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SYNTHESIS OF A NEW HETEROCYCLIC MOLECULE WITH AN OXADIAZOLE MOIETY AND ITS BIOLOGICAL ASSESMENT

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ABSTRACT:
In the present study a series of 1,3,4 oxadiazoles have been synthesized by multistep reaction scheme. Sebacic acid dihydrazides was used as the starting material. The structure of the newly synthesized derivatives were established by the combined practice of elemental analysis, IR,1HNMR, and Mass spectrometry. We report the synthesis, biological assessment of 1,3,4 oxadiazole substituted derivatives as novel potential antibacterial agent.

KEYWORD: Heterocyclic compound ,1,3,4 oxadiazoles derivative, Spectroscopic Study, pharmacological activities, oxadiazole.

INTRODUCTION:

Recently the oxadiazole chemistry has been developed extensively and is still developing .Most of the drug are used clinically [I,II] which comprise oxadiazole moiety in association with various heterocyclic rings. 1,3,4 Oxadiazole are important heterocyclic compound which are synthetically useful and biologically active, literature survey revealed that 1,3,4 oxadiazoles are related to wide range of pharmacological activities.[III]. Some,1,3,4Oxadiazole and their derivatives are reported in the literature [IV-XI].1,3,4 Oxadiazolines-2-thio and 1,2,5 oxadiazole derivatives are found to be active against HIV [XII-XIII] . The compound possessing 1,3,4oxadiazole ring system reported [XIV-XX] to show area broad spectrum of Sbiological properties like analgesic and anti-inflammatory, antibacterial and antifungal activities. The most often used synthetic route for 1,3,4oxadiazole includes synthesis of 1,8 Bis(2-arylamino 1,3,4oxadiazole-5-yl)octane has been carried out by the action of I_2/KI on Bis(N-aryl/alkyl) thiocarbamido sebacic acid diamide substituted 1,3,4 oxadiazoles have been shown to be effective against a wide range of gram positive and gram negative bacteria[XXI-XXIII].

MATERIAL AND METHOD:

Experimental protocol: All the chemical reagent and solvent on a Perkin of analytical grade were purchased from Merek analytical thin layer chromatography was carried out on TLC plates coated with silica gel G for reaction monitoring and for determination of retardation

factor .Melting point for newly synthesized derivatives were determined on digital melting point apparatus and were found uncorrected. The carbon and Hydrogen analysis was carried out on 'Carlo Erbo 1106 analyser. The IR Spectra were recorded on a Perkin Elmer 577; Spectrometer using Nujol Method 1H NMR Spectra were recorded by utilizing 400 and 300 MHZ Bruker Spectrometer indicating chemical shift value and TMS was taken as an internal reference .Thermo LCQ Deca XP Max spectrometer was utilized for Mass spectra.

New synthetic approach for novel series of 1,3,4 oxadiazole is shown in scheme -I The starting material Bis-(N-aryl/alkyl) thiocarbamido sebacic acid diamide was obtained by the reaction with molecular iodine in presence of alkaline ethanolic medium .The required diamides were synthesized by the condensation of different aryl/alkyl isothiocyanate and sebacic acid dihydrazide. The purity of synthetic compound was checked by TLC and were established on the basis of chemical transformation ,elemental analysis,1HNMR and Mass spectral studies.

EXPERIMENTAL:

The parent compound sebacic acid dihydrazide was (1) prepared by refluxing the mixture of sebacic acid (0.01mole) and thionyl chloride (0.02 mole) for 20 min .This was transformed in to sebacic acid dihydrazide followed by addition of hydrazine hydrate(0.02mole.). The reaction mixture cooled and on basification with dilute ammonium hydroxide solution. It afforted a free base.

Synthesis of bis (-N-o-tolyl thiocarbamido) sebacic acid diamide(2a):

Sebacic acid dihydrazide (1) (0.01mole) and o-tolyl isothiocyanate (0.02 mole) in chloroform (10ml) was refluxed for 2 hrs. The chloroform distilled off a granular solid mass was obtained . It was crystallised from ethanol and identified as bis (N-o-tolyl thiocarbamido) sebacic acid diamide(2a) 78% m.p 202^{o}C.Similarly other thiocarbamides (2b-g) were obtained using different aryl/alkyl isothiocyanates and the related product were isolated in good yield.

Synthesis of 1,8 Bis –(2-arylamino 1,3,4 oxadiazole -5-yl)Octane(3):

A paste of bis (N-o-tolyl thiocarbamido) sebacic acid diamide(2a) (0.01mole) was prepared in chloroform and solution of iodine in ethanolic potassium hydroxide containing potassium iodide was added to it drop by drop with constant stirring , initially the colour of iodine was disappeared therefore excess of iodine was added till no further decolourisation of violet colour of iodine was observed. The evolution of hydrogen sulphide gas was observed .The reaction mixture was allowed to stand overnight at room temperature.It was repeatedly washed with petroleum ether followed by addition of ethanol and crystalised from ethanol and identified as 1,8 bis (2-o-tolylamino-1,3,4 oxadiazole-5-yl)octane.(3a).

3b-g were prepared from2b-g, **3a** (89%) m.p 188(Found: C,67.58;H,6.45;N,18.16,Calcd. for $C_{26}H_{32}N_60_2$ C,67.82;H,6.95,;N,18.26, **3b** (82%) m.p196 (Found:C,67.70;H,6.60;N,18.34; Calcd for $C_{26}H_{32}N_6O_2$ C,67.82;H,6.95;N,18.26) **3c** (78%)m.p 182(Found: C,68.00;H,6.70;N,18.98; Calcd. For $C_{26}H_{32}N_6O_2$,C,67.82;H,6.95;N,18.26) **3d** (85%)m.p186(Found C,66.05;H,7.00;N19.92 Calcd. for $C_{30}H_{36}N_6O_4$,C,66.12;H,6.80,;N,15.06) **3e** (85%)m.p186(Found C,57.02;H,5.03,;N,16.73 Calcd. for $C_{24}H_{26}N_6O_2Cl_2$ C,57.48;H,5.18,;N,16.76) **3f** (87%)m.p 195(FoundC,61.03;H,5.08;N,16.42,Calcd.for $C_{24}H_{26}N_6O_2Cl_2$C,57.48;H,5.18,N16.76) **3g** (72%) m.p188 (Found C,61.03,; H,9.14; N,21.04, Calcd. for $C_{20}H_{20}N_6O_2$,C,61.22;H,9.18;N,21.42)

Table1: Spectral data of 1,8 bis (N-aryl/alkylamino1,3,4 oxadiazol-5yl) octane(3a-g)

Compound	IR Spectra(KBR $cm^{-1)}$	1H NMR(DMSO.D_6,δ)
3a	3221(NH-Stret..),2926(CH-Stret.),1600(C=N Stret.)1488(Ar-C=C Stret.,1300(C-N Stret.)1181(C-O Stret.)1221(N-N Stret)	8.0(S,2H,NH- Proton)6.5-7.6(m,8H,Ar.-H Proton)2.3(S,6H,Ar.CH_3 Proton),1.2-3.25(m,6H,$(CH_2)_8$ Proton)
3b	1223(N-N Stret.)1185(C-O Stret.,)1299(C-N Stret.)1488(Ar C=C Stret.)1600(C=N Stret.)2926(Aliphatic-CH-Stret.,3221(NH- Stret.)	1.23-1.26(m,16H,$(CH_2)_8$ Proton)2.4(s,6H,Ar CH_3-Proton)6.4-7.6(m,8H,Ar-H-Proton)8.00(S,2H,NH- Proton)
3c	1320(C-N Stret.)1180(C-O Stret.)1221(N-N Stret.)1487(Ar.C=C Stret.)1600(C=N Stret.),3221(NH Stret.),2926(Aliphatic CH-Stret.)	6.5-7.4(m,8H,Ar-H proton)2.5-(S,6H,Ar-CH_3 Proton)1.3-3.26(m,16H,$(CH_2)_8$)8.01(S,2H,NH-Proton)
3d	2932(Aliphatic C-H Stret.),1620(C=N Stret.),3221(NH- Stret. 1488(Ar.C=C Stret.)1310(C-N Stret.) 1181(C-O Stret,)1221(N-N Stret.)	2.4(S,6H,Ar.H Proton)6.5-7.7(m,8H,Ar.HProton)8.01(S,2H,NH-Proton)1.2-3.25(m,16H,$CH_2)_8$ Proton)
3e	1181(C-O Stret.),1600(C=N Stret.)3221(NH-Stret.),2922(Aliphatic CH- Stret.)1218(C-O Stret.)1488(Ar.C=C Stret.)1320(C-N Stret.)	1.2-3.25(m,16H,$(CH_2)_8$)8.01(S,2H,NH-Proton) 6.4-7.4(m,8H,Ar-H Proton)2.3(s,6H,Ar-CH_3,Proton)
3f	1620(C=N Stret.)2930(Aliphatic CH-Stret.)1488(Ar.C=C Stret.)1300(C-N Stret.)1181(C-O Stret.)1221(N-N Stret.)3221(NH-Stret.)	8.01(S,2H,NH- Proton)6.5-7.6(m,8H,Ar-H Proton)2.3(s,6H,Ar-CH_3 Proton)1.2-3.25(m,16H,$(CH_2)_{8)}$
3g	2926(Aliphatic -CH Stret.)3223(NH-Stret.)1601(C=N Stret.)1300(C-N Stret.)1480(Ar-C=C Stret.)1181(C-O Stret.)1221(N-N Stret.)	2.4(S,6H,Ar-CH_3)1.5-3.26(m,16H,(CH2)8)8.02(S,2H,NH-)6.5-7.6(m,8H,Ar-H)

General procedure for the synthesis of 1,8 bis (2 aryl/alkylamino3,3, diacetyl1,3,4 oxadiazole- 5yl)octane(4).

In a round bottom flask (10ml) a mixture of 1,8 bis -2-aryl/alkylamino 1,3,4 oxadiazole-5yl octane(3)(0.01mole)acetic anhydride(0.02mole) and glacial acetic acid was gradually added with magnetic stirring. After two hours of stirring crushed ice was added to the solution in a similar manner. Compound 4a-g were synthesized and the resultant solid was seperated ,dried and recrystalised from aqueous ethanol.**4a(72%)m.p**185(Found:C,66.32;H,6.62;N,16.63,Calcd.for$C_{30}H_{36}N_6O_4$ C,66.17;H,6.61;N15.44),**4b**(78%)m.p192(Found:C,C,66.07;H,6.70;N,15.72 Calcd.$C_{30}H_{36}H_6O_4$,C,66.17,;H,6.61;N,15.44)**4c**(84%)m.p181(Found,C,66.12;H,6.80;N,15.06, Calcd.for$C_{30}H_{36}N_6O_4$C,66.17;H,6.61;N,15.44)**4d,(78%)**m.p171(Found:C,64.92;H,6.80;N,16.30,Calcd.for$C_{28}H_{32}N_6O_4$,C,65.11;H,6.20;N,16.27)**4e**(70%)m.p197(Found:C,57.03;H,5.05;N,14.36Calcd.for$C_{28}H_{30}N_6O_4Cl_2$,C,57.43;H,5.12;N,14.36)**4f**(87%)m.p191(Found:C,57.12:H,5.16

:N,14.12,Calcd.for$C_{28}H_{30}N_6O_4Cl_2$,C,57.43;H,5.12;N,14.37)**4g**(76%)m.p200(Found:C,60.10; H,8.72;N17.07.Calcd.for C,60.10;H,8.72;N,17.07).

Table II: Spectral data of 1,8 Bis (N-arylimino3,3,diacetyl 1,3,4 oxadiazol-5-yl) Octane (4a-g)

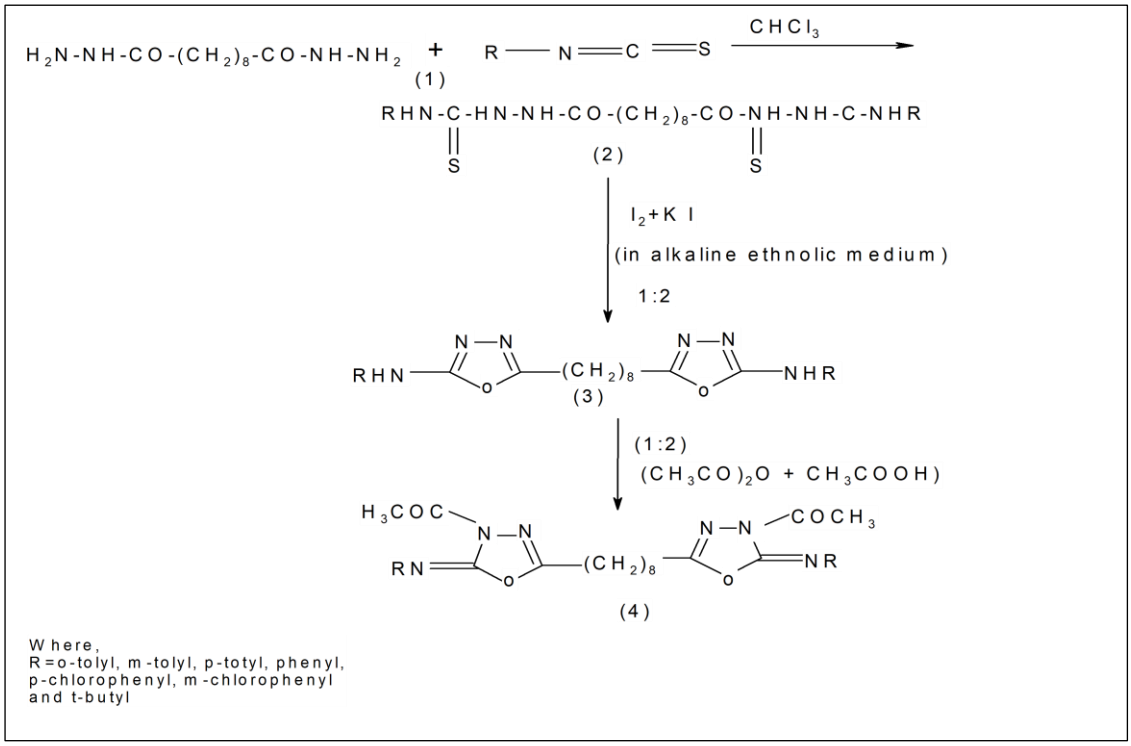
Compound	IR Spectra (KBR cm^{-1})	1^H NMR(DMSO.D_6,δ)
4a	2926(Aliphatic CH-Stret.1600(C=N Stret.)1488(Ar-C=C)Stret,1300(C-N Stret.)1650(C=O Stret,1221(N-N Stret.)	1.23-3.41(m,8H,Ar-HProton),7.1-7.2(m,8H,Ar-HProton),2.66(S,6H,ArCH_3-Proton),2.17(S,6H,$COCH_3$)Proton))
4b	1220(N-N Stret.)1640(C=O Stret).1300(C-N Stret.)1488Ar C=C Stret.)1600(C=N Stret.)2927(Aliphatic-CH-Stret.)	1.23-3.41(m,16H,$(CH_2)_8$ Proton.2.70(S,6H Ar.CH_3 -Proton),7.2-7.4(m,8H,Ar-H-Proton).2.66(s,6H),2.17(S,CO-CH_3gr.)
4c	1320(C-N Stret.,1660(C=O Stret.)1221(N-N Stret.,1488(Ar.C=C Stret.)1600(C=N Stret).2930(Aliphatic CH-Stret.)	6.5-7.4(m,8H.Ar-H Proton),2.70,(S,6H,Ar-H Proton),1.23-3.4(m,16H$(CH_2)_8$),2.19(s,6H,CO-CH_3 Proton)
4d	2930(AliphaticC-H Stret.)1600(C=N Stret.).1488(Ar.C=C Stret.)1312(C-N Stret.),1652(C=O Stret.,1222(N-N Stret.)	2.66(s.6H,Ar-CH_3 Proton)7.1-7.2(m.8H.Ar-HProton),2.17(S,6H,CO-CH_3 Proton),1.24-3.41(m,16H,$(CH_2)_8$ Proton)
4e	1650(C=O Stret.),1600(C=N Stret.)2930(Aliphatic CH-Stret.),1224(N-N Stret.),1488(Ar.C=C),1318(C-N Stret.),	1.22-3.42(m,16H.$(CH_2)_8$,)7.1-7.2(m.8H,Ar-H Proton),2.16(s,6H,CO-CH_3 Proton)
4f	1616(C=N Stret.),2932(Aliphatic CH- Stret.)1490(Ar.C=C Stret.,1321(C-N Stret).1645(C=O Stret.)1221(N-N Stret.)	7.00-7.2(m,8H,Ar-H Proton)2.29(S,6H,CO-CH_3 Proton),1.23-3.40(m,16H,()$CH_2)_8$
4g	2926(AliphaticCH-Stert.),1601(C=N Stret.)1300(C-N Stret.),1480(Ar.-C=CStret.)1621(C=O Stret.)1221(N-N Stret.)	2.62(S,6H,Ar-CH3)1.21-3.38(m,16H,$(CH_{2)8}$,7.1-7.4(m,8H,Ar-H),2.20(S,6H,CO-CH_3)

RESULT AND DISCUSSION:

Scheme 1 shows the order of the reaction used to synthesize the title compound. The various compounds produced' spectral and physicochemical data are provided. The combination of phenyl isothiocyanate and sebacic acid dihydrazide produced bis.Naryl/alkyl thiocarbamido sebacic acid diamide.Melting point, TLC, chemical testing, and IR and 1^HNMR spectrum data were used to establish the compound's purity and structure, respectively. The characteristic peaks of the IR spectra were CH stretching at 3080 cm^{-1}, C-O stretching at 1180 cm^{-1}, and NH stretching at 1480 $cm^{-1.}$ When ethanolic molecular iodine was combined with bis N-aryl/alkyl thiocarbamido sebacic acid diamide, 1,3,4 oxadiazol-5-yl-octane (3) was the resultant compound.Melting point, TLC, IR, 1^HNMR, and mass spectral data were

used to establish the purity of compound. IR spectra revealed the characteristic peak. Aliphatic CH-Streatching at 2926, NH-Stretching at 1221 cm-1, and C=N 1600 cm-1 stretching, Ar C=C 1488 cm^{-1} stretching, 1300 cm^{-1} for C-N stretching, 1181 cm^{-1} for C-O stretching, and 1221 cm^{-1} for N-N stretching.3,3 diacetyl 1,3,4 oxadiazol-5-yl-octane was produced when this 1,3,4 oxadiazol was treated with acetic anhydride and glacial acetic acid.The purity of compound was confirmed by melting point ,TLC,and structure was confirmed by IR,1HNMR and Mass spectra showed the characterstic peak of aliphatic CH-streatching at 2926cm-1,C=N streatching at 1600,C=C streatching at 1488cm-1,N-N streatching at 1221cm-1,C-N Streatching at 1300cm-1,C-Ostreatching 1650cm-1.The other compound (4a-g) were prepared by extending the acetylation reaction to other compound (3a-g)and gave the title compound(4a-g).

Scheme-1



ANTIBACTERIAL ASSAY:

In the present study antimicrobial activity of the synthesized compound were studied by the cup plate diffusion method.To evaluate the antibacterial activity standard drug Ampicilin.The bacterial organism used included both gram positive and gram negative strains like S.aureus, B. subtilis ,proteus vulgaris,sensitivity plate were seeded with a bacterial inoculum of $1x10^6$ CIU/ML and each (Diameter 10mm) was loaded with 0.1ml of test compound solution in DMF so that the concentration of each test compound was 100ug/ml.Which were previously dipped in different concentration of test sample and incubated for 24hrs.After incubation the diameter of the incubation zones were measured and from these values minimum inhibitory concentration biological activities were calculated.[XXIV-XXVI]

All the synthesized compound of oxadiazole in the present study showed significant activity against bacteria employed at the concentration of 100ug/ml.The zone of inhibition of synthesized compound are been summarised in the following table.

TABLE 3. Antimicrobial activity of 1,8 bis (N-aryl/alkylamino1,3,4oxadiazol-5yl) octane. (3a-g) (Diameter of inhibition zone in mm.) (Concentration 100g/ml).

Organism	**1,8 bis (N-aryl/alkylamino1,3,4oxadiazol-5yl) octane**						
	3a	3b	3c	3d	3e	3f	3g
S. aureus	+ +	+ +	+ + +	-	+ + +	-	+
B. subtilis	-	+ +	+ +	+	+	-	+
P. vulgaris	+	+	+ + +	+	+ + +	+ +	+

(-) = Inactive (12 mm and less)
(+) = Weakly active (13-16 mm)
(+ +) = Moderately active (17-20 mm)
(+ + +) = Highly active (21 mm and above)

Compound (**3c**) and (**3e**) shown much more activity against the organism s.aureus and p.vulgaris.Compound (**3b**) shown enhanced activity against s.aureus and B.subtilis.Majority of the compound were found inactive against B.subtilis. Moderately active against. S. aureus.

ANTIFUNGAL ASSAY:

The title compound (**3a-g**) were also screened for their antifungal activity using paper disc method. Paper disc used were of 6mm diameter, which were soaked in 1 and 2% solution of the compound in DMF .The tested fungus was A. Niger .the zones of inhibition were recorded after incubation for 48hrs at 35^0c .

TABLE 4. Antifungal activity of 1,8 bis (N-aryl/alkylamino1,3,4oxadiazol-5yl) octane (3a-3g) (Diameter of inhibition zone in mm) (Concentration 100g/ml).

Organism	**1,8 bis (N-aryl/alkylamino1,3,4oxadiazol-5yl) octane**						
	3a	3b	3c	D	3e	3f	3g
A. niger 1%	-	+ +	+ + +	-	-	+ + +	+ +
A, niger 2%	+ +	+	+ + +	+	+	+ + +	-

(-) = Inactive (12 mm and less)
(+) = Weakly active (13-16 mm)
(+ +) = Moderately active (17-20 mm)
(+ + +) = Highly active (21 mm and above)

Compound (3c) and (3f) were shown high activity against A. Niger where as other compound shown low to moderate activity.

CONCLUSION:

In the present study all the synthesized compound containing oxadiazol moiety were derived from different characterized by physicochemical ,spectral analysis and biological activity. All the compound were found to posses antibacterial and antifungal activity. Compound showed the significant antibacterial and antifungal activity. The result of this investigation motivates us to synthesized similar other related compound and evaluate them for a wide range of biological activity.

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