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Synthesis, Characterization and Biological Evaluation of some 2, 3-dihydroquinazolinone coupled 5, 5-disubstituted imidazolidine-2,4-diones

[1]Bhadreshkumar R Sudani and [2]Vikas A Desai Sudani

[1]Government Engineering College, Valsad-396001, India. (Affiliated to Gujarat Technological University, Near Visat Three Roads, Visat - Gandhinagar Highway, Chandkheda, Ahmedabad, Gujarat-382424, India.
[2]Department of Chemistry, B. K. M. Science College, Valsad-396 001(Affiliated to Veer Narmad South Gujarat University, Udhna-Magdalla Road,Surat-395 007, State-Gujarat, India)

Abstract: The aim of the present work is to synthesize and find out the biological importance of the series of the designed 2, 3-dihydroquinazolinone coupled 5, 5-disubstituted imidazolidine-2,4-diones compounds. 4-(4-oxoquinazolin-3(4H)-yl)benzene-1-sulfonyl chloride is obtained by the reaction between 4-aminobenzene-1-sulfonyl chloride and 4H-benzo[d] [1,3]oxazin-4-one. This compound was than condensed with 5, 5-disubstituted imidazolidine-2, 4-diones compounds. And four novel compounds were prepared in moderate yields. The structures of all four derivatives have been characterized on the basis of physical properties of the molecule and satisfactory spectral (IR, ^{1}H NMR) data. These compounds were evaluated for their antimicrobial activity against Gram (+) and Gram (–) bacteria as well fungal organism. is evaluated. The compounds showed lower to moderate level of drug like properties.
Keywords : Imidazolidinone, oxoquinazolin, hydantoin, antimicrobial activity.

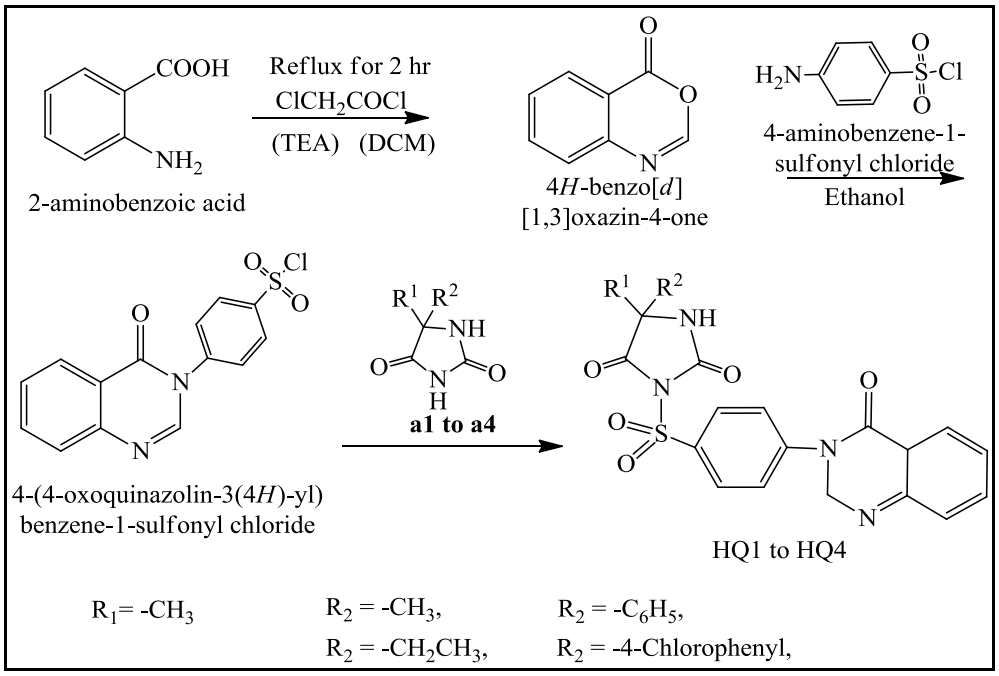
Introduction:

Hydantoins and their derivatives are well known for their medicinal and many important non-medicinal applications. [1-5] In the vast literature study it is found that these derivatives are frequently applied as anticonvulsant[6], Antibacterial[7], Antidiabetic[8], Antiviral[9], Anti-HIV[10] and many more. As well the quinazolinone derivatives are also well exploited for their medicinal and pharmaceutical applications viz. CNS depressant and anticonvulsant[11] antibacterial and antifungal[12] antimicrobial[13] and so many allied applications. Both these moieties are much more active against different microbes and pathogens in order to avail maximum effectiveness we designed some coupled derivatives of quinazolinone and hydantoin compounds. Literature study indicated that there is no significant work is available towards this concept.

In the present work four molecules were designed with their structures (Scheme-1) and synthesized accordingly. These structures were characterized by spectroscopic analysis. For getting antimicrobial characteristics they were also evaluated for their antimicrobial activities.

Experimental:

Synthesis process was involved five steps. In the first step **(*Step-I)*** 5, 5-disubstituted hydantoins (**a1 to a4)** were synthesized according to available literature methods.[6, 14-15] In the second step ***(Step-II)*** 4H-benzo[d][1,3]oxazin-4-one was prepared according to previously reported methods.[16-17] In the third step ***(Step-III)*** *4-(4-oxoquinazolin-3(4H)-yl)benzene-1-sulfonyl chloride* was prepared by the reaction between 4H-benzo[d][1,3]oxazin-4-one (the product of **Step-II**) and 4-aminobenzene-1-sulfonyl chloride (1:1) in presence of ethanol under refluxing condition for 12 Hrs. The resulting product was precipitated with pH adjustment at 6.5 to 6.9. This product was then allowed to react with the products of ***Step-I*** (5, 5-disubstituted hydantoins) at 40 to 45^{o} C with constant stirring for 3 Hrs. After completion of TLC check the reaction mixture was cooled at room temperature, then, poured on ice-cold water, stirred and filtered. Solid obtained were re-crystallized in methanol.



Scheme-1: Synthesis rout of the Hydantoin Quinazolizonone derivative

After further purification all the four samples were used to measure their melting points. And one selected samples was sent for analytical testing Viz. IR spectroscopy and ^{1}H NMR spectroscopy. The list of compounds **(HQ1 to HQ4)** synthesized in this series is given in the **Table-1** with M.F., M.W. and IUPAC names see and for Physical properties see **Table-2**.

Table-1: M.F., M.W. and IUPAC names of the compounds of the series

Comp. Code	R_1	R_2	M.F. M.W. g/mol	IUPAC Name
HQ1	$-CH_3$	$-CH_3$	$C_{19}H_{16}N_4O_5S$ 412.42	5,5-dimethyl-3-((4-(4-oxoquinazolin-3(4H)-yl) phenyl)sulfonyl)imidazoli dine-2,4-dione
HQ2	$-CH_3$	$-CH_2CH_3$	$C_{20}H_{18}N_4O_5S$ 426.10	5-ethyl-5-methyl-3-((4-(4-oxoquinazolin-3(4H)-yl) phenyl) sulfonyl)imidazolidine-2,4-dione
HQ3	$-CH_3$	$-C_6H_5$	$C_{24}H_{18}N_4O_5S$ 474.49	5-methyl-3-((4-(4-oxoquinazolin-3(4H)-yl) phenyl)sulfonyl)-5-phenylimidazolidine-2,4-dione

HQ4	$-CH_3$	-4-Chloro phenyl	$C_{24}H_{17}ClN_4O_5S$ 508.93	5-(4-chlorophenyl)-5-methyl-3-((4-(4-oxoquina zolin-3(4H)-yl)phenyl) sulfonyl) imidazolidine-2,4-dione

Table-2: Physical properties of compounds prepared in series

Compound Code	M.P. °C	Yield %	Elemental Analysis							
			C%		H%		N%		Cl%	
			Cal	Found	Cal	Found	Cal	Found	Cal	Found
HQ1	103	61	55.33	55.34	3.91	3.87	13.58	13.56	-	-
HQ2	98	47	56.33	56.31	4.25	4.26	13.14	13.11		
HQ3	92	76	60.75	60.73	3.82	3.81	11.81	11.77		
HQ4	141	43	56.64	56.60	3.37	3.75	11.01	10.98	6.97	6.95

After completing the analytical tests for structural correlation with the data the samples were then tested for the antimicrobial activity potency tests.

Results and Discussions:

The spectral data of the synthesized compounds HQ1 to HQ4

Compound (HQ1): **5,5-dimethyl-3-((4-(4-oxoquinazolin-3(4H)-yl) phenyl) sulfonyl) imidazolidine-2,4-dione**

IR (KBr pellets Cm^{-1}): 3265 (N-H str. Amine), 3040 (C-H Aromatic), 1744, 1630 (>C=O str.), 1140 (S=O str. sulfonyl); *^1H NMR (DMSO, 400 MHz)*: δ 12.19 (s, 1H, -N-H ring) δ 8.72-7.65 (m, 8H, Ar=H), δ 2.31 (q, 2H, $-CH_2-$) δ 1.29 (s, 6H, $-CH_3$)

Compound (HQ2): **5-ethyl-5-methyl-3-((4-(4-oxoquinazolin-3(4H)-yl) phenyl) sulfonyl) imidazolidine-2,4-dione**

IR (KBr pellets Cm^{-1}): 3280 (N-H str. Amine), 3087 (C-H Aromatic), 1749, 1642 (>C=O str.), 1370 (C-H str. alkyl), 1138 (S=O str. sulfonyl), ; *^1H NMR (DMSO, 400 MHz)*: δ 12.35 (s, 1H, -N-H ring) δ 8.80-7.63 (m, 9H, Ar=H), δ 3.21 (s, 1H, -CH-), δ 2.31 (d, 2H, $-CH_2-$) δ 1.25 (s, 6H, $-CH_3$)

Compound (HQ3): **5-methyl-3-((4-(4-oxoquinazolin-3(4H)-yl) phenyl)sulfonyl)-5-pheny limidazolidine-2,4-dione**

IR (KBr pellets Cm^{-1}): 3265 (N-H str. Amine), 3040 (C-H Aromatic), 1744, 1630 (>C=O str.), 1140 (S=O str. sulfonyl); *^1H NMR (DMSO, 400 MHz)*: δ 12.22 (s, 1H, -N-H ring) δ 8.89-7.74 (m, 13H, Ar=H), δ 3.23 (s, 1H, -CH-), δ 1.32 (s, 3H, $-CH_3$)

Compound (HQ4): **5-(4-chlorophenyl)-5-methyl-3-((4-(4-oxoquina zolin-3(4H)-yl)phenyl) sulfonyl) imidazolidine-2,4-dione**

IR (KBr pellets Cm^{-1}): 3324 (N-H str. Amine), 3070 (C-H Aromatic), 1710, 1620 (>C=O str.), 1124 (S=O str. sulfonyl), 765 (C-Cl str halogen); *^1H NMR (DMSO, 400 MHz)*: δ 12.34 (s, 1H, -N-H ring) δ 8.76-7.79 (m, 12H, Ar=H), δ 7.33 (d, 2H, -CH=CH-), δ 3.12 (d, 2H, -CH=CH-), δ 1.31 (s, 3H, $-CH_3$)

From the above analytical and spectral data (IR, ^{1}H-NMR) of all four synthesized compounds were in full agreement with proposed structures.

Biological activities:

All the newly synthesized compounds HQ1 to HQ4 were tested for their antimicrobial activity against 2 gram +ve bacterial organism (***E. coli*** & ***P. aeruginosa***), 2 gram –ve bacterial organisms (***S. aureus*** & ***S. pyogenus***) as well as 3 fungal organisms (***C. albicans, A. niger*** & ***A. clavatus***) by Broth dilution method. The minimal inhibition concentrations of different compounds and the standard drugs are given in the **Table-3.** The effects of unknown compounds were compared with the standard drugs like ***Gentamycin, Ampicillin Chloramphenicol, Norfloxacin*** &***Ciprofloxacin for antibacterial tests*** *and* ***Nystatin & Greseofulvin*** for anti fungal activity tests.

Table-3: Antibacterial and antifungal activities of compound HQ1 to HQ4

Compound	Minimalinhibition Concerntation *(µg/mL)*						
	Bacterial stains				Fungal stains		
	E. coli	***P. aeruginosa***	***S. aureus***	***S. pyogenus***	***C. albicans***	***A. niger***	***A. clavatus***
HQ1	250	500	250	200	500	250	250
HQ2	200	200	125	100	100	250	100
HQ3	62.5	250	200	250	250	500	500
HQ4	100	125	50	100	500	1000	250
Gentamycin	**0.05**	**1**	**0.25**	**0.5**	--	--	--
Ampicillin	**100**	--	**250**	**100**	--	--	--
Chloramphenicol	**50**	**50**	**50**	**50**	--	--	--
Norfloxacin	**10**	**10**	**10**	**10**	--	--	--
Ciprofloxacin	**25**	**25**	**50**	**50**	--	--	--
Nystatin	--	--	--	--	**100**	**100**	**100**
Greseofulvin	--	--	--	--	**500**	**100**	**100**

Here from the above data it indicates that compound HQ is having good activity against ***E. coli (gram +ve)*** while compound HQ4 is having good activity against ***S. aureus (gram –ve)*** as well the compound HQ2 is moderately active towards ***S. aureus*** & ***A. clavatus (fungal stains)***. The remaining compound HQ1 is not sp active compound against either of the microbial stains.

Conclusion:

In conclusion, we have reported some novel N-substituted quinazolinone-benzenesulfonyle and imidazoline-2,4dione derivatives, in which hydantoin moiety is linked with quinazolinone via benzene sulfonyl group. These compounds possess good to moderate antimicrobial activity. Further change in active groups on phenyl group may give more fruitful bioactivity.

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