"Greener Approach for Synthesis, Characterization and Biological Activity of α-Cyno Chalcones using Deep Eutectic Solvent"

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Abstract:

In present work we here report novel methodology for synthesis of α-cyno chalcones using Deep Eutectic Solvent (DES). Deep Eutectic Solvent of Cholin chloride and $ZnCl_2$ (1:2) is an efficient green solvent for the synthesis of α-cyno chalcones via knovengel condensation of benzoyl acetonitrile and aromatic aldehyde. DES affords high yield of products in short reaction time. The some synthesized compounds were tested for their antibacterial and antifungal activity. The results indicated that the compounds show antifungal activity and antibacterial activity.

Keywords: α-cyno chalcones, Deep Eutectic Solvent, Cholin Chloride-$ZnCl_2$,Green Chemistry, Antimicrobial activity.

1. Introduction:

In the recent year DES has gained an enormous attention from the scientific community, and the number of reported articles in the literature has grown enormously. Deep Eutectic Solvents (DES) is widely used to promote chemical reactions and a number of reviews have endorsed the use of DES in organic synthesis. The quaternary ammonium salts react with hydrogen bond donar such as urea, citric acid, glycerol, carboxylic acid, and amide yields Deep Eutectic Solvent (DES) by complexation reaction. The first eutectic mixture of cholin chloride and urea was introduced by Abbott and co-workers. DES have emerged as a green alternative to conventional Ionic liquid as their physical and chemical properties similar to those of an ionic liquid such as low vapour pressure ,non volatile inspite of this they do have some advantages as cheaply available ,easy preparation, non toxic, and biodegradable.

Current research have focused on the use of DESs as solvent as well as catalyst for various organic reactions such as cycloaddition reaction, Perkin reaction, Pall Knorr reaction, Sonogashira cross-coupling reactions, Kabachnik–Fields reaction, to afford the corresponding products in excellent yields with high selectivity.

It is well known that Chalcones are α-β unsaturated carbonyl compound with two aromatic rings obtained by Claisen–Schmidt condensation of aromatic aldehyde with acetophenone in presence of suitable condensing agents. Chalcone are used as intermediates for many reactions have been shown to possess remarkable biological activities such as anti-inflammatory, anti-bacterial, anti-viral, anti-cancer, The development of an economical and rapid

methodology for synthesis of chalcone is highly essential. Here we report Choline chloride-$ZnCl_2$ based deep eutectic solvent as green solvent for the synthesis of α cyno chalcone.

2. Experimental Section

2.1. Material and Equipment:

All chemicals such as aldehydes, Benzoyl actonitrile, choline chloride and deep eutectic solvent component are commercially available and were purchased from Merck and SD Fine Chemical Ltd and are synthetic grade. ^1H spectra were recorded on 400 MHz, 500 MHz NMR spectrometer and ^{13}C-NMR on a 100 MHz Varian mercury plus spectrometer, using DMSO as solvent chemical shifts have been expressed in (ppm) downfield from TMS. All melting points were recorded on Buchi melting point apparatus presented in degrees and are uncorrected. All the reactions are monitored by thin layer chromatography (TLC) with UV light

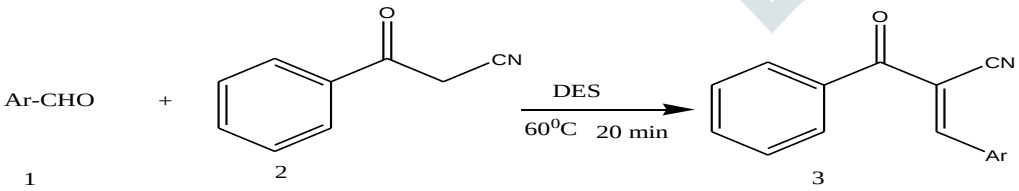
2.2. Deep Eutectic Solvent Preparation:

The DES was prepared by reported procedure. Choline chloride (10 mmol) and Zinc chloride (20 mmol) were placed in a round bottom flask and heated to 70 to 80^{0}C, after 15 to 20 min, a homogenous colorless liquid was obtained , which was used directly for the reactions without purification

2.3. Experimental Procedure:

A mixture of benzoyl acetonitrile (1 mmol) and aromatic aldehydes (1 mmol) in ChCl:$ZnCl_2$(1:2)DES (1gm) the reaction mixture was heated to 60^{0}C for 20 minutes and then was cooled to room temperature slowly. The reaction completion was monitored by TLC (Hexane: Ethyl acetate (8:2). After completion of the reaction, the reaction mixture was diluted with water (5 mL). The DES being soluble in water hence passes in the aqueous layer. The solid was separated by filtration and was washed with (1:1) ethanol–water. . The products were recrystallized from ethanol to give pure corresponding compounds. The DES was recovered from the filtrate by evaporating the water phase under vacuum.

Scheme -I



1 2 3

Ar=a)4-ClC_6H_4 h)=3,4di $OMeC_6H_3$
b)=4-$NO_2C_6H_4$ i)=4-MeC_6H_4
c)=4-OHC_6H_4 j)=2,4,5tri $OMeC_6H_2$
d)=3-ClC_6H_4 k)=4-PhC_6H_4
l)=1Naphaldehyde
f)=3-$NO_2C_6H_4$ m)=2Thiophene
g)=4-$OMeC_6H_4$ aldehyde

2.4. Selected data:

2-benzoyl-3-(4-chlorophenyl)acrylonitrile (3a): IR (KBr) υ: [Cm^{-1}] 1517(C=C), 1666 (enone -C=O str.), 2216 (-CN), 2812 (Aromatic C-H str); 1H NMR (400 MHz, DMSO-d6): 6.962 (d ,J= 8.8Hz, 2H, Ar-H), 7.570 (t, J=7.6Hz, 2H, Ar-

H), 7.681 (t, J=7.6Hz, 1H, Ar-H), 7.796 (d , J=7.6Hz, 2H, Ar-H), 8.012 (d, J=8.8Hz, 2H, Ar-H), 8.012 (s, 1H, NC-C=CHAr) ; 13C NMR (250 MHz, DMSO): δ = 105.80, 116.91, 118.09, 123.29, 129.13, 129.52, 133.34, 134.63, 136.75, 156.19, 163.52, 190.60

2-benzoyl-3-(4-nitrophenyl)acrylonitrile (3b):IR (KBr) υ: [Cm^{-1}] 1595 (C=C), 1627 (enone -C=O str.), 2216 (-CN), 2935 (Aromatic C-H str), 1448 (-NO_2); 1H NMR (500 MHz, DMSO-d6): 7.623 (t, J=7.5Hz, 2H, Ar-H), 7.755 (t, J=7.5Hz, 1H, Ar-H), 7.932 (d, J=7.5Hz, 2H, Ar-H), 8.273 (d, J=9Hz, 2H, Ar-H), 8.437 (d, J=9Hz, 2H, Ar-H), 8.310 (s, 1H, NC-C=CHAr), 13C NMR (250 MHz, DMSO): δ =114.53, 116.45, 124.58, 129.33, 130.14, 132.06, 134.22, 135.57, 138.36, 149.60, 153.45, 189.57

2-benzoyl-3-(4-hydroxyphenyl)acrylonitrile(3c): IR (KBr) υ: [Cm^{-1}] 1579 (C=C), 1666 (enone -C=O str.), 2216 (-CN), 2877 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6): 6.967 (d, J=8.5Hz, 2H, Ar-H), 7.592 (t, J=7.5Hz, 2H, Ar-H), 7.688 (t, J=7.5Hz, 1H, Ar-H), 7.803 (d, J=7.5Hz, 2H, Ar-H), 8.019 (d, J=8.5Hz, 2H, Ar-H), 8.035 (s, 1H, NC-C=CHAr), 10.879 (s, 1H, O-H), 13C NMR (250 MHz, DMSO) :δ =105.81, 116.90, 118.09, 123.30, 129.13, 129.52, 133.34, 134.62, 136.75, 156.20, 163.50, 190.59

2-benzoyl-3-(3-chlorophenyl)acrylonitrile(3d): IR (KBr) υ: [Cm^{-1}] 1583 (C=C), 1663 (enone -C=O str.), 2208 (-CN), 2912 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6): 7.633 (m, 3H, Ar-H), 7.728 (t, 2H, Ar-H), 7.895 (d, 2H, Ar-H), 8.054 (d, 1H, Ar-H), 8.125 (s, 1H, Ar-H), 8.178 (s, 1H, NC-C=CHAr), 13C NMR (250 MHz, DMSO) :δ=112.49, 116.78, 129.29, 129.36, 130.02, 130.70, 131.57, 133.02, 134.04, 134.26, 134.36, 135.80, 154.32, 189.85

2-benzoyl-3-(4-bromophenyl)acrylonitrile(3e): IR (KBr) υ: [Cm^{-1}] 1581 (C=C), 1674 (enone -C=O str.), 2212 (-CN), 2924 (Aromatic C-H str) ;1H NMR (500 MHz, DMSO-d6): 7.604 (t, J=7.5Hz, 2H, Ar-H), 7.730 (t, J=7.5Hz, 1H, Ar-H), 7.850 (d ,J=8.5Hz, 2H, Ar-H), 7.894 (d, J=7.5Hz, 2H, Ar-H), 8.016 (d, J=8.5Hz, 2H, Ar-H), 8.158 (s, 1H, NC-C=CHAr), 13C NMR (250 MHz, DMSO): δ =111.51, 116.97, 127.48, 129.26, 129.93, 131.50, 132.86, 132.94, 133.94, 135.93, 154.82, 189.97

2-benzoyl-3-(3-nitrophenyl)acrylonitrile (3f): IR (KBr) υ: [Cm^{-1}] 1590 (C=C), 1671 (enone -C=O str.), 2217 (-CN), 2922 (Aromatic C-H str); 13C NMR (250 MHz, DMSO): δ = 113.62, 116.56, 124.55, 125.49, 127.35, 128.45, 129.31, 131.29, 133.90, 135.38, 136.77, 148.49, 153.62, 189.74

2-benzoyl-3-(4-methoxyphenyl)acrylonitrile(3g): IR (KBr) υ: [Cm^{-1}] 1562 (C=C), 1645 (enone -C=O str.), 2222 (-CN), 2935 (Aromatic C-H str), 1271 (Ar-OMe); 1H NMR (500 MHz, DMSO-d6) :3.337 (s, 3H, H-OCH_3), 7.192 (d, J=9Hz, 2H, Ar-H), 7.591 (t, J=7.5Hz, 2H, Ar-H), 7.707(t, J=7.5Hz, 1H, Ar-H), 7.829 (d, J=7.5Hz, 2H, Ar-H), 8.132 (d, J=9Hz, 2H, Ar-H), 8.108 (s, 1H, NC-C=CHAr), 13C NMR (250 MHz, DMSO) :δ=56.28, 107.22, 115.47, 117.86, 124.78, 129.18, 129.63, 133.50, 134.11, 136.56, 155.86, 164.08, 190.46

2-benzoyl-3-(3,4,-dimethoxyphenyl)acrylonitrile(3h): IR (KBr) υ: [Cm^{-1}] 1568 (C=C), 1660 (enone -C=O str.), 2200 (-CN), 2953 (Aromatic C-H str), 1263 (Ar-OMe); 1H NMR (500 MHz, DMSO-d6) :3.837(s, 3H, H-OCH_3), 3.877(s, 3H, H-OCH_3), 7.218(d, J=8.5Hz, 1H, Ar-H), 7.595 (t, J=7.5Hz, 2H, Ar-H), 7.708 (t, J=7.5Hz, 1H, Ar-H), 7.783(d, J=8.5Hz, 1H, Ar-H), 7.808 (s, 1H, Ar-H), 7.838 (d, J=7.5Hz, 2H, Ar-H), 8.098 (s, 1H, NC-C=CHAr), 13C NMR (250

MHz, DMSO): δ =56.01, 56.43, 107.23, 112.41, 113.59, 118.00, 124.84, 127.30, 129.19, 129.61, 133.48, 136.61, 149.19, 154.04, 156.21, 190.51

2-benzoyl-3-(4-methylphenyl)acrylonitrile(3i): IR (KBr) υ: [Cm^{-1}] 1570 (C=C), 1667 (enone -C=O str.), 2213 (-CN), 2916 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6): 2.506(s, 3H, H-CH_3), 7.418 (d, J=8Hz, 2H, Ar-H), 7.597 (t, J=7.5Hz, 2H, Ar-H), 7.717(t, J=7.5Hz, 1H, Ar-H), 7.850 (d, J=7.5Hz, 2H, Ar-H), 8.001 (d, J=8Hz, 2H, Ar-H), 8.118 (s, 1H, NC-C=CHAr), 13C NMR (250 MHz, DMSO): δ =21.85, 109.56, 117.38, 129.22, 129.57, 129.77, 130.42, 131.48, 133.71, 136.24, 144.80, 156.16, 190.29

2-benzoyl-3-(2,4,5-trimethoxyphenyl)acrylonitrile (3j):IR (KBr) υ: [Cm^{-1}] 1613 (C=C), 1649 (enone -C=O str.), 2212 (-CN), 2939 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6) :3.781 (s, 3H, H-OCH_3), 3.879(s, 3H, H-OCH_3), 3.955(s, 3H, H-OCH_3), 6.816(s, 1H, Ar-H), 7.580(t, J=7.5Hz, 2H, Ar-H), 7.688 (t, J=7.5Hz, 1H, Ar-H), 7.777 (d, J=7.5Hz, 2H, Ar-H), 7.972 (s, 1H, Ar-H), 8.372 (s, 1H, N-H), 8.372 (s, 1H, NC-C=CHAr), 13C NMR (250 MHz, DMSO): δ=56.27, 56.77, 57.32, 97.74, 105.21, 110.29, 111.67, 118.56, 129.06, 129.37, 133.21, 137.05, 143.29, 149.19, 156.76, 157.36, 190.69

2-benzoyl-3-(4-phenylphenyl)acrylonitrile(3k): IR (KBr) υ: [Cm^{-1}] 1576 (C=C), 1672 (enone -C=O str.), 2215 (-CN), 2932 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6): 7.444-8.212 (m, 5H, Ar-H), 7.444-8.212 (m, 9H, para Ph-Ar-H), 8.185 (s, 1H, NC-C=CHAr) 13C NMR (250 MHz, DMSO): δ =110.77, 117.371, 127.485, 127.818, 129.175, 129.255, 129.638, 129.868, 131.268, 132.108, 133.819, 136.180, 138.985, 145.072, 155.583, 190.231.

2-benzoyl-3-(1-naphthyl)acrylonitrile(3l): IR (KBr) υ: [Cm^{-1}] 1600 (C=C), 1663 (enone -C=O str.), 2221 (-CN), 3064 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6): 7.627-8.280 (m, 5H, Ar-H),7.627-8.280 (m, 7H, napthyl-H),8.827(s, 1H, NC-C=CHAr) 13C NMR (250 MHz, DMSO):δ=114.643, 116.863, 124.097, 125.961, 127.461, 128.300, 128.367, 129.290, 129.384, 129.691, 130.033, 131.255, 133.294, 133.515, 133.984, 136.186, 154.482, 189.930

3m) IR (KBr) υ: [Cm^{-1}] 1553 (C=C), 1660 (enone -C=O str.), 2204 (-CN), 2923 (Aromatic C-H str); 1H NMR (500 MHz, DMSO-d6): 7.377 (t, 1H, Thiophene-H), 7.591 (t, J=7.5Hz, 2H, Ar-H), 7.705 (t, J=7.5Hz, 1H, Ar-H), 7.824 (d, J=7.5Hz, 2H, Ar-H), 8.083 (d, 1H, Thiophene-H), 8.263 (d, 1H, Thiophene-H), 8.447 (s, 1H, NC-C=CHAr) 13C NMR (250 MHz, DMSO): δ=106.179, 117.540, 129.189, 129.427, 129.530, 133.499, 136.456, 136.541, 137.890, 141.149, 148.990, 189.862

3. Result and Discussion:

Our contribution is intended to extend scope of Deep Eutectic solvent for the synthesis of α-cyno chalcones and describe application of DES as catalyst for Knoevenagel condensation reaction between aromatic aldehyde and benzoyl acetonitrile. To examine catalytic suitability of DES at the beginning the reaction of para-chloro benzaldehyde(1), and Benzoyl actonitrile(2)in absence of catalyst at 60^0C was employed as model reaction this reaction does not proceed within 24 hours.

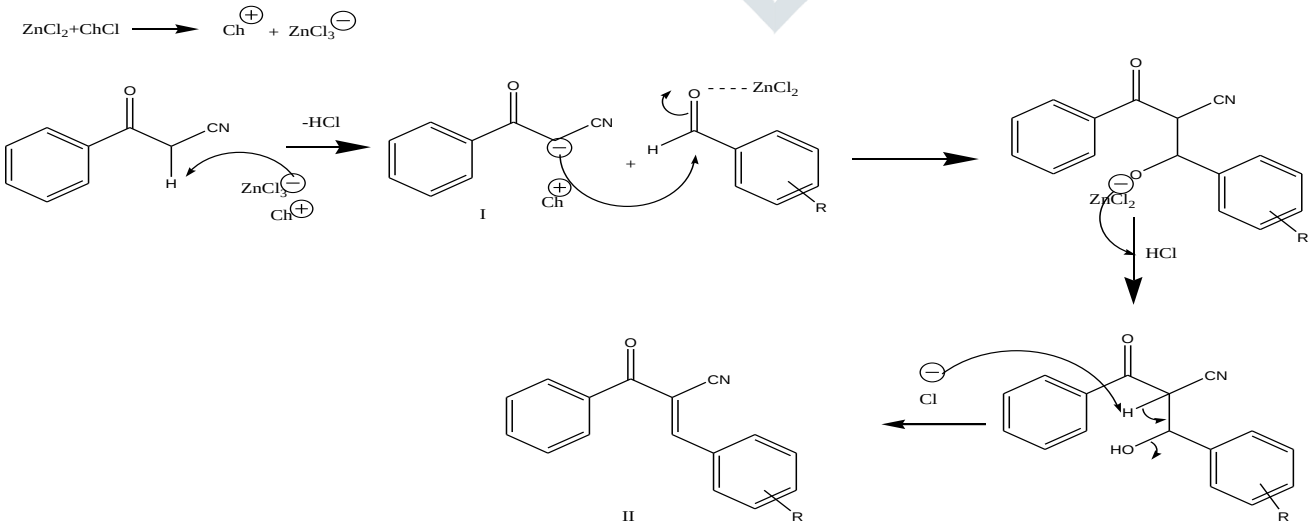
Deep eutectic solvent (DES) is a powerful solvent accomplishing a variety of organic reaction. when the reaction was performed in Choline chloride-$ZnCl_2$ (1:2) at room temp the yield of the model reaction was less than 20% .We then study the reaction at elevated temperature (40 to 80^0C) the result indicates that Choline chloride –$ZnCl_2$ was found to be most effective for this transformation at temp 60^0C in 20 min and gave exclusively the desired product with high yield up to 92% yield. Various DESs were employed on model reaction to determine efficiencies of DES and the results are summarized in Table no.2 It should be noted that other DES solvents supported formation of the target product in moderate yield . Therefore, ChCl: $2ZnCl_2$ has been considered as the best DES for this reaction Thus, under these optimized conditions, various structurally diverse aromatic aldehydes were reacted with benzoyl acetonitrile the corresponding results are listed in Table.no1. As shown, the aromatic aldehydes substituted with electron releasing and electron-withdrawing groups undergo this reaction with equal efficiency. The products were characterized by using FTIR, ^{1}H NMR, ^{13}C NMR spectra.

Furthermore, the reaction was carried out by using different amount of DES (Deep Eutectic solvent) at 60^0C and the results are summarized in table no. 3 .The optimal amount of the DES was determined to be 1.0 g . The higher amounts of the DES have no significant effect on the yield and reaction time, as shown in Table no.3.

One of the most important benefits of applying DES in organic synthesis is their potential reusability. After completion of the reaction, 5 ml water was added to reaction mixture. The DES being soluble in water, filtered the reaction mixture, DES was recovered from the filtrate by evaporating the water phase under vacuum. The recycled DES could be reused up to three cycles with only a slight decrease in its activity, as shown in Table no.4.

On the basis of experimental results and the literature, plausible mechanisms for the formation of α-cyno chalcones are shown in fig. This mechanism has been based on acidic nature of choline cation and $ZnCl_3^-$ anion act as Lewis base it activate benzoyl acetonitrile so that deprotonation of C-H bond take place to form intermediate I then nucleophilic attack on carbonyl group of aldehydes take place to form α-cyno chalcones II.

3.1.Reaction Mechanism:



3.2.In Vitro antimicrobial activity:

Among the all synthesized compound eight compounds are tested for antimicrobial study against microorganism a)Gram negative :E.coli ,b)Gram positive S.aureus ,Fungi c)C.albicans d)A. niger as shown in table no.5. The compounds were tested by agar diffusion method at a concentration of 100μg/mL [22]. The zone of inhibition was measured in mm and Chloromphenicol and Amphotericin-B were used as reference drugs.

The results of these studies of compounds revels that compound possess significant antifungal and antibacterial activity as shown in table no. From the antifungal screening results it has been observed that compound 3i and 3m possess excellent activity against C.albicans while compound 3d possess excellent activity against A.niger .In case of antibacterial screening, all tested compounds shows moderate activity. Antibacterial screening data shows compound 3band 3f possess good activity against E.coli while compound 3f possess good activity against S.aureus .

Table No.1

synthesis of α cyno chalcones derivatives under optimized conditions

Entry	Ar	Product	Yield%	M.P. Observed	M.P. Reported
1	4-ClC_6H_4	3a	92	180^0-185^0C	
2	4-$NO_2C_6H_4$	3b	90	140^0-145^0C	
3	4-OHC_6H_4	3c	75	180^0-182^0C	
4	3-ClC_6H_4	3d	74	115^0-120^0C	
5	4-BrC_6H_4	3e	82	100^0-102^0C	
6	4-$NO_2C_6H_4$	3f	75	115^0-118^0C	
7	4-$OMeC_6H_4$	3g	90	95^0-98^0C	96-97[21]
8	3,4di-$OMeC_6H_3$	3h	87	95^0-98^0C	
9	4-MeC_6H_4	3i	86	85^0-88^0C	88-89[21]
10	2,4,5-tri$OMeC_6H_2$	3j	88	190^0-195^0C	
11	4-PhC_6H_4	3k	86	115^0-120^0C	
12	1Naphaldehyde	3l	88	112^0-115^0C	
13	2 thiohene aldehyde	3m	90	110^0-112^0C	

Table No.2

Comparing different DESs in optimizing reaction of p-chlorobenzaldehyde(1 mmol) ,benzoyl acetonitrile(1 mmol)& DES(1 gm)

Entry	Solvent	Temperature	Yield(%)
1	Absence of solvent	60^0C	NR
2	ChCl: $ZnCl_2$ (1:2)	RT	Trace < 20
3	ChCl: $ZnCl_2$ (1:2)	40^0C	70
4	ChCl: $ZnCl_2$ (1:2)	50^0C	82
5	ChCl: $ZnCl_2$ (1:2)	60^0C	92
6	ChCl: $ZnCl_2$ (1:2)	80^0C	92
7	ChCl: Urea (1:2)	60^0C	80
8	ChCl: Citric acid (1:2)	60^0C	72
9	ChCl: Oxalic acid(1:2)	60^0C	75
10	ChCl: Glycerin (1:3)	60^0C	60
11	ChCl: Malonic acid (1:2)	60^0C	68
12	ChCl: $SnCl_2$ (1:2)	60^0C	82

Table No.3

Optimization of catalyst for the reaction of para-chloro benzaldehyde and Benzoyl acetonitrile

Entry	Quantity of Catalyst in gram	Yield %
1	0.5	76
2	1.0	92
3	1.5	92
4	2.0	92

Table No.4

reusability of DES for the reaction of p-chloro benzaldehyde and benzoyl acetonitrile

Sr. No.	Number of Runs	Yield %
1	Fresh	92
2	First	90
3	Second	87
4	Third	82

Table No. 5

antimicrobial activity of α cyno chalcones compounds.

Sr.no.	Compound	E. coli	S. aureus	C. albicans	A. niger
1	3b	7.55	7.64	6.20	8.26
2	3d	6.92	7.01	-	11.87
3	3f	7.81	11.25	-	-
4	3i	6.92	7.11	8.22	9.34
5	3j	-	-	-	-
6	3k	-	-	-	-
7	3l	7.43	7.30	6.19	-
8	3m	6.92	7.09	8.57	8.49
STD	Chloromphenicol	18.39	23.72	NA	NA
STD	Amphotericin-B	NA	NA	10.22	14.27

4. Conclusion:

In Summary, we have demonstrated an green, efficient and simple method for synthesis of α-cyno chalcones by reaction of benzoyl acetonitrile and aromatic aldehydes using low cost, non toxic , biodegradable deep eutectic solvent. This procedure have significance advantages offered in terms of simple work up ,easy to separate the solvent, high isolated product yield. Further the compounds were screened for their antibacterial and antifungal activity. The compounds 3d shows antifungal activity 83.18% as compared with standard A.niger while compounds 3i and 3m shows antifungal activity 80.46% and 83.85 % with standard C.albicans.

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