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RECENT SYNTHETIC APPROACHES TO OXADIAZOLE AND THIADIAZOLE DERIVATIVES AS BIOLOGICALLY POTENT ANTI INFLAMMATORY AGENTS

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ABSTRACT
This research focused on clubbing different heterocyclic molecules having diverse biological action to produce potentially active derivatives of oxadiazole and thiadiazole. In the present study we have revealed a new synthetic approach for synthesizing novel oxadiazole and thiadiazole derivatives. Synthesis of 1, 3, 4 – Oxadiazole and Thiadiazole were carried out by the reaction between chalcone and isonicotinic acid hydrazide, followed by cyclizationwith propyl phosphonic anhydride for Oxadiazole and Hurd Mori reaction for Thiadiazole. Purity of the compounds ascertained consistency by TLC and melting point determination. The structure of newly synthesized compounds was characterized by IR, HNMR, MASS Spectral analysis. By comparing the results of all compounds, we havereached in a conclusion that 3a5 and 3b5 can be considered as potent antiinflammatory agents.

KEYWORDS: Chalcone, Oxadiazole, Thiadiazole, anti-inflammatory.

INTRODUCTION

Chalcones are 1, 3-diphenyl-2-propene-1-one, consist of two aromatic rings are interconnected by highly electrophilic three carbon α, and β-unsaturated carbonyl system that assumes linear or nearly planar structure. They containing keto ethylinic group (-CO-CH=CH-). Chalcones possess conjugated double bonds and completely delocalized π- electron system on both benzene rings. The presenceof a reactive and unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity.

Oxadiazole is a five membered heterocylic compound containing one oxygen atom and twonitrogen atoms. It is considered to be derived from furan by substitution of two -CH= groups with two pyridine type nitrogen (-N=). Oxadiazole and their derivatives had been reported to exhibit several biological activities like, antiinflammatory, antifungal, antibacterial, anticonvulsant, and mono amino oxidase inhibition. It occurs in various isomeric forms like, 1, 2, 3-oxadiazole, 1, 2, 5-oxadiazole, 1, 2, 4- oxadiazole and 1, 3, 4-oxadiazole. However, 1, 3, 4 and 1, 2, 4- oxadiazole are better known, and more widely studied by researchers, because of theirimportant chemical and biological properties. In chemistry, thiadiazoles are a sub family of azole compounds. Structurally they arefive membered heterocyclic compounds containing two nitrogen and a sulfur atom, and two double bonds, to give an aromatic ring. Four possible structures exist depending on the relative positions of the heteroatoms such as 1, 2, 3- thiadiazole, 1, 2, 4- thiadiazole, 1, 2, 5-

thiadiazole and 1,3,4- thiadiazole. It exhibits a wide variety of pharmacological activities such as anticancer, antitubercular, antibacterial, antifungal, antimicrobial, antiinflammatory, analgesic, anticonvulsant, diuretic and antisecretory activity. This study aims to synthesize potentially active novel derivatives of oxadiazole and thiadiazole by incorporating different heterocyclic moieties and substituting different functional groups. Synergism may occur due to the incorporation of two or more moiety that results in the formation of highly potent compound.

MATERIALS AND METHOD

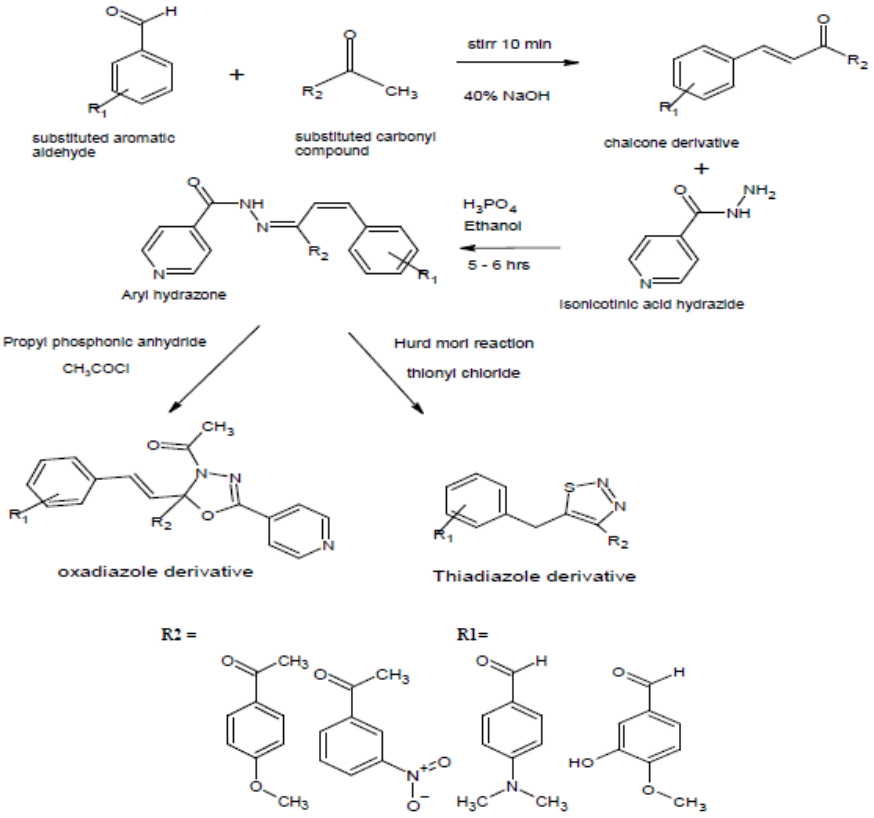
Synthesis and Characterization

All the chemicals and reagents used in this research work were analytical or practicalgrade. The compound procured were purified and dried using standard methods before use, wherever necessary. Melting point of the synthesized compounds were determined by open capillary method, Infra-Red spectra of the synthesized compounds are recorded using JASCO FT-IR spectrophotometer. Proton NMR spectra of synthesized compounds are recorded in D2O on Bruker ultra-shield DPX 400 spectrophotometer. Mass spectra of the synthesized compounds are recorded by using LC-MSD Trap-SL 2010 A- Purity of the compound ascertained by TLC over precoated, preactivated glass plates with appropriate solvent systems. Purity of the compounds are confirmed by single spot in TLC and consistency in the Rf value.

Pharmacological activity: Anti-inflammatory studies

Antiinflammatory activity of synthesized compounds are evaluated by Carrageenan induced paw oedema in rats from Devaki Amma Memorial college of Pharmacy, Chelembra, Malappuram.

EXPERIMENTAL SECTION



General Procedure for the preparation of chalcone derivatives

Dissolve 0. 01 mol benzaldehyde and 0.01 mol acetophenone in 10 ml 95% ethanol in 25 ml Erlenmayer flask and equipped with magnetic stirrer bar. 3.5 ml of NaOH solution was added to the reaction flask and stirred for 10 min. Cooled the mixture until the crystal formation was completed. Added 2ml of ice cold ethanol and allow to air dry. Rycrystallized from 95% ethanol.

General procedure for the synthesis of aryl hydrozones

A mixture of isonicotinic acid hydrazide (1.81 mM) and chalcones (1.81 mM) in absolute ethanol 20 ml and catalytic amount of H3PO4 was refluxed for 10 hours. Reaction completion wasmonitored by thin layer chromatography (TLC). Reaction mixture was then poured on to crushed ice, solid separated was filtered and dried. Crude compound was purified by recrystallization using hot water to get pure aryl hydrozones as color less solid.

General procedure for the synthesis of oxadiazole derivatives

A mixture of aryl hydrozones (Schiff's base) derivative, Propyl phosphonic anhydride (T3P) (10 mM) and acetyl chloride (15 volume) was refluxed for 8 hours. Progress of the reaction was monitored by Thin Layer Chromatography. After completion of the reaction, reaction mixture was cooled to room temperature and excess acetyl chloride was removed by the addition of saturated sodium bicarbonate solution to obtain crude compound.[49]

General procedure for synthesis of thiadiazole derivatives

An excess amount of thionyl chloride was stirred at 0^0c and the corresponding hydrazones were added in several portions. The mixture were stirred at room temperature until no more hydrogen chloride was produced. The remaining thionyl chloride was evaporated under vaccum and the residue was washed with diethyl ether. Recrystallisation from hot water.[70]

Synthesis of 1-[2-{(E)-2-[4-(dimethylamino)phenyl]ethenyl}-2-(3-nitrophenyl) ethenyl - 5- (pyridin-4-yl)-1,3,4- oxadiazol-3(2H)-yl]ethan-1-one (3a5)

A mixture of aryl hydrozones (Schiff's base) (2a5) derivative, Propyl phosphonic anhydride (T3P) (10 mM) and acetyl chloride (15 volume) was refluxed for 8 hours. Progress of the reaction was monitored by Thin Layer Chromatography. After completion of the reaction, reaction mixture was cooled to room temperature and excess acetyl chloride was removed by the addition of saturated sodium bicarbonate solution to obtain crude compound.

Synthesisof1-{2-[E]-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-2-(Metthoxyphenyl- ethenyl-5-(pyridin-4-yl)-1,3,4-oxadiazole-3(2H)-yl}ethan-1-one (3a6)

A mixture of aryl hydrozones (Schiff's base) (2a6) derivative, Propyl phosphonic anhydride (T3P) (10 mM) and aceticyl chloride (15 volume) was refluxed for 8 hours. Progress of the reaction was monitored by Thin Layer Chromatography. After completion of the reaction, reaction mixture was cooled to room temperature and excess acetyl chloride was removed by the addition of saturated sodium bicarbonate solution to obtain crude compound.

Synthetic procedure for N, N-dimethyl-4-{[4-(3-nitrophenyl)-1, 2, 3-thiadiazol-5- yl]methyl}aniline (3b5)

An excess amount of thionyl chloride was stirred at 0^0c and the corresponding hydrazones (2a5) were added in several portions. The mixture were stirred at room temperature until no more hydrogen chloride was produced. The remaining thionyl chloride was evaporated under vaccum and the residue was washed with diethyl ether. Recrystallization from hot water.

Pharmacological evaluationAnimals

Albino mice of swiss strains and wistar rat were used for the pharmacological and toxicological studies. The animal's experimental protocol has been approved by our Institutional Animal Ethics Committee (IAEC) registration no: DAMCOP/IAEC/045.

Acute toxicity study

The acute oral toxicity study was carried out on Swiss Albino mice as per the guidelines No: 423 given by theorganization for Economic Co- operations and Development (OECD 423, 1988).

Antiinflammatory study

Acute Antiinflammatory study by Carrageenan induced paw edema in rat

This method is the most commonly used method for the evaluation of antiinflammatory drugs.

Group1: Control (normal saline)

Group2: Standard group (Indomethacin 10mg/kg body weight)

Group3:Oxadiazole derivative (lower dose+ higher dose)

Group4: Thiadiazole derivative (lower dose+higher dose)83

RESULTS

Table 1 Preliminary characterization of synthesized compounds. Table 2: Spectral analysis of synthesized compounds. Figure 1: Histogram showing Antiinflammarory effect of derivative 3a5 by carrageenan induced paw edema. Figure 2: Histogram showing Antiinflammarory effect of derivative 3a5 by carrageenan induced paw edema.

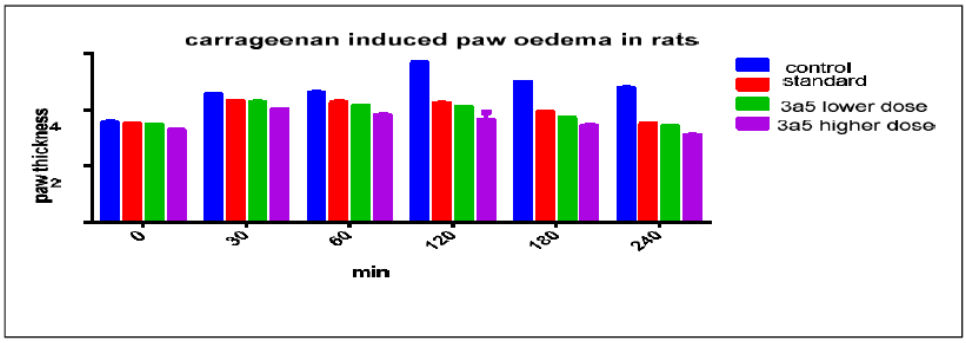


Figure 1: Histogram showing Antiinflammarory effect of derivative 3a5 by carrageenanInduced edema.

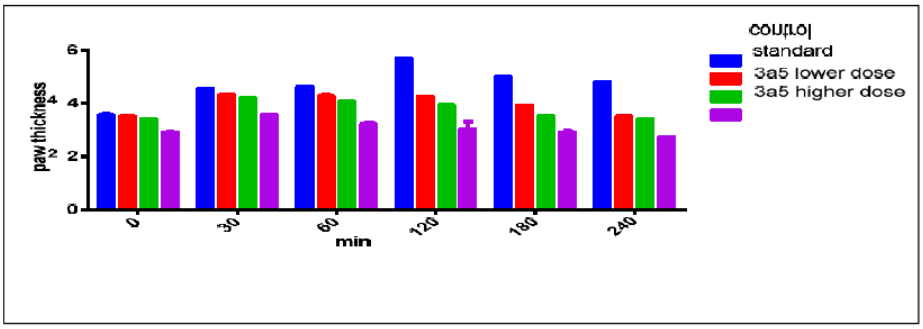


Figure 2: Histogram showing Antiinflammarory effect of derivative 3b5 byinduced paw edema.

Table 1: Preliminary characterization of synthesized compounds.

Compound code	Molecular formula	Molecular weight	Melting Point (^{0}c)	Percentage Yield	Rf value
3a5	$C_{25}H_{23}N_5O_4$	457.49	200	60	0.6
3a6	$C_{25}H_{23}N_3O_5$	445.48	195-200	65	0.6
3b5	$C_{17}H_{16}N_4O_2S$	340.1	100-130	75	0.7

Table 2: Spectral analysis of synthesized compounds.

Compoundcode	IR peaks(cm	^{1}HNMR (δ valueinPPM)	^{13} C NMR(δ value in PPM)	Mass spectral detals
3a5	3020 (Ar C-H str) ; 2934 (CH_3 str); 1700(C=O str) ; 1342 (C-N str) ; 1099 (C-O str) ; 1527 (NO_2 str)	6.54-7.12 (D, 4H, CH-Benzene), 2.02-2.86 (S, 9H, CH_3), 8.02-8.84 (D, 4H,CH-pyridine), 7.45-8.12 (4H, CH-	23.8, 39.83, 40.00, 40.33, 40.331, 82.4, 114.20, 114.21, 119.1, 122.21, 124.1, 124.11, 124.7, 126.30, 127.31,	Base peak atm/z value411 Molecular ion peak(M+H)atm/z value457 Molecularweight of the compound is457.49
		Benzene) 6.34-6.66 (D, 2H,ethylene)	127.311, 129.5, 129.7, 141.6, 148.2, 148.8, 149.5, 149.51, 155, 168.6.	
3a6	3655 (O-H str) ; 3011 (Ar C-H str) ; 2825 (O-CH_3 str) ; 1780 (C=O str) ; 1599 (CH=CH alkene str) ; 1300(C=N str) ; 1030.77 (C-O str)	6.57-6.69 (D, 3H, CH-Benzene), 2.02-3.73 (S, 9H, CH 3), 6.70-7.08 (D, 4H, CH-Benzene), 8.02-8.34 (D, 4H, CH-Pyridine), 5.0 (D, 1H,-OH), 6.34-6.66(D, 2H, Ethylene)	23.8, 55.9, 56.2, 83.4, 112, 114.1, 114.2, 116.8, 120.1, 124.0, 124.1, 126.5, 128,128.1, 128.2, 129.7, 133, 133.1, 138, 149.5, 149.51, 151.3, 155, 158.7, 168.	Base peak atm/z value150 Molecular ion peak(M+H)atm/z value445 Molecular weight of the compound is 445.48
3b5	3100 (Ar C-H str) ; 2945 (CH_3 str) ; 1588 (NO_2 str) ; 1501(N=N str) ; 1431 (C=C str) ;1365 (C-N str) ; 800 (C-S str)	6.47-6.88 (D, 4H, CH-Benzene, 3.81(D, 2H, CH_2), 7.58-8.41 (D, 4H, CH-Benzene), 2.85-2.851 (S, 6H,CH_3.)	28.9, 40.3, 40.31, 40.32, 114.0, 114.01, 121.1, 121.11, 125.8, 128.9, 130.0, 130.12, 133.6, 134.0, 146.6, 148.9, 158.2.	Base peak atm/z value329 Molecular ion peak(M+H)atm/z value340 Molecular weight of the compound is 340.1

DISCUSSION

Synthesis of oxadiazole and thiadiazole derivatives were carried out by fusing chalcone with isonicotinic acid hydrazide, followed by cyclization for oxadiazole derivatives and, by Hurd Mori reaction for Thiadiazole derivatives. Purity of the compounds were ascertained consistency by TLC and melting point determination. The structure of newly synthesized compounds were characterized by IR, HNMR, MASS Spectral analysis. From the antiinflammatory study by carrageenan induced paw edema method it is revealed that compounds 3a5 and 3b5 have shown better reduction in the carrageenan induced paw edema when compared to standard. The compound 3a5 and 3b5 with a dose of 400mg/kg have shown better antiinflammatory activity than the dose of 200mg/kg.

From these results and observation it was found that in future these newly synthesized 1, 3, 4 – Oxadiazole and 1,2,3 Thiadiazole derivatives can be developed as a lead molecules in antiinflammatory, drug discovery process.

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