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In silico studies and β-cyclodextrin mediated neutral synthesis of 4-oxo-4,5,6,7-tetrahydroindoles of potential biological interest

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ABSTRACT

Prompted by the *in silico* docking study predictions the first β-cyclodextrin (β-CD) mediated synthesis of 4-oxo-4,5,6,7-tetrahydroindoles in water was achieved *via* a 3-component reaction under neutral conditions. A range of compounds was prepared by using this environmentally friendly method in good yields (82–92%). The catalyst β-CD could be recovered and recycled. The *in silico* docking studies predicted chorismate mutase (CM) inhibitory properties of some of the tetrahydroindoles synthesized that was supported by the results of subsequent *in vitro* assay.

The conversion of chorismate to prephenate in the shikimate biosynthetic pathway involves a Claisen rearrangement catalysed by the enzyme called chorismate mutase or CM (EC 5.4.99.5). This is a key step leading to the generation of essential amino acids, phenylalanine and tyrosine. Thus inhibition of CM is believed to hamper the supply of nutrients to the organism. Moreover, due to its presence in bacteria, fungi and higher plants but not in human [1–3] targeting CM is regarded as one of the promising strategies for the discovery of new antibacterial agents. Over the years various efforts have been devoted towards the identification of inhibitors of CM either via screening of existing compound library or design, synthesis and screening of new molecules [2]. While several heterocyclic class has been explored for this purpose the potential of 4-oxo-4,5,6,7-tetrahydroindoles as inhibitors of CM has not been assessed previously. Indeed, a relevant compound e.g. microindolinone A (**A**, Fig. 1) though was isolated from a deep-sea-derived actinomycete Microbacterium sp. MCCC 1A11207 but its effects on bacterial cells are not studied [4]. Notably, the utility of 2-aryl-4,5,6,7-tetrahydro-1*H*-indole (**B**, Fig. 1) as an anti-hepatitis C virus targeting scaffold has been reported [5] whereas sirtuin inhibitory

potential of another class of tetrahydroindole derivatives have been explored [6]. Very recently, antibacterial activities of related compounds e.g. fused pyrrole derivatives has been described [7]. Nevertheless, due to our long standing interest in the pharmacological evaluation of pyrrole derivative [8,9] as well as CM inhibitors [2] we became curious about potential CM inhibitory properties of 4-oxo-4,5,6,7-tetrahydroindole derivatives (**C**, Fig. 1) derived from **A** and **B**.

The virtual screening of molecules *via* their docking into the target protein in silico is considered as one of the fascinating approaches in Med Chem efforts [10]. The researchers employ this technique for a variety of purposes and therefore applications of docking studies has increased dramatically over the last decade. In our effort, to verify the merit of the framework **C** for the identification of potential inhibitor of CM the docking study [11] of two representative molecules e.g. **C-1** and **C-2** was performed using AutoDock Vina and the binding energies are presented in Table 1. Based on a previous study [11a] we pursued the interface site of *Mtb*CM for docking of our molecules. The comparable binding energies of these molecules with the known inhibitor [11b] (**D**) suggested that molecules based on framework **C** might inhibit the CM too. Indeed, the molecule **C-1** formed hydrophobic / Vander Wall interactions with the hydrophobic residues and hydrophobic regions of polar and charged residues (see Fig. S-1, Suppl. data). Similar interactions were also observed for the molecule **C-2** (see Fig. S-2, Suppl. data).

There are not many methods known for the synthesis of compounds containing the 4-oxo-4,5,6,7-tetrahydroindole framework. For example, synthesis [12] of this class of compounds was carried

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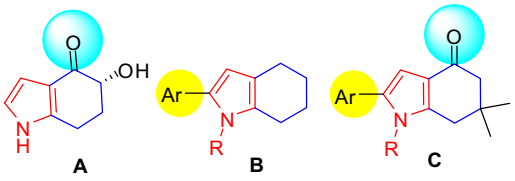
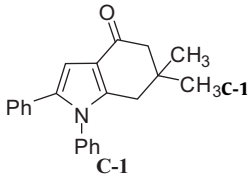
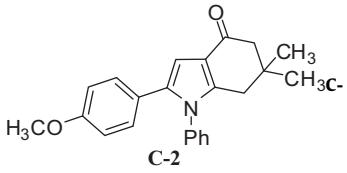
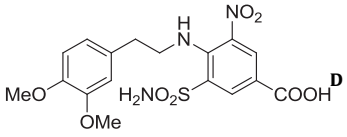


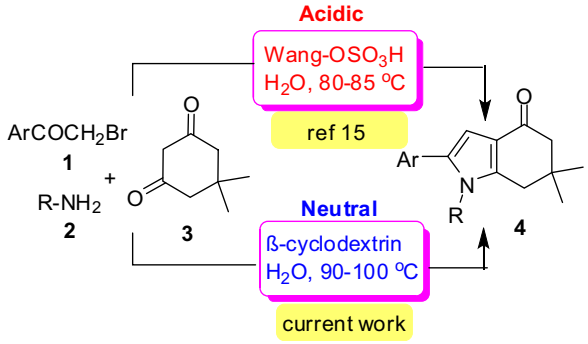
Fig. 1. The bioactive 4,5,6,7-tetrahydroindole derivative **A** and **B** and the target framework **C**.

Table 1
Docking of molecules into *MtbCM*.

Molecules	AutoDock Vina score (Kcal/mol)
 C-1	−7.3
 C-2	−7.5
2	
 D	−7.3

out (i) *via* the K_2CO_3 mediated reaction of phenacyl bromide with dimedone followed by the reaction with aniline in presence of HOAc [12a] or (ii) *via* a sulfamic acid (H_2NSO_3H) mediated three component reaction in the absence of any solvent under ball milling conditions [12b]. or (iii) other methods [12c,d]. Alternatively, 4-oxo-4,5,6,7-tetrahydroindole derivatives were synthesized *via* the reaction of aryl glyoxal with 3-(aryl/aralkyl amino)-cyclohex-2-enone [13].

Multicomponent reactions (MCRs), known for over 150 years since the report of Strecker's synthesis [14a] of α-amino cyanides in 1850 are generally defined as synthetic protocols that allow assembly of three or more substrates in a regio- and stereoselective manner to afford complex organic molecules [14b]. These protocols offer significant advantages (e.g. operational simplicity, atom economy etc) over the stepwise construction of complex molecules and hence have become powerful tools for the direct and one-pot access to a variety of molecules including heterocyclic compounds [14c]. Thus the dramatic rise in applications of MCRs in all fields of organic synthesis is not surprising [14d]. Recently, 3-component approach has been reported for the preparation of 4-oxo-4,5,6,7-tetrahydroindoles *via* the reaction of phenacyl bromide (**1**), primary amine (**2**) and dimedone (**3**) in water (Scheme 1) [15]. While, a range of compounds was prepared efficiently by using this green methodology the process however involved the use of acidic Wang-OSO_3H as a catalyst. Notably, the preparation of this catalyst from the Wang resin required the use of a harmful and lachrymator agent i.e. chlorosulfonic acid [16]. Thus, establishing a better and neutral method that is free from the use of hazardous or acidic agents was desirable. The reactions assisted by cyclodextrin (CD) in aqueous or other media have been explored [17–21] for the



Scheme 1. The reported and current synthesis of 4-oxo-4,5,6,7-tetrahydroindole derivatives.

development of economic and eco-friendly methodologies that are thought to be the central focus of green and sustainable chemistry. Cyclodextrins, the inexpensive and commercially available cyclic oligosaccharides [22] [consisting of α-(1,4) linked glucose units] contain non-polar cavities at center (Fig. 2) that are less hydrophilic than water and allow selective binding of substrates thereby facilitating the reactions with high selectivity. Indeed, this supramolecular catalysis involves reversible formation of host–guest complexes *via* noncovalent bonding that actually facilitates the reaction [21b]. Nevertheless, in addition to their remarkable inclusion capabilities with small organic molecules, nontoxic nature and water solubility, and the favorable properties amenable for eco-friendly approaches prompted us focusing on CDs. Herein we report the β-cyclodextrin (β-CD) mediated efficient and neutral synthesis of 4-oxo-4,5,6,7-tetrahydroindole derivatives (**4**) in pure water (Scheme 1). To the best of our knowledge the use of β-CD for the synthesis of compound **4** has not been explored previously.

At the beginning the reaction of 2-bromo-1-phenylethanone (**1a**), aniline (**2a**) and dimedone (**3**) was examined in the absence or presence of a range of commercially available catalysts either in water or in other organic solvents (Table 2). These reactions were performed nearly at refluxing temperature of the solvent used for 6 h. While the reaction did not proceed well in the absence of a catalyst (entry 1, Table 2) or in the presence of $NaHSO_3$-SiO_2 (entry 2, Table 2) the use of 5–15% w/w INDION 225H as a catalyst improved the yield of desired product **4a** significantly (entries 3–5, Table 2). Indeed, the use of 10% w/w of this catalyst afforded the best product yield (entry 4, Table 2) though it was not the maximum. Changing the catalyst to β-CD maintained the product yield in the range 58–75% when the reaction was performed in solvents such as PEG-400, MeOH, MeCN, i-PrOH (entries 8–11, Table 2), *n*-BuOH, DMF, DMA or 1,4-dioxane. Indeed, no significant improvement in product yield was observed when water was used as solvent (entry 12, Table 2). However, the reaction temperature was 60–65 °C instead of refluxing temperature of the solvent used in

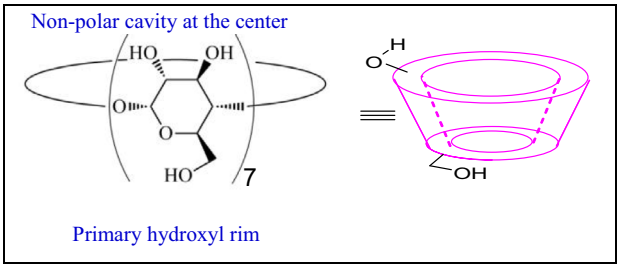
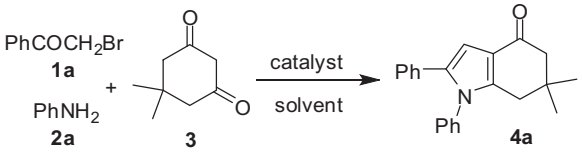


Fig. 2. β -Cyclodextrin (β-CD).

Table 2
Study to establish the optimized reaction conditions.[a]



Entry	Catalyst (%w/w)	Solvent	Temp (°C)	Yield (%)[b]
1	No catalyst	H_2O	90–100	15
2	$NaHSO_3$–SiO_2 (10)	H_2O	90–100	20
3	INDION 225H (5)	H_2O	90–100	50
4	INDION 225H (10)	H_2O	90–100	70
5	INDION 225H (15)	H_2O	90–100	75
8	β-CD (10)	PEG-400	90–100	75
9	β-CD (10)	MeOH	60–65	58
10	β-CD (10)	MeCN	80–85	68
11	β-CD (10)	i-PrOH	80–85	60
12	β-CD (10)	H_2O	60–65	76
13	β-CD (10)	H_2O	80–85	80
14	β-CD (10)	H_2O	90–100	90
15	β-CD (20)	H_2O	90–100	90

[a]Reaction conditions: phenacy bromide **1a** (1.0 mol), amine **2a** (1.0 mol), dimedone **3** (1.2 mol) and a catalyst in a solvent for 6 h.
[b]Isolated yields

this case. Hence the reaction was performed at higher temperature e.g. at 80–85 °C when an improvement in product yield was observed (entry 13, Table 2). Further increase in reaction temperature to 90–100 °C increased the yield to 90% (entry 14, Table 2). Notably, all these reactions were performed using 10 mL of solvent. Increase in volume of water used (to 15 or 20 mL) decreased the reaction rate whereas decrease in volume (to 5 mL) affected the product yield. Similarly, these reactions were carried out using w/w 10% β-CD and increase in catalysts quantity did not improve the product yield (entry 15, Table 2). Thus, the conditions of entry 14 i.e. 10% w/w of β-CD in water at 90–100 °C were found to be optimum in terms of product yield.

We then examined the recovery and reuse of the catalyst used i.e. β-CD in the synthesis of 4-oxo-4,5,6,7-tetrahydroindole derivative **4a**. Accordingly, after completion of the reaction (1st run) the mixture was cooled to room temperature and extracted with dichloromethane (10 mL). The aqueous layer separated containing β-CD was collected and left overnight at 5 °C when because of its low solubility the β-CD was precipitated at lower temperature. After filtration and proper drying it was used for the next reaction involving **1a** (1.0 mmol), **2a** (1.0 mmol) and **3** (1.2 mmol) in water a reaction vessel. The reaction was carried out at 90–100 °C for 6.5 h. The recyclability of the catalyst was examined for up to four cycles and results are summarized in Table 3. It is evident that the product **4a** could be obtained in each cycle without significant loss of product yield up to the third cycle and a marginal loss of yield (~5%) was observed after the fourth cycle.

Having established the optimized reaction conditions a range of analogues of **4a** were prepared using the β-CD-mediated MCR (Table 4). The phenacyl bromide (**1**) containing electron donating e.g. OMe and electron withdrawing group e.g. CN was employed for this purpose. Similarly, a range of aromatic / aliphatic amines (**2**) were employed in this MCR. The aromatic amines may contain mono substituent like Me, F, Cl or Br group or combination of two substituents like Me and Me or Me and Cl. The α -naphthyl amine was also employed in this MCR. The aliphatic amine may contain a cyclopropyl ring or a linear hydrocarbon chain. The reaction proceeded smoothly in all these cases affording the desired product in good to excellent yield. However the use of *p*-nitoaniline as the amine component (**2**) under the conditions employed was not successful indicating the limitation of the current MCR. Nevertheless, as reported earlier [18] the reaction proceeded well when dimedone (**3**) was replaced by pentane-2,4-dione (**5**) affording the polysusbtituted pyrrole derivatives (**6**) in 88–92% yield (Scheme 2). The duration of the reaction was somewhat lower in these cases perhaps due to

the use of relatively higher reaction temperature though the product yields were comparable. Thus the current MCR is amenable for the synthesis of two different class of *N*-heterocyclic compounds depending on the nature of 1,3-diketone employed. Notably, the use of other cyclic 1,3-diketone e.g. cyclohexane-1,3-dione (**7**) in place of dimedone (**3**) afforded the desired product i.e. 1,2-diphenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (**4o**) (albeit in low yield i.e. 33%) when reacted with 2-bromo-1-phenylethanone (**1a**) and aniline (**2a**). However, the MCR did not afford the desired product when cyclopentane-1,3-dione was used in place of **3**. Nevertheless, all compounds synthesized were characterized by spectral (NMR, IR, and HRMS) data. The partial ^1H and ^{13}C NMR data of a representative compound **4a** is presented in Fig 3. It is evident that the C-3 pyrrole proton appeared at ~ 6.8 δ in the ^1H NMR spectra whereas the presence of two CH_2 groups was indicated by the appearance of two singlets near ~ 2.5 and ~ 2.4 δ. Additionally, the two Me groups appeared at ~ 1.1 δ. The presence of C=O group was confirmed by the ^{13}C signal at 193.4 ppm in the ^{13}C NMR spectra whereas C-3 of pyrrole ring appeared at 105.6 ppm. The ^{13}C NMR signals at 52.1 and 37.0 ppm were due to the two CH_2 groups. Further the ^{13}C NMR signals at 28.6 and 35.5 ppm were due to the two Me groups and the carbon bearing these groups, respectively.

A plausible reaction mechanism [22] for the formation of compound **4** via the β-CD mediated MCR is presented in Scheme 3 that

Table 3
Recyclability of the catalyst in the MCR of **1a**, **2a** and **3** to afford **4a** under the reaction condition of entry 14 of Table 2.

Cycle	Time (h)	Yield (%)
1st	6.0	90
2nd	6.5	90
3rd	7.0	88
4th	8.0	85

Table 4
β-CD mediated synthesis of 4-oxo-4,5,6,7-tetrahydroindole derivatives (**4**).[a]

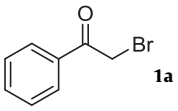
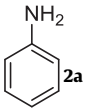
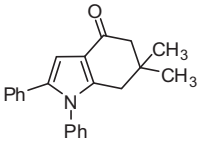
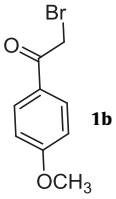
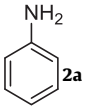
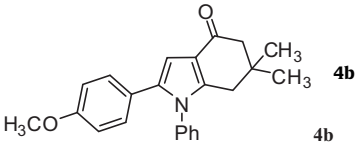
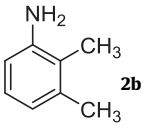
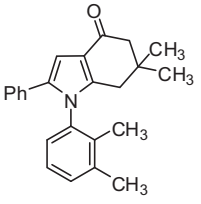
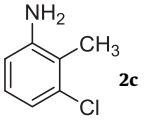
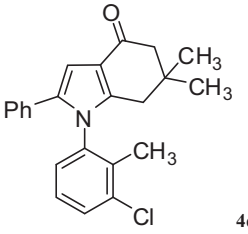
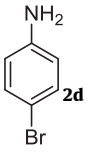
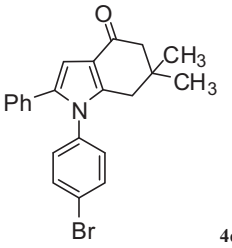
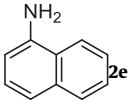
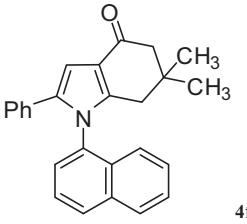
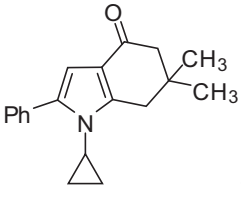
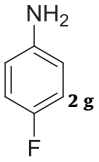
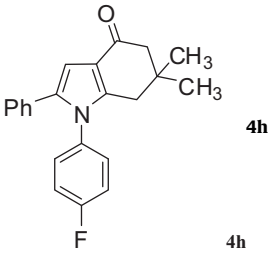
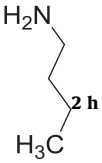
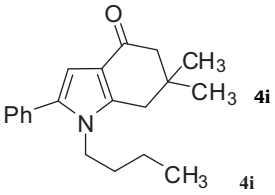
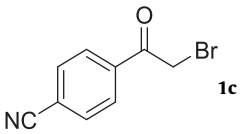
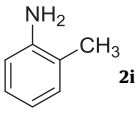
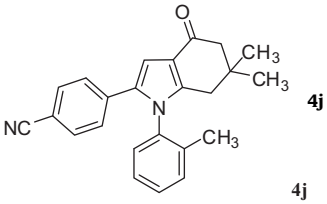
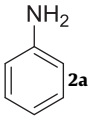
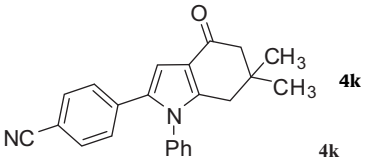
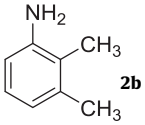
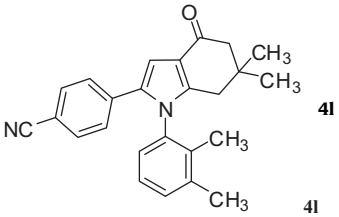
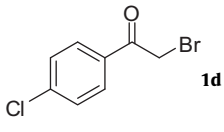
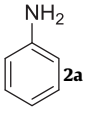
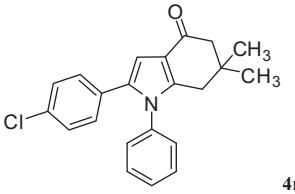
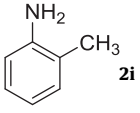
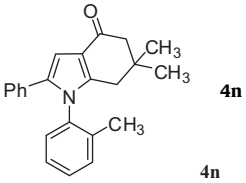
Entry	Phenacyl bromide (**1**)	Amine (**2**)	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **4a**	90
2	 **1b**	 **2a**	 **4b**	82
3	**1a**	 **2b**	 **4c**	92
4	**1a**	 **2c**	 **4d**	88
5	**1a**	 **2d**	 **4e**	87
6	**1a**	 **2e**	 **4f**	90
7	**1a**	 **2f**	 **4g**	86

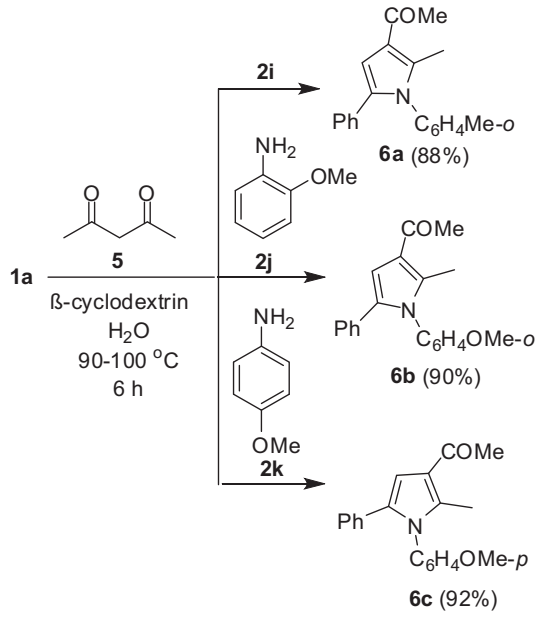
Table 4 (*continued*)

Entry	Phenacyl bromide (**1**)	Amine (**2**)	Product	Yield[b] (%)
8	**1a**	 **2 g** **2g**	 **4h** **4h**	87
9	**1a**	 **2 h** **2h**	 **4i** **4i**	88
10	 **1c** **1c**	 **2i** **2i**	 **4j** **4j**	86
11	**1c**	 **2a** **2a**	 **4k** **4k**	82
12	**1c**	 **2b** **2b**	 **4l** **4l**	85
13	 **1d** **1d**	 **2a** **2a**	 **4m** **4m**	84
14	**1a**	 **2i** **2i**	 **4n** **4n**	88

[a] All reactions were carried out using phenacyl bromide **1** (1 mmol), amine **2** (1 mmol), dimedone **3** (1.2 mmol) and β-cyclodextrin (10% w/w) in water (10 mL).
[b] Isolated yield.

involved the formation of a β-CD complex from the primary rim of the cylinder. The β-CD is often presented as a doughnut-shaped truncated cone [23a,b] as shown in Scheme 3. It is known that the primary hydroxy groups (–CH_2OH) of glucose units are located on the narrower rim of the cone (making β-CDs soluble in water), whereas the secondary hydroxy groups (>CHOH) remain on the wider side (Fig 2 and Scheme 3).

Nevertheless, since the MCR was less efficient in the absence of β-CD (entry 1, Table 2), the catalyst appeared to play an important role in increasing the efficiency of the reaction especially by activating the bromo group of the phenacyl bromide (**1**) in addition to aiding the water solubility of all the reactants (because of its ability [24] to form inclusion complexes with reactants). A subsequent nucleophilic attack by the dimedone (**3**) *via* its enol



Scheme 2. β -CD mediated synthesis of polysustituted pyrrole derivatives (**6**).

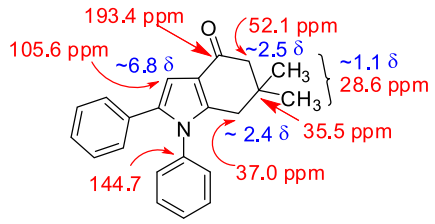
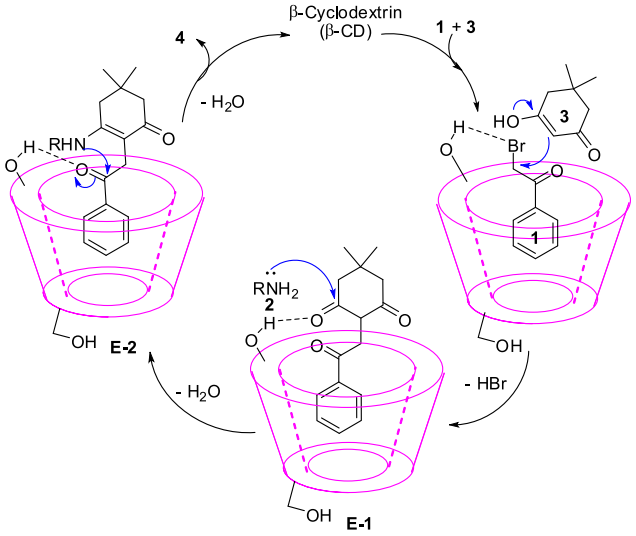


Fig. 3. Partial representation of ^{1}H and ^{13}C NMR spectral data of compound **4a.**



Scheme 3. Proposed reaction mechanism for the formation product **4**.

form on the bromo group bearing carbon was also facilitated by β-CD afforded the tri-keto intermediate **E-1**. On further reaction with amine (**2**) the **E-1** afforded an enamine intermediate **E-2** that on intramolecular cyclization furnished the desired product **4**. In order to gain evidences on intermediacy of **E-1** in the reaction of **1a**, **2a** and **3** (under the conditions of entry 14, Table 2) was halted after 2 h when the tri-keto compound i.e. 5,5-dimethyl-2-(2-oxo-2-phenylethyl)cyclohexane-1,3-dione (see Supplementary data) was isolated though in low yield after usual work-up.

In an initial study most of the 4-oxo-4,5,6,7-tetrahydroindole derivatives (**4**) synthesized were tested for their CM inhibitory properties *in vitro* [25,26] using an assay that involved measurement of catalytic activity of enzyme (CM) in the conversion of chorismate (substrate) to prephenate. The known inhibitor [11b] **D** (Table 1) was used as a reference compound (IC_{50} < 10 mM). The compound **4a**, **4b** and **4h** showed significant inhibition i.e. 43.67 ± 3.14, 49.92 ± 1.74 and 59.6 ± 2.51% of CM respectively when tested at 50 μM. This was supported by the docking of **4h** into the CM (Fig. 4). While **4h** showed similar interactions as observed for the molecule **C-1** (or **4a**) and **C-2** (or **4b**) an additional hydrophobic interaction with LYS60 (that was not present in earlier two molecules) along with other interactions was observed in this case. This perhaps justified the better binding energy (-7.6 Kcal/mol) as well as activities of **4h** over **C-1** (or **4a**) and **C-2** (or **4b**). While detailed pharmacological studies of this class of compounds are currently ongoing the compound **4h** appeared to be of further interest in view of the fact that tuberculosis is a leading cause of death worldwide.

In summary, the first β-CD mediated synthesis of 4-oxo-4,5,6,7-tetrahydroindoles in water has been achieved *via* a 3-component reaction of phenacyl bromide (**1**), primary amine (**2**) and dimedone (**3**). A range of compounds was prepared by using this environmentally friendly method in good yield (82–92%). The catalyst β-CD could be recovered and recycled. Being neutral and free from the use of any metal / hazardous catalyst the methodology appeared to have advantages over to the previously reported methods for the synthesis of this class of compounds. The *in silico* docking studies predicted chorismate mutase (CM) inhibitory properties

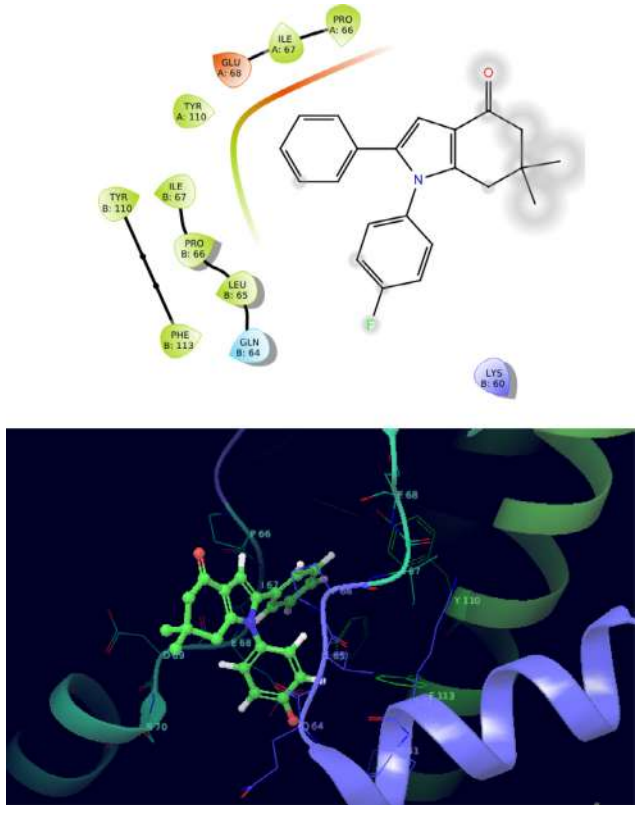


Fig. 4. 2D followed by 3D interaction diagram between interface residues of *Mtb*CM (where red color indicates A chain and orange is B chain) (PDB code: 2FP2) and **4h** that were prepared in Maestro visualizer (Schrödinger, LLC).

of some of the tetrahydroindoles synthesized that was supported by the results of *in vitro* assay. Indeed, the compound **4h** appeared to be best among them. Thus, our effort facilitated identification of a new class of potential inhibitors of CM and further studies are in progress towards this direction. Overall, the current work involving green chemistry approaches, small organic molecules and their in silico as well as pharmacological studies would be of further interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151972.

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