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Synthesis and Characterization of New Coumarin Derivatives and Evaluating of its Biological Activity

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Abstract : Nine compounds of N, N substituted diquinolinone-2 were synthesized from the reaction of coumarin with diamines (4,4'-sulfonyldianiline,6-methyl-1,3,5-triazine-2,4-diamine, 6-phenyl-1,3,5-triazine-2,4-diamine, pyridine-2,6-diamine, 4-methylbenzene-1,3-diamine, 2,6-diaminopyrimidin-4-ol,1,2,4-triazole-3,5-diamine, 4,4'-methylenedianiline). The structural formula of the synthesized compounds was confirmed by physical and spectroscopic methods(^{1}H- NMR, ^{13}C- NMR, I.R, UV-VIS, elemental analysis, and mass spectral data) .The synthesized compounds were screened for their antibacterial activity against four microorganisms *Staphylococcus aureus, Bacillus. subtilis, Escherichia Coli* and *Klebsiella pneumonia,* and they were found to exhibit good to moderate antibacterial activity.
Keywords: Coumarin, diamine, Antibacterial activity, *E. coli*, *K. pneumonia, S. aureus, B. subtilis.*

Introduction

Coumarins and its derivatives represent one of the most active classes of Heterocyclic compounds, possessing a wide spectrum of biological activities[1].It has stimulated extensive research in biology, organic chemistry and medicine, due to their antibiotic, anti-coagulant[2,3],anticancer[4], anti-inflamatory[5],and anti-HIV properties. A number of natural or synthetic derivatives of coumarin have found pharmaceutical applications[6],Coumarins are nowadays an important group of organic compounds that are used as additives to food and cosmetics[7], optical brightening agents[8],and dispersed fluorescent and laser dyes. The derivatives of coumarin usually occur as secondary metabolites present in seeds, roots and leaves of many plant species. Their function is far from clear, though suggestions include waste products, plant growth regulators[9].Therefore,it is utmost importance, that the synthesis of coumarin and its derivatives should be achieved by a simple and effective method. The synthesis of this heterocyclic nucleus is of current interest. Coumarins have been synthesized by several methods including Von Pechman, Knovenagel, and Reformatsky reactions[10]. 2-quinolone derivatives were found to be associated with various biological activities such as antitumor[11],antimalarial[12],antiplatelet[13], antidepressant[14],antiulcer[15], plant virucides[16,17], antioxidant activity[18], and herbicides[19].Many substituted quinoline-2-one derivatives have recently craned great interest in chemotherapy as anti-tumor drugs[20,21].Alsoa number of quinolones are excellent reservoir of bioactive substances[22]. 2- Quinolones are also valuable intermediates in organic synthesis; since they are easily converted into 2-chloro and 2-aminoquinoline derivatives[23].Some Schiff bases bearing heterocyclic residues possess biological activities, such as analgesic, antiviral, antifungal and anticancer[24].Transition metals have varying utility and interesting chemistry. Coordination compounds are important due totheir role in biological and chemical systems in various ways.

Material and Methods

General Procedures

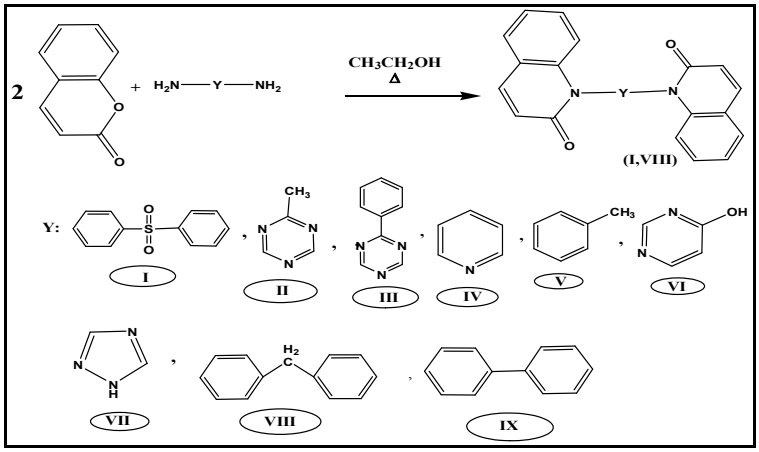
Melting points were determined in open glass capillaries on Agallenkamp apparatus and are uncorrected.TLC was performed to assess the reactions and the purity of the products.IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar-330 FT-IR spectrometer and noteworthy absorption values (cm^{-1}) alone are listed.^{1}H and ^{13}C NMR Spectra were recorded at 400 MH_ZBruker AMX using $CDCl_3$ as solvent .The ESI+ve MS spectra were recorded on a Bruker Daltonics LC-MS Spectrometer .Satisfactory microanalysis was obtained on carloErba 1106 CHN analyzer.

Chemical and Starting Materials

Coumarin, diamine :4 ,4'-sulfonyldianiline ,6-methyl-1,3,5-triazine-2,4-diamine ,6-phenyl-1,3,5-triazine-2,4-diamine,pyridine-2,6-diamine,4-methylbenzene-1,3-diamine,2,6-diaminopyrimidin4-ol, 3,5-Diamino-1,2,4-triazol,4,4'-methylenedianiline, Ethanol all materials from sigma-aldrich.

General procedure for synthesis of N, N substituted diquinolinone-2 (I-VIII):

2.92gr(0.02 mole)Coumarin, 2.48 gr (0.01 mole) 4,4'-sulfonyldianiline ,1.25gr (0.01mole)6-methyl-1,3,5-triazine-2,4-diamine, 1.87gr(0.01mole)6-phenyl-1,3,5-triazine-2,4-diamine,1.09gr (0.01mole)pyridine-2,6-diamine,1.22gr(0.01mole)4-methylbenzene-1,3-diamine,1.26 gr (0.01 mole) 2,6-diaminopyrimidin-4-ol,0.99 gr (0.01 mole) 3,5-Diamino-1,2,4-triazol,1.98 gr (0.01 mole)4,4'-methylenedianiline were refluxed in (50 ml) Ethanol for (12) hrs. The reaction mixture was filtered off while hot and the filtrate was allowed to cool .The solvent was evaporated to dryness and the residue was recrystallized from methanol (Scheme**1**).The Tables (**I, II, III, IV**) showed physical properties, elemental analysis data and spectral data.

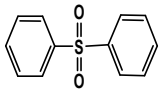
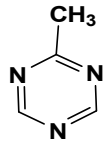
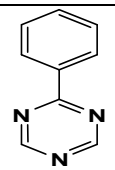
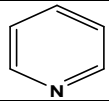
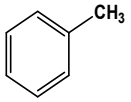
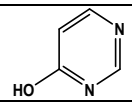
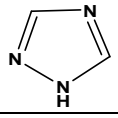
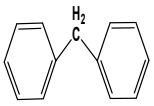
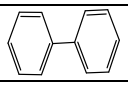


Scheme (1) Synthesis of coumarin derivatives

Antimicrobial activity

All newly synthesized compounds were test for their in vitro growth inhibitory activity against a standard strain of pathogenic microorganism including Gram –positive bacteria and Gram - negative bacteria (*Escherichia coli,Bacillus*)Antibacterial activity was done by the disk diffusion method[25].*Bacillus subtilis*, *Escherichia Coli and Klebsiella pneumonia* were sub cultured in BHI medium and incubated for 18hrs at 37°C, and then the bacterial cells were suspended, according to the McFarland protocol in saline solution to produce a suspended of about 10^{-5}CFU ml^{-1}, 10µL of this suspension was mixed with 10 mL of sterile antibiotic agar at 40°C and poured onto an agar plate I a laminar flow cabin. Five paper disks(6.0mm diameter) were foxed onto nutrient agar plate. One mg of each test compound was dissolved in 100 mL DMSO to prepare stock solution from stock solution different concentration 100,250,500,1000 ppm of each test compound were prepared . These compounds of different concentration were poured over disk plate on to it. Streptomycin was used as standard drug (positive control) DMSO poured disk was determined by the formation of an inhibitory zone after 24hrs of incubation at 37°C. **Table1** reports the inhibitory zones (mm) of each compound and the control.

Table (I): Physical properties of compounds (I-IX).

Comp. No.	Y	M.P (^oC)	Yield (%)	Molecular Weight	Molecular formula	color	U.V($CHCl_3$) λ max (nm)
I		**244**	**70**	504	$C_{30}H_{20}N_2O_4S$	yellow	295
II		**278-280**	**65**	381	$C_{22}H_{15}N_5O_2$	White	298
III		**234**	**75**	443	$C_{27}H_{17}N_5O_2$	white	300
IV		**245**	**60**	365	$C_{23}H_{15}N_3O_2$	white	310
V		**360**	**70**	378	$C_{25}H_{18}N_2O_2$	white	280
VI		**291**	**60**	382	$C_{22}H_{14}N_4O_3$	White	316
VII		**285**	**60**	355	$C_{20}H_{13}N_5O_2$	white	317
VIII		**275**	**70**	454	$C_{31}H_{22}N_2O_2$	white	318
IX		**265**	**77**	440	$C_{30}H_{20}N_2O_2$	white	319

Results and Discussion

The product (I-IV) was formed from the reaction of two molecule of coumarin and mole of amine. The infrared of products exhibited characteristic peak at 1723.25 cm^{-1} due to ν (C=O) group and no absorption band due to NH_2 group. Compound (V) show absorption at (1720.60) cm^{-1}due to (C=O). Compound (VI) show absorption at (1635.23)cm^{-1}due to (C=N) The UV spectra showed λmax at 298-316.^{1}H-NMR for compounds (I-VI)shows multiple signals at (6.57-8.42ppm) due to aromatic proton of cumarin. ^{1}H-NMR for compounds (II)show single signal at (2.44ppm) due to(CH_3)group, also ^{1}H-NMR for compounds (V) show single signal at (2.12ppm) due to(CH_3)group and ^{1}H-NMR for compound (VI) show signals at (11.53ppm) due to hydroxyl proton and for compound (VII)show signal at (13.5 ppm) due to (NH) OF triazole, ^{1}H-NMR for compound (**VIII**) show signals at (3.96ppm) due to (CH_2)AND signal at (7.21,7.69,7.21) due to diphenylmethane, ^{1}H-NMR for compound (**IX**) show signals at (7.77,7.87 ppm) due to biphenyl.

^{13}C-NMR of compounds (**I-IX**) showed signals at (118-132ppm) due to aromatic carbons ofcoumarin and signal at (159.3ppm) due to C=O**.** ^{13}C-NMR spectrum of compound (**I**) showed signal at (120.1,129.2,130.9,140.9ppm) due to aromatic carbons of sulfonyl, ^{13}C-NMR spectrum of compound (**II**) showed single signal at (24.5 ppm) due to CH_3 group ,and signal at (180.7,176.8,176.8ppm) due to aromatic Carbone oftriazine.^{13}C-NMR spectrum of compound (**III**) showed signal at (127.5,129.2,131.1,134ppm) due to (Ar-TRIAZINE), and signal at (120.4,139.5,130,128,124.2,128.1,129.5,132.1) ppm due to aromatic carbons

of aromatic ring of (quinoline). ^{13}C-NMR spectrum of compound (**IV**) showed signals at (110.1,153.3,139.1,153.3ppm) due to aromatic carbons of Pyridin.^{13}C-NMR spectrum of compound (**V**) showed single signals at(17.6ppm) due to CH_3 group and signal at (159.3ppm) due to (C=O) and signals at (108.2,137.4,139.8,119.9,124.4,130.8 ppm) due to aromatic carbons of toluene, ^{13}C-NMR spectrum of compound (**VI**) showed signal at(88.9,168.5,169.1,160.2ppm) due toaromatic Carbone of pyrimidol-4,^{13}C-NMR spectrum of compound (**VII**) showed signal at (157.2ppm) due to triazole and signal at (159.3ppm) due to (C=O) and ^{13}C-NMR spectrum of compound (**VIII**) showed signal at(41.3ppm) due to (CH_2) and signal at (130.6,131,139.4,131,130.6,121.5 ppm) due to Ar of diphenylmethane,^{13}C-NMR spectrum of compound (**IX**) showed signal at (115.6,140.8,128.8,133.3 ppm) due to Ar ofbiphenyl[26, 27].

Table (II) FT-IR Spectral data for compounds (I-IX)

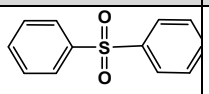
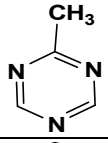
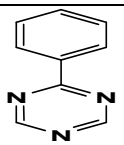
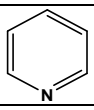
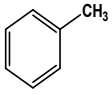
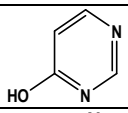
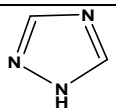
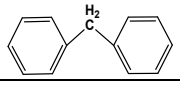
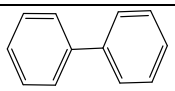
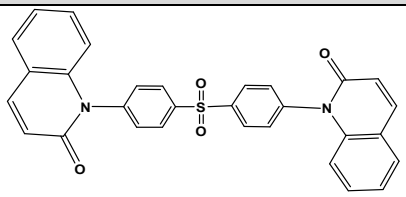
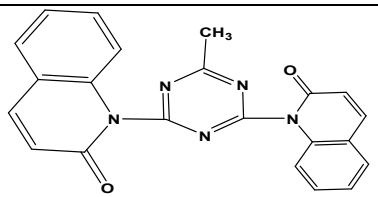
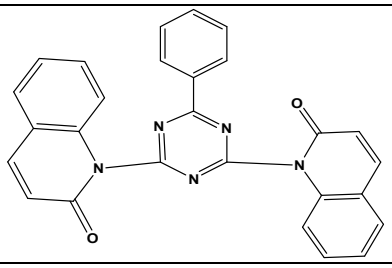
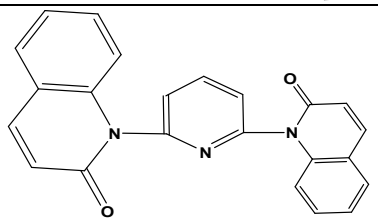
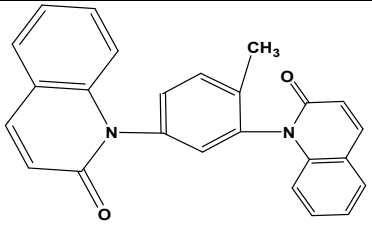
Comp. No.	Y	υ (C–H) cm^{-1}	υ(C=C) cm^{-1}	C=O	Others
I		3045	1592	1730.7	1230.36(asymmetric –SO_2-) 1155.28(symmetric-SO_2-stretch)
II		3212.4	1546.5	1711.5	
III		3145.7	1540	1735	
IV		3085	1560	1733.4	
V		3095	1465.3	1731.6	
VI		3038	1533.7	1725.5	3284.18(OH)
VII		3060.2	1483.3	1735.6	
VIII		3046.7	1537.8	1736.6	
IX		3070.6	1586.5	1737.6	

Table (III) Depicted Elemental Analysis (C.H.N) of Synthesis Compounds

Compounds	Calc.			Found		
	H%	N%	C%	H%	N%	C%
I	4	5.55	71.41	4	5.53	71.40
II	3.96	18.36	69.28	3.90	18.39	69.20
III	3.86	15.79	73.13	3.80	15.70	73.10
IV	4.14	11.50	75.60	4.10	11.43	75.40
V	4.79	7.40	79.35	4.70	7.49	78.46
VI	3.69	14.65	69.10	3.70	14.70	69.20
VII	3.69	19.71	67.60	3.70	20.70	67.80
VIII	4.88	6.16	81.92	4.65	6.15	80.98
IX	4.58	6.36	81.80	4.60	6.30	82.12

Table (IV) ^{1}H-NMR and ^{13}C-NMR spectral data for some of the prepared compounds.

Comp. No.	Compd. Structure	^{1}H-NMR spectra data	^{13}C-NMR spectra data
I		6.57,7.14,7.31, 7.36,7.76,8.42(12H,Ar-coumarin),7.81, 7.98(8H,Ar-sulfonyl)	118,128.8,127,137.1,127.5,129.5,1 39.5,120.4(16C,Ar-coumarin),159.3(2C,2C=O),120.1, 129.2,130.9,140.9(12C,Ar-sulfonyl)
II		2.44(3H,CH_3),6 .57,8.42,7.36,7. 14,7.31,7.76(12 H,Ar-coumarin)	24.5(1C,CH_3),120.4,139.5,130,128 .8,124.2,128.1,129.5,132.1(8C,Ar-coumarine), 159.3(2C,2C=O),180.7,176.8,176. 8(3C,Ar-triazine)
III		6.57,7.36,7.14, 7.31,7.76(12H, Ar-coumarin),7.41, 7.51,8.28(5H,p henyl -1.3.5-triazine)	120.4,139.5,130,128.8,124.2,128.1 ,129.5,132.1(16C,Ar-coumarin),159.3(2C,2C=O),127.5, 129.2,131.1,134.1(6C,Ar),164.6,17 7.6(3c,Ar-1.3.5-triazine)
IV		6.56,8.42,7.36, 7.14,7.31,7.76(12H,Ar-coumarin),5.92, 7.04,5.92(3H,A r-pyridin)	120.4,139.5,130,128.8,124.2,128.1 ,129.5,132.1(8C,Ar-cumrin),159.3(2C,2C=O),110,153. 3,139.1,153.5(5C,Ar-pyridin)
V		6.57,8.42,7.36, 7.14,7.31,7.76(12H,CH3),2.12 (3H,CH3),7.19, 7.43,8.01(3H,A r)	120.4,139.5,127.5,129.5,118.1,128 .8,127,137.1(16C,Ar-coumarin),159.3(2C,2C=O),17.6(1 C,CH3),108.2,137.4,139.8,119.9,1 24.4,130.8(6C,Ar)

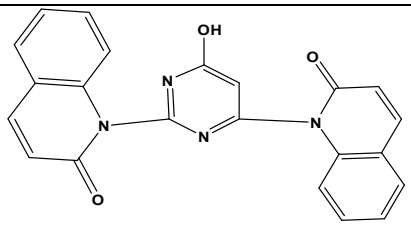
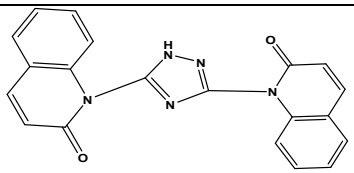
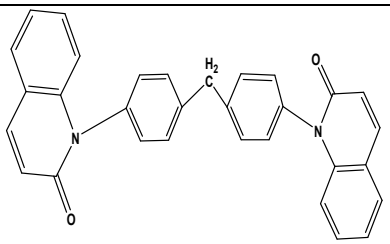
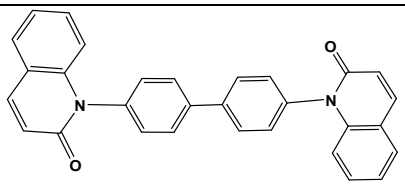
VI		6.57,8.42,7.36, 7.14,7.31,7.76(12H,Ar-coumarin),11.5 3(1H,OH-PYRIMIDINO L)	159.3(2C,2C=O),120.4,139.5,130, 128.8,124.2,128.1,129.5,132.1 (8C,Ar-coumarin), 88.9,168.5,169.1,160.2(4C,Ar-pyrimidinol)
VII		6.57,8.42,7.36, 7.14,7.31,7.76(12H,Ar-coumarin),13.5 (1H,NH)	159.3(2C,2C=O),120.4,139.5,130, 128,124,128.1,129.5,132.1(16C,Ar -coumarine) ,157.2,157.2(2C,triazole)
VIII		3.96(2H,CH_2),6 ..57,8.42,7.36,7 .14,7.13,7.76(1 2H,Ar-coumarin),7.21, 7.69,7.21(8H,A r-dipheny lmethane)	41.3(1C,CH2),130.6,131,139.4,13 1,130.6,121.5(12C,Ar-diphenylmethane),159.3(2C,2C=O),120.4,139.5,127.5,129.5,118.1,12 8.8,127,137.1(16C,Ar-coumarin)
IX		6.57,8.42,7.36, 7.14,7.31,7.76(12H,Ar-coumarin),7.77, 7.87(8H,Ar-biphenyl)	159.3(2C,2C=O),120.4,139.4,127. 5,129.5,118.1,128.8,127,137.1(16 C,Ar-coumarin),115.6,140.8,128.8,133.3 (12C,Ar-biphenyl)

Table (V) Antimicrobial activity of the prepared compounds (I-IX).

Compound	Zone of inhibition (mm)			
	Gram positive bacteria		Gram negative bacteria	
	S. aureus	***B. subtilis***	***E. coli***	***K. pneumonia***
I	**10 ± 0.16**	**7 ± 0.23**	**6.5 ± 0.18**	**6.5 ± 0.11**
II	**11 ± 0.32**	**9 ± 0.17**	**7 ± 0.14**	**7 ± 0.42**
III	**14 ± 0.22**	**13 ± 0.12**	**6.2 ± 0.33**	**7 ± 0.25**
IV	**15 ± 0.19**	**14 ± 0.34**	**6.1 ± 0.13**	**9 ± 27**
V	**12 ± 0.10**	**15 ± 0.15**	**8 ± 0.24**	**7 ± 0.09**
VI	**14 ± 0.26**	**10 ± 0.18**	**9 ± 0.37**	**7 ± 0.39**
VII	**15 ± 0.21**	**9 ± 0.11**	**9 ± 0.17**	**7.5 ± 0.27**
VIII	**16 ± 0.16**	**7 ± 0.25**	**8 ± 0.22**	**6 ± 0.14**
IX	**17 ± 0.31**	**16 ± 0.12**	**14 ± 0.33**	**7 ± 0.29**
Streptomycin*	**15 ± 0.17**	**12 ± 0.26**	**9.5 ± 0.13**	**9.5 ± 0.37**

Dataaremean ± SDofthreeindependentexperiments. * Positive control.

Antimicrobial activity

The antimicrobial activity of both categories of compounds was determined by the disc diffusion method[28]. Thein vitro antimicrobial activity was carried out in two gram positive bacteria, and two gram negative bacteria,the gram positive bacteria used were *Staphylococcus aureus* and *Bacillus subtilis*, gram negative bacteria used were *Escherichia coli* and *Klebsiella pneumonia*.The compounds were tested at a concentration of 100µg/mL in Dimethylsulfoxide. The zoneof inhibition was compared after 24 hrs of incubation at 37°C against Ciprofloxacin (100µg/ml) as standards for comparison of antibacterial activity

(Table V). In general, all synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism (*S. aureus, B. subtilis, E. coli, K. pneumonia)* peculiar against (*S. aureus, B. subtilis*).

Conclusions

The main aim of the present study is to synthesize and investigate the antimicrobial and anti-corrosion activity of new heterocyclic derivatives containing coumarin ring with the hope of discovering new structures serving as potential broad spectrum antimicrobial agents and anti-corrosion agents. Compounds (**I-IX**) which contain functional moiety is most potent against bacterial it's showed good antimicrobial activity.

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