SYNTHESIS AND ANTI-BACTERIAL SCREENING OF SOME NOVEL (2-SUBSTITUTED BENZYLIDENE) IMINO-5-(4'ACETAMIDO PHENOXY METHYL)-1, 2, 4-OXADIAZOLE

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ABSTRACT: A series of some novel aryl oxadiazole derivatives were prepared by the condensation of compounds containing primary aromatic amine and aryl aldehydes to give respective Schiff's bases. The compounds were characterized by Mp, TLC, spectral data (U.V, IR, NMR and Mass) and screened for anti-bacterial activity. Almost all the synthesized compounds showed good activity against all the microbes compared to the standard employed.

KEYWORDS: - Anti-bacterial, Oxadiazole, Schiff's bases, IR, NMR.

1. INTRODUCTION

Modern drug design, as compared with classical approach- "*Let's make a change on an existing compound or synthesize a new structure and see what happens*"- has undergone a rapid evolution as an approach to solving a drug design problem (1).

Heterocyclic compounds form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature (2). One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three-dimensional representations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

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Heterocycles play an important role in biological processes because the side group of the most typical and essential constituent of living cells, DNA and RNA are based on aromatic heterocycles (3).

In the field of heterocyclic chemistry, 5-membered O-containing heterocyclic ring occupied a unique place due to their various biological properties. Oxadiazoles are considered as an important pharmacophore in medicinal chemistry encompassing wide spectrum of biological activities such as anti-inflammatory (4), antifungal (4), antibacterial (5), antitubercular (5), anticonvulsant (6), anti-cancer (7), and antiviral activity (8). Paracetamol moiety posses antipyretic, anti-inflammatory and anti-rheumatic properties. Hence an attempt was made to incorporate oxadiazole moiety to paracetamol nucleus to explore the activity.

2. MATERIALS AND METHODS

2.1 Materials

Pure drug of paracetamol was supplied as a gift sample by Strides arcolab limited Bangalore. All the other chemicals were purchased from merk chemi-

cals, Bangalore. Melting points were determined in open capillaries on Precision Melting Point Apparatus. The purity of the compounds was checked by TLC using precoated TLC plates (E. Merck Kieselguhr $60F_{254}$) taking $CHCl_3$:CCl_4 (8:2) as solvent system. The IR spectra were recorded on a Shimadzu IR spectrophotometer as KBr pellets and the wave numbers were given in cm^{-1} .NMR and MASS spectra were taken from IISc bangalore.

2.2. Experiment

The synthetic strategies adopted to obtain the target compounds are depicted in scheme I

2.2.1. Ethyl(4-acetamidophenoxy)acetate(I)

A mixture of paracetamol (0.2 mol), ethyl chloroacetate (0.2mol) and anhydrous K_2CO_3 (0.3 mol) in dry acetone (300 ml) was refluxed on a water bath for 16 hr, cooled and filtered. From filtrate excess acetone was removed by distillation. The reaction mixture was poured into ice cold water and stirred well. The resultant product was filtered, washed with water and crystallised from methanol to yield pure ethyl-(4-acetamidophenoxy) acetate(I) (9).

2.2.2. 2-(4'-acetamido phenoxy)acetohydrazide

A mixture of ethyl-(4-acetamidophenoxy) acetate (0.1 mol), and hydrazine hydrate (0.3 mol) in ethanol (100 ml) was refluxed for 3 hr. Excess of ethanol was removed by distillation. On cooling 2-(4'-acetamidophenoxy) acetohydrazide began to separate. It was collected by filtration and recrystallized from aqueous ethanol (6).

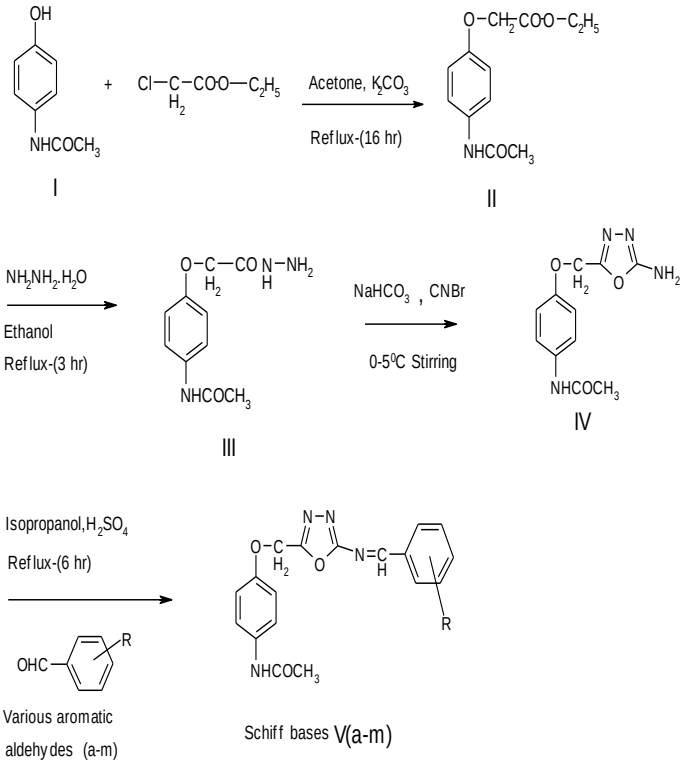
2.2.3. 2-amino-5-(4'-acetamidophenoxymethyl)-1,3,4-oxadiazole

To a suspension of 2-(4'-acetamido phenoxy) acetohydrazide (0.1 mol) in 200ml methanol $NaHCO_3$ (14.77gm) was added and cooled to 0-5° C with vigorous stirring. Solid cyanogen bromide (0.15mol) was added in single portion followed by addition of 20 ml methanol. The reaction mixture was stirred at 0-5°C for 2 hr. The cooling bath was allowed to warm up to ambient temperature over a 2 hr period and the reaction was continued for an extra hr at room temperature. The reaction mixture was stirred in an open flask for 1 hr. The precipitated product was collected by filtration, washed with water, dried and recrystallized from 95% ethanol (6).

2.2.4. 2-(substituted benzylidene) imino-5-(4'-acetamidophenoxy methyl)-1,3,4-oxadiazole.

A mixture of 2-amino-5-(4'-acetamidophenoxy methyl)-1,3,4-oxadiazole (0.01 mol) and the required aryl aldehydes (0.01 mol) in isopropanol (30 ml) and catalytic amount of sulphuric acid (1ml) was subjected to reflux for 6 hr. The reaction mixture was cooled to room temperature. The solid separated was filtered, washed with isopropanol and recrystallized with suitable solvents (4).

Scheme I



3. RESULTS AND DISCUSSION

The present work is bonafide and novel for the syntheses and characterization of some novel

Table 1 Physical and spectral Data of the Synthsized Compounds

Comp	M.P. (ºC)	% Yield	Mol. Formula	R_f Value	UV λ_{max} (nm)	IR (KBr)cm^{-1}
II	99	62.5	$C_{12}H_{15}O_4N$	0.60	254	1172.73 (O-C_2H_5); 1221.43 (Ar-O-C).
III	196	81	$C_{10}H_{13}O_3N_3$	0.55	298	3342.46 (NH_2 str); 1228.04 (Ar-O-C).
VI	206	70	$C_{11}H_{12}O_3N_4$	0.69	285	1091.18 (C-O); 1648(C=N).
Va	216	48.2	$C_{20}H_{21}N_5O_3$	0.85	335	1558.33 (N=CH); 1093.82 (C-O).
Vb	221	54.5	$C_{19}H_{18}N_4O_3$	0.74	338	1598.42 (N=CH); 3066.17(Ali C-H).
Vc	213	52.2	$C_{20}H_{19}N_4O_5$	0.78	340	1586.97 (N=CH); 1247.59 (OCH_3).
Vd	223	60.5	$C_{18}H_{16}N_4O_3Cl$	0.66	342	763.10 (C-Cl); 1594. 46 (N=CH).
Ve	218	55.4	$C_{19}H_{18}N_4O_4$	0.81	349	1582.92 (N=CH); 1253.17 (OCH_3).
Vf	224	63.4	$C_{18}H_{15}N_5O_5$	0.86	357	1530.6,1347.86(N=O);1583.54(N=CH).
Vg	210	57.6	$C_{18}H_{16}N_4O_4$	0.76	361	3568.46 (O-H); 1592.31 (N=CH).
Vh	212	58.4	$C_{18}H_{16}N_4O_4$	0.79	371	3595.12 (O-H); 1585.92 (N=CH).
Vi	225	60.2	$C_{18}H_{16}N_4O_3$	0.77	366	1596.07 (N=CH); 1442.50 (Ar C=C).
Vj	222	62.5	$C_{18}H_{16}N_4O_3Cl$	0.64	373	777.10 (C-Cl); 1595.56 (N=CH).
Vk	219	54.8	$C_{19}H_{18}N_4O_5$	0.82	384	3510.99 (O-H); 1579.89 (N=CH).
Vl	220	62.7	$C_{18}H_{15}N_5O_5$	0.83	381	1536.6,1351.08(N=O);1589.52(N=CH)
Vm	215	54.4	$C_{21}H_{22}N_4O_6$	0.62	391	1583.73 (N=CH); 1251.54 (OCH_3).

Table 2 Antibacterial activity data

Comp	R	*S.aureus*	*B.subtilis*	*E.coli*	*K. pneumoniae*
Va	4''-Dimethylamino	05	02	06	03
Vb	4''-Methyl	06	05	02	07
Vc	3'',4''-Dimethoxy	05	04	02	03
Vd	2''-Chloro	09	11	10	08
Ve	4''-Methoxy	05	08	NA	NA
Vf	2''-Nitro	07	06	07	08
Vg	2''-Hydroxy	06	03	03	04
Vh	4''-Hydroxy	05	04	NA	NA
Vi	H	05	04	NA	NA
Vj	4''-Chloro	11	12	14	11
Vk	4''-hydroxy-3''-methoxy	05	07	NA	NA
Vl	3''-Nitro	08	07	08	07
Vm	3'',4'',5''-Trimethoxy	04	05	NA	NA
Ampicillin	----------	12	12	19	12

oxadiazoles as anti-bacterial agents.Synthesis starts with etherification of N-(4-hydroxyphenyl) acetamide with ethylchlroacetate in presence of anhydrous K_2CO_3 using dry acetone as reacting medium to give compound II. Hydrazinolysis of II with three fold equimolar amount of hydrazine hydrate gave 2-(4' acetamidophenoxy methyl) acetohydrazide III. Formation of the compounds II & III were confirmed by Mp, TLC and IR spectra.

The obtained hydrazide was treated with CNBr in presence of $NaHCO_3$ to get 2-amino-5-(4'-acetamidophenoxy methyl)-1,3,4-oxadiazole which was confirmed by Mp,TLC, IR (table 1).

The ^1H NMR (DMSO) specra showed $-NH_2$ chemical shift at 4.87 ppm and mass spectrum showed its molecular ion peak at m/z 249(M^+). The desired title compounds were synthesized by refluxing compound IV and various aromatic aldehydes in

isopropylalcohol with catalytic amount of sulphuric acid. All the compounds were confirmed by Mp, TLC and IR spectra (table 1). ^{1}H NMR (DMSO) specra of two compounds with R substitution as 4''dimethylamino and 4''chlro showed enamine hydrogen shift at 8.48 and 8.5 respectively. Synthetic route is depicted in Scheme I.

The synthesized compounds were characterized by their Mp, TLC, UV, IR, NMR, and Mass spectra. All melting points were determined in open capillaries and are uncorrected formation and purity of the compounds (table 1) was routinely checked by TLC using precoated TLC plates (E. Merck Kieselguhr $60F_{254}$). Solvent system used was $CHCl_3$:CCl_4 (8:2) and spots were located by UV fluorescence. The UV spectra was recorded on shimadzu spectrometer, IR were recorded using KBr pellets on shimadzu IR spectrophotometer

Anti-bacterial activity

All the title compounds (Va-m) were screened for antibacterial activities at 500µg/ml concentrations. The test organisms chosen were S.aureus, B.subtilis, E.coli, K.pneumoniae. Agar dilution method was used to measure the activity (5). The zones of inhibition were measured in mm at the end of 24 h and represented in table 2. It was observed that both electron donating and electron withdrawing groups on the aldehydic phenyl ring of the compounds influence the activity. But aldehydic phenyl ring containing electron withdrawing group had shown more promising result. Among all the compounds tested Vj and Vd showed good activity against all the microbes.

4. CONCLUSION

From the present work it was observed that the compounds with both electron donating and electron withdrawing groups on the aldehydic phenyl ring of the compounds influenced the activity. But compounds containing electron withdrawing group had shown more promising results. Compouds Vj and Vd having substituents 4''chloro and 2''chloro respectively showed good anti-bacterial activity compared to the standard employed.

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