I J R B A T, Issue (XIII) Volume (II) May 2025: 64-76 e-ISSN 2347 – 517X

A Double-Blind Peer Reviewed & Refereed Journal OPEN ACCESS Original Article

INTERNATIONAL JOURNAL OF RESEARCHES IN BIOSCIENCES, AGRICULTURE AND TECHNOLOGY

 www.ijrbat.in

ULTRASOUND STIMULATED ONE POT SYNTHESIS OF NOVEL PYRIMIDINE-CHALCONE HYBRIDS: ANTIMICROBIAL SCREENING AND MOLECULAR MODELLING

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Communicated: 24.11.2024	Revision: 15.01.2025 & 27.01.2025 Accepted: 23.02.2025	Published: 31.05.2025

ABSTRACT:

An expeditious, efficient and eco-friendly method for one pot synthesis of novel pyrimidine-chalcone hybrids under ultrasound irradiations using Alumina supported Na_2CO_3 as a green catalyst has been developed and reported. The present method is safe, mild and effective affording excellent yields of novel pyrimidine-chalcone hybrids within shorter reaction times. All the synthesized compounds were characterized using melting point, IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral study. Newly synthesized compounds were screened for their in vitro antibacterial activities against *S. abony, S. epidermidis* and *E. coli* microorganisms. Molecular modelling studies viz., Lipinski rule of five, drug likeness, drug scores, toxicity profiles and other physico-chemical properties of drugs were performed using Molinspiration and Osiris softwares available online and verified experimentally.

KEYWORDS:- Ultrasound Irradiation, Condensation, Solid Support, Pyrimidine-Chalcones, Molecular Modelling

INTRODUCTION:

The molecular hybridization is current concept of rational drug design approach. With the help of this approach, new potent chemical entities are gained from the combination of two or more pharmacophore skeletons from different bioactive compounds into a single molecular setting. By using this concept, medicinal chemists hope that the new hybrid molecules will possess better selectivity, affinity, efficacy, multiple modes of action, less undesirable side effects, least interactions between different drug molecules, reduced drug resistance and lower cost as compared with the individual parent drugs molecules, [1]. Molecular hybridization might be analogous to conventional combination therapy; however with the exception that the two pharmacophores are covalently linked and available as a single entity. This concept motivated us to design and synthesize novel

http://doi.org/10.29369/ijrbat.2025.010.2.0008

pyrimidine-chalcone hybrids using mild, green and clean chemical technology. Chalcone are obtainable in plentiful in the plant kingdom. They are α, β unsaturated ketones having reactive keto ethylene moiety in their skeleton that provides an active binding sites to different microorganisms. It is well-known concept that most natural or synthetic chalcones are highly active with extensive pharmaceutical and medicinal applications [2]. They are significant active pharmaceutical intermediates in the synthesis of many finished pharmaceuticals [3]. Recently, the members of chalcone family signified bulk of life saving pharmacological and medicinal properties like anti-bacterial [4], anti-fungal, anti-malarial [5], anti-oxidant [6], anti-inflammatory [7], anti-cancer [8], anti-microbial [9], anti-protozoal [10], anti-HIV, anti-viral [11], anti-diabetic, cardiovascular, anti-allergic [12], anti-ulcer, anti-leishmanial [13], and anti-tubercular activities [14]. The Pyrimidine skeleton is one of great important core to chemists as well as biologists as it is available in a large variety of naturally occurring compounds and in clinically useful molecules having diverse biological activities [15-16]. These include anti-cancer [17] and anti-viral [18] activities. Currently, there are nine AIDS cracking agents which are in clinical use, e.g. DDC, AZT, DDI are pyrimidine derivatives to name a few [19] and their activity are revealed in the pyrimidine skeleton.

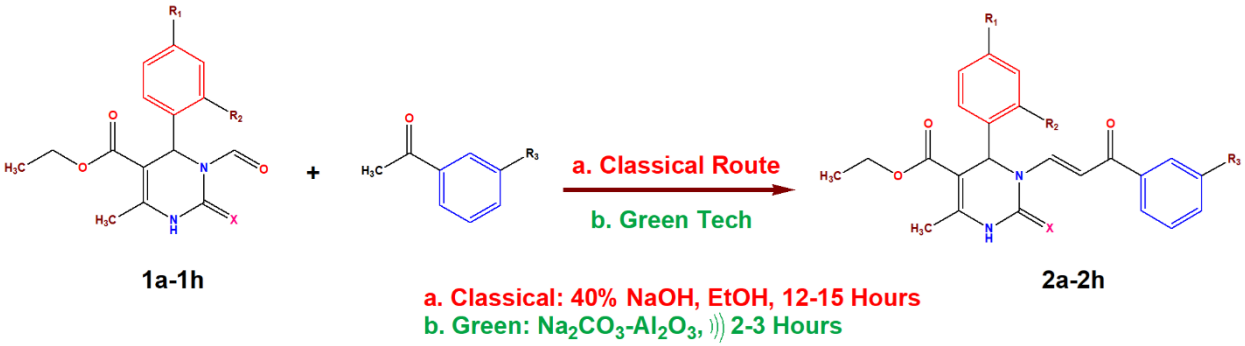
Literature review study specified that several methods and reagents over the years for classical Claisen Schmidt condensation to synthesize chalcone skeletons. Those were alkaline alumina [20], zinc chloride, Lewis acid such as dry HCl gas, BF_3, $AlCl_3$ [21], Mg–Al-OBu hydro calcite [22], strong alkalis with phase transfer catalysts [23], $Ba(OH)_2$ in ethanol [24], calcined $NaNO_3$/phosphate [25], potassium phosphate, microwave [26] and ultrasonic reaction conditions [27]. Recently, many scientist developed and reported synthetic protocol for chalcone using p-TSA catalyst [28], catalyst free [29] and by using other traditional methods [30]. However, above-mentioned methodologies suffer from one or more drawbacks like harsh reaction conditions, use of corrosive catalyst, longer reaction times, tedious work up or low atom economy. Recently, there is a growing interest in application of heterogeneous catalysts for the synthesis of chalcone, that are reported in the literature [31], however there is no report of the use of Na_2CO_3/Al_2O_3 as a catalyst in combination with ultrasound. This is a need of hour to explore mild, better, cheap, safe, and environmentally friendly experimental techniques to carry out chemical transformations under an important premise of green chemistry. One such technique includes application of ultrasonic irradiation from ultrasonicator on reaction mixtures and on solid surfaces, which has emerged as a useful methodology for achieving better yields of the products, a significant reduction in reaction time, and a reduction or elimination of environmentally detrimental solvents. For these reasons, ultrasonic assisted synthesis has clearly become a rapidly growing field of study especially for various organic conversions. Ultrasonic irradiation leads to the acceleration of numerous catalytic reactions as well as in homogeneous and heterogeneous systems and we had previously reported one such conversion using K_2CO_3/Al_2O_3 mediated ultrasound synthetic system [32]. Thus, due to the varied pharmacological profile of this class of compounds and in continuation of our research in this area [32-33] and our interest in green chemistry lead us to synthesized differently substituted ethyl-1, 2, 3, 6-tetrahydro-1-(3-(2-hydroxyphenyl)-3-oxo-1-propenyl)-4-methyl-2-oxo/thioxo-6-phenylpyrimidine-5-carboxylates(Pyrimidine-Chalcone Hybrids) (2a-2h) as shown in **Scheme1**.

http://doi.org/10.29369/ijrbat.2025.010.2.0007

RESULTS AND DISCUSSION

CHEMISTRY

We have reported the efficient green synthesis, antimicrobial activity and molecular modelling of the substituted ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxyphenyl)-3-oxo-1-propenyl)-4-methyl-2-oxo/thioxo-6-phenyl pyrimidine-5-carboxylates (Chalcone) 2a-k, using Sodium carbonate over solid supported alumina, under ultrasound irradiation in minimum amount of ethanol. The obtained results, which are in the form of comparative study between classical and presented green technology, are given in **Table 1**. There was no progress of reaction, when a base catalyzed reaction was carried out at room temperature. It was witnessed that pyrimidines skeleton did not undergo nucleophilic addition reaction easily at ambient temperature.



Scheme 1: Comparative synthesis of Pyrimidine-chalcone hybrids

To develop and activate the course of reaction in frontward path, we amplified the reaction timings and conditions. The preferred products were obtained by the classical method with average yields and more time was needed for the completion of reaction. These results forced and encouraged us to explore novel, ecofriendly, efficient and quick method for the synthesis of Pyrimidine-chalcone hybrids. The solid supported catalyst, Na_2CO_3 is readily available, low-priced, mild and safe which can be easily handled and removed from the reaction mixture. Thus, the extraordinary catalytic activities along with its operating simplicity make this process suitable for the synthesis of medicinally important chalcone hybrids. It is found that the condensation reaction in less solvent conditions in the presence of ultrasonic irradiation worked well and the products were obtained in excellent yields within less reaction time and no by products were formed. The plausible mechanistic pathway appears to involve basic media of Na_2CO_3 which activates both carbonyl function, thereby making carbonyl and methyl groups readily enolisable which in turn undergoes condensation and derived α- β unsaturated carbonyl group with loss of water molecule to produce products 2a-2h **(Scheme 2)**.

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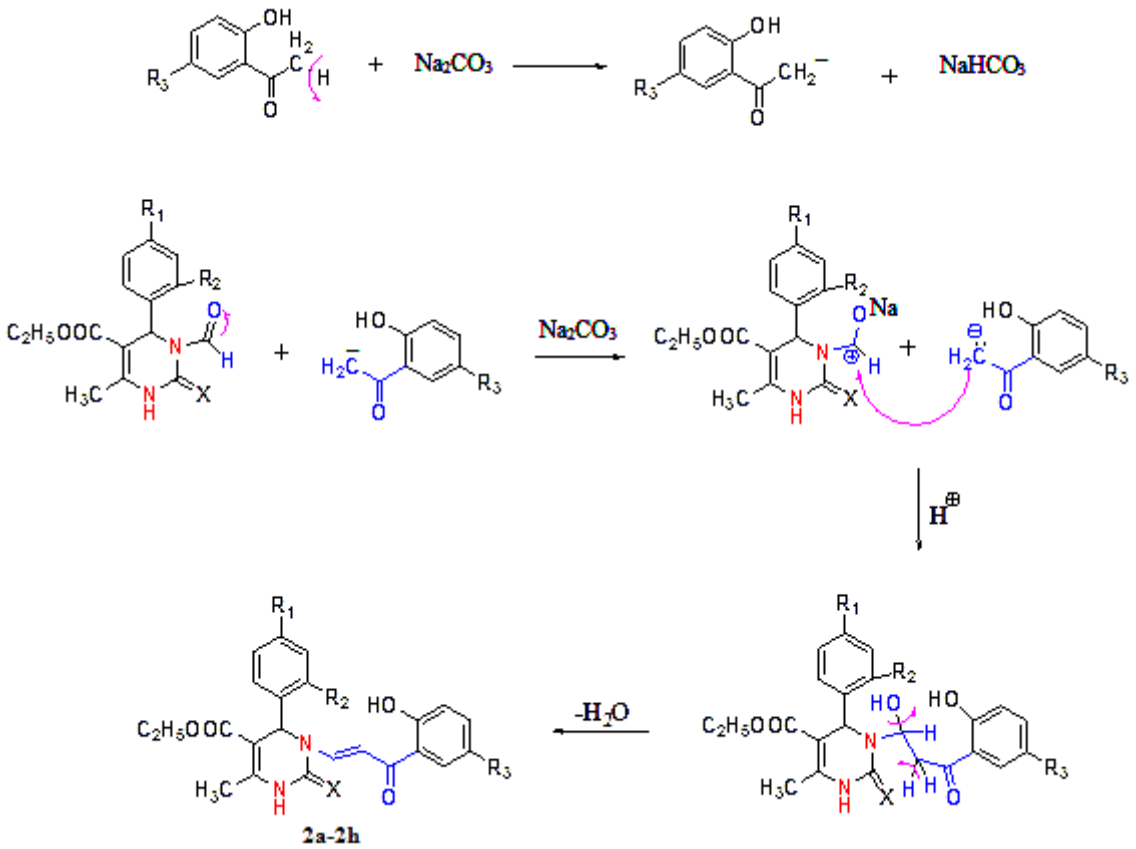

Scheme 2: The plausible mechanistic pathway in synthesis of Pyrimidine-chalcone hybrids

The structural composition of synthesized substituted Ethyl-6-methyl/chloro-2-oxo/thioxo-3-(3-oxo-3-(m-tolyl)-prop-1-en-1-yl)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylates (2a-2h) were confirmed by using IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic techniques. The IR spectrum of compound 2a displayed sharp absorption bands at 3195 (N-H str.), 3105 (=C-H str.), 3068 (C-H, Ar), 2930 (C-H, Methyl), 1675 (C=O str.), 1605 (C=C str.), 1475 (C=C str.). The ^{1}HNMR spectrum of 2a explained the presence of two methyl group by appearance of the two different peaks, triplet at ∂ 1.14 & singlet at ∂ 1.50 which integrating for three protons respectively. A singlet at ∂ 2.23 indicated the presence of methyl protons on aromatic ring integrating for three protons. The C-H_{α} and C-H_{β} protons of 2a appeared as two doublets at ∂ 5.20 and ∂ 8.25 integrating for one proton each. Compound 2a showed singlets at ∂ 5.42 and 8.31 (N-H) for the protons in pyrimidine ring. It also presents double doublets integrating for nine protons from ∂ 7.24-42 in an aromatic region. In the ^{13}C-NMR spectrum of the compound 2a, the signals belonging to the same carbon groups were recorded at 182.8, 166.8, 162.9, 158.8, 153.9, 141.4, 127.9, 127.7, 126.2, 102.9, 62.8, 56.9, 36.1, 22.1, 13.8 and 13.7. The product 2a was analyzed for $C_{24}H_{22}N_2O4_5$, which exhibited molecular ion peak at m/z 404 [M^{+}].

http://doi.org/10.29369/ijrbat.2025.010.2.0007

Table 1: Comparative study of classical synthesis and green technology in the synthesis of Pyrimidine-chalcone hybrids

Compound	R_1	R_2	R_3	X	Classical Synthesis 40% NaOH, EtOH		Green Technology Na_2CO_3-Al_2CO_3-Ultrasonics	
					Time (Hours)	Yield (%)	Time (Hours)	Yield (%)
2a	H	H	CH_3	O	14	75	3.0	84
2b	Cl	H	CH_3	O	13.5	72	2.5	81
2c	H	H	CH_3	S	12	69	2.0	82
2d	Cl	H	CH_3	S	12.5	71	2.0	86
2e	H	H	Cl	O	14	68	2.5	84
2f	Cl	H	Cl	O	14	64	3.0	75
2g	H	H	Cl	S	13.5	65	2.5	83
2h	Cl	H	Cl	S	13.5	62	3.0	75

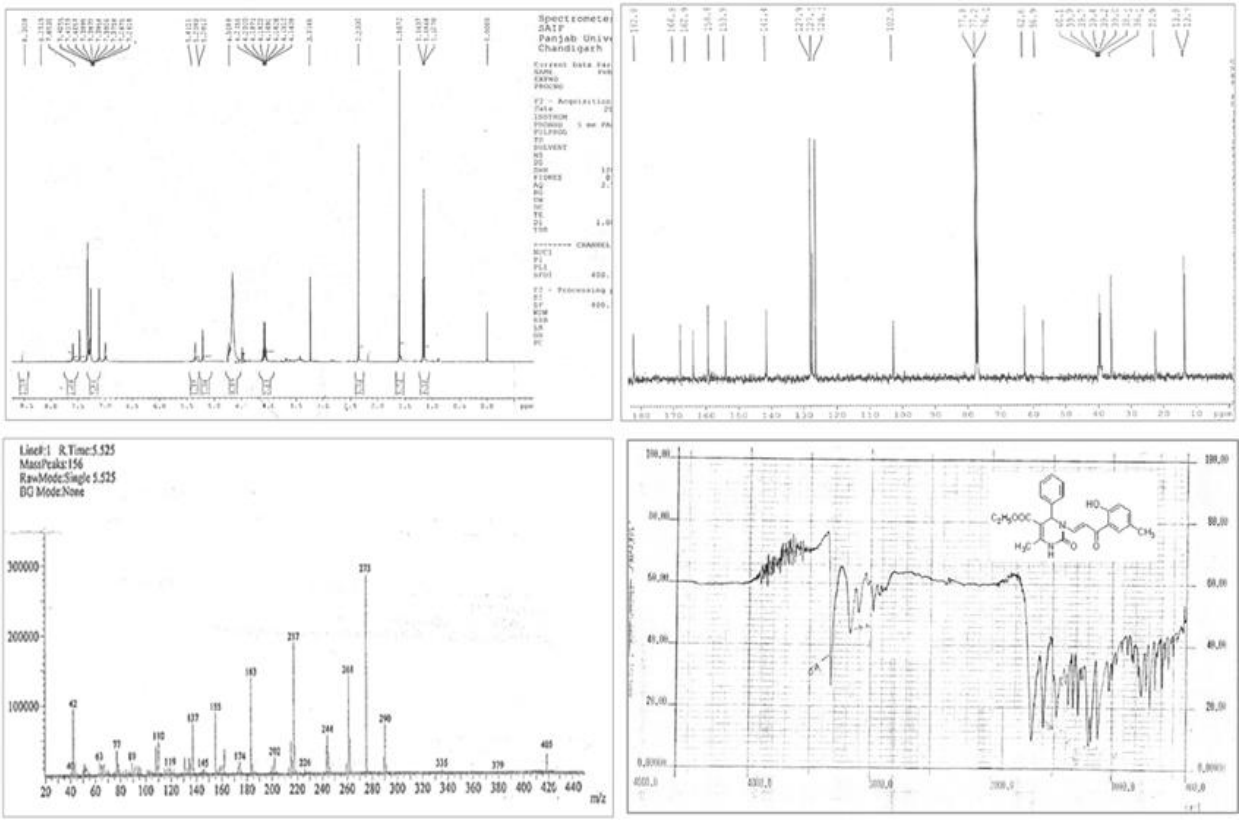

Figure 1: ^{1}H-NMR, ^{13}C-NMR, Mass & IR Spectra of compound 2a

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ANTIBACTERIAL ACTIVITY

The antibacterial activity of compounds 2a-2h has been assayed at the concentration of 100-µg disc^{-1} against strains of pathogenic bacteria. Initially, susceptibility testing was carried out by measuring the inhibitory zone diameters on nutrient agar (NA) with conventional paper disc method; and the inhibitory zone diameter were read and rounded off to the nearest whole numbers (mm) for analysis. The results of inhibitory effects of compounds 2a-2h against these organisms are given in **Table 2**. The results were compared with standard Streptomycin. The antibacterial screening results revealed that *E. coli* is highly sensitive to the all the tested compounds (2a-2h), followed by S. *epidermis* and S. *ebony*. It has been observed that the presence of substituent at R_1 and the variation of X (O and S) of pyrimidine ring played a vital role in the potency of antibacterial activities. From the mentioned data in table 1, it is observed that all the pyrimidine-chalcone hydrids showed excellent activities against *E. Coli,* more than that for Streptomycin. Moreover, compound 2h possessed broad spectrum of biological activities against all the tested organisms and its activities are more or close to the drug used for comparison. In general, It can be concluded that the presence of –Cl substituents at R_1 and R_3 along with X = S, are responsible for the potency of synthesized pyrimidine-chalcone hydrids.

Table 2. Antimicrobial-Screening Results of Synthesized Compound (2a-2h)

Entry	S. abony	S. epidermidis	E. coli
2a	-	16mm	15mm
2b	12mm	15mm	24mm
2c	12mm	12mm	21mm
2d	11mm	-	13mm
2e	-	-	22mm
2f	18mm	14mm	26mm
2g	14mm	13mm	25mm
2h	21mm	26mm	27mm
SD	25mm	-	29 mm

SD – Streptomycin, (-) No zone

MOLECULAR MODELLING

Calculation and analysis of toxicity profiles and drug likeness scores by Osiris [35-37]

We have calculated and reported the toxicity risk and other drug relevant properties like ClogP, solubility, drug likeness and drug score of the synthesized compounds **(**2a-2h) using Osiris software available online. Toxicity risk alerts are a sign that the drawn structure could be harmful concerning the risk category specified. Moreover, overall drug score values indicate the qualification of considered compound as a drug. Osiris Property Explorer predicts the molecule's potential mutagenic, tumorigenic, reproductive, or other risks. It helped to calculate various drug relevant properties of chemical structures likewise. From the data evaluated in **Table 3** indicates that all the compounds are non-toxic,

http://doi.org/10.29369/ijrbat.2025.010.2.0007

non-mutagenic, non-tumorigenic, non-irritating with no reproductive effects when run through the mutagenicity assessment system comparable with standard drugs used. Low hydrophilicities and so high log P values may cause poor absorption or permeation. Log P value, which must not be greater than 5.0. On this basis, all the compounds are having log P values are under the appropriate criteria. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, an occasional solubility goes together with a nasty absorption and so the overall aim is to avoid poorly soluble compounds. There are quite 80% of the drugs on the market which have an (estimated) log S value greater than -4 and compounds 2a-2h are well under this value. **Table 3** shows drug likeness and drug score of compounds (2a-2h). The reported compounds showed acceptable solubility, moderate to good drug likeness and drug score as compared with standard drug used. It is observed based on Osiris data that most potent compound is 2h and least potent compounds are 2e, 2d and 2a. It was supported by the antibacterial activities data in Table 2.

Table 3: Toxicity risks and Osiris calculations

Compd.	MW	Toxicity risk				Osiris calculations			
		MUT	TUMO	IRRI	REP	CLP	S	D-L	D-S
2a	404					3.47	-4.74	-0.19	0.58
2b	439					4.08	-5.48	+0.94	0.62
2c	421					3.83	-8.82	-1.25	0.46
2d	455					4.44	-5.56	-0.06	0.50
2e	425					3.74	-5.13	-0.07	0.56
2f	459					4.34	-5.87	+1.00	0.58
2g	441					4.10	-5.21	-1.12	0.45
2h	475					4.70	-5.95	+0.05	046
SD	581					-7.83	-0.96	0.83	0.43

: Non-toxic; : Slightly toxic; : Highly toxic. MUT: Mutagenic; TUMO: Tumorigenic; IRRI: irritant; REP: reproductive effective. CLP: cLogP, S: Solubility, DL: Drug-likeness, DS: Drug-Score. SD: Streptomycin

Calculations of Molecular Properties (QSAR) and Drug likeness Score against receptors by Molinspiration [36-37]

Prediction of biological activities by Molinspiration software which calculates drug likeness score against GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI) and other enzyme inhibitors (EI) and molecular properties. Molecular Polar area (TPSA) has been shown to be a good descriptor characterizing drug absorption, including intestinal absorption,

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bioavailability, Caco-2 permeability and blood-brain barrier penetration. Prediction results of compounds (2a-2h) and molecular properties (TPSA, NV, GPCR ligand, KI, NRL, PI, EI and ICM) are valued in **Table 4**. Polar area (PSA) values are important properties for the prediction of per oral bioavailability of drug molecules Therefore, we have got calculated PSA values for compounds (2a-2h) and compared them with the values obtained for traditional drugs Chloramphenicol and Streptomycin. Molecules with PSA values of 140 A^0 or more are expected to exhibit poor intestinal absorption. **Table 4** shows that every compound is within this limit. To support this contention, note that only few compounds have just one violation of the Rule of 5. Two or more violations of the Rule of 5 suggest the probability of problems in bioavailability. Few compounds have just one violation of the Rule of 5 with only a few compounds have zero violation.

Table 4: Physico-chemical properties and molinspiration calculations

Compd	Molinspiration calculations					Drug-likeness					
	TPSA	N/OH	NV	Nrotb	VOL	GPCRL	ICM	KI	NRL	PI	EI
2a	75.71	1	0	7	373.88	-0.31	-0.32	-0.82	-0.44	-0.57	-0.40
2b	75.71	1	1	7	387.41	-0.30	-0.31	-0.81	-0.45	-0.59	-0.42
2c	58.64	1	0	7	382.76	-0.54	-0.50	-1.00	-0.70	-0.77	-0.55
2d	58.64	1	1	7	396.29	-0.53	-0.49	-0.99	-0.70	-0.78	-0.56
2e	75.71	1	1	7	370.85	-0.28	-0.26	-0.81	-0.45	-0.57	-0.39
2f	75.71	1	1	7	384.39	-0.27	-0.25	-0.79	-0.43	-0.55	-0.38
2g	58.64	1	1	7	379.73	-0.51	-0.44	-1.00	-0.71	-0.77	-0.53
2h	58.64	1	1	7	393.27	-0.49	-0.42	-0.96	-0.69	-0.74	-0.51
SD	336	16	3	9	497.00	-0.09	-0.16	-0.17	-0.18	-0.65	-0.38

TPSA: Total polar surface area, O/NH: O—HN interaction, NV: Number of violation, VOL: Volume, ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand. PI: Protease inhibitor; EI: Enzyme inhibitor. SD: Streptomycin

Drug likeness includes properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and adaptability and presence of miscellaneous pharmacophores features influence the behavior of molecule on living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and plenty of others. Activity of all eight compounds and standard drugs were rigorously analyzed under six criteria of known successful drug activity within the areas of GPCR ligand

http://doi.org/10.29369/ijrbat.2025.010.2.0007

activity, ion channel modulation, kinase inhibition activity, and nuclear receptor ligand activity. Results are shown for all compounds in **Table 4** by means of numerical assignment. Likewise all compounds have consistent negative values altogether categories and numerical values conforming and similar to that of normal drugs used for comparison. Therefore, it has readily seen that each one the compounds are expected to possess near similar activity to the standard drug used based upon these six rigorous criteria of drug likeness, which was supported by the antibacterial activities data in Table 2.

EXPERIMENTAL SECTION

All chemicals were obtained from Sigma Aldrich and S. D. Fine chemical companies and used without further purification. All solvents were distilled prior to use. The purity of the synthesized compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck) coated aluminum plates, visualized by iodine vapors. Developing solvents were n-Hexane-ethylacetate (7:3). Melting points were determined by an open capillary method and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded from CDCl3 solution on a Brucker Avance II 400 (400 MHz) NMR Spectrometer. Chemical shifts are reported in ppm using TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR spectrophotometer using KBr discs. Mass spectra were recorded by using Shimadzu gas chromatograph coupled with QP5050 Spectrometer at 1-1.5 eV. Spectra lab model UCB 40D ultrasonicator with a frequency of 40 kHz and a nominal power of 250 Watt was used for the ultrasonic mediated synthesis of pyrimidine-chalcone hybrids. Antimicrobial screening was performed at the Department of Microbiology & Biotechnology, S. P. College, Chandrapur, Maharashtra, India.

Classical Method for general synthesis of substituted Ethyl-6-methyl/chloro-2-oxo/thioxo-3-(3-oxo-3-(m-tolyl)-prop-1-en-1-yl)-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates (2a-2h)

In a 50 mL RB Flask, substituted acetophenones (0.011mol) and ethyl 1-formyl-1, 2, 3, 6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenylpyrimidine-5-carboxylates **(1a-1h)** (0.01mol) were dissolved in the 20 mL ethanol by warming the mixture and it was stirred for 05 Minutes. To this, 40% solution of 0.03 mol NaOH was added and the reaction mass was stirred at room temperature for 12-15 hours. After the completion of reaction, as monitored by TLC, the reaction was subsequently quenched by ice cold 1:1 HCl, until the reaction mixture became acidic. The formed precipitate was filtered, washed and dried. The products were recrystallized from rectified spirit to give crystal of chalcone **(2a-2h)**. The purity of the synthesized compounds were checked by TLC using Benzene: ethyl acetate (7:3) as eluent.

Ultrasound stimulated Na_2CO_3-Al_2O_3 catalyzed general synthesis of substituted Ethyl-6-methyl/chloro-2-oxo/thioxo-3-(3-oxo-3-(m-tolyl)-prop-1-en-1-yl)-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates (2a-2h)

Substituted acetophenones (0.011mol), ethyl 1-formyl-1, 2, 3, 6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenylpyrimidine-5-carboxylates **(1a-1h)** (0.01mol) and 15 mol% Na_2CO_3 was dissolved in 5 mL dichloromethane. The reaction mixture was absorbed on 1.5 g neutral Al_2CO_3 and air-dried. The mixture was irradiated with small amount of ethanol (5 mL) in the water bath of Spectra lab model UCB 40D ultrasonicator with a frequency of 40 kHz and a power of 250 Watt for the time slots given in Table 1. After completion of reaction, as monitored by TLC, 20 mL ethanol was added to the reaction mixture.

http://doi.org/10.29369/ijrbat.2025.010.2.0007

Inorganic material was filtered out and the filtrate was poured in ice cold 1:1 HCl solution. Obtained solid products were separated by filtration and recrystallized from rectified spirit to get the desired pyrimidine-chalcones in 75-86 % yields. The purity of the products was checked using TLC from Benzene: ethyl acetate (7:3) as eluent.

Ethyl-6-methyl-2-oxo-3-(3-oxo-3-(m-tolyl)-prop-1-en-1-yl)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbo -xylate (2a). Pale Yellow crystal**;** mp 120-125^{0}C; IR (KBr disc), ν, cm^{-1}: 3195 (N-H), 3105 (=C-H), 3068 (C-H, Ar), 2930 (C-H, Methyl), 1675 (C=O), 1605 (C=C), 1475 (C=C), 1090 (C-O); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.60 (s, 3H), 2.23 (s, 3H), 4.14-4.20 (q, 2H), 5.20 (d, 1H), 5.42 (s, 1H), 7.24-7.59 (m, 8H), 8.25 (d, 1H), 8.31 (s, 1H, N-H); ^{13}C-NMR (400 MHz, CDCl3, δ ppm): 182.8, 166.8, 162.9, 158.8, 153.9, 141.4, 127.9, 127.7, 126.2, 102.9, 62.8, 56.9, 36.1, 22.1, 13.8, 13.7; DI-MS: m/z 404 [M] $^+$

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-3-(3-oxo-3-(m-tolyl)-prop-1-en-1-yl)-1,2,3,4-tetrahydropyrimi-dine-5-carboxylate (2b). Yellow crystal**;** mp 110-115^{0}C; IR (KBr disc), ν, cm^{-1}: 3190 (N-H), 3100 (=C-H), 3065 (C-H, Ar), 2935 (C-H, Methyl), 1670 (C=O), 1610 (C=C), 1470 (C=C), 1095 (C-O), 680 (C-Cl); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.70 (s, 3H), 2.32 (s, 3H), 4.13-4.23 (q, 2H), 5.20 (d, 1H), 5.64 (s, 1H), 7.24-7.59 (m, 8H), 8.21 (d, 1H), 8.48 (s, 1H, N-H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 182.5, 166.8, 162.9, 158.9, 153.9, 141.4, 127.9, 126.2, 102.9, 62.8, 56.9, 36.1, 22.8, 13.7, 13.6; DI-MS: m/z 439 [M] $^+$

Ethyl-6-methyl-3-(3-oxo-3-(m-tolyl)prop-1-en-1-yl)-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2c). Brown crystal**;** mp 125-130^{0}C; 3200 (N-H), 3110 (=C-H), 3070 (C-H, Ar), 2935 (C-H, Methyl), 1665 (C=O), 1615 (C=C), 1475 (C=C), 1110 (C=S), 1095 (C-O), ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.62 (s, 3H), 2.24 (s, 3H), 4.14-4.23 (q, 2H), 5.20 (d, 1H), 5.42 (s, 1H), 7.23-7.59 (m, 8H), 8.24 (d, 1H), 8.32 (s, 1H, N-H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 182.4, 166.7, 162.2, 158.8, 153.9, 141.2, 127.1, 127.2, 126.9, 102.8, 62.8, 56.9, 36.2, 22.5, 13.7, 13.5; DI-MS: m/z 421 [M] $^+$

Ethyl-4-(4-chlorophenyl)-6-methyl-3-(3-oxo-3-(m-tolyl)prop-1-en-1-yl)-2-thioxo-1,2,3,4-tetrahydropyrimi -dine-5-carboxylate (2d). Yellow crystal**;** mp 102-107^{0}C; IR (KBr disc), ν, cm^{-1}: 3192 (N-H), 3107 (=C-H), 3067 (C-H, Ar), 2930 (C-H, Methyl), 1678 (C=O), 1615 (C=C), 1475 (C=C), 1105 (C=S), 1092 (C-O), 686 (C-Cl); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.68 (s, 3H), 2.30 (s, 3H), 4.13-4.25 (q, 2H), 5.20 (d, 1H), 5.62 (s, 1H), 7.24-7.45 (m, 8H), 8.22 (d, 1H), 8.46 (s, 1H, N-H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 182.9, 166.9, 162.9, 158.8, 153.9, 141.4, 127.9, 127.7, 126.4, 102.9, 62.8, 56.5, 36.1, 22.1, 13.9, 13.7; DI-MS: m/z 455 [M] $^+$

Ethyl-3-(3-(3-chlorophenyl)-3-oxoprop-1-en-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2e). Yellow crystal**;** mp 145-150^{0}C; IR (KBr disc), ν, cm^{-1}: 3198 (N-H), 3105 (=C-H), 3068 (C-H, Ar), 1677 (C=O), 1613 (C=C), 1478 (C=C), 1090 (C-O), 676 (C-Cl); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.60 (s, 3H), 4.12-4.24 (q, 2H), 5.12 (d, 1H), 5.32 (s, 1H), 7.24-7.42 (m, 8H), 8.24 (d, 1H), 8.42 (s, 1H, N-H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 182.8, 166.1, 162.2, 158.8, 153.9, 141.4, 127.9, 127.4, 126.4, 102.8, 62.6, 56.9, 36.0, 22.5, 13.7, 13.5; DI-MS: m/z 425 [M] $^+$

Ethyl-4-(4-chlorophenyl)-3-(3-(3-chlorophenyl)-3-oxoprop-1-en-1-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro- pyrimidine-5-carboxylate (2f). Dark yellow crystal; mp 130-135^{0}C; 3205 (N-H), 3108 (=C-H), 3070 (C-H, Ar), 1680 (C=O), 1615 (C=C), 1480 (C=C), 1095 (C-O), 678, 682 (C-Cl);); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.62 (s, 3H), 2.34 (s, 3H), 4.12-4.24 (q, 2H), 5.12 (d, 1H), 5.36 (s, 1H), 7.26-7.59 (m,

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8H), 8.26 (d, 1H), 8.45 (s, 1H, N-H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 182.5, 166.2, 162.8, 158.9, 153.9, 141.4, 127.8, 127.4, 126.4, 102.8, 62.8, 56.8, 36.2, 22.1, 13.8, 13.6; DI-MS: m/z 459 [M]$^+$

Ethyl-3-(3-(3-chlorophenyl)-3-oxoprop-1-en-1-yl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimi- dine-5-carboxylate (2g). Yellow crystal; mp 110-115^{0}C; 3197 (N-H), 3107 (=C-H), 3065 (C-H, Ar), 1677 (C=O), 1619 (C=C), 1476 (C=C), 1109 (C=S), 1097 (C-O), 685 (C-Cl); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.60 (s, 3H), 4.12-4.20 (q, 2H), 5.11 (d, 1H), 5.34 (s, 1H), 7.26-7.42 (m, 8H), 8.25 (d, 1H), 8.43 (s, 1H, N-H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 182.9, 166.9, 162.8, 158.8, 153.9, 141.4, 127.9, 127.4, 126.4, 102.1, 62.8, 56.9, 36.2, 22.1, 13.8, 13.6; DI-MS: m/z 441 [M]$^+$

Ethyl-4-(4-chlorophenyl)-3-(3-(3-chlorophenyl)-3-oxoprop-1-en-1-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahy- dropyrimidine-5-carboxylate (2h). Yellow crystal; mp 100-105^{0}C; 3192 (N-H), 3101 (=C-H), 3072 (C-H, Ar), 1685 (C=O), 1618 (C=C), 1485 (C=C), 1105 (C=S), 1094 (C-O), 675, 689 (C-Cl); ^{1}H-NMR (DMSO, 400MHz) δ 1.14 (t, 3H), 1.60 (s, 3H), 2.32 (s, 3H), 4.14-4.22 (q, 2H), 5.10 (d, 1H), 5.34 (s, 1H), 7.26-7.42 (m, 8H), 8.25 (d, 1H), 8.43 (s, 1H, N-H); ^{13}C-NMR (400 MHz, DMSO - d6, δ ppm): 182.9, 166.8, 162.8, 158.8, 153.9, 141.4, 127.8, 127.1, 126.8, 102.8, 62.83, 56.8, 36.2, 22.1, 13.8, 13.6; DI-MS: m/z 475 [M]$^+$

ANTIBACTERIAL SCREENING TEST

The antibacterial activity of the synthesized compounds 2a-2h was studied against three human pathogenic bacteria, viz *E.coli* (ATCC No. 8739), *S.abony* (NCTC No. 6017) and *S.epidermidis* (NCTC No. 8853, ATCC No. 12228). For the detection of antibacterial activities, Kirby aurer method was employed. Chloromphenicol and Streptomycin were used as standard antibiotics for the antibacterial test. Nutrient agar (NA) was used as the basal medium for test bacteria. These agar media were inoculated with 1mL of the 24 hr liquid cultures containing 10^7 microorganisms/mL. The incubation time was 12 hr at 37^{0}C for bacteria. Discs with only DMSO were used as control. The diameter (in mm) of the observed inhibition zones were taken as a measure of inhibitory activity.

CONCLUSIONS

A simple, mild, expeditious, efficient and eco-friendly method for one pot synthesis of novel pyrimidine-chalcone hybrids under ultrasonic irradiations using Alumina supported Na_2CO_3 as a green catalyst with excellent yields has been developed. Various reported drawbacks like harsh reaction conditions, use of corrosive catalyst, longer reaction times, and tedious work up procedures or low atom economy have been wiped out through this method. It is established that the presence of –Cl substituents at R_1 and R_3 along with X = S, are accountable for the potency of synthesized pyrimidine-chalcone hydrids and this is in good agreement with the calculated data obtained through molecular modelling.

ACKNOWLEDGEMENT

Authors acknowledged to the Department of Pharmacy, RTM, Nagpur University, Nagpur for IR spectral analysis, SAIF, Chandigarh for ^{1}H-NMR ^{13}C-NMR spectral analysis, Mass analysis, and Department of Microbiology & Biotechnology, S. P. Collage, Chandrapur, Maharashtra, India for antimicrobial screening. Author would like to thank Academic Affairs, Center for Health Studies, Prince Sultan Military Medical City, Riyadh, Saudi Arabia for literature referencing and molecular modelling data.

DECLARATION OF INTEREST

The authors report and declare that there are no financial, personal and professional conflicts of interest. The authors alone are responsible for the content and writing of the research Paper.

http://doi.org/10.29369/ijrbat.2025.010.2.0007

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