Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2015, 4 (6): 1858-1864

(International Peer Reviewed Journal)

Short Communication

Synthesis And Biological Screening Of Some Novel Quinazolinone And Quinazoline Thiones Derivatives

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Accepted on 10th November 2015

ABSTRACT

Many of the quinazolinones derivatives show antibacterial, antifungal, antiviral, antitumor, anticonvulsant activities as well as the inhibitory effects for thymidylate synthase and poly- (ADP-ribose) polymerase[1-10].On the other hand, quinazolinone ring containing substituted amino thiazole nucleus also exhibit various pharmacological activities. To keeping the above fact in the mind, we have synthesized substituted thiazolyl quinazoline-4(3H) one and substituted thiazolyl quinazoline-4(3H)-thione derivatives. In this work, some novel quinazolinones derivatives have been synthesized in two steps, in the step-I, various substituted benzoxazin-4(3H) one are prepared by the reaction of anthranilic acid and benzoyl chloride /acetic anhydride/propanoic anhydride. In step II, prepared substituted benzoxazine -4(3H) one, are coupled with various substituted thaizole compounds. The resulting novel thiazolyl quinazolinone derivatives were characterized by 1_H NMR spectra & mass spectral analysis. To broaden the scope of pharmacological activity of above prepared compound; sulphur group has been introduced in quinazolinone ring using phosphorous pentasulfide as sulfonation agent to synthesize thiazolyl quinazoline-4(3H) thione derivatives. The resulting novel thiazolyl quinazoline-4(3H) thione derivatives were characterized by1_H NMR spectra and mass spectral analysis.

Keywords: Anthranilic acid, substituted 2-aminothiazole, quinazoline-4(3H)-4 one, Quinazoline-4(3H)-4 thione, NMR & Mass & biological activity.

INTRODUCTION

Since many years there has been an increasing interest in the chemistry of 4(3H)-quinazolinones, because of their broad biological activities. Many of the quinazolinones derivatives shows 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 tyrosine kinase inhibitor [12]. In light of the increasing interest among chemist and biologists in their synthesis and bioactivity of quinazolinones derivatives, expecting an enhancement of biological activity sites, we have introduced two potential bioactivity sites; a quinazolinone moiety and thiazole ring in my system. Most common anticancer molecule which is currently in the market having quinazolinone ring system and to enhance biological activity of quinazolinone compounds, ketone

functionality is substituted with other aromatic moieties. Tyrosine kinase-targeting anti-cancer drugs (Figs. 1-5).

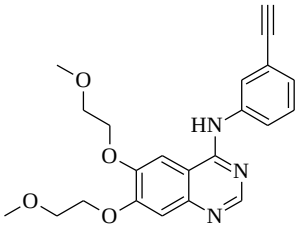


Fig. 1 Erlotinib (Anticancer)

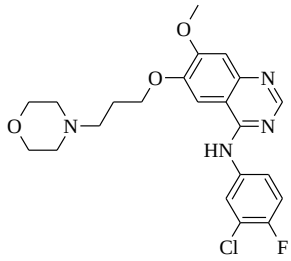


Fig.2 Gefitinib (Anticancer)

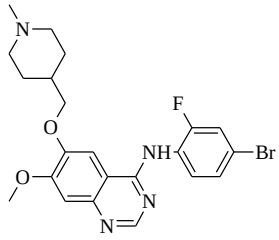


Fig. 3. Vandetanib (Anticancer)

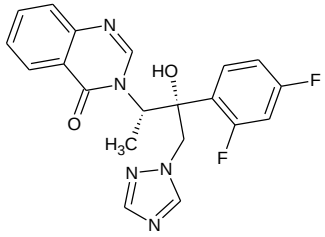


Fig.4. Albaconazole (antifungal)

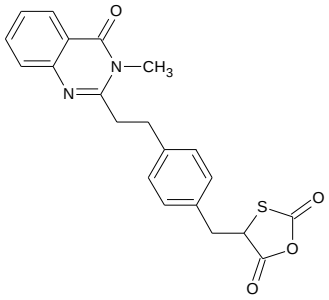
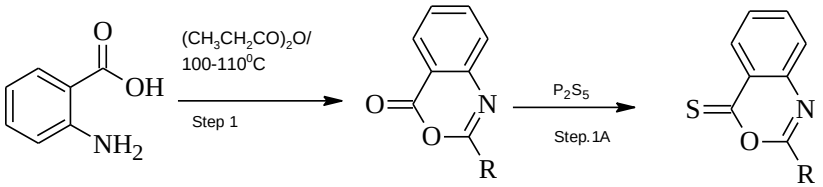


Fig.5. Balaglitazone (Antidiabetic &hyperlipedimic)

MATERIALS AND METHODS

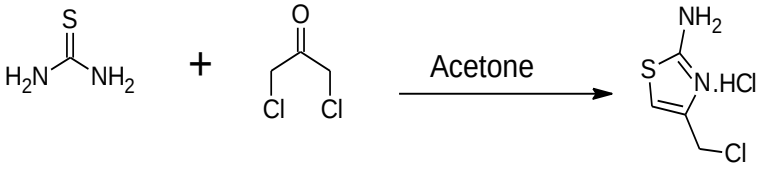
The purity and reaction progress were monitored by thin layer chromatography (TLC) in silica gel (MN-kieselge G, 0.2 nm thickness and $CHCl_3$ and methanol (9:1) were used as mobile phase the TLC were visualized under 254 nm ultraviolet light as well as the staining with iodine and potassium permagnate. 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 1.

Step-I Synthesis of 2-substituted-3, 1 benzoxazin-4-one

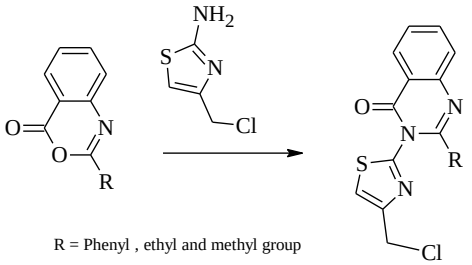


R = Methyl, ethyl , phenyl

Synthesis of (2-amino-1, 3-thiazol-4-yl) methanol

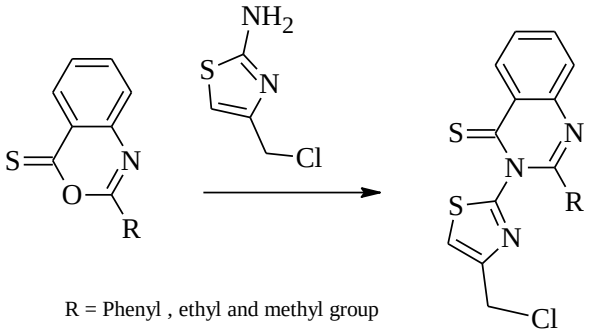


Step-II Synthesis of (3-[4-(chloromethyl)-1, 3-thiazol-2-yl]-2-ethylquinazolin-4(3*H*)-one



R = Phenyl , ethyl and methyl group

Step-IIA Synthesis of 3-[4-(chloromethyl)-1, 3-thiazol-2-yl]-2-ethylquinazolin-4(3*H*)-thione



R = Phenyl , ethyl and methyl group

Scheme 1

Synthesis and spectral analysis of prepared quinazolinone compounds and yield, characterization data were given in table-1

Synthesis of 2-phenyl-3, 1 benzoazine-4-one (PBO-1): 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 (PBO-2): To a solution of anthranilic acid (0.1 mol) and in acetic anhydride (0.2 mol) was reflux 6 h 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. This was purified in methanol.

Synthesis of 2-ethyl-3, 1 benzoazine-4-one (PBO-3): 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 quinazoline 4-thione compounds [13-17]

Synthesis of 2-phenyl-3, 1 benzoazine-4-thione (PBT-1): To a solution of 2-phenyl-3, 1 benzoazine-4-one (0.1mol) in THF (10 mL) was added phosphorous pentasulfide (0.03mol) lot wise in 1 h and reaction mixture stirred again d for 3 h at room temperature. The reaction mixture washed with 5% NaOH solution. Material extracted in ethyl acetate and again washed with water. The solvent distilled off under reduced pressure and cool to room temperature to afforded yellow coloured compound.

Synthesis of 2-methyl-3, 1 benzoazine-4-thione (PBT-2): To a solution of 2-methyl-3, 1 benzoazine-4-one (0.1mol) in THF (10 mL) was added phosphorous pentasulfide (0.03mol) lot wise in 1 h and reaction mixture stirred again d for 3 h at room temperature. The reaction mixture washed with 5% NaOH solution. Material extracted in ethyl acetate and again washed with water. The solvent distilled off under reduced pressure and cool to the room temperature to afforded yellow coloured compound.

Synthesis of 2-ethyl-3, 1 benzoazine-4-thione (PBT-3): To a solution of 2-ethyl-3,1 benzoazine-4-one (0.1mol) in THF (10 mL) was added phosphorous pentasulfide (0.03mol.) lot wise in 1h and reaction mixture stirred again d for 3 h at room temperature. The reaction mixture washed with 5% NaOH solution. Material extracted in ethyl acetate and again washed with water. The solvent distilled off under reduced pressure and cool to the room temperature to afforded yellow colored compound.

Synthesis of 3-[4-(chloromethyl)-1,3-thiazol-2-yl]-2-phenylquinazolin-4(3*H*)-one (PTQ-1): To solution of (0.1mol) 2-phenyl-3,1 benzoazine-4-one in 15 mL dry pyridine was added 4-(chloromethyl)-1, 3-thiazol-2-amine (0.2mol) in lot wise and reaction was stirred continued. The resulted reaction mixture was refluxed for 10 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.

Synthesis of 3-[4-(chloromethyl)-1, 3-thiazol-2-yl]-2-methylquinazolin-4(3*H*)-one (PTQ-2): To solution of (0.1mol) 2-methyl-3,1 benzoazine-4-one in 15 ml dry pyridine was added 4-(chloromethyl)-1, 3-thiazol-2-amine (0.2mol) in lot wise and reaction was stirred continued. The resulted reaction mixture was refluxed for 10 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

Synthesis of 3-[4-(chloromethyl)-1, 3-thiazol-2-yl]-2-ethylquinazolin-4(3*H*)-one (PTQ-3): To solution of (0.1mol) 2-ethyl-3,1 benzoazine-4-one in 15 mL dry pyridine was added 4-(chloromethyl)-1, 3-thiazol-2-amine (0.2mol) in lot wise and reaction was stirred continued. The resulted reaction mixture was refluxed for 10 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.

Synthesis of 3-[4-(chloromethyl)-1,3-thiazol-2-yl]-2-phenylquinazolin-4(3*H*)-thione (PTT-1): To solution of (0.1mol) 2-phenyl-3,1 benzoazine-4-thione in 15 mL dry pyridine was added 4-(chloromethyl)-1, 3-thiazol-2-amine (0.2mol) in lot wise and reaction was stirred continued. The resulted reaction mixture was refluxed for 10 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.

Synthesis of 3-[4-(chloromethyl)-1,3-thiazol-2-yl]-2-methyllquinazolin-4(3*H*)-thione (PTT-2): To solution of (0.1mol) 2-methyl-3,1 benzoazine-4-thione in 15 mL dry pyridine was added 4-(chloromethyl)-1, 3-thiazol-2-amine (0.2mol) in lot wise and reaction was stirred continued. The resulted reaction mixture was refluxed for 10 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 desired compound.

Synthesis of 3-[4-(chloromethyl)-1,3-thiazol-2-yl]-2-ethylquinazolin-4(3*H*)-thione (PTT-3): To solution of (0.1mol) 2-ethyll-3, 1 benzoazine-4-thione in 15 mL dry pyridine was added 4-(chloromethyl)-1, 3-thiazol-2-amine (0.2mol) in lot wise and reaction was stirred continued. The resulted reaction mixture was refluxed for 10 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 desired compound.

Table1. Yield and characterization data

Compd.	**Molecular formula**	**Melting point(^{0}C)**	**% yield**	**Spectral data of the synthesized compounds [18-20]**	
				Mass (M+1)	**^{1}H NMR, δ (ppm), CDCl3 (400MHZ)**
PBO-1	$C_{14}H_9NO_2$	118	85	224.2	7.25-7.59(4H,m),7.67-7.69(1H,d),7.80-7.83(1H,m), 8.22-8.31 (3H,m)
PBO-2	$C_9H_7NO_2$	105	*85*	162.2	2.24-2.63(3H,s),7.11-7.29(2H,m),7.77-7.81 (1H,d), 8.13-873 (1H,m)
PBO-3	$C_{10}H_9NO_2$	120	80	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)
PBT-1	C_4H_9NOS	135-138	85	240.28	7.15-7.39(4H,m),7.35-7.39(1H,d),7.80-7.83(1H,m), 8.22-8.31 (3H,m)
PBT-2	C_9H_7NOS	128-131	90	178.2	2.20-2.33(3H,s),7.21-7.29(2H,m),7.77-7.81 (1H,d), 8.13-873 (1H,m)
PBT-3	$C_{10}H_9NOS$	121-123	88	191.24	1.18-1.42(3H,m),2.40-2.65(2H,m),7.07-7.57 (2H,m), 7.76-7.80 (1H,t),8.15-8.17(1H,d)
PTQ-1	$C_{18}H_{12}ClN_3OS$	152-154	65	354.8	2.18-2.42(2H,s),6.97-6.98(1H,d),7.04-7.05 (1H,d), 7.15-7.18(1H,t),7.51-7.63(3H,m),7.65-7-70(1H,t), 7.89-7.91(1H,d),8.05-8.07(2H,d),8.88-8.9(1H,d)
PTQ-2	C13H10ClN3OS	145-147	85	292.7	2.20-2.33(3H,s),2.18-2.42(2H,s),6.97-6.98 (1H,d), 7.04-7.05(1H,d),7.15-7.18(1H,t),7.51-7.63(2H,m)
PTQ-3	C14H12ClN3OS	140-141	90	306.8	2.20-2.33(3H,s),2.18-2.42(2H,s),6.97 6.98 (1H,d), 7.04-7.05(1H,d),7.15-7.18 1 H,t), 7.51 -7.63 (2H,m)
PTT-1	C14H12ClN3OS2	172	75	370.8	2.18-2.42(2H,s),6.97-6.98(1H,d),7.04-7.05 (1H,d), 7.15-7.18(1H,t),7.51-7.63(3H,m),7.65-7-70(1H,t) 7.89-7.91(1H,d),8.05-8.07 (2H,d), 8.88-8.9(1H,d)
PTT-2	C13H10ClN3OS2	152	70	308.7	1.24-1.63(3H,s),2.18-2.42(2H,s),6.97-6.98 (1H,d) 7.04-7.05(1H,d),7.15 7.1 8(1H,t), 7.51-7.63(2H,m)
PTT-3	C14H12ClN3OS2	165	65	322.7	1.14-1.53(3H,s),2.18-2.42(2H,s),1.18-1.42(2H,s), 6.97-6.98(1H,d),7.04-7.05(1H,d),7.15-7.18 (1H,t),7.51-7.63(2H,m)

RESULTS AND DISCUSSION

1n the recent work attempts has been made to undertake the synthesis of quinazoline 4(3H)-one and quinazoline 4(3H)-thione derivative by two step process. Total nine novel quinazolinone and quinazoline thione derivatives 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 propanoic anhydride in presence of pyridine base and different solvents. The desired quinazolinone and quinazolinone thione compounds were prepared from coupling between benzoxazinone, benzoxazine thione and 4-(chloromethyl)-1, 3-thiazol-2-amine.

APPLICATIONS

Antimicrbial actvity: The prelimnary in vitro antimicribial actvity of stnthesiezed 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*.

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, 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.

Comp.	E.coli.	S. typhi	S. aureous	B. subtlis	candida albicans
PTQ 1	++	++	+++	--	--
PTQ-2	--	+	++	+	--
PTQ-3	++	+	+	--	--
PTT-1	+++	+++	+++	--	--
PTT-2	+	---	++	+	++
PTT-3	++	++	---	+	--
Erythromycin	+++	+	++	++	++
Sreptomycin	+++	++	NT	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 PTQ-1 showed remarkable actvity agianst gram positive S.aureous and PTT-1 also showed remarkable actvity agianst gram positive S.aureous.B.subtilis and gram negative E.coli. All of the afermentioned compund showed antimicrbial actvity comparable to the used positive control drug. In addition compound PTQ-1 & PTT-1 proved to be most active broad spectrum antimicrobial agent.

ACKNOWLEDGMENTS

Author is thankful to faculty of chemistry Nrain P.G College Shikohabad for their support and cooperation for providing research facilities and author is also thankful to HBTI Kanpur, IIT Delhi & CDRI Lucknow for library support spectral analysis and biological activity of the compound.

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