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Synthesis and evaluation of quinazolinthione derivatives as antibacterial agents

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ABSTRACT

Quinazolinthione is a heterocyclic compound with a unique place in the field of medicinal chemistry. The comprehensive study summaries the different derivative of quinazolinthione derivative along with their chemistry, evaluated for their antibacterial activity. The structures of all newly synthesized compounds were confirmed by FT-IR, Mass spectroscopy, ^{1}HNMR spectral data. The synthesized compound were screened for antibacterial activities (500 µg,1000µg) against (both Gram *+ve* and Gram *–ve*) *Escherichia coli*, *Pseudomonas aeruginosa.*

Key words: Chalcone, Quinazolinthione, cyclohexanone, antibacterial.

INTRODUCTION

Quinazolinthione is a bicyclic compound consisting of a pyrimidine system fused at 5, 6 with benzene ring having broad spectrum of medicinal values. Quinazoline is a heterocyclic compound with a unique place in the field of medicinal chemistry. [1-2] Quinazoline and their derivative are building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganism and animals.[3] In light of the growing number of application in recent year, there has been an enormous increase in the interest among biologist and chemist in their synthesis and bioactivity of quinazolinone derivatives.[4] Compound containing 2(1H)-quinazolinone ring system have showed anticancer,[5] anticonvulsant,[6] antituborcular,[7] activity analgesic,[8] antimicrobial.[9] Quinazolinone frequently used in medicine, such as quinethazone and metolazone and are used in medicine, as diuretics.[10] As our interest in search for bioactive heterocycles, synthetically accessible heterocyclic template (quinazoline) capable of bearing some potential pharmacophore to elicit and enhance the inherent biological activity.[11-12] The quinazolinthione antibacterial have emerged as an area of immense interest because of their broad spectrum of in vitro chemotherapeutic efficiency. [13] However, the current quinolones suffer from some drawbacks such as limited activity against a number of clinically important gram positive such as *Streptococcus pneumonia*, *Streptococcus pyrogen*, *Staphyloccus aureus* and *enterococcus*, low activity against anaerobes and increasing quiulones resistance among many pathogens. [14-15] In view of newer antibacterial is focused on synthesis and evaluation of quinazolinthione derivatives.

MATERIAL AND METHODS

All the chemicals were of synthetic grade and commercially. Melting points were determined by open capillary method. The synthesized compound characterized by FT-IR, ^{1}HNMR and mass spectroscopy. IR spectroscopy recorded by Perkin Elmer FT-IR (89258). The pellets were prepared in KBr press model M-15 techno search instruments. A ^{1}HNMR spectrum was recorded by Bruker avance (400 MHz) spectrometer in CDCl3 with tetramethysilane as internal standard (chemical shifts in δ ppm). The mass spectra of the compounds were carried out in Agilent 1100 series LC-MSD.

Synthesis and characterization of quinazolinthione derivatives: *Step 1: Synthesis of chalcone derivatives (1):* Cyclohexanone (0.01mol)

and an aldehyde (0.01 mol) were taken in reaction vessel and dissolved in ethanol. To this solution alcoholic potassium hydroxide was added. Then the reaction mixture was allowed to stand at room temperature for an hour with occasional shaking. A yellow crystalline solid that resulted was filtered and washed with small quantities of ethanol and dried. The product was purified by recrystallization from methanol to get a yellow crystalline solid.

Step 2: 4-phenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thiones (2): A mixture of chalcone derivative (0.01mol) and thiosemicarbazide hydrochloride (0.01mol) and alcoholic solution of KOH were taken into a reaction flask and heated under reflux for 3hr. The excess of solvent was removed by distillation. The concentrate was then diluted with cold water and cooled further. The solid mass thus resulted was filtered, washed with small portion of cold water and dried. It was purified by recrystallization from alcohol to get colorless crystalline solid. The synthetic route of synthesized compound shown in **Fig No. 1.**

Characterization of the quinazolinthione derivatives: The synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectral analysis.

ANTIBACTERIAL ACTIVITY

The antibacterial activity of all synthesized compounds was determined by disc diffusion method. All human pathogenic bacteria viz. *Escherichia coli, Pseudomonas aeruginosa* were procured from Department of Life science, SGRRITS Dehradun. The nutrient agar medium and peptone diameter were punched from whatman No.1 filter paper. Stock solution of synthesized compounds diluted in dimethyl sulphoxide (1% DMSO) to give final concentration of 500µg/ml and 1000µg/ml. a reference standard for both gram positive and gram negative bacteria was made by dissolving accurately weighed quantity of ciprofloxacin (500µg/ml, 1000µg/ml) respectively in sterile distill water separately. The incubation was carried at 33° – 37° C for 48 hours. All the experiment was carried out in triplicate. Simultaneously, controls were maintained by employing 0.1 ml of DMSO which did not reveal any inhibition.

RESULT AND DISCUSSION

In this study we have prepared new 4-pheyl-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thiones. The initial step in the synthetic method involved the synthesis of five different chalcones from cyclohexone and different substituted benzaldehyde, followed by cyclization with thiosemicarbazide. The physical constants were shown in **Table No.1**.

The synthesized compound characterized by FT-IR, ^{1}HNMR and Mass spectroscopy. In IR spectrum the absorption bands for stretching of NH_2, NH, C-H, C=C and C=S for quinazolinthione in compound IA-IE were in good agreement with standard value reported in literature. The mass spectra of synthesized compound IA-IE showed molecular ion peaks as M^+ and M^++1. The spectral data of compound shown in **Table No. 2**.

All the fives synthesized compounds were studied for their antibacterial activity. It was found that compound IC (4-chlorophenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thiones) has shown maximum activity against *E.coli* at both concentration 500µg/ml and 1000 µg/ml, whereas IC (4-chlorophenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thiones) has shown maximum activity against *Pseudomonas aeruginosa* at only 500 µg/ml. The compound ID (4-aminophenyl-3,4,5,6,7,8-hexahydroquinazolinone-2(1H)-thiones) & IE (4-phenyl-3,4,5,6,7,8-hexahydroquinazolinone-2(1H)-thiones) has shown moderate activity against *E.coli* at both concentration, whereas ID & IE has shown moderate activity against *Pseudomonas aeruginosa* at 1000 µg/ml. The compound IA (4-phenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thiones) showed least activity against *Pseudomonas aeruginosa* only at 1000 µg/ml whereas compound IA showed no activity against *E.coli* at both concentration. The zones of inhibition of the compounds on the bacteria were shown in **Table No.3.**

CONCLUSION

A new series of 4-phenyl substituted quinazoline-2(1H)-thiones were synthesized. The synthesized compound were characterized by FT-IR, ^{1}HNMR, Mass spectroscopy and evaluated for Antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa*. . The screening result revealed that the compound (IA – IE) showed significant antibacterial activity at both 500µg/ml and 1000µg/ml concentration levels when compare with standard drug (Ciprofloxacin).

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Table No. 1. Physical constants of the synthesized compounds:

Compound Code	R	R^1	Mol. Formula	Melting Point^{o} C	% Yield	Mol. Wt
IA	H	H	$C_{14}H_{17}N_3S$	80-85	25%	259.05
IB	H	Br	$C_{14}H_{17}BrN_3S$	135-140	15%	338.96
IC	H	Cl	$C_{14}H_{17}ClN_3S$	78-82	35%	294.51
ID	H	$N(CH_3)_2$	$C_{16}H_{22}N_4S$	95-100	45%	302.06
IE	H	OH	$C_{14}H_{17}N_3OS$	80-85	15%	275.05

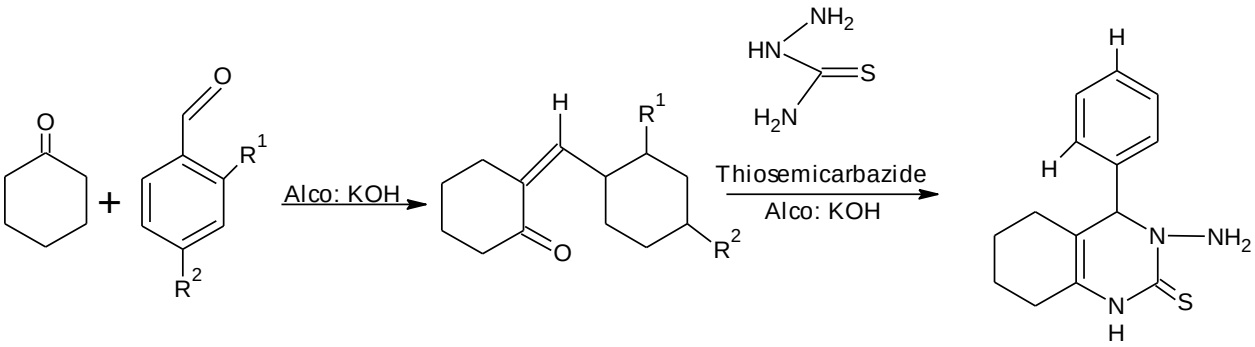
Table No. 2 : The spectral data of the compound:

No.	IR(cm-1)	^{1}H NMR (δ in CDCl3, ppm)	Mass (ESI)
IA	3435.48 (NH_2, str), 3057.24 (NH, str), 2928 (C-H, str), 1598.17 (C=C, str), 1338 (C-C, str)	7.80(s, 1H), 7.27.32(m,5H,Ar-H), 6.95(s,H at S), 1.32-1.34(m,8H, cyclic), 2.81(s, 2H at 1^0N)	m/z(relative intensity%): 264.2$[M]^+$ (100)
IB	508.75 (C-Br, str), 3436.21(NH_2, str), 3289.19(NH, str), 1090.61(C=S, str)	7.88(s,1H), 7.30-7.37(m,5H,Ar-H), 6.81(s,1H at S), 1.45-1.47(m,8H, cyclic), 2.85(s,2H at 1^0N)	m/z(relative intensity%): 342.1$[M]^+$ (100)
IC	824.1(C-Cl, str), 3436.21 (NH_2, str), 3283 (NH, str),1090.6 (C=S, str)	7.80(s,1H), 7.26-7.32(m,5H,Ar-H), 6.84(s,1H at S), 1.58-1.61(m,8H, cyclic), 2.70(s,2H at 1^0N).	m/z(relative intensity%): 294.1$[M]^+$(59)
ID	3409.28 (NH_2, str), 1184.15 (C=S, str), 1360.42 (-C-N, str)	7.96(s,1H), 7.53-7.57(m,5H,Ar-H), 2.54(s,2H,at 1^0N), 6.73(m, 1H at S), 1.70-1.76(m,8H,cyclic)	m/z(relative intensity%): 303$[M+1]^+$(2.57) 338$(M+2H_2O)^+$(1.53)
IE	3433.95 (NH_2, str), 1182 (C=S, str), 1361.22 (C-O, str, ether), 945.15 (C=S, str).	7.81(s,1H), 7.39-7.43(m,5H,Ar-H), 6.67(m,1H at S), 2.50(s,2H,at 1^0N), 1.74-1.78(m,8H,cyclic)	m/z(relative intensity%): 274.3$[M+1]^+$(1.1) 295.2$[M+H_2O]^+$(20)

Table No. 3: Zone of inhibition obtained on bacteria

Compound Code	*E. Coli*				*Pseudomonas aeruginosa*			
	500 µg/ml in mm	**% Inhib.**	**1000 µg/ml in mm**	**% Inhib.**	**500 µg/ml in mm**	**% Inhib.**	**1000 µg/ml in mm**	**% Inhib.**
IA	-	-	-	-	-	-	6.7	20.56%
IB	2.8	20.24%	8.5	28.81%	6.1	40.65%	16.8	51.27%
IC	6.1	44.58%	14.25	48.30%	10.5	69.21%	16.1	49.24%
ID	5.8	41.93%	5.8	19.77%	9.5	62.62%	17.83	54.32%
IE	4.1	30.12%	11.75	39.83%	7.8	51.63%	17.50	54.32%
Ciprofloxacin	13.83	-	29.5	-	15.17	-	32.83	-
DMSO	-	-	-	-	-	-	-	-

Fig No. 1: Synthetic route to the title compounds



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