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SYNTHESIS & PHARMACOLOGICAL EVALUATION OF SOME 1, 3, 4-OXADIAZOLE DERIVATIVES

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Abstract

In present investigation, a new series of the 2,5-disubstituted 1,3,4-oxadiazole derivatives were synthesized by the reaction between benzoyl chloride and various chloro, nitro benzoyl chloride with oxasemicarbazide and these synthesized compounds were isolated & purified by TLC & Column chromatographic method & evaluated for their antibacterial activities. The antibacterial activity of these compounds were examined against gram positive & gram negative bacteria by the help of Dish diffusion method. All the synthesized compounds were characterized by 1H NMR, IR and Mass Spectroscopic method.

Keywords: 1, 3, 4-oxadiazole, antibacterial activity.

Introduction:

Oxadiazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. The derivatives of oxadiazole nuclei showed diverse biological activities such as Antibacterial, anti-inflammatory, anticonvulsant, anticancer, anti-tubercular, anthelmintic, analgesic, CNS depressant & other activities.1 The synthesized compounds 2,5-disustituted 1,3,4-oxadiazole derivatives were evaluated for their antibacterial and anti-inflammatory activies. The antibacterial drugs are designed to inhibit or kill the infecting organism, microbes such as bacteria, fungi etc. & to have no or minimal effect on the recipient and Antibiotic are the substances produced by micro-organism, which suppress the growth of or kill other micro-organism at very low concentration.2 Anti-inflammatory are use for the prevention & cure of inflammation and pain including musculoskeletal disorders such as rheumatic arthritis, osteoarthritis etc. all drugs grouped in this class have analgesic, antipyretic, anti-inflammation. NSAIDS agents inhibit the cycloxygenase steps (COX 1 extensively, besides COX 2) thereby preventing the formation of prostaglandin endoperoxidase (PGG2 & PGH2) & TXA2. & other prostaglandins and consequently reducing the sign & symptoms of inflammation.[pandeya S.N., 2008] These agents are used to relieve swelling, redness, pain and fever associates with inflamed joints is an for long time.3

Experimental:

Various chemicals are used during synthesis was supported by Merk and the melting point was measured on melting point apparatus in open capillary tube method and are uncorrected.IR spectra were recorded on PERKIN ELMER RX 1

Spectrophotometer in KBr solution, 1H NMR spectra were recorded on BRUKER DRX – 400 MHz Spectrophotometer in DMSO-d6 using TMS as internal Standard.(chemical shift in ? ppm). And the Mass spectra were recorded on JEOL-AccuTOF JMS-T100LC Mass spectroscopy.

Materials and methods:

General Procedure for the preparation of Oxasemicarbazide:

Calcium oxide (0.17 mol.) was dissolved in the ethanol (100 ml.) and stand for overnight in closed bottle after overnight distilled the ethanol then sodium metal (0.09 mol.) was added into the distilled ethanol (25 ml) & stirred well for ½ hr. And the semicarbazide HCl (0.1 mol.) was added into the above mixture & stirred well. Then filtered the residue and dried well. The excess solvent was evaporated from the product. The crude product Oxasemicarbazide was used for the reaction process.

General Procedure for the preparation of 2, 5-disubstituted 1,3,4-oxadiazole derivatives:

The ratio of Aromatic acids (0.01 mol.) and phosphorus pentachloride (0.01 mol.) and excess amount of benzene were taken in the round bottom flask, shake well then fitted with air condenser with calcium chloride guard tube and refluxed the mixture on water bath for 30 min. at 500 C. After 30 min. the excess POCl3 was distilled out then the residue was proceed for the next step. The Oxasemicarbazide (0.033 mol.) was added into the respected Acid chloride & refluxed for 3-6 hr. after refluxed the mixture the excess benzene was distilled out then cool and neutralized with aq. NaHCO3, filter and the crude product was dried well & recrystallized with methanol. The progress of the reaction was monitored by checking the TLC.

Purification of the compounds:

The fraction of compounds was collected by regular checking of TLC & finally the compounds were purified by thin layer chromatography using silica gel G coated glass TLC plates & preparative plate with the solvent system ethyl acetate : pet. ether : methanol (3:1:2drops) & spot were developed in both UV chamber and Iodine vapours chamber.The compounds were also purified by the column chromatography using silica gel (60-120 mess) & silica gel GF columns with solvent system ethyl acetate : pet. Ether: methanol (3:1:2 drops).

Compounds characterization:

C_a:[N-(5-Phenyl-[1,3,4]oxadiazole-2-yl)-benzamide]: IR (KBr,cm^{-1}) 3393(NH),1654(C=O),1081(N-N), 1370 (C-O-C).^{1}HNMR(DMSO–d_6 ,δ, ppm) 8.13(1H,s,NH),2.7(2×5H,m,aromatic) ,Mass m/z (%): Found: C=64.02,H=3.91,N=14.94,O =11.38

C_b:[3-Chloro-N-[5-(3-Chloro-Phenyl)-[1,3,4]Oxadiazole-2yl]benzamide]:IR(KBr,cm^{-1})3304(NH),1665(C=O),1112(N-N),1347(C-O-C),^{1}HNMR(DMSO–d_6,δ,ppm)766.3(C-Cl).7.91(1H,d,NH), 3.4(5H,s,aromatic) Mass m/z (%):Found C=53.87,H=2.69,N=12.56,O =9.57,

Cc:[4-Chloro-N-[5-(4-Chloro-Phenyl)-[1,3,4]Oxadiazole-2-yl]benzamide]:IR(KBr,cm^{-1})3304(NH),1665(C=O),1112(N-N), 1347(C-O-C), 713.8(C-Cl) ^{1}HNMR(DMSO–d_6 ,δ, ppm)

8.19(1H,d,NH)7.97.95(5H,m,aromatic)Mass,m/z(%):Found:C=53.87,H=2.69,N=12.56,O=9.57,

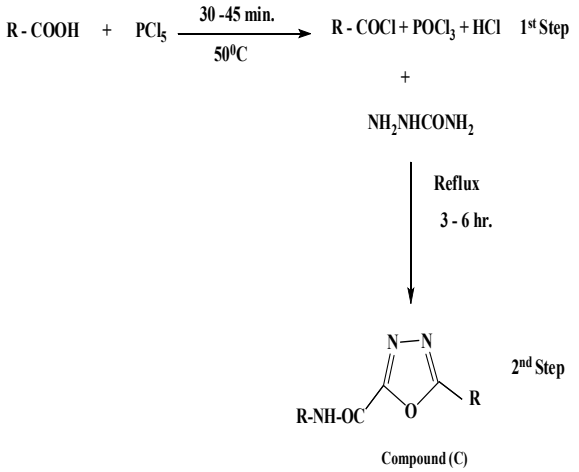
Cd:[4-Nitro-N-[5-(4-Nitro-Phenyl)-[1,3,4]Oxadiazole-2-yl]benzamide]IR(KBr,cm^{-1})3214(NH),1665(C=O),1112.6(N-N),1347(C-O-C),769.2(C-NO_2).^{1}HNMR(DMSO–d_6,δ,ppm) 8.41(1H,d,NH) 8.31-8.36(4H,t, aromatic). Mass,m/z(%):Found:C=52.45,H=2.62,N=20.39,O= 27.97.

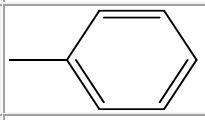
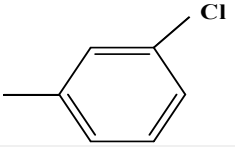
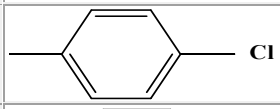
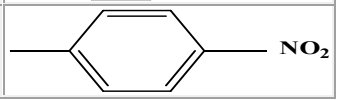
Antibacterial activity (by Disc diffusion Method):

The synthesized compounds were tested for their antimicrobial activity against gram positive S.aureus, B.subtilis and gram negative E.coli, P.aeruginosa bacteria by dish diffusion method. Ciprofloxacine were used as standard drug for antimicrobial studies. Nutrient agar (Beef extract 10 gm, Peptone 10 gm, NaCl 5 gm, Agar 20 gm, unfired water 1000 ml) was employed as culture media for antimicrobial studies. The ingredient were dissolved in water & adjust pH 7.2 to 7.4 by using dilute alkali/acid & autoclave at 1200c for 20 min. then nutrient agar media was transferred to the petri dish . 5 µg/dish concentration of the test compound are prepared & DMF was used as vehicle & ciprofloxacine 10 µg/dish was used as standard.Nutrient agar plates were prepared aspectically to get a thickness of 5-6 mm. the plate were allowed to solidify & inverted to prevent condensate falling on the agar surface. The plate was dried at 37 0C just before inoculation. After inoculation the sterilized dish for the test drugs were placed in the petri dishes, incubated the petri dish at 370C for about 18-24 hr. after placing them in the refrigerater. The average zone diameter of the plate were measured & record.4

Result and Discussion

Scheme: 1



Compounds	R
C_a	
C_b	
C_c	
C_d	

The 1,3,4-oxadiazole and their derivatives were synthesized by the new method of the solution of acid & phosphorus penta chloride & then performed the cyclization by the oxasemicarbazide to obtained the new drug. the reaction was found to be successful producing good yields.

Table:1: Some physical properties of compounds (Ca – Cd):

Compounds	Molecular formula	m.p. (^{0}c)	Yield (%)	Solubility	Rf value	Mwt.	Colour
Ca	C15H11N3O2	211	72	Methanol & DMSO	0.742	265.2	Off white
Cb	C15H9N3O2Cl2	213	78	Methanol & DMSO	0.688	334.16	Yellowish white
Cc	C15H9N3O2Cl2	212	81	DMSO	0.678	334.16	White
Cd	C15H9N5O6	271	78	Methanol & DMSO	0.662	355.26	yellowish white

Table.2; Antibacterial Activity :

Zone of inhibition in mm.								
Compounds	**S.aureus (zone of inhibition in mm)**	**% inhibition**	**B. subtilis (zone of inhibition in mm)**	**% inhibition**	**E-coli (zone of inhibition in mm)**	**% inhibition**	**P.aeruginosa (zone of inhibition in mm)**	**% inhibition**
C1	15	60	18	69.23	16	57.14	17	68
C2	13	52	15	57.69	14	50	20	80
C3	17	68	20	76.8	12	42.84	18	72
C4	16	64	17	65.28	15	53.55	16	64
Ciprofloxacine	25	100	26	100	28	100	25	100

The synthesized compounds were evaluated for their Antibacterial activity against gram positive & gram negative bacteria by the help of Disc-diffusion method. The antibacterial activity was observed at 5 µg/dish of concentration. few compounds like compound C2 & C3 were show good antibacterial activity while remaining compounds C1 & C4 showed moderate & less antibacterial activity when compared with that of standard drug Ciprofloxacin.

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