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Preparation, characterization and biological activity studies of benzoxaizne derivatives

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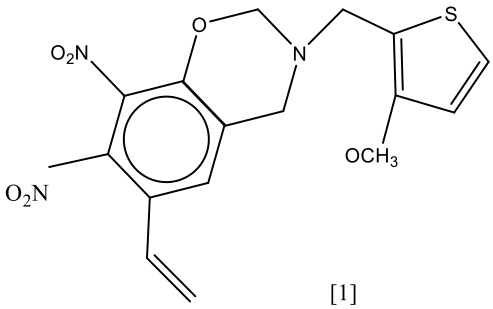
Abstract
Two new benzoxazines were synthesized by treatment of 4-hydroxy-2,3 dinitrostyrene with 1-(3methoxythiophene-2-yl)- N-methylmethanamine and 2-amino-3,4,5trimethoxyphenol with oxalyl chloride.
The new benzoxazine derivatives were checked by different spectral techniqur (IR,[1] H-NMR, MS and elemental analysis) the new compounds (c-1) and (c-2) were studied for antibacterial and antifungal activities.

Keywords: Benzoxazine, synthesis, biological activity

Introduction
Benzoxazines show a wide range of biological activity which are key molecules for the synthesis of various pharmaceutical agents as antifungal [1], antimicrobial [2]. There are only few reports suggesting the antimicrobial properties of benzoxazine derivatives so for [3, 4]. However, the primary benzoxazine is insoluble which may affect its application in the field of biology. Herein, carbon dots derived from benzoxazin monomers (BZM-CDs) were designed, and their effect in blocking the (JEV, ZIKV and DENV) and non eveloped virues (porcine parvovirus, PPV and adeno virus associated virus, AAV) were ill equipped to infect the cultured cells. It was observed that BZM-CDs directly interacted with virious, which in turn, prevented the entry of virions into the host cell.these suggested the broad spectrum
Therapeutic potential of benzoxazine monomer derived nanoparticles against phylogenetically related and unrelated viruses [5, 6]. benzoxazines derivatives. recently, rick Morrison and co-workers discovered that 2-morpholino-substituted -1,3 benzoxazine compounds exhibit high to moderate DNA-PK inhibition activity (Ca. 0.28-6.80 μMIC_{50}). The most potent compound found in the series was pyridine -3yl methoxy derivative (L-27) with an IC_{50} =0.28 μM [7]. Benzoxazine derivatives also display various biological activities such as anticancer [8], antimicrobial [9], antifungi [10], antiplatelet [11], and antituberculosis activities [12].

Experimental part
Instrumentation
All melting points were measured on a Gallenkamp melting apparatus and uncorrted.The IR spectra of compounds were recorded on shimadzu IR Affinity FTIR spectrophotometer using KBr discs and the values are expressed inδ cm^{-1}. The ^{1}H-NMR spectra of compound were recorded on Bruker Avance 400 MHz NMR spectrophotometer using DMSO as an internal standard and the values are expressed in δ ppm. The elemental analyasis of the compounds were recorded on a perkin – Elmer 2400 CHN elemental analyzer.
The mass spectra were recorded on a GCMS-QP-1000EX mass spectrometer at (70ev). All the chemical reactions were monitord by TLC.
Synthesis of 7, 8 dinitro -6- vinyl -3 {3methoxy (2 methyl amino) thiophene-1.3benzoxazine (C-1).
Amixture of 4-hydroxy - 2, 3 dinitrosyrene (8, 7 gm, 50mmol) paraformaldehyde (1, 5gm, 50mmole) and 1-(3methoxythiophene- 2- yl) –N- methylmethanamine (7,85gm, 50mmole) in DMF (100ml) was heated under reflux for 8hrs. The reaction mixture was cooled.the solid that separated was filtered off, dried and recrystallized from ethanol to give (C-1)

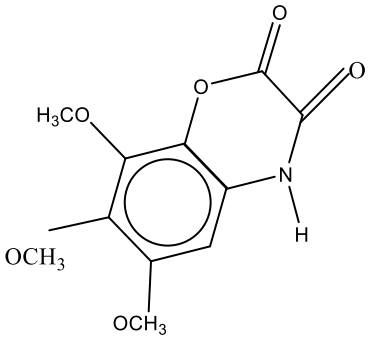


[1]

Fig 1: 7, 8 dinitro -6- vinyl -3 {3methoxy (2 methyl amino) thiophene-1.3benzoxazine (C-1).

Synthesis of 5, 6, 7 trimethoxy {1, 4} benzoxazine -2, 3 diones (C-2):

In around bottom flask 250ml dissolve (16,3gm,0.1mole) of 2-amino-3,4,5 trimethoxyphenol in 100ml ethanol then add (12,6gm,0.1mole) of oxalyl chloride, stirr the mixture at room temperature for 2hrs then add 2ml of piperidine. The mixture was heated to reflux for 10hrs and keep overnight. The solide was separated by filtration. The solid was recrystallized from ethanol.



[2]

Fig 2: 5, 6, 7 trimethoxy {1,4} benzoxazine -2,3 diones (C-2)

Results and discussion:

Spectroscopic studies of 7, 8 dinitro – 6- vinyl – 3 – (3-methoxy (2methyl amino) thiophene -1,3 benzoxazine (C-1):

The infrared spectrum of (1) table (2) exhibit a strong band at 1640cm^{-1} due to ע (C=C), the short string band observed at 945cm^{-1} assigned toע (C-S-C) stretching of thiophene ring.

The peaks noticed at 3079 and 3034 cm^{-1} are assigned to ע CH stretching of aromatic ring. Furthermore, the IR spectrum displayed two bands at 1023 and 1218 cm^{-1} due to (C-O-C), and the peak at 1179 cm^{1} due to (C-N-C).

The ^{1}HNMR spectrum of (C-1) in deuterated DMSO showed a singlet singlet at 3,71ppm due to OCH_3, the new peaks at 396ppm and 4,99 ppm are assigned to the Ar-CH_2- N and O-CH_2-N in oxazine ring, respectively. Furthermore, a singlet signal at 3.25 ppm due to (CH_2) also the ^{1}HNMR spectrum exhibit doublet signal at 7,41 and 7,72 ppm due to protons of thiophene ring, as well as multiplets in range 7,08-7,23 ppm due to phenyl protons. moreover, the ^{1}H-NMR spectrum of compound (C-1) displayed triplet signal at 6,80 ppm due to (CH= CH_2) and doublet signal at 6,53 ppm due to (-CH=CH_2). The mass spectrum of compound (1) showed the absence of the moleculr ion peak [M] $^{+}$ at m/e 378 (86.24%) for formula $C_{16}H_{16}N_3SO_6$. Furthermore, the abserved fragmentation peaks 359 (32, 19%), 352 (49, 23%), 348(65, 36%), 332 (54, 10%), 266 (83, 29%), 251(2, 14%), 128(100%), 78(44, 07%).

Spectrscpic studies of 5, 6, 7 trimethoxy (1, 4) benzoxazine – 2, 3 diones (C-2):

The infrared spectrum of (2) table (2) displayed a strong band at 1665cm^{-1} corresponding to ע (C=O) (lactone),as well as the IR spectrum exhibited absorption band at 3218cm^{-1} due to (N-H). the ^{1}H-NMR spectrum of the (C-2) in deuterated DMSO-d_6 table (2)exhibited from low field to high field, the following signals (δ /ppm): 8,13(S,H,NH),7,65(S,1H,Ar-H)and 3,81(3S,9H,3OCH_3).

The mass spectrum of compound (2) exhibited the molecular ion peak [M]$^{+}$ at m/e 253 (67%) indicating the molecular formula $C_{11}H_{11}NO_6$, beside other fragemnts which are in accordance with the proposed structure 238(44%), 223(45%), 193(71%),163(80%),149(93%).77(100%).

Biological activity

Measurement of antimicrobial activity using diffusion disc method:

Antibacterial and antifungal activities of some synthesized compound were screened using the disc diffusion method. All the tested compounds showed antibacterial and antifungal activity and these activities were compared to standard amoxicillin, the results of antimicrobial studies are given in table 3, the antimicrobial activity of newly synthesized benzoxazines was conducted against gram positive and gram negative groups namely staphylococcus aureus and Escherichia coli respectively as well as Aspergillus flavus and candida albicans as tested fungi by disc diffusion method. Amoxicillin was employed as reference standard to compare the results.

Each test compare was dissolved in dimethyl sulphoxide (DMSO). The concentration of DMSO solutions was 0.1 mg/ml.

Table 1: Physical characterization of compounds

Compound No.	M.P/C°color	Solvent yield	MF(M.wt)	Elemental analysis calc/found			
				C%	H%	N%	S%
C-1	220-222	Ethanol	$C_{16}H_{15}N_3SO_6$	50,78	4,26	11,10	8,47
	Yellow	79	378,381	50,11	3,76	10,88	7,91
C-2	184-186	Ethanol	$C_{11}H_{11}NO_6$	52,17	4,37	5,53	
	Brown	90	253,208	51,82	3,95	4,79	

Table 2: Spectroscopic for (c-1) and (c-2)

Compound No.	IR(KBr) עcm^{-1}	^{1}HNMRδ(PPm)	MS,Mm/z (%) relevan
C-1	עC=C 1640 עC-S-C945 עC-O-C1023 1218 עC-N-C 1179	3,71(S,3H, OCH_3) 3,96(S,2H, Ar, CH_2N) 4,99(S,2H, O-CH_2-N) 3,25(S,2H, CH_2) 7,41;7,72(d-thiophen ring) 7,08-7,23(m,1H, Ar-H) 6,80(t,2H, CH=CH_2) 6,53(t,1H, CH=CH_2)	378(86, 24%) 359(32,19%),352(49,23) 348(65,36%),332(54,10%) 266(83,29%), 251(27,14%), 128(100%), 78(44,07%)
C-2	עN-H3218 עC=O1665(Lacton)	8,13(S, H, NH) 7,65(S,1H, Ar-H) 3,81(3S,9H,3OCH_3)	378(86,24%),359(32,19%) 352(49,23%),348(65,36%),332(54,10%), 266(83,29%),251(72,14%), 128(100%), 78(44,07%)

Table 3: The inhibition zone diameter of some benzoxazine derivatives

Sample/ standard	Inhibition zone diameter (mm/mg sample)			
	***Staphylococcus aureus* (G+)**	Escherichia coli **(G-)**	***Candida albicans* (fungus)**	***Aspergillus***
c-1	21	23	16	12
c-2	17	20	0.0	0.0
Amoxicillin	30	32	24	21

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