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Research Article

SYNTHESIS, CHARACTERIZATION AND MICROBIAL ACTIVITY OF SOME 2-SUBSTITUTED-3-BENZENE SULPHONAMIDO-4(3H)-QUINAZOLINONES; AN EXPERIMENTAL AND THEORETICAL APPROACH

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ABSTRACT

Quinazolinone derivatives with substituents at 3rd position were found to be biologically active due to their diverse pharmacological and chemical properties. The present work involves synthesis of 2-substituted-3-benzene sulphonamido-4(3H)-quinazolinones from the reaction between 3-amino-2-substituted-4(3H)-quinazolinones and various 4-substituted benzene sulphonyl chlorides. All the synthesized compounds were characterized based on IR, NMR and Mass spectral data. The antibacterial activity for all the synthesized compounds was evaluated. In the present investigation the Quantitative structure activity relationship (QSAR) and quantum mechanical properties were also computed employing HyperChem 7.5 software. The orientations of frontier molecular orbitals which are important for the prediction of the reactivity were computed employing HyperChem 7.5 software. The computed highest occupied molecular orbitals (HOMO) for all the synthesized compounds infer that electron density is more localized on quinazolinone ring nitrogen at 3rd position. Such an observation would attribute towards more reactive nature of ring nitrogen. The computed QSAR parameter substituent's hydrophobicity constant 'π' is greater for chloro derivatives than other compounds which are in accordance of experimentally observed greater activity of the chloro compounds against bacteria.

Keywords: Quinazolinones, Sulphonyl chlorides, HyperChem 7.5 software, QSAR properties, Antibacterial activity.

INTRODUCTION

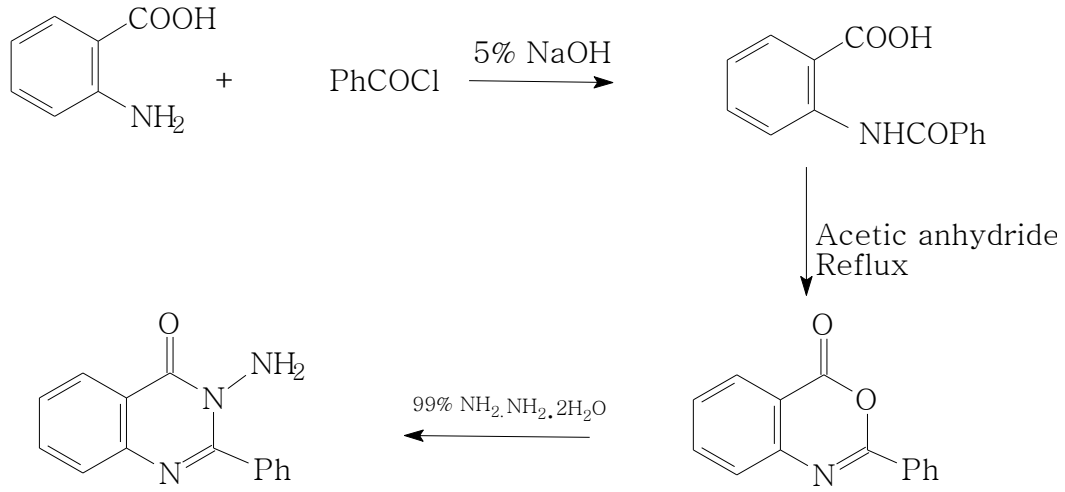
Over the past decade, the synthesis of privileged classes of heterocyclic molecules has become one of the main areas of interest in synthetic chemistry [1,2]. These important structures have gained much attention owing to their potential role as ligands which are capable of binding multiple biological targets[3]. Among nitrogen containing privileged class of molecules, substituted quinazolinones and quinazolines are considered as important therapeutic scaffolds[4,5]. Quinazolin-4(3H)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds [6]. Compounds containing 4(3H)-quinazolinone ring system have been reported to possess different biological activities depending on the nature of substituent's in the ring system such as antibacterial[7], antifungal[8], antitubercular[9], antiviral, anti-cancer[10] and anticonvulsant activity. Because of this established biological activity of quinazolin-4(3H)-ones and its derivatives, we concentrated on the synthesis, characterization of series of benzene sulphonamides using 2-substituted -3-amino-4(3H)-quinazolinones and various 4-substituted benzene sulphonyl chlorides. The QSAR properties and quantum mechanical properties for synthesized compounds were computed using HyperChem 7.5 software. The antibacterial activity of the synthesized compounds was evaluated.

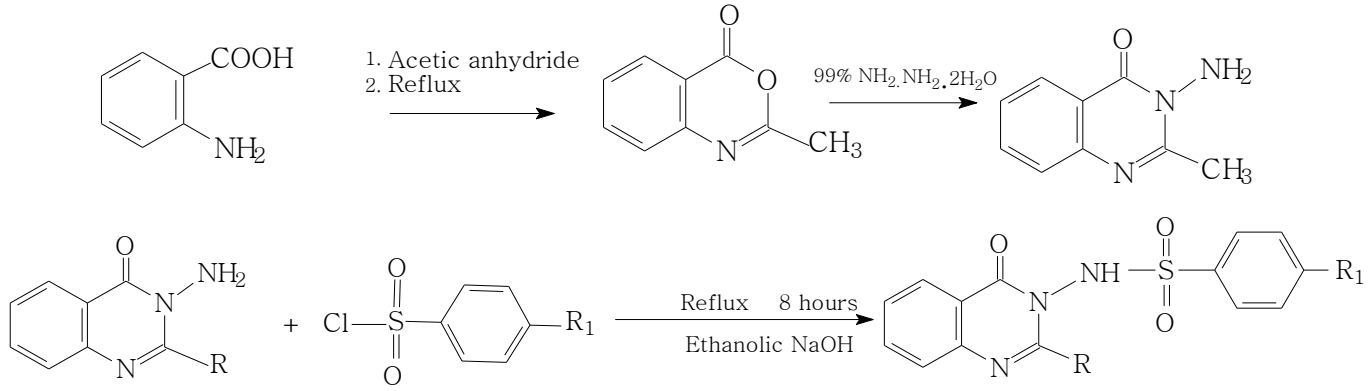
MATERIALS AND METHODS

All chemicals used were of laboratory grade and procured from Merck and Sigma Aldrich.

Synthesis of N-(4-Oxo-2-substituted-3,4-dihydroquinazolin-3-yl)-4-substituted benzene sulfonamide:

All the compounds were synthesized from 2-substituted-3-amino-4(3H)-quinazolinones. An equimolar mixture of 2-substituted-3-amino-4(3H)-quinazolinones and 4-substituted benzene sulphonyl chlorides were refluxed in ethanolic NaOH for 8hrs. The progress of the reaction was monitored by TLC using chloroform-ethyl acetate solvent system. The solid separated was filtered dried and recrystallized from ethanol. The sequence of reactions is given in scheme-1.





Substituent	1	2	3	4	5	6	7
R	CH_3	CH_3	CH_3	CH_3	Ph	Ph	Ph
R_1	H	CH_3	Cl	NO_2	H	CH_3	Cl

Scheme 1

Spectral studies

IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra were recorded for the characterization of the synthesized compounds. The spectral data of IR (KBr) on Bruker TENSOR 27 FT-IR Spectrophotometer, NMR on Bruker Biospin Avance-111400 MHz spectrometer and Mass on LCMS-2010A Shimadzu were recorded and tabulated in table -1

Computational studies

The pKa values of synthesized compounds were calculated using ChemAxon, which is an advanced java based chemical editor for drawing chemical structures. Using ChemAxon software various structure based calculations were performed by calculator plug-in. The pKa values are presented in table -2.

For computing QSAR and quantum mechanical properties the structure of the molecules was drawn using HyperChem 7.5 software. Geometry optimization was carried out by ab Initio method. The geometry optimized structure of N-(4-Oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-4-methyl benzene sulfonamide is given in fig-1.

Antimicrobial studies

The antibacterial activity of all synthesized compounds 1-7 were tested against seven pathogenic bacteria, viz; Bacillus subtilis, Pseudomonas fluorescence, Pseudomonas aerogenosa, Kleibsella pneumonia, streptococcus pneumonia, E.coli and Staphylococcus aureus, by disc diffusion technique. Compounds 1-7 were dissolved in DMSO and the discs were dipped in the respective compounds and placed on the Petri dishes which were inoculated with the specific organisms against a control of DMSO. After 24hours the zone of inhibition was measured. The details of the activity are furnished in table-3

RESULTS AND DISCUSSION

IR spectra of all the compounds displayed characteristic stretching frequencies of N-H, C=O, S=O and N-S. ^{1}H-NMR spectrum of each compound exhibited signal corresponding to N-H proton which is further confirmed by deuterium exchange studies.^{13}C-NMR spectra recorded signals corresponding to carbonyl and other aromatic carbon atoms. Molecular mass of the compounds is confirmed from mass spectral data.

Table 1: Spectral data of the synthesized compounds 1-7

S. No.	R	R_1	IR	NMR(δppm)	Mass (m/z)
1	CH_3	H	3616-3546 cm^{-1} (N-Hr), 3061 cm^{-1} (Ar C-H), 1622 cm^{-1} (C=O), 1510 cm^{-1} (C=N), 1446 cm^{-1} (C-N),1389 cm^{-1}(Ar C=C),1320 cm^{-1}(S=O)1210-1175 cm^{-1}(N-S).	^{1}H-NMR: 2.37 (s,3H, CH_3), 5.79 (s, 1H,N-H), 7.4-8.1 (9H,Ar-H) ^{13}C-NMR: 40.42 (CH_3), 125.45-128.40(Ar-C), 148(C=O)	316 (M+1)
2	CH_3	CH_3	3466-3378 cm^{-1} (N-H), 3039 cm^{-1} (Ar C-H), 1648 cm^{-1} (C=O), 1540cm^{-1} (C=N),1453 cm^{-1} (C-N), 1320 cm^{-1} (S=O), 1193-1133 cm^{-1} (N-S).	2.2 (s,3H, CH_3), 2.5 (s,3H,CH_3), 5.85 (s, 1H,N-H),7.1 (4H,Ar-H), 7.4 (4H,Ar-H)	330 (M+1)
3	CH_3	Cl	3615-3545 cm^{-1} (N-H), 3091 cm^{-1} (Ar C-H), 1622 cm^{-1} (C=O), 1587 cm^{-1} (C=N), 1481 cm^{-1} (C-N),1395 cm^{-1} (Ar C=C),1369 cm^{-1}(S=O), 1213,1176,1134 cm^{-1} (N-S), 759 cm^{-1} (C-Cl).	2.5 (s,3H,CH_3), 5.8 (s, 1H,N-H),7.4 (4H,Ar-H), 7.6 (4H,Ar-H)	349(M+1)
4	CH_3	NO_2	3456 cm^{-1} (N-H), 3091 cm^{-1} (Ar C-H), 1642 cm^{-1} (C=O), 1595 cm^{-1} (C=N), 1456 cm^{-1}(C-N),1379 cm^{-1} (Ar C=C),1325 cm^{-1}(S=O), 1199-1130 cm^{-1} (N-S).	2.5 (s,3H,CH_3), 5.8 (s, 1H,N-H),7.4 (4H,Ar-H), 7.6 (4H,Ar-H)	361(M+2)
5	Ph	H	3615-3545 cm^{-1} (N-H), 3091 cm^{-1} (Ar C-H), 1623 cm^{-1} (C=O), 1586 cm^{-1} (C=N), 1481 cm^{-1} (C-N),1395 cm^{-1} (S=O), 1175-1134 cm^{-1}(N-S).	^{1}H-NMR: 7.36-7.61 (14H,Ar-H),8.1(s,1H,N-H) ^{13}C-NMR: 126-147 (Ar-C), 164(C=O)	378 (M+1)
6	Ph	CH_3	3483-3377 cm^{-1} (N-H), 3036 cm^{-1} (Ar C-H), 1648 cm^{-1} (C=O), 1540 cm^{-1} (C=N), 1481 cm^{-1} (C-N),1395 cm^{-1}(Ar C=Cr),1336 cm^{-1}(S=O),1193-1133 cm^{-1}(N-S).	1.4 (s,3H, CH_3), 5.1 (s,1H,NH), 6.2-7.2(13H,Ar-H)	390(M-1)
7	Ph	Cl	3617-3546 cm^{-1} (N-H), 3061 cm^{-1} (Ar C-H), 1622 cm^{-1} (C=O), 1530 cm^{-1} (C=N), 1447 cm^{-1} (C-N),1378 cm^{-1}(S=O), 1211,1176,1135 cm^{-1} (N-S), 737 cm^{-1} (C-Cl).	7.33-7.36 (9H,Ar-H),7.62-7.64(4H,Ar-H), 8.1(1H,N-H)	412 (M+1) peak

In the present investigation the QSAR parameters were computed employing HyperChem 7.5 software and pKa values from ChemAxon software. QSAR properties like surface area, volume, hydration energy, log P, refractivity, polarisability, mass were determined by single point method and data is presented in table-2.

QSAR properties allow calculation and estimation of a variety of molecular descriptors commonly used in quantitative structure activity relationship (QSAR) studies. The QSAR data analysis represents an attempt to relate structural descriptors of compounds with their physicochemical properties and biological activities. The σ, Hammet's substituent constant and π, substituent hydrophobicity constant are important physicochemical properties of QSAR studies. Hence these values were calculated from pKa and log p values computed. Hammet's substituent constant 'σ' gives information about nature of substituent whether electron withdrawing or electron releasing. Substituent hydrophobicity constant 'π' value gives information about hydrophobic nature of the substituent.

As surface area is increasing, the steric contribution of the substituent is increasing, which in turn increases the refractivity value. Change in refractivity value affects the biological activity. The pKa value for the electron releasing substituent's is more when compared to parent compound and its derivatives with electron withdrawing groups. The σ and π values calculated from the computed data are in good agreement with the expected data. The π and molecular property parameter free energy are linearly dependent. From the data it is evident that, the 'π' value is greater for chloro substituent and its free energy is also high when compared to other derivatives.

Table 2: The Free Energy and QSAR Parameters of synthesized compounds 1-7

	1	2	3	4	5	6	7
Free energy (Kcal/mole)	$-0.813x10^5$	$-8.677x10^5$	$-11.128x10^5$	$-7.5313x10^5$	$-9.610x10^5$	$-7.376x10^5$	$-12.464x10^5$
Surface area(A^2)	414.65	467.22	450.86	472.59	437.74	483.05	475.22
Surface area grid(A^2)	500.20	533.59	523.05	536.98	570.39	599.94	598.26
Volume(A^3)	841.00	893.43	886.16	905.96	994.34	1046.20	1040.78
Hydration Energy (Kcal/mol)	-7.90	-6.95	-7.583	-12.94	-8.10	-6.90	-7.76
Log p	7.77	8.41	8.46	7.56	9.85	10.32	10.37
Refractivity(A^3)	82.03	87.15	86.95	88.93	102.28	107.32	107.09
Polarisability(A^3)	31.99	33.28	33.37	33.28	39.27	41.10	41.20
Mass(amu)	315.35	329.37	349.79	360.34	377.42	391.44	411.86
PKa	5.25	5.47	4.70	4.66	5.25	5.47	4.70
σ	0	-0.22	0.55	0.59	0	-0.22	0.55.
Π	0	0.64	0.69	-0.21	0	0.47	0.52

Quantum mechanical calculations for orbitals have been widely used to study donor and acceptor properties of molecules. The frontier molecular orbitals are significant parameters for the prediction of the reactivity of a chemical species. The HOMO and LUMO orbital diagrams generated for N-(4-Oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-4-methyl benzene sulfonamide were given in fig-2 & fig-3. The diagram of HOMO in all synthesized compounds infers that electron density is more localized on quinazolinone ring nitrogen at 3rd position and adjacent N & S atoms. These results would attribute towards more reactive nature of ring nitrogen.

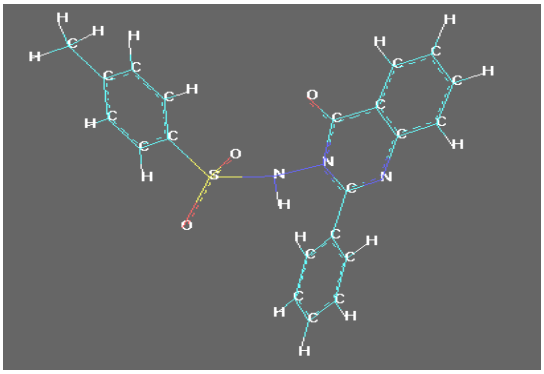


Fig. 1: HyperChem Ab Initio- Geometry optimized N-(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-4-Methyl benzene sulfonamide

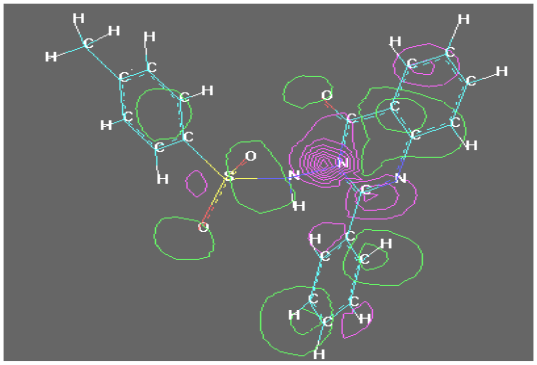


Fig. 2: Highest occupied Molecular Orbitals of N-(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-4-Methyl benzene sulfonamide

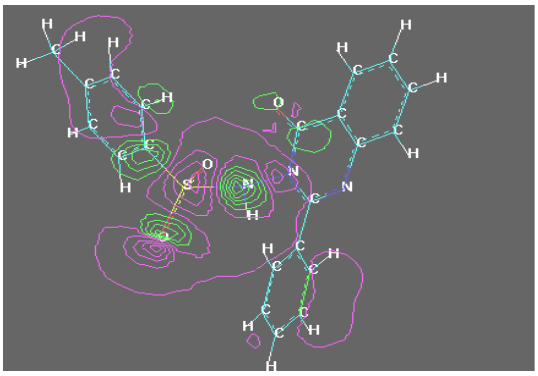


Fig. 3: Lowest Unoccupied Molecular Orbitals of N-(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-4-Methyl benzene sulfonamide

Introduction of substituents such as chloro, nitro and methyl at para position showed considerable variation in activity against some organisms. N-(4-Oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-4-chloro benzene sulfonamide showed more antibacterial activity when compared to all other compounds.

Table 3: Antibacterial activity of the synthesized compounds (1-7)

	Bacillus subtilis	Pseudomonas fluorescence	Pseudomonas aerogenosa	Kleibsella pneumonia	streptococcus pneumonia	E.coli	Staphylococcus aureus
1	+	+	++	+++	+	++	+
2	+	++	++	+++	-	-	++
3	+++	+++	+++	+++	+++	++	++++
4	+	+	++	-	+	-	-
5	+++	++	+++	+++	++++	++++	+++
6	++	+	+	+	+++	++	+++
7	++++	++	++++	++++	++++	++	+++

+ indicates very week activity, ++ indicates week activity,

+++ indicates moderate activity, ++++ indicates good activity

CONCLUSIONS

In summary, the presented method of preparation of 2-substituted-3-benzene sulphonamido-4(3H)-quinazolinones and their derivatives from appropriate 3-amino-2-substituted-4(3H)-Quinazolinones and substituted benzene sulphonyl chlorides in ethanolic NaOH is very convenient, rapid and gives good to moderate yields. The computed highest occupied molecular orbitals (HOMO) for all the synthesized compounds infer that electron density is more localized on quinazolinone ring nitrogen at 3rd position, which attributes towards more reactive nature of ring nitrogen. The QSAR parameters and quantum mechanical calculations obtained from the computational calculations using Hyperchem7.5 software were correlated with their structural and biological activity. It was also found that the synthesized compounds displayed good to moderate antibacterial activity against wide range of micro organisms.

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