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Molecular diversity from the three-component reaction of 2-hydroxy-1,4-naphthaquinone, aldehydes and 6-aminouracils: a reaction condition dependent MCR†

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The three-component reaction of 2-hydroxy-1,4-naphthaquinone, aldehydes, and 6-aminouracil derivatives in acetic acid/water (1 : 1; v/v) under microwave heating conditions provides 1,4-dihydropyridines fused with naphthaquinone and pyrimidines. On the other hand the same reaction combinations under conventional reflux conditions provide acyclic trisubstituted methane derivatives. Using these tuneable reaction conditions a series of polycyclic fused N-heterocycles has been synthesized. The notable features of this methodology are a simple metal-free one-pot operation, easy purification process, use of the green solvent water, short reaction time and good to moderate yields of the products.

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Introduction

One-pot multicomponent reactions (MCRs) have emerged as an efficient tool for benign synthesis of functionalized heterocycles by virtue of their convergence, productivity, facile execution, and generation of highly diverse and complex products from easily available starting materials in a single operation.¹ MCRs are very useful to access “privileged medicinal scaffolds”, especially, for synthesizing various N-heterocyclic compounds which are key constituents of a wide range of both natural and synthetic bioactive compounds.^{2,3} Microwave assisted multi-component reactions have drawn remarkable attention from organic and medicinal chemists considering their green features. MW irradiation provides enhanced reaction rates, higher yields of products, better selectivity, rapid optimization of reactions and several ecofriendly advantages.⁴ Further, in comparison with organic solvents, water is a non-toxic, non-corrosive, non-explosive and is readily available solvent. These properties along with the network of hydrogen bonds, large surface tension, high polarity and high specific heat capacity make it both economical and environmentally friendly and thus suitable as a green solvent.^{5,6} According to the current synthetic requirements and from green perspective, environmentally benign multicomponent procedures employing microwave methodology in aqueous medium are particularly welcome.

Polycyclic fused N-heterocycles have attracted much attention due to their presence in biologically active natural products and pharmaceuticals. They display a wide range of biological activities such as antifungal, antibacterial, antineoplastic, anti-cancer, antiplasmodial, and as DNA intercalators.⁷ The presence of several functional groups in one molecule often proves useful to find better bioactivities of compounds. Further, literature survey shows that fused polycyclic N-heterocycles containing naphthaquinone,^{8–10} 1,4-dihydro pyridine^{11–13} and pyrimidine¹⁴ moieties are important in discovering new bioactive compounds due to their fascinating molecular structure and remarkable pharmacological efficiency. This class of building blocks are useful for treating Alzheimer’s disease¹⁵ and also exhibit anti-tumor,¹⁶ antimicrobial,¹⁷ anti-diarrhea,¹⁸ and

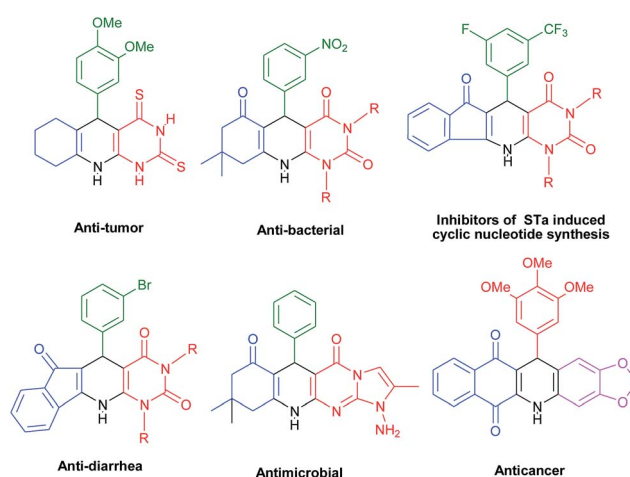


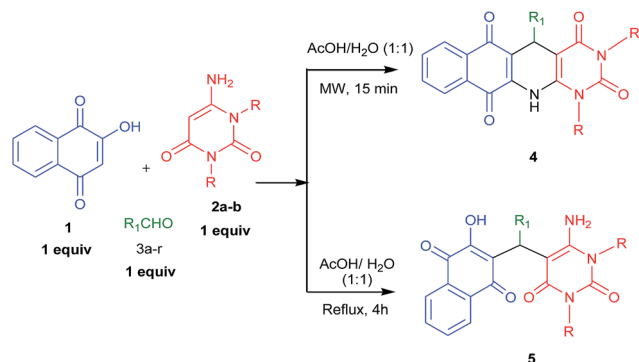
Fig. 1 Examples of pharmaceutically important fused polycyclic N-heterocycles and their activities.

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Scheme 1 Formation of 4 and 5 in different reaction conditions from the three component reactions.

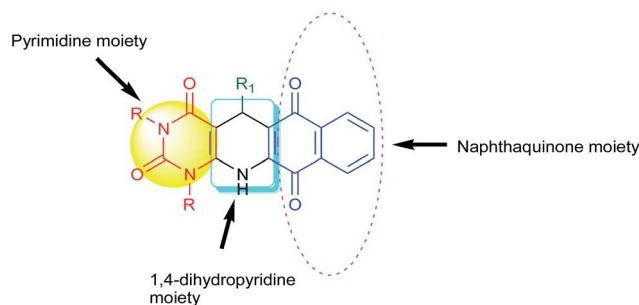


Fig. 2 Product having three important bioactive moieties.

anti-cancer activities.¹⁹ Some of the pharmacologically active fused polycyclic N-heterocycles are shown in Fig. 1.

6-Aminouracil is considered as a very popular and useful starting material for the synthesis of heterocyclic scaffolds

using multicomponent reaction.²⁰ Recently various research groups have explored 6-amino uracil in multicomponent reactions to construct fused heterocycles.²¹

Considering the importance of fused polycyclic N-heterocycles having naphthaquinone, 1,4-DHP and pyrimidine moieties in pharmaceutical and chemical domains, and also as a part of our continuous effort on the synthesis of highly functionalized or fused heterocycles,^{22–24} we turned our attention to design a three component reaction of 2-hydroxy-1,4-naphthaquinone (1), 6-aminouracils (2) and aldehydes (3). In acetic acid/water (1 : 1) under reflux conditions we ended with acyclic products 5 (Scheme 1). Interestingly, when we carried out the same reaction under microwaves in acetic acid/water (1 : 1), we ended with fused polycyclic N-heterocycles 4 (Scheme 1). It consists of three important bioactive moieties naphthaquinone, 1,4-dihydropyridine and pyrimidine (Fig. 2).

Results and discussion

For the preliminary investigation, reaction of 2-hydroxy-1,4-naphthaquinone 1, 1,3-dimethyl-6-aminouracil 2a and 4-methyl benzaldehyde 3c was chosen as model reaction. In the presence of acetic acid under the reflux conditions, this combination provided 75% of acyclic product 5ac within 5 h (Table 1, entry 1) and we did not get our desired three component cyclic product 4ac under this reaction conditions. Next, we attempted to get the cyclized product by varying various parameters of the reaction, such as using microwave heating, solvent *etc.* Interestingly, the same model reaction provided 77% yield of the corresponding fused polycyclic N-heterocyclic product 4ac and 12% of acyclic product 5ac, after microwave heating at 130 °C for 15 minutes in acetic acid medium (Table 1, entry 2). The product 4ac was fully characterized by recording

Table 1 Optimization of reaction conditions^a

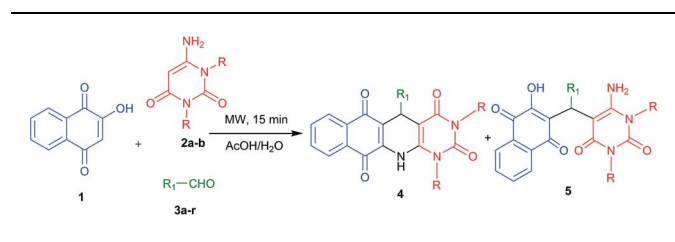
| Entry | Solvent | Reaction conditions | Yield ^b (%) 4ac/5ac | Time (h/min) |
|-------|---------------------------------|---------------------|--------------------------------|--------------|
| 1 | AcOH | Reflux | 0/75 | 5 h |
| 2 | AcOH | MW | 77/12 | 15 min |
| 3 | H ₂ O | MW | 66/15 | 15 min |
| 4 | EtOH | MW | 51/12 | 15 min |
| 5 | DMSO | MW | 0/53 | 15 min |
| 6 | PEG-400 | MW | 0/72 | 15 min |
| 7 | AcOH/H ₂ O (1 : 1) | Reflux | 0/80 | 5 h |
| 8 | AcOH/EtOH (1 : 1) | MW | 76/15 | 15 min |
| 9 | AcOH/H ₂ O (1 : 1) | MW | 90/8 | 15 min |
| 10 | AcOH/DMF (1 : 1) | MW | 56/21 | 15 min |
| 11 | AcOH/CH ₃ CN (1 : 1) | MW | 68/14 | 15 min |
| 12 | AcOH/DMSO (1 : 1) | MW | 48/40 | 15 min |

^a Reactions were carried out in 1.0 mmol scale with 1 : 1 : 1 ratio of 2-hydroxy-1,4-naphthaquinone, 1,3-dimethyl-6-aminouracil and 4-methyl benzaldehyde in 2 ml solvent. ^b Isolated yields.



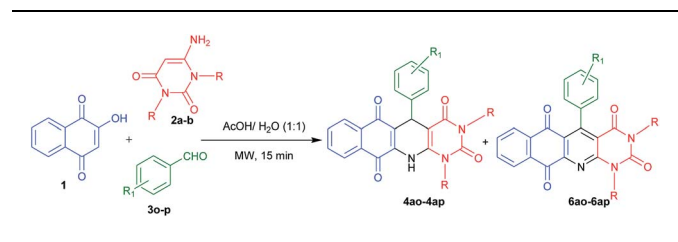
IR, ^1H & ^{13}C NMR as well as HRMS. Encouraged by this positive result, the same set of reaction was performed in various solvents under microwave heating and the results are summarized in Table 1 (entries 3–6). Interestingly, it has been observed that when the reaction was performed in the presence of protic solvents like AcOH, H_2O , and EtOH it gives cyclic product **4ac** as major and acyclic product **5ac** as minor product (Table 1 entries 2–4). But when the reaction was performed in DMSO and PEG-400, only acyclic product **5ac** was observed (Table 1, entries 5 and 6). To further investigate, we also performed the same model reaction using mixed solvent like acetic acid and other solvent (1 : 1) under reflux as well as microwave reaction conditions (Table 1, entries 7–12). Among them, acetic acid/water (1 : 1) under microwave heating was found as optimum reaction conditions in terms of yield obtained (Table 1, entry 9).

In order to explore the scope of this multicomponent reaction, a wide variety of aldehydes **3a–r** were reacted with 2-hydroxy-1,4-naphthaquinone **1** and aminouracil derivatives **2a–b** under the optimized reaction conditions and the results are

Table 2 Scope of the reaction^a

| Entry | R | R ₁ | % yield ^b of 4 | % yield ^b of 5 ^c | |
|-------|-----------------|---|---------------------------|--|---------------|
| 1 | CH ₃ | C ₆ H ₅ | 4aa | 79 | 5aa 13 |
| 2 | CH ₃ | 4-ClC ₆ H ₄ | 4ab | 87 | 5ab 10 |
| 3 | CH ₃ | 4-CH ₃ C ₆ H ₄ | 4ac | 90 | 5ac 8 |
| 4 | CH ₃ | 4-OCH ₃ C ₆ H ₄ | 4ad | 85 | 5ad 10 |
| 5 | CH ₃ | 4-CH(CH ₃) ₂ C ₆ H ₄ | 4ae | 82 | 5ae 12 |
| 6 | CH ₃ | 4-NO ₂ C ₆ H ₄ | 4af | 64 | 5af 32 |
| 7 | CH ₃ | 4-FC ₆ H ₄ | 4ag | 71 | 5ag 25 |
| 8 | CH ₃ | 2-ClC ₆ H ₄ | 4ah | 90 | 5ah — |
| 9 | CH ₃ | 3-BrC ₆ H ₄ | 4ai | 78 | 5ai 18 |
| 10 | CH ₃ | Naphthyl | 4aj | 85 | 5aj — |
| 11 | CH ₃ | 2-OCH ₃ C ₆ H ₄ | 4ak | 92 | 5ak — |
| 12 | H | C ₆ H ₅ | 4ba | 89 | 5ba — |
| 13 | H | 4-OCH ₃ C ₆ H ₄ | 4bd | 91 | 5bd — |
| 14 | H | 4-CH(CH ₃) ₂ C ₆ H ₄ | 4be | 87 | 5be — |
| 15 | H | 4-FC ₆ H ₄ | 4bg | 89 | 5bg — |
| 16 | H | 2-ClC ₆ H ₄ | 4bh | 87 | 5bh — |
| 17 | H | 3-BrC ₆ H ₄ | 4bi | 92 | 5bi — |
| 18 | H | 2-OCH ₃ C ₆ H ₄ | 4bk | 96 | 5bk — |
| 19 | H | 2-CH ₃ C ₆ H ₄ | 4bl | 93 | 5bl — |
| 20 | H | 2,6-DiCH ₃ C ₆ H ₃ | 4bm | 87 | 5am — |
| 21 | H | 4-BrC ₆ H ₄ | 4bn | 87 | 5bn — |
| 22 | H | 4-CNC ₆ H ₄ | 4bo | 78 | 5bo — |
| 23 | CH ₃ | Cyclohexyl | 4aq | — | 5aq 81 |
| 24 | CH ₃ | Butyl | 4ar | — | 5ar 79 |

^a Reactions were carried out in 1.0 mmol scale with 1 : 1 : 1 ratio of 2-hydroxy-1,4-naphthaquinone, 1,3-dimethyl-6-aminouracil and 4-methylbenzaldehyde in acetic acid/water (1 : 1) in microwave. ^b Isolated yields. ^c For full characterization of compounds **5**, please see ref. 22.

Table 3 Scope of the reaction^a

| Entry | R | R ₁ | % yield ^b of 4 | % yield ^b of 6 | |
|-------|-----------------|---|---------------------------|---------------------------|---------------|
| 1 | CH ₃ | 4-CNC ₆ H ₄ | 4ao | 38 | 6ao 52 |
| 2 | CH ₃ | 3-NO ₂ C ₆ H ₄ | 4ap | 35 | 6ap 58 |

^a Reactions were carried out with 1 : 1 : 1 ratio of 2-hydroxy-1,4-naphthaquinone, 1,3-dimethyl-6-aminouracil and 4-methylbenzaldehyde in acetic acid/water (1 : 1) under microwave irradiation. ^b Isolated yields.

summarized in Table 2. It is notable that the characteristics of **2a–b** and **3a–r** had an important influence on the final products. In most of the cases when **2a** was employed, cyclic product **4** was obtained as major and acyclic product **5** as minor product (Table 2, entries 1–7 and 9). However, in the cases of 2-chlorobenzaldehyde **3h**, naphthaldehyde **3j** and 2-methoxybenzaldehyde **3k**, we obtained exclusively cyclic product and

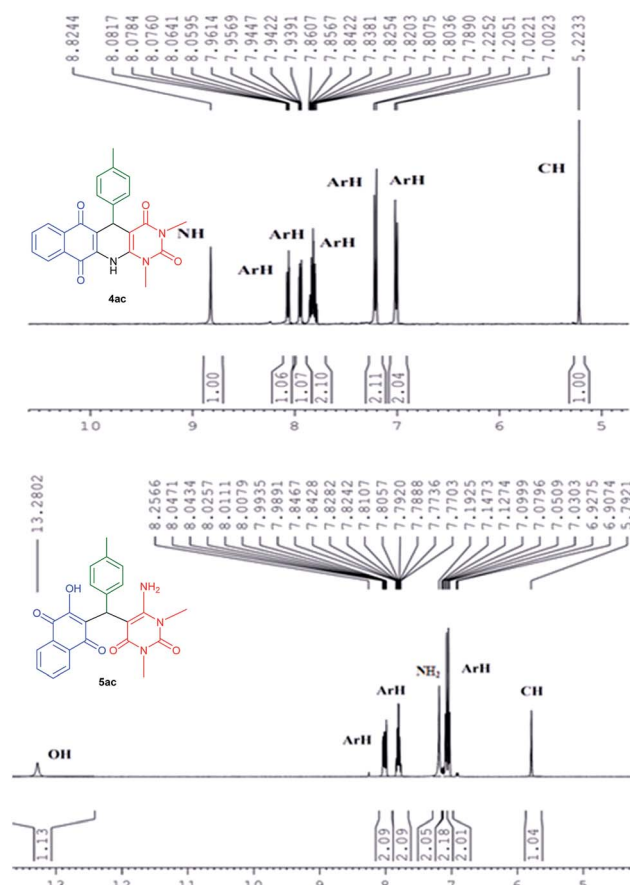


Fig. 3 Comparison of ^1H NMR spectra of cyclic product **4ac** with acyclic product **5ac**.



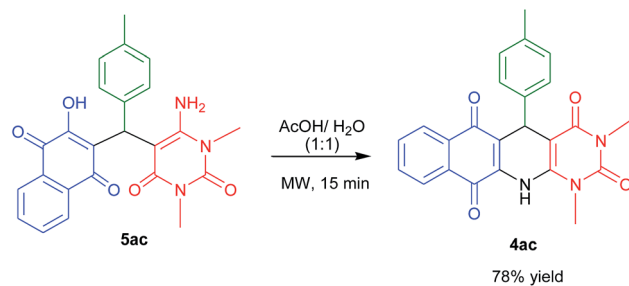
no acyclic product (Table 2, entries 8, 10 and 11) was observed. Further, when 6-aminouracil **2b** was tested with **1** and different substituted aldehydes **3(a, d-e, g-i, k-o)** only cyclic products were observed (Table 2, entries 12–22). Next we examined some aliphatic aldehydes such as cyclohexyl carboxaldehyde **3q** and butyraldehyde **3r**. Unfortunately, they provided acyclic product only (Table 2, entries 23 and 24). However, when 4-cyanobenzaldehyde **3o** and 3-nitrobenzaldehyde **3p** were used, we obtained **6ao** and **6ap** along with **4ao** and **4ap** (Table 3, entries 1 and 2) respectively.

All the products were fully characterized by IR, ^1H NMR, ^{13}C NMR spectroscopy as well as HRMS. The formation of **4** and **5** were ascertained from NMR spectroscopy with compound **4ac** and **5ac** (Fig. 3). As a representative case, ^1H NMR of **4ac** was interpreted by the presence of a singlet at 8.82 for –NH proton, 8.08–7.00 ppm for eight Ar-H protons, and singlet at 5.22 for CH proton. While, ^1H NMR of **5ac** was characterized by the presence of a singlet at 13.28 for –OH proton, 8.26–7.77 and 7.15–6.90 ppm for eight Ar-H proton and two singlets at 7.19 and 5.79 for –NH₂ and –CH protons respectively. From this it is clear that the product **4ac** is the fused polycyclic N-heterocycle whereas the acyclic product is **5ac** where free –NH₂ and –OH groups are present.

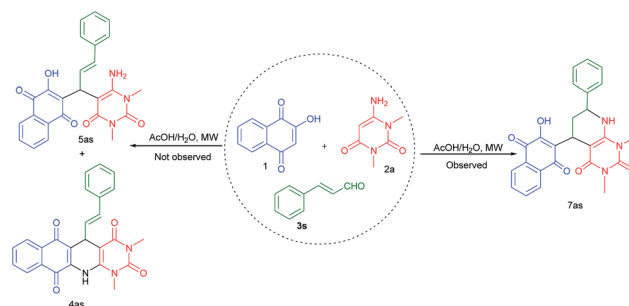
The formation of product **4**, can be explained by the proposed mechanism, as shown in Scheme 2. The reaction is initiated by an acetic acid assisted aldol condensation to provide **A** which transforms to **B** after elimination of water molecule. Then **B** reacts with 6-aminouracil derivatives **2a–b** in a Michael-type fashion and gave **C** which undergoes intramolecular condensation followed by tautomerization to give the corresponding product (**4**).

Next, we attempted to convert acyclic product which we obtained under reflux conditions to the corresponding cyclic products. For that we have treated the acyclic product **5ac** in acetic acid/water (1 : 1) under MW heating for 15 min and the corresponding cyclic product **4ac** was obtained in 78% yield (Scheme 3).

Finally, we explored cinnamaldehyde an α,β -unsaturated aldehyde in this three component reaction under the similar reaction conditions. To our surprise, this aldehyde did not provide expected acyclic product **5as** or cyclic product **4as**, instead of these a novel unexpected cyclic product **7as** was obtained as shown in Scheme 4.



Scheme 3 Synthesis of cyclic product from the acyclic one.



Scheme 4 Synthesis of unexpected product **7as** from the reaction of cinnamaldehyde, 2-hydroxy-1,4-naphthaquinone and **2a**.

Conclusions

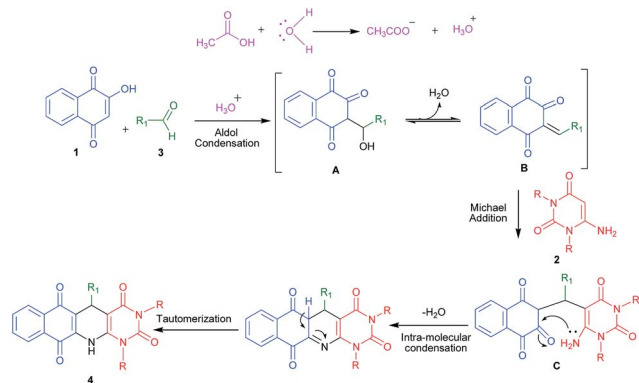
In conclusion, we have demonstrated the effects of reaction conditions on the formation of two types of products from the three-component reaction of 2-hydroxy-1,4-naphthaquinone, aldehydes and 6-aminouracils. This method is a green tool for the synthesis of fused polycyclic N-heterocycles in acetic acid/water under microwave heating. The main advantages of this method are (i) easy purification process of the products avoiding column chromatographic purification, (ii) high atom economy of the reaction (iii) use of water as solvent, (iv) short reaction time, (v) good yields of the products and (vi) environmentally benign procedures. Considering the presence of naphthaquinone and pyrimidine moiety fused with 1,4-DHPs, it is expected that these products will exhibit promising bioactivities.

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Scheme 2 Proposed mechanism.



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