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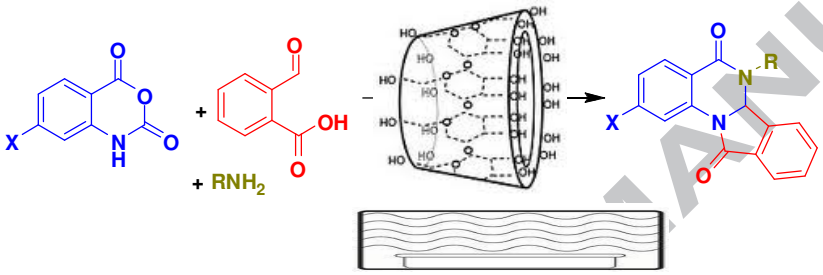

β-CD mediated MCR in water under microwave irradiation afforded dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives of pharmacological interest.

β-Cyclodextrin mediated MCR in water: Synthesis of dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives under microwave irradiation

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Abstract. We report a faster and greener approach for the synthesis of dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives of potential pharmacological interest *via* a β-CD mediated MCR in water under microwave irradiation.

Keywords: β-CD; MCR; water; dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione; microwave

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Multi-component reactions[1,2] (MCRs) that provide diversity based combinatorial library of small molecules required by pharmaceutical and agrochemical industries are of great demand when performed under green conditions. Such methodologies often address the growing concern about environmental safety and hazard. Since performing chemical reactions in water in the presence of a catalyst derived from biomass enhances the greenness of the process, the development of such economic and eco-friendly methodologies therefore is the central focus in the area of green and sustainable chemistry. Recently, cyclodextrin-mediated reactions in aqueous media have been explored for this purpose.[3] Being cyclic oligosaccharides, cyclodextrins (CDs) possess cavities (Fig. 1), that are less hydrophilic than water and bind substrates selectively thereby catalyzing the reactions with high selectivity (indeed, these reactions are facilitated by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding). Additionally, CDs are

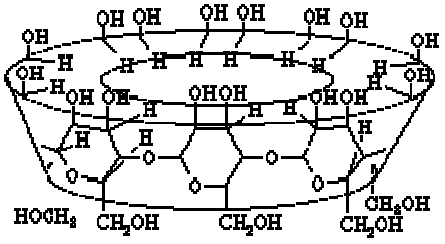
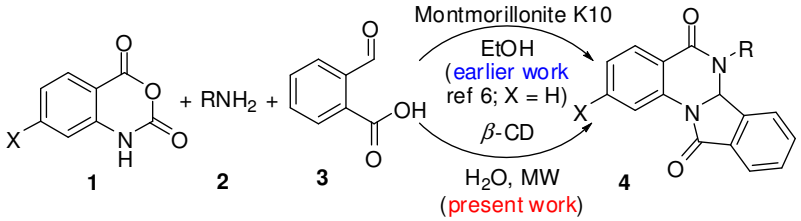


Fig. 1. A view of cyclodextrin.

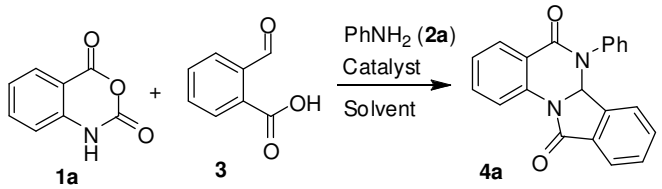
nontoxic and considered to be metabolically safe.[3a] Due to the importance of TNF-α (Tumor Necrosis Factor-alpha) inhibition[4a] in the treatment of inflammatory disorders such as rheumatoid arthritis, Crohn's disease, and ulcerative colitis, a monoclonal antibody i.e. infliximab[4b] has been discovered and is being used as a TNF-α inhibitor. In our effort to design and synthesize novel small molecules[5] as inhibitors of TNF-α, we have recently reported[6] the synthesis of 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones (**4**, Scheme 1) as potential inhibitors. In continuation of this research, we required a wide variety of close analogues for our SAR (Structure Activity Relationship) studies. In order to develop a robust and faster synthesis of this class of compounds, CDs attracted our attention due to their favorable properties amenable to eco-friendly approaches. During recent years microwave assisted reactions[7-11] have gained considerable attention in organic synthesis especially in the area of drug discovery. These green processes have remarkable advantages over the reactions performed under conventional heating. Herein we report a greener synthesis of **4** mediated by *β*-CD in water under microwave irradiation (Scheme 1).



Scheme 1. Earlier and present synthesis of **4.**.

Initially, the reaction of isatoic anhydride (**1a**), aniline (**2a**) and 2-formylbenzoic acid (**3**) was examined in the presence of a range of commercially available catalysts in water under microwave

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst (w/w%)	Heating time		Conversion (%)
		Microwave[b] (min)	Conventional (h); 90-100 ºC	
1	Iodine (20)	10	14-16	30
2	*p*-TSA (10)	10	14-16	45
3	*p*-TSA (20)	10	14-16	55
4	*p*-TSA (30)	10	14-16	55
5	$NaHSO_3$ –SiO_2 (10)	10	14-16	45
6	$NaHSO_3$ –SiO_2 (20)	10	14-16	50
7	INDION 225H (5)	10	14-16	55
8	INDION 225H (15)	10	14-16	70
9	INDION 225H (25)	10	14-16	71
10	*β*-CD (5)	10	14-16	70
11	*β*-CD (10)	10	14-16	80 (78,77,75)[c]
12	*β*-CD (15)	10	14-16	80
13	No catalyst	10	14-16	15
14	*β*-CD (15)	10	--	65[d]
15	*β*-CD (15)	10	--	50[e]
16	*β*-CD (15)	10	--	60[f]

[a]All the reactions were carried out using isatoic anhydride **1a** (1.0 mmol), aniline **2a** (1.2 mmol), 2-formylbenzoic acid **3** (1.0 mmol) and catalyst in water (5 mL).

[b]The reaction mixture was irradiated in a CEM Explorer microwave.

[c]Recovered aqueous *β*-CD was used.

[d]*i*-PrOH was used in place of water.

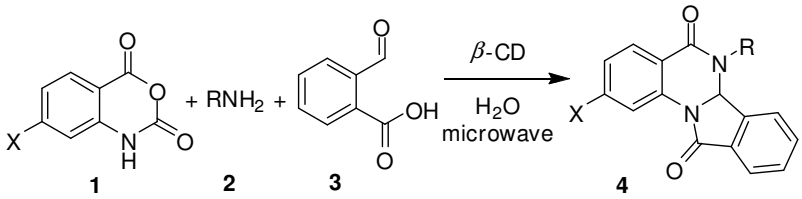
[e]MeOH was used in place of water.

[f]1,4-Dioxane was used in place of water.

and conventional heating separately (Table 1). While the reaction proceeded in the presence of I_2 (entry 1, Table 1), *p*-TSA (entries 2-4, Table 1), $NaHSO_3$-SiO_2 (entry 5 and 6, Table 1), or INDION 225H (entries 7-9, Table 1) affording the desired product **4a**, the degree of conversion varied from 30 to 71% depending on the nature and quantity of catalyst used. Improved conversion was observed when 10 w/w% of *β*-CD was used (entry 11 vs 10 and 12, Table 1). An increase in reaction time from 10 min to 15 min did not improve the degree of conversion significantly. The poor conversion in the absence of a catalyst (entry 13, Table 1) indicated its key role in the present MCR. Thus, *β*-CD was found to be the catalyst of choice and was used for our further studies. As expected, all these reactions required much longer time (14-16 h) when performed under conventional heating as compared to microwave heating (entries 1-13, Table 1). The role of other solvent e.g. *i*-PrOH, MeOH or 1,4-dioxane was also examined and found to be less effective (entries 14-16, Table 1). To test the recyclability of the catalyst, the aqueous *β*-CD was recovered after usual work-up with organic solvent and reused[12] to afford **4a** without changing of the degree of conversion significantly (entry 11, Table 1).

We then performed the *β*-CD-mediated MCR[12] using various aromatic and aliphatic amines **2** (Table 2). Substituents like Br and Cl or electron donating OMe and Bu^t or electron withdrawing CN and CO_2Me groups on the aryl ring were well tolerated and afforded **4** in good to excellent yields. Aliphatic amines e.g. methyl, cyclopropyl or 2-phenylethanamine or N^1,N^1-dimethylpropane-1,3-diamine as well as disubstituted aromatic amines and α-naphthyl amine also participated well in the MCR. The presence of a chloro group on the aryl ring of **1** was tolerated (entries 18 and 19, Table 2). Overall, nineteen compounds were prepared by using this methodology and all the synthesized compounds were characterized by spectral (NMR, IR, and HRMS) data. A chiral HPLC performed using the compound **4i** and **4p** individually indicated the presence of a 1:1 mixture of both enantiomers in both cases (see ESI for chromatograms).

Table 2. β-CD mediated synthesis of 6-substituted-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones in water under microwave.[a]



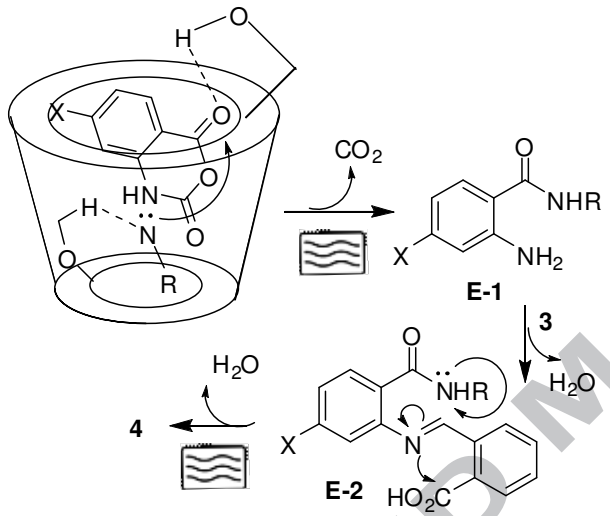
Entry	Compd (**1**); X =	Amine (**2**); R =	Product (**4**)	Yield[b] (%)
1	**1a**; H	**2a**; Ph	**4a**	70
2	**1a**; H	**2b**; CH_2Ph	**4b**	88
3	**1a**; H	**2c**; c-propyl	**4c**	85
4	**1a**; H	**2d**; $CH_2C_6H_4OMe$-*p*	**4d**	85
5	**1a**; H	**2e**; C_6H_4Br-*p*	**4e**	77
6	**1a**; H	**2f**; $CH_2C_6H_3Cl_2$-o,*p*	**4f**	80
7	**1a**; H	**2g**; $(CH_2)_3NMe_2$	**4g**	75
8	**1a**; H	**2h**; α-Naphthyl	**4h**	75
9	**1a**; H	**2i**; C_6H_4Me-*p*	**4i**	85
10	**1a**; H	**2j**; C_6H_4CN-*p*	**4j**	60
11	**1a**; H	**2k**; $C_6H_4(Bu^t)$-*p*	**4k**	85
12	**1a**; H	**2l**; $C_6H_4(CO_2Me)$-*p*	**4l**	70
13	**1a**; H	**2m**; $CH_2C_6H_4Cl$-*p*	**4m**	77
14	**1a**; H	**2n**; $C_6H_3(Cl\text{-}o)Me$-*m*	**4n**	72
15	**1a**; H	**2o**; $(CH_2)_2C_6H_5$	**4o**	87
16	**1a**; H	**2p**; Me	**4p**	95
17	**1a**; H	**2q**; $C_6H_3Me_2$-*o,m*	**4q**	80
18	**1b**; Cl	**2r**; C_6H_4Me-*p*	**4r**	81
19	**1b**; Cl	**2s**; Me	**4s**	90

[a]All the reactions were carried out using isatoic anhydride **1** (1.0 mmol), amine **2** (1.2 mmol), 2-formylbenzoic acid **3** (1.0 mmol) and β-CD (w/w 10%) in water (5 mL) under microwave.[12]

[b]Isolated yield.

Based on the earlier ^{1}H NMR studies indicating the association of isatoic anhydride and cyclodextrin during the reaction[3a] and formation of a β-CD complex from the primary rim of the cylinder, a plausible scheme for the present β-CD mediated MCR is shown in Scheme 2. Since the

MCR is less efficient in the absence of β-CD, the catayst appears to play an important role in increasing the efficiency of the reaction especially by activating the anhydride carbonyl group of **1** in addition to aiding the water solubility of all the reactants. A subsequent nucleophilic attack by the amine **2** on the activated carbonyl carbon was also facilitated by β-CD leading to the generation of 2-amino-*N*-arylbenzamide intermediate **E-1** *in situ*. Once formed, the **E-1** then reacts with 2-formylbenzoic acid (**3**) affording the second intermediate **E-2**. The azomethine moiety of **E-2** subsequently participates in an intramolecular concurrent cyclization involving the carboxylic acid and amide group to give the desired product **4**.



Scheme 2. Plausible scheme for the β-CD-mediated MCR under microwave irradiation.

In conclusion, we have described for the first time a β-CD mediated MCR in water under microwave irradiation affording a faster and greener approach for the synthesis of dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives of potential pharmacological interest. The methodology worked under neutral conditions and is free from the use of any metal catalyst. It is amenable for the synthesis of diversity based library of small molecules required by pharmaceutical / chemical industries.

Acknowledgements

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12. **General procedure for the preparation of compound 4a:** To a mixture of **1a** (1.0 mmol), **2a** (1.2 mmol), and **3** (1.0 mmol) in water (5.0 mL) was added β-CD (w/w 10%). The reaction vessel was sealed with a pressure cap and irradiated in a CEM Explorer microwave for 10 min at 120 °C (300 W). The progress of the reaction was monitored by TLC. After completion of the reaction (1st run) the mixture was cooled to room temperature and extracted with dichloromethane (10 mL). The organic layer was collected and filtered through celite. The celite was washed with dichloromethane (5.0 mL). The combined filtrate was concentrated and

the residue was purified by column chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane (0-30%) to give the desired product. **Reuse of *β*-CD**: The aqueous layer separated containing *β*-CD was collected. To this was added **1a** (1.0 mmol), **2a** (1.2 mmol) and **3** (1.0 mmol) in a reaction vessel that was then sealed with a pressure cap and irradiated in a CEM Explorer microwave for 10 min at 120 °C (300 W). Up to four cycles of recyclability of the catalyst was examined. **Recovery of *β*-CD:** the aqueous layer was left overnight at 5 °C. Due to its low solubility the *β*-CD was precipitated at lower temperature. It was then filtered, dried and used for the next reaction.