Current Chemistry Letters 9 (2020) 183–198

Contents lists available at GrowingScience

Current Chemistry Letters

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Synthesis of 1, 3-diaryl-2-propene-1-one derivatives using Tripotassium phosphate as an alternative and efficient catalyst and study its cytotoxic and antimicrobial properties

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C H R O N I C L E

Article history:
Received October 26, 2019
Received in revised form
February 25, 2020
Accepted March 23, 2020
Available online
March 23, 2020

Keywords:
Synthesis
Chalcones
Tripotassium phosphate
2-Methoxyethanol
Cytotoxic activity
Antimicrobial activity

A B S T R A C T

A series of fourteen chalcone was synthesized via. Claisen–Schmidt condensation between substituted 2- hydroxyl acetonaphthones and substituted benzaldehyde in presence of tripotassium phosphate (K_3PO_4) catalyst. The reaction was carried out by conventional method using 2-methoxyethanol. The procedure is simple and efficient in terms of reaction time, easy workup and isolation of products and yields. *In-vitro* all these synthesized compounds were screened and evaluated for the cytotoxic and antimicrobial activity. It was found that these compounds had significant cytotoxic activity in comparison with standard 5-flurouracil. The compounds 3a, 3b, 3h, 3f and 3l were screened by MTT assay against liver cancer cell line-HepG2. Among these, the compound **3b** and **3c** showed LC50 values of 997.14 µM/ml and 284.13 µM/ml., respectively. The remaining compounds did not display the LC50 values. The compound **3l** displayed the strongest cytotoxic activities with IC50 value of 91.85 µg/ml against liver cancer cell line. The Chalcone **3a**, **3f**, **3h** and **3e** demonstrated excellent antimicrobial activity and the remaining were moderately active against tested pathogens. The antimicrobial effects of all the tested compounds are due to the presence of pharmacological active substituent in the basic nucleus of Chalcones. Therefore, the present study leads to the development of new class of anticancer and antimicrobial inhibitory candidates.

1. Introduction

α, β-unsaturated carbonyl systems are commonly known as Chalcones. These are some important naturally occurring flavonoids in many plants or are synthetically prepared[1]. They are biogenic key precursors of flavonoids in many plants[2, 3]. They also exhibit the wide range of biological properties such as antiviral, anti-inflammatory, antimicrobial[4,5], cytotoxicity[6-8], analgesic, antimitotic, antitumor, antiulcerative and antipyretic properties[9].The α,β-unsaturated ketones, possess reactive ketoethylenic group, which makes it enormous important in organic synthesis. In addition, these compounds are useful as intermediates for the synthesis of various heterocyclic compounds[10]. They also helpful in material science field viz. non-linear optics, optical limiting, electrochemical sensing, Langmuir films and photo initiated polymerization.

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doi: 10.5267/j.ccl.2020.3.001

Useful and known method for the preparation of chalcones is the condensation of acetophenones with aldehydes in the presence of the alkali. Claisen-Schmidt condensation is the classical method in which aldehydes reacted with ketone in presence of aqueous alkaline bases[11], barium hydroxide or Lithium hydroxide[12]. Chalcone synthesis also achieved by various methods by using microwave irradiation[13-15], ultrasound irradiation[16], grinding technique[17-20], Suzuki reaction[21] and by using diverse catalyst like anhydrous K_2CO_3[9], NaOH-Al_2O_3[1], $SOCl_2$[22], KF / natural phosphate[23], Potassium phosphate[24], CaO, NH_4OH[25], Na_2CO_3[26],natural phosphate/lithium nitrate[27], silica-sulphuric acid[28],Iodine[29],NaOH[30-31]and KOH[32].

Commercially available K_3PO_4 is found to be interesting catalyst for the synthesis of titled compounds since this is thermally stable and inexpensive [24]. In view of these observations, herein for the first time we introduce a simple and convenient approach for chalcone synthesis using tripotassium phosphate in combination with 2-methoxyethanol as reaction solvent (Scheme 1, Table 5).

2. Results and Discussion

2.1. Chemistry

Tripotassium phosphate is capable of catalyzing the aldol condensation and Claisen-Schimdt reaction. In model reaction, anhydrous tripotassium phosphate catalyzed claisen-schimdt condensation between different substituted 2-acetyl-1-naphthol and substituted benzaldehyde was carried out (Scheme 1, Table 5). Optimization of reaction conditions is of importance for the synthesis of titled compounds. The type of solvent was investigated and the reaction was performed by using various solvent such as MeOH, EtOH, AcOH, DMSO, DMF, acetonitrile and 2-methoxyethanol. To study the effectiveness of K_3PO_4 using different reaction solvent, we performed the experiment in which mixture of substituted 2-hydroxy acetonaphthone (0.01 moles) and substituted benzaldehyde (0.01 moles) was dissolved in MeOH, EtOH, AcOH, DMSO, DMF, acetonitrile and 2-methoxyethanol. Weighed accurately and transferred 0.02mole (4.24g) of anhydrous K_3PO_4 into each reaction solution. The reaction mixture was refluxed till the completion and progress of the reaction as monitored by TLC in Hexane: Ethyl acetate (4:1). In light of the above experiment, we found that 2-methoxyethanol as an efficient reaction medium in terms of clean reactions, inexpensive and ecofriendly. The comparison and optimization using various reaction solvent for synthesis of Chalcones is made in terms of reaction time and yields (Table 6, Fig.3). The combination of 2-methoxyethanol and K_3PO_4 found to be convenient route for the preparation of Chalcones. Structures of all newly synthesized chalcones were confirmed by the spectral analysis like FTIR, ^{1}H NMR,C^{13}NMR,Mass and elemental analysis. FTIR analysis was performed by potassium bromide pellet technique. All the spectra showed the characteristic bands at 3234-3438 cm^{-1} , 1617-1634 cm^{-1} and 1490-1607 cm^{-1} for the corresponding –OH, C=O and aromatic C=C bond stretch respectively. ^{1}H NMR was performed on spectrometer at 500 MHz, spectra showed the characteristic singlet at δ(13.90-16.00), doublet at δ(6.50-7.70, J=16 Hz) and multiplet at δ (7.50-8.70) for phenolic, α-β olefinic and aromatic protons respectively. Mass spectrometric analysis was performed on the LCMS, each spectrum showed the characteristic molecular in peak at respective molecular mass of compound. These results are in confirmation with the formation of product.

2.2. Cytotoxic activity

These synthesized compounds were screened for the cytotoxic activity in terms of their ability to fatal the live cells of organism *Artemia salina*. Cytotoxic activity was evaluated in percentage mortality. *In-vitro* assay was performed with treatment of different sample concentration 1μM/ml, 10 μM/ml, 100μM/ml and 1000 μM/ml on the 10 shrimps of live cells of *Artemia salina*. Blank and test solutions were incubated at room temperature (28˚C-30˚C) under the condition of strong aeration for 24 hours. Percentage mortality was determined by measuring the viable count in the stem of capillary against

light background. All the compounds were showed the significant cytotoxic activity (Table 1). Compounds **3b** and **3c** were showed the LC50 values.

Percentage mortality = (Total nauplii - alive nauplii/total nauplii) ×100

From the Table 1, we have observed that all the compounds demonstrated the significant cytotoxic activity in terms of the % mortality of live cells of organism *Artemia salina.* The compounds **3b** and **3c** represented the 997.14 µM/ml and 284.13 µM/ml LC50 values, respectively. These values indicate that **3b** and **3c** were more potent than other compounds. The compounds **3b** and **3c** had -Cl and -OH substituent at *para* position of benzene ring. From this observation, it can be concluded that substituent –Cl and –OH at *para* position of benzene ring leads the significant cytotoxic activity.

Table 1. Cytotoxic activity in terms of Percentage mortality

Compound	**(%)Percentage Mortality** Sample Concentration(µM/ml)				**LC50 Value (µM/ml)**
	1	**10**	**100**	**1000**	
3a	70	70	80	80	ND
3b	30	40	40	50	997.14
3c	40	30	60	70	284.13
3d	90	100	100	100	ND
3e	90	90	100	100	ND
3f	90	90	100	100	ND
3g	90	90	100	100	ND
3h	90	80	100	100	ND
3i	90	90	100	100	ND
3j	90	90	100	100	ND
3k	90	100	100	100	ND
3l	100	100	100	100	ND
3m	100	90	100	100	ND
3n	90	100	100	100	ND

ND-Not detected

*2.3 MTT Assay of compounds **3a, 3b, 3f, 3h** and **3l**.*

The growth inhibitory activity of intended compounds against liver cancer cells (HepG2) was evaluated *in-vitro* by MTT assay. As presented in Fig.1, all compounds displayed inhibitory activity against liver cancer cell. The IC_{50} values for compounds **3a**, **3b**, **3f**, **3h** and **3l** were represented in Table 2. It was observed that compound **3b, 3f** and **3l** were shown 416.66 µg/ml, 536.66µg/ml and 91.85µg/ml IC_{50} values, respectively (Table 2). The compound **3b** has –Cl substituent at *para* position, **3h** has –2Cl substituent at *meta* and *para* position and **3l** has -2OH substituent at *meta* and *para* position of benzene ring. From this observation, it can be concluded that the substituent –Cl and –OH at *para* position of benzene ring leads to the significant potency.

Table 2. The IC50 values of compound 3a, 3b, 3f, 3h and 3l against liver cancer cell line

Compound	**In vitro inhibition of liver cancer cell (HepG2) (IC50,µg/ml)**
Standard 5-flurouracil	97.75
3a	>1000
3b	416.66
3f	>1000
3h	536.66
3l	91.85

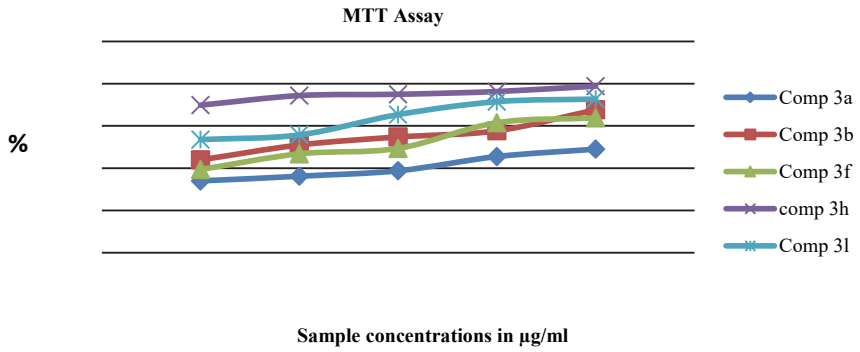


Fig.1. Inhibitory activity of compounds **3a**, **3b**, **3f**, **3h** and **3l** on liver cancer cell was incubated with indicated concentrations for 24 h.

2.4 Antimicrobial activity

Table 3.Activity index of the compounds **(3a-3n)**

Compound	Antibacterial				Antifungal	
	Gram positive bacteria		Gram negative bacteria			
	S.aureus		*E.coli*		*C.albicans*	
	Mean value of Zone of inhibition (in mm)	Activity Index (A.I.)	Mean value of Zone of inhibition (in mm)	Activity Index (A.I.)	Mean value of Zone of inhibition (in mm)	Activity Index (A.I.)
3a	21.55	**1.2471**	15.17	**0.8358**	17.45	**1.03132**
3b	10.22	0.5914	15.88	**0.8749**	13.95	**0.82447**
3c	13.36	0.7731	13.19	0.7267	11.29	0.66726
3d	11.39	0.6591	12.09	0.6661	16.12	**0.95272**
3e	13.9	**0.8044**	12.44	0.6854	11.93	0.70508
3f	14.05	**0.8131**	12.67	**0.6981**	14.6	**0.86288**
3g	12.25	0.7089	14.04	**0.7736**	No zone	-
3h	13.55	**0.7841**	15.08	**0.8309**	14.25	**0.84220**
3i	11.2	0.6481	11.77	0.6485	No zone	-
3j	10.23	0.5920	12.39	0.6826	13.02	0.76950
3k	11.15	0.6453	12.32	0.6788	No zone	-
3l	14.2	**0.8218**	12.88	**0.7096**	13.04	**0.77069**
3m	12.93	0.7483	10.19	0.5614	13.87	**0.81974**
3n	13.08	0.7569	11.55	0.6364	13.86	**0.81915**
DMSO	No zone	-	No zone	-	No zone	-
Ampicilin Standard	17.28	-	18.15	-	-	-
Fluconazole Standard	--	-	---	-	16.92	-

These synthesized compounds were screened for the antibacterial activities against Gram positive bacteria *Staphylococcus aureus* (ATCC6538) and Gram negative bacteria *Echerchia coli* (ATCC8739) and were screened for antifungal activity against *Candida albicans* (ATCC10231) by Agar cup method. Standard drugs Ampicilin and Fluconazole were used as antibacterial and antifungal drug for results comparison. Two bacterial stains were incubated for 24 hr at 35˚C and the single fungal stain was incubated for 48 hr at 25˚ C along with antibacterial and antifungal standard. For antibacterial and antifungal screening, culture medium was soyabean casein digest agar and sabourauds dextrose agar respectively. Stock solution (1 mg/ml) was prepared by dissolving compound in dimethylsulfoxide. All the studies were carried out in triplicates and average zone was reported in final reading. The activity index (A.I.) of all the compounds is calculated by following formula, the results are summarised in Table 3 and the average zone of inhibition against the pathogens is graphically presented in Fig.2.

$$\text{Activity Index (A.I.)} = \frac{\text{Mean zone of inhibition of derivatives}}{\text{Zone of inhibition of Standard drug}}$$

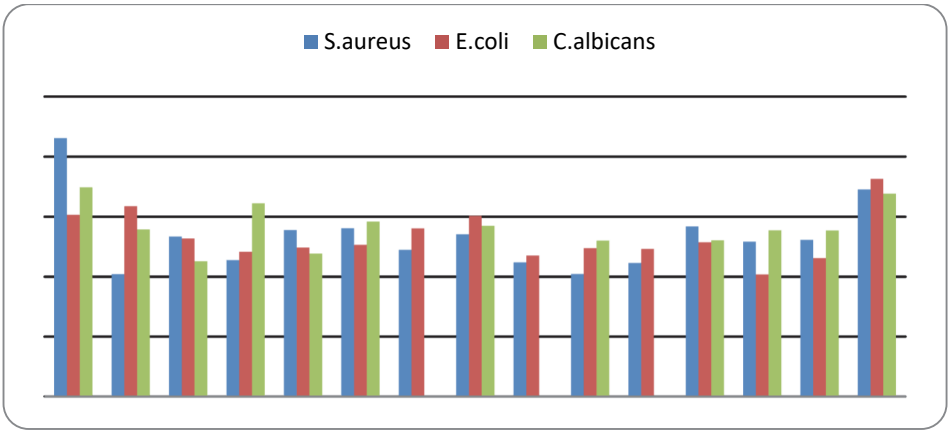


Fig. 2. Zone of inhibition of compounds against pathogens

From Table **3**, various observations are drawn, the compounds **3a**, **3f**, **3h** and **3e** were shown the significant antibacterial and antifungal activity against the *Staphylococcus aureus, Echerchia coli* and *Candida albicans* respectively. The compound **3a** is bearing the 2-OH and -3I substituent, **3f** and **3h** are bearing -Br, -2Cl substituent whereas **3e** possess the -Br and 2-OH substituent. These observed results support the structure activity relationship at the varying structural features of the molecules. The presence of multiple hydroxyl and halogen substituent in compounds **3a**, **3f**, **3h** and **3e** lead to the significant antimicrobial activity. The compound 3j contains -2Br substituent, it showed moderate antibacterial activity against *Echerchia coli.* The compounds **3b** and **3g** associated with -Br, -Cl and -Br,-OH substituent respectively, they showed moderate antibacterial activity against *Echerchia coli.* Also the compounds **3i** and **3k** associated with -Br, $-NO_2$, $-(CH_3)_2$ substituent showed good antibacterial activity instead did not show the antifungal activity. Activity index of all the compounds is summarized in the Table 3.

2.4.1. Minimum inhibitory concentration (MIC)

The minimum inhibitory concentration of synthesized chalcones were performed at the concentrations 1.0, 0.5, 0.25 and 0.12 mg/ml, the results of MIC are given in Table 4. From the table, it looks that the compound **3a** showed the best minimum inhibitory concentrations (0.12 mg/ml) against the antibacterial and antifungal organisms. The compound **3b** and **3h** showed better MIC 0.50 mg/ml, 0.25 mg/ml and 0.25 mg/ml against *Staphylococcus aureus, Echerchia coli* and *Candida albicans* respectively. Also, the compound **3f** showed the moderate MIC 0.25 mg/ml, 0.50 mg/ml and 0.25

mg/ml against antibacterial and antifungal organisms. The compounds **3i** and **3k** showed the good MIC 1.0 mg/ml against the antibacterial organisms (Table 4). From the comparative study, it is revealed that the compounds bearing the multiple halogen and hydroxyl groups have moderate inhibition activity, however compounds bearings nitro, methoxy groups reduce the inhibition activity.

Table 4. MICs of chalcone derivatives **(3a-3n)**

Compound	Antibacterial								Antifungal			
	Gram positive bacteria				Gram negative bacteria							
	S.aureus				*E.coli*				*C.albicans*			
	1.0	0.5	0.25	0.12	1.0	0.5	0.25	0.12	1.0	0.5	0.25	0.12
3a	-	-	-	-	-	-	-	+	-	-	-	-
3b	-	-	+	+	-	-	-	+	-	-	-	+
3c	-	+	+	+	-	+	+	+	-	+	+	+
3d	-	+	+	+	-	+	+	+	-	-	-	+
3e	-	-	+	+	-	+	+	+	-	+	+	+
3f	-	-	-	+	-	-	+	+	-	-	-	+
3g	-	+	+	+	-	-	+	+	+	+	+	+
3h	-	-	+	+	-	-	-	+	-	-	-	+
3i	-	+	+	+	-	+	+	+	+	+	+	+
3j	-	+	+	+	-	+	+	+	-	+	+	+
3k	-	+	+	+	-	+	+	+	+	+	+	+
3l	-	-	-	+	-	-	+	+	-	-	+	+
3m	-	+	+	+	-	+	+	+	-	-	-	+
3n	-	+	+	+	-	+	+	+	-	-	-	+
Ampicilin Standard	-	-	-	+	-	-	-	+				
Fluconazole Standard									+	+	+	+

The positive sign (+) indicate growth on plate, negative sign (-) indicate no growth on plate.

3. Conclusions

In present study, we have developed method using tripotassium phosphate as an efficient green catalyst for the synthesis of chalcones. Tripotassium phosphate is nontoxic, cheaper and economic. It provides greater reaction conditions coupled with clean products, increased yield and better economy. Newly synthesized compounds were characterized by IR, ^{1} H NMR, C^{13} NMR, mass spectral data and elemental analysis. All results are in agreement with the structural confirmation. These compounds were screened for their antimicrobial activity. Antimicrobial activity was studied against the gram positive bacteria *Staphylococcus aureus* and gram negative bacteria *Echerchia coli* and antifungal pathogen *Candida albicans* with MICs of 0.12, 0.25, 0.50 and 1.0 mg/ml. From the antimicrobial study, it was concluded that the compounds **3a, 3f, 3h** and **3e** having multiple halogen and hydroxyl substituent show significant antibacterial activity. The synthesized compounds were screened for cytotoxic activity against the organism *Artemia salina*. They showed significant cytotoxic activity. Further, the compounds **3a**, **3b**, **3f**, **h** and **3l** were evaluated for anticancer activity by MTT assay against the liver cancer cell (Hep G2). The compounds **3b, 3h** and **3l** represented significant anticancer activity. They have chloro and hydroxyl substituent at *para* position of benzene ring. These studies reveal the antimicrobial and anticancer potency of the 1, 3-diaryl-2-propene-1-one derivatives.

Acknowledgements

The authors are very thankful to Panjab University, Chandigarh for Instrumental Analysis and Radial Microbiotech services for biological activities.

4. Experimental

4.1. Materials and Methods

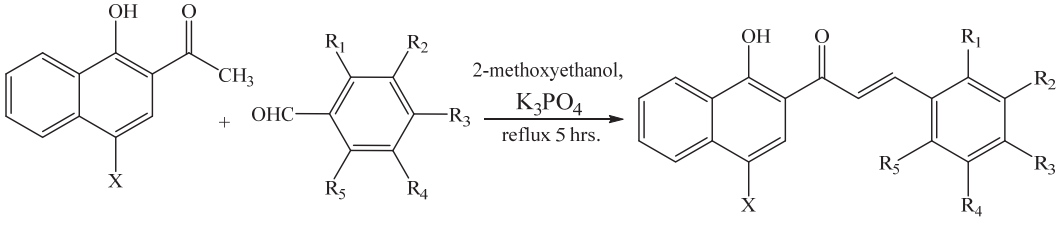
Starting material alpha naphthol, all the aldehydes, solvents were purchased from the Loba chemicals. Zinc chloride and tripotassium phosphate was purchased from the Sigma Aldrich chemicals and were used without purification. TLC plate, Silica gel 60 F_{254}, Aluminum backed was purchased from the Merck. The progress of the reaction was monitored by TLC. Acetyl naphtol was synthesized by the acylation reaction of alpha naphthol in presence of zinc chloride and acetic acid solvent. Halo ketones were prepared from alpha naphthol according to literature procedure[33-35]. Melting points were determined in open glass capillaries on Veego, VMP-D, Melting Point System, are uncorrected. FTIR spectra were recorded as KBr pellets on a Perkin Elmer System 2000 and Shimadzu spectrophotometer. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance NEO500 Spectrometer at 500 MHz. Mass spectra were recorded on LCMS.

4.2. General Procedure for Synthesis of 1, 3-diaryl-2-propene-1-one

A mixture of substituted 2-hydroxy acetonaphthone (0.01 moles) and substituted benzaldehyde (0.01 moles) were dissolved in 20 ml of 2-methoxyethanol. Weighed accurately and transferred 0.02mole (4.24g) of anhydrous K_3PO_4 in to reaction solution. The reaction mixture was refluxed for 5 hours and progress of the reaction was monitored by TLC in Hexane: Ethyl acetate (4:1). After completion of refluxing, reaction mixture was cooled and poured into 20 ml of ice-water, stirred then treated with dil.HCl to precipitate crude solid product. Solid mass observed were filtered, washed with sufficient amount of water and dried under vacuum. The crude product was purified by column chromatography to give pure sample.

4.3. Column Chromatography

Silica gel was used as stationary phase and a mixture of hexane and ethyl acetate was used as mobile phase in the proportion 8:2. Initially weighed the 20 g of silica gel in the beaker and prepared the slurry in hexane. The bottom of the column was plugged with a piece of glass wool just above the stopcock. Slurry was transferred gradually in the column through funnel, ensured that column packing should be free from gap. Solvent was allowed to drain until just before the silica gel and the solvent front meet. 100 mg of sample was dissolved in 1 ml of ethyl acetate. Added sample solution on the top of column using pipette. Remainder of the column was filled with 4.0 ml of hexane. Stopcock was opened gradually and flow rate was adjusted as a single drop per 30 seconds to achieve well separation of mixture. 2.0 ml of fractions were collected in each test tube. Additionally mobile phase was used until the desired compounds have been eluted. The test tube was identified by using TLC that contains desired product and then mixed all of the same fractions. The solvent was evaporated to get isolated pure product. The structures of products were confirmed by the physical and spectral characterization.



1 **2** **3a-n**

Tripotassium phosphate supported basic catalyst for synthesis of Chalcones

Scheme 1

Table 5. Synthesis of chalcone **(3a-3n)**

Sr.No	Compound	X	R_1	R_2	R_3	R_4	R_5
1	3a	I	OH	I	H	I	H
2	3b	Br	H	H	Cl	H	H
3	3c	Br	H	H	OCH_3	H	H
4	3d	Br	H	OCH_3	OH	H	H
5	3e	Br	H	H	Br	H	H
6	3f	Br	Cl	H	H	H	Cl
7	3g	Br	H	H	OH	H	H
8	3h	Br	Cl	H	Cl	H	H
9	3i	Br	H	H	NO_2	H	H
10	3j	Br	H	H	F	H	H
11	3k	Br	H	H	$N(CH_3)_2$	H	H
12	3l	Br	H	OH	OH	H	H
13	3m	I	H	OCH_3	OCH_3	H	H
14	3n	I	H	OH	OH	H	H

Table 6. Optimization of reaction condition for chalcone synthesis

Entry	Solvent	Quantity (ml)	Time (h)	Yield (%)
1	Methanol	40	10	52
2	Ethanol	35	9.0	66
3	Acetic acid	35	10.5	59
4	DMSO	30	8.0	62
5	DMF	30	8.5	63
6	Acetonitrile	25	7.0	57
7	**2-Methoxy ethanol**	20	5.0	81

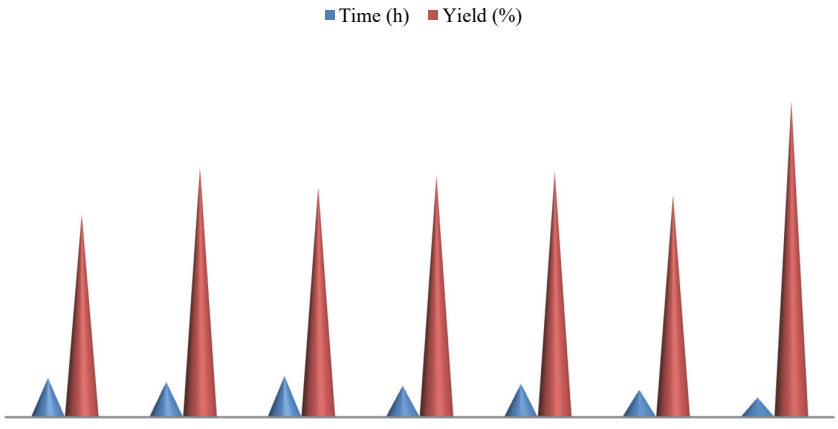


Fig. 3. Optimization of reaction condition for chalcone synthesis

4.4 Physical and Spectral Data

The synthesized compounds were purified by column chromatography. All the compounds were colored in nature. The compounds were dried; finely powdered and melting points were recorded. FTIR analysis was performed by potassium bromide pellet technique. All the spectra showed the characteristic bands at 3234-3438 cm^{-1}, 1617-1634 cm^{-1} and 1490-1607 cm^{-1} for the corresponding –OH, C=O and aromatic C=C bond stretch respectively.^{1}H NMR was performed on spectrometer at 500 MHz, spectra showed the characteristic singlet at δ(13.90-16.00), doublet at δ(6.50-7.70, J=16 H_z) and

multiplet at δ (7.50-8.70) for phenolic, α-β olefinic and aromatic protons respectively. C^{13}NMR was also performed on spectrometer at 500 MHz, spectra showed the singlet at δ (204.00-205.00), multiplet at δ (110.00-167.00) and singlet at δ (55.00-56.00) for carbonyl carbon, aromatic carbon and methoxy carbon respectively (Fig.3). Mass spectrometric analysis was performed on the LCMS, each spectra showed the characteristic molecular ion peak at respective molecular mass of compound. Elemental analysis was performed on ThermoFinnigan elemental analyser; obtained values were comparable with the theoretical values. These results are in confirmation with the formation of product. Following are the spectral and physical details of each compound.

3-(2-Hydroxy-3, 5-Diodo-phenyl)-1-(4-Iodo-1-hydroxyl-naphthalen-2-yl)-propenone (3a)

Brown solid, Yield, 81%.Melting point, 205^0C.FTIR (KBr, cm^{-1}): 3419(OH),1628(C=O),1577,1540(ring C=C),^{1}H NMR (DMSO,500 MHz):δ5.19(s,1H, OH), δ6.90(d, *J*=16Hz 1H,Hα), δ7.46(d, *J*=16Hz 1H,Hβ), δ7.66-8.37(m,7H,Ar-H), δ13.90(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ205.11(C=O), δ115.57-161.76(Aromatic carbon), δ82.87-90.51(C-I). MS m/z:667(M^+),471,385,269,249,181,179.Anal.Calc for $C_{19}H_{11}O_3I_3$:C,34.13;H,1.65;I,57.04.Found: C,34.18;H,1.72;I,57.11.

3-(4-Chloro-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3b)

Yellow solid, Yield, 76%.Melting point, 118^0C.FTIR(KBr, cm^{-1}): 3415(OH),1631(C=O),1577,1490(ring C=C),^{1}H NMR(500 MHz,DMSO) δ6.74(d, *J*=16Hz 1H,Hα), δ7.54(d, *J*=16Hz 1H,Hβ), δ7.66-8.64(m,9H,Ar-H), δ15.02(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.98(C=O),δ114.84-136.17(Aromatic carbon,),MS m/z:387(M^+),375,315,249,181,179.Anal.Calc for $C_{19}H_{12}O_2BrCl$:C,58.76;H,3.09;X(Br+Cl),29.64.Found: C,58.84;H,3.15;X(Br+Cl),29.72.

3-(4-methoxy-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3c)

Yellow solid, Yield, 84 %.Melting point, 166^0C.FTIR(KBr, cm^{-1}): 3430(OH),1630(C=O),1607,1563(ring C=C),^{1}H NMR(500 MHz,DMSO)δ3.86(s,3H, –OCH_3), δ7.05(d, J=16Hz 1H,Hα), δ7.61(d, J=16Hz 1H,Hβ), δ7.70-8.70(m,9H,Ar-H), δ15.31(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ(204.90),δ114.95-162.44(Aromatic carbon),δ55.96(O-CH_3).MS m/z:383(M^+),336,281,255,199,97.Anal.Calc for $C_{20}H_{15}O_3Br$:C,62.66;H,3.92;Br,20.89.Found: C,62.74;H,3.96;Br,20.92.

3-(4-Hydroxy-3-methoxy-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3d)

Orange solid, Yield, 79 %.Melting point, 180^0C.FTIR(KBr, cm^{-1}): 3424(OH),1627(C=O),1604,1559(ring C=C),^{1}H NMR(500 MHz,DMSO)δ3.91(s,3H, –OCH_3), δ5.30(s,1H, –OH),δ6.88(d, J=16Hz 1H,Hα), δ7.46(d, J=16Hz 1H,Hβ), δ7.63-8.67(m,8H,Ar-H), δ15.44(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.55(C=O), δ110.10-163.63(Aromatic carbon), δ 56.49(O-CH_3). (MS m/z:399(M^+),397,385,281,263,181,149,97.Anal.Calc for $C_{20}H_{15}O_4Br$:C,60.15;H,3.76;Br,20.05.Found: C,60.23;H,3.81;Br,20.10.

3-(4-Bromo-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3e):

Brown solid, Yield, 73 %.Melting point, 198^0C.FTIR(KBr, cm^{-1}): 3400(OH),1624(C=O),1589,1568(ring C=C),^{1}H NMR(500 MHz,DMSO) δ6.78(d, J=16Hz 1H,Hα), δ7.46(d, J=16Hz 1H,Hβ), δ7.69-8.41(m,9H,Ar-H), δ13.98(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ205.25(C=O),δ110.71-167.09(Aromatic carbon).MS

m/z:432(M^+),419,265,263,249,201,157,97,79.Anal.Calc for $C_{19}H_{12}O_2Br_2$:C,52.78;H,2.78;Br,37.04.Found: C,52.85;H,2.85;Br,37.12.

3-(2, 6-Dichloro-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3f)

Brown solid, Yield, 79 %.Melting point, 230^0C.FTIR(KBr, cm^{-1}): 3235(OH),1617(C=O),1577,1553 (ring C=C),^{1}H NMR(500 MHz,DMSO) δ6.52(d, J=16Hz 1H,H_α), δ7.42(d, J=16Hz 1H,H_β), δ7.69-8.40(m,8H,Ar-H), δ14.00(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ205.15(C=O),δ110.61-161.16(Aromatic carbon).MS m/z:422(M^+),377,325,283,263,255,249,181,97.Anal.Calc for $C_{19}H_{11}O_2BrCl_2$:C,54.03;H,2.61;X(Br+Cl),35.78.Found: C,54.11;H,2.68;X(Br+Cl),35.84.

3-(4-Hydroxy-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3g)

Brown solid, Yield, 77 %.Melting point, 215^0C.FTIR(KBr, cm^{-1}): 3238(OH),1625(C=O),1591,1565(ring C=C),^{1}H NMR(500 MHz,DMSO)δ5.31(s,1H, –OH), δ6.88(d, J=16Hz 1H,H_α), δ7.67(d, J=16Hz 1H,H_β), δ7.70-8.65(m,9H,Ar-H), δ14.06(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.95(C=O),δ110.39-161.38(Aromatic carbon).MS m/z:369(M^+).Anal.Calc for $C_{19}H_{13}O_3Br$:C,61.79;H,3.52;Br,21.68.Found: C,61.84;H,3.59;Br,21.74.

3-(2, 4-Dichloro-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3h)

Brown solid, Yield, 74 %.Melting point, 211^0C.FTIR(KBr, cm^{-1}): 3400(OH),1621(C=O),1590,1568(ring C=C),^{1}H NMR(500 MHz,DMSO) δ6.82(d, J=16Hz 1H,H_α), δ7.41(d, J=16Hz 1H,H_β), δ7.51-8.37(m,8H,Ar-H), δ14.00(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.75(C=O),δ110.22-161.55(Aromatic carbon).MS m/z:422(M^+),421,419,395,265,255,199,173,97.Anal.Calc for $C_{19}H_{11}O_2BrCl_2$:C,54.03;H,2.61;X(Br+Cl),35.78.Found: C,54.11;H,2.67;X(Br+Cl),35.82.

3-(3-Nitro-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3i)

Yellow solid, Yield, 75 %.Melting point, 220°C.FTIR(KBr, cm^{-1}): 3369(OH),1624(C=O),1591,1567(ring C=C),^{1}H NMR(500 MHz,DMSO) δ6.85(d, J=16Hz 1H,H_α), δ7.46(d, J=16Hz 1H,H_β), δ7.66-8.39(m,9H,Ar-H), δ14.00(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.61(C=O),δ110.00-161.77(Aromatic carbon.MS m/z:399(M^+),398,384,339,311,267,265,221.Anal.Calc for $C_{19}H_{12}O_4BrN$:C,57.29;H,3.02;Br,20.10;N,3.52.Found: C,57.34;H,3.11;Br,20.10;N,3.58.

3-(4-Fluoro-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3j)

Yellow solid, Yield, 82 %.Melting point, 247^0C.FTIR(KBr, cm^{-1}): 3432(OH),1625(C=O),1606,1571(ring C=C),^{1}H NMR(500 MHz,DMSO) δ6.81(d, J=16Hz 1H,H_α), δ7.44(d, J=16Hz 1H,H_β), δ7.67-8.37(m,9H,Ar-H), δ13.99(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ205.17(C=O),δ110.70-161.05(Aromatic carbon).MS m/z:371(M^+),339,325,281,265,255,181,97.Anal.Calc for $C_{19}H_{12}O_2BrF$:C,61.46;H,3.23;X(Br+F),26.69.Found: C,61.54;H,3.27;X(Br+F),26.75.

3-(4-N-Dimethylamino-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3k)

Red solid, Yield, 84 %.Melting point, 162^0C.FTIR(KBr, cm^{-1}): 3434(OH),1625(C=O),1565,1503(ring C=C),^{1}H NMR(500 MHz,DMSO)δ3.72(s,6H,two $–CH_3$), δ6.78(d, J=16Hz 1H,H_α), δ7.64(d, J=16Hz 1H,H_β), δ7.67-8.68(m,9H,Ar-H), δ14.00(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.87(C=O),δ111.54-153.06(Aromatic carbon).MS

m/z:396(M^+),339,325,281,255,199,97.Anal.Calc for $C_{21}H_{18}O_2BrN$:C,63.64;H,4.38;Br,20.20;N,3.54.Found: C,63.69;H,4.44;Br,20.20;N,3.60.

3-(3, 4-Dihydroxy-phenyl)-1-(4-Bromo-1-hydroxyl-naphthalen-2-yl)-propenone (3l)

Brown solid, Yield, 79%.Melting point, 180^0C.FTIR(KBr, cm^{-1}): 3431(OH),1625(C=O),1592,1567(ring C=C),^{1}H NMR(500 MHz,DMSO)δ5.18(s,2H,two –OH), δ6.81(d, J=16Hz 1H,H_α), δ7.42(d, J=16Hz 1H,H_β), δ7.68-8.37(m,8H,Ar-H), δ13.99(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ205.03(C=O),δ110.56-161.19(Aromatic carbon).MS m/z:385(M^+),377,325,283,265,249,165,97.Anal.Calc for $C_{19}H_{13}O_4Br$:C,59.22;H,3.38;Br,20.78.Found: C,59.29;H,3.41;Br,20.83.

3-(3, 4-Dimethoxy-phenyl)-1-(4-Iodo-1-hydroxyl-naphthalen-2-yl)-propenone (3m)

Orange solid, Yield, 75 %.Melting point, 161^0C.FTIR(KBr, cm^{-1}): 3432(OH),1624(C=O),1586,1565(ring C=C),^{1}H NMR(500 MHz,DMSO)δ3.92(s,6H,two –OCH_3), δ6.91(d, J=16Hz 1H,H_α), δ7.35(d, J=16Hz 1H,H_β), δ7.51-8.38(m,8H,Ar-H), δ13.98(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.28(C=O),δ110.38-164.65(Aromatic carbon),δ76.84-85.70(C-I),δ55.99-56.19(O-CH_3).MS m/z:460(M^+),459,312,311,97.Anal.Calc for $C_{21}H_{17}O_4I$:C,54.78;H,3.70;I,27.61.Found: C,54.82;H,3.77;I,27.68.

3-(3, 4-Dihydroxy-phenyl)-1-(4-Iodo-1-hydroxyl-naphthalen-2-yl)-propenone (3n)

Brown solid, Yield, 71 %.Melting point, 180^0C.FTIR(KBr, cm^{-1}): 3432(OH),1624(C=O),1586,1565(ring C=C),^{1}H NMR(500 MHz,DMSO)δ5.20(s,2H,two –OH), δ6.78(d, J=16Hz 1H,H_α), δ7.29(d, J=16Hz 1H,H_β), δ7.58-8.33(m,8H,Ar-H), δ13.96(s,1H, OH). ^{13}C NMR (DMSO, 500MHz):δ204.11(C=O),δ115.28-162.14(Aromatic carbon),δ78.84-86.15(C-I).MS m/z:432(M^+),401,357,341,313,311,299,269,127,97.Anal.Calc for $C_{19}H_{13}O_4I$:C,52.78;H,3.01;I,29.40.Found: C,52.81;H,3.08;I,29.44.

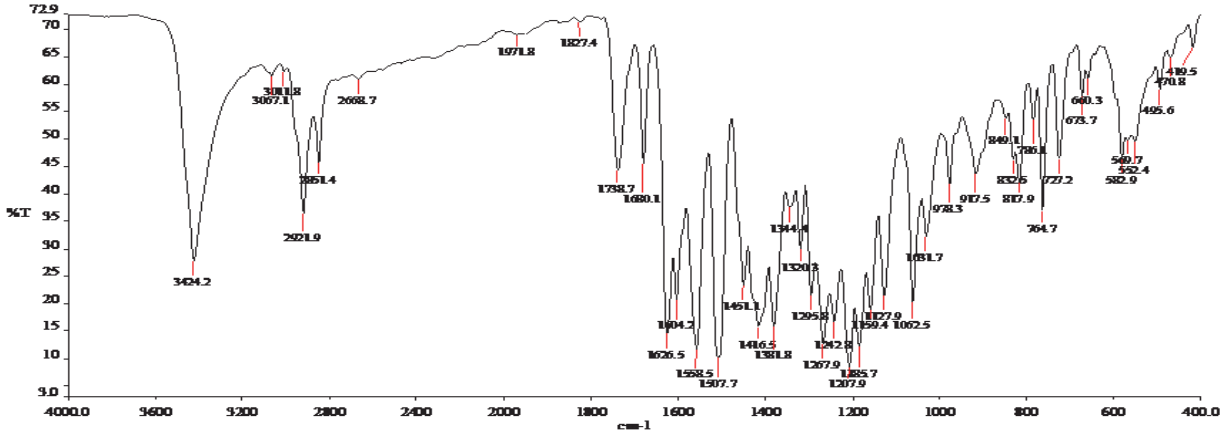


Fig. 4. IR spectrum of compound 3d

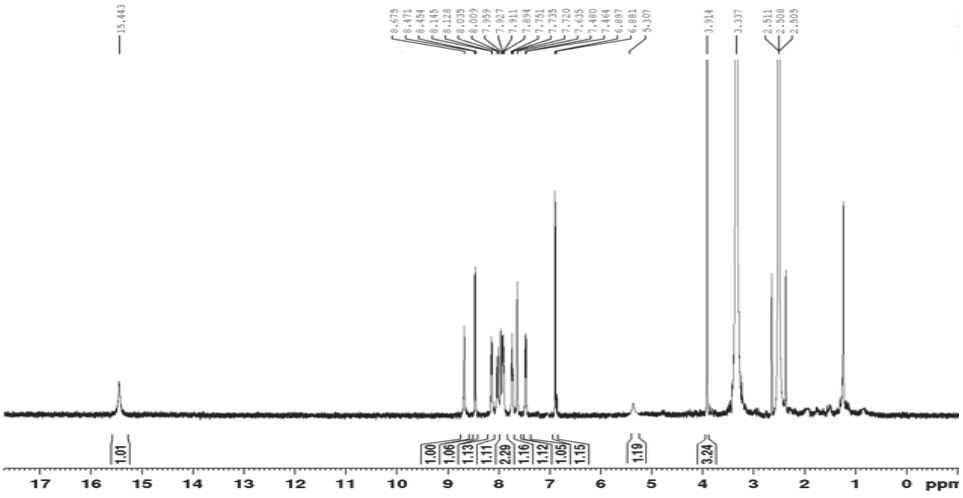


Fig. 5. ^{1}H NMR spectrum of compound 3d

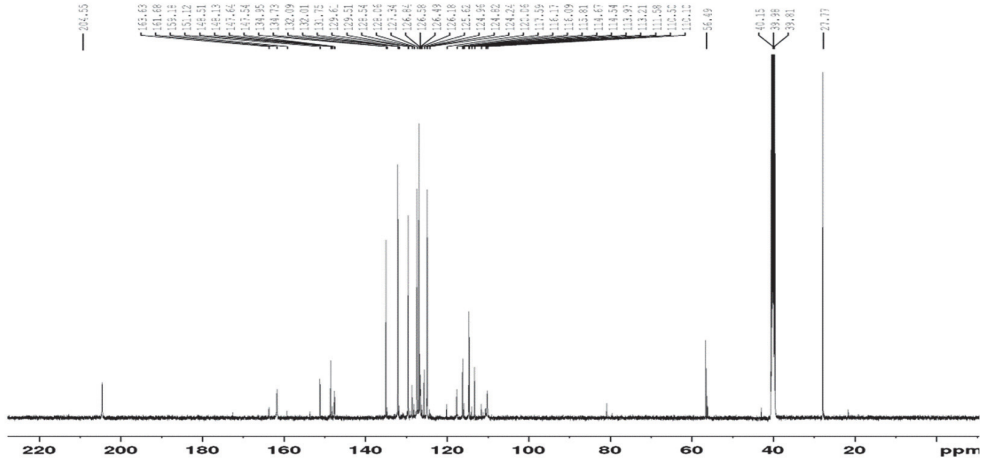


Fig. 6. C^{13} NMR spectrum of compound 3d

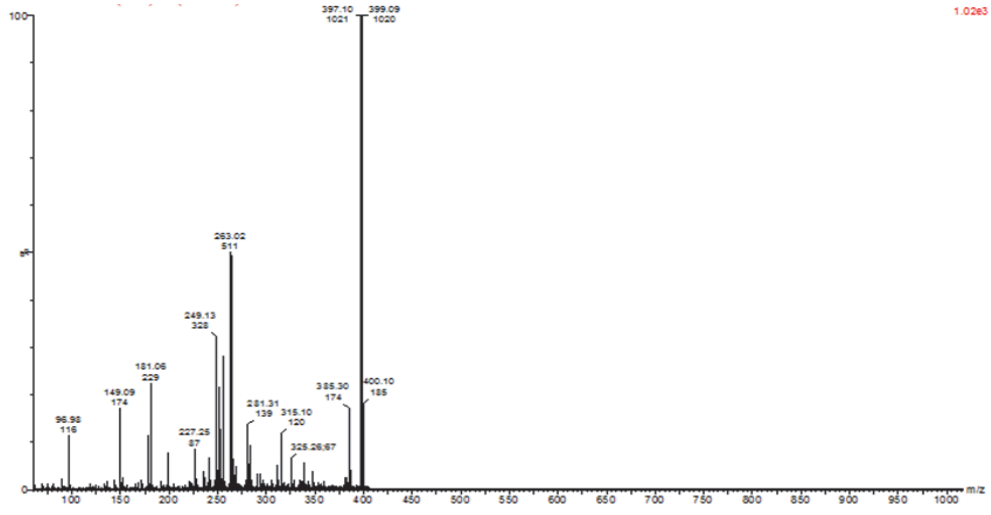


Fig.7. MS spectrum of compound 3d

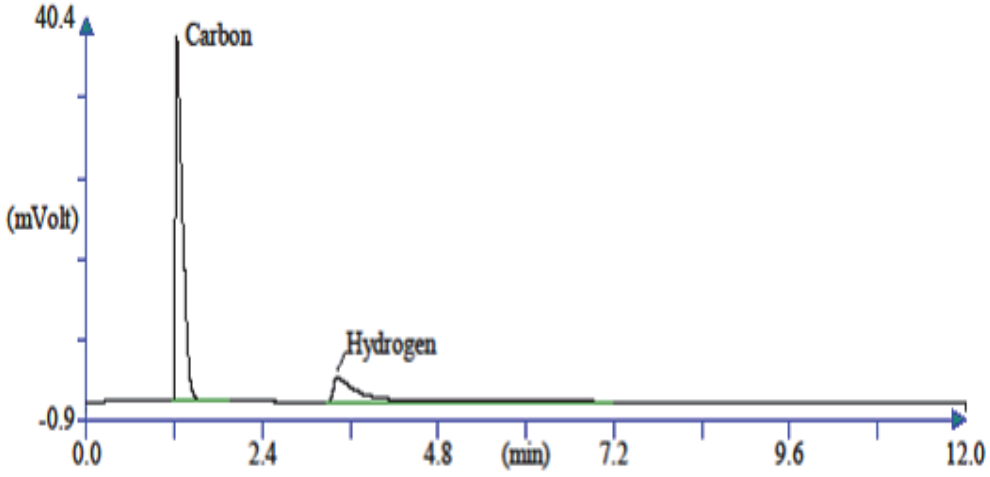


Fig. 8. CHN spectrum of compound 3d

4.5. Cytotoxic activity

Cytotoxic activity was screened against the organism *Artemia salina* for 24 hr *in-vitro* assay. Sample solutions were prepared in dimethylsulfoxide (DMSO) solvent. Different sample concentrations such as 1µM/ml, 10 µM/ml, 100µM/ml and 1000 µM/ml were prepared from each compound. For the test, 96 well plates were used. In each test tube, 0.1 ml of brine solution and 10 shrimps was added then treated with each sample solutions. For blank control, 0.1 ml of brine solution and 10 shrimps was added in a test tube and well plates were incubated at room temperature (28˚C-30˚C) under the condition of strong aeration for 24 hours. After incubation, nauplii were counted in the stem of capillary against light background. The percentage mortality was obtained by the following formula

Percentage mortality = (Total nauplii- alive nauplii)/ Total nauplii × 100

*4.6. MTT Assay for the compounds **3a, 3b, 3f, 3h** and **3l**.*

Liver cancer cell line (HepG2) was cultured at concentration 10^4 cells per well in 100 µl culture medium in 96 well flat bottom microplates overnight. Control wells were incubated with DMSO (0.2% in PBS) and cell line. Various sample concentrations of each compound such as 200 mg/ml, 400 mg/ml, 600mg/ml, 800mg/ml and 1000 mg/ml were prepared in dimethylsulfoxide. All samples were incubated in triplicate. Controls were maintained to determine the control cell survival and the percentage of live cells after culture. Cell cultures were incubated for 24 h at 37˚C and 5 % CO_2 in CO_2 incubator. After incubation, medium was removed completely and added 20 µl of MTT reagent (5 mg mL^{-1} in PBS) to each well. Then cells were incubated for 4 h 37˚C and 5 % CO_2 in CO_2 incubator. The resulting formazan crystals were dissolved in 200 µl DMSO and absorbance was measured spectrophotometrically at 550 nm after 10 minute incubation at 37˚C. The inhibition induced by each tested compound at indicated concentrations was calculated by the following formula.

% inhibition = Control absorbance-test absorbance/ control absorbance

4.7 In-vitro Antimicrobial Screening

In vitro antimicrobial screening of the compounds were performed for their antibacterial and antifungal activities by Agar cup plate method. Amipicilin and fluconazole were used as standard for antibacterial and antifungal activities respectively. Stock solutions (1mg/ml) of all the compounds and

standards were prepared in dimethylsulfoxide. From the stock solutions, 100 µl of volume was used to inoculate.

The gram positive bacterial slant *Staphylococcus aureus* (ATCC6538) and gram negative bacterial slant *Echerchia coli* (ATCC8739) were incubated with growth media Soyabean casein digest agar in incubator at condition 35˚C for 24 hr. The fungal slant *Candida albicans* (ATCC10231) was incubated with growth media sabourauds dextrose agar in incubator at condition 25˚C for 72 hr. After incubation, picked up the well grown slant and inoculated in saline solution and vortexes to uniform suspension. Adjusted the O.D. of the culture with saline water at 530 nm on calorimeter and at viable count was 1x 10^7 colony forming unit (CFU/ml). These culture suspensions were inoculated on Mueller-Hinton agar, and plates were bored by cork borer (6 mm) to create wells. Added a volume of 100 µl of sample solution in to each well. Two controls were maintained for each test. These included reference drug control and blank control. Then plates were incubated for bacteria at 35˚C for 24 hrs and for the yeast and mould incubated at 25˚C for 48 hrs to examine the zone of inhibition. All the experiments were performed in triplicate and the average zone of inhibition was reported.

4.8 Minimum inhibitory concentration (MIC)

The *Staphylococcus aureus, Echerchia coli* and *Candida albicans* suspension was prepared after incubation of each slant for 24 hrs in incubator. O.D. of the culture was earlier adjusted at 1x10^7colony forming unit (CFU/ml). The determination of minimum inhibitory concentrations of the synthesized compounds was carried by agar dilution method. Various serial dilutions of synthesized compounds 1 mg/ml, 0.5 mg/ml.0.25 mg/ml and 0.12.5 mg/ml were prepared in dimethylsulfoxide. 1x10^7 cells were inoculated on Mueller-Hinton agar, and then plates were punched by cork borer (6 mm) to create wells. The volume 100 µl of various sample concentrations were added in to the well. Then plates were incubated for bacteria at 35˚C for 24 hrs and for the yeast and mould incubated at 25˚C for 24 hrs to examine the zone of inhibition. Two controls that is, one with reference standard and other without standard or test was maintained for each test. By visual inspection, the lowest concentration of test solution with no detectable bacterial growth was considered as minimum inhibitory concentration.

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