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Design, Synthesis and Characterization of Novel 1 ,3,4-Oxadiazole Dimers from Benzoic acids

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Abstract: 1,3,4-oxadiazoles are five membered heterocycles containing one oxygen and two nitrogen atoms at position 1, 3 and 4 position respectively. As with the azoles, this is also an electronegative ring system with weak basic characteristics due to the inductive effects of the extra hetero atoms. Oxadiazoles are susceptible to nucleophilic attack as because it readily undergoes ring cleavage with aqueous acid or base hence both carbon positions are substituted (2,5-disubstituted). 1,3,4-oxadiazoles can be synthesized by a number of methods but we have synthesized 1,3,4-oxadiazoles starting from benzoic acids or their corresponding esters. Benzoic acids were converted to the esters and subsequently into their hydrazides. Then oxadiazole nucleus was synthesized by oxidative cyclisation of hydrazides using phosphorus oxychloride. The structures of the compounds were confirmed by analytical techniques.
Keywords: 1,3,4-oxadiazole, Benzoic acids, Dimers, Monomers.

INTRODUCTION:

Oxadiazole nucleus is continuously drawing interest for development of newer drug moiety. Due to its wide range of activities viz. anticancer, antibacterial, antifungal, antimalarial, anticonvulsant, anti-inflammatory, etc. a steady research is going on in oxadiazole nucleus[1-7].

In recent years, a wide range of research has been done in the field of anticancer drug development. Since oxadiazole nucleus has shown quite good response as an anticancer agent, hence this nucleus has become an interest in the field of research. Among different types of oxadiazole nucleus containing molecules, many 2,5-disubstituted 1,3,4-oxadiazoles had shown better anticancer activities. One of such compound of 2,5-disubstituted 1,3,4-oxadiazole class- A-204197 had been proven useful for the treatment of neoplastic diseases in *in vivo* studies as an antimitotic agent[51]. Hence our prime target was to synthesize dimers of 2,5- disubstituted 1,3,4-oxadiazoles for potent anticancer activity.

Oxadiazole types of heterocyclic compounds contain oxygen and two nitrogen atoms. These derivatives are synthesized by both conventional as well as microwave assisted. Dimers are the molecules having two units of monomers containing same nucleus, which are either directly linked with each other or joined by a bridge of non interactive chains. Dimers are generally planner molecules, large in size hence their DNA binding site is much enlarged in comparison to the small size monomeric units of different nucleus containing molecules. These molecules generally act as DNA intercalating agents.[8-15]

Chemistry:- Substituted benzoic acids were used for the synthesis of different monomers of 2,5-

disubstituted 1,3,4-oxadiazoles. In this process, the various substituted benzoic acids were esterified by using ethanol and conc. H_2SO_4 and refluxed for 4 hour.In the next step, these synthesized esters were converted to corresponding hydrazides using hydrazine hydrate and ethanol by refluxed for 4 hour. These hydrazides were cyclized with substituted benzoic acids in the presence of phosphorus oxychloride and toluene refluxed for 8 hour to get the monomeric units containing oxadiazole nucleus. The dimers of different 2,5-disubstituted 1,3,4-oxadiazole monomers were synthesized by $sncl_2$ and methanol for 4 hour.

EXPERIMENTAL:

Material and Methods

Reagents, starting materials and solvents were purchased from common commercial suppliers (CDH, S.D. Fine, Loba, E. Merch, Lancaster, etc

The melting points were determined in open capillary method on a Jindal melting point apparatus and are reported uncorrected. 1H NMR spectra were recorded in MeOD (unless otherwise indicated) on a Bruker DRX-300 spectrometer with Me_4Si as the internal standard. IR absorption spectra were recorded on Jasco FT/IR - 470 PLUS, using KBr by diffuse reflectance method. Mass spectra were recorded on a Waters ZQ 4000 spectrometer operating in the electrospray (ES) mode. UV-absorption studies were done on Shimadzu Pharmaspec-UV 1700 spectrophotometer to find out λ_{max} of the compounds. The elemental analysis (CHN analysis) was done on a Perkin Elmer CHN rapid analyzer. All the compounds gave satisfactory analysis within ± 0.4% of the theoretical values**.** The purity and the reactions progress were monitored by thin layer chromatography using silica gel-G on glass plate as stationary phase and different polarity of solvents as mobile phase. Visualization was accomplished with UV light and/or iodine vapour. Compounds were named following IUPAC rules as applied by AUTONOM, PC software for nomenclature in organic chemistry.

Synthesis of DOXD-01

Dimer (DOXD-01) [1] was synthesized from oxadiazole monomer OXD-A. The monomer (2.3 gm, 8 mmol) was taken with 3.136 gm of potassium carbonate (32 mmol) and 40 ml of dry DMF in a round bottom flask. To this mixture, 0.34 gm of dichloromethane (4 mmol) was added and the mixture was stirred at room temperature for approximately 30 hr. Once the reaction was completed, the reaction mixture was poured into 80 ml of water and this aqueous solution was extracted with diethyl ether (20 ml × 3). The extracts were combined and washed with cold water (20 ml × 5) and brine solution (20 ml × 4) then passed through dried sodium sulphate. The organic solvent was evaporated to get dimer product and was dried and recrystallised, and yield of DOXD-01 was 11.78%.. TLC was monitored with petroleum ether : Ethyl acetate (9:1).

Synthesis of DOXD-02

Dimer (DOXD-02) [2] was synthesized from oxadiazole monomer OXD-A. The monomer (2.3 gm, 8 mmol) was taken with 3.136 gm of potassium carbonate (32 mmol) and 40 ml of dry DMF in a round bottom flask. To this mixture, 0.748 gm of dibromoethane (4 mmol) was added and the mixture was stirred at room temperature for approximately 30 hr. The compound was separated from the mixture as per the earlier procedure. and yield of DOXD-02 was 18.51%.. TLC was monitored with petroleum ether : Ethyl acetate (9:1).

Synthesis of DOXD-03

Dimer (DOXD-03) [3] was synthesized by simultaneous synthesis of two oxadiazole nucleus in a bicarboxylic acid compound by the process similar to the synthesis of oxadiazole monomers described earlier. For the synthesis of dimer [3], terepthalic acid (1,4-dicarboxy benzoic acid) was used as the starting material. Initiatly, 3.2 gm of terepthalic acid (0.02 mol) was esterified to both of its acidic group by refluxing it with 0.4 mol of ethanol for 4 hr in the presence of few drops of conc. H_2SO_4. Then the ester (2) was converted to its corresponding hydrazide (3) by refluxing 2.22 gm of it with 0.03 mol of hydrazine hydrate in the presence of ethanol for 4 hr. In the next step, 1.94 gm of the hydrazide of terepthalic acid (0.01 mol) was cyclized by refluxing it for 8 hr in the presence of 3.6 gm of 3,5-dimethoxy benzoic acid (0.02 mol) and 0.5 mol of $POCl_3$ in toluene as solvent to get the dimer . and yield of DOXD-03 was 72.72%.. TLC was monitored with petroleum ether : Ethyl acetate (9:1).

Synthesis of DOXD-04

Dimer (DOXD-04) [4] was also synthesized by the similar way as that of the dimer [3] using aliphatic dicarboxylic acid ester – diethyl malonate (1) as the starting material. The ester was converted to its corresponding hydrazide (2) by refluxing 1.6 gm (0.01 mol) of it with 0.015 mol of hydrazine hydrate in the presence of ethanol for 4 hr to get white coloured product. In the next step, 1.32 gm of the hydrazide of diethyl malonate ester (0.01 mol) was cyclized by refluxing it for 8 hr in the presence of 3.0 gm of 4-methoxy benzoic acid (0.02 mol) and 0.5 mol of $POCl_3$ in toluene as solvent to get the dimer . and yield of

DOXD-04 was 74.41%.. TLC was monitored with petroleum ether : Ethyl acetate (9:1).

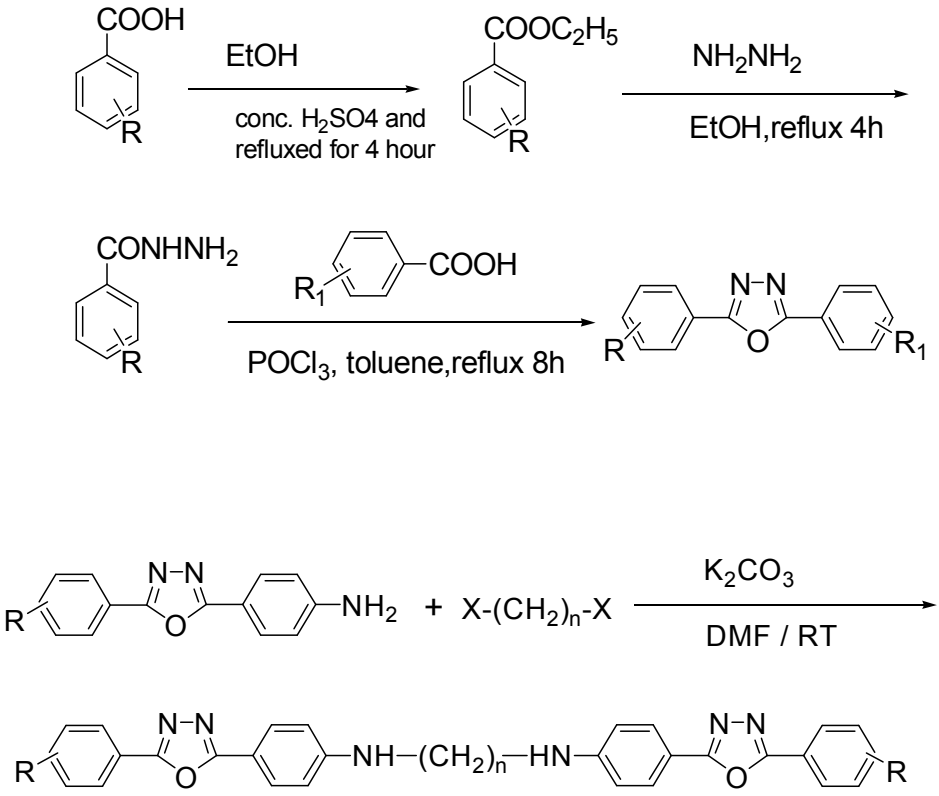
Synthesis of DOXD-05

Dimer (DOXD-05) [5] was synthesized by coupling the monomer OXD-B and monomer OXD-C by ether linkage in the presence of microwave radiation. Both OXD-B (1.43 gm, 0.005 mol) and OXD-C (1.3 gm, 0.005 mol) were taken in a flask along with 1.9 gm (0.02 mol) of K_2CO_3 and few ml of DMF. The mixture was then placed in a microwave apparatus at 80% intensity and the reaction was allowed to continue for 6 min with interval of 2 min after every exposure of 1 min. After completion of the reaction, the reaction mixture was cooled and poured into ice cold water to get the precipitate of the product. The precipitate was dried and recrystallised. and yield of DOXD-05 was 66.67%.. TLC was monitored with petroleum ether : Ethyl acetate (9:1).

Synthesis of DOXD-06

Dimer (DOXD-06) [6] was synthesized by treating monomer OXD-A with ethyl acetoacetate in microwave radiation. Monomer OXD-A (2.97 gm, 0.01 mol) was taken in a flask along with 1.3 gm of ethyl acetoacetate and few ml of triethylamine. This mixture was then placed in a microwave apparatus at 20% intensity and the reaction was allowed to continue for 8 min 30 sec with interval of 2 min after every exposure of 1 min. After completion of the reaction, the reaction mixture was cooled and poured into ethanol to get the precipitate of the product. The precipitate was dried and recrystallised. and yield of DOXD-06 was 57.14%.. TLC was monitored with petroleum ether : Ethyl acetate (9:1).

Scheme 1: synthesis of 1,3,4 oxadiazole monomer and dimer



R= NO_2, Cl, OH, C_2H_5COO

Table 1: Molecular structure and IUPAC name of the synthesized compounds

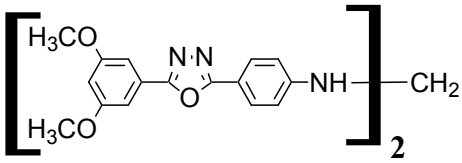
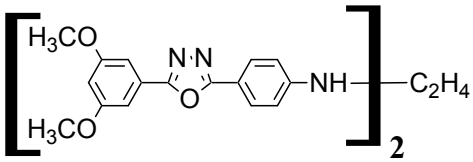
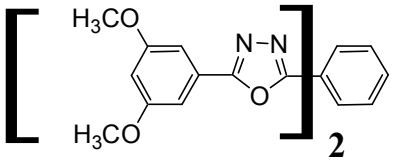
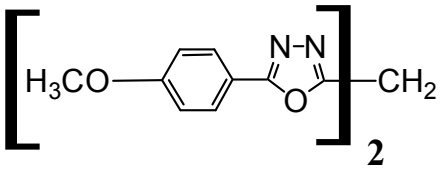
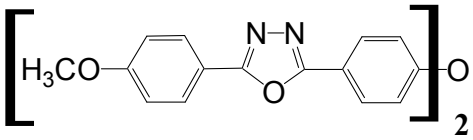
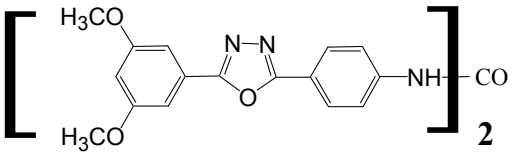
Code	IUPAC Name	Structure
DOXD-01	Bis-{4-[5-(3,5-dimethoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amino methane.	
DOXD-02	Bis-{4-[5-(3,5-dimethoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amino ethane.	
DOXD-03	1,4-Bis-[5-(3,5-dimethoxy-phenyl)-1,3,4-oxadiazole-2yl] benzene.	
DOXD-04	Bis-[5-(p-methoxy-phenyl)-1,3,4-oxadiazol-2-yl] methane	
DOXD-05	Bis-4-[5-(4-methoxy-phenyl)-[1,3,4] oxadiazol-2-yl]-phenyl ether.	
DOXD-02	1,3-Bis-4-[5-(4-methoxy-phenyl)-[1,3,4] oxadiazol-2-yl]-phenyl urea.	

Table 2: Physicochemical characters of the synthesized compounds

Compound Code	Melting Point ^{o}C	Rf Value	% Yield	λ_{max} nm	
				$CHCl_3$	DMSO
DOXD-01	182	0.65	11.78	309.0	-
DOXD-02	189	0.60	18.51	306.5	-
DOXD-03	241	0.58	72.72	-	286.5
DOXD-04	143	0.51	74.41	259.5	-
DOXD-05	154	0.47	66.67	-	305.0
DOXD-06	359	0.54	57.14	-	293.5

Table 3: Spectrocopial data of the 1,3,4 oxadiazole derivatives.

Compound Code	SPECTRAL DATA
DOXD-01	**IR (KBr/Cm^{-1}) : 1042(C-O-C),1064(Ar C-O-C Aliphatic),1308(CN),2935(C-H),1541(C=N),3333(NH)** **^{1}H NMR(300MHz, δ/ppm in MeOD$_4$):** δ 6.6(m,14H,Benzene),4.2(t,2H,NH),3.8(s,12H,OCH$_3$),1.3(t,2H,CH$_2$)
DOXD-02	**IR (KBr/Cm^{-1}) : 1159(C-O-C),1312(C-N),2920(CH),1541(C=N),3451(N-H)** **^{1}H NMR(300MHz, δ/ppm in MeOD$_4$):** δ6.6(m,14H,CHBenzene),3.8(t,2H,NH),3.72(s,6H,OCH$_3$),1.5(t,4H,CH$_2$)
DOXD-03	**IR (KBr/Cm^{-1}) : 1020(C-O-C),1269(Ar C-O-C-Aliphatic),2986(CH),1540(C=N),**
DOXD-04	**IR (KBr/Cm^{-1}) :1026(C-O-C),1267(Ar C-O-C-Aliphatic),2986(C-H),1540(CN)** **^{1}H NMR(300MHz, δ/ppm in MeOD$_4$):6.9(m,8H,CH Benzine),3.8(s,6H,OCH$_3$),2.2(s,2H,CH$_2$)**
DOXD-05	**IR (KBr/Cm^{-1}):963(C-O-C Sym),1073(C-O-C),1070(Ar C-O-C Aliphatic),1541(CN)** **^{1}H NMR(300MHz, δ/ppm in MeOD$_4$):** 7.0(m,16H,CH Benzine),3.8(s,6H,OCH$_3$)
DOXD-06	**IR (KBr/Cm^{-1}) :999(C-O-C),1338(C-N),1540(C=N),1679(C=O),3415(N-H)**

RESULTS AND DISCUSSION:

All compounds were in conformity with the structure envisaged by spectral data (UV, IR, H^{1}NMR, Mass and Elemental analysis) (Table 3). In mass spectral analysis, all the synthesized molecules showed molecular ion (M$^+$) peak characteristic of their molecular weight which confirms their formation. The structures of the synthesized compounds were elucidated from the results obtained from various characterizations,I.e UV, IR, H^{1}NMR, Mass and Elemental analysis . The TLC of these synthesized compounds was done by using silica gel G glass plates and petroleum ether:ethyl acetate mixture (8:2) as developing solvent. After developing the chromatograms in iodine chamber, the R_f value were calculated and the results obtained show that all these synthesized compounds have entirely different R_f values. λ_{max} of the compounds were measured by dissolving in suitable solvents and the λ_{max} of each compound was determined, IR spectra of the compounds were obtained by IR spectrophotometer using IR standard potassium bromide as reference. Various peaks obtained for different functional groups of individual compounds. PNMR spectra of the samples were determined using TMS (tetramethyl silane) as internal reference in instrument BRUKER AVANCE II 400 spectrometer. Mass spectra of the samples were determined by LC-Mass spectroscopic analysis in instrument Varian Inc. 500 MS Ion Trap.

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