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Synthesis and Antiviral Activities of Some 2,3-Disubstituted Quinazoline Derivatives

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In the search of new leads towards potent antiviral agents 2,3-disubstituted quinazoline derivatives were synthesized and tested for their antiviral activity. Anthranilic acid (**1**) on treatment with an aromatic acid chloride in pyridine gives 2-aryl-4-oxo-3H-benzoxazines (**2**) which in turn reacts with *p*-amino benzoic acid (PABA) to afford 2-aryl-3-*p*-carboxylatophenyl-4-oxo-3*H*-quinazolines (**3**). The compound **3** further reacts with amido alcohols in the presence of conc. H_2SO_4 resulting 3-[benzoic acid-(3-phthalimidomethyl/3-ethyl-3*H*-2-phenyl-4-oxo-quinazolinyl/1-ethyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)]-2-aryl-3H-quinazoline-4-ones (**4**). The resulting compounds **4a-f** have been evaluated for their *in vitro* and *in vivo* antiviral activity against JEV and HSV type-I. The synthesized compounds were characterized through their physical and chemical analysis. The obtained results can be used as the key step for the building of novel chemical entities with interesting antiviral activity compare with the standard drugs.

Keywords: Antiviral activities, 2,3-Disubstituted quinazoline derivatives.

INTRODUCTION

Quinazoline and its derivatives are versatile nitrogen containing heterocyclic compounds, demonstrating a broad spectrum of biological and pharmacological activities in animal as well as in human beings[1,2]. The chemistry and pharmacology of quinazolines have been of great interest to medicinal chemists. Wedding in 1885 synthesized the first quinazolines and later on, extensive work on this nucleus was done for the amelioration of human suffering from various diseases and many drugs incorporating this nucleus were developed. The designing and devolvement of selective non-nucleoside inhibitors of virus polymerases is an emerging area of research activity. Interest in discovering non-nucleoside inhibitor of virus polymerases increase after the pronounced antiviral activity of 2-(α-hydroxybenzyl)benzimidazole (HBB) and methisazone which are truly the selective inhibitors of RNA polymerase[3,4] subsequently other synthetic compounds were developed and assayed for their antiviral activity. Amongst various synthetic compounds quinazolines have been demonstrated to be potential candidate molecules against several strains of virus since such compound exhibit varying degree of virus inhibition properties against semliki forest disease virus (SFV)[5], Ranikhet disease virus (RDV)[6], Encephalomyocarditis virus (EMCV)[7], Japanese encephalitis virus (JEV)[8] and Herpes simplex virus type-I (HSV-I)[9], Interest in quinazolones chemistry has increased many folds because of their association with varying degree of antiviral activity against animal and plant viruses[10-12]. These valid observations led the authors to undertake the synthesis of 2,3-disubstituted quinazolones in order to study their antiviral activity against both, RNA and DNA viruses.

EXPERIMENTAL

Melting points of the compounds were determined in open glass capillaries in the Toshniwal melting points apparatus and recorded values are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer 157 spectrophotometer in region ν_{max} 4000-400 cm^{-1} and ^1H NMR and ^{13}C NMR spectra were recorded on Brooker DRX 200 MHz spectrophotometer using $CDCl_3$ as solvent (TMS as internal standard with chemical shift in δ, ppm). Mass spectra were recorded on Hitachi-Elmer model RMV-7 spectrometer at 70 eV.

Synthesis of 2-aryl-4-oxo-3,1-benzoxazines (2): The titled compound was prepared according to the method described in the literature[13]. Anthranilic acid (0.1 mol) was dissolved in anhydrous pyridine (50 mL) by stirring slowly at room temperature. The solution was cooled to 0 °C and an aromatic acid chloride (0.2 mol) was added drop wise slowly with constant stirring. After complete addition, the reaction mixture was further stirred for 0.5 h at room temperature and kept for 1 h. The dense mass, thus obtained, was diluted with deionized water (50 mL) and treated with 5 % $NaHCO_3$

solution (50 mL) to remove any unreacted acid. When the effervescence ceased, it was filtered off and washed with deionized water in order to remove the adhered pyridine and inorganic materials. The crude benzoxazines thus prepared, were dried and recrystallized using dilute ethanol.

2-Phenyl-4-oxo-3,1-benzoxazines: m.p.: 122-123 °C. Yield 75 % (Found: N, 6.11 %: $C_{14}H_9NO_2$ requires N, 6.27 %).

2-Styryl-4-oxo-3,1-benzoxazines: m.p.: 209-210 °C. Yield 60 % (Found: N, 5.56 %: $C_{16}H_{11}NO_2$ requires N, 5.62 %).

Synthesis of 2-aryl-3-*p*-carboxylatophenyl-4-oxo-3*H*-quinazolines (3) The compound **3** was prepared according to the method described in the literature[14]. A mixture of 2-aryl-4-oxo-3,1-benzoxazines (0.05 mol) (**2**) and *p*-amino benzoic acid (0.05 mol) in dry pyridine (50 mL) was heated under reflux for 6 h under anhydrous reaction conditions and then allowed to cool at room temperature. The reaction mixture was then treated with dilute hydrochloric acid (5 mL) and stirred. The solid thus separated was filtered off and washed with deionized water to remove pyridine. The crude quinazolones was dried under vacuum and recrystallized from dilute ethanol.

2-Phenyl-3-benzoic acid)-4-(3*H*)-quinazolones: m.p.: 199-200 °C. Yield 65 % (Found: N, 8.75 %: $C_{21}H_{14}N_2O_3$ requires N, 8.91 %).

2-Styryl-3-(4-benzoic acid)-4-(3*H*)-quinazolones: m.p.: 159-160 °C. Yield 61 % (Found: N, 8.55 %: $C_{23}H_{16}N_2O_3$ requires N, 8.23 %).

Synthesis of N-hydroxymethyl phthalimide: The titled compound was prepared according to the method described in the literature[15]. A mixture of phthalimide (0.1 mol), formalin (0.25 mol) and anhydrous potassium carbonate (1 g) was dissolved in water (50 mL) by heating on a water bath for 5 min. The resultant solution was stirred for 15 min and then refluxed on a sand-bath for 2 h. On cooling, a solid separated out which was filtered off and washed repeatedly with ice-cold water. The solid thus obtained, was dried and recrystallized from ethanol. A colorless needle was obtained. m.p., 149-150 °C, Yield-75 %.

Synthesis of 7-hydroxy-4-methyl coumarin: The titled compound was prepared according to the method described in the literature[16]. A mixture of resorcinol (5.5 g) and ethyl acetoacetate (6.35 mL) with 75 % H_2SO_4 (50 mL) in a 100 mL conical flask heated on the water bath at 100 °C for 0.5 h. Cool the resulting dark green solution and stir in to crushed ice. Filter off the crud product and wash with water to remove impurities and recrystallized from methanol. A pale yellow plate was obtained. m.p. 185-186 °C, Yield 85 %.

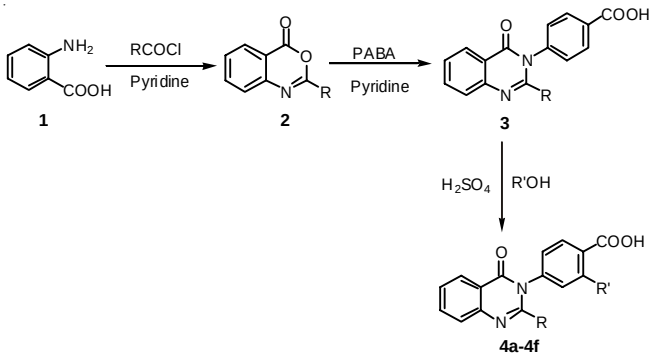
Synthesis of 2-aryl-3-(hydroxyl ethyl)-4-(3*H*)-quinazoline/1-hydroxyethyl-7-hydroxy-4-methyl-2-oxo-quinoline: The titled compound was prepared according to the method described in the literature[17]. A mixture of 2-aryl-4-oxo-3,1-benzoxazines **(2)** (0.05 mol)/7-hydroxy-4-methyl coumarin (0.05 mol) was dissolved in dry pyridine (50 mL) and stirred vigorously followed by adding β-aminoethenol (0.05 mL) in portion with constant shaking. Subsequently reaction mixture was refluxed for 6 h and then allowed to cool, which is treated with dilute hydrochloric acid. The solid separated out was filtered off washed with water and dried over silica gel. It is recrystallized from ethanol.

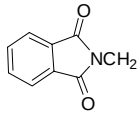
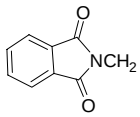
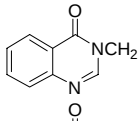
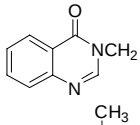
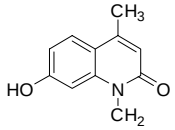
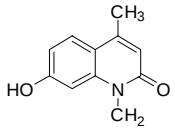
2-Phenyl-3-(hydroxyethyl)-4-(3*H*)-quinazolone: m.p.: 164-165 °C. Yield 80 % (Found: N, 10.55 % $C_{16}H_{14}N_2O_2$ requires N, 10.53 %)

2-Styryl-3-(hydroxyethyl)-4-(3*H*)-quinazolone: m.p.: 108-109 °C. Yield 75 % (Found: N, 9.54 % $C_{18}H_{16}N_2O_2$ requires N, 9.58 %)

1-Hydroxyethyl-7-hydroxy-4-methyl-2-oxo-quinoline: m.p.: 172-173 °C. Yield 75 % (Found: N, 6.10 % $C_{12}H_{13}NO_2$ requires N, 6.39 %)

Preparation of 3-[benzoic acid-(3-phthalimido methyl/3-ethyl-3H-2-phenyl-4-oxo-quinazolinyl/1-ethyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)]-2-aryl-3*H*-quinazoline-4-ones (4a-f): The method of Tscherniac[17] was followed for amido alkylation of compound **3**. A mixture of compound **3** and N-hydroxy methyl phthalimide/2-aryl-3-(ethanoic acid)-4-(3*H*)-quinazoline/1-ethanoic acid-7-hydroxy-methyl-2-oxo-quinoline (0.01 mol) was dissolved in minimum quantity of conc. H_2SO_4 in cold conditions and stirred for 1 h then left overnight. A solid is separated out after pouring the content in ice cold water, which is filtered off and washed with water to remove sulphonated products. After drying under vacuum it is recrystallized from ethanol (**Scheme-I**).



Compound No.	R	R'
4a	Phenyl	
4b	Styryl	
4c	Phenyl	
4d	Styryl	
4e	Phenyl	
4f	Styryl	

Scheme-I

3-[Benzoic acid-(3-phthalimido methyl)]-2-phenyl-3H-quinazoli-ne-4-ones (4a): IR (KBr) (ν_{max} in cm^{-1}): 1610 (C=N str.), 1686 (Ph-N-C=O str.), 1755 (CH_2-N=C=O str.), 3000 (Phenolic- COOH str.); ^{1}H NMR (δ, ppm) ($CDCl_3$): 4.89 (m, 2H), 7.29-7.99 (m, 16H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (δ, ppm) ($CDCl_3$): 35.8, 119.1, 119.5, 120.9, 122.4, 124.0, 126.1, 127.4, 127.6, 128.7, 128.8, 128.9, 130.2, 130.3, 132.1, 132.3, 132.5, 133.5, 137.8, 138.3, 151.3, 160.9, 164.0, 168.2 & 169.4; Mass (*m/z*): 456, 445, 313, 247, 145, 119, 105 (base peak), 396 and 376.

3-[Benzoic acid-(3-phthalimido methyl)]-2-styryl-3H-quinazolin e-4-ones (4b): IR (KBr) (ν_{max} in cm^{-1}): 1610 (C=N str.), 1686 (Ph-N-C=O str.), 1755 (CH_2-N=C=O str.), 3000 (Ar -COOH str.); ^{1}H NMR (δ, ppm) ($CDCl_3$): 4.89 (m, 2H), 7.29-7.99 (m, 16H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (δ, ppm) ($CDCl_3$): 35.8, 112.0, 119.1, 119.5, 120.9, 122.4, 124.0, 126.1, 127.4, 127.6, 128.7, 128.8, 128.9, 130.2, 130.3, 132.1, 132.3, 132.5, 133.5, 137.8, 138.3, 151.3, 160.9, 164.0, 168.2 & 169.4; Mass (*m/z*): 456, 445, 313, 247, 145, 119, 105 (base peak), 396 and 376.

3-[Benzoic acid-(3-ethyl-3H-4-oxo-quinazolinyl)]-2-phenyl-3H-quinazoline-4-ones (4c): IR (KBr) (ν_{max} in cm^{-1}): 1610 (C=N str.), 1686 (Ph-N-C=O str.), 1755 (CH_2-N=C=O str.), 3000 (Ar -COOH str.); ^{1}H NMR (δ, ppm) ($CDCl_3$): 4.46 (m, 2H), 7.29-7.99 (m, 16H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (δ, ppm) ($CDCl_3$): 38.6, 119.1, 119.5, 120.9, 122.4, 127.4, 128.7, 128.8, 128.9, 130.2, 130.3, 133.5, 137.8, 138.3, 147.1, 147.5, 151.3, 160.9, 164.0, & 169.4; Mass (*m/z*): 456, 445, 313, 247, 145, 119, 105 (base peak), 396 and 376.

3-[Benzoic acid-(3-ethyl-3H-4-oxo-quinazolinyl)]-2-styryl-3H-quinazoline-4-ones (4d): IR (KBr) (ν_{max} in cm^{-1}): 1610 (C=N str.), 1686 (Ph-N-C=O str.), 1755 (CH_2-N=C=O str.), 3000 (Ar -COOH str.); ^{1}H NMR (δ, ppm) ($CDCl_3$): 4.46 (m, 2H), 7.29-7.99 (m, 16H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (δ, ppm) ($CDCl_3$): 38.6, 112.0, 119.1, 119.5, 120.9, 122.4, 127.4, 128.7, 128.8, 128.9, 130.2, 130.3, 133.5, 137.8, 138.3, 147.1, 147.5, 151.3, 160.9, 164.0, & 169.4; Mass (*m/z*): 456, 445, 313, 247, 145, 119, 105 (base peak), 396 and 376.

3-[Benzoic acid-(1-ethyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)]-2-phenyl-3H-quinazoline-4-ones (4e): IR (KBr) (ν_{max} in cm^{-1}): 1610 (C=N str.), 1686 (Ph-N-C=O str.), 1755 (CH_2-N=C=O str.), 3000 (Ar -COOH str.); ^{1}H NMR (δ, ppm) ($CDCl_3$): 1.71 (s, 3H), 4.22 (m, 2H), 5.0 (s, 1H, OH), 6.35 (q, 1H), 7.06-7.99 (m, 15H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (δ, ppm) ($CDCl_3$): 20.8, 38.2, 41.5, 61.6, 106.3, 111.4, 119.4, 119.8, 120.7, 120.9, 122.2, 122.4, 126.4, 127.4, 128.0, 128.7, 128.8, 131.5, 133.5, 135.2, 135.8, 136.7, 138.2, 139.0, 147.1, 148.8, 157.9, 160.9, 161.8 & 164.0; Mass (*m/z*): 456, 445, 313, 247, 145, 119, 105 (base peak), 396 and 376.

3-[Benzoic acid-(1-ethyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)]-2-styryl-3H-quinazoline-4-ones (4f): IR (KBr) (ν_{max} in cm^{-1}): 1610 (C=N str.), 1686 (Ph-N-C=O str.), 1755 (CH_2-N=C=O str.), 3000 (Ar -COOH str.); ^{1}H NMR (δ, ppm) ($CDCl_3$): 1.71 (s, 3H), 4.22 (m, 2H), 5.0 (s, 1H, OH), 5.6 (m, 1H), 6.6 (m, 1H), 7.06-7.99 (m, 16H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (δ, ppm) ($CDCl_3$): 20.8, 38.2, 41.5, 61.6, 106.3, 111.4, 112.0, 119.4, 119.8, 120.7, 120.9, 122.2, 122.4, 126.4, 127.4, 128.0, 128.7, 128.8, 131.5, 133.5, 135.2, 135.8, 136.7, 138.2, 139.0, 147.1, 148.8, 157.9, 160.9 & 161.8; Mass (*m/z*): 456, 445, 313, 247, 145, 119, 105 (base peak), 396 and 376.

Antiviral activity: All the six synthesized compounds **(4a-f)** were evaluated for their antiviral activity against two animal viruses *viz*., JEV (P20778) and HSV-I (753166) originally obtained from National Institute of Virology Pune (India). Antiviral activity was performed *in vitro* (Vero cells) and *in vivo* (Swiss-albino-mico). Both the viruses were maintained by introcerebral passages of 1-3 days old suckling Swiss albino-mice. Vero cell were maintained in minimum essential medium (MEM) (Sigma, USA) with 10 % foetal bovine serum (FBS) (Gibco, USA) and 100 units of penicillin 100 µg of streptomycin and 40 µg mL^{-1} of gentamycin were added. Cytotoxicity as well as antiviral assay of the compounds was performed in 96 well µL plates (non-clone Denmark) by the standard method. For *in vivo* testing the treated and untreated mice were observed for 21 days post infection. Upon the termination of experiment the percent protection and the mean survival time (MST) in day were calculated.

RESULTS AND DISCUSSION

The method of Tscherniac[17] was followed for the synthesis of 3-[benzoic acid-(3-phthalimido methyl/3-ethyl-3*H*-2-phenyl-4-oxo-quinazolinyl/1-ethyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)]-2-aryl-3*H*-quinazoline-4-ones **(4a-f).** The synthesized compounds were characterized by elemental analysis, FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral data (Table-1).

All the compounds **(4a-f)** investigated for their anti-JEV and anti-HSV-I activity (Tables 2 and 3), were found active both *in vitro* and *in vivo* studies. The maximum percentage inhibition was 55 % in *in vivo* studies as compared to *in vitro* studies for anti-JEV activity and on the other hand the maximum percentage inhibition was 56 % in *in vitro* studies for anti-HSV-1 activity.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF 3-[BENZOIC ACID-(3-PHTHALIMIDO METHYL/3-ETHYL-3*H*-2-PHENYL-4-OXO-QUINAZOLINYL/1-ETHYL-7-HYDROXY-4-METHYL-2-OXO-QUINOLINYL)]-2-ARYL-3*H*-QUINAZOLINE-4-ONES (**4a-f**)

Comp. No.	R	R'	m.p. (°C)	Yield (%)	m.f.	N (%)	
						Found	Calcd.
4a	Phenyl	Phthalimido methyl	120-122	75	$C_{30}H_{19}N_3O_5$	8.82	8.87
4b	Styryl	Phthalimido methyl	160-164	70	$C_{32}H_{21}N_3O_5$	8.83	8.41
4c	Phenyl	3-Ethyl-3*H*-2-phenyl-4-oxo-quinazolinyl	135-140	65	$C_{37}H_{26}N_4O_4$	9.93	9.96
4d	Styryl	3-Ethyl-3-2-phenyl-4-oxo-quinazolinyl	158-160	65	$C_{39}H_{28}N_4O_4$	9.49	9.52
4e	Phenyl	1-Ethyl-7-hedroxy-4-methyl-2-oxo-quinazolinyl	139-141	61	$C_{33}H_{25}N_3O_5$	8.10	8.15
4f	Styryl	1-Ethyl-7-hydroxy-4-methyl-2-oxo-quinazolinyl	162-164	55	$C_{35}H_{27}N_3O_5$	8.09	8.12

TABLE-2
ANTI-JEV ACTIVITY DATA OF 3-[BENZOIC ACID-(3-PHTHALIMIDO METHYL/3-ETHYL-3*H*-2-PHENYL-4-OXO-QUINAZOLINYL/ 1-ETHYL-7-HYDROXY-4-METHYL-2-OXO-QUINOLINYL)]-2-ARYL-3*H*-QUINAZOL-INE-4-ONES (**4a-f**)

Compd. No.	R	R'	*in vitro*			TI	CPE inhibition (%)	*in vivo*		Protection (%)
			Dose (µg/mL)	CT_{50} (µg/mL)	EL_{50} (µg/mL)			Dose (µg/ mouse/day)	MST (days)	
4a	Phenyl	Phthalimidomethyl	500-4	500	125	04	40	200	7	55
4b	Styryl	Phthalimidomethyl	500-4	500	100	05	50	200	4	40
4c	Phenyl	3-Ethyl-3*H*-2-phenyl-4-oxo-quinazolinyl	500-4	500	125	04	40	200	7	35
4d	Styryl	3-Ethyl-3-2-phenyl-4-oxo-quinazolinyl	500-4	500	100	05	50	200	4	42
4e	Phenyl	1-Ethyl-7-hedroxy-4-methyl-2-oxo-quinazolinyl	500-4	500	125	04	40	200	7	30
4f	Styryl	1-Ethyl-7-hydroxy-4-methyl-2-oxo-quinazolinyl	500-4	500	100	05	50	200	4	40

CT_{50}= 50 % cytotoxic concentration; EC_{50} = 50 % effective concentration; TI = Therapeutic index; CPE = Cytopathic effect; MST = Mean survival time.

TABLE-3
ANTI-HSV-I ACTIVITY DATA OF 3-[BENZOIC ACID-(3-PHTHALIMIDO METHYL/3-ETHYL-3*H*-2-PHENYL-4-OXO-QUINAZOLINYL/1-ETHYL-7-HYDROXY-4-METHYL-2-OXO-QUINOLINYL)]-2-ARYL-3*H*-QUINAZOL-INE-4-ONES (**4a-4f**)

Compd. No.	R	R'	*in vitro*			TI	CPE inhibition (%)	*in vivo*		Protection (%)
			Dose (µg/mL)	CT_{50} (µg/mL)	EL_{50} (µg/mL)			Dose (µg/ mouse/day)	MST (days)	
4a	Phenyl	Phthalimidomethyl	500-4	250	7.8	32	45	200	7	40
4b	Styryl	Phthalimidomethyl	500-4	250	15.62	16	26	200	4	20
4c	Phenyl	3-Ethyl-3*H*-2-phenyl-4-oxo-quinazolinyl	500-4	250	7.8	32	55	200	7	10
4d	Styryl	3-Ethyl-3-2-phenyl-4-oxo-quinazolinyl	500-4	250	62.5	04	55	200	4	10
4e	Phenyl	1-Ethyl-7-hedroxy-4-methyl-2-oxo-quinazolinyl	500-4	250	62.5	04	56	200	7	20
4f	Styryl	1-Ethyl-7-hydroxy-4-methyl-2-oxo-quinazolinyl	500-4	250	125	02	20	200	4	30

CT_{50}= 50 % cytotoxic concentration; EC_{50}= 50 % effective concentration; TI= Therapeutic index; CPE= Cytopathic effect; MST= Mean survival time.

Conclusion

In present study, the synthesis of 3-[benzoic acid-(3-phthalimido methyl/3-ethyl-3*H*-2-phenyl-4-oxo-quinazolinyl/ 1-ethyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)]-2-aryl-3*H*-quinazoline-4-ones **(4a-f)** is described. The structures of the synthesized compounds were confirmed and characterized by elemental analysis and spectral studies. It was observed that some of the synthesized compounds showed excellent anti-JEV and anti-HSV-I activities.

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