Supramolecular biomimetic catalysis by β-cyclodextrin for the synthesis of new antimicrobial chromeno[4,3-b]quinolin-isonicotinamides in water

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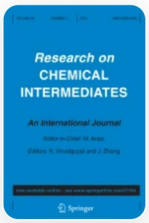

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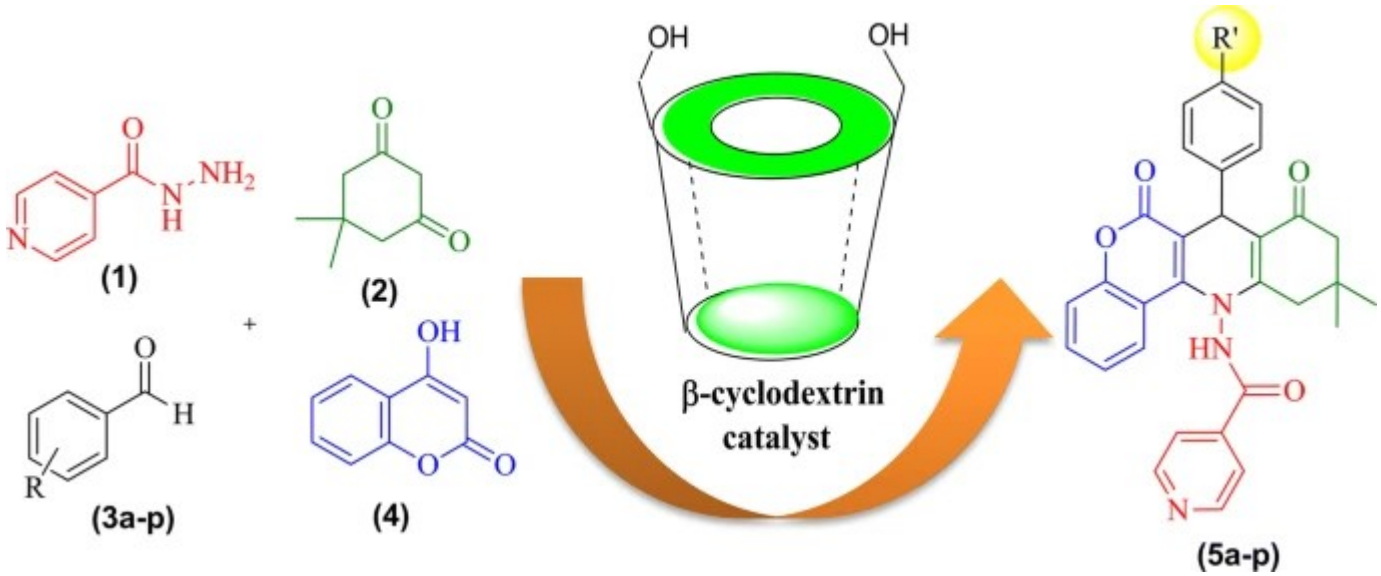
Abstract

Herein, a fast and convenient protocol for the synthesis of new isoniazid fused chromeno[4,3-b]quinolin was achieved through biomimetic catalysis by cyclodextrin in the water at 60–65 °C. The present investigation involves attractive characteristics such as the use of water as the reaction medium, one-pot conditions, short reaction periods, easy work-up/purification

and reduced waste production. This method provides a green route for the synthesis of targeted scaffolds and also a wide substrate scope for several substituted aldehydes to provide good yields of the corresponding products. Furthermore, the catalyst can be easily recovered by simple filtration and reused several times without any substantial loss in activity. Our study also discloses the antimicrobial screening of new chromeno[4,3-b]quinolin-isonicotinamides against four bacterial and three fungal strains.

Graphic Abstract



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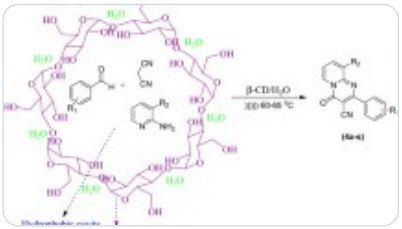

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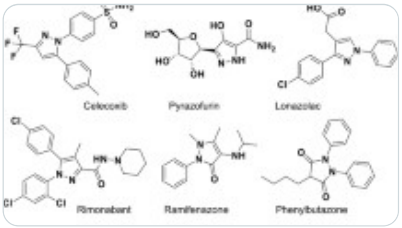

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Introduction

During the past decade, ecological requirements have pressed chemists to develop clean catalytic processes and technologies [1,2,3]. The fusion of two emergent areas, supramolecular catalysis and green chemistry, holds the answer to an environmentally sustainable society [4,5,6]. Supramolecular biomimetic catalysis is a rapidly expanding discipline which has benefited from the development of both homogeneous catalysis and supramolecular chemistry [7,8,9,10]. Cyclodextrins, which are cyclic oligosaccharides (pockets), consist of 7-D(+)-glucopyranose units with 7-primary and 14-secondary alcoholic -OH functionalities and can accommodate various guest molecules into its truncated cone-shaped hydrophobic cavity [11,12,13,14]. Due to their remarkable inclusion capabilities with small organic molecules, more recent interests focus on organic reactions catalyzed by cyclodextrins. They catalyze reactions by supramolecular catalysis through non-covalent bonding, as seen in enzymes. These reactions can be carried out effectively in water, which is an environmentally benign solvent under neutral conditions, and also do not generate any toxic waste products [15,16,17,18,19,20,21].

Chromenoquinolines are an important and privileged class of heterocyclic scaffolds in medicinal chemistry having chromone as a natural pharmacophore [22, 23]. Chromenoquinoline derivatives are of interest having promising biological and pharmacological activities such as anti-proliferative [24], bacteriostatic [25], ulcerogenic, anti-inflammatory, anticancer, glucocorticoid modulators, progesterone and 5-HT receptor antagonist [26,27,28,29,30,31,32] (Fig. 1). Isoniazid and its derivatives being *N*-containing heterocycles have gained prominence in medicinal chemistry due to their variety of biological activity such as anti-mycobacterial [33], anti-bacterial [34], anti-virus [35], antifungal [36], anti-tumor [37, 38], anti-analgesic [39, 40] and anti-convulsant activities. Among the various activities of its derivatives, the anti-TB activity is remarkable [41, 42]. Recently, hybridization of bioactive molecules has been one of the hottest topics in medicinal chemistry, which is on the basis of the combination of two or more different pharmacophore moieties of

different bioactive substances resulting in a new molecule [43, 44]. Therefore, we decided to club these two heterocycles in one molecular framework through Michael-initiated ring closure reaction to obtain new hybrids chromeno[4,3-b]quinolin-isonicotinamides.

Fig. 1

Representative chromeno-based bioactive compounds

The literature survey reveals that very few synthetic methods have been developed to obtained chromeno[4,3-b]quinolins. Khurana et al. [45] and Foroumadi et al. [46] carried synthesis of chromeno[4,3-b]quinolins via multicomponent approach in ethylene glycol and *n*-PrOH solvents, respectively. In the literature, some reports are available to prepare structurally different chromenoquinolines with hopes to find new therapeutically active compounds [47,48,49,50,51,52,53,54].

However, these methods are having drawbacks like long reaction time, use of volatile organic solvents and metal catalysts. Recently, we have reported the reaction of 4-hydroxycoumarin, aldehyde and active methylene compound such as malononitrile and urea in the presence of catalyst β-cyclodextrin for the formation of dihydropyranochromene and chromenopyrimidine-2,5-diones under aqueous medium [55]. Therefore, we have now extended our work with the application of cyclodextrin for the synthesis of new hybrids chromeno[4,3-b]quinolin-isonicotinamides as attractive candidates for biological evaluation.

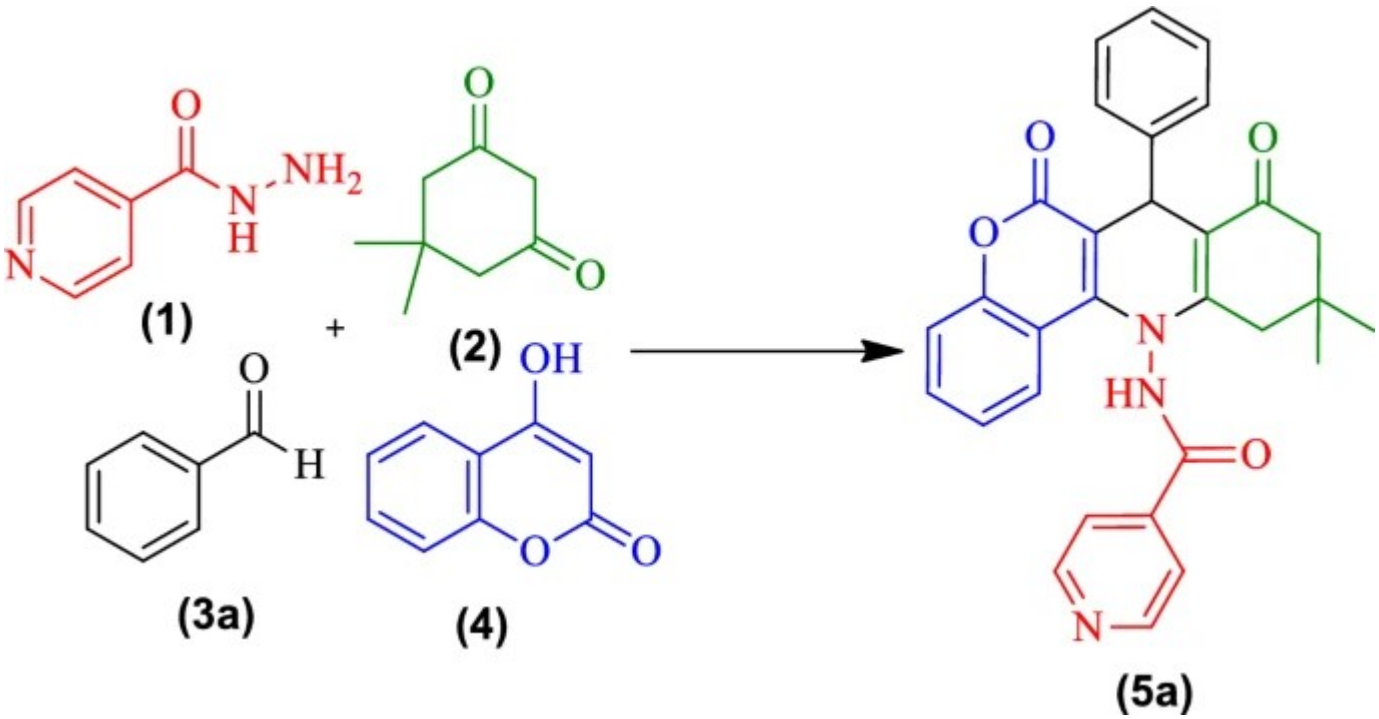
Against this background, and also in the context of our interest in the synthesis of biologically important heterocycles via multicomponent and domino reactions [56,57,58,59], we report

here the green preparation of a library of pharmacologically relevant fused polyheterocyclic systems containing a chromeno[4,3-b]quinolin and isoniazid structural fragments by a process that combines the use of aqueous media with the synthetic efficiency associated with MCRs, providing a convergence of reaction and environmental economies.

Result and discussion

In our initial studies, we attempted to optimize the reaction conditions for the domino multicomponent reaction between isoniazid, dimedone, benzaldehyde and 4-hydroxycoumarin as model substrates (Scheme 1).

Scheme 1



Synthesis of *N*-(10,10-dimethyl-6,8-dioxo-7-phenyl-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamide (5a)

We commenced our study with the optimization of the model reaction by the reported procedure in ethylene glycol as a medium. A mixture of isoniazid and dimedone was stirred in

ethylene glycol for 30 min; then, aldehyde and 4-hydroxycoumarin were added into it. First, there is formation of intermediate *N*′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)isonicotinohydrazide; then, we obtained the product *N*-(10,10-dimethyl-6,8-dioxo-7-phenyl-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamide (5a) with 89% yield in 2 h at 60 °C. We found that there is formation of new hybrid *N*-(10,10-dimethyl-6,8-dioxo-7-phenyl-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamide (5a). Therefore, to optimize the reaction conditions, we performed this domino sequential addition multicomponent reaction in various solvents such as deep eutectic mixture (ChCl–2Urea), polyethylene glycol, glycerol and the product obtained in 56, 72 and 46% yield within 1 h at 60 °C (Table 1).

Table 1 Formation of *N*-(10,10-dimethyl-6,8-dioxo-7-phenyl-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamide (5a)[a] using different catalyst and solvent systems

In recent years, there has been an upsurge in developing low cost and reliable methods by using water as a medium for synthetic transformations. Water promotes or accelerates the reactions and acts as an excellent supporting medium with numerous advantages including the ease of product isolation, non-toxicity, nonflammability, high heat capacity and a strong tendency for hydrogen bonding. Water as a solvent has been selected by nature to carry out all kinds of chemical transformations no matter whether substrates are soluble or insoluble [60,61,62,63,64]. Considering this, we decided to carry out the model reaction in water using catalysts such as CTAB, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin (β-CD), *p*-TSA and SDS to solubilize the organic reactants. We found that the desired product 5a obtained in 78, 63, 92, 49, 81 and 69% yield at 60 °C (Table 1, entries 6–11) within 1 h. No product was detected when the reaction was performed in water without the above catalyst (Table 1, entry 5) which demonstrated that catalyst is necessary to facilitate the cyclocondensation of reactants. The presence of β-CD renders the formation of 5a in high yield. Therefore, this forced us to further study the influence of water/β-cyclodextrin on the reaction outcome.

After accomplishing the optimum yield in β-CD and water system, we studied the effect of

temperature variation and catalyst concentration; the rate of reaction, as well as the yield of 5a, was conserved while reducing the temperature to 60 °C (Table 1, entry 12). The rate of reaction and product yield was decreased when the above reaction was conducted at room temperature. Further increasing the reaction temperature to 80 °C, the yield of the product turned lower. To determine the appropriate concentration of the catalyst β-CD, we investigated the model reaction at different concentrations of β-CD such as 5, 10, 15, 20 and 25 mol%. The product was formed in 62%, 74%, 89%, 92% and 92% yield, respectively (Table 1, entry 13). This indicates that 20 mol% of β-CD is sufficient to carry out the reaction smoothly.

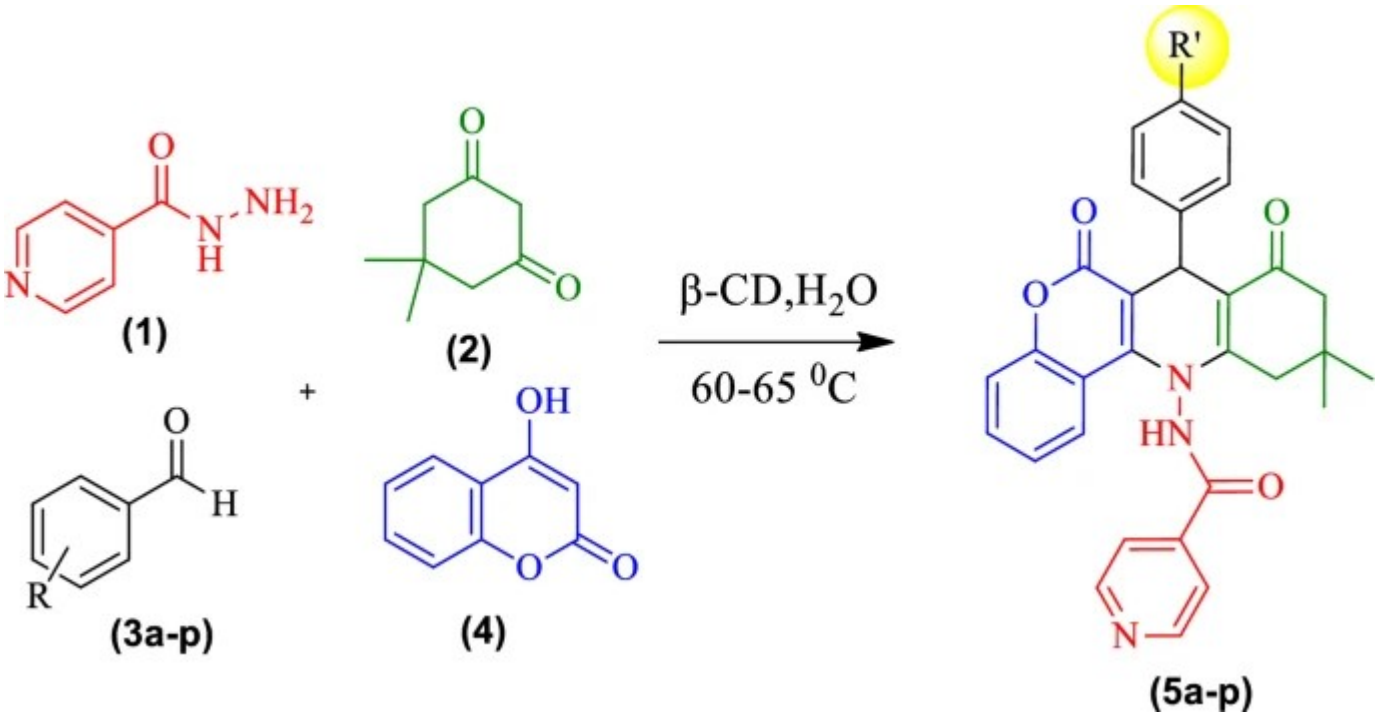
Moreover, excellent results were obtained when the reactions were performed with β-CD as a catalyst using water (92% yield) as solvents. Inferior results were obtained with CH_3CN and DMF (40 and 39% yield). EtOH, MeOH and *iso*-PrOH give the average yield (82, 76 and 69%) of the product 5a using β-CD as a catalyst (Table 2). However, β-CD in aqueous media was selected as solvent–catalyst system for the further reactions.

Table 2 Optimization of solvents for synthesis of *N*-(10,10-dimethyl-6,8-dioxo-7-phenyl-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamide (5a)[a]

Encouraged by the remarkable results obtained with the above reaction conditions, and to show the generality and scope of this new protocol, a wide range of substituted aromatic/heteryl aldehydes were used for the synthesis of variety of chromeno[4,3-b]quinolin-isonicotinamides (5a–p) in aqueous β-CD under optimized conditions, with the results as shown in Table 3. Aromatic aldehydes with several functionalities such as either mono-, di- or tri-substituted -Me, -OMe, -Cl, -Br, -F, -OH and $-NO_2$ were found to be compatible under the optimized reaction condition. Heteroaromatic aldehydes such as thiophene-2-carbaldehyde and pyridine-3-carbaldehyde were equally acquiescent to these conditions (Table 3, entries 15–16) (Scheme 2).

Table 3 Physical data of *N*-(7-(Substituted phenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamides (5a–p)[a]

Scheme 2



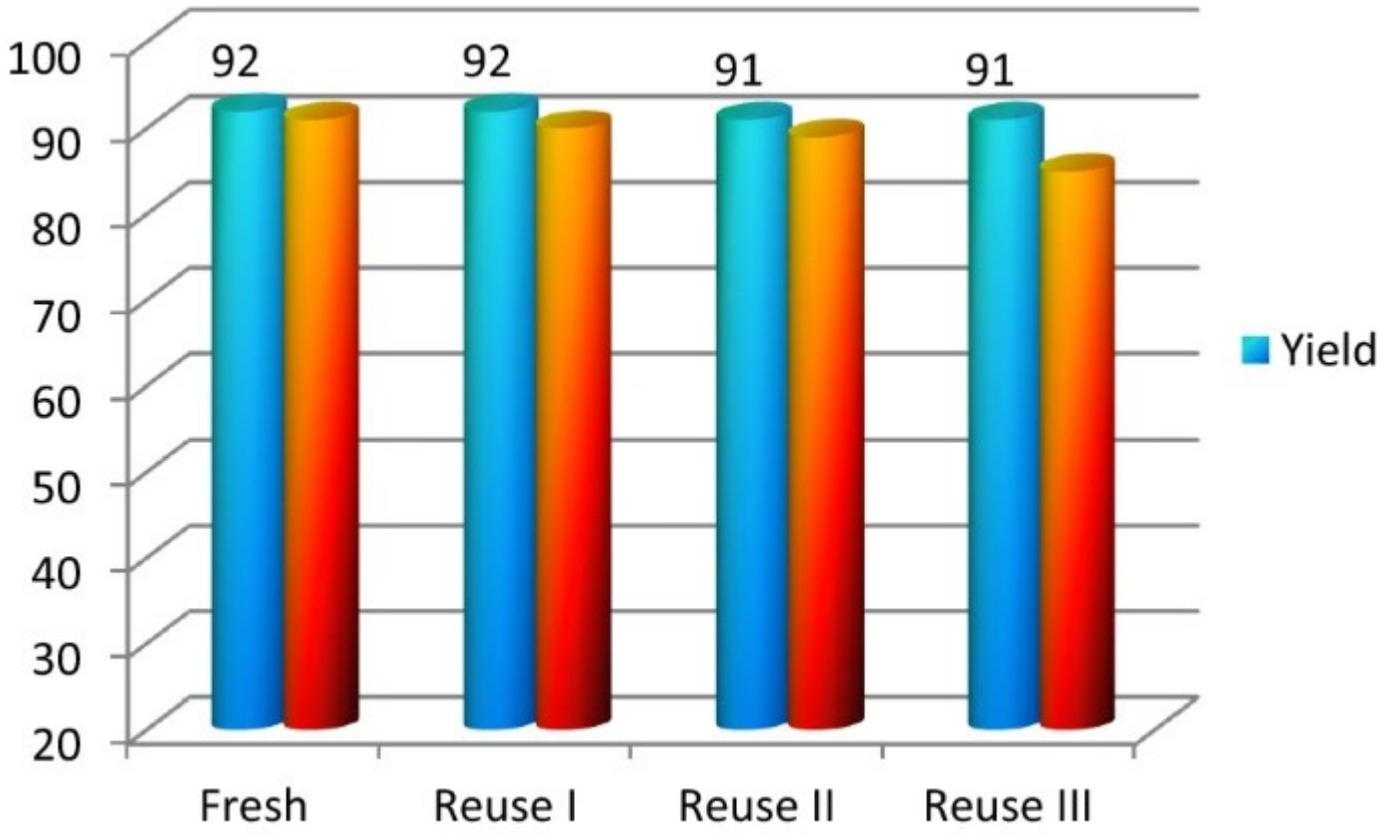
Synthesis of *N*-(7-(substituted phenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamides (5a–p)

Recycling of catalyst

After the completion of the reaction, the corresponding solid product was isolated by simple filtration and washed with hot water. The filtrate is having soluble β-CD. To the filtrate, acetone (5 mL) was added dropwise with stirring at room temperature giving a white turbid solution of precipitated β-CD which was cooled to 5 °C. Cyclodextrin was recovered by filtration, dried and reused. The catalyst β-CD was almost quantitatively recovered, and no significant loss in yield was observed (Fig. 2). The recycled β-CD was utilized in the reaction with the same substrates, and the results are shown in Fig. 2. The reusability of the catalyst

was studied for three reaction cycles (using the fresh catalyst) for the synthesis of compounds, and only a marginal decrease in the yield of the desired product was observed.

Fig. 2



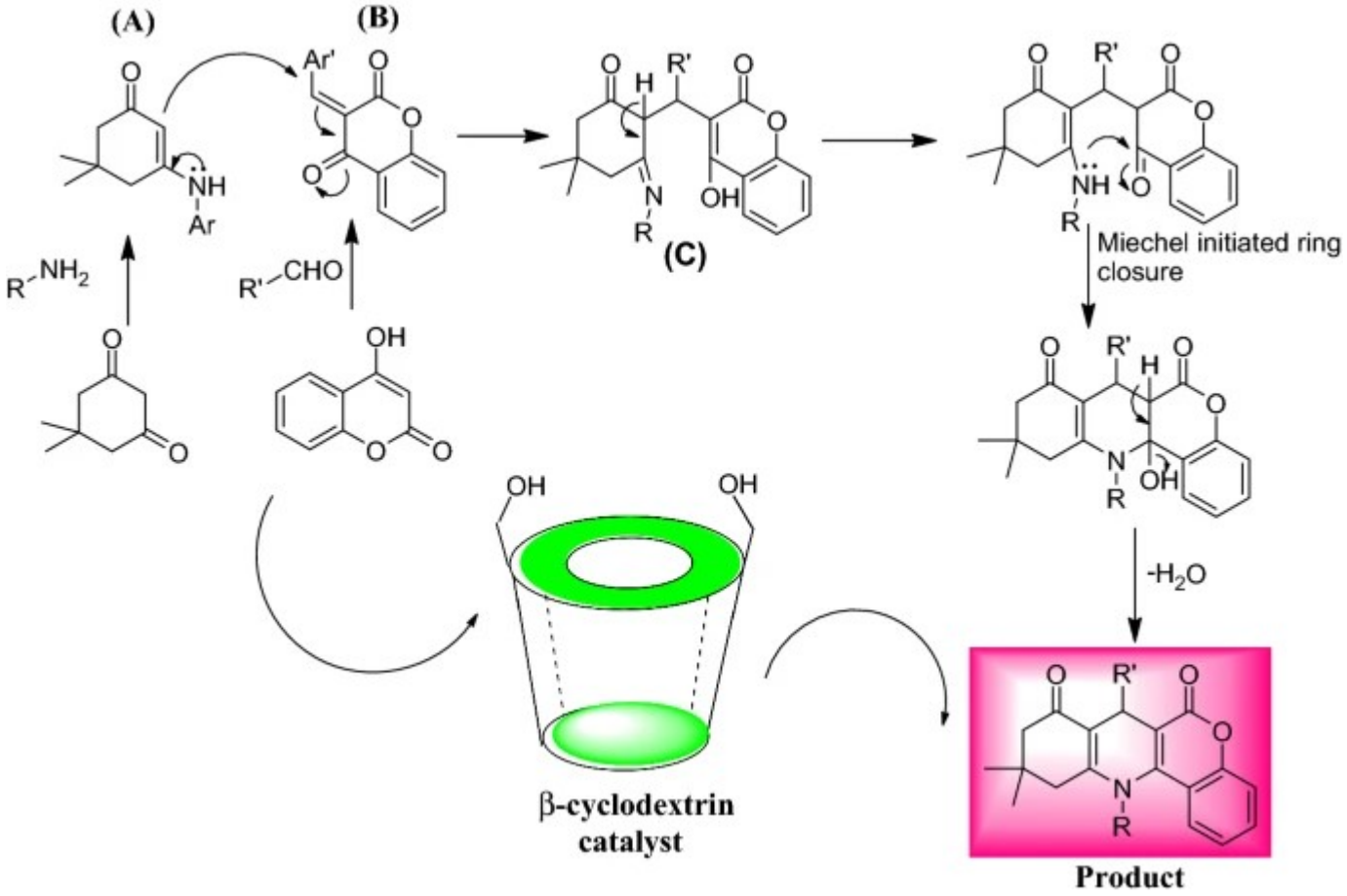
Reuse and recovery of β-cyclodextrin and its effect on yield

Plausible reaction mechanism

Cyclodextrins (CDs) act as a model of the host molecule in supramolecular chemistry. Host molecules may chelate guest molecules (with definite stability, selectivity and kinetic features), react with them (with definite rate, selectivity, turnover) and, finally, release the products, thus regenerating the reagents for a new cycle. β-CD catalyzes chemical reactions by supramolecular catalysis involving reversible construction of host–guest relations via non-covalent bonding such as that in enzymes. This type of interaction between β-CD units and reactants intensifies the local concentration of substrate and keeps the substrate near the catalytic active center; hence, this accelerates the rate of reaction and provides excellent

substrate selectivity [65, 66]. A mechanistic rationale portraying the probable sequence of events is given in Scheme 3.

Scheme 3



Plausible reaction mechanism for the synthesis of chromeno[4,3-b]quinolin-isonicotinamides (5a–p)

We supposed that the reaction may proceed via the formation of *N*′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)isonicotinohydrazide (A) and 3-(arylmethylene)chroman-2,4-dione intermediates (B) in the truncated cone-shaped cavity of β-CD. The amines and dimedone might be forming non-covalent complexes with hydroxyl group of β-CD and enhancing the localized concentration of the amines and dimedone resulting in nucleophilic addition and formation of intermediate *N*′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)isonicotinohydrazide (A). Likewise aldehydes and 4-hydroxycoumarin might be forming non-covalent reversible

supramolecular complexes with β-CD in the cavity, enhancing the localized concentration of the aldehydes and 4-hydroxycoumarin resulting in the Knoevenagel condensation and formation of intermediate 3-(arylmethylene)chroman-2,4-dione (B). Subsequent Michael addition occurs with the in situ formed intermediates (C), followed by intramolecular cyclization, dehydration to give the final product 5a.

Biological activity

Newly synthesized *N*-(7-(substituted phenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamides (5a–p) were tested for the antimicrobial activity against four pathogenic bacteria and three fungi including *Escherichia coli, P. aeruginosa, Staphylococcus aureus*, *Bacillus subtilis, Candida albicans, Aspergillus Niger and A. Flavus* in vitro using Ampicillin, Ciprofloxacin and Miconazole used as positive controls. The results are summarized in Table 4. Among the series, compounds 5f and 5c are the most potent showing inhibitory activity against all the selected bacterial and fungal strains. Compounds 5e, 5h, 5k and 5n showed significant anti-bacterial activity against *S. aureus*, *B. subtilis* bacterial strains. Compounds 5b and 5n exhibited good inhibitory activity against *A. Niger.* Compounds 5b, 5l and 5 m inhibited the *C. albicans* more potently.

Table 4 Antimicrobial screening of *N*-(7-(substituted phenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamides (5a–p)

Experimental

Reagents and instrumentation

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 Bruker Avance 400 and Bruker Topspin spectrometer operating at 400 and 700 MHz using $CDCl_3$ and 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

LCMS/MS Instrument. CHNS analysis was performed on ThermoFisher Flash EA112 Series Analyzer. The purity of each compound was checked by TLC using silica-gel, $60F_{254}$ aluminum sheets as adsorbent and visualization were accomplished by iodine/ultraviolet light.

General procedure for synthesis of 7-(substituted phenyl)-10,10-dimethyl-12-(5-phenylthiazol-2-yl)-9,10,11,12-tetrahydro-6*H*-chromeno[4,3-b]quinolin-6,8(7*H*)-diones

A mixture of isoniazid (8) (4 mmol), dimedone (2) (4 mmol) and β-cyclodextrin (20 mol%) in 20 ml of water was placed in round-bottomed flask, and the contents were stirred at 60–65 °C for 15 min. 4-Hydroxycoumarin (4) (4 mmol) and aromatic aldehydes (3a–p) (4 mmol) were then added to the reaction mixture, and the mixture was stirred at 60–65 °C. The progress of the reaction was monitored by TLC using ethyl acetate–petroleum ether as eluent. After completion of the reaction, the reaction mixture was allowed to cool at room temperature. The solid separated was collected by filtration at the pump. The products were purified by crystallizing from hot ethanol.

Spectral data of compounds

N-(10,10-dimethyl-6,8-dioxo-7-phenyl-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-yl)isonicotinamide (5a)

IR (ATR, υ cm^{-1}) Characteristic absorptions: 674, 813, 1028, 1221, 1441, 1611, 1662, 2325, 2714, 2860, 3044, 3218, 3411; ^{1}H NMR (700 MHz, DMSO-*d*6 δ ppm): 1.04–1.06 (m, 6H, CH_3), 2.05–2.16 (m, 2H, CH_2), 2.24–2.46 (m, 2H, CH_2), 4.87 (s, 1H, CH), 7.19–7.37 (m, 4H, Ar–H), 7.53–7.76 (m, 3H, Ar–H), 8.39 (s, 1H, Ar–H), 8.68–8.72 (m, 3H, Ar–H), 9.12 (s, 1H, Ar–H), 9.69 (s, 1H, Ar–H), 10.08 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO-*d6*) δ 28.17, 52.53, 60.52, 72.54, 74.18, 82.61, 101.96, 117.43, 121.86, 121.99, 122.76, 125.52, 129.65, 129.84, 131.31, 131.70, 133.69, 139.89, 140.21, 141.58, 144.50, 149.19, 150.77, 151.64, 162.29, 164.67, 167.05, 193.27; MS (scanning mode, ESI^+): m/z 492 (M^+); Anal. calcd. For $C_{30}H_{25}N_3O_4$: N, 8.55; C, 73.30; H, 5.13; Found: N, 8.50; C, 73.36; H, 5.09%.

N-(10,10-Dimethyl-6,8-dioxo-7-(p-tolyl)-8,9,10,11-tetrahydro-6*H*-chromeno[4,3-b]quinolin-12(7*H*)-

yl)isonicotinamide (5b)

IR (ATR, υ cm^{-1}) Characteristic absorptions: 672, 817, 1028, 1226, 1613, 1664, 1653, 3042, 3222, 3407; ^{1}H NMR (700 MHz, DMSO-*d6* δ ppm): 1.08–1.10 (m, 6H, CH_3), 2.03–2.12 (m, 2H, CH_2), 2.28–2.50 (m, 5H, CH_2, CH_3), 4.85 (s, 1H, CH), 7.28–7.46 (m, 4H, Ar–H), 7.64–7.88 (m, 2H, Ar–H), 8.43 (s, 1H, Ar–H), 8.75–8.79 (m, 3H, Ar–H), 9.09 (s, 1H, Ar–H), 9.95 (s, 1H, Ar–H), 10.83 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO-*d6*) δ 21.71, 28.12, 50.89, 60.57, 73.26, 74.07, 82.27, 102.04, 118.30, 121.36, 121.96, 123.52, 127.75, 129.26, 129.93, 130.76, 131.65, 134.41, 139.41, 140.68, 140.90, 145.60, 149.71, 150.76, 151.20, 161.16, 164.32, 166.27, 193.48; MS (scanning mode, ESI^+): m/z 506.4 (M^+); Anal. calcd. For $C_{31}H_{27}N_3O_4$: N, 8.31; C, 73.65; H, 5.38; Found: N, 8.29; C, 73.61; H, 5.40%.

N-(7-(4-Bromophenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6H-chromeno[4,3-b]quinolin-12(7H)-yl)isonicotinamide (5e)

IR (ATR, υ cm^{-1}) Characteristic absorptions: 680, 817, 1010, 1200, 1358, 1487, 1593, 2955, 3181, 3455; ^{1}H NMR (700 MHz, DMSO-*d6* δ ppm): 1.03 (s, 6H, CH_3), 2.06 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 4.85 (s, 1H, CH), 7.00–7.23 (m, 5H, Ar–H), 7.31–7.88 (m, 4H, Ar–H), 8.36 (s, 1H, Ar–H), 8.89–8.91 (m, 2H, Ar–H), 9.78 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO-*d6*) δ 28.15, 55.87, 60.36, 72.59, 73.48, 82.05, 91.09, 104.13, 112.34, 114.26, 119.87, 120.10, 122.63, 123.68, 125.61, 128.67, 131.21, 132.70, 41.72, 144.77, 147.32, 148.59, 149.93, 150.37, 152.88, 161.93, 164.93, 166.03, 167.53, 191.51; MS (scanning mode, ESI^+): m/z 570.3 (M^+); Anal. calcd. For $C_{30}H_{24}BrN_3O_4$: N, 7.37; C, 63.17; H, 4.24; Found: N, 7.41; C, 63.15; H, 4.21%.

N-(7-(4-(Dimethylamino)phenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6H-chromeno[4,3-b]quinolin-12(7H)-yl)isonicotinamide (5g)

IR (ATR, υ cm^{-1}) Characteristic absorptions: 674, 841, 997, 1263, 1322, 1410, 1512, 1673, 2960, 3182, 3565; ^{1}H NMR (700 MHz, DMSO-*d6* δ ppm): 1.03–1.06 (m, 6H, CH_3), 2.07–2.09 (m, 2H, CH_2), 2.25–2.33 (m, 2H, CH_2), 3.77 (s, 6H, CH_3), 4.49 (s, 1H, CH), 7.13–7.29 (m, 5H, Ar–H), 7.45–7.64 (m, 2H, Ar–H), 7.80–7.99 (m, 3H, Ar–H), 8.48 (s, 1H, Ar–H), 8.91 (s, 1H, Ar–H), 9.99 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO-*d6*) δ 28.35, 29.25, 36.10, 46.85, 47.08, 50.49, 50.71, 59.90, 73.03, 103.98, 105.69, 113.83, 115.99, 120.06, 123.08, 123.30, 128.15, 129.05, 129.29,

133.14, 135.29, 139.20, 142.86, 146.49, 146.87, 148.59, 149.26, 161.26, 161.48, 163.67, 164.54, 167.75, 192.63; MS (scanning mode, ESI^+): m/z 535.6 (M^+); Anal. calcd. For $C_{32}H_{30}N_4O_4$: N, 10.48; C, 71.89; H, 5.66; Found: N, 10.45; C, 71.92; H, 5.62%.

N-(7-(8-Methoxynaphthalen-1-yl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6H-chromeno[4,3-b]quinolin-12(7H)-yl)isonicotinamide (5l)

IR (ATR, υ cm^{-1}) Characteristic absorptions: 662, 828, 1025, 1161, 1248, 1363, 1553, 1599, 1653, 2957, 3445; ^1H NMR (700 MHz, DMSO-*d6* δ ppm): 1.02–1.15 (m, 6H, CH_3), 2.09–2.26 (m, 2H, CH_2), 2.31–2.51 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 4.95 (s, 1H, CH), 6.25–6.44 (m, 2H, Ar–H), 6.79–7.29 (m, 4H, Ar–H), 7.51–7.64 (m, 2H, Ar–H), 7.87–7.99 (m, 3H, Ar–H), 8.42 (s, 1H, Ar–H), 8.76–8.91 (m, 2H, Ar–H), 9.89 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO-*d6*) δ 28.25, 50.37, 55.79, 60.65, 73.37, 74.23, 82.72, 103.63, 117.71, 121.45, 121.63, 123.57, 127.14, 129.89, 129.98, 130.63, 131.71, 133.90, 139.47, 140.79, 140.95, 145.28, 149.69, 150.70, 151.36, 161.67, 164.29, 166.56, 193.54; MS (scanning mode, ESI^+): m/z 572.2 (M^+); Anal. calcd. For $C_{35}H_{29}N_3O_5$: N, 7.35; C, 73.54; H, 5.11; Found: N, 7.31; C, 73.58; H, 5.15%.

N-(7-(2,6-Dichlorophenyl)-10,10-dimethyl-6,8-dioxo-8,9,10,11-tetrahydro-6H-chromeno[4,3-b]quinolin-12(7H)-yl)isonicotinamide (5m)

IR (ATR, υ cm^{-1}) Characteristic absorptions: 667, 842, 1025, 1237, 1383, 1433, 1563, 1616, 1664, 2361, 3299; ^1H NMR (700 MHz, DMSO-*d6* δ ppm): 1.03–1.06 (m, 6H, CH_3), 2.07–2.13 (m, 2H, CH_2), 2.28 (s, 2H, CH_2), 4.85 (s, 1H, CH), 7.18–7.37 (m, 2H, Ar–H), 7.50–7.97 (m, 7H, Ar–H), 8.71–8.85 (m, 2H, Ar–H), 10.85 (s, 1H, NH); ^{13}C NMR (176 MHz, DMSO-*d6*) δ 28.12, 50.50, 60.37, 72.82, 74.08, 81.83, 91.52, 102.26, 103.09, 112.79, 116.21, 116.59, 116.82, 122.16, 123.53, 124.12, 130.77, 131.43, 131.87, 133.59, 135.55, 135.98, 140.01, 145.01, 149.93, 150.37, 153.95, 162.40, 166.27 190.06; MS (scanning mode, ESI^+): m/z 560.4 (M^+); Anal. calcd. For $C_{30}H_{23}Cl_2N_3O_4$: N, 7.50; C, 64.29; H, 4.14; Found: N, 7.54; C, 64.31; H, 4.11%.

Conclusion

A diverse library of biologically functional new chromeno[4,3-b]quinolin-isonicotinamides was synthesized by supramolecular catalysis of domino multicomponent reaction in aqueous β-cyclodextrin. This domino strategy allows rapid cyclization by Michael addition of in situ generated intermediates for 16 desired target skeletons in excellent yields. The present protocol offers prominent advantages of shorter reaction times, simple operational procedure, being practically robust and extensive substrate scope. The proficient catalytic activity of the β-cyclodextrin in this cyclocondensation reaction will definitely accumulate to the already existing synthetic methodologies which make the present domino process more convenient and eco-friendly. All the synthesized chromeno[4,3-b]quinolin-isonicotinamides (5a–p) were examined for their potential in vitro antimicrobial activity. Compounds 5c and 5f show excellent anti-bacterial activity.

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Ethics declarations

Conflict of interest

The authors declare that they have no conflict of interest.

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