations,<sup>6,7</sup> direct catalytic asymmetric

aldol, Mannish and Michael.<sup>8–10</sup> Polysubstituted heterocyclic *ortho*-quinones,<sup>11</sup> pyridines,<sup>12</sup> acridine derivatives,<sup>13</sup> pyrans and thiopyrans,<sup>14</sup> and quinolines.<sup>15</sup>

Coumarin moieties are involved in plants<sup>16</sup> and showed anticoagulation, antiviral,<sup>17</sup> anti-inflammatory,<sup>18</sup> antibacterial<sup>19</sup> and anticancer<sup>20</sup> activities. Fused pyrimidines,<sup>21</sup> chomenopyrimidine,<sup>22</sup> and pyrimidines have also been reported as having anti-viral, anti-tumor, anti-inflammatory, and antihypertensive activities,<sup>23–25</sup> as well as being calcium channel modulators<sup>26</sup> and antimicrobial agents.<sup>27–29</sup> Coumarin derivatives (Fig. 1A) have become drugs such as the anticoagulants warfarin,<sup>30a</sup> acenocoumarin,<sup>30b</sup> and phenprocoumon,<sup>30c</sup> all acting as vitamin K antagonists, the choleretics armillarisin A,<sup>31a</sup> hymecromone (umbelliferone),<sup>31b</sup> and the antibiotic novobiocin<sup>32</sup> which is a potent inhibitor of bacterial DNA gyrase (GyrB). Some drugs such as Lamivudine,<sup>33a</sup> Raltegravir,<sup>33b</sup> Imatinib,<sup>34a,b</sup> Erlotinib<sup>34c,d</sup> and Lapatinib<sup>35</sup> are types of drugs with pyrimidine core (Fig. 1B).

Thus as part of our research aimed at development of synthetic methodologies using environmentally benign catalysts through MCRs,<sup>36</sup> we wish to report herein a metal free efficient and facile protocol for the three-component synthesis of fused pyrimidines in the presence of L-proline as an organo-catalyst in water at 70 °C, accompanied by moderate to good enantioselectivity (Scheme 1).

## 2. Materials and methods

### 2.1 Experimental

All reagents such as L-proline, 4-hydroxy coumarin, aldehydes *etc.* were analytical grade and have more than 98% purity. <sup>1</sup>H

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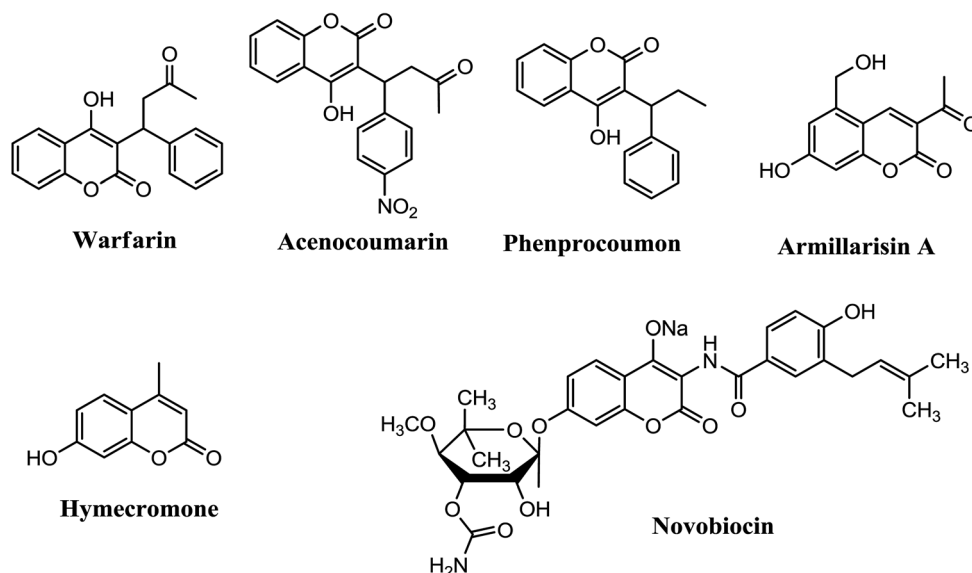
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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra07517d

A



B

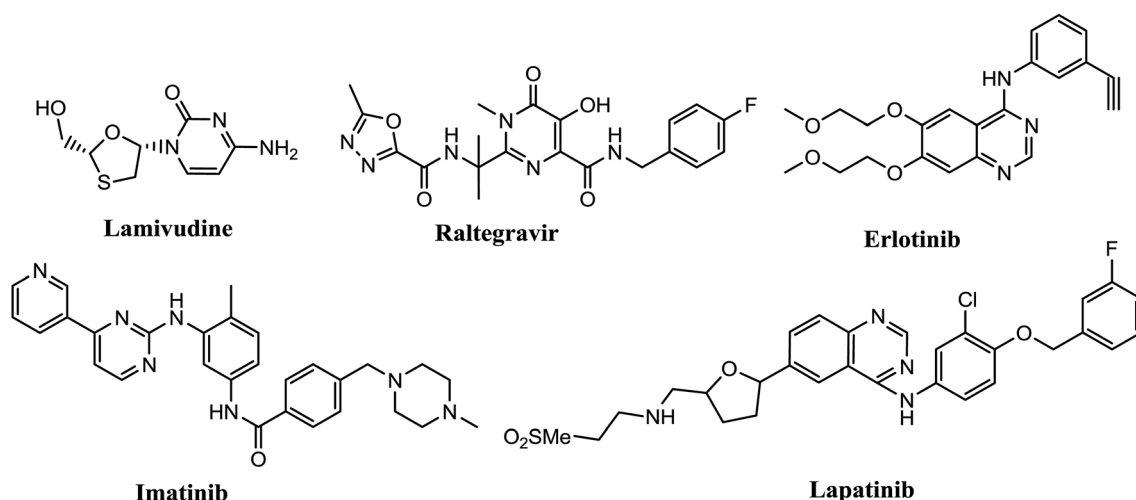


Fig. 1 Some drugs with coumarin and pyrimidine core.

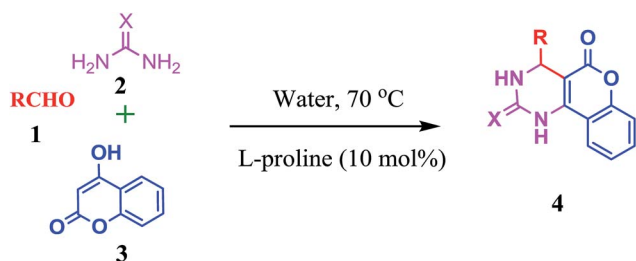
and  $^{13}\text{C}$  NMR spectra were recorded on BRUKER AVANCE II 500 NMR spectrometer using  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  as solvent. Purity of the compound was checked by TLC. MS 1927 microwave starter kit was used for microwave reactions. Reaction was carried out under microwave conditions at 300 W

in open to air conditions. E-Merck precoated TLC plates, RANKEM silica gel G for preparative thin-layer chromatography were used. Melting points were determined in open capillary and are uncorrected.

Table 1 Optimization of solvents<sup>a</sup>

Entry	Solvents	Time (h)	Yield (%)
1	Water	3.0	90
2	Toluene	5.0	40
3	DMF	7.5	41
4	Ethanol	4.0	35
5	Acetonitrile	5.5	40
6	THF	5.0	53

<sup>a</sup> Reaction conditions: 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol) and urea (5 mmol) using L-proline (10 mol%).



Scheme 1 Synthesis of fused pyrimidines.



Table 2 Screening of catalysts<sup>a</sup>

Entry	Catalysts	Time (h)	Yield (%)
1	L-Proline (2 mol%)	8.0	61
2	L-Proline (5 mol%)	4.0	77
3	L-Proline (10 mol%)	3.0	90
4	L-Proline (15 mol%)	3.0	90
5	<i>p</i> -TSA (10 mol%)	10.0	49
6	TEA (10 mol%)	8.0	59
7	CaCl <sub>2</sub> (10 mol%)	10.0	60
8	H <sub>2</sub> SO <sub>4</sub> (10 mol%)	160	70
9	Sulphamic acid (10 mol%)	180	42

<sup>a</sup> Reaction conditions: 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol) and urea (5 mmol) using water.

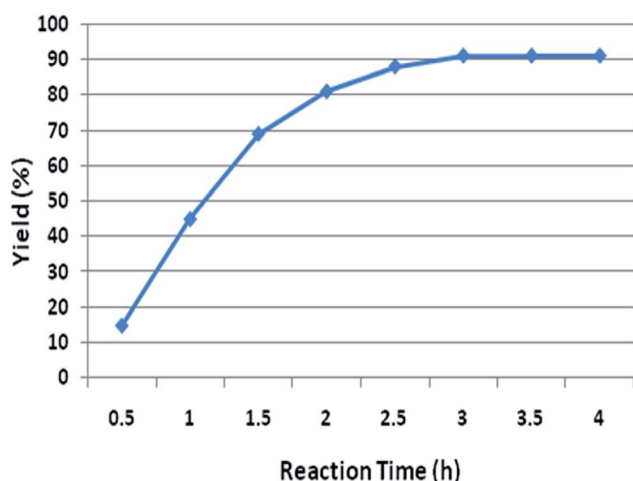


Fig. 2 Comparison of reaction time with respect to yield.

## 2.2 Typical procedure for synthesis

In a 50 mL, 3 necks round bottom flask, charged appropriate aldehydes (5 mmol), 4-hydroxy coumarin (5 mmol) and urea/thiourea (5 mmol), water (10 mL) and L-proline (10 mol%). Stir the reaction mass and reflux at 70 °C. Reaction completion has monitored by TLC analysis. After reaction completion (monitoring by TLC), filtered the solid mass under vacuum then suck dried the solid and solid was recrystallized in ethanol.

## 3. Results & discussion

Initially study has been started with screening of solvents in one-pot reaction 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol) and urea (5 mmol). Reaction was efficiently promoted in water according to screening results as compared to other catalysts (Table 1, entry 1).

Above screening results revealed that the solvent plays a key role in this transformation. For instance, a best yield was obtained when water was utilized as medium (Table 1, entry 1). Nevertheless, when other solvents, such as toluene, DMF, ethanol, acetonitrile and THF were employed, we observed average yield of **4a** even after 7.5 h at 70 °C (Table 1, entries 2–6). Additionally, water is an eco-friendly, cheaper, safe solvent and preferred as medium for clean synthesis. In respect of solvent selection, water has been selected as solvent or aqueous medium. Subsequently, same reaction has been done with different catalysts and results are shown in Table 2. As indicated in Table 2, good yield was obtained in the presence of L-proline (Table 2, entry 3). However, other catalysts (such as *p*-TSA, TEA, CaCl<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, sulphamic acid) have been afforded moderate yield with higher reaction time (Table 2, entries 5–9). In the screening part, we have examined acids, amine and metal salt as catalysts. However, all catalysts showed some activity but were not efficient. L-Proline has dual functionality and both free NH and COOH groups of L-proline are essential for efficient transformation. L-Proline easily form iminium complex, this may be due the fact that protonation of amine moiety of catalyst which subsequent easily react with aldehyde. Protonation of amine may be easily achieved after dipolar structure of acid and amine resultant high yield was obtained due to combine effect of acid and amine moiety. Rest of catalysts have not this dual functionality or nature to catalyze the reaction efficiently results low yield was achieved.

After screening of solvents and catalysts, loading of catalyst has been evaluated in one pot condensation (Table 2, entries 1–4). Screening results have shown that catalyst amount play a crucial role in completion of reaction. Excellent yield was obtained with 10 mol% of L-proline which could not be raised by increasing the catalyst loading. Accordingly, 10 mol% of catalyst loading was acceptable for this transformation. The reaction was then conducted at different time interval, such as

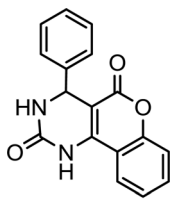
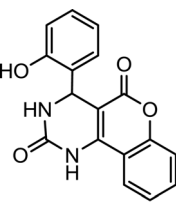
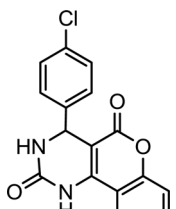
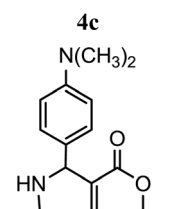
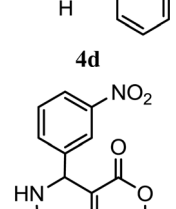
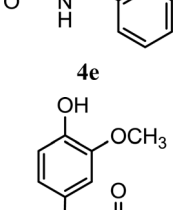
Table 3 Comparison of present methodology with reported catalysts

Entry	Catalyst	Solvent	Conditions	Time (h/min)	Yield (%)	ee <sup>c</sup>	Reference
1	HCl/chloro sulphonic acid	MeOH	60 °C	8.0 h	96	—	37
2	HCl	EtOH	Reflux/MW <sup>a</sup>	12 h	94	—	38
3	HCl	MeOH	Reflux	Overnight	59	—	39
4	Chloro sulphonic acid	—	60 °C/US <sup>b</sup>	30 min	92	—	40
5	HCl	EtOH	Reflux	12 h	74	—	41
6	HCl/silica gel/acidic alumina/montmorillonite-K10 clay	MeOH	110 °C/MW <sup>a</sup>	4–6 min	60/83/90/85	—	42
7	K <sub>2</sub> CO <sub>3</sub>	EtOH/H <sub>2</sub> O	Reflux/MW <sup>a</sup>	7 h	53	—	43
8	VCl <sub>3</sub>	Acetonitrile	Reflux	2 h	82	—	44
9	L-Proline	Water	MW <sup>a</sup>	10 min	90	98	Present work

<sup>a</sup> Microwave conditions. <sup>b</sup> Ultrasonication. <sup>c</sup> ee = enantiomeric excess.



**Table 4** Synthesis of library of fused pyrimidines under conventional method and microwave irradiation

Entry	Product	Time (h/min)		Yield (%)		ee%
		CH <sup>a</sup>	MW <sup>b</sup>	CH	MW	
1	 <b>4a</b>	3.0 h	10 min	90	92	98
2	 <b>4b</b>	4.5 h	8.0 min	88	86	89
3	 <b>4c</b>	5.0 h	10 min	83	86	91
4	 <b>4d</b>	4.5 h	10 min	83	85	86
5	 <b>4e</b>	4.5 h	8.0 min	82	81	83
6	 <b>4f</b>	5.0 h	5.0 min	89	87	89

**Table 4** (Contd.)

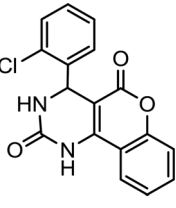
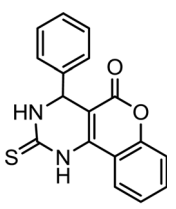
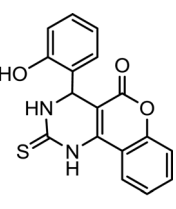
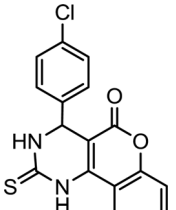
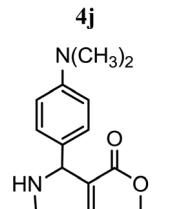
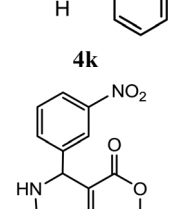
Entry	Product	Time (h/min)		Yield (%)		ee%
		CH <sup>a</sup>	MW <sup>b</sup>	CH	MW	
7	 <b>4g</b>	5.0 h	10 min	89	88	90
8	 <b>4h</b>	5.0 h	10 min	92	91	93
9	 <b>4i</b>	5.0	8.0 min	93	92	96
10	 <b>4j</b>	5.0 h	10 min	92	90	92
11	 <b>4k</b>	5.0 h	10 min	91	92	97
12	 <b>4l</b>	5.0 h	8.0 min	87	85	85



Table 4 (Contd.)

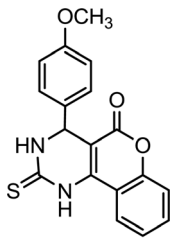
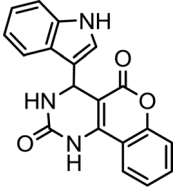
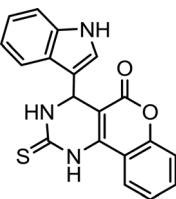
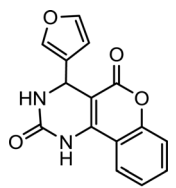
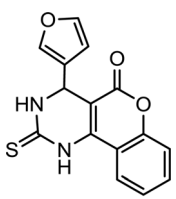
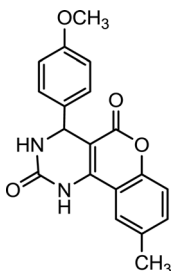
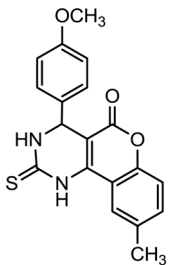
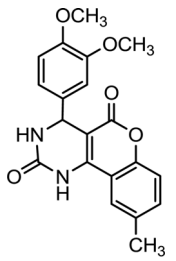
Entry	Product	Time (h/min)		Yield (%)		ee%
		CH <sup>a</sup>	MW <sup>b</sup>	CH	MW	
13		5.0 h	5.0 min	90	88	90
	<b>4m</b>					
14		5.0 h	5.0 min	90	91	91
	<b>4n</b>					
15		5.0 h	8.0 min	79	83	84
	<b>4o</b>					
16		5.0 h	5.0 min	83	85	88
	<b>4p</b>					
17		5.0 h	10 min	83	83	86
	<b>4q</b>					
18		4.5	10 min	80	83	84
	<b>4r</b>					

Table 4 (Contd.)

Entry	Product	Time (h/min)		Yield (%)		ee%
		CH <sup>a</sup>	MW <sup>b</sup>	CH	MW	
19		4.5	10 min	81	82	89
	<b>4s</b>					
20		5.0	10 min	77	81	85
	<b>4t</b>					

<sup>a</sup> CH = conventional heating. <sup>b</sup> MW = microwave conditions.

0.5 h, 1.0 h, 1.5 h, 2.0 h, 2.5 h, 3.0 h, 3.5 h and 4.0 h, to determine the optimum time for this transformation. It can be concluded that after 3 h time interval, highest yield (91%) was obtained (Fig. 2).

There are few reports in literature for synthesis of 3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione/thione derivatives using 4-hydroxy coumarin, aldehydes and urea/thiourea in the presence of homogeneous and heterogeneous catalysts. Reported methods show that researchers have used acids such as HCl<sup>37–39,41,42</sup> and chloro sulphonic acid<sup>37,40</sup> which has drawbacks such as longer reaction time,<sup>37–39,41</sup> harsh reaction conditions such as ultrasonication used,<sup>38,40,42,43</sup> higher temperature (60 °C, 110 °C and reflux), hazardous solvent (MeOH, EtOH and ACN)<sup>37–39,41–44</sup> and often lower yield.<sup>39–43</sup> Although the ultrasonication technology has been shown feasible on a small scale, the commercialization of sonolysis is still a challenge due to its high energy requirement.<sup>45</sup> On the other hand, vanadium chloride has been used as catalyst<sup>44</sup> with lower yield, hazardous solvent (ACN) and higher temperature. Many studies have been revealed that exposure of vanadium may cause respiratory dysfunction,<sup>46</sup> hematological and biochemical alterations, and renal toxicity<sup>47</sup> reproductive and developmental toxicity immunotoxicity, mutagenicity<sup>48</sup> and neurotoxicity may also occur.<sup>49</sup> All above reported methods have at least one mentioned drawback resultant there is need to develop a methodology



which remove all drawback in a single procedure. It is important to note that the previous above methods reported in the literature do not show any asymmetric induction, however target compound has a chiral centre. To solve this problem, L-proline was used as enantioselective organocatalyst in water as environmental benign solvent under microwave conditions and shown good enantioselectivity. Several advantages offered by this method such as its generality, simplicity, high yields and environmental friendly solvent used (Table 3).

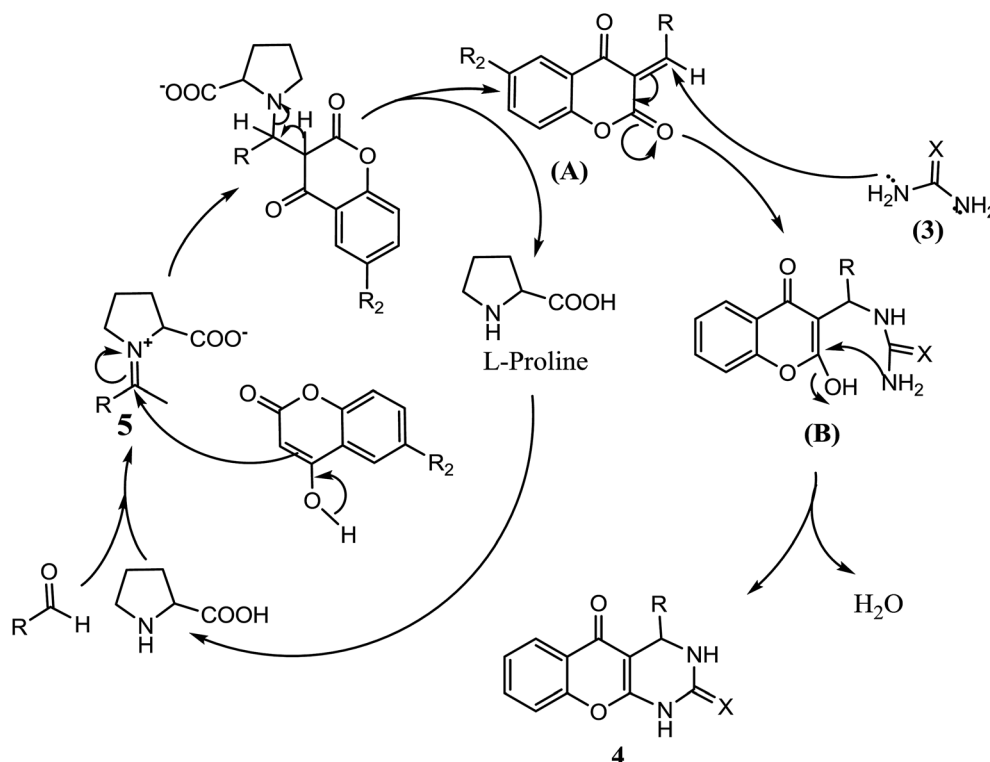
To explore the catalytic activity of L-proline, the scope the present methodology has been applied in the synthesis of various substituted fused pyrimidines. Different electron donating and electron withdrawing substituents have been investigated and results are incorporated in Table 4. From Table 4, the reaction was performed smoothly with *para* substituents and synthesized compounds have been characterized by spectroscopic analysis. Copy of all  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra is placed in the ESI† and confirmed the proposed structure of heterocycles.

Energy transfer depends on the thermal conductivity which is relatively slow and insufficient upon conventional heating resultant higher reaction time is required for completion of reaction. In contrast, microwave conditions are required minimum time to complete the reaction. Apart from this, the advantages of numerous microwave (MW) induced reactions over conventional reactions, and their utility in organic synthesis, have been fully recognized in the last two decades.<sup>50</sup> To minimize the reaction time, reaction has performed under microwave conditions. The results showed that reaction has completed within 5–10 minutes with good yield under

microwave conditions as compared to conventional heating. Therefore, microwave irradiation reducing the reaction time with good enantioselectivity (Table 4). The enantiomeric excess of the compounds synthesized was determined by employing chiral HPLC using OD-H column. Excellent enantioselectivity upto 98% ee was obtained (Table 4, entry 1). For the rest of the compounds enantiomeric excess was found to be in the range of 83% ee to 97% ee. It is important to note that the previous methods reported in the literature do not show any asymmetric induction (Table 3).

Synthesized compounds **4a–4t** were confirmed by spectroscopic analysis.  $^1\text{H}$  NMR of compound **4a** showed characteristic signal at  $6.36\delta$  as singlet due to 4-H, multiplet for nine hydrogens of aromatic rings in the downfield region between  $7.09$ – $7.39\delta$  and two singlet has been arisen at  $7.60$  and  $7.90$  for  $-\text{NH}$ . Likewise derivatives **4d**, **4k** and **4f** demonstrated the singlet at  $3.11\delta$  for six hydrogens of  $\text{N}(\text{CH}_3)_2$  and singlet at  $3.73\delta$  for  $\text{OCH}_3$  respectively.  $^{13}\text{C}$  NMR of compound **4a** showed characteristic signal at  $36\delta$  for C-1 carbon, signal at  $104$  has been assigned for C-2 carbon, other characteristic signal for ketonic carbon (C-4 and C-11) exhibited at  $164\delta$  and  $165\delta$ . Derivatives **4d**, **4k** and **4f** have been showed characteristic signal at  $45$  and  $56\delta$  for  $-\text{N}(\text{CH}_3)_2$  and  $\text{OCH}_3$  group. Mass spectra as well as elemental analysis also confirmed the structure of final product.

A plausible mechanism for reaction of 4-hydroxy coumarin (**1**), aldehydes (**2**), and urea/thiourea (**3**) to synthesis of fused pyrimidines (**4**) is depicted in Scheme 2. Based on literature, L-proline having dual functionality as acid and base can catalyze aldol related reactions such as Knoevenagel condensation as well as Michael addition.<sup>51</sup> Previous study has shown that



Scheme 2 Plausible reaction mechanism.





Knoevenagel condensation reaction efficiently catalyzed by amino acid catalyst and supports present mechanistic pathway.<sup>52</sup> The reaction presumably proceeds through initial activation of the aldehyde by L-proline to form an iminium complex<sup>53</sup> which further facilitates the Knoevenagel condensation to produce intermediate which pursue by Michael addition of urea/thiourea (3) on double bond of intermediate (A) to form intermediate (B). Furthermore, carbonyl and amino corner of the Michael adduct B was condensed through intramolecular cyclization to give desire target (4).

To support the plausible mechanism, proposed reaction intermediate (A) has been isolated and characterized. First of all reaction of 4-hydroxy coumarin and 2-hydroxy benzaldehyde has been carried out in optimized reaction conditions and formed the intermediate (A). Further intermediate (A) has been isolated and characterized by <sup>1</sup>H and <sup>13</sup>C NMR. Characterization data and literature have also been supported the structure of intermediate (A).<sup>54</sup> Then isolated intermediate (A) was react with third component (urea) and achieved the product (4b). Present investigation has confirmed proposed mechanistic pathway by which target compound was achieved.

## 4. Conclusions

In conclusion, an enantioselective and metal free L-proline catalyzed protocol for the synthesis of fused pyrimidines with good yield in water as a green solvent using urea/thiourea, aldehydes and 4-hydroxy coumarin. Environmental benign one pot strategy has been explored with L-proline successfully which generate a green platform in future for enantioselective synthesis of novel molecules in water. Operational simplicity, metal-free approach, compatibility with various aldehydes and 4-hydroxy coumarin, simple se of workup, neat and clean synthesis are notable advantages of this protocol. In term of green solvent, an environmental benign solvent *i.e.* water was used which is very inexpensive and having reactivity and selectivity toward reaction media. Most notable feature of this methodology is enantioselective synthesis with more than 98% ee.

## Conflicts of interest

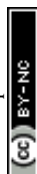
There are no conflicts to declare.

## Acknowledgements

Authors are grateful thanks to the IPC Ghaziabad, India for performing <sup>1</sup>H and <sup>13</sup>C NMR spectra.

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