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Research Article

β -CYCLODEXTRIN – GLYCERIN AS A VERSATILE GREEN SYSTEM FOR SYNTHESIS OF 2-AMINO-TETRAHYDRO-4*H*-CHROMENES

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ABSTRACT

Environmental safe synthesis of 2-amino-tetrahydro-4*H*-chromenes in *β*-Cyclodextrin – glycerinwas achieved by one pot three-component condensation of aromatic aldehydes, malononitrile and dimedone at ambient temperature without the addition of any other catalyst. This synthetic path is inexpensive, efficient, as well as user friendly.

Keywords: *β*-CD-glycerine, aqueous medium, 2-amino-tetrahydro-4*H*-chromenes.

INTRODUCTION

In recent years growing awareness of environmental safety has been attracted worldwide concern towards the use of renewable sources and reduction of waste. In the present work, we use *β*-CD in combination with glycerin in aqueous medium for the synthesis of 2-amino-tetrahydro-4*H*-chromenes at ambient temperature.

Cyclodextrins (CDs) are interesting supramolecules and are cyclic oligosaccharides with the ability to encapsulate a broad range of guest molecules showing host-guest chemistry[1,2]. Now a day's *β*-CD has been extensively used in organic synthesis as catalyst[3,4], as they are naturally occurring material, inexpensive and biodegradable.

As a key component of organic reactions, solvents are more important for making the process environment benign. High boiling point, low vapour pressure, non-toxic, inexpensive, recyclable, wide range of solubility of compounds, are the mandatory requirements of an ideal solvent for organic transformations. Though Breslow highlighted that the rate of many organic reactions in water can be increased tremendously due to hydrophobic effects but the low solubility power of organic compounds restricts the use of water as solvent in organic synthesis. According to literature, glycerin is used as a high-valued starting material in the beverages, chemicals[5], drugs, soaps and food industries[6]. It has been reported that glycerin is used as an excellent solvent, in which many organic compounds are readily soluble than in water and alcohol [7,8]. To the best of our knowledge, glycerin acts as Hydrotrope (surface active comound) and is a green and sustainable option to organic solvents. The crystal structure study of *β*-CD complexed with glycerol·7.2 H_2O has been reported in literature[9] this inspired us to use *β*-CD-Glycerin system in organic transformation.

2-amino-tetrahydro-4*H*-chromene derivatives represent an important class of bioactive molecules. They are often used in cosmetics, pigments [10] and utilized as potential agrochemicals[11]. Some derivatives of chromenes constitute a core skeleton of many natural products[12] and bioactive molecules which seize various pharmacological actions, such as antiallergic, antitumor and antibacterial[13]. Several techniques and modified catalysts have been reported for synthesis of 2-amino-tetrahydro-4H-chromene derivatives. Use of microwave[14], grinding[15], reflux[16], phase transfer catalyst[17], solid supported catalyst[18] and ionic liquids[19] are some representatives from

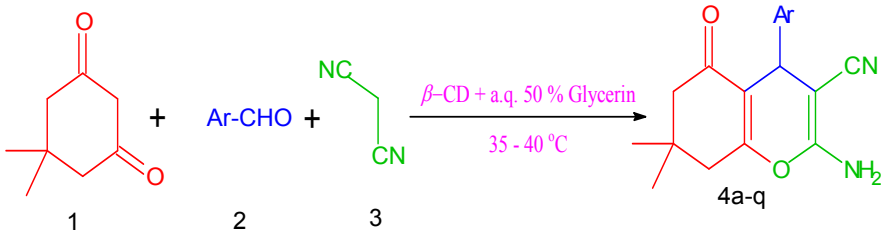
literature. In addition to this, use of inorganic[20], organic[21] and modified catalysts have been reported. Most of the reported methods involved the use of expensive catalyst, prolonged reaction time, toxic solvents, tedious work up procedure, low yields of products and consumption of energy. We violet such traditional disadvantages in present work and make it environmentally more adored.

Our research efforts are to develop novel catalytic system which allows the use of water as a suitable solvent for wide range of organic transformation[22a,b,c] herein we would like to report the novel, green system for the synthesis of chromenes in water without the addition of any other catalyst at ambient temperature.

EXPERIMENTAL

Chemical and apparatus

β-CD was purchased from Himedia and all remaining chemicals from s. d. Fine chem. Limited (India), Sigma Aldrich, Spectrochem. These chemicals were used as such without further purification. Melting points were determined in an open capillary and are uncorrected. Infrared spectra were recorded on Perkin Elmer FT-IR spectrometer. The samples were examined as KBr discs ~5% *w/w*. NMR spectra were recorded on Bruker Avon 300 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal reference. LCMS were recorded on Thermo LCQ Tune Spectrometer. (Scheme)



Scheme. Synthesis of 2-amino-tetrahydro-4H-chromene derivatives

General procedure

In a 50 mL round bottom flask, *β-CD* (0.227 gm) was added to 15 mL aq. 50% glycerin (*v/v*) and heated (35- 40°C) under stirring to obtain homogeneous solution. Equimolar quantityof aryl aldehyde, malononitrile and dimedone(1 mmole each) was mixed to this homogeneous solution and reaction mixture was stirred at 35-40 °C. The reaction was monitored by TLC by using Petroleum Ether : Ethyl acetate :: 8:2 as mobile phase. The product was filtered off, washed with water (15 mL x 3) and then recrystallized from ethyl acetate and acetone (8:2) to afford the corresponding pure 2-amino-tetrahydro-4*H*-chromene in good yield.

RESULT AND DISCUSSION

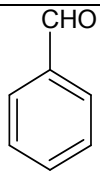
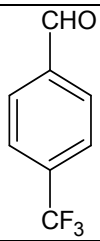
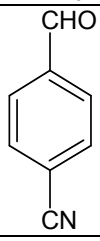
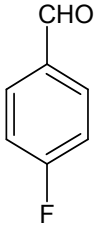
In present work we have developed novel method for the synthesis 2-amino-tetrahydro-4*H*-chromenes by means of one-pot, three-component condensation of aromatic aldehydes, malononitrile and dimedone in aqueous medium using *β*-CD and glycerin system. In order to study the best useful system, we performed different sets of reaction and observations are given in **Table 1**. We observed that the use of *β*-CD (0.227 gm) in 15 mL water (**Table 1a**), amongst the various aldehydes used only p-Chloro benzaldehyde undergo reaction with 30% yield while in aq. 50 % glycerin (*v/v*) (**Table 1b**) slight increase in yield (40%) of same reaction. In the third set of reaction tremendous increase in the yield of product upto 90% by using *β*-CD (0.227 gm) with aq. 50% glycerin (*v/v*) 15 mL (Table 1c) was observed. In this case it is clear that aq. 50% glycerin played versatile role to enhance the solubility of *β*-CD and thus helped to form inclusion complex in solution very easily.

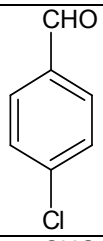
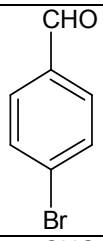
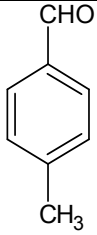
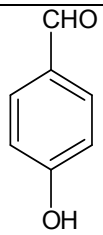
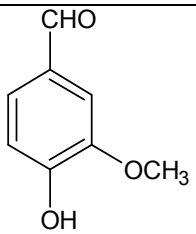
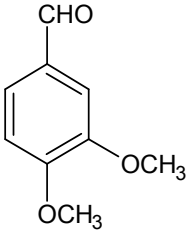
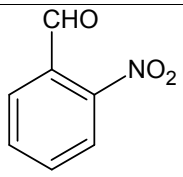
Table 1: Reaction conditions for the synthesis of 2-amino-tetrahydro-4*H*-chromene derivatives

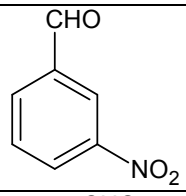
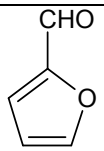
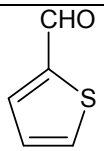
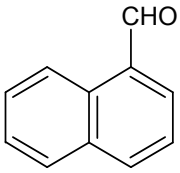
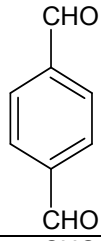
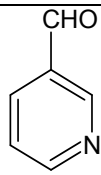
Sr. No.	Aldehyde	a		b		c	
		β-CD (0.227 gm) in 15 mL water		aq. 50 % glycerin (*v/v*) 15 ml		*β*-CD (0.227 gm) -aq. 50 % glycerin (*v/v*) 15 mL	
		Time (Hrs.)	Yield (%)	Time (Hrs.)	Yield (%)	Time (Hrs.)	Yield (%)
1	Benzaldehyde	4.0	10	4.0	20	2.0	**90**
2	4-Chloro benzaldehyde.	4.0	30	4.0	40	0.5	**90**
3	4-Hydroxy benzaldehyde	4.0	00	4.0	00	3.0	**80**
4	Vanillin	4.0	00	4.0	00	6.0	**80**
5	3,4-Dimethoxy benzaldehyde	4.0	00	4.0	00	4.0	**75**
6	Furan-2-carboxaldehyde	4.0	10	4.0	10	4.0	**92**
7	1-Naphthaldehyde	4.0	00	4.0	00	8.0	**70**

To explore the generality of *β*-CD and aq. glycerin system, the reactions of different aromatic as well as heterocyclic aldehydes with malononitrile and dimedone were performed and the results are given in **Table 2**. Halogen and cyano substituted as well as heterocyclic aldehydes are good guest molecules for *β*-CD than the remaining substituted aldehydes. Novel derivatives **(Table 2; Entries 2, 15, 16)** of 2-amino-tetrahydro-4*H*-chromene were confirmed by spectroscopic characterization such as IR, ^{1}HNMR, ^{13}CNMR, DEPT, LCMS which are in good agreement with proposed structure. *β*-CD – Glycerin system works well for sterically hindered aldehydes **(Table 2; Entries 9, 10, 15, 16)** with satisfactory results.

Table 2: Synthesis of 2-amino-tetrahydro-4*H*-chromene derivatives[a].

Entry	Aldehyde	Product	Time (Hrs.)	Yield[b] (%)	Melting Point (°C)	
					Observed	Literature
1		**4a**	2.0	90.0	225	228-230[16]
2		**4b**	0.25	92.0	235-240	-------
3		**4c**	0.25	96.0	220-225	220-225[23]
4		**4d**	0.25	93.0	180-185	184-186[16]

5		**4e**	0.5	90.0	210-215	208-210[16]
6		**4f**	0.5	95.0	210	205-202[16]
7		**4g**	0.5	90.0	210-215	220-222[16]
8		**4h**	3.0	80.0	215-220	206-208[21]
9		**4i**	6.0	80.0	230	227-228[21]
10		**4j**	4.0	75.0	175	170-173[25]
11		**4k**	0.5	80.0	228	225-230[25]

12		**4l**	0.5	83.0	210	207-209[25]
13		**4m**	4.0	92.0	190-200	218-220[21]
14		**4n**	4.0	95.0	210-220	216[20]
15		**4o**	8.0	70.0	210-215	----------
16		**4p**	2.0	85.0	270-275	--------
17		**4q**	0.5	93.2	205	203[24]

[a]Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), β-CD (0.227 gm) - aq. 50 % glycerin (v/v) 15 mL at 35-40 [o]C. [b]Isolated yield.

In plausible mechanism **(Fig 1)** the formation of hydrogen bonding between hydroxyl group of *β*-CD and glycerin in presence of water enhances the solubility of *β*-CD and also facilitates the deprotonation of malononitrile to form its carbanion. The latter attacked the carbonyl group of the aromatic aldehyde followed by dehydration to yield Knovenagel product.

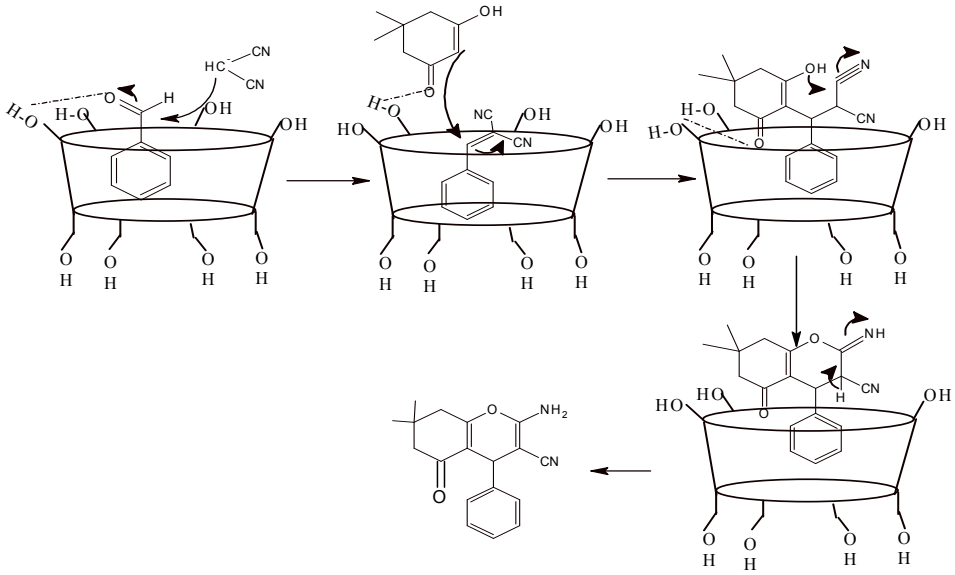


Fig. 1: Plausible mechanism for synthesis of 2-amino-tetrahydro-4H-chromene derivatives

Then Michael addition of dimedone with Knovenagel product, which on cyclization yield 2-amino-tetrahydro-4*H*-chromene. *β*-CD catalyzed reactions involved the reverse formation of host-guest complex by hydrogen bonding. The size, shape as well as hydrophobicity of guest molecules are responsible for host-guest complex (Inclusion complex) which modifies the physicochemical properties of guest molecule mostly in terms of water solubility[26].

β-CD is cyclic oligosaccharide which consist of (α-1,4)-linked α-D-glucopyranose units **(Fig 2a)**. To confirm the role of glycerin we compared the ^{1}HNMR of *β-CD* in D_2O **(Fig 2b)** and ^{1}H NMR of *β*-CD + Glycerin in D_2O **(Fig 2c)**.

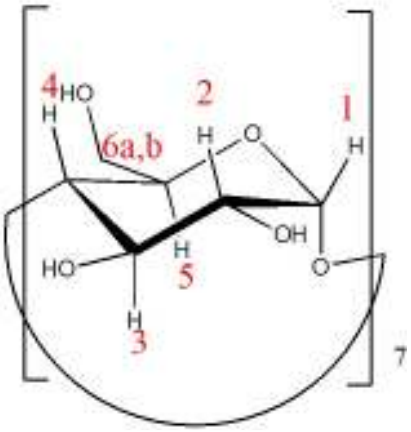


Fig. 2a: Structure of *β*-CD

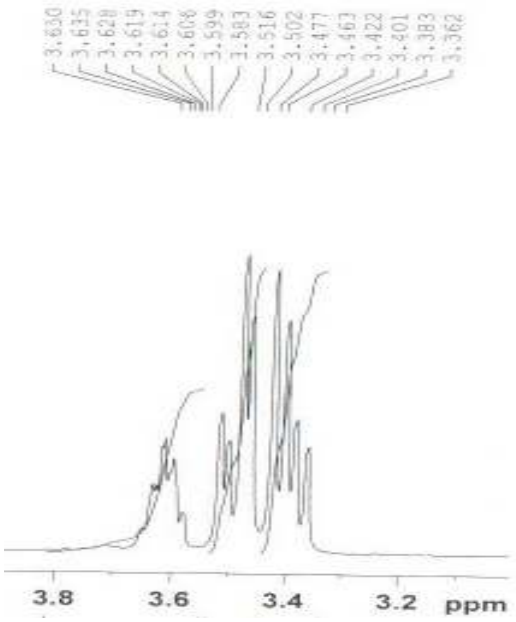


Fig. 2b: ^{1}H NMR Spectrum of β-CD in D_2O

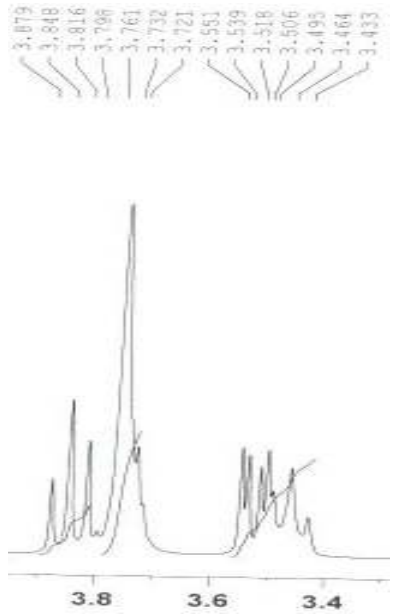


Fig. 2c:^{1}HNMR Spectrum of β-CD + Glycerin in D_2O

The ^{1}HNMR spectrum of *β*-CD in D_2O **(Fig 2b)** shows two multiplates in between δ 3.87 to δ 3.72 ppm and at δ 3.55 to 3.43 ppm, for hydrogens of carbon C2, C3, C4, C5 and C6 in glucose unit.

In the ^{1}HNMR spectrum of *β*-CD + Glycerin in D_2O **(Fig 2c)** protons appeared as three multiplates from δ 3.65 to δ 3.36 ppm, upfield shift of protons confirms the bonding between hydrogen attached to glycerin and *β*-CD which facilitates the formation of inclusion complex with substrate to yield the desired product.

CONCLUSION

In summary we have reported novel approach for the synthesis of 2-amino-tetrahydro-4*H*-

chromene derivatives using combination of *β*-CD and aq. glycerin. This protocol implies mild reaction condition, easy work up procedure and high yield of products. The combination of a biodegradable catalyst, a green solvent and one pot three component reaction, the developed synthetic method is cost effective, less toxic to environment and good contribution to chromene synthesis.

ACKNOWLEDGEMENT

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SPECTROSCOPIC DATA

2-amino-7,7-dimethyl-5-oxo-4-(4'-trifliuromethylphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 2, Entry 2, 4b)

Mp (^oC):235-240 ^oC; IR (KBr,ν, cm^{-1}): 3346 (NH_2), 2967 (C-H), 2191 (CN), 1661 (C=O); ^{1}HNMR(300 MHz, DMSO-d_6, δ): 7.44-7.41 (m, 4H, Ar-H), 6.82 (bs, 2H, NH_2), 3.26 (s, 1H, Chiral-H), 2.49 (s, 2H, $\underline{CH_2}$–C=O), 2.49-2.07 (m, 2H, CH_2), 1.08 (s, 3H, CH_3), 0.97 (s, 3H, CH_3);^{13}CMR (75 MHz, DMSO-d_6, δ): 195.43, 162.71, 158.99, 148.51, 146.12, 119.57 (CN), 131.48, 129.33, 126.14, 124.18, 123.58, 112.87, 58.11, 50.47, 36.01, 32.18, 29.07 (CH_3), 27.28 (CH_3); DEPT (75 MHz, DMSO-d_6, δ): 131.48, 129.32, 124.17, 124.12, 123.63, 50.45 (CH_2,down), 40.47 (CH_2,down), 35.99, 29.08 (CH_3), 27.28 (CH_3); LCMS (ESI) *m/z*: 385.18 (M + Na).

2-amino-7,7-dimethyl-5-oxo-4-(4'-bromophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 2, Entry 6,4f)

Mp (^oC): 210 ^oC ; IR (KBr, ν, cm^{-1}): 3330 (NH_2), 2965 (C-H), 2193 (CN), 1665 (C=O); ^{1}HNMR (300 MHz, DMSO-d_6, δ): 7.35-7.32 (d, 2H,J= 8.1 Hz, Ar-H), 7.086-7.059 (d, 2H, J= 8.1, Ar-H), 6.480 (bs, 2H, NH_2),4.19(s, 1H, Chiral-H), 2.43 (s, 2H, $\underline{CH_2}$–C=O), 2.00 (s, 2H, CH_2), 1.06 (s, 3H, CH_3), 0.97 (s, 3H, CH_3) ; ^{13}CNMR (75 MHz, DMSO-d_6, δ): 195.32, 162.19, 158.81, 143.80, 131.33, 129.60, 120.45(CN), 113.23, 58.80, 50.61, 40.32, 32.13, 30.94, 27.58 ; DEPT (75 MHz, DMSO-d_6, δ): 131.33, 129.6, 50.53(CH_2,down), 40.54(CH_2,down), 35.54, ; LCMS (ESI) *m/z*: 395.04 (M + Na).

2-amino-7,7-dimethyl-5-oxo-4-(4'-methylphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 2, Entry 7, 4g)

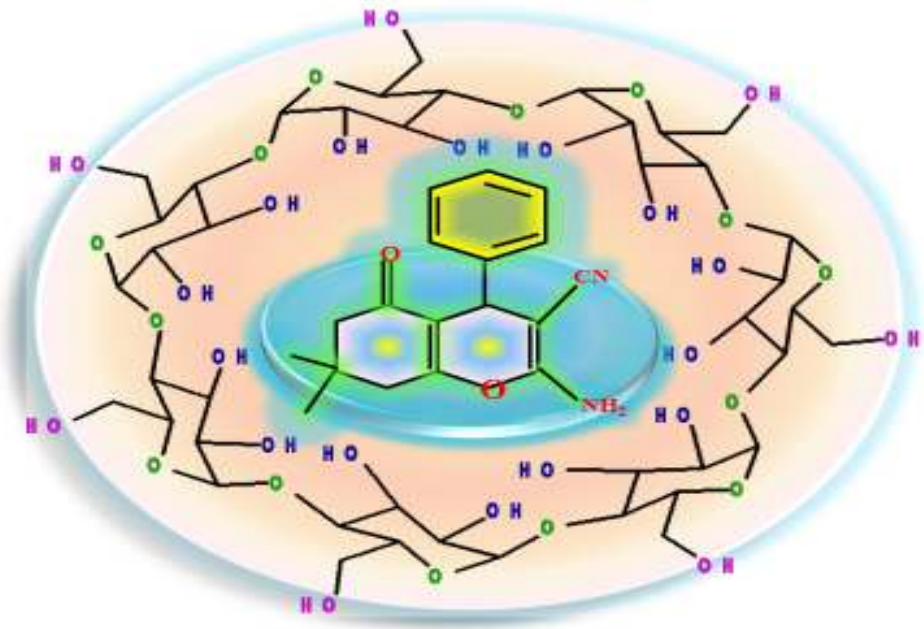
Mp (^oC): 210-215 ^oC; IR (KBr, ν, cm^{-1}): 3425 (NH_2), 2957 (C-H), 2191 (CN), 1666 (C=O), 1639 (C=C), 1602 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.017 (s, 4H, Ar-H), 6.3 (bs, 2H, NH_2), 4.175 (s, 1H, Chiral-H), 2.427 (s, 2H, CH_2–C=O), 2.255 (s, 3H, CH_3), 1.969 (s, 2H, CH_2), 1.970(s, 3H, CH_3), 0.981 (s ,3H, CH_3); ^{13}CNMR (75 MHz, DMSO-d_6, δ): 195.36 (C=O), 161.81, 158.64, 141.54, 135.92, 129.04, 128.79, 128.55, 128.32, 127.45, 120.0 (CN), 113.84, 59.93, 50.65, 44, 32.50, 29.04(CH_3), 27.53(CH_3), 21.08 (CH_3, Aryl), DEPT (75MHz, DMSO-d_6, δ):129.04, 127.44 (Ar-H), 50.63(CH_2,down), 40.61 (CH_2,down), 35.43 (Chiral, CH), 29.05, 27.53 (CH_3), 21.09 (Ar.CH_3); LCMS (ESI) m/z:331.18 (M + Na).

2-amino-7,7-dimethyl-5-oxo-4-(1'-naphthyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 2, Entry 15,4o)

Mp (^oC):210-215 ^oC; IR (KBr, ν, cm^{-1}): 3320 (NH_2), 2958 (CH), 2185 (CN), 1658 (C=O), 1595 (C=C); ^{1}HNMR (300 MHz, DMSO-d_6, δ): 8.38-7.21 (m,7H, Ar-H), 6.80 (s, 2H, NH_2), 5.12 (s, 1H, Chiral-H), 2.57-2.50 (d, 2H, CH_2–C=O), 2.24-2.19 (d, 2H, CH_2), 1.10 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}CNMR (75 MHz, DMSO-d_6, δ): 195.68 (C=O), 162.7, 158.8, 142.15, 133.73, 131.73, 128.68, 127.32, 126.06, 125.83, 125.52, 123.89, 119.88 (CN), 114.05, 113.22 (C=C), 59.47, 50.56, 30.63, 28.99 (CH_3), 27.66 (CH_3); DEPT (75 MHz, DMSO-d_6,δ): 128.69, 127.31, 126.07, 125.85, 125.52, 123.88, 50.54 (CH_2,down), 40.46 (CH_2,down), 39.93 (Chiral CH), 28.99 (CH_3), 27.64 (CH_3); LCMS (ESI) m/z: 367.2 (M + Na).

2-amino-7,7-dimethyl-5-oxo-4-[2'-amino-7',7'-dimethyl-5'-oxo-4'-(phynyl)-5',6',7',8'-tetrahydro-4H-chromene-3'-carbonitrile]-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (Table 2, Entry 16, 4p)

Mp (^oC):270-275 ^oC; IR(KBr, ν, cm^{-1}): 3394 (NH_2), 2961 (CH), 2199 (CN), 1660 (C=O), 1604 (C=C); ^{1}HNMR (300 MHz, DMSO-d_6, δ): 7.02 (s, 4H, Ar-H), 6.42 (bs, 4H, two NH_2), 4.16 (s, 2H,two Chiral-H), 2.42 (s, 4H, two CH_2–C=O), 2.15 (s, 4H, two CH_2), 1.05 (s, 6H, two CH_3), 1.01 (s, 6H, two CH_3); ^{13}CMR (75 MHz, DMSO-d_6, δ): 195.56 (C=O), 162.4, 158.81, 142.91, 128.75, 127.30, 120.20 (CN), 113.55, 59.84, 50.61, 35.26, 28.26 (CH_3), 27.95 (CH_3); DEPT (75 MHz, DMSO-d_6, δ):127.29, 50.59 (CH_2,down), 40.59 (CH_2,down), 35.26, 28.84 (CH_3), 27.95 (CH_3); LCMS (ESI) *m/z*: 533.26 (M + Na).



GRAPHICAL ABSTRACT

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