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ORIGINAL PAPER

Straightforward multicomponent synthesis of pyrano[2,3-d] pyrimidine-2,4,7-triones in β-cyclodextrin cavity and evaluation of their anticancer activity

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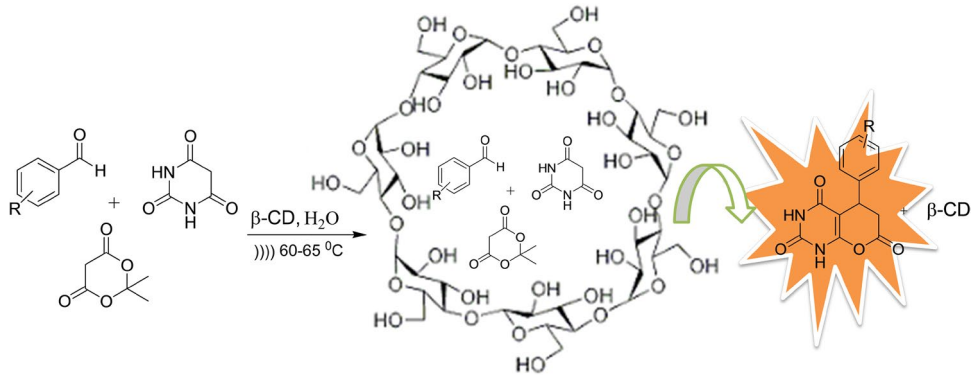
Abstract

In the present study, we have developed an efficient and green method for the synthesis of pyrano[2,3-d]pyrimidine-2,4,7-triones employing β-cyclodextrin as a catalyst in aqueous media from substituted aldehydes, barbituric acid and meldrum acid. The reactions were performed under mild conditions to afford biologically active target molecules in excellent yields. All the synthesized compounds are evaluated for their in vitro anticancer activity against HePG-2 (Human liver cancer cell line) and MCF-7 (Human breast cancer cell line). Among them **4c, 4j, 4k, 4l** and **4m** were active and potent anticancer agents.

Graphical abstract



Keywords Anticancer activity · β-Cyclodextrin · Multicomponent reaction · Pyrano[2,3-d]pyrimidine-2,4,7-triones

Introduction

Cancer being the second foremost cause of death worldwide, a number of experiments have been going on to develop compounds having minor or no side effects. The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry [1–3]. Pyrano[2,3-d]pyrimidine-2,4,7-triones are such active molecules having pyrimidinone as immensely important pharmacophore, owing to their potent antitumor activity [4, 5] in the treatment of B16 melanoma and P388 leukemia [6]. The pyrano-fused pyrimidines have emerged as promising scaffolds because of their broad spectrum of biological activities,

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such as antimicrobial [7–9], antiplatelet [10], antifungal [11], as well as anticonvulsant [12] activities. Compounds which having a uracil moiety in the skeleton of an organic molecule are distinguished themselves as heterocycles of profound chemical and biological significance [13–16]. Barbituric acid or 6-hydroxy uracil is a heterocyclic compound that possesses anti-neoplastic [17], antiviral [18], antibiotic [19], and anti-inflammatory [20] activities. Many synthetic drugs of barbituric acid motif-based derivatives and chemotherapeutic agents are well known (Fig. 1) [12–23].

In this context development of green alternative multicomponent reactions (MCRs) has attracted much attention as these reactions produced important biological scaffolds [24] and various designer as well as marketed drugs in an environment-friendly pathway. Water is the greenest solvent among all and accordingly it has been widely used as the reaction medium for straightforward organic transformations as well as in MCRs [25].

However, few reports have appeared in the literature on the synthesis of pyrano[2,3-d]pyrimidine-2,4,7-triones [27, 28] and no reports are available on its biological screening. With this background and as part of our ongoing program toward the development of greener chemical approaches for the synthesis of biologically relevant intermediates and heterocyclic moieties [29–31], herein, we wish to report a straightforward, efficient, clean, and high-yielding MCR protocol for the one-pot facile synthesis of biologically relevant diverse and densely functionalized 5-aryl-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-triones heterocyclic scaffolds and their anticancer activity.

Experimental

General: all the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz using DMSO solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm Mass spectra were recorded on a Sciex, Model; API 3000 LC–MS/MS Instrument. The purity of each compound was checked by TLC using silica-gel, $60F_{254}$ aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

General procedure for the synthesis of pyrano[2,3 *d*] pyrimidine-2,4,7-triones (4a-r)

A mixture of substituted benzaldehydes (**1a–r**) (4 mmol), meldrum acid (**2**) (4 mmol), barbituric acid (4 mmol) and β-cyclodextrin (20 mol%) in water (15 ml) was subjected to ultrasonication at 65 °C. Progress of the reaction was monitored by thin-layer chromatography. After 60 min, reaction mixture was cooled to room temperature, filtered and washed with hot water. Obtained solid was crystallized by ethanol:DMF.

Synthesized compounds characterized by IR, ^{1}H NMR and are in good agreement with those reported in the literature [27, 28].

Experimental procedure for MTT assays

The stock solutions of test compounds were prepared in DMSO. After 24 h incubation, different concentrations (2, 4, 6, 8 μM) of compounds, made by serial dilution in culture medium, were added in 48 h incubation. The final concentration of DMSO was 0.01% in each well. A separate well containing 0.01% DMSO only was run as DMSO control, which was found inactive under applied conditions. The cell growth was determined using MTT (3-(4,5-dimethylthiazol-2-yl))-2,5-diphenyl tetrazolium bromide (Sigma) reduction assay, which is based on ability of viable cells to reduce a soluble yellow tetrazolium salt to blue farmazan crystal [32, 33]. Briefly, after 48 h of treatments, 10μl of MTT dye, prepared in phosphate-buffered saline (PBS) was added to all wells. The plates were then incubated for 4 h at 37 °C. Supernatant from each well was carefully removed, formazan crystals were dissolved in 100 μL of DMSO and absorbance at 540 nm wavelength was recorded and each concentration was tested in threefold. The IC_{50} values were determined as concentration of compounds that inhibited cancer cell growth by 50%.

Spectral analysis

5,6-dihydro-5-phenyl-1H-pyrano[2,3-d] pyrimidine-2,4,7(3H)-trione (4a)

FTIR (ATR υ cm-1) characteristic absorptions: 3207 (N–H stretching), 3083 (Ar–H stretching), 2844 (C–H stretching),

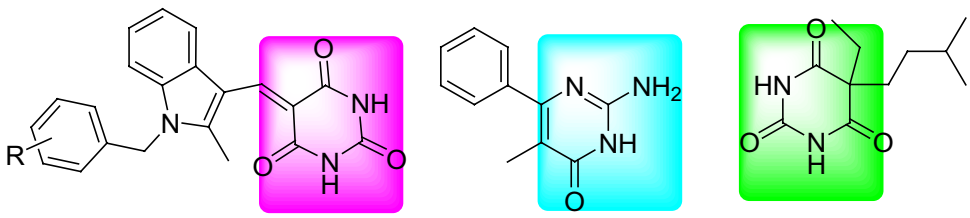


Fig. 1 Representative biologically active molecules that posses pyrimidinone and uracil structural motif

1184 (C–O–C stretching), 1690(C=O stretching); ^{1}H-NMR (400 MHz, DMSO-*d6*, δ ppm): 3.29–3.37 (dd, 1H, –CH_2), 3.55–3.65 (dd, 1H, –CH_2), 4.9–5.1 (*t*, 1H, *J* = *7.2 Hz*, CH), 7.52–7.59 (d, 2H, *J* = *8 Hz*, Ar-H), 8.02–8.09 (*d*, 2H, *J* = *8 Hz*, Ar-H), 8.24 (s, 1H, Ar–H), 11.26 (s, 1H, –NH) and 11.41 (s, 1H, –NH).

Results and discussion

Chemistry

Recently, growing awareness about environmental safety and global warming has attracted worldwide concern towards use of renewable sources and reduction of waste. This has shifted paradigm towards the use of eco-friendly and green protocols in organic synthesis [34, 35]. A catalyst derived from biomass and green solvent increases the greenness of a process. Cyclodextrins are those produced from starch by means of enzymatic conversion. They catalyse reactions by supramolecular catalysis through non-covalent bonding, forming reversible host–guest complexes just like enzymes [36–40]. Among the cyclodextrins β-cyclodextrin is useful both from an economic and environmental point of view, apart from being non toxic, metabolically safe and readily recoverable and reusable. In this work, we report the use of β-cyclodextrin as a catalyst in the synthesis of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-triones (**4a-r**) in aqueous medium (Scheme 1).

To find out the best experimental conditions for the preparation of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-triones, a model reaction, involving the 3-component annulation between benzaldehyde (**1a**), meldrum acid (**2a**) and barbituric acid (**3**) was selected.

In this study, a model reaction was conducted by sequential addition of aldehyde, meldrum acid and barbituric acid at room temperature in the absence of β-CD to obtain the corresponding 5-aryl-5,6-dihydro-1H-pyrano[2,3-d] pyrimidine-2,4,7-triones (**4a**) in aqueous medium. It was observed that there was no product formation even after heating for longer time. Cyclodextrin can boost solubility in water and reduce toxicity by complexation. Cyclodextrins contain hydrophobic cavities inside and hydrophilic hydroxyl groups outside. These macrocycles act as host molecules and form stable complexes with hydrophobic compounds. Thus, we performed model reaction using 20 mol% β-CD in water at room temperature the product was obtained in moderate yield (71%). The reaction was found to be sluggish at room temperature; however, by increasing the temperature to 60 °C, the corresponding product (**4a**) was obtained in 89% yield within 5 h (Scheme 1). No product formation was detected in the absence of cyclodextrin, which clearly demonstrates the catalytic role of cyclodextrin. This result indicates that catalyst plays a critical role in this reaction.

US irradiation offers an alternative energy source which is ordinarily accomplished by heating [41–44]. Ultrasound-assisted reactions proceed by acoustic cavitation phenomenon, that is, the formation, growth, and collapse of bubbles in the liquid medium. During the collapse of a cavity, high local temperatures and pressures arise which lead to increase in the rate of reactions [45–48]. Considering the synthetic utility of ultrasonication, we performed the model reaction using β-CD under ultrasonication, it was observed that the corresponding product was obtained in 96% yield within 1 h at 65 °C. Here ultrasonication reduces the reaction time from 5 h to 1 h. Therefore all the reactions were carried under ultrasonication.

The three most common cyclodextrins are α, β and γ-species having 6, 7 and 8 sugar molecules, respectively, in the ring system. Efforts were made to carry out the cyclocondensation using α, β and γ-species in water under ultrasound irradiation. Based on screening results in Table 1, β-CD is the best catalyst among others. Low conversions were observed with either α- or γ-cyclodextrin because of the size of cavities. Cavity of α-CD might be too small to hold three reagents and the cavity of γ-CD was too big compared to β-CD. This observation is in a good agreement with the known fact that β-CD has usually one order of magnitude higher affinity for the benzene derivatives as compared to α- and γ-CD [49–52]. No product formation was detected in the absence of cyclodextrin under ultrasonication, which clearly demonstrates the catalytic role of cyclodextrin. Therefore, β-CD was preferred as a catalyst for this reaction.

Scheme 1 Synthesis of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d] pyrimidine-2,4,7-triones (**4a-r**)

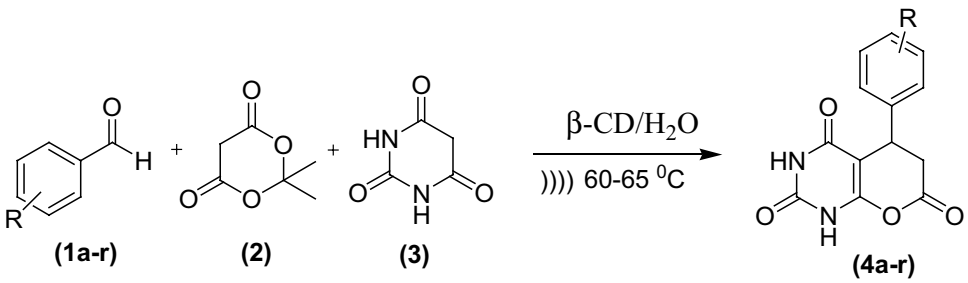


Table 1 Formation of pyrano[2,3 d]pyrimidine-2,4,7-triones (**4a**) using different catalysts in aqueous medium

Entry	Catalyst	Time (h)	Concentration (mol%)	Yield (%)
1	Water	15	–	No condensation
2	α-Cyclodextrin	9	20	45
3	β-Cyclodextrin	1	10, 15, 20, 25	72, 89, 96 and 96
4	γ-Cyclodextrin	5	20	39

[a]Reaction conditions: benzaldehyde (**1a**) (3 mmol), barbituric acid (**2**) (3 mmol), meldrum acid (**3**) (3 mmol), water, at 65 °C

[b]Isolated yield

Table 2 Optimization of solvents for synthesis of pyrano[2,3 d] pyrimidine-2,4,7-triones (**4a**)

Entry	β-Cyclodextrin (mol %)	Solvent	Yield (%)
1	20	Water	96
2	20	EtOH	65
3	20	MeOH	67
4	20	DMF	45
5	20	Acetonitrile	51

[a]Reaction conditions: benzaldehyde (**1a**) (3 mmol), barbituric acid (**2**) (3 mmol), meldrum acid (**3**) (3 mmol) at 65 °C

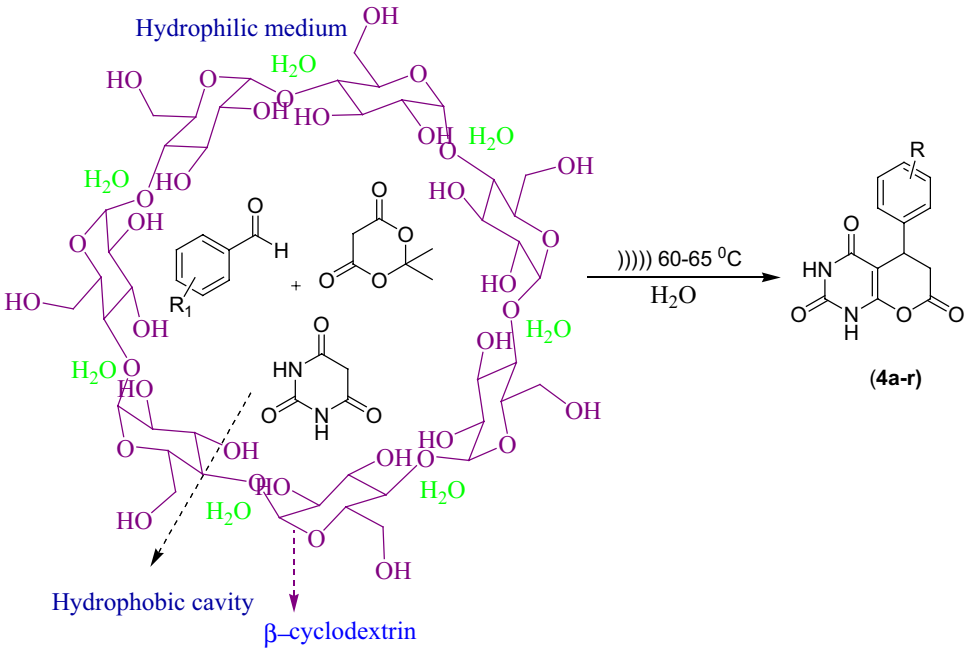
[b]Isolated yield

To optimize the catalyst, the model reaction was carried out at different concentration of β-CD in water. As catalyst concentration is a important factor that exclusively affects the reaction rate and product yield. To study this, the reaction was performed at different concentrations of β-CD, i.e., 10, 15, 20 and 25 mol%, and gave the product in 72, 89, 96 and 96% yield, respectively (Table 1). Thus, it is clear that reaction rate was positively influenced by increasing catalyst concentration up to 20 mol% and then became static on further increasing the catalyst concentration. It means that the presence of 20 mol% of β-CD was sufficient for catalyzing the reaction effectively in the forward direction.

We also screened different solvents such as water, EtOH, MeOH, DMF and acetonitrile with cyclodextrin as catalyst. Among all these solvents, water was found to play an effective role in this transformation affording highest yields due to better solubility of cyclodextrin in water. (Table 2). Therefore, water was selected as the solvent system for this transformation.

A variety of structurally divergent aldehydes possessing a wide range of functional groups (Scheme 2) was selected to understand the scope and generality of the β-CD-promoted cyclocondensation reaction to form pyrano[2,3-d]pyrimidine-2,4,7-triones and the results are summarized

Scheme 2 Synthesis of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d] pyrimidine-2,4,7-triones (**4a-r**)



in Table 3. The results showed that substituted aryl aldehydes containing either electron-donating or electron-withdrawing groups gave the analogous products in good yields at short reaction times (Table 3). We have also used aliphatic aldehyde, butaraldehyde and β-CD also afforded the respective pyrano[2,3-d]pyrimidine-2,4,7-trione (**4r**) in good yield.

Table 3 Scope of the substrate for the synthesis of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d] pyrimidine-2,4,7-triones (**4a–r**) in aqueous β-CD

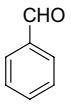
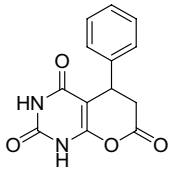
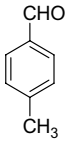
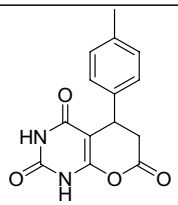
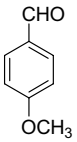
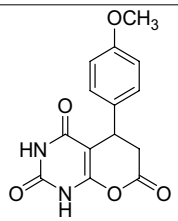
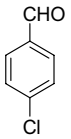
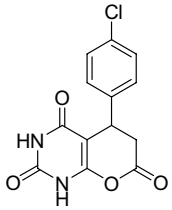
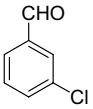
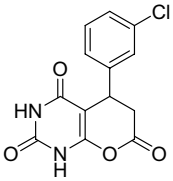
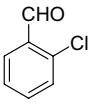
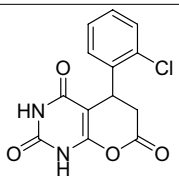
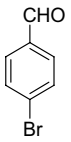
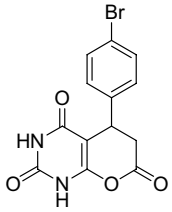
Sr. No.	Aldehydes	Structure	Yield (%)	Melting Point (°C)
1			96	254-256
2			90	260-261
3			92	291-293
4			88	282-284
5			78	268-270
6			84	242-244
7			84	273-275

Table 3 (continued)

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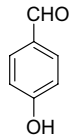
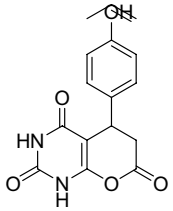
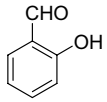
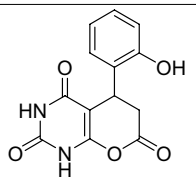
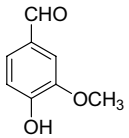
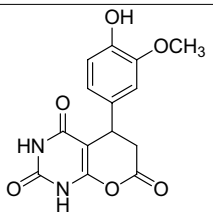
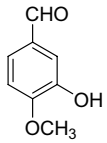
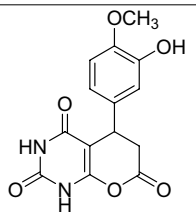
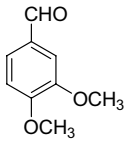
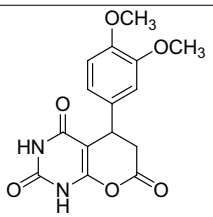
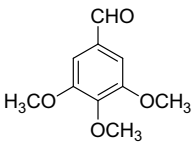
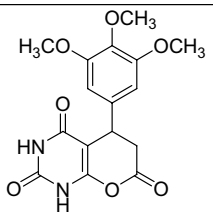
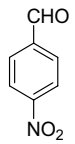
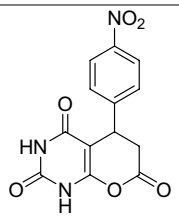
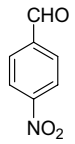
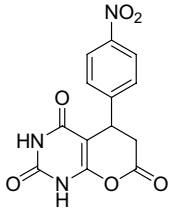
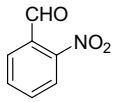
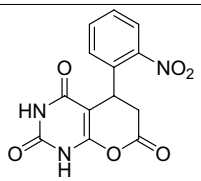
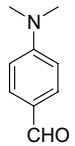
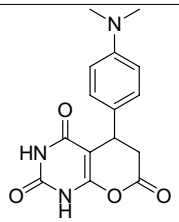
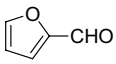
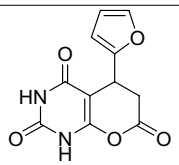
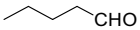
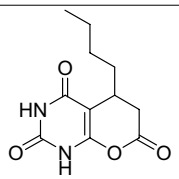
8			93	>300
9			83	290-292
10			82	280-282
11			80	290-291
12			84	281-282
13			90	268-270
14			81	249-251

Table 3 (continued)

Sr. No.	Aldehydes	Structure	Yield (%)	Melting Point (°C)
14			81	249-251
15			75	216-218
16			94	280-282
17			82	294-295
18			75	243-245

[a]Reaction conditions: substituted benzaldehyde (**1a–o**) (4 mmol), meldrum acid (**2**) (4 mmol), barbituric acid (**3**) (4 mmol), β-cyclodextrin (20 mol%), at 65 °C

[b]Isolated yield

[c]Melting points are in good agreement with those reported in the literature [27, 28]

Biological activity

In vitro anticancer evaluation of synthesized compounds (4a–r)

All the synthesized pyrano[2,3-d]pyrimidine derivatives were evaluated for their in vitro anticancer activity against HePG-2 (Human liver cancer cell line) and MCF-7 (Human breast cancer cell line) by MTT assay using 5-Flurouracil as standard drug. The result obtained for in vitro anticancer activity is reported in Table 4. The IC_{50} (μM) value means concentration required to inhibit 50% of cancer cells growth.

From the close examination of IC_{50} values, it is observed that **4c, 4j, 4k, 4l** and **4m** were active and potent anticancer agents among the synthesized derivatives **4a–r**. The compound **4j** was found to be the most potent anticancer agent against HePG-2 with IC_{50} value 6.8 μM and 5-FU showed IC_{50} value 7.9 μM against HePG-2. This proves that compound **4j** was more active than the standard drug 5-FU against HePG-2. The compound **4 k** bearing para-methoxy and ortho-hydroxy group on phenyl ring was found to be second most active anticancer agent against HePG-2 with IC_{50} value 8.8 μM. The compound **4 m** bearing 3,4,5-trimethoxy group on phenyl ring was found to be most active anticancer agent against MCF-7 with IC_{50} value 6.6 μM.

Table 4 In vitro anticancer activity of synthesized compounds (**4a–r**)

Compounds	HePG-2 IC_{50} μM	MCF-7
4a	46.3	44.9
4b	35.9	43.6
4c	10.6	23.4
4d	28.6	26.2
4e	32.7	38.8
4f	38.1	42.1
4g	36.3	27.5
4h	8.2	22.2
4i	16.4	34.5
4j	6.8	10.9
4k	8.8	14.5
4l	8.9	20.8
4m	17.2	6.6
4n	15.6	33.2
4o	26.7	40.1
4p	30.3	47.4
4q	48.8	49.5
4r	> 50	> 50
5-FU	7.9	5.4

IC_{50} values are the concentrations in micro-molar needed to inhibit cell growth by 50%; *5-FU* 5-flurouracil used as standard drug, *HePG-2* Human liver cancer cell line, *MCF-7* Human breast cancer cell line

The compound **4 m** was found to be equipotent to standard drug 5-FU.

Structure activity relationship (SAR) studies for these compounds demonstrated that the phenyl ring substituted at para position (**4b, 4c, 4d, 4 g, 4 h, 4n, 4p**) was more active than those substituted at ortho (**4f, 4i, 4o**). Compounds with para-position substitution on phenyl ring were more active than those with ortho-position substitution, suggesting that there might be a sterric hindrance effect due to ortho-position substitution on the phenyl ring. Replacement of phenyl ring with furan and alkyl group decreased the in vitro anticancer activity. The compound **4 h** bearing para-hydroxy is more active than that of **4i** with ortho-hydroxy group on the phenyl ring. The anticancer activity for derivatives bearing an electron-withdrawing group such as chlorine or bromine were found to be less active in comparison to derivatives bearing an electron donating polar group such as methoxy, hydroxy. The **4q** and **4r** were found to be least active anticancer agents among the synthesized derivatives.

Conclusion

In summary, we have presented an elegant and simple methodology for a one-pot multicomponent synthesis of pyrano[2,3 *d*]pyrimidine-2,4,7-triones in water under supramolecular catalysis. The operational simplicity, mild reaction conditions, short reaction time, high yields (75–96%) and environmental friendliness are the notable features of this procedure. Indeed, a wide range of aldehydes was converted to the corresponding pyrano[2,3 *d*]pyrimidine-2,4,7-triones using this method. To the best of our knowledge, this is the first report of anticancer activity of pyrano[2,3 *d*] pyrimidine-2,4,7-triones. Compounds **4c, 4j, 4k, 4l** and **4m** from the series (**4a–r**) were active against HePG-2 (Human liver cancer cell line) and MCF-7 (Human breast cancer cell line).

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