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Synthesis, Charactrisation and Pharmacological Evaluation of Novel Brominated Triazolyl Quinazolinone Derivatives

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ABSTRACT

*In the present study a series of novel brominated triazolyl quinazolinone derivatives were synthesized by the addition of ammonia and propargyl bromide to brominated 2-Phenyl-benzo[1,3]oxazin-4-one [I] to give brominated O-, N-alkylnyl quinazolinones [III, IV]. These compounds when treated with alkyl azide in DMSO using copper sulphate as catalyst, gives brominated 4-((1H-1,2,3-triazol-4-yl)methoxy)-2-phenylquinazoline **[V]** and brominated 3-((1H-1,2,3-triazol-4-yl)methyl)-2-phenylquinazoline-4-one[VI] and their derivatives. These synthesized compounds were characterized by TLC, IR, [1]HNMR and Mass spectra. All these compounds were evaluated for their antibacterial and antifungal activity using minimum inhibitory concentration (MIC) values (Zone of inhibition method). Some of them are found to be moderate to good biologically active compounds.*

Key words: *Brominated Quinazolinones, Triazoles, [1]HNMR, IR, Mass and Antimicrobial activity.*

INTRODUCTION

Quinazolinone is a keto-quinazoline compound. It is a versatile lead molecule for designing potential bioactive agents. Quinazolinones and their derivatives like 4(3H)-quinazolinones are of considerable interest because of their biological applications, such as, antibacterial [1], analgesic [2], anti-inflammatory [3, 4], antifungal [5], antimalarial [6], antihypertensive [7], CNS depressant [8], anticonvulsant [9], antihistaminic & local anaesthetic [10], antiparkinsonism [11], antiviral and cancer activities [12]. Series of quinazolinones were found to be potent nonnucleoside reverse transcriptase inhibitors (NNRTIs) of human immuno- deficiency virus type -1 (HIV-1) [13]. Structure activity relationship studies of quinazolinone ring system revealed in various literatures [14-16].

Triazoles are aromatic compounds similar to the pyrazole and imidazole, but with an additional nitrogen atom in the ring structure. These compounds have received much attention because of their wide range of applications as light stabilizers, fluorescent whiteners, optical brightening agents, corrosion retardants, dyestuffs, asymmetric dihydroxylation catalysts, photosensitizers fungicidal, herbicidal, cytostatic, virostatic, antiinflammatory, anti-HIV, antimicrobial, antihistaminic, anticonvulsant, hypnotic, CCK antagonists, antiulcer, and β-adrenergic receptor agonists [17].

Click chemistry is a modular approach and its applications are enormously increasing in all aspects of drug discovery. This methodology gives access to triazole-based drug molecules in a controlled fashion and lays the foundation for a fragment-based approach to drug discovery.

Considering all these applications of quinazolinones and triazoles which were reported to be more potent and less toxic, it has been felt worthwhile to take up the present investigation in an effort to incorporate triazole ring system into quinazolinone derivatives with methylene bridge to synthesize novel O- and N-alkynyl triazolyl quinazolinones as antimicrobial agents.

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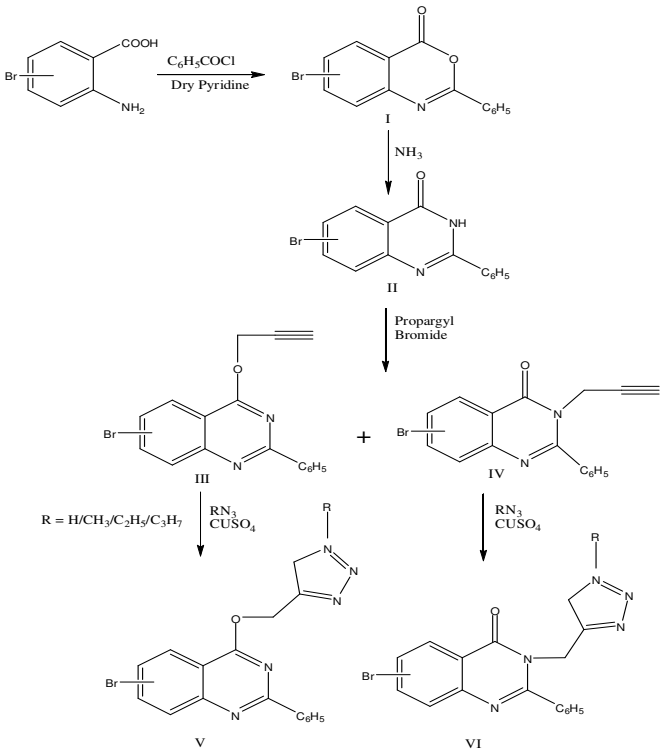
MATERIALS AND METHODS

All the chemicals used were Aldrich, Fluka and Merck company. Thin layer chromatography (TLC) was performed on E.Merk AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were determined in a Perkin-Elmer transform (FTIR spectrum). ^{1}H NMR spectra were recorded on varian EM-360(400MHz mercury plus) spectrometer in DMSO or $CDCl_3$ and calibrated using solvent signals. All chemical shifts recorded in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS at energy of ionizing electron equal to 70ev.

Brominated-2-phenyl-benzo(1,3)oxazin-4-one [1] was prepared from Mono bromo anthranilic acid, by cyclization with benzoyl chloride in the presence of dry pyridine. By treating compound [I] with ammonia, Brominated-2-phenylquinazolin-4-one [II] was synthesized. In equimolar ratio the synthesized compound was allowed to react with propargyl bromide in presence of anhydrous potassium carbonate in dry acetone as a solvent. This results in the formation of both Brominated O- and N-alkynyl quinazolinones [III and IV]. Since O-alkynylated product was comparatively less polar than the N-alkynylated product, they were separated using column chromatography. The Brominated O-alkynyl quinazolinone [III] was treated with alkyl azide in DMSO using Copper sulphate as catalyst and resulted in the formation of substituted-1,2,3-triazolo quinazolinone derivatives [V]. The reaction is considered to take place via 1,3-dipolar cycloaddition of alkyl azide to alkynyl quinazolinones through a preformed copper acetylide complex formation. The synthesized Brominated triazolyl quinazolinone derivatives were characterized by both physical and spectral data. These compounds were evaluated for their antimicrobial activity. The melting points of newly synthesized compounds were determined with an electro thermal melting point apparatus.

Scheme:



The derivatives of synthesized compounds V were prepared by substituting R = H, CH_3, C_2H_5, C_3H_7 groups. The obtained substituted products were also characterized, and screened for their antimicrobial activities.

Synthesis of Bromo quinazolinone derivatives:

Bromination of anthranilic acid:

Anthranilic acid was dissolved in glacial acetic acid and cooled below 15^0C by keeping in ice bath. Then bromine in acetic acid was added drop wise till the reddish brown colour of the bromine persisted. Then the mixture was filtered under suction pump and then washed with benzene. The obtained product contains mixture of mono and di bromo anthanilic acid. After drying the product, it was boiled with water containing conc.HCl and filtered while hot under suction. The insoluble residue was extracted twice with boiling water. The filtrate upon cooling yielded precipitate of mono bromo anthranilic acid.

STEP – 1: Synthesis of Brominated 2-Phenyl-benzo(1,3)oxazin-4-one:[I]

To an ice cold solution of mono bromo anthranilic acid (0.10moles) in dry pyridine, benzoyl chloride (0.20moles) was added. The mixture was stirred for 4–5hrs, then poured into 250ml of ice cold water and 2 to 3 drops of dilute HCl was added. The separated solid was recrystallized from ethanol.

Molecular formula: $C_{14}H_8BrNO_2$, Molecular weight: 302, Solubilty: $CHCl_3$, Percentage Yield: 82%, M.P; 100-105°C, R_f; 0.47 (hexane and ethyl acetate)

STEP – 2: Synthesis of Brominated 2-Phenyl quinazolin-4(3H)-one: [II]

To the Compound (I) (0.01moles), ammonia (10ml) was added and the mixture was allowed to stirr for about 7hrs. TLC was monitored during the reaction. After stirring the reaction mixture was filtered, washed with water and dried.

Molecular formula: $C_{14}H_9BrN_2O$, Molecular weight: 301, Solubilty: $CHCl_3$, Percentage Yield: 84%, M.P; 200-204°C, R_f; 0.48 (hexane and ethyl acetate).

STEP – 3: Synthesis of Bromo Propargylated quinazolinones: [III and IV]:

Compound II (3mmole) and potassium carbonate (6mmoles) in acetone (20ml) was taken in a two-necked flask. To the mixture, propargyl bromide (6mmoles) was added drop-wise and the reaction was heated under reflux for five hours. The mixture was concentrated *in vacuo* and added to the ice-cold water. The separated product was collected by filtration. The bromo O- and N-propargylated products were separated by column chromatography.

Brominated 2-Phenyl quinazolin-4-ol-but-1-yne [III]:

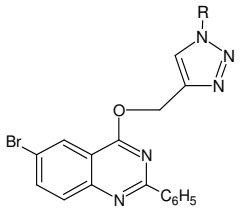
Molecular formula: $C_{18}H_{13}BrN_2O$, Molecular weight: 353, Solubilty: $CHCl_3$, Percentage Yield: 90%, M.P; 155-157°C, R_f; 0.4 (hexane and ethyl acetate).

Brominated 2-Phenyl-4-(prop-2-ynyl) quinazolin-4(3H)-one [IV]:

Molecular formula: $C_{17}H_{13}BrN_2O$, Molecular weight: 341, Solubilty: $CHCl_3$, Percentage Yield: 90%, M.P; 105-110°C, R_f; 0.4 (hexane and ethyl acetate).

STEP – 4: Synthesis of Bromo Triazolyl quinazolinone derivatives: [V]

Brominated Alkynyl quinazolinones (0.001mole) and copper sulphate (0.001moles) were taken in dimethyl formamide in a round-bottomed flask and cooled to O^0C. Then weighed amount of alkyl azide was added drop wise and the reaction mixture was stirred for 12 hours. The mixture was concentrated *in vacuo* and poured into the crushed ice. The crude brominated triazolyl quinazolinone product was collected by extraction with ethyl acetate and then purified the product by passing through a column packed with silica gel.



.V

S.No	Compound	R	Molecular formula	Molecular weight	Melting point (°C)	% yield
1	Va	H	$C_{17}H_{12}BrN_5O$	382	>300	88
2	Vb	CH_3	$C_{18}H_{14}BrN_5O$	396	174-176	74
3	Vc	C_2H_5	$C_{19}H_{16}BrN_5O$	410	155-158	69
4	Vd	C_3H_7	$C_{20}H_{18}BrN_5O$	424	167-169	70

Compound [Va]:

4-((1H-1,2,3-triazol-4-yl)methoxy)-6-bromo-2-phenylquinazoline:

IR (KBr, cm^{-1}): 3379 (ν N-H), 3077(CH, aromatic), 2929 (CH str in CH_2), 1630 (N=N), 1577 (C=N str), 1143 (C-O-C str), 1081 (N-N), and 750-730 (C-Br). **^{1}H NMR** ($CDCl_3$, δ ppm) 3.7(s, 3H, N-CH_3), 5.2 (d, 2H, OCH_2), 7.3 (d, 1H, Ar-H), 7.5-7.6. (t, 3H, Ar-H), 7.8-7.9 (t, 1H, Ar-H), 8.1- 8.3 (m, 3H, Ar-H), 8.45 (s, 1H, triazole-H). MS (EI). m/z 383 (M+1).

Compound [V b]:

6-Bromo-4-((1-methyl-1H-1,2,3-triazol-4-yl)methoxy)-2-phenylquinazoline:

IR (KBr, cm^{-1}): 3379 (ν N-H), 3077 (CH, aromatic), 2929 (CH str in CH_2), 1630 (N=N), 1577 (C=N str), 1143 (C-O-C str), 1081 (N-N), and 750-730 (C-Br).**^{1}H NMR** ($CDCl_3$, δ ppm) 3.7(s, 3H, N-CH_3), 5.2 (d, 2H, OCH_2), 7.3 (d, 1H, Ar-H), 7.5-7.6. (t, 3H, Ar-H), 7.8-7.9 (t, 1H, Ar-H), 8.1- 8.3 (m, 3H, Ar-H), 8.45 (s, 1H, triazole-H). MS (EI).m/z 397 (M+1).

Compound [V c]:

6-Bromo-4-((1-ethyl-1H-1,2,3-triazol-4-yl)methoxy)-2-phenylquinazoline:

IR (KBr, cm^{-1}): 3379 (ν N-H), 3077(CH, aromatic), 2929 (CH str in CH_2), 1630 (N=N), 1577 (C=N str), 1143 (C-O-C str), 1081 (N-N) and 750-730 (C-Br). ^{1}H NMR ($CDCl_3$, δ ppm) **^{1}H NMR** ($CDCl_3$, δ ppm): 0.8-0.9(t, 3H, CH_3), 1.2-1.4 (m, 2H, CH_2), 4.45(s, 2H, N-CH_2), 5.25 (s, 2H, OCH_2), 7.2-7.3(t, 4H, Ar-H), 7.4-8.2 (m, 7H, Ar-H), 8.45 (s, 1H, triazole-H)MS (EI). m/z 411 (M+1).

Compound [V d]:

6-Bromo-2-phenyl-4-((1-propyl-1H-1,2,3-triazol-4-yl)methoxy)quinazoline:

IR (KBr, cm^{-1}): 3379 (ν N-H), 3077(CH, aromatic), 2929 (CH str in CH_2), 1630 (N=N), 1577 (C=Nstr), 1143 (C-O-C str), 1081 (N-N) and 750-730 (C-Br). ^{1}H NMR ($CDCl_3$, δ ppm, **^{1}H NMR** ($CDCl_3$, δ ppm): 0.8-0.9(t, 3H, CH_3), 1.2-1.4 (m, 2H, CH_2), 4.45(s, 2H, N-CH_2), 5.25 (s, 2H, OCH_2), 7.2-7.3(t, 4H, Ar-H), 7.4-8.2 (m, 7H, Ar-H), 8.45 (s, 1H, triazole-H). MS (EI). m/z 425 (M+1).

Antimicrobial Activity:

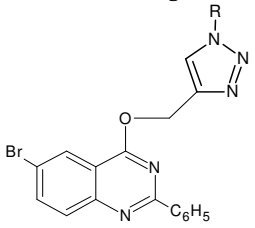
All the newly synthesized compounds were screened for their antibacterial and antifungal activities. For antibacterial study microorganisms employed were E-coli, K.pneumonia (gram –ve bacteria), S.aureus, B.subtilis (gram +ve bacteria). For antifungal study microorganism employed was Candida albicans. Both antibacterial and antifungal activities were investigated by using filter paper strip method in nutrient agar medium, and Sabouraud dextrose of czapexs dox agar medium by using drug standards Streptomycin and Fluconazole. The compounds were tested invitro for their antibacterial activity which are pathogenic to human beings. The Inoculation period for the test organisms in nutrient agar media was found to be 37± 1ºC for 24hrs, whereas for antifungal activity the zone of inhibition in mm was measured after 24 hrs of inhibition at 25^{0}C.

RESULTS AND DISCUSSIONS

Formation of 4-((1H-1,2,3-triazol-4-yl)methoxy)-6-bromo-2-phenylquinazoline **(V a-d)** were confirmed by recording their IR, ^{1}H NMR and Mass spectral analysis. **IR** spectrum of compound Va showed absorption bands at 3379, 3077, 2929, 1630, 1577, 1143, 1081 and 750 cm^{-1} due to ν N-H, aromatic C-H, C-H stretching in methylene group, N=N, C=N, C-O-C str, N-N and C-Br respectively**. ^{1}H NMR** spectrum ($CDCl_3$, δ ppm) of representative compound **(Va)** show a specific pattern of signals. A Singlet at δ 3.7 ppm was appeared for three protons of N-CH_3 group. A doblet at δ5.2 ppm was appeared for two protons of O-H. A doblet at δ 7.3 ppm was appeared for one proton of aryl group (Ar-H). A triplet was appeared at δ 7.5-7.7 ppm due to three protons of aromatic ring. A triplet was appeared at δ 7.8-7.9 ppm due to single proton of aromatic ring. A multiplet was appeared at δ 8.1-8.3 ppm integrated to three protons of aromatic ring. A singlet was appeared at δ 8.45 ppm due to single proton of triazole moiety. Similarly the mass spectrum was recorded and reported as (M+1) values. For the compound Va the molecular weight 383 is consistent with the molecular formula $C_{17}H_{12}BrN_5O$. The values for the remaining compounds have been presented under the experimental part.

From the antimicrobial study the results conclude that among the newly synthesized Bromo triazolyl quinazolinones Vb exhibited good antibacterial activity against K.pneumoniae, E-coli, S,aureus, B.subtilis, the compounds Va and Vb exhibited relatively high antifungal activity against the species.

Table No. 2: Antibacterial and antifungal activities of compounds V



code	R	Antibacterial (IC_{50})				Antifungal (IC_{50})
		E. Coli	K. Pneumonia	S. Aureus	B. Subtilis	Candida albicans
Va	H	319	282.1	260.4	349.6	385.7
Vb	CH_3	206.7	301.4	323.4	72.2	390.2
Vc	C_2H_5	340.6	276	319	267.5	480.6
Vd	C_3H_7	282.4	348.8	319	329.9	410.9

CONCLUSION

In conclusion the Synthesis, Characterization, Pharmacological analysis of 4-((1H-1,2,3-triazol-4-yl)methoxy)-6-bromo-2-phenylquinazoline and its derivatives were done. The representative analogues were Screened for in vitro antibacterial and antifungal activities. The biological evaluation showed that the molecules Vb showed better antibacterial activity where as Va, and Vb exhibited relatively high antifungal activity. The results were in agreement with the experimental observations.

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