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Synthesis, Characterization and evaluation of Antibacterial Activity of some 3-Substitutedphenylquinazoline -2,4-diones

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ABSTRACT

In the present study a series of 3-substitutedphenylquinazoline-2,4-diones ***1(a-m)*** *have been synthesized from isatoic anhydride with substituted aromatic amines. The structure of these compounds has been established on the basis of their analytical and spectral data. All the compounds have been screened for their in vitro antibacterial activity at MIC level (minimum inhibitory concentration) against Bacillus subtillis, Staphylococcus aureus, Escherichia. coli, and pseudomonas aeruginosa. Most of the synthesized compounds showed promising antibacterial activity compare to the standard drug ciprofloxacin.*

Keywords: Quinazoline, Antibacterial Activity, substituted amines, Minimum inhibitory concentration.

INTRODUCTION

Quinazoline-2,4-dione heterocyclic nucleus is found to exhibit a broad range of biological activities such as antibacterial [1-4], anti-inflammatory [5], anti-tubercular [6], anticonvulsant [7], hypoglycemic [8], analgesic [9], antifungal [10-11], antiviral [12], antidepressant [13] and anti-parkinsonism [14] activities.

In view of these importance of quinazoline-2.4-diones, the present work is carried out towards the synthesis of 3-substituted phenylquinazoline-2,4-diones using isatoic anhydride with different aromatic primary amines in presence of acetic acid (Scheme1). The newly synthesized compounds were screened for their possible antimicrobial activity.

MATERIALS AND METHODS

Experimental

All the chemicals were obtained from commercial and used after further purification. The melting points of the synthesized compounds were taken in open capillary and are uncorrected. The Purity of the compounds was checked by micro TLC using pet ether:ethyl acetate (8:2) as mobile phase and the spots were observed under iodine. IR spectra were recorded in KBr on a shimadzu FT-IR 8400 spectrophotometer. ^{1}H NMR spectra were obtained using AMX-400 liquid state spectrometer at 400MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on GCMS solution. Elemental analysis (C, H, N) of these newly synthesized compounds were performed on a Carlo Erba-1108 elemental analyzer.

General procedure for the synthesis of 3-substitutedquinazoline-2,4-diones
An equimolar mixture of isatoic anhydride (0.01mol) and substituted aromatic amines (0.01mol) were taken in a 100 mL round bottom flask and refluxed for about 12 h in alcohol in presence of few drops of acetic acid. The progress of the reaction was monitored by TLC. The contents were then poured into crushed ice and the solid obtained was collected, re-crystallized from ethanol water (8:2).

3-(4-Methylphenyl)quinazolin-2,4(1*H*,3*H*)-dione (2a)
Isatoic anhydride (1.63g,0.01mol), 4-methylaniline (1.08ml, 0.01mol): Yield 37%, m.p 140-142 ^{o}C: IR (KBr,cm^{-1}): 3365 (NH), 3036 (Ar-H), 1665 (C=O), 1438 (CH_3), ^{1}H NMR ($CDCl_3$,δppm) 2.3 (s,3H,CH_3), 6.6-7.4 (m,8H,Ar-H), 8.6 (s,1H, NH). MS (m/z): 253 Anal. Calcd for $C_{15}H_{12}N_2O_2$ C, 71.42; H, 4.79; N, 11.10. Found: C, 71.39; H, 4.81; N, 10.99.

3-(2-Methoxyphenyl)quinazolin-2,4(*1H,3H*)-dione (2b)
Isatoic anhydride (1.63g, 0.01mol) 2-methoxyaniline (1.25ml, 0.01mol): Yield39%, m.p170-172 ^{o}C: IR(KBr,cm^{-1}): 3360 (NH),3040 (Ar-H) 1655 (C=O). ^{1}HNMR($CDCl_3$,δppm) 3.5(s,3H,OCH_3), 6.7-7.9(m,8H,Ar-H), 9.1(s,1H,NH). MS (m/z): 269 Anal. Calcd for $C_{15}H_{12}N_2O_3$ C, 67.16; H, 4.51; N, 10.44. Found: C, 67.00; H, 4.6; N, 10.38.

3-(4-Methoxyphenyl)quinazolin-2,4(*1H,3H*)-dione (2c)
Isatoic anhydride (1.63g,0.01mol), 4-methoxy aniline (1.24ml,0.01mol): Yield 42%, m.p 110-112 ^{o}C: IR(KBr,cm^{-1}): 3362 (NH), 3031 (Ar-H), 1661 (C=O),^{1}H NMR ($CDCl_3$, δppm) 3.5 (s, 3H, OCH_3) 6.5-7.8 (m, 8H, Ar-H), 9.2(s, 1H, NH). MS (m/z): 269 Anal. Calcd for $C_{15}H_{12}N_2O_2$ C, 67.16 ; H, 4.51; N, 10.44. Found: C, 67.00; H, 4.96; N, 10.41.

3-(4-Methoxy-2-nitrophenyl)quinazolin-2,4(1H,3H*)*-dione (2d)
Isatoic anhydride (1.63g, 0.01mol), 4-methoxy-*2*-nitroaniline (1.52ml, 0.01mol): Yield 48%, m.p 285-287 ^{o}C IR (KBr, cm^{-1}) 3225(NH), 3070(Ar-H),1649(C=O),752(Ar-NO_2). ^{1}HNMR ($CDCl_3$, δppm) 3.5 (s, 3H, OCH_3) 7.6-6.5 (m, 7H, Ar-H), 9.2(s,1H,NH). MS (m/z): 314 Anal. Calcd for $C_{15}H_{11}N_3O_5$ C, 57.51; H, 3.54; N, 13.41. Found: C, 57.53; H, 3.50; N, 13.44.

3-(4-acetylphenyl)quinazolin2,4(*1H,3H*)-dione (2e)
Isatoic anhydride (1.63g, 0.01mol), 4-aminoacetophenone (1.35ml, 0.01mol):Yield 28%, m.p 115-120 ^{o}C: IR (KBr, cm^{-1}): 3335 (NH), 3064 (Ar-H), 1660 (C=O).^{1}H NMR ($CDCl_3$, δppm) 3.3 (s,3H,CH_3), 6.7-7.8 (m, 8H, Ar-H), 8.4 (s, 1H, NH). MS (m/z): 281 Anal. Calcd for $C_{16}H_{12}N_2O_3$ C, 68.56; H, 4.32; N, 9.99. Found: C, 68.58; H, 4.29; N, 10.1.

5-(2,4-Dioxo-1,4-dihydroquinazolin-3(*2H*)-yl)-2-hydroxybenzoic acid (2f)
Isatoic anhydride (1.63g, 0.01mol), 5-aminosalicylicacid (1.53ml, 0.01mol): Yield 35%, m.p 164-166 ^{o}C: IR (KBr, cm^{-1}): 3645 (OH), 3336 (NH), 3119 (Ar-H), 2372 (COOH), 1660 (C=O), ^{1}H NMR ($CDCl_3$, δppm) 4.3 (s, 1H, COOH), 6.5-7.4 (m, 7H, Ar-H), 7.7 (s, 1H, OH), 8.4 (s, 1H, NH). MS (m/z): 299 Anal. Calcd for $C_{15}H_{10}N_2O_5$ C, 60.41; H, 3.38; N, 9.39. Found: C, 60.43; H, 3.41; N, 9.36.

3-(4-Aminobenzenesulfonicacid)quinazolin-2,4(*1H,3H*)-dione (2g)
Isatoic anhydride (1.63g, 0.01mol), 4-aminobenzenesulfonicacid (1.95ml, 0.01mol): Yield 25%, m.p 130-132 ^{o}C: IR (KBr, cm^{-1}): 3341 (NH), 3068 (Ar-H), 1666 (C=O). ^{1}H NMR ($CDCl_3$, δppm) 6.8-7.6 (m, 8H, Ar-H), 8.3 (s, 1H, NH), 7.9 (s, 1H, OH). MS (m/z): 319 Anal. Calcd for $C_{14}H_{10}N_2O_5S$ C, 52.83; H, 3.17; N, 8.80. Found: C, 52.85; H, 3.15; N, 8.75.

3-(4-Chlorophenyl)quinazolin-2,4(*1H,3H*)-dione (2h)
Isatoic anhydride (1.63g,0.01mol), *4*-chloroaniline (1.29ml,0.01mol):Yield 49%, m.p 180-182 ^{o}C: IR(KBr, cm^{-1}): 3365 (NH), 3075 (Ar-H),1650 (C=O), 754 (C-Cl).^{1}H NMR ($CDCl_3$, δppm) 6.6-7.6 (m, 8H, Ar-H), 9.4 (s, H, NH). MS (m/z): 273 Anal. Calcd for $C_{14}H_9ClN_2O_2$ C, 61.66; H, 3.33; N, 10.27. Found: C, 61.69; H, 3.35; N, 10.19.

3-(2-Chloro-5-nitrophenyl)quinazolin-2,4(*1H,3H*)-dione (2i)
Isatoic anhydride (1.63g,0.01mol), 2-chloro-5-nitroaniline (1.73ml,0.01mol):Yield 45%, m.p108-110 ^{o}C: IR (KBr, cm^{-1}): 3362 (NH),3045 (Ar-H), 1662 (C=O), 1530 (C-NO_2), 753 (C-Cl). ^{1}H NMR ($CDCl_3$,δppm) 6.6-7.8 (m,7H.Ar-H), 9.3 (s,1H, NH). MS (m/z): 318 Anal. Calcd for $C_{14}H_8ClN_3O_4$ C, 52.93; H, 2.54; N, 13.23. Found: C, 52.90; H, 2.57; N, 13.25.

3-(4-Bromophenyl)quinazolin-2,4(*1H,3H*)-dione (2j)
Isatoic anhydride (1.63g,0.01mol), *4*-bromoaniline (1.73ml,0.01mol): Yield 35%, m.p 140-142 ^{o}C: IR (KBr, cm^{-1}): 3356 (NH), 3039 (Ar-H), 1664 (C=O), 698 (C-Br), ^{1}H NMR ($CDCl_3$,δppm) 7.1-8.6 (m, 8H, Ar-H), 9.4 (s,1H,NH). MS (m/z): 318 Anal. Calcd for $C_{14}H_9BrN_2O_2$ C, 53.02; H, 2.86; N, 8.83. Found: C, 52.98; H, 2.92; N, 8.85.

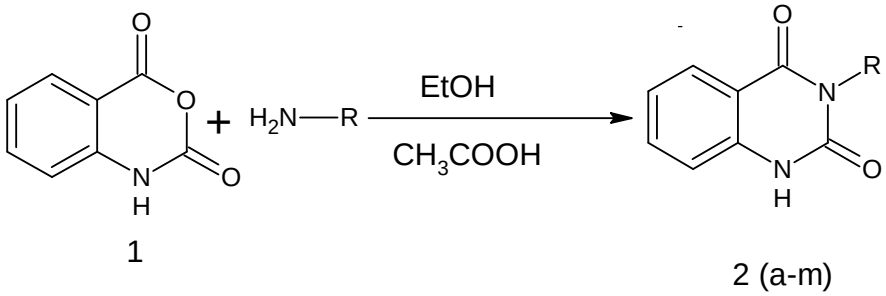
3-(2-Nitrophenyl)quinazolin-2,4(*1H,3H*)-dione (2k)
Isatoic anhydride (1.63g, 0.01mol), 2-nitroaniline (1.38g, 0.01mol): Yield 52%, m.p190-192 ^{o}C IR (KBr,cm^{-1}): 3227(NH), 3115(Ar-H), 1651(C=O), 1516(C-NO_2). ^{1}H NMR ($CDCl_3$, δppm) 7.2-8.5 (m,8H,Ar-H), 9.3 (s,1H,NH). MS (m/z): 284 Anal. Calcd for $C_{14}H_9N_3O_4$ C, 59.37; H, 3.20; N, 14.84. Found: C, 59.31; H, 3.24; N, 14.89.

3-(4-Nitrophenyl)quinazolin-2,4(*1H,3H*)-dione (2l)
Isatoic anhydride (1.63g, 0.01mol), 4-nitroaniline (1.38g, 0.01mol): Yield 46%, m.p 280-282 ^{o}C: IR (KBr,cm^{-1}) 3363(NH),3070 (Ar-H), 1654(C=O), 752(Ar-NO_2). ^{1}H NMR ($CDCl_3$, δppm) δ 7.5-8.6 (m, 8H, Ar-H), 9.2 (s,1H,NH). MS m/z 253 m^{+} Anal. Calcd for $C_{15}H_{12}N_2O_2$ C, 71.42; H, 4.79; N, 11.10. Found: C, 71.34; H, 4.85; N, 10.99. MS (m/z): 284 Anal. Calcd for $C_{14}H_9N_3O_4$ C, 59.37; H, 3.20; N, 14.84. Found: C, 59.34; H, 3.23; N, 14.88.

4-(2,4-Dioxo-1,4-dihydroquinazolin-3(*2H*)-yl)benzoic acid (2m)
Isatoic anhydride (1.63g, 0.01mol), 4-amino benzoic acid (1.37g, 0.01mol): Yield 39%, m.p 206-208 ^{o}C: IR (KBr, cm^{-1}): 3340 (NH), 3034 (Ar-H), 2365 (COOH), ^{1}H NMR ($CDCl_3$, δppm) 4.2 (s, 1H, COOH), 6.6-7.5 (m, 8H, Ar-H), 8.2 (s, 1H, NH). MS (m/z): 283 Anal. Calcd for $C_{15}H_{10}N_2O_4$ C, 63.83; H, 3.57; N, 9.92. Found: C, 63.85; H, 3.55; N, 9.94.

Compounds	R
2a	4-CH_3 C_6H_4
2b	2-OCH_3 C_6H_4
2c	4-OCH_3 C_6H_4
2d	4-OCH_3, 2-NO_2 C_6H_3
2e	4-$COCH_3$ C_6H_4
2f	2-OH, 4-COOH C_6H_3
2g	4-SO3H C_6H_4
2h	4-Cl C_6H_4
2i	2-Cl, 5-NO_2 C_6H_3
2j	4-Br C_6H_4
2k	2-NO_2 C_6H_4
2l	4-NO_2 C_6H_4
2m	4-COOH C_6H_4

Scheme.1



1 2 (a-m)

Antibacterial activity
The *in vitro* antibacterial activity of synthesized compounds was carried out following the method described in literature [15] against two gram positive bacteria *Bacillus subtillis*, *Staphylococcus aureus* and two gram negative bacteria *Escherichia. coli*, and *pseudomonas aeruginosa* by well diffusion method using nutrient agar as the medium. Ciprofloxacin was used as standard. The stock solution (1mg in 1ml of DMSO) was prepared by dissolving the compound in DMSO and the solution was serially diluted in order to find Minimum Inhibitory Concentration (MIC) values. In a typical procedure, a well was made on the agar medium inoculated with microorganisms in a Petriplate. The well was filled with the test solution and the plate was incubated for 48 h for bacteria at 37^{o}C. During

the period, the test solution diffused and the growth of the inoculated microorganisms was affected. The inhibition zone was developed was measured and recorded.

RESULTS AND DISCUSSION

Antibacterial activity MIC values were depicted in **Table.1.** Quinazoline derivatives with appropriate substituent's mainly amine or substituted amine on the 4th position and either halogens or electron rich substituent's on the 6 and 8 position known to promote activity against bacteria. All the synthesized compounds evaluated for anti bacterial activity against gram positive and gram negative organisms *Bacillus subtillis*, *Staphylococcus aureus* and *Escherichia coli*, *pseudomonas aeruginosa* respectively. All the compounds exhibited moderate to excellent antibacterial activity. The compounds 2c, 2e, 2g and 2m were found to be more active against both gram positive and gram negative bacterial species. However remaining compounds also showed significant activity and results can be comparable with the standard drug ciprofloxacin. The antibacterial activity data were tabulated in Table.1. The increase in antibacterial activity may be considered in light of Overtone's concept [16] and Tweedy's chelation theory [17]. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage only of lipid-soluble materials due to which liposolubility is an important factor controlling the antimicrobial activity.

In the compounds 2c, 2e, 2g and 2m due to the presence of different substituent's like methyl, methoxy, acetyl, sulphonic acid and carboxylic groups at specific position in phenyl ring alters the polarity of the molecule by delocalization of π- electrons and may enhances the lipophilicity nature of the compounds and facilitates the easy passage through the cell membrane of bacteria thereby inhibits the growth of bacteria.

Table.1. *Invitro* antibacterial activity of compounds and their inhibition zone (MIC) in mm

	Antibacterial activity							
	E.coli		***B.subtilis***		***P.aeruginosa***		***S.aures***	
Comps. \Conc. (µg)	**100**	**200**	**100**	**200**	**100**	**200**	**100**	**200**
2a	23	27	18	24	20	28	27	33
2b	19	25	29	31	27	29	20	24
2c	24	29	26	30	23	27	25	32
2d	4	7	25	29	26	28	19	21
2e	24	28	21	26	30	33	34	36
2f	23	27	23	26	24	27	18	21
2g	32	36	27	32	34	36	32	35
2h	27	32	26	33	23	26	28	34
2i	23	26	24	27	30	34	31	33
2j	24	27	31	34	31	33	27	30
2k	5	7	10	12	26	32	30	32
2l	17	19	18	21	19	22	3	4
2m	27	33	26	31	14	18	31	35
Std	27	32	24	27	25	28	27	30
Control	-	-	-	-	-	-	-	-

Standard is ciproflaxin, Control is dimethyl sulfoxide (DMSO)

CONCLUSIONS

The target molecules were synthesized and characterized by different spectral analysis and screened for antibacterial activity. All the newly synthesized compounds were showed moderate to excellent antibacterial activity compared to standard drug ciprofloxacin.

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REFERENCES

[1] P. T. Tuan, L. E. Edmund, A. S. Michael, M. D. John, H. D. Showalter, J. G. Stephen, A.S. Martin, E. J. Themis, *Bioorg. Med. Chem. lett*., **2004**, 14, 4405.

[2] P. M. Bedi, V Kumar, M. P. Mahajan. *Bioorg Med Chem. letters*., **2004**, 14, 5211.
[3] Vivek Gupta, Sushil K. Keshaw, VarshaJatava, Pradeep Mishra. *Med.Chem.Res.*, **2008**, 17 , 205.
[4] A. Mahr. EI-Hashash, B. Dala, Guirguis, A. Yaser. EI- Badry. *Der Pharma Chemica*., **2011**, 3, 147.
[5] V. Algarsamy, M. Gopinath, P. Parthiban, B. SubbaRao, K. Murali, V. Rajasolomon. *Med.Chem. Res.*, **2011**, 20, 946.
[6] J. Kunes, J. Bazant, M. Pour, K. Waisser, M. Slosarek, J. Janata *Farmaco*., **2000**, 55, 725.
[7] M. Nagwa, Abdel Gawad, Hanan Hanna Georgey, M. Rihan Youssef, A. Nehad. E.I. sayed. *Med.Chem.Res*., **2011**, 20, 280.
[8] J. R. Vishnu, Farhanullah, K.T. Brajendra, K. S. Arvind. *Bioorg.Med.Chem*., **2003**, 11, 2439.
[9] A. S. Hosam, A. O. Nermen, H. Ahmed, Monstafa. *Molecules*., **2011**, 16, 10187.
[10] S. N. Pandeya, D. Sriram, G. Nath, E. D. Clercq. *Pharmaceutica Acta Helvetiae*., **1999**, 74, 11.
[11] M. M. Ghorab, S. M. Abdel-Gawad, M. S. A EI-Gaby. *Farmaco*., **2000**, 55, 249.
[12] Tun-Cheng Chien, Chien-Shu Chen, Fang-Hwa Yu, Ji-wang Chern. *Chem. Pharm. Bull.*, **2004**, 52, 1422.
[13] S. Chaki, T. Funakoshi, S. Hirota-Okuno, M. Nishiguchi, T. Shimazaki, M. Lijima, *J. Pharma. Exp. Therap*., **2005**, 313, 831.
[14] S. Kumar, H. Kaur, I. Singh, M. Sharma, P. Vishwakarma, K. K. Saxena, *World. J. Chem.*, **2009**, 4, 195.
[15] Saeed-ur-Rehman, Muhammad Ikram, Sadia Rehman, Alia Faiz, Shahnawaz, *Bull. Chem. Soc.*, *Ethiop*. **2010**, 24, 201.
[16] H. M. Parekh, P. B. Pansuriya, M. N. Patel, *Polish J. Chem*., **2005**,79,1843.
[17] B. G. Tweedy, *Phytopathology*, **1964**, 55, 910.