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ORIGINAL ARTICLE

Synthesis of per-substituted hydrophilic and hydrophobic β-cyclodextrin derivatives

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Abstract The aim of this work was to synthesize new cyclodextrin derivatives from native β-cyclodextrin by allylation reactions and indium metal in aqueous and organic medium. The resulted products could be used to prepare a new hydrophilic pharmaceutical active ingredient. A hydrophobic derivative can also be prepared by the same method. Indeed, the allylation reactions allow the creation of a stereogenic centers and the introduction of an allyl group lead to development of various functionalization of CD sites. Natural β-cyclodextrin was treated with allyl bromide and sodium hydride in dimethylformamide (DMF) at room temperature, which resulted in the formation of *O*-perallylated β-cyclodextrin A_1 (98%). Through successive reactions of oxidation, reduction and allylation, the latter was converted into per 2, 3, 6-tri-*O*-(2-hydroxypent-4-enyl) β-cyclodextrins A_4 (40%). Others derivates of CD type B_3 and C_3 were synthesized by series of reaction to give multifunctionalized cyclodextrins with yield of 25 and 30%, respectively.

Keywords *O*-perallylated β-CD · Per 2, 3, 6-tri-*O*-(2-hydroxypent-4-enyl) β-CD · Hydrophobic · Hydrophilic · Indium

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Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with truncated cylindrical shapes and are composed of six, seven or eight glucose units (α-, β- and γ-CD, respectively) [1].

CDs have a hydrophobic internal cavity and hydrophilic external part, which provide interesting properties and specific complexation abilities with guest molecules including compounds with aromatic moieties. Due to the ability to form a complex with host molecule, CDs have found a wide range of applications in pharmaceutical field, food additives, chromatography and enzyme mimicking [2, 3]. The complexation could be achieved either by chemical modification of hydroxyl groups present on the outer surface of the CDs or by their relative hydrophobic interactions. Bartsch and Croft investigated the chemical modification of cyclodextrins [4], however, these modifications were difficult to control due to problems arising from steric and statistical factors imposed by the torus structure and the large number of hydroxyl groups [5]. The natural CDs, in particular β-CD, are of limited aqueous solubility (e.g., solubility β-CD in pure water at ∼25 °C is 18.5 g/L). Consequently, the synthesis of new CD derivatives is needed to improve both the apparent solubility of hydrophobic drugs and their release mechanism. To our knowledge, the only application of CD was conducted in extended releases where derivatives ethylated polymers of CD or CDs were used [6].

The preparation of CD derivatives by allylation reaction [7, 8] could be conducted in aqueous and organic medium. Indeed, the allyl groups could be grafted [9] effectively into various positions of CDs skeleton leading to novel intermediates following an oxidation reaction. Two strategies were investigated. First, per [2, 3, 6-tri-*O*-(2-hydroxypent-4-enyl) β-CD] A_4 with yield of 40% was obtained by reacting the per-*O*-allyl-ß-CD A_1 with periodate and allyl

bromide in the presence of indium in water at room temperature (20 °C ± 1 °C) in which all hydroxyl groups were substituted by a chain of five carbons. Second, other type of CD derivatives in an organic medium were synthesized mainly [2, 3-di-*O*- methyl, 6-*O*-(2 hydroxy, 2 propenyl) pent-4enyl]-*β*-CD B_3 and 3-*O*-methy-3, 6-di-*O*-(2-hydroxyprop-3-enyl) pen-4-enyl *β*-cyclodextrins C_3. The product B_3 was resulted after the reduction of ester to an alcohol functional group, which took place between B_2 and allylmagnesium chloride in tetrahydrofuran at −78 °C. The compound C_3 was obtained by reacting the allylmagnesium chloride through C_2 under the same conditions as B_3.

Materials and methods

β-CD was obtained from Roquette, France and dried in a vacuum oven at 80°C for 48 h. Tetrahydrofuran, chloroform, dimethylformamide, dichloromethane, methanol and sodium hydride were obtained from VWR-France. The reagents allyl bromide, 4-methylmorphine N-oxide monohydrate, Osmonim tetroxide, allylmagnesium chloride, sodium periodate and acetate bromide were obtained from Acros organics, France. The purified water was obtained using Millipore Super Q system and degassed prior to use. The methylation of CDs was performed in anhydrous conditions, under inert atmosphere and in a round bottomed vessel fitted with reflux condenser and a dropping funnel. The silica gel for the purification is obtained from VWR, France.

Per (2, 3, 6-tri-*O*-allyl)-*β*CD A_1

β-cyclodextrin (2.07 g; 1.82 mmol) was dissolved in 90 mL of anhydride DMF while heating and stirring. The obtained clear solution was added drop wise to cold (0 °C) suspension of NaH (60% dispersion in mineral oil), (2 g, 83 mmol, 2.2 equiv per OH group in cyclodextrin). The suspension was stirred for 1 h at 0–5 °C while adding allyl bromide (15 mL, 172 mmol, 4.5 equiv per –OH group in CD) drop wise. The resulting mixture was first stirred for 1 h at 0–5 °C and 24 h at room temperature. At this point, TLC showed the formation of a single product. The reaction was quenched by addition of 5 mL methanol. Dimethylformamide and excess allyl bromide were removed by evaporation under diminished pressure. The obtained residue was partitioned between 200 mL of EtOAc and 30 mL of water, the organic layer was washed twice with (2 × 50 mL) of saturated NaCl and dried over Na_2SO_4 then evaporated. The purification of *O*-perallylated CDs was obtained by using a flash silica gel column and an eluent composed of 9.5:0.5 (v/v) dichloromethane/methanol then characterized by NMR as given below.

^{1}H NMR (300 MHz, $CDCl_3$)

6.10–6.03 (m, 7H, $OCH_2CH = CH_2$), 6.04–5.92 (m, 14 H, $OCH_2–CH = CH_2$), 5.44–5.26 (m, 21 H, $OCH_2CH = CH$H), 5.23(d, 7 H, *J* 3.4 Hz, H-1), 5.24–5.14 (m, 21 H, $OCH_2CH = CH$H), 4.57–4.35 (dd, 14H, *J* 12.1, 5.4 Hz, OCH*H*$CH = CH_2$), 4.30–4.06 (m, 28 H, OCH*H*$CH = CH_2$), 3.96 (dd, 7 H, *J* 10.5, 2.4 Hz, H-6), 3.90–3.64 (m, 21 H, H-3, H-4 and H-5), 3.58 (d, 7 H *J* 10.5 Hz, H-6′), 3.35 (dd, 7 H, *J* 9.4,3.4 Hz, H-2).

^{13}C NMR (300 MHz, $CDCl_3$)

138.0–137.56 (OCH_2–*C*H=CH_2), 119.03–118.86 (OCH_2CH=*C*H_2), 101.27 (C-1), 82.68 (C-3), 81.76 (C-2), 81.86 (C-4), 75.09 (O*C*H_2CH=CH_2), 73.69(C-5), 71.65 (C-6).

Per 2, 3, 6-tri-*O*-(2-hydroxypent-4 enyl)- *β*CD A_4

The compound A_1 (3 g, 1.5 mmol) was dissolved in mixture of acetone/water (20/10 mL). After 30 min, the mixture was added to 4-methylmorphine N-oxide monohydrate (1.98 g, 7 mmol, 5 eq) and Osmonim tetroxide (7 g, 60 mmol, 40 eq). The obtained solution had a black color and stirred for 24 h then treated twice with ethyl acetate (2 × 30 mL) and washed twice with water (2 × 30 mL).The aqueous layer was treated with saturated aqueous $Na_2S_2O_3$ (2 × 15 mL), water (15 mL) and filtered then evaporated. Finally, the obtained product was purified by silica gel column chromatography and water: methanol (9.5:0.5) as eluent, which contained 98% of compound A_2 (2, 3, 6-tri-*O*-(2-3 dihydroxypropyl)-*β*CD). In addition, the compound A_2 (0.5 g, 186 mmol) was dissolved in 10 mL water at room temperature and (2.5 g, 12 mmol, 64 eq) of $NaIO_4$ was slowly added. After 1 h of stirring, the solution was filtered then indium (1.5 g, 13 mmol, 70 eq), bromide allyl (1.5 g, 13 mmol, 70 eq) and 2 mL of tetrahydrofuran were added, respectively. The mixture was stirred for 24 h at room temperature. Then analyzed by TLC where it showed tree spots. The mixture was stirred again for 1 h at room temperature. Finally, the medium was acidified and extracted with ethyl acetate (3 × 30 mL) and the resulted two layers were then separated and NMR was conducted.

^{1}H NMR $CDCl_3$ 300 MHz A_4

5.97(m, 21H, $OCH_2CH(OH)CH_2CH$=CH_2), 5.86 (m, 42H, $OCH_2CH(OH)CH_2CH$=CH_2), 5.43–5.3 (d, 7 H, J 3.5 Hz, *H-1*), 4.41 (br, OCH_2CH(*OH*)CH_2CH=CH_2), 4.32(m, 42H, $OCH_2CH(OH)CH_2CH$=CH_2), 3.90 (*H-6*), 3.66–3.55 (14 H, *H-3*, *H-4*), 3.22 (7 H, *H-2*), 3.75 (m, 7H, *H-5*), 3.52 (*H-6′*), 2.07-(42H, O*C*$H_2CH(OH)CH_2CH$=CH_2), 2.57 (m, 21H, $OCH_2CH(OH)CH_2CH$=CH_2).

^{13}C NMR $CDCl_3$ 300 MHz

136.0 ($OCH_2CH(OH)CH_2CH{=}CH_2$),116.86 ($OCH_2CH(OH)CH_2CH{=}CH_2$), 99.33 (*C-1*), 80.96 (*C-3*), 80.46 (*C-2*), 81.68 (*C-4*), 76.74 ($OCH_2CH(OH)CH_2CH{=}CH_2$), 72.79 ($OCH_2CH(OH)CH_2CH{=}CH_2$), 73.63(*C-5*), 71.70 (*C-6*).

[2, 3-di-*O*- methyl, 6-*O*-(2hydroxy, 2 propenyl) pent-4-enyl]-*β*-CD B_3

The first step was the reaction of ethyl bromoacetate with 2, 3-*O*-dimethyl-*β*CD B_1 which led to per-2, 3-*O*-dimethyl-6-*O*-AcEt) *β*CD B_2. This compound was isolated with a good yield. The compound B_2 was transformed into per 2, 3-*O*-dimethyl-6-*O*-(2hydroxy 2-propenyl) pent-4 enyl *β*CD B_3. The reduction of the ester to alcohol function by allylmagnesium chloride at −78 °C gave the formation of two allylic substitutions on the same carbon. The compound B_3 was characterized by NMR and the results were given below.

^{1}H NMR $CDCl_3$ 300 MHz, B_3

6.03(m, $OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 5.90(m, $OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 5.17 (d, 7 H, J 3.5 Hz, *H-1*), 4.33(m, $OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 3.65 (m 7 H, *H-5*), 3.95–3.85 (12 H, *H-6, 6′*), 3.65 (21H, *O-Me*$_3$), 3.50 (7 H, *H-3*), 3.51 (21H, *O-Me*$_2$), 3.20 (7 H, J 9.5 Hz, *H-2*), 2.12 ($OCH_2C(OH)[CH_2CH{=}CH_2]_2$).

^{13}C NMR $CDCl_3$ 300 MHz

136.31 ($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 116.68–115.70 ($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 99.33 (*C-1*), 81.96 (*C-3*), 81.26 (*C-2*), 80.60 (*C-4*), 75.09 (($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), *74*–70 (($OCH_2C(OH)[CH_2CH{=}CH_2]_2$),70.97 (*C-5*), 67.0(*C-6*), 61.54 (3-*O-CH*$_3$), 59.09 (2-*O-CH*$_3$).

3-*O*-methy-3, 6-di-*O*-(2-hydroxyprop-3-enyl) pen-4-enyl *β*-cyclodextrins C_3

1 g of heptakis (3-*O*-methyl)-*β*-CD was dissolved in 50 mL of dry DMF by stirring. The solution was then added dropwise to a cooled (0 °C) suspension of NaH (1.2 g, 60% dispersion in mineral oil). The resulted mixture was firstly stirred for 15 min at 0–5 °C, then for 45 min at 25 °C, finally, 1 mL ethyl bromoacetate was added drop wise at 0–5 °C to the aforementioned solution which gave a yellowish color. The mixture was stirred at room temperature for 24 h and quenched by addition of 100 mL water then extracted with (3 × 30 mL) Chloroform ($CHCl_3$). The organic layer was washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated. The purified product, Per (2, 6-di-*O*-AcEthyl-3-*O*-methyl)-*β*-CD C_2, was obtained using a flash silica gel column and eluent composed of hexane–EtOAc (3:1) (v/v). Under the action of chloride on allylmagnesium through C_2 in defined conditions, we obtained the compound C_3 which was purified and characterized by NMR.

^{1}H NMR $CDCl_3$ 300 MHz, C_3

6.0–5.85 (m, $OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 5.20–5.15(m, $OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 5.12–5.3 (d, 7 H, J 3.5 Hz, *H-1*), 4.50–3.98(m, $OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 3.84 (*H-6*), 3.70 (m, 7H, *H-5*), 3.58 (m, *H-4*), 3.55 (21H, *O-Me3*), 3.54 (*H-6′*), 3.42 (7 H, *H-3*), 3.22 (7 H, *H-2*), 2.12–2.65 ($OCH_2C(OH)[CH_2CH{=}CH_2]_2$).

^{13}C NMR $CDCl_3$ 300 MHz

136.31 ($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 116.68–115.70 ($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 98.73 (*C-1*), 81.96 (*C-3*), 81.26 (*C-2*), 80.60 (*C-4*), 75.09 (($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 74–70 (($OCH_2C(OH)[CH_2CH{=}CH_2]_2$), 70.97 (*C-5*), 67.0(*C-6*), 59.09 (2–*O–CH*$_3$).

Results and discussion

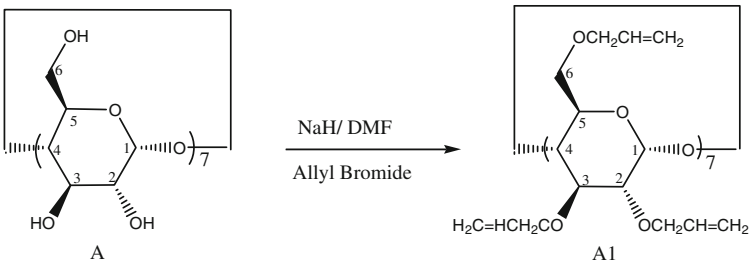
The *O*-perallylation of native CD was conducted according to the procedure described by Badi et al. [10, 11] in which the synthesis was conducted at higher temperature conditions (60 °C). Briefly, natural CD was dissolved in dimethylformamide by heating and stirring. A clear solution was obtained and added to NaH suspension in dried DMF then the allylation reaction with allyl bromide was conducted at low temperature 0 °C. Interestingly, this method led to a reproducible allylation yield of the native *β*-CD. Consequently, *O*-perallylated *β*-CD was obtained with 98% yield (Scheme 1).

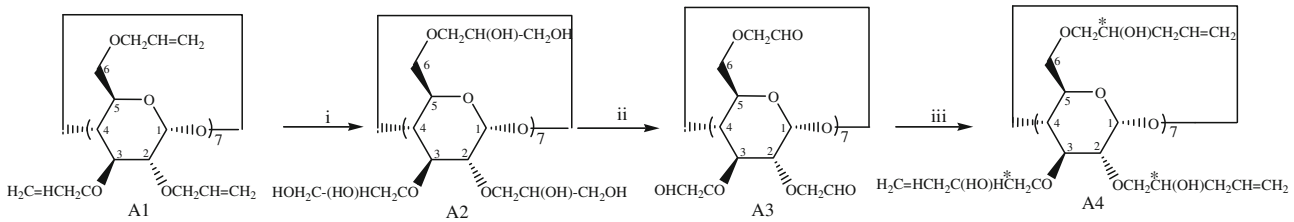
Per-2, 3, 6-tri-*O*-(2-hydroxypent enyl-4)-*β*CD A_4

The formation of compound A_4 was conducted in four steps as shown in Scheme 2

The formation of per-(2,3, 6) tri-*O*-(1,2) dihydroxypropyl *β*CD (diol) intermediate was obtained by an oxidation of allyl function group using osmium tetroxide (O_4Os), the reaction was conducted in the presence of 4 methylmorphine-N-oxide monohydrate (NMO) [12]. This powerful oxidant has the ability to transform the allylated *β*CD into per-(2, 3, 6) tri-*O*-(1, 2) dihydroxypropyl *β*CD A_2 with a yield of 98%. Per-(2, 3, 6) tri-*O*-(1, 2) dihydroxypropyl *β*CD (diol) underwent a reduction reaction by $NaIO_4$ forming an aldehyde. Under the action of allyl bromide and

Scheme 1 Allylation reaction, Reagents and conditions (i): NaH, DMF and Allyl Bromide





Scheme 2 Oxidation, reduction and allylation reaction, Reagents and conditions (i): Acetone, H_2O; NMO, OsO_4; (ii, iii) $NaIO_4$, H_2O, THF, In, Allyl Bromide, 25 °C, 24 h

in the presence of indium, the compound 2, 3, 6-tri-*O*-(2-hydroxypent enyl-4)-*β*CD A_4 was formed with a yield of 40%. The obtained compound has a chain of five carbons containing both double bond, hydroxyl group and an asymmetric carbon. FT-IR spectra of compound A_4 showed a characteristic absorption band –OH at 3600 to 3200 cm^{-1}, *C*=*C* absorption band at 1660.31 cm^{-1}, =C–H absorption band at 3098 cm^{-1}, alkane type $–CH_3$, $–CH_2$ and –CH absorption band at 2934.34 cm^{-1}. Additionally, the absorption band of aldehyde was observed in the spectrum of intermediate A_3. NMR spectra of the compound A_4 indicated the allyl protons at 5.97 ppm C*H*=CH_2, and 5.86 ppm CH=CH_2; the anomeric proton at 5.43–5.3 ppm d, 7 H, J 3.5 Hz, *H-1*) and the signal for the hydroxyl group at 4.41 ppm *OH*.

2, 3-*O*-dimethyl-6-*O*-(2hydroxy 2-propenyl) pent-4 enyl *β*CD B_3

The formation of compound B_3 was conducted in three steps as shown in Scheme 3.

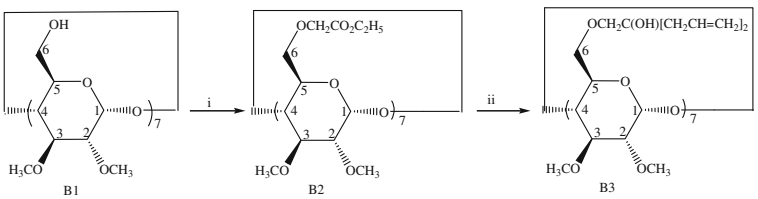
The reaction of ethyl bromoacetate with 2, 3-*O*-dimethyl-*β*CD B_1, which led to 2, 3-*O*-dimethyl-6-*O*-AcEt) *β*CD B_2 with a good yield. The latter was transformed into per 2, 3-*O*-dimethyl-6-*O*-(2hydroxy 2-propenyl) penta-4 enyl *β*CD B_3. The reduction of the ester to an alcohol by allylmagnesium chloride at −78 °C led to the formation of two allylic substitutions on the same carbon. The analysis of compound B_3 by FT-IR showed a peak at 3436–3626.97 cm^{-1}suggesting the presence of OH functions, the decrease of the intensity peak at this region was mainly due to the methylation of secondary hydroxyl group. A peak at 1090.30 cm^{-1} represented ether groups *O*CH_3; peak at 1639.32 cm^{-1} corresponded to group of alkenes *C*=*C*; peak at 2856–2925 cm^{-1} indicated the presence of alkanes group $–CH_2–$CH and peak at 880–995 cm^{-1} corresponded to substituent's =CH, $=CH_2$. NMR spectra for the compound B_3 indicated the allyl protons: at 6.03 ppm C*H*=CH_2, 5.90 ppm CH=CH_2, and 4.33 ppm CH_2CH=CH_2; the anomeric proton at 5.17 ppm d, 7 H, J 3.5 Hz, *H-1*; and the methoxy group's at 3.65 ppm 7x *O-Me*$_3$, 3.51 ppm 7x*O-Me*$_2$.

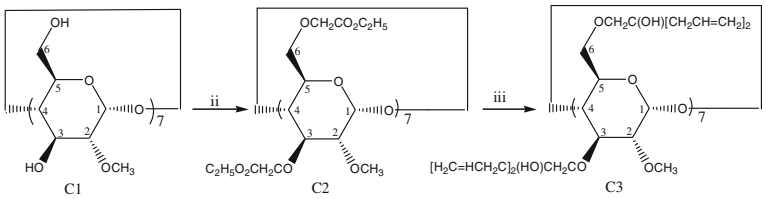
2-*O*-methy-3, 6-di-*O*-(2-hydroxyprop-3-enyl) pen-4-enyl *β*-cyclodextrins C_3

This synthesis was achieved in a tree-step procedure as demonstrated in Scheme 4.

The 2-*O*-methyl *β*-CD C_1 was reacted with ethyl bromoacetate in dimethylformamide in the presence of a base, which gave 2-*O*-methyl-3, 6-di-*O*-(EtOAc) *β*-CD C_2.

Scheme 3 Functionalization of various sites of the 2,3 di-*O*-methyl *β*CD, Reagents and conditions (i): DMF, NaH, $C_4H_7BrO_2$; (ii, iii) THF, $MgCl_2CH_2CHCH_2$, −78 °C, 20 min





Scheme 4 Functionalization of various sites of the 2-*O*-methyl βCD, Reagents and conditions (i): DMF, NaH, $C_4H_7BrO_2$; (ii) THF, $MgCl_2CH_2CHCH_2$, −78 °C, 20 min

This compound was dissolved in tetrahydrofuran at −78 °C then the allylmagnesium chloride was added to give 2-*O*-methy-3,6-di-*O*-(2 hydroxyprop-3enyl)pen-4-enyl β-CD C_3. Analysis of compound C_3 was found in the same type of B_3 absorption bands but with more or less strong intensities. NMR spectra for the compound C_3 indicated the allyl carbons at 136.31 ppm *C*H=CH_2 and at 116.68–115.70 ppm CH=*C*H_2, the carbon at 98.73 ppm C-1, and the methoxy group at 59.09 ppm 2-*O*–CH_3.

Conclusion

It is well known that allyl groups could be introduced effectively into various positions of the CD skeleton. The oxidation of the allylic functions and substitution of alcohol groups opened an access to novel hydrophilic intermediate of CDs with improved physicochemical proprieties. A variety of ketones and aldehydes underwent indium-mediated allylation in water leading to the homoallylic alcohols with relatively significant yields. Allylic iodides and bromides are equally reactive. Indium could also mediate the allylation of aldehydes and ketones efficiency in water [13]. In pure aqueous or partially aqueous medium, the allyl-indium is easily generated in situ by reacting the allyl halides with the indium. It was noticed during the synthesis of compound A_4 that the yield of allyl group substitution is greater in the presence of indium. Yet, chemically synthesized β-CDs derivatives in aqueous medium in presence of indium metal have been optimized and the desired products were obtained with higher yield. In regard to compounds B_3 and C_3, we showed the ability to substitute different groups in three β-CD sites. However, the results obtained were composed of isomers mixture. The use of allylmagnesium chloride for reduction of ester group was efficient and produced a convenient yield which was 25 and 30%, respectively. Unlike the intermediate A_2, A_3, and B_2 which were soluble in an aqueous medium, the final products A_4, B_3 and C_3 were insoluble in water. All synthesized CDs derivatives have a variety of substitutions that could easily be evolved by substitution reactions, addition, oxidation and metathesis to give another compounds with different physicochemical properties [14]. The presence of different substituent (A_4, B_3, C_3) could be an asset to the formation of stable complexes with drug substances. All of these properties are unique for these new CD derivatives compared to those written in the literature [7]. These CDs derivatives could be suggested as useful excipients for chemical and/or pharmaceutical applications.

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