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SYNTHESIS, CHARACTERIZATION, INSILICO PREDICTION AND ANTI MICROBIAL ACTIVITY OF CHALCONE DEIVATIVES

G Mercy Beula*, P Venkateswara Rao

Department of Pharmaceutical Chemistry, Vikas College of Pharmacy, Vissanapeta, Krishna Dist, Andhra Pradesh, India

ABSTRACT

A novel series of six different derivatives of some NSAID chalcones were synthesized and characterized by physical & spectral interpretations like m.p., FT-IR & H^1 NMR are confirmed. The derivatives of some NSAID chalcones were prepared from chalcone derivatives and hydrazine. The initial compounds for synthesizing derivatives are paracetamol ,aspirin and different aldehydes. The synthesized compounds are useful as a lead compounds for various diseases like antiulcer, antitumour, herbicidal, antifungal activites some infectious diseases. The derived chalcone pyrazoline derivatives were characterized by thin layer chromatography, infra-red spectroscopic and NMR methods. The biological activity was tested and found to have anti-microbial activity against bacteria like *E.coli* (Gram negative organism), *Pseudomonas aeuroginosa* (Gram negative organism), *Staphylococcus aureus* (Gram positive organism) and Fungal Organism of *Sacchromyces Species, Aspergillus Niger, Candida Albicans* using filter-paper disc method. Most of the compounds exhibit mild to moderate anti bacterial activity as well as anti fungal activity against all the microbes tested.

Key Words: NSAID chalcones, insilico prediction, antimicrobial activity

Author for correspondence:
G Mercy Beula
Department of Pharmaceutical Chemistry, Vikas College of Pharmacy, Vissanapeta, Krishna Dist, Andhra Pradesh, India.
E mail: mercybeula28@gmail.com

INTRODUCTION

Chalcones are the compounds where aromatic substituents are introduced at the terminal position of the system -C=C-C=O. So, chalcones are characterized by their position of an Ar (A)-CO-CH=CH-Ar (B) - in which two aromatic rings A and B are linked by an aliphatic three carbon chain. Chalcones (1,3-diaryl-2-propen-1-ones) belong to the flavanoid family. Chemically they consist of open-chain flavanoid inwhich the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. Chalcones are the precursors in the biosynthesis of anthocyanins and flavones. Chalcones and substituted chalcones can be synthesized in laboratory by Claisen-Schmidt condensation of acetophenone or substituted acetophenones with aromatic aldehydes. An interesting feature of chalcones is that they serve as starting materials for the synthesis of various heterocyclic compounds such as pyrimidines, pyrazolines, indazoles,

flavones, flavonols, flavanones, aurones and benzoyl coumarones as well as certain compounds like deoxybenzoins and hydantions which are of some therapeutic value. The chalcones are α, β-unsaturated ketones containing the reactive keto-ethylenic group (-COCH=CH-). The chalcones are coloured compounds because of the presence of the chromophore (-COCH=CH-).

Many studies have shown that chalcones are compounds of great chemical and pharmacological interest because they exhibit many biological activities such as anti-microbial[1], anti-tumor[2], anti-malarial[3], cytotoxic[4,5] anti-depressant[6], anti-inflammator[7], anti-HIV[8] and anti-cancer[9].

They have close relationship with flavones, aurones, tetralones and aziridines. Chalcones and their derivatives find application as artificial sweeteners, scintillator, polymerization catalyst organic brightening agent, stabilizer against heat, visible light, ultraviolet light and aging. 3,2',4',6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside has been used as synthetic sweetener and is 2200 times sweeter than glucose. They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g. (a) phenyl hydrazine, (b) 2-amino thiophenol etc. The chalcones have been found useful in elucidating structure of natural products like hemlock tannin, cyanomaclurin, ploretin, eriodictyol and homo eriodictyol, naringenin etc.

The literature survey reveals that chalcone derivatives reported to possess antiulcer, antitumour, herbicidal, antifungal activites. Therefore it was thought that preparing substituted pyrazoline derivatives of some NSAID chalcones would probably result in compounds of having high biological activities towards many diseases. In keeping view the biological importance and medicinal utility of the substituted pyrazoline derivatives of some NSAID chalcones, the present study involves synthesis of some substituted pyrazoline derivatives of some NSAID chalcones, characterizing them and evaluating their biological activity.

MATERIALS AND METHODS

Synthesis of some NSAID chalcones

To aceto group containing molecules like paracetamol or acetyl salicylic acid (0.01 moles) added aromatic aldehydes (0.01 moles) in ethanol(20 ml) and catalytic quantity of sodium hydroxide. The mixture was stirred for 2 to 3 hours at room temperature using magnetic stirrer, the reaction was monitored by TLC and it was kept at room temperature and then cooled in an ice bath. After filtration,the product was washed with ethanol (5 ml) followed by distilled water, dried and crystallized from ethanol to yield a pure chalcones (Fig-1).

Synthesis of pyrazoline derivatives of some NSAID chalcones

To the different chalcones (0.01 moles) added glacial acetic acid (10 ml) and hydrazine hydrate 99% (0.01 moles). Refluxed for 8 hour on water bath ay 80^0C and cool it. The resulting solid was filtered, washed with distilled water. Recrystallized from ethanol and drying in desicators (Fig-1).

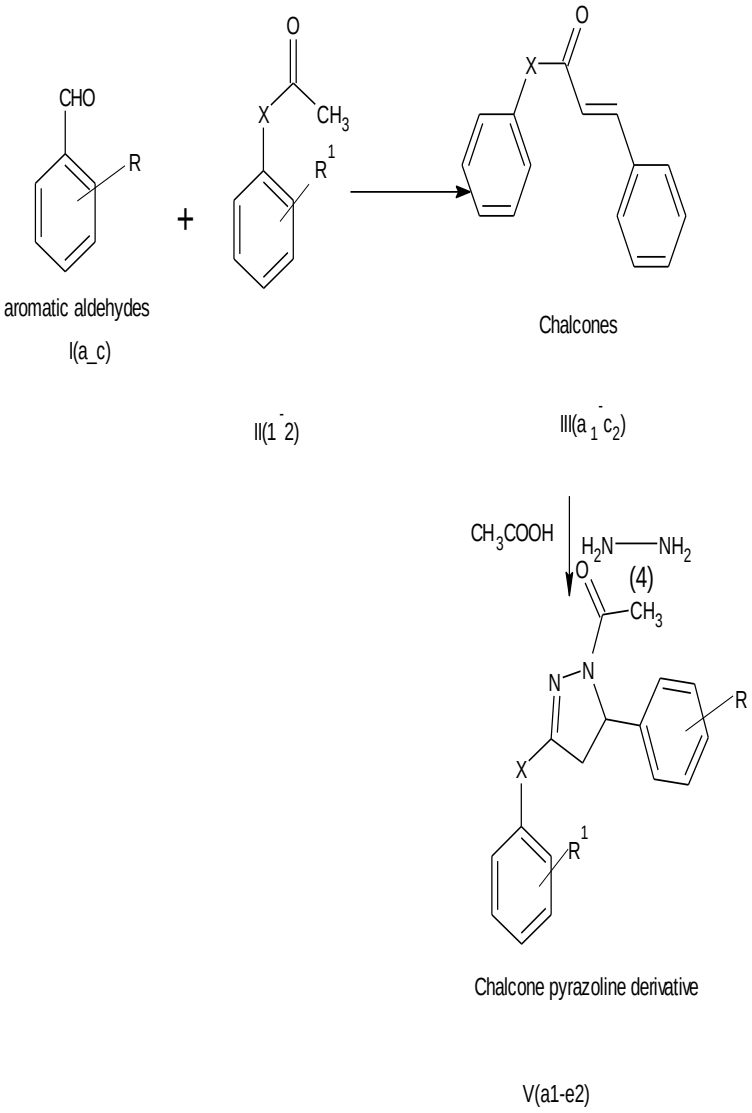

Fig-1 scheme of the synthesis

Insilico prediction

Molinspiration

Molinspiration offers broad range of chem informatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. Our products support also fragment-based virtual screening, bioactivity prediction and data visualization. Calculation of molecular physicochemical properties relevant to drug design and QSAR, including logP, molecular polar surface area (PSA), and the Rule of 5 descriptors. Calculation of activity score and drug-likeness for GPCR ligands, ion channel modulators and kinase inhibitors (interactive virtual screening), choose the "Predict Bioactivity" option. More information about calculation of bioactivity score and virtual screening (Fig-2).

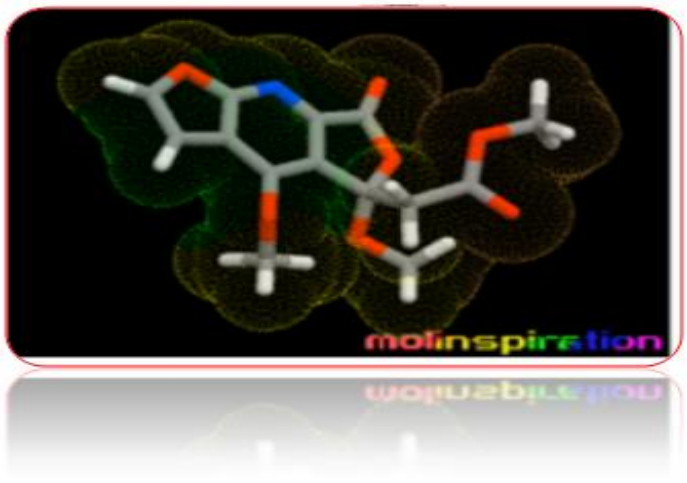

Fig-2 Molinspiration

Antibacterial activity

The Peptone, Beef extract, Yeast extract , Sodium chloride , Agar-Agar were collected in their respective proportions in conical flask previously filled with100 ml distilled water and dissolved in water.

The P^H of the medium was adjusted to 7.4 the P^H was tested using universal indicator paper, which showed green color at P^H 7.4.

Then it was transferred to Conical flask and sealed with non-absorbent cotton and sterilized by autoclaving at 121°C (15 lbs pressure) for 30 minutes. Then poured aseptically into sterile petridishes.

The standard drug tetracycline disc was placed on the media and the whatmann filter disc (5mm diameter) were cut and filled into vials plugged with cotton. These vials were kept in hot air oven at 160°C for 30 minutes for sterilization. Then it was soaked in synthesized compounds separately and evaporated to dryness and then kept on the media (5mm height). One more disc immersed in DMSO and kept on the media as control. It was kept in the incubator for a period of 24 hrs at 37°C. Observations were made for the zone of inhibition around the synthesized compounds and compared with that of standard (10-15).

RESULTS AND DISCUSSION

A practical synthetic route to pyrazoline derivatives of some NSAID chalcones containing a hydrazine moiety were synthesized by the condensation of intermediate chalcones formed from different NSAID's like Paracetamol and Aspirin with Hydrazine hydrate in presence of GAA as cyclisation agent is presented. All the synthesized compounds are purified by recrystallization and the structures of all compounds are confirmed via a wide range of spectroscopic techniques like FT-IR & H^1 NMR and physical characterization like m.p. The completion of the reaction was confirmed by TLC using chloroform: methanol (9:1) as solvent system and melting point. The values and interpretation data's are shown in the table-10.

Table-1 Physico chemical parameters of synthesized compounds

S. no	Compound	Molecular formula	Molecular weight	Composition	Melting point^0 (c)	Percentage yield	R_f value
1	**V(a_1)**	$C_{17}H_{16}N_4O_4$	340.33	C(59.99%) H(4.74%) N(16.46%) O(18.80%)	359.11^0 c	72.26%	0.784
2	**V(a_2)**	$C_{18}H_{15}N_3O_6$	369.32	C(58.54%) H(4.09%) N(11.38%) O(25.99%)	276.18^0 c	70.04%	0.724
3	**V(b_1)**	$C_{17}H_{15}Cl_2N_3O_2$	364.22	C(56.06%) H(4.15%) Cl(19.47%) N(11.54%) O(8.79%)	243.5^0 c	68.64%	0.812
4	**V(b_2)**	$C_{18}H_{14}Cl_2N_2O_4$	393.22	C(54.98%) H(3.59%) Cl(18.03%) N(7.12%) O(16.28%)	326.27^0 c	73.13%	0.696
5	**V(c_1)**	$C_{18}H_{19}N_3O_3$	325.36	C(66.45%) H(5.89%) N(12.91%) O(14.75%)	340.2^0 c	66.17%	0.756
6	**V(c_2)**	$C_{19}H_{18}N_2O_5$	354.35	C(64.40%) H(5.12%) N(7.91%) O(22.58%)	261.23^0 c	70.5%	0.736
7	V d_2	$C_{17}H_{15}N_5O_6$	385.33	C(52.99%) H(3.92%) N(18.17%) O(24.91%)	266.28^0 c	72.04%	0.713
8	V d_2	$C_{18}H_{14}N_4O_8$	414.32	C(52.18%) H(3.41%) N(13.52%) O(30.89%)	267.55^0 c	69.34%	0.742
9	V e_1	$C_{17}H_{16}FN_3O_2$	313.32	C(65.17%) H(5.15%) F(6.06%) N(13.41%) O(10.21%)	315.27^0 c	71.23%	0.719
10	V e_2	$C_{18}H_{15}FN_2O_4$	342.32	C(63.15%) H(4.42%) F(5.55%) N(8.18%) O(18.70%)	298.18^0 c	72.08%	0.663

Activity prediction

The biological activity spectra of the chalchonepyrazoline derivatives were obtained by PASS software. The predictions were carried out on the basis of analysis of training set containing about 10000 drugs and biologically active compounds. This set consider as reference compounds for known chemical compounds as well as different biological activities. Percent activity (pa) and inactivity (pi) of compounds have been represented in table. It can be seen from the results of PASS that most probable activities are Anti-inflammatory, Antiallergic and Antiasthmatic. The present work is an attempt to plan synthesis according to application of the compound. It would save unnecessary waste of chemicals as well as time. The Molinspiration virtual screening is fast (100,000 molecules may be screened in about 30 minutes) and therefore allows processing of very large molecular libraries. Validation tests performed on various target classes (includingkinase inhibitors, various GPCR targets, different enzymes etc.,) show 10 to 20- fold increases in hit rate in comparison with standard / random selection of molecules for screening. Log p is used in QSAR and rational drug design as a measure of molecular hydrophobicity. Hydrophobicity affects drug absorption, bioavailability, drug-receptor interaction ,metabolism of molecules as well as their toxicity. Any title compound did not show significant lipophilic activity.number of rotatable bonds is a simple topological parameter and is a measure of molecular flexibility.Molecular volumes were found to be within lipinsky's limit ***i.e.***(less than 500 dalton) all substituted chalchonepyrazoline derivatives were found to be in limit with respect to lipinsky's rule.

All the values of the synthesized compounds were found to be in compliance with standard values stated according to the Lipinsky's rule of five. This demonstrates that all the synthsesized compounds possess good permeation and availability

Anti microbial activity

All the synthesized compounds are evaluated for their invitro anti-microbial activity against bacteria like *E.coli* (Gram negative organism), *Pseudomonas aeuroginosa* (Gram negative organism), *Staphylococcus aureus* (Gram positive organism) and Fungal Organism of *Sacchromyces Species, Aspergillus Niger, Candida Albicans* using filter-paper disc method (Table-2,3).

The compounds were tested at a concentration level of 200µg/disc and the results were compared with that of tetracycline, fluconazole as a reference drug at 50µg/ml. All the compounds have shown significantantibacterial activity and moderate antifungalactivity. With the suitable molecularmodification of these compounds can prove aspotent antimicrobial agents in future.

Table-2 Anti fungal activity

S.no	Compound	Anti Fungal activity		
		C.albicans	*A.niger*	*Sacchromyces*
1	Standard 2	15	14	11
2	v(a1)	6.5	7	8
3	v(a2)	5	5	7
4	v(b1)	12	7	9
5	v(b2)	5	6	4.5
6	v(c1)	7	7	8
7	v(c2)	5.5	6	7
8	v(d1)	7.5	6.5	4.5
9	v(d2)	7	6	7.5
10	v(e1)	5.5	6	7
11	v(e2)	7	5.5	6

Table-3 Anti Bacterial Activity

S.no	Compound	Anti Bacterial activity		
		E.coli	*P. aeuroginosa*	*S. aureus*
1	Standard 1	10	12	11
2	v(a1)	7	9	7
3	v(a2)	9	7	6
4	v(b1)	11	9	7
5	v(b2)	7	5.5	4.5
6	v(c1)	10	9	7
7	v(c2)	8	6.5	7
8	v(d1)	6.5	6	5.5
9	v(d2)	7.5	6	6.5
10	v(e1)	5.5	6.5	7
11	v(e2)	7	5.5	6.5

CONCLUSION

The novel derivatives of some NSAID chalcones were synthesized and characterized by thin layer chromatography, Infra-red spectroscopic and NMR method. It have been prepared in good yields from readily available starting material and evaluated their *invitro* anti microbial activity. Biological results indicates that new derivatives of some NSAID chalcones shows moderate antimicrobial effect compared with standards. Hence the compounds might be promising new antimicrobial agent. The biological activity spectra of the derivatives of some NSAID chalcones were obtained by PASS software. It can be seen from the results of PASS that most probable activities are **Anti-inflammatory, Antiallergic, Anti microbial and Antiasthmatic**. It would save unnecessary waste of chemicals as well as time. This chapter continues with possible future direction from this line of investigation and concludes with a discussion on larger contexts surrounding my research.

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