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Research Article

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Synthesis, characterization, docking studies and bio-efficacy evaluation of novel chalcones

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ABSTRACT

TwoNovel Chalcones(2E)-3-[3-(4-Methylphenyl)-1-phenyl-1H-pyrazol-4-yl]-1-(naphthalen-2-yl)prop-2-en-1-one ***(1a)*** *and (2E)-3-(1H-Indol-3-yl)-1-(naphthalen-2-yl) prop-2-en-1-one* ***(1b)****were synthesized and characterized by using spectral techniques like IR, [1]H NMR, [13]C NMR and GC-MS.In general, these compoundsshowed better anti-bacterial activity. The newly synthesized compounds were docked with inflammatory protein (Pdb id: 2X6L)from the result it has been clearthat compound* ***(1a)****has highgold score.*

Keywords: Chalcones;antibacterial activity;Docking Studies.

INTRODUCTION

The name chalcones was given by Kostanecki and Tambor. The chalcones, two aromatic rings are linked by analiphatic three carbon chain which bears a very good synthon so that variety of novel heterocyclics with good pharmaceutical profile can be designed. These are α, β unsaturated ketone containing reactive ketoethylenic group –CO-CH=CH- and are coloured compounds because of the presence of the chromophore. –CO-CH=CH- , which depends on the presence of the other auxochromes [1].

Studieson the bioavailability of Aromatic Chalcones from natural sources are limited, but synthetic Aromatic Chalcones have been reported to have a wide range of biological properties,especially anticancer, antibacterial [2-4], anti-inflammatory [5], cytotoxicity [6], and anti-tumor [7].

Indoles are one of the most important nitrogen containing heterocyclic molecules, found extensively in biological system which play vital role in biochemical process [8].Indole derivatives are used as neuroprotective agent affecting oxidative stress[9], neurotransmitter serotonin[10] (5-HT 5-hydroxytriptamine) involved in various physiological functions such as appetite, sleep, body temperature, indolodioxane is found to be active hypertensive agent[11], INF55 is an inhibitor of NorA efflux pump in the human pathogenic bacterium staphylococcus aureus[12]. Different indole derivatives like tryptans are used as antimigrain and anti-inflammatory[13, 14], anticonvulsant[15], antimicrobial[16], antimalarial[17] and anticancer[18].

On the other hand, pyrazoles are of interest as potent bioactive molecules. The pyrazole moiety is a versatile lead molecule in pharmaceutical development and has a wide range of biological activities [19]. Besides being biologicallly active they are also used as usefulsynthons in organic synthesis[20-22].Pyrazolechalcones and their

derivatives have been reported to possess anti-inflammatory, analgesic, antimicrobial, antitumor, antioxidant and xanthenes dehydrogenase [23].

Microwave assisted organic synthesis (MAOS) has become increasingly popular in recent years to improve the yields and shorten reaction time in a variety of reactions [24, 25].Hence, in continuation of our interest onpyrazol and indol derivatives,[26]the utility of microwave irradiation in organic synthesis and the evaluation of different classes of heterocyclic nucleus as anti cancerbioactive compounds[27, 28].In this paper we envisioned to design and synthesize the chalcone based substituent pyrazoland Indolthrough microwave and non-microwave method as well as study their antibacterial activity.

EXPERIMENTAL SECTION

Experimental protocols

Several instruments were used to characterize the compounds obtained in the experiments. Infrared (IR) spectra were recorded on a Shimadzu 8000 as KBr pellet for solid samples. ^{1}H and ^{13}C NMR (spectra) were recorded by using Bruker Advance spectrometer (400 and 100 MHz) with $CDCl_3$ as the solvent. Hewlett Packard Model 6890 series II a gas chromatography was used in this study. The capillary column of Ultra 1 (fused silica column) which composed 100% dimethyl poly cyclohexane was used. The spectra of gas chromatography-mass spectrometry (GCMS) were recorded using a Hewlett Packard Model 5980 a gas chromatography and a Hewlett Packard Model 5989 a mass spectrometer.

Thin layer chromatography (TLC) was conducted using thin layer aluminum plate Merck pre-coated silica gel F254 of 0.2 mm in thickness. The spots were viewed under ultraviolet (UV) light, followed by spraying the plate with *p*-anisaldehyde. Column chromatography (CC) was performed on silica gel Merck 70-230 mesh. The melting point of the individual compound was recorded with Leica Galen III melting apparatus.

General Procedure for Synthesis of Chalcone:

Conventional heating method:

A solution of ketone (1g, 5.85mmol) and aldehyde (1.54g, 5.85mmol) were dissolved in ethanol (20 ml) under stirring in a round bottle flask, and aqueous KOH (50%, 10 ml) was added drop wise. The mixture was stirred at room temperature until it solidified. The progress of the reaction was mentioned by TLC. After completion of the reaction mixture was poured into ice water, and extracted with chloroform. The extracts solution was evaporated under reduced pressure and recrystallized from absolute ethanol to give Chalcones.

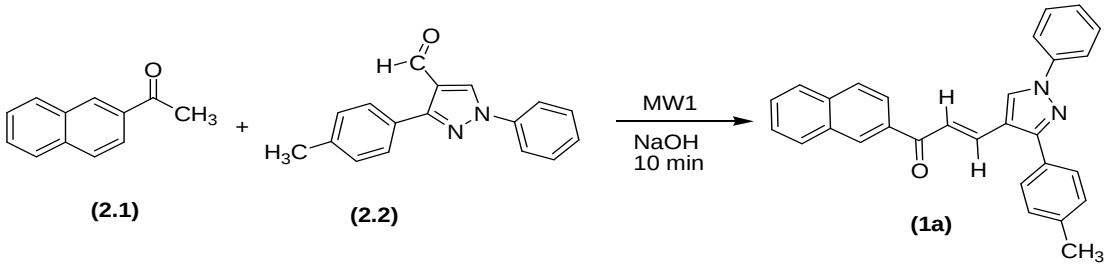
Microwave Irradiation method:

A solution of ketone (1g, 5.85mmol) and aldehyde (1.54g, 5.85mmol) were dissolved in ethanol (8 ml) in a beaker to this solution added 50%NaOH (10 mL). The reaction mixture was irradiated under microwave at 180 watts for 8 min. with an interval of 30 sec. The progress of the reaction was mentioned by TLC. After completion of the reaction the reaction mixture was poured into ice water, neutralized with dilute HCl and extracted with chloroform. The filtered solution was evaporated under reduced pressure and recrystallized from absolute ethanol to give the product.

Microwave method Vs conventional method

Chalcones(2*E*)-3-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1 (naphthalen-2-yl)prop-2-en-1-one(**1a**) and (2*E*)-3-(1*H*-Indol-3-yl)-1-(naphthalen-2-yl) prop-2-en-1-one (**1b**) were synthesized using designed microwave method and non-microwave method. Table 1 summarizes the comparison of two methods in terms of reaction time and yield and emphasizes the advantages of microwave reaction in addition to solvent less conditions, increased conversion etc.

Synthesis of (2*E*)-3-[3-(4– Methylphenyl)–1–phenyl-1*H*–pyrazol–4–yl]-1-(naphthalene-2-yl) prop-2-en-1-one (1a).



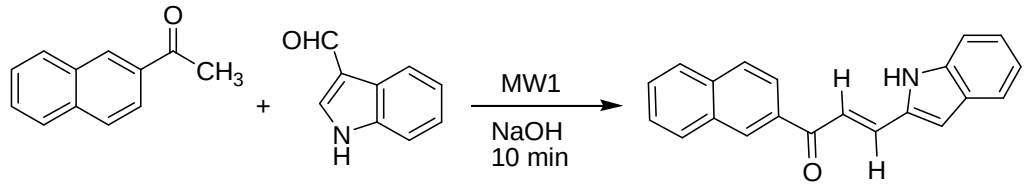
(2.1) **(2.2)** **(1a)**

Scheme 1*:* Synthesis of (2E)-3-[3-(4-Methylphenyl)-1-phenyl-1H-pyrazol-4-yl]-1-(naphthalene-2-yl) prop-2-en-1-one (1a)

The synthesis of (2*E*)-3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl-1-(naphthalene-2-yl) prop-2-en-1-one**(1a)** was carried out via the Claisen-Schmidt condensation of commercially available 1-(Naphthalen-2-yl)ethan-1-one**(1)**in the presence of NaOH (50%) as a base in ethanol. The reaction was initiated by removal of a proton from the α-carbon of naphthalene-1-carbaldehyde to form a resonance stabilized enolate ion by the base. This was followed by the nucleophilicenolate attacks on the electrophilic carbonyl carbon of 3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **(2)** resulting in a new carbon-carbon bond formation. This reaction joined the α-carbon of 1-(Naphthalen-2-yl) ethan-1-one **(1)** to the carbonyl carbon of 3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **(2)** to form intermediate. The final step of this reaction was protonation and deprotonation by hydroxide ion to form (2*E*)-3-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(naphthalene-2-yl) prop-2-en-1-one **(1a)** as a light yellow solid in (89%) yield.

Analytical data: For $C_{29}H_{22}N_2O$: IR (KBr) 1659 (C=O), 1597 (C=N) cm^{-1}. GCMS: m/z; 415 $[M+H]^+$.^{1}H-NMR ($CDCl_3$, 400 MHz,): 2.73(s, 3H, CH_3), 7.31-7.33(d, 1H, Cα-H) 7.35-7.37(d, 1H, Ar-H), 7.48-7.64(m, 8H, Ar-H), 7.80-7.95(m, 7H, Ar-H), 7.97-8.05(dd, 1H, Ar-H), 8.39(s, 1H, Pyrazole proton). ^{13}C-NMR(100 MHz, $CDCl_3$,δ ppm), 189.90, 153.97, 139.50, 138.65, 135.63, 135.46, 132.58, 129.76, 129.69, 129.50, 129.44, 129.26, 128.74, 128.52, 127.84, 127.19, 126.84, 124.49, 123.85, 121.47, 119.39, and118.35.

Synthesis of (2*E*)-3-(1*H*-Indol-3-yl)-1-(naphthalen-2-yl) prop-2-en-1-one (1b)



(2.1) **(2.3)** **(2b)**

Scheme 2: Synthesis of (2E)-3-(1H-Indol-3-yl)-1-(naphthalen-2-yl) prop-2-en-1-one (2b)

The synthesis of (2*E*)-3-(1*H*-Indol-3-yl)-1-(naphthalen-2-yl) prop-2-en-1-one **(2b)** was achieved by the Claisen-Schmidt condensation. The reaction was carried out in the presence of strong base (NaOH 50%) in ethanol and the resulting product was a yellow solid (77.35%).

Analytical data: For $C_{21}H_{15}NO$: IR (KBr) 1677 (C=O), and 1565 (C=N) cm^{-1}. GCMS: m/z; 298 $[M+H]^+$. ^{1}H-NMR spectrum:(400 MHz, $CDCl_3$)δ:7.25-7.29(m, 2H, Ar H), 7.52-7.53(m, 1H, Ar-H), 7.61-7.67 (m, 3H, Ar-H), 7.81-7.85(d,1H,Cβ-H), 7.96-8.17(m,6H,Ar-H),8.22-8.24(d,1H, Cα-H),8.84(s,1H,Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$,δppm), The signal resonated downfield at δ 197.85 was attributed for (C=O) and the other peaks observed at δ: 139.13, 137.36, 135.18, 1135.01, 134.18, 133.04, 130.13, 129.86, 129.52, 128.57, 127.60, 126.88, 125.19, 124.26, 123.04, 122.65, 120.54, 115.25 and 112.81.

Antibacterial activity:

The antibacterial activities of synthesized Chalcones s were conducted against *Staphylococcus aureus*, *Pseudomonas aeruginosa* [29]. The antimicrobial activity was performed by filter paper disc plate method [30, 31] at concentration 100 μg/mL and reported in Table-3. Streptomycin was used as standard for antibacterial.

Molecular docking simulation

Automated docking is used to determine the orientation of synthesized compounds binding with inflammatory protein. The protein structure file 2X6L is taken from PDB (www.rcsb.org/pdb) [32].

The binding interactions can be ascertained by docking the inhibitors into the active site of the protein. The GOLD 3.01[33], program was used to calculate the docking modes of inflammatory protein inhibitors into the active site of the homology modeled protein structure. It employs genetic algorithm in which the information about the ligand conformation and hydrogen bonding is encoded in chromosome. GOLD considers complete ligand flexibility and partial protein flexibility and the energy functions are partly based on conformational and non bonded interactions. Several types of scoring functions such as Gold Score, Chem score and User-defined score are available. The Gold Score was opted to rank order the docked conformations.

RESULTS AND DISCUSSION

A variety of novel chalcones were synthesized via Claisen-Schmidt condensation and microwave of substitutedIndol and pyrazol. Work up procedure is simple and yield of the product is excellent. All the newly synthesized Chalcones

were characterized by their chemical, physical andspectral analysis data and are further subjected to antimicrobial studies which exhibits moderate to good activity.

Table1: Comparison of microwave and conventional (non-microwave) methods used for the synthesis of Chalcones

compound	Reaction time		Yield (%)	
	Conventional method	Microwave method	Conventional method	Microwave method
1a	5h	8 min	85	89
2b	6h	10 min	62.35	77.35

Table 2: Physicochemical analysis of synthesized compounds

Compounds	Mol. Formula	Mol. weight	MP (^{o}C)
1a	$C_{29}H_{22}N_2O$	414.50	202
2b	$C_{21}H_{15}NO$	297.35	284

Antibacterial activity

The results obtained in this study indicate a considerable difference in antibacterial activity among the two newly synthesized compounds. Compound **1a** containing substituent pyrazolexhibited significant antibacterial activity against pathogenic bacterial strains. Its bio-controlling potency is per with that of the standard antibiotic Streptomycin[34].

Table3: Antibacterial activity of the synthesized compounds against pathogenic bacterial strains

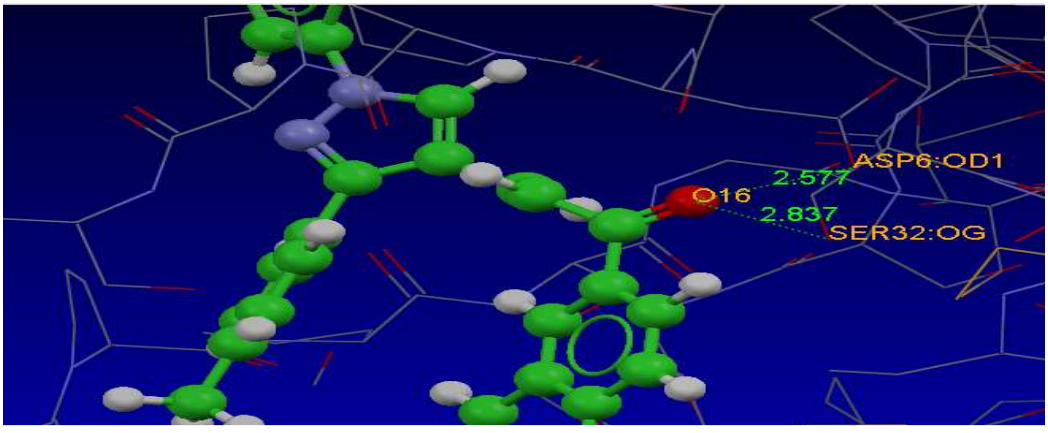
Clinical strains	Diameter of zone of inhibition (mm)		
	Compound **1a**	Compound **2b**	Streptomycin
Staphylococcus aureus	17.60 ± 0.10	14.90 ± 0.10	22.60 ± 0.10
Pseudomonas aeruginosa	16.40 ± 0.10	15.60 ± 0.10	19.20 ± 0.10

Docking Studies of ChalconeAnalogues

Docking with GOLD (Genetic Optimization for Ligand Docking)

An attempt was made to dock the inhibitors using the superimposition of the Aromatic chalcone molecules with structure of 2X6L.Then, using the knowledge of the active site, an atom was defined representing the center of the active site residues, that is SER in A chain and the atom number used for docking is 1293 (taken from the protein atomic coordinates of all the active site molecules). From this point, the search was carried out in 15 A^0 radius (since this was found to be the optimum). In the 2X6L complex, the binding interactions of the 3D conformation of shows that the inhibitors are located in the center of the active site, and are stabilized by Vader Waals interactions, hydrogen bonding and hydrophobic interactions. A total of 2 ligands were docked into the active site of the 2X6L site by using GOLD 3 .0.1.The calculated binding Gold score are given in table 4 and type of interactions in best molecules are given in table 4.The interactions of ligands with protein are maximum by Vander Waals interactions. The GOLD score values are very similar in the two top solutions. The difference between the consecutive best two runs of a particular ligand is less and this indicates the stabilization of a particular Ligand at the active sites. The docking studies of the molecules are showing good fitness score and Vander Waals interactions.

1a



2b

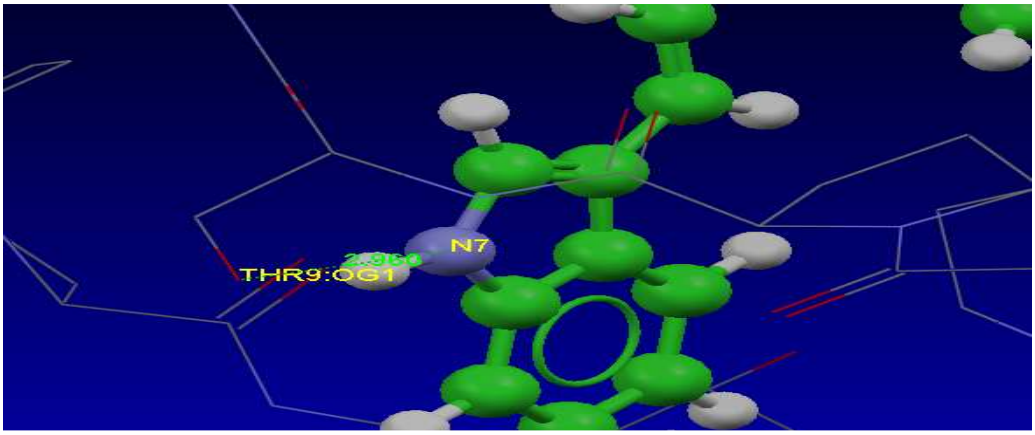


Figure 2: The binding modes of compounds 1a, 2b with the active site of inflammatory protein 2X6L

Table 4: Docking scores from GOLD

compounds	H –Bond Donor-Acceptor	Bond Length (Å)	Vander Waals interactions	Bond Length (Å)	Gold Score
1a	O16-SER32:OG	2.577	C3-PRO7:CD	2.863	25.3598
	O16-ASP6:OD1	2.837	C28-GLY4:CA	2.627	
			O16-SER5: O	2.534	
2b	N7-THR9:OG1	2.960	C17- PRO7:CD	2.890	24.2824
			O6-PRO7:CD	2.162	

CONCLUSION

To conclude, We have established an easy, high yielding convenient and green methods for the synthesis of (2*E*)-3-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(naphthalen-2-yl)prop-2-en-1-one **(1a)**, (2*E*)-3-(1*H*-Indol-3-yl)-1-(naphthalen-2-yl) prop-2-en-1-one **(1b)**.The antibacterial study show that compounds **1a**, showed better zone of inhibition.Molecular docking study gave us good information about the interaction mode of pyrazol with 2X6L active site. Compound **1a** has ability to make hydrogen bonds with amino acid residues SER32, ASP6 and GLY4 in 2X6L active site.

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