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Synthesis, Characterization and Biological Activity of Novel Quinazolinone Compounds

Pankaj k. Singh and Rakesh K. Paliwal*

*Department of chemistry, Narain Degree College, Shikohabad-205135, Uttar Pradesh, **INDIA**

Email: rkpaliwal.skb@gmail.com

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ABSTRACT

A series of novel quinazolinone compounds were synthesized by two steps. In step 1, various 2-substituted-3, 1-benzoxazin-4-ones are prepared by the reaction of anthranilic acid and acetic anhydride/benzoyl chloride and propanoic anhydride. In step II, 2-substituted-3, 1-benzoxazin-4-one which were prepared in step I, were condensed with different substituted aromatic amine to produce various quinazolinone compounds. The resulting quinazoline-4(3H)-one compounds were characterized by ^{1}H *NMR spectra & mass spectral analysis. Synthesized novel quinazolinone compounds evaluated for their biological activity, although the synthesized compound were prepared for targeting antiviral & anticancer activity but synthesized compound so far has been tested for antibacterial &antifungal activity. Among synthesized compound exhibited good antibacterial & antifungal activity.*

Keywords: Anthranilic acid, substituted aromatic amine, quinazolinone-4(3H)-one, antimicrobial activity.

INTRODUCTION

The quinazolinone core presents in various derivatives which form an important class of compound, as they are present in large family of product with their broad biological activities. They generally show useful therapeutic and pharmacological properties such as antibacterial, antifungal, antiviral, antitumor, antimalarial[1-9] diuretic, sedative and hypotension, antihypertensive[10], antitubercular[11], anti HIV, anticonvulsant Antiviral, anticancer [11], hypolipedimic, analgesic activities and also known to act as protein tyrosinkinase inhibitor [12]. Some marketed drugs having quinazoline and quinazolinone moiety are given in figs.1-3.

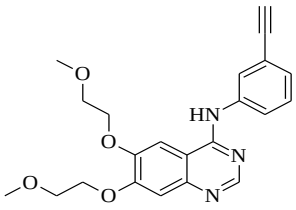


Fig 1. Erlotinib (Anticancer)

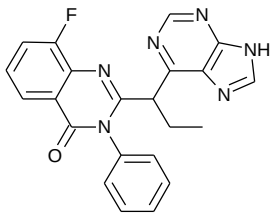


Fig 2.Antihaemetological cancer

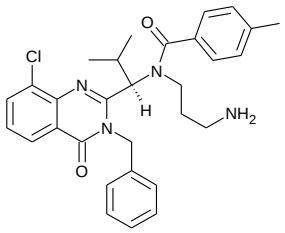
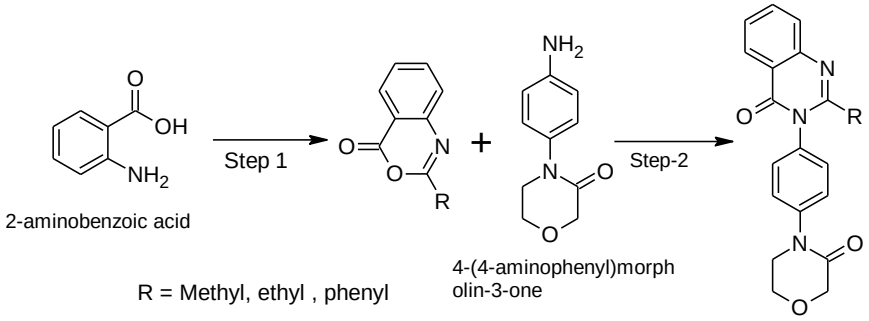


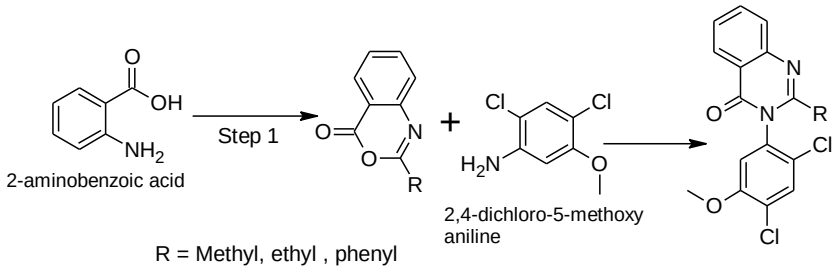
Fig 3. Ispinesib (Totreatsolid tumer)

MATERIALS AND METHODS

The purity and reaction progress were monitored by thin layer chromatography (TLC) in silica gel (MN-kieselge G, 0.2 nm thickness and $CHCl_3$ and methanol (9:1) were used as mobile phase the TLC were visualized under 254 nm ultraviolet light as well as the staining with iodine and potassium permagnate.The structure of the synthesized compound was characterized by 1_H NMR spectra were obtained on a broker 400 MHz spectrometer with CDCl3 as a solvent.Tetramethylsilane (TMS) served as an internal reference and chemical shift δ (ppm). Mass spectra were recorded by MAT GC MS. Synthetic route for synthesis of compound in Scheme-1and scheme-2



Scheme 1: Synthesis of 3-[4-(3-oxomorpholin-4-yl) phenyl]-2-substituted quinazolin-4(3*H*)-one



Scheme 2: Synthesis of 3-(2,4-dichloro-5-methoxyphenyl)-2-substitutedquinazolin-4(3*H*)-one

Synthesis of benzoxazinone compounds: The yields and characterization data were given in table 1

Synthesis of 2-phenyl-3, 1 benzoazine-4-one (PB): To a solution of anthranilic acid (0.1 mol) and in pyridine (20 mL) was added benzoyl chloride (0.02 mol.), and the mixture was stirred for 1 h at room temperature. The reaction mixture was washed with 5% sodium carbonate solution (20 mL) to remove the pyridine and unreacted benzoyl chloride, again washed with water and then filtered, dried to get crude product which was further purified in ethyl acetate and hexanes solvent mixture afforded the pure compound.

Synthesis of 2-methyl-3, 1 benzoazine-4-one (MB): To a solution of anthranilic acid (0.1 mol) and in acetic anhydride (0.2 mol) was reflux 6 hr under anhydrous conditions. Product formation was monitored by TLC. The excess acetic anhydride distilled off under reduced pressure and cooled to room temperature to afforded pale yellow crude product which was purified in methanol.

Synthesis of 2-ethyl-3, 1 benzoazine-4-one (EB): To a solution of anthranilic acid (0.1mol) and in propionic anhydride (0.2mol) was reflux 6 h under anhydrous conditions. Product formation was monitored by TLC. The excess propionic anhydride distilled off under reduce pressure and cooled to room temperature to afforded pale yellow sold as crude product, this was further purified in methanol.

Synthesis of oxomorpholinyl quinazoline 4-(3H)-one compounds [13-15]

Procedure for the preparation of 3-[4-(3-oxomorpholin-4-yl) phenyl]-2-phenylquinazolin-4(3*H*)-one (PMQ): To solution of (0.1mol) 2-phenyl-3,1 benzoazine-4-one in 15 mL acetic acid was added 4-(4-aminophenyl)morpholin-3-one (0..15mol) in one lot and reaction was stirred continued. The resulted reaction mixture was heated to 100^0 C for 5-6 h. After the reaction was completed cool the reaction mixture and reaction mixture was poured in to ice with continuous stirring. The compound was crystallized and filter, dried to provided off white colored compound.

Procedure for the preparation of 2-methyl-3-[4-(3-oxomorpholin-4-yl) phenyl] quinazolin-4(3H)-one (MMQ): To solution of (0.1mol) 2-methyl-3,1 benzoazine-4-one in 15 ml glacial acetic acid was added 4-(4-aminophenyl)morpholin-3-one (0..15 mol) in one lot and reaction was stirred continued. The resulted reaction mixture was heated at 100^0 C for 5-6 h. After the reaction was completed cool the reaction mixture and reaction mixture was poured in to ice with continuous stirring. The compound was crystallized and filter, dried to provided compound.

Procedure for the preparation of 2-ethyl-3-[4-(3-oxomorpholin-4-yl) phenyl] quinazolin-4(3H)-one (EMQ): To solution of (0.1mol) 2-ethyl-3,1 benzoazine-4-one in 15 mL glacial acetic acid added 4-(4-aminophenyl)morpholin-3-one (0.15 mol) in one lot and reaction was stirred continued. The resulted reaction mixture was refluxed for 5-6 h. After the reaction was completed cool the reaction mixture and reaction mixture was poured in to ice with continuous stirring. The compound was crystallized and filters, dried to provide desired compound.

Synthesis of 2, 4 dichloro methoxy phenyl quinazoline 4-(3H)-one compounds [16, 17]

Procedure for the preparation 3-(2,4-dichloro-5-methoxyphenyl)-2-phenylquinazolin-4(3H)-one (PPQ): To solution of (0.1mol) 2-phenyl-3,1 benzoazine-4-one in 15 mL glacial acetic acid added 2,4-dichloro-5-methoxyaniline (0.15 mol.) in one lot and reaction was stirred continues. The resulted reaction mixture was refluxed for 5-6 h. After the reaction was complete reaction mixture was cooled to room temperature. The compound was crystallized in hexane and filter, dried to provide desired compound.

Procedure for the preparation 3-(2,4-dichloro-5-methoxyphenyl)-2-methyl lquinazolin-4(3H)-one (PMQ): To solution of (0.1mol) 2-methyl-3,1 benzoazine-4-one in 15 mL glacial acetic acid added 2,4-dichloro-5-methoxyaniline(0.15 mol) in one lot and reaction was stirred continued. The resulted reaction mixture was refluxed for 5-6 h. After the reaction was completed reaction mixture was cooled to room temperature. The compound was crystallized in hexane and filter, dried to provide desired compound.

Procedure for the preparation 3-(2,4-dichloro-5-methoxyphenyl)-2-ethyl lquinazolin-4(3H)-one (PEQ): To solution of (0.1mol) 2-ethyl-3,1 benzoazine-4-one in 15 mL glacial acetic acid added 2,4-dichloro-5-methoxyaniline (0.15 mol) in one lot and reaction was stirred continued. The resulted reaction mixture was refluxed for 5-6 h. After the reaction was completed reaction mixture was cooled to room temperature. The compound was crystallized in hexane and filter, dried to provide desired compound.

Table 1

Compound	Yield (%)	Melting point	Spectral data of synthesized compound [18-21]	
			Mass (m+1)	1_H NMR(ppm),CDCl3(400MHZ)
PB	85	118	224.3	7.25-7.59(4H,m),7.67-7.69(1H,d),7.80-7.83(1H,m),8.22-8.31(3H,m)
MB	90	105	162.15	2.24-2.63(3H,s),7.11-7.29(2H,m),7.77-7.81(1H,d),8.13-873 (1H,m)
EB	80	120	176.2	1.19-1.52(3H,m),2.46-2.75(2H,m),7.07-7.57(2H,m),7.76-7.80 (1H,t), 8.15-8.17(1H,d)
PMQ	65	167	398.3	3.64-3.80(2H,m),4.11-4.12(2H,m),4.29(2H,s),7.15-7.18(1H,d), 7.15 (1H,d),7.23(1H,m)
MMQ	73	142	336.4	2.18(3H,s), 3.64-3.80(2H,m),4.11-4.12(2H,m),4.29(2H,s), 7.17-7.18 (1H,d),7.75(1H,d),7.24(1H,m)
EMQ	63	144-148	350.4	1.31-1.33(3H,m)2.73-2.78(2H,m), 3.64-3.80(2H,m),4.11-4.12 (2H,m), 4.29(2H,s),7.15-7.18(1H,d),7.15(1H,d),7.23(1H,m)
PPQ	54	167-168	412.25	3.98(3H,s),6.90(1H,s),7.65(1H,s),7.42-7.46(3H,m)8.01-8.02(1H,m)
PMQ	63	135	351.21	3.98(3H,s),2.22-2.24(3H,s),7.11 (1H,s),7.65-7.67(1H,s)
PEQ	72	156-157	364.35	1.35-1.39(3H,m),2.78-2.80(2H,m),3.98(3H,s),7.09(1H,s),7.59(1H,s)

RESULTS AND DISCUSSION

In this work attempts has been made to undertake the synthesis of novel quinazoline 4(3H)-one by two step process. Total six novel quinazolinone and compounds were synthesized and characterized by spectral analysis. For this purpose the required 2-phenyl-3, 1 benzoazine-4-one, 2-methyl-3,1 benzoazine-4-one and 2-ethyl-3, 1 benzoazine-4-one were prepared through reaction between anthranilic acid and benzoyl chloride, acetic anhydride and propionic anhydride in presence of pyridine base & solvents. Novel quinazolinone compounds were prepared by coupling between benzoxazine 4-one with 4-(4-aminophenyl) morpholin-3-one and benzoxazine 4-one coupled with 2, 4-dichloro-5-methoxyaniline.

APPLICATIONS

Antimicrbial actvity: The preliminary in vitro antimicribial activity of synthesized compound were screened agianst the gram positive bacteria *Staphylococus aureous*, *Bacilus subtlis* and pathogenus fungi *candida albicans* and gram negative bacteria *Salmonella typhi and Escherichiacoli* (Table 2)
Nutrient agar plate were seeded 0.1ml of 24 h cultures, cylindrical plug were removed from agar plate using sterile cork borer and 100µg of the tested compounds (1mg mL^{-1}, DMSO) were added to well in triplicate. Blank solvent was used as control.plates inoculated with tested bacteria were incubated at 37^0C, while those of fungi incubated at 30^0C. The result were taken after 24 h incubation and were recorded as average diameter of inhibition zone in mm.

Table 2. Antimicrobial screening results for the tested compounds at 1mg mL^{-1} of concentration.[22, 23]

Comp.	*E.coli.*	*S. typhi*	*S. aureous*	*B. subtlis*	*candida albicans*
PMQ	++	++	--	++	--
MMQ	--	+	--	++	+
EMQ	+++	+	--	---	--
PPQ	+++	+++	--	++	--
PMQ	+	---	++	++	+
PEQ	++	+++	--	---	+
Erythromycin	+++	+	++	++	++
Streptomycin	+++	++	NT	---	NT

Inactive (Inhibition zone < 10mm),+, moderate actvity (inhibition zone 10-15mm),++, active (inhibition zone 15-20),+++, marked actvity (Inhibition zone >20), NT: not tested.

CONCLUSIONS

All of the newly synthesized compunds were subjected to antimicrbial screening by the in vitro cup plate technique using erythromycin and streptomycin as positive control. Compund EMQ and PPQ showed remarkable actvity agianst gram positive S.aureous and PEQ also showed remarkable actvity agianst gram positive S.aureous.B.subtilis and gram negative E.coli. All of the afermentioned compound showed antimicrbial actvity comparable to the used positive control drug. In addition compound EMQ,PPQ and PEQ proved to be most active broad spectrum antimicrobial agent.

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AUTHORS' ADDRESSES

1. **Rakesh Kumar paliwal**
Ex Principal Narain Degree college
37A Mehra colony, Shikohabad Fiozabad,
Uttar Pradesh-283135 (India)
Email: rkpaliwal.skb@gmail.com Tel: 7500775550
2. **Pankaj k. singh**
23E/16 Dabouli Ratanlal Nagar Kanpur
Uttar Pradesh -208022 (India)
Email: singh9788@gmail.com Tel: 9899252218