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## Graphical Abstract

**β-Cyclodextrin-propyl sulfonic acid: a new and eco-friendly catalyst for one-pot multi-component synthesis of 3, 4-dihydropyrimidones *via* Biginelli reaction**

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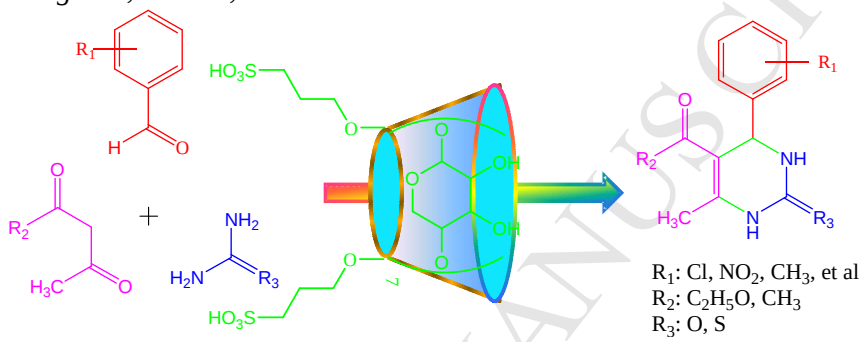


$R_1$: Cl, $NO_2$, $CH_3$, et al
$R_2$: $C_2H_5O$, $CH_3$
$R_3$: O, S

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# *β*-Cyclodextrin-propyl sulfonic acid: a new and eco-friendly catalyst for one-pot multi-component synthesis of 3, 4-dihydropyrimidones *via* Biginelli reaction

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ABSTRACT

*β*-Cyclodextrin-propyl sulfonic acid (*β*-CD-PSA) is reported as a new and eco-friendly catalyst for the synthesis of 3, 4-dihydropyrimidinones from one-pot multi-component reaction of aromatic aldehydes, 1, 3-dicarbonyl compounds and urea or thiourea under solvent-free conditions. The present methodology offers several advantages, such as shorter reaction time, high yields, mild reaction conditions and a simple work-up procedure. Furthermore, *β*-CD-PSA is inexpensive, biodegradable, and can be reusable. It could be reused six-times without a significant loss of catalytic activity.



## 1. Introduction

Multi-component reactions (MCRs) have been proven to be remarkably successful in generating molecular complexity in a single synthetic operation, and shown simple procedures, high atom-economy and high selectivity due to the formation of carbon-carbon and carbon-heteroatom bonds in one-pot.[1] Owing to their bond forming efficient, MCRs are the preferred approach in the drug discovery process.[2] The Biginelli reaction is one of the most important MCRs that offer an efficient route to produce multi-functionalized 3, 4-dihydropyridin-2(*1H*)-ones/3, 4-dihydropyridin-2(*1H*)-thiones (DHPMs). DHPMs and their derivatives have been receiving considerable attention because they exhibit a wide of biological and pharmacological properties, such as antiviral, antibacterial, antitumor, anticancer, antihypertensive and most importantly, as calcium channel modulators.[3] The great potential of DHPMs in pharmaceutical fields has accordingly triggered growing interest in their synthetic study.

The most simple and straightforward produce, reported by Biginelli more than 100 years ago, involves the one-pot three-component condensation of an aldehyde, *α*, *β*-ketoester and urea.[4] Unfortunately, this original protocol suffers from the harsh conditions, long reaction times and frequently low yields. This has led to the development of new improved methodologies for the Biginelli reaction, involving the use of a number of catalysts such as ionic liquids or supported ionic liquids,[5] $H_4PMo_{11}VO_{40}$,[6] $SiO_2$-$H_2SO_4$,[7] $Fe_3O_4$-MWCNT,[8] $CaF_2$,[9] TMSCl,[10] $NbCl_5$,[11] $Ce(C_{12}H_{25}SO_3)_3$,[12] $ErCl_3$,[13] $Gly(NO_3)$,[14] IBX,[15] SBA-15-$PrSO_3H$,[16] Mo/$\gamma$-$Al_2O_3$,[17] bentonite/PS-$SO_3H$,[18] mesoporous $SiO_2$-$H_2PO_3$,[19] PS-PEG-$SO_3H$,[20] Amberlyst-70,[21] Carbon-$SO_3H$,[22] $Fe_3O_4$/PAA-$SO_3H$,[23] nano-$\gamma$-$Fe_2O_3$-$SO_3H$,[24] $Fe_3O_4$@$Nb_2O_5$,[25] and so on. DHPMs have also been synthesized under microwave[19, 26] and ultrasound irradiations[8, 27]. However, these methodologies suffer from one or more shortcomings such as unsatisfactory yields, prolonged reaction times, used of toxic organic solvents, requirement of excess of reagents or catalysts and harsh reaction conditions. Therefore, the development of an eco-friendly and efficient methods using novel catalyst for Biginelli reaction is still in great demand.

Cyclodextrins (CDs) are macrocyclic oligosaccharides possessing hydrophobic cavities that bind substrates selectively *via* noncovalent interactions, and this outstanding property enables them to be used in various applications.[28] Native *β*-CD and chemical modification of CDs has been employed as a phase transfer catalyst in organic synthesis reactions, such as Azide-alkyne cycloaddition reaction, aza-Michael addition, and so on.[29] Recently, hydrochloric-*β*-CD,[30] sulfonated *β*-CD[31] and *β*-CD[32] have been used as catalyst for the Biginelli reaction. These methods made some achievements, but there suffer from one or more shortcomings such as required a co-catalyst, used hazardous and corrosive regent and prolonged reaction times. Based on these issues, develop green method exploit new functionalized CDs is necessary.

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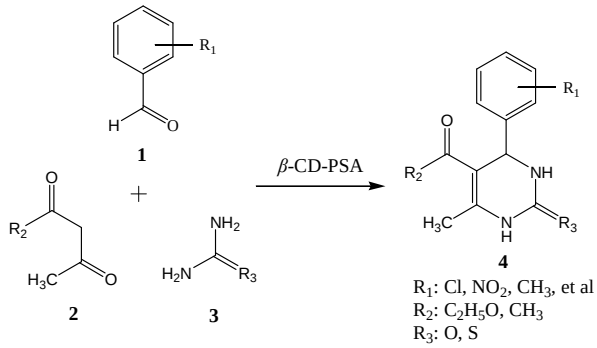
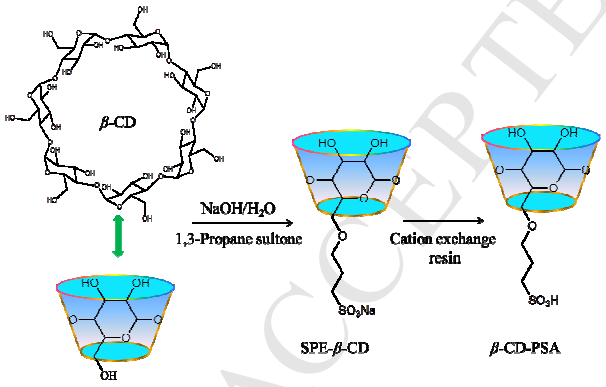
In this context, we wish to report a *β*-cyclodextrin functionalized by propyl sulfonic acid (*β*-CD-PSA), which is obtained from available and inexpensive staring materials. We introduce *β*-CD-PSA successfully as an efficient and eco-friendly catalyst for the one-pot synthesis of 3, 4-dihydropyrimidinones under solvent-free conditions with good to excellent yields (Scheme 1). To the best of our knowledge, this is the first report on the use of *β*-CD-PSA in Biginelli reaction.




Scheme 1 One-pot synthesis of 3, 4-dihydropyrimidinones catalyzed by *β*-CD-PSA

## 2. Results and discussion

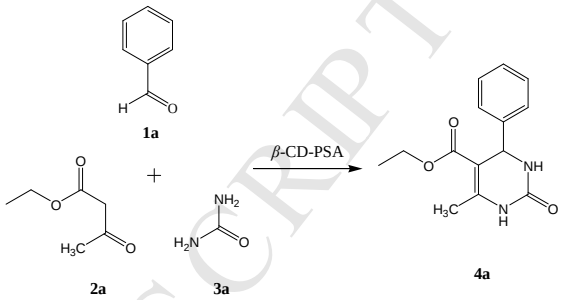
The detailed preparation for *β*-CD-PSA is shown in Scheme 2. First, commercially available *β*-CD was reacted with 1, 3-propane sultone in NaOH solution to afford sulfopropyl ether *β*-cyclodextrin (SPE-*β*-CD), which was further treated with acidic resin to give *β*-CD-PSA. *β*-CD-PSA was identified by FT-IR spectroscopy, $^{1}$H NMR, $^{13}$C NMR and elemental analysis. The average degree of substitution for *β*-CD-PSA was estimated from $^{1}$H NMR spectroscopy, and it was about 5.04. The loading amount of propyl sulfonic acid per g catalyst was also determined by elemental analysis, which is 2.45 mmol/g. The radio of C/S was also used to calculate the average degree of substitution. It was 4.99. The results from different methods are in agreement with each other.




Scheme 2 synthesis of *β*-CD-PSA

In order to optimize the conditions, we carried out the reaction of benzaldehyde (**1a**), ethyl acetoacetate (**2a**) and urea (**3a**) as a model reaction. The results are summarized in Table 1. Initially, when the model reaction was carried without any catalysts at room temperature and 80 ℃, no desirable product was observed even after prolonging reaction time. It indicated that the catalyst should be absolutely necessary for this reaction (Table 1, entry 1-2). The same reaction was performed in presence of 2 mol% *β*-CD-PSA at room temperature, 50 ℃, 80 ℃ and 100 ℃, the yields were 18%, 65% 91% and 92%, respectively (Table 1, entry 3-6). No improvements in the reaction rates and yields were observed from increasing and decreasing the amount of *β*-CD-PSA from 2 mol% (Table 1, entry 7-8). Next, the reaction was carried out in various solvents as well as under solvent-free conditions. Typically, solvents such as ethanol, $H_2O$, $CH_3CN$, THF, DMF, EtOAc, and $ClCH_2CH_2Cl$ were chosen for comparison. As a result, the yields were not ideal, only range from 49% to 84%. For this reaction, it proceeded most readily to give the highest yield of the product **4a** under solvent-free conditions (Table 1, entry 9-15). Therefore, the optimal conditions were determined as that the reaction was catalyzed by 2 mol% *β*-CD-PSA under solvent-free conditions at 80 ℃.

Table 1. Optimization of reaction conditions for the synthesis of **4a** [a]




| Entry | Solvents | T (℃) | Amount (mol%) | Time(min) | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 | Solvent-free | rt. | -- | 120 | NR[c] |
| 2 | Solvent-free | 80 | -- | 120 | NR[c] |
| 3 | Solvent-free | rt. | 2 | 120 | 18 |
| 4 | Solvent-free | 50 | 2 | 30 | 65 |
| 5 | Solvent-free | 80 | 2 | 20 | 91 |
| 6 | Solvent-free | 100 | 2 | 20 | 92 |
| 7 | Solvent-free | 80 | 1 | 20 | 85 |
| 8 | Solvent-free | 80 | 3 | 20 | 93 |
| 9 | $H_2O$ | 80 | 2 | 20 | 76 |
| 10 | $CH_3CH_2OH$ | reflux | 2 | 20 | 84 |
| 11 | $ClCH_2CH_2Cl$ | reflux | 2 | 30 | 58 |
| 12 | EtOAc | reflux | 2 | 30 | 62 |
| 13 | THF | reflux | 2 | 30 | 49 |
| 14 | $CH_3CN$ | 80 | 2 | 30 | 70 |
| 15 | DMF | 80 | 2 | 30 | 78 |

[a] Reaction condition: benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol) and urea (2.4 mmol), catalyst: *β*-CD-PSA, solvent-free or solvent (5 mL).
[b] Isolated yield. [c] No reaction was observed.

To compare the efficiency of our catalyst with the reported catalysts for the synthesis of DHPMs, we have tabulated the results of these catalysts to promote the synthesis of compounds **4a** from benzaldehyde, ethyl acetoacetate and urea, in Table 2. The results showed that *β*-CD-PSA is a better catalyst with respect to reaction times and yields of the products.

With the optimal conditions, we tended to investigate the generality and limitation of this method. The reaction of various aromatic aldehydes, 1, 3-dicarbonyl compounds and urea or thiourea were explored under the optimal conditions to produce a series of structurally diverse DHPMs. The results are summarized in Table 3. Most of the reactions proceeded very efficiently. Various aromatic aldehydes containing electron-withdrawing and electron-donating substituents at *ortho*, *meta* or *para*-positions show equal ease towards the product formation in high yields ranging from 82% to 93% (Table 3, entry 1-10). We

also found that ethyl acetoacetate and acetylacetone could be used to synthesize DHPMs successfully also with high yields (Table 3, entry 11-16). Thiourea was applied in the reaction instead of urea which successfully led to the corresponding DHPMs in good to excellent yields (Table 3, entry 17-24).

Table 2. Comparison of different catalysts for the synthesis of **4a**

| Entry | Catalyst | Condition | Time | Yield(%) | Ref. |
|---|---|---|---|---|---|
| 1 | *β*-CD-PSA | Solvent-free/80 ℃ | 20 min | 91[a] | This work |
| 2 | *β*-CD | Solvent-free/100 ℃ | 3 h | 85[a] | 32 |
| 3 | *β*-CD-$SO_3H$ | Solvent-free/100 ℃ | 2 h | 83[a] | 31 |
| 4 | *β*-CD-HCl | EtOH/ reflux | 8 h | 92[a] | 30 |
| 5 | nano-γ-$Fe_2O_3$-$SO_3H$ | Solvent-free/60 ℃ | 3 h | 95[a] | 24 |
| 6 | PS-PEG-$SO_3H$ | Dioxane/80 ℃ | 10 h | 86[a] | 20 |
| 7 | $Fe_3O_4$/PAA-$SO_3H$ | Solvent-free/rt. | 120 min | 90[a] | 23 |
| 8 | Bentonite/PS-$SO_3H$ | Solvent-free/120 ℃ | 30 min | 89[a] | 18 |
| 9 | $[(CH_3)_3NC_3H_6SO_3H][HSO_4]$ | $H_2O$/90 ℃ | 10 min | 94[a] | 5b |
| 10 | Carbon-$SO_3H$ | $CH_3CN$/80 ℃ | 4 h | 90[a] | 22 |
| 11 | Amberlyst-70 | $H_2O$/90 ℃ | 3 h | 81[c] | 21 |
| 12 | $SiO_2$-$H_2PO_3$ | Solvent-free/60 ℃ | 2.5 h | 92[a] | 19 |
| 13 | $ErCl_3$ | Solvent-free/120 ℃ | 30 min | 92[b] | 13 |
| 14 | Mn@PMO-IL | Solvent-free/75 ℃ | 45 min | 97[a] | 5e |
| 15 | IBX | $H_2O$/60 ℃ | 2.5 h | 90[a] | 15 |
| 16 | $CaF_2$ | EtOH/ reflux | 2 h | 98[c] | 9 |
| 17 | $Ce(C_{12}H_{25}SO_3)_3$ | EtOH/80 ℃ | 8 h | 93[a] | 12 |
| 18 | $Fe_3O_4$-MWCNT | EtOH/ ultrasound Irradiation/50 ℃ | 20 min | 98[c] | 8 |

[a] Isolated yield. [b] GC/MS data. [c] Not mark.

Table 3. Synthesis of DHPMs catalyzed by *β*-CD-PSA under solvent-free conditions[a]

| Entry | $R_1$ | $R_2$ | $R_3$ | Product | time | Yield(%)[b] |
|---|---|---|---|---|---|---|
| 1 | H | $C_2H_5O$ | O | **4a** | 20 | 91 |
| 2 | *p*-Cl | $C_2H_5O$ | O | **4b** | 20 | 90 |
| 3 | *o*-Cl | $C_2H_5O$ | O | **4c** | 20 | 86 |
| 4 | *p*-$NO_2$ | $C_2H_5O$ | O | **4d** | 20 | 92 |
| 5 | *m*-$NO_2$ | $C_2H_5O$ | O | **4e** | 20 | 84 |
| 6 | *o*-$NO_2$ | $C_2H_5O$ | O | **4f** | 20 | 82 |
| 7 | *p*-$CH_3$ | $C_2H_5O$ | O | **4g** | 15 | 93 |
| 8 | *p*-OH | $C_2H_5O$ | O | **4h** | 25 | 80 |
| 9 | *p*-$OCH_3$ | $C_2H_5O$ | O | **4i** | 25 | 88 |
| 10 | *p*-$N(CH_3)$ | $C_2H_5O$ | O | **4j** | 20 | 90 |
| 11 | H | $CH_3$ | O | **4k** | 30 | 88 |
| 12 | *p*-Cl | $CH_3$ | O | **4l** | 30 | 85 |
| 13 | *p*-$NO_2$ | $CH_3$ | O | **4m** | 25 | 90 |
| 14 | *p*-$CH_3$ | $CH_3$ | O | **4n** | 30 | 86 |
| 15 | *p*-OH | $CH_3$ | O | **4o** | 30 | 76 |
| 16 | *p*-$OCH_3$ | $CH_3$ | O | **4p** | 30 | 81 |
| 17 | H | $C_2H_5O$ | S | **4q** | 30 | 86 |
| 18 | *p*-Cl | $C_2H_5O$ | S | **4r** | 30 | 90 |
| 19 | *o*-Cl | $C_2H_5O$ | S | **4s** | 30 | 85 |
| 20 | *p*-$NO_2$ | $C_2H_5O$ | S | **4t** | 25 | 91 |
| 21 | m-$NO_2$ | $C_2H_5O$ | S | **4u** | 25 | 88 |
| 22 | *p*-$CH_3$ | $C_2H_5O$ | S | **4v** | 25 | 90 |
| 23 | *p*-$OCH_3$ | $C_2H_5O$ | S | **4w** | 30 | 83 |
| 24 | *p*-OH | $C_2H_5O$ | S | **4x** | 30 | 78 |

[a] Reaction condition: aromatic aldehydes (2 mmol), 1, 3-dicarbonyl compounds (2 mmol), urea or thiourea (2.4 mmol), β-CD-PSA (0.02 mmol), 80 ℃.
[b] Isolated yield.

To increase the catalyst worth, its recyclability was tested upon the synthesis of compound **4a**. After completion of the reaction, water was added and the reaction mixture was filtered. The solution of *β*-CD-PSA was dried under vacuum for recycling catalyst in next run. The procedure was repeated and the results indicated that the catalyst could be recycled six-times with only a slight loss of catalytic activity (Fig. 1).

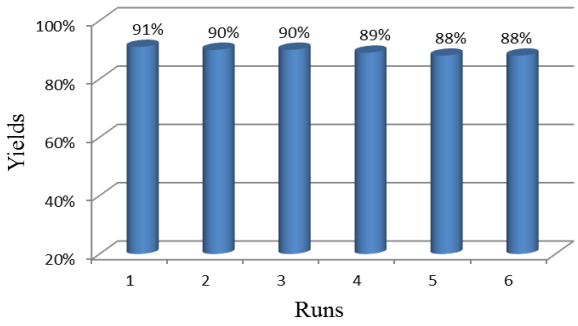



Fig. 1 Reusability of *β*-CD-PSA for the synthesis of **4a**

The recovered catalyst after six runs had no obvious change in structure, referring to FT-IR spectrum in comparison with fresh catalyst (Fig. 2). Furthermore, the loading amount of propyl sulfonic acid after using six-times was determined by elemental analysis, and which was 2.38 mmol/g. These results indicate that the catalyst was very stable and could endure this reaction's conditions.

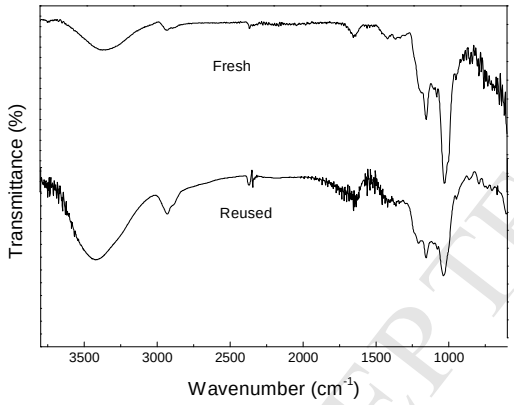
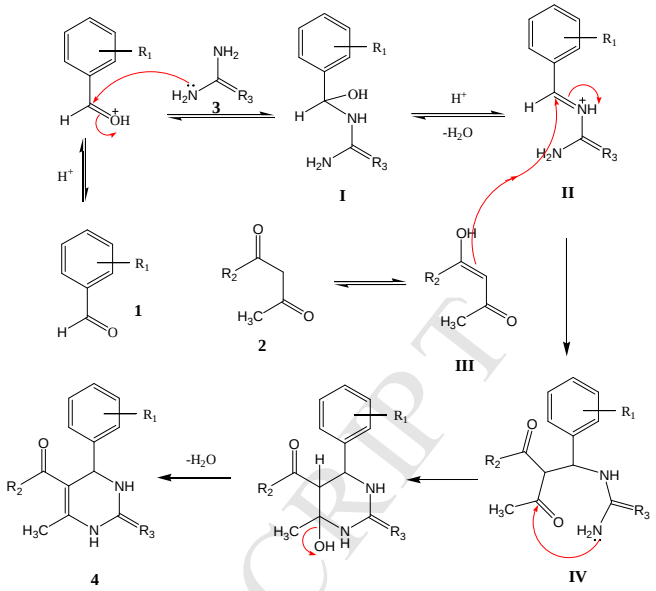



Fig. 2 FT-IR spectrum comparison of the fresh catalyst and the catalyst used after six-times

Although we have not established the mechanism of reaction experimentally, a possible explanation is proposed in Scheme 3, on the basis of the literature and substrate trends. The *β*-CD-PSA as a BrØnsted acid participate in the reaction which activate the aldehyde **1** followed by nucleophilic addition of urea or thiourea **3** forming the *N*-acylimine intermediate **I**. Then the iminium intermediate **II** generated, which is the key rate-determining step, acts as an electrophile for the nucleophilic addition of the enol form of the *β*-keto ester **III**. The ketone carbonyl of the resulting open-chain of the resulting open-chain ureide adduct **IV** undergoes intramolecular cyclocondensation with the urea $NH_2$ followed by dehydration to give the cyclized product **4**.




Scheme 3 Plausible mechanism for the synthesis of DHPMs catalyzed by *β*-CD-PSA

## 3. Conclusion

In summary, we have developed a facile, efficient and eco-friendly procedure for the one-pot synthesis of 3, 4-dihydropyrimidinones from a multi-component reaction of aromatic aldehydes, 1, 3-dicarbonyl compounds and urea or thiourea using *β*-CD-BSA as a powerful catalyst under solvent-free conditions. *β*-CD-BSA is easily prepared from commercially available starting materials. The notable advantages of this method are high catalytic activity, short reaction time, excellent yields, reusability of catalyst, simple work-up and mild reaction conditions. Thus, this procedure is a better and more practical alternative for green chemistry.

## 4. Experimental section

### 4.1 General

Melting points were determined on an X6-data microscopic melting points apparatus and were uncorrected. FT-IR spectra were recorded on a BRUKER VECTER 22 (KBr). NMR spectra were obtained from solution $D_2O$ or DMSO-$d_6$ with TMS as internal standard using a BRUKER AVANCE III (400 MHz) spectrometer. Elemental analysis was performed on an Elementar VARIOEL III spectrometer.

### 4.2 Synthesis of *β*-CD-PSA

First, *β*-CD (1 g) was dissolved in NaOH solution (5M, 10 mL) in a 50 mL round bottom flask at 75 ℃. To the solution, 1, 3-propane sultone (1.1 g) was added dropwise. Then the mixture was stirred for 4 h. The reaction solution was cooled to room temperature, which was adjusted to neutral using HCl solution (3 M). The mixture was dropped in ethanol to afford sulfopropyl ether *β*-cyclodextrin (SPE-*β*-CD).

Second, the acidic resin was activated in a saturated aqueous solution of NaCl for 1 day, followed by the treatment of 2.5 wt % NaOH aqueous solution for 80 min, and then washed with distilled water until pH 7.0, and finally it was treated with 5.0 wt % HCl aqueous solution for 12 h. Afterwards, the resin was transferred to a column and washed with deionized water until the eluent reached pH 7.0.

Lastly, the sodium salt of SPE-*β*-CD (0.5 g) was dissolved in water (100 mL), and the solution was allowed to flow through the acidic resin column at a speed of 20 drops per minute. The acidic eluent was collected and then freeze-dried for 12 h to obtain *β*-CD-PSA product.

FT-IR (KBr, cm-1): 3354, 2930, 2365, 1653, 1361, 1153, 1030, 791, 700. $^1$H NMR (400 MHz, $D_2O$): $\delta$ 5.01-5.11 (m, $C_1$-H), 3.49-3.8 (m, -OC$H_2$C$H_2$C$H_2$S$O_3$H and CH), 2.95 (s, -OC$H_2$ C$H_2$C$H_2$S$O_3$H), 1.98 (s, -OC$H_2$C$H_2$C$H_2$S$O_3$H). $^{13}$C NMR (101 MHz, $D_2O$): δ 80.92, 72.72, 72.00, 71.68, 69.48, 60.18, 47.91, 47.68, 24.50, 24.28. Anal. Found: C 33.52, S 7.834, H 6.67.

4.3 General procedure for the synthesis of 3, 4-dihydropyrimidinones

A mixture of aldehyde 1 (2 mmol), 1, 3-dicarbonyl compounds (ethyl acetoacetate or acetylacetone, 2 mmol), urea or thiourea (2.4 mmol), and *β*-CD-PSA (0.02 mmol) was stirred at 100 ℃ for the appropriate time (monitored by TLC). Then, water (5 mL) was added and the reaction mixture filtered. The solution of *β*-CD-PSA was dried under vacuum for recycling catalyst in next run. Pure 3, 4-dihydropyrimidinones were afforded by evaporation of the solvent followed by recrystallization from ethanol. All were characterized by spectral data and comparison of their physical data with the literature.

The spectral (FT-IR, $^1$H NMR, $^{13}$C NMR) and analytical data for some selected 1-amidoalkyl-2-naphthols are presented below:

*Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (Table 3, entry 1): white crystals, mp.: 201-202 ℃. FT-IR (KBr, cm$^{-1}$): 3246, 3119, 2978, 1726, 1649, 1466, 1292, 1223, 1094, 783, 700. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.21 (s, 1H, NH), 7.75 (s, 1H, NH), 7.32 (m, 2H, ArH), 7.24 (m, ArH, 3H), 5.14 (d, *J*= 3.2 Hz, 1H, CH), 3.98 (q, *J* = 7.1 Hz, 2H, C$H_2$), 2.24 (s, 3H, C$H_3$), 1.09 (t, *J* = 7.1 Hz, 3H, C$H_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 165.81, 152.61, 148.85, 145.33, 128.87, 127.75, 126.72, 99.70, 59.67, 54.42, 18.26, 14.55.

*5-Acetyl-6-methyl-4-p-tolyl-3,4-dihydropyrimidin-2(1H)-one* (Table 3, entry 14): white crystals, mp.: 168-170 ℃. FT-IR (KBr, cm$^{-1}$): 3289, 1699, 1616, 1512, 1466, 1423, 1389, 1364, 1327, 1265, 1236, 1184, 1140, 1105, 999, 964, 793, 733, 685. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.17 (s, 1H, NH), 7.79 (s, 1H, NH), 7.12 (s, 4H, ArH), 5.21 (d, *J*= 3.0 Hz, CH, 1H), 2.26 (m, 6H, Ar-C$H_3$ and C$H_3$CO), 2.08 (s, 3H, C$H_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 194.79, 152.60, 148.43, 141.78, 136.97, 129.52, 126.83, 110.00, 54.01, 30.71, 21.12, 19.35.

*Ethyl-4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetra-hydropyrimidine-5-carboxylate* (Table 3, entry 18): Light yellow solid, mp.: 193-194 ℃. FT-IR (KBr, cm$^{-1}$): 3423, 3327, 2361, 1672, 1574, 1458, 1327, 1283, 1198, 1119, 748, 669. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.41 (s, 1H, NH), 9.69 (s, 1H, NH), 7.43 (d, *J*= 8.4 Hz, ArH, 2H), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 5.16 (d, *J*= 3.4 Hz, 1H, CH), 4.00 (q, *J*= 6.9 Hz, C$H_2$, 2H), 2.29 (s, 3H, C$H_3$), 1.09 (t, *J*= 7.1 Hz, 3H, C$H_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 174.69, 165.46, 145.87, 142.85, 132.73, 129.08, 128.79, 100.73, 100.00, 60.14, 53.90, 17.66, 14.48.

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## References and notes


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**Supplementary Material**

Supplementary related to this article can be found at…

# Supporting Information

*β*-Cyclodextrin-propyl sulfonic acid: a new and eco-friendly catalyst for one-pot multi-component synthesis of 3, 4-dihydropyrimidones *via* Biginelli reaction

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## Table of Contents





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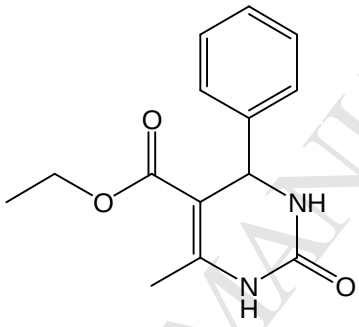
## Spectral data of *β*-CD-PSA and selected compounds

## Spectral data of *β*-CD-PSA

FT-IR (KBr, cm-1): 3354, 2930, 2365, 1653, 1361, 1153, 1030, 791, 700. $^{1}$H NMR (400 MHz, $D_2O$): $\delta$ 5.01-5.11 (m, $C_1$-H), 3.49-3.8 (m, -OC$H_2$C$H_2$C$H_2$S$O_3$H and CH), 2.95 (s, -OC$H_2$ C$H_2$C$H_2$S$O_3$H), 1.98 (s, -OC$H_2$C$H_2$C$H_2$S$O_3$H). $^{13}$C NMR (101 MHz, $D_2O$): δ 80.92, 72.72, 72.00, 71.68, 69.48, 60.18, 47.91, 47.68, 24.50, 24.28.

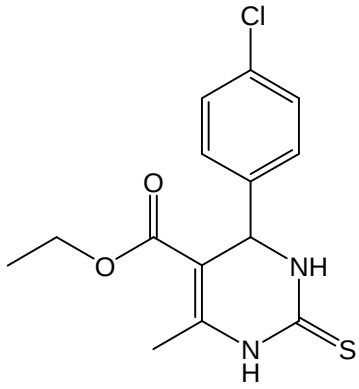
## Spectral data of selected compounds

*Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate:*



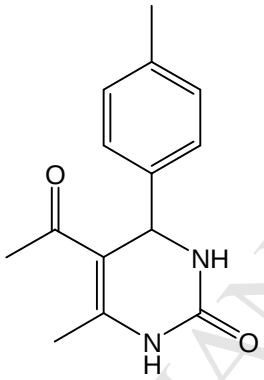

white crystals, mp.: 201-202 ℃. FT-IR (KBr, $cm^{-1}$): 3246, 3119, 2978, 1726, 1649, 1466, 1292, 1223, 1094, 783, 700. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 9.21 (s, 1H, NH), 7.75 (s, 1H, NH), 7.32 (m, 2H, ArH), 7.24 (m, ArH, 3H), 5.14 (d, *J*= 3.2 Hz, 1H, CH), 3.98 (q, *J* = 7.1 Hz, 2H, $CH_2$), 2.24 (s, 3H, $CH_3$), 1.09 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 165.81, 152.61, 148.85, 145.33, 128.87, 127.75, 126.72, 99.70, 59.67, 54.42, 18.26, 14.55.

*Ethyl-4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxyl ate:*



white crystals, mp.: 168-170 ℃. FT-IR (KBr, $cm^{-1}$): 3289, 1699, 1616, 1512, 1466, 1423, 1389, 1364, 1327, 1265, 1236, 1184, 1140, 1105, 999, 964, 793, 733, 685. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 9.17 (s, 1H, NH), 7.79 (s, 1H, NH), 7.12 (s, 4H, ArH), 5.21 (d, *J*= 3.0 Hz, CH, 1H), 2.26 (m, 6H, Ar-$CH_3$ and $CH_3CO$), 2.08 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 194.79, 152.60, 148.43, 141.78, 136.97, 129.52, 126.83, 110.00, 54.01, 30.71, 21.12, 19.35.

*5-Acetyl-6-methyl-4-p-tolyl-3,4-dihydropyrimidin-2(1H)-one:*




Light yellow solid, mp.: 193-194 ℃. FT-IR (KBr, $cm^{-1}$): 3423, 3327, 2361, 1672, 1574, 1458, 1327, 1283, 1198, 1119, 748, 669. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.41 (s, 1H, NH), 9.69 (s, 1H, NH), 7.43 (d, *J*= 8.4 Hz, ArH, 2H), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 5.16 (d, *J*= 3.4 Hz, 1H, CH), 4.00 (q, *J*= 6.9 Hz, $CH_2$, 2H), 2.29 (s, 3H, $CH_3$), 1.09 (t, *J*= 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 174.69, 165.46, 145.87, 142.85, 132.73, 129.08, 128.79, 100.73, 100.00, 60.14, 53.90, 17.66, 14.48.

**Copies of FT-IR, $^{1}H$ and $^{13}C$ NMR spectra of selected Compounds**

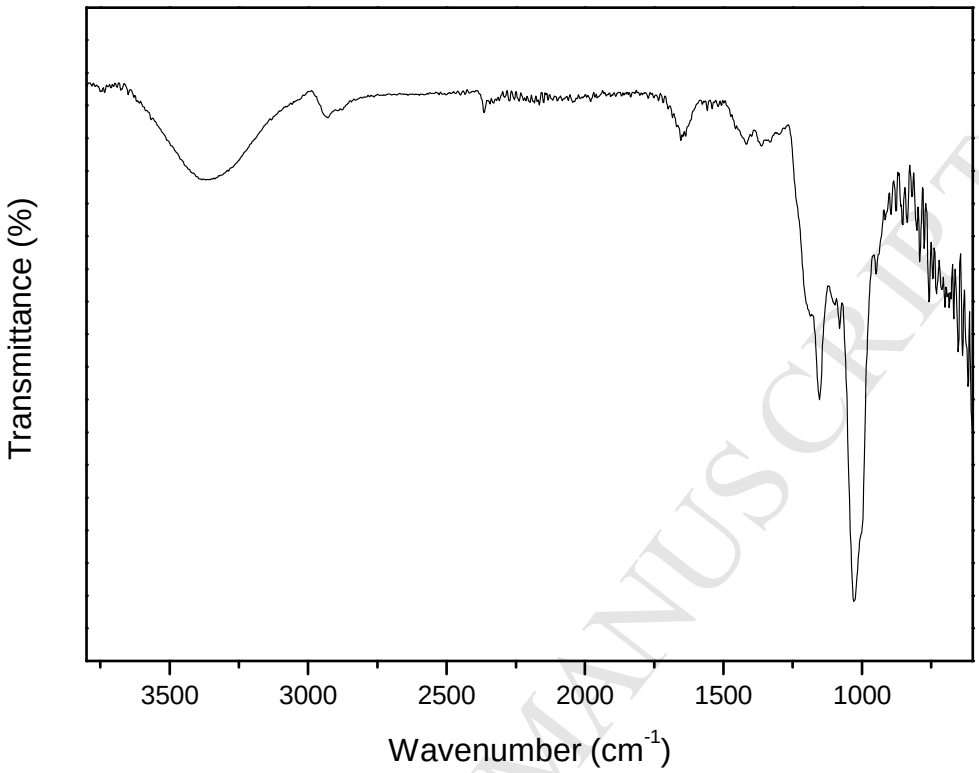



Fig. S1 FT-IR spectrum of *β*-CD-BSA in KBr

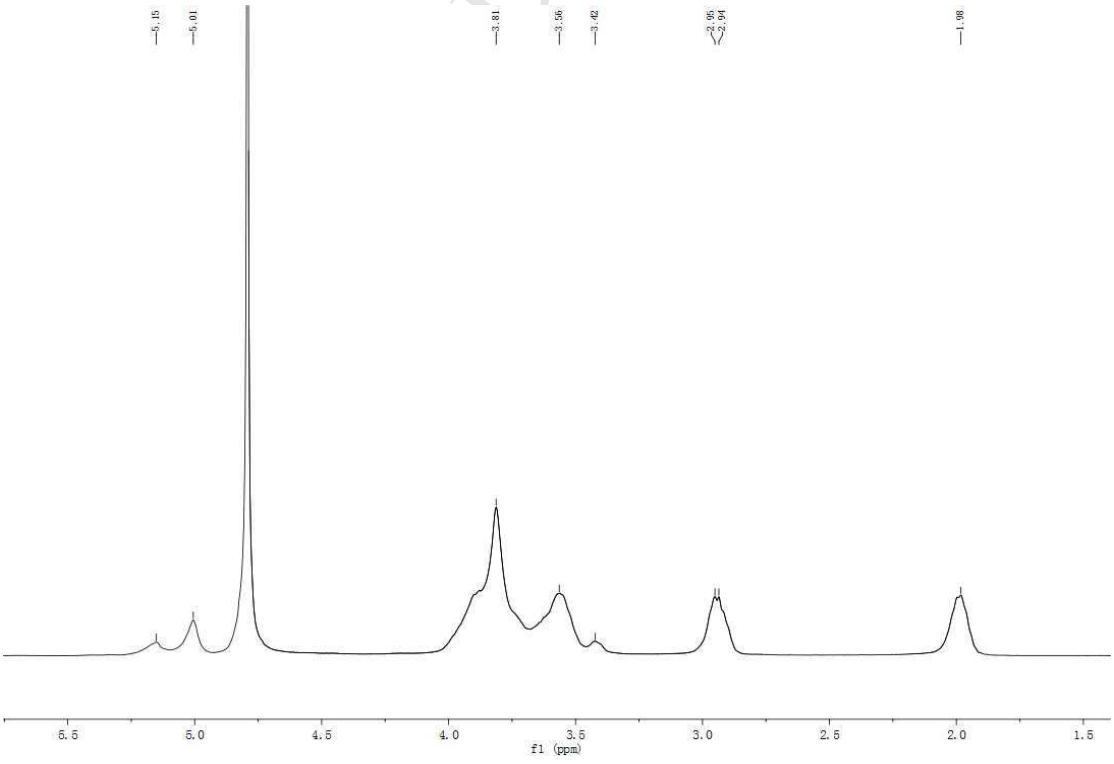



Fig. S2 $^{1}H$ NMR spectrum of *β*-CD-BSA in $D_2O$

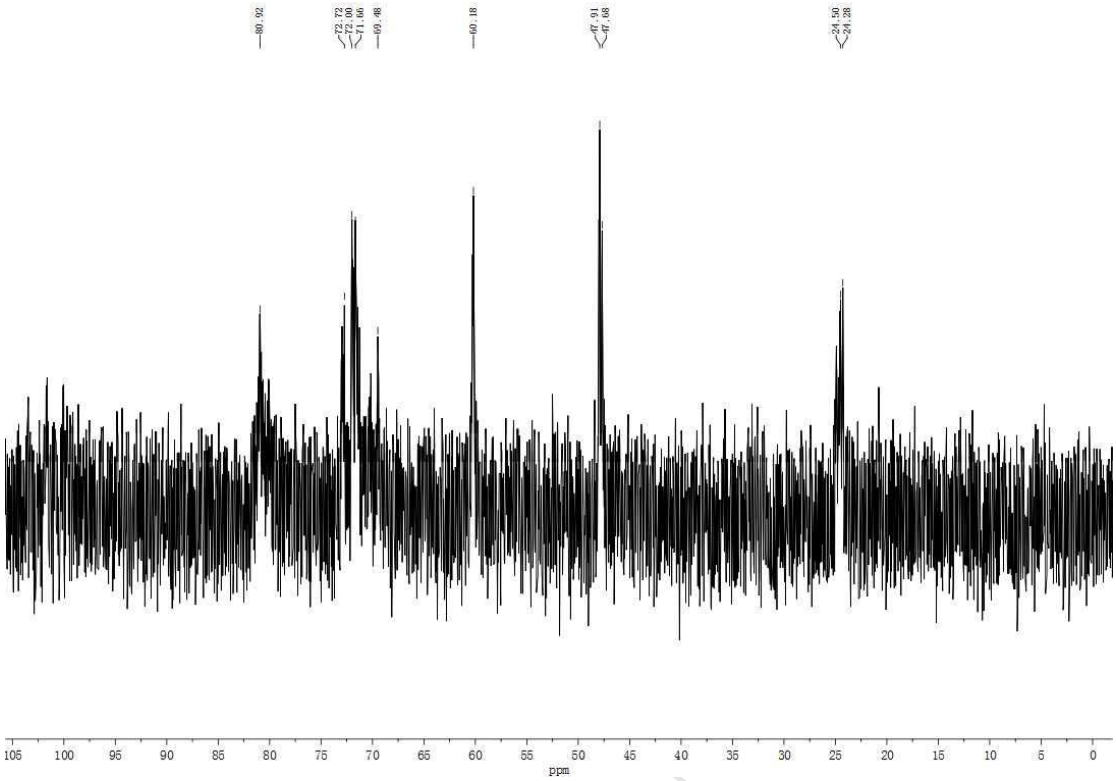



Fig. S3 $^{13}C$ NMR spectrum of $\beta$-CD-BSA in $D_2O$

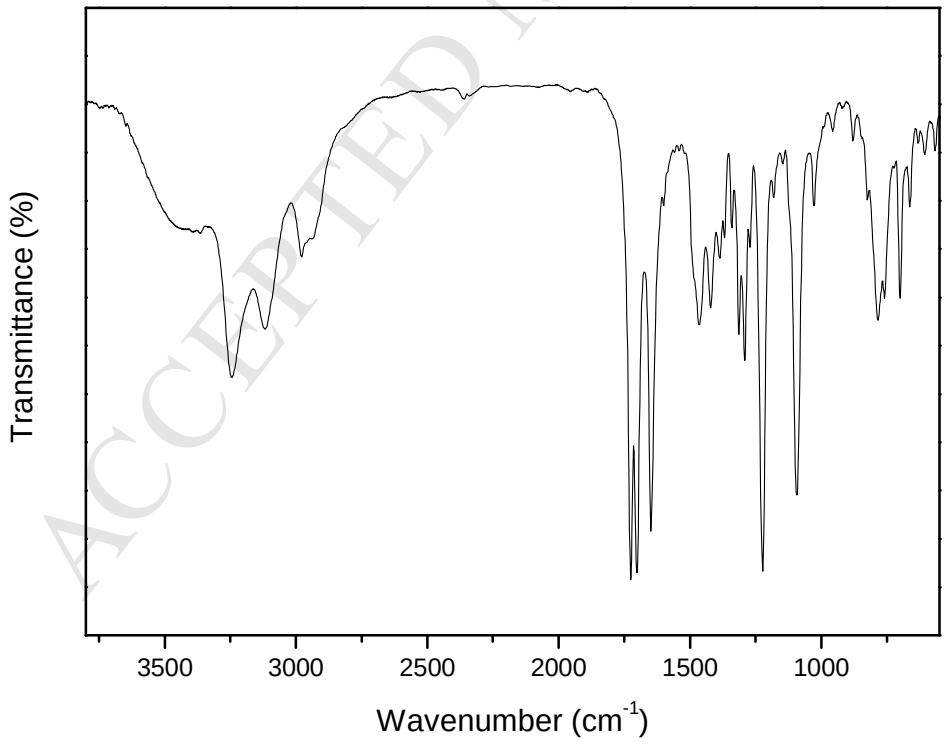



Fig. S4 FT-IR spectrum of compound **4a**

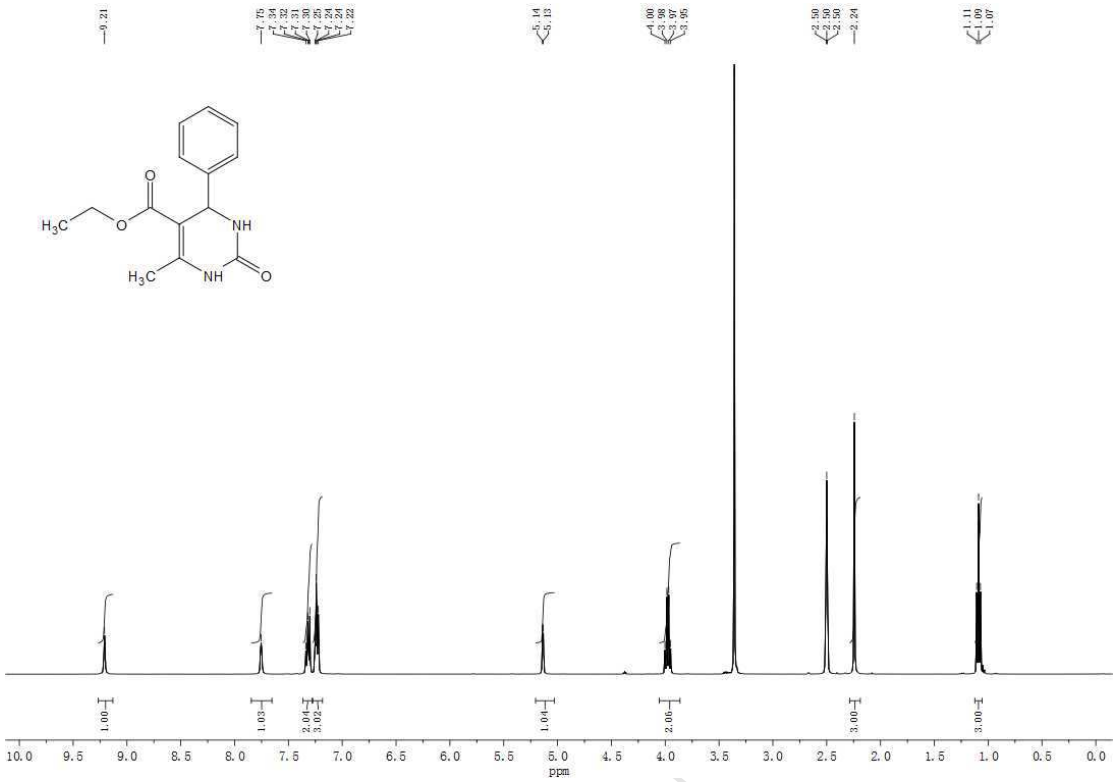



Fig. S5 $^{1}$H NMR spectrum of compound **4a**

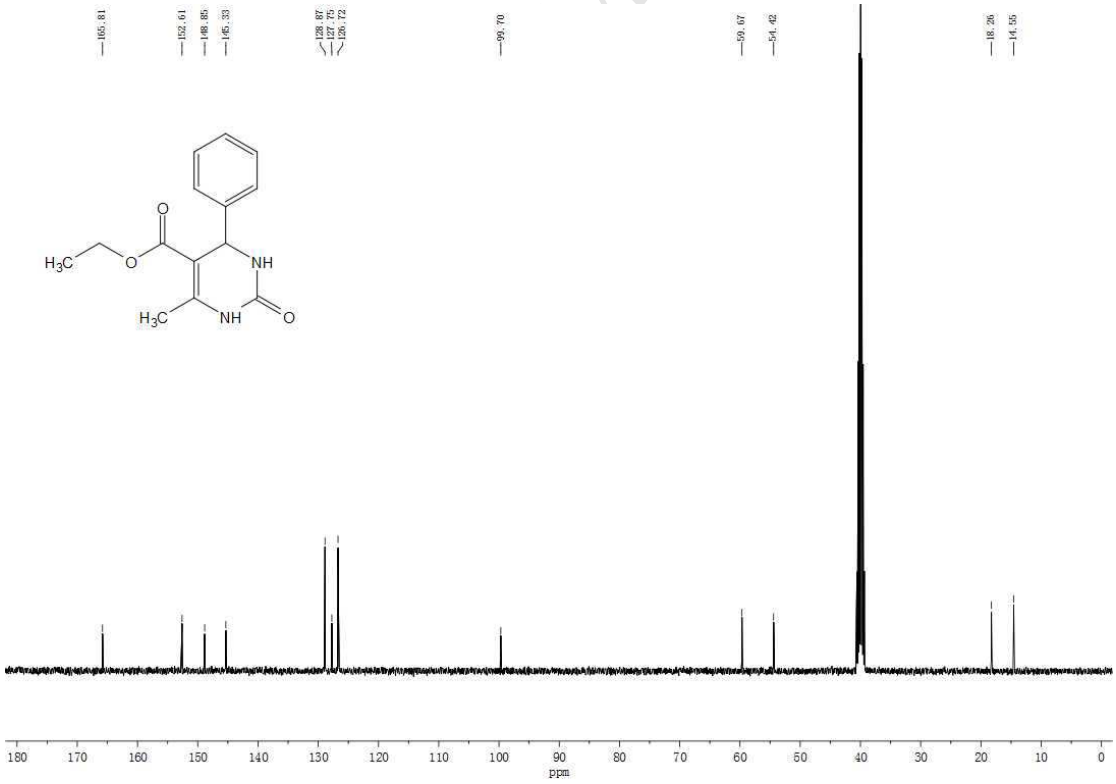



Fig. S6 $^{13}$C NMR spectrum of compound **4a**

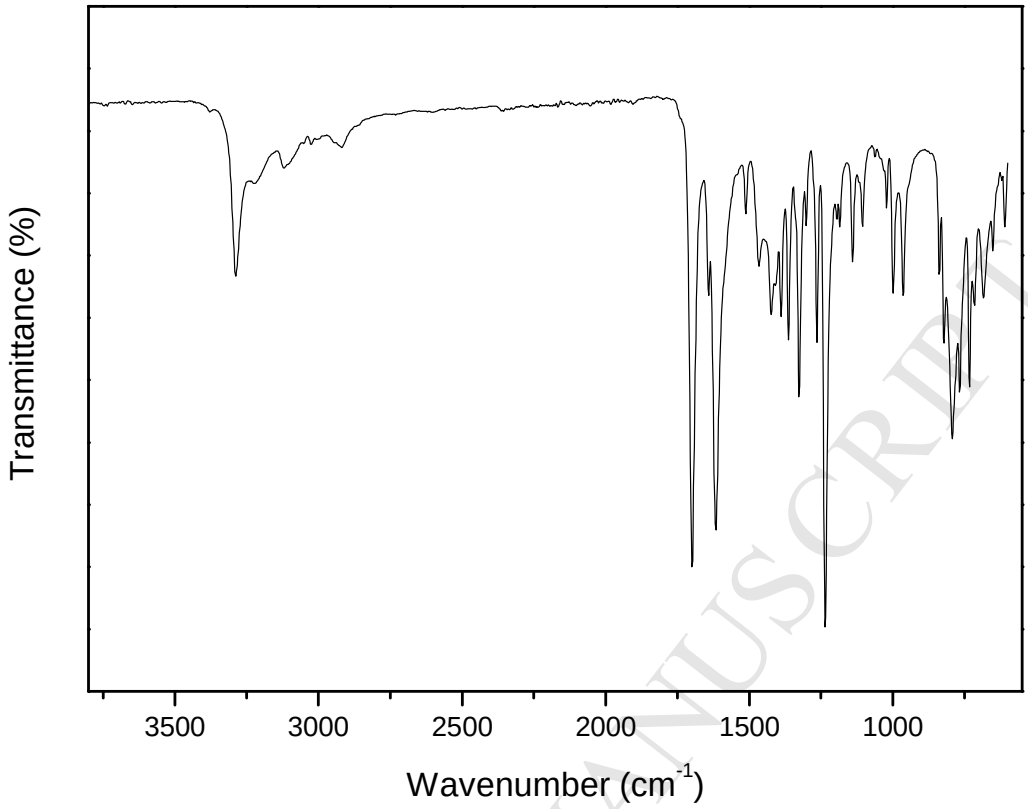



Fig. S7 FT-IR spectrum of compound **4n**

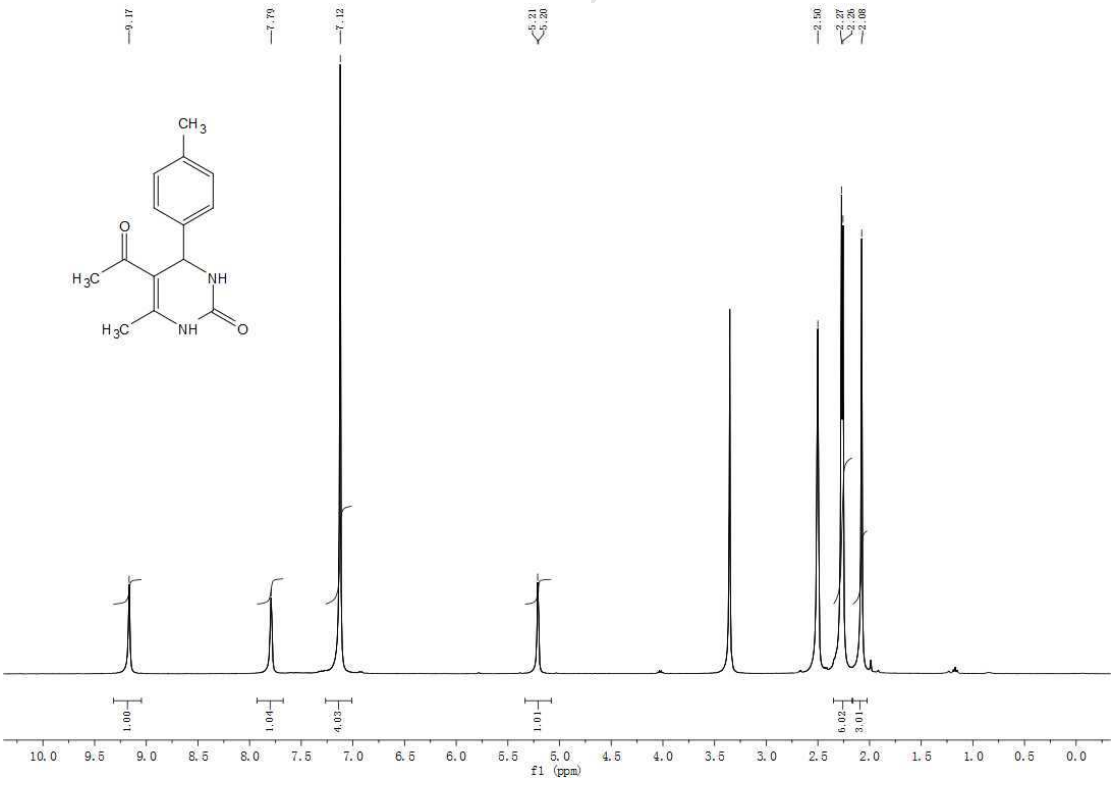



Fig. S8 $^{1}$H NMR spectrum of compound **4n**

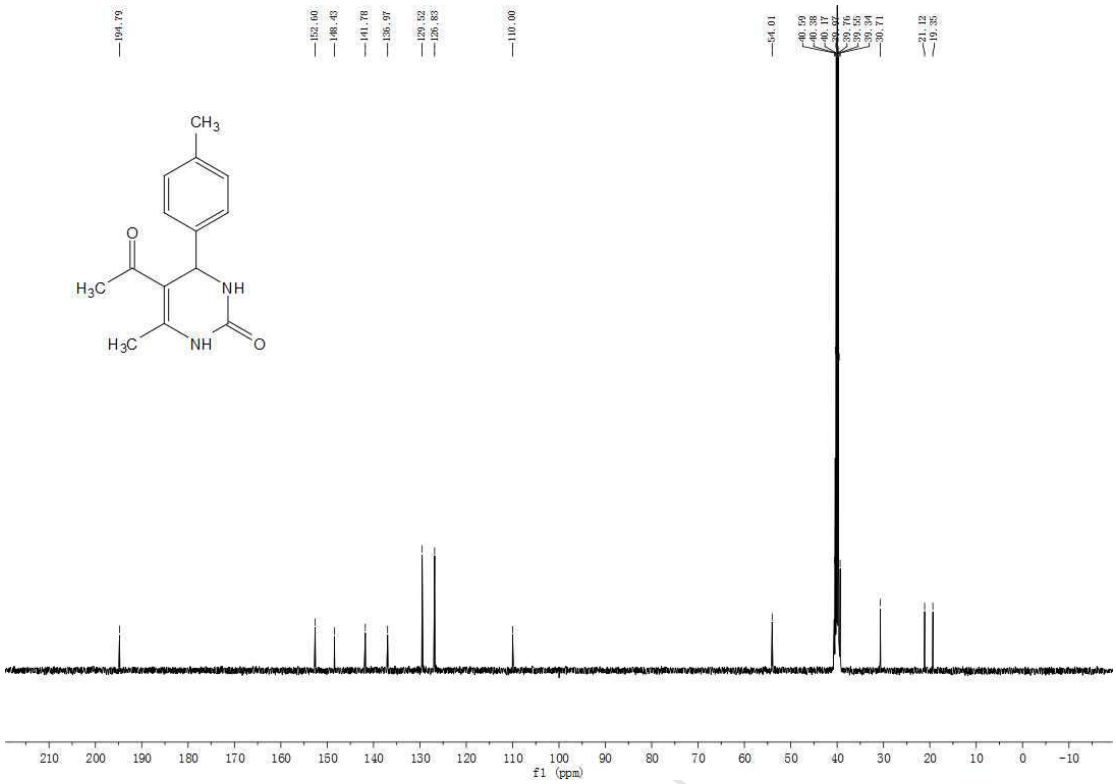



Fig. S9 $^{13}$C NMR spectrum of compound **4n**

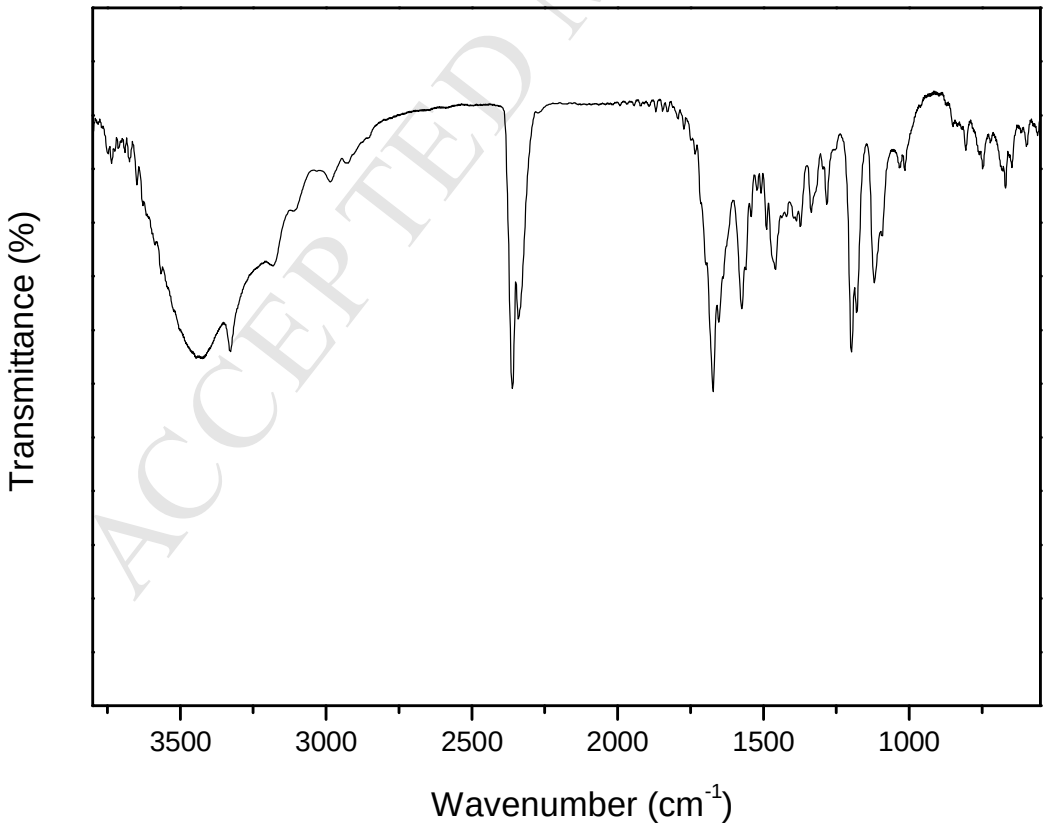



Fig. S10 FT-IR spectrum of compound **4r**

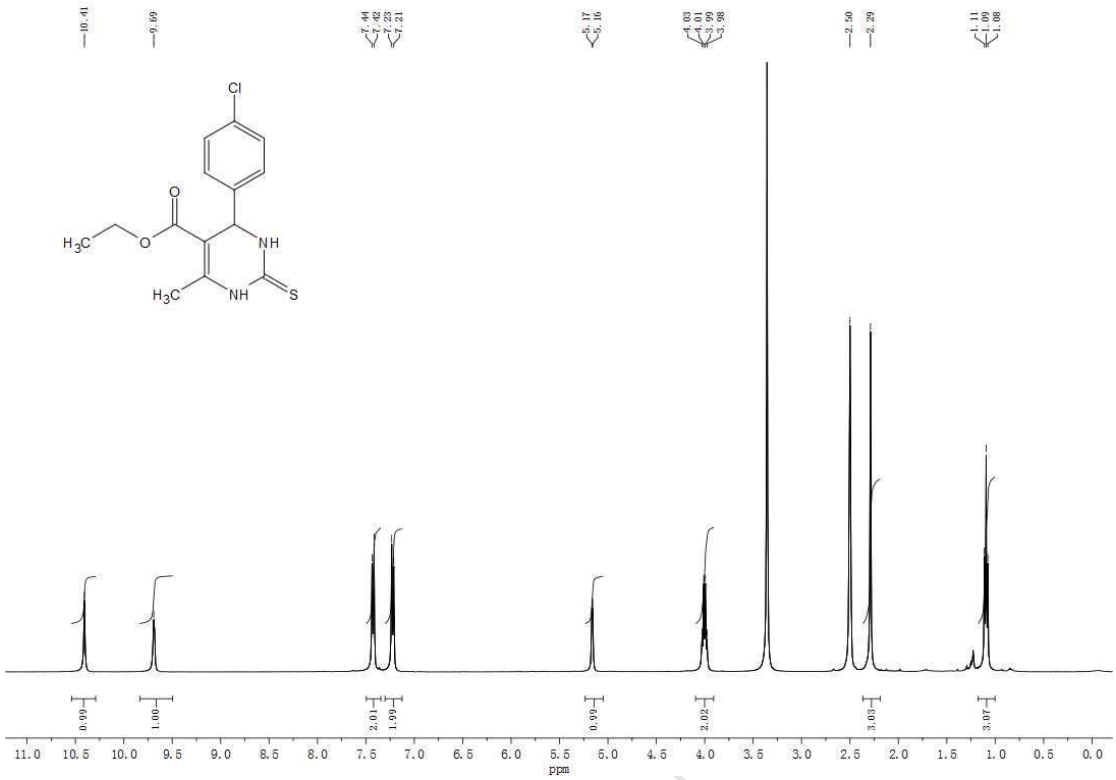



Fig. S11 $^{1}$H NMR spectrum of compound **4r**

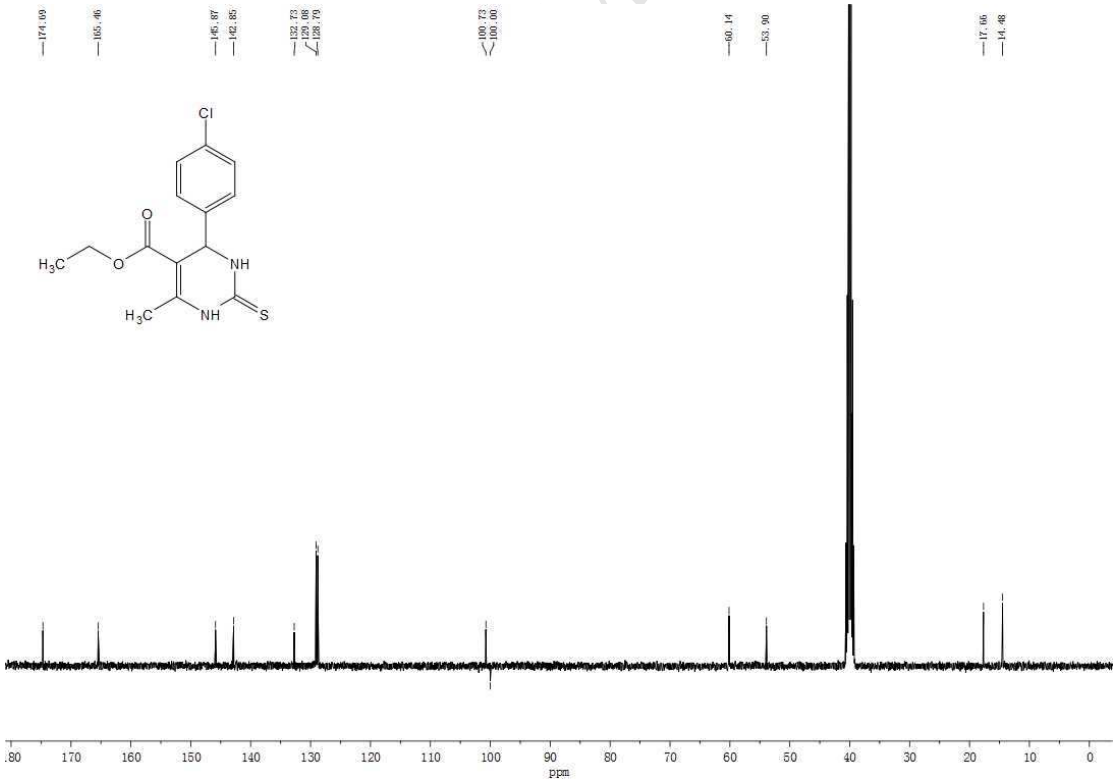



Fig. S9 $^{13}$C NMR spectrum of compound **4r**