IJPSR (2012), Vol. 3, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 July, 2012; received in revised form 28 August, 2012; accepted 29 October, 2012

SYNTHESIS OF QUINAZOLINONE DERIVATIVES AND THEIR ANTIMICROBIAL EVALUATION

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Keywords:
Quinazolinone, Antibacterial activity, Antifungal activity

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QUICK RESPONSE CODE

IJPSR:
ICV- 5.07

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ABSTRACT

Some new series of 3-(4-substituted-phenyl)- 2-thioxo-2,3-dihydroquinazolin-4(1H)-one, 3-(4-substituted-phenyl)-2-(methylthio)quinazolin-4(3H)-one and 3-(4-substituted-phenyl)-2-hydrazinylquinazolin-4(3H)-one were synthesized by cyclization of 4-substituted-phenylcarbamodithioate with methyl anthranilate followed by reaction with dimethylsulphate and then prepared compound was refluxed with hydrazinehydrate respectively. The starting material 4-substituted-phenylcarbamodithioate was synthesized from 4-substituted-aniline. The title compounds were investigated for antibacterial and antifungal activity by disc diffusion technique. Compound IIa, IIb and IIIa showed moderate activity against *B. subtilis*, *E. coli* and *A. niger* as compared to standard drug. Compound IIIb and Iva exhibited good activity against *A. niger.* Compound IIIc and IVc was found to be most active compound against *E. coli* and moderately active against *B. subtilis* and *A. niger*, of the prepared series.

INTRODUCTION: The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including analgesic-anti-inflammatory [1], antibacterial [2], antimalarial [3], CNS depressant- anticonvulsant [4], antihistaminic [5], antiviral [6], antitumor [7] and antitubercular [8] activities.

The present work is an effort towards the development and identification of new molecules for antibacterial and anti-fungal activity.

On this basis, we synthesized some 3-(4-substituted-phenyl)-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one, 3-(4-substituted-phenyl)-2-(methylthio)quinazolin-4(3H)-one and 3-(4-substituted-phenyl)-2-hydrazinyl quinazolin-4(3H)-one the title compounds, we aimed to synthesize these compounds by a novel innovative route [9] (**Figure 1, Reaction Scheme**). The synthesized compounds were tested for their antibacterial and anti-fungal activities.

MATERIALS AND METHODS: Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded in potassium bromide disks on a Perkine Elmer Model-398 spectrometer. The ^{1}H spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive).

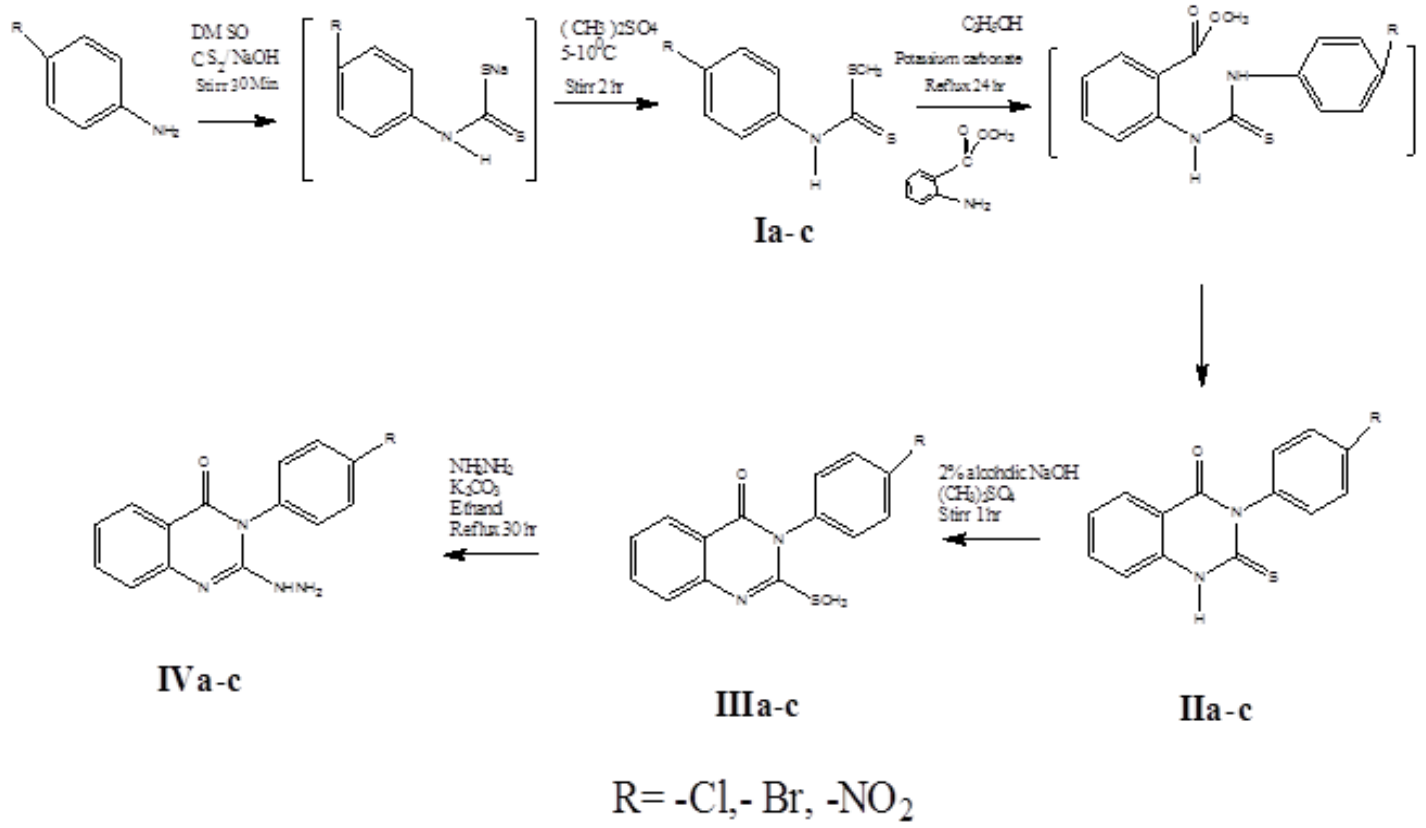

FIGURE 1 REACTION SCHEME

The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform methanol (9:1) as a solvent system. Iodine was used as a developing agent. All microbial strains used in present study were obtained from Institute of Microbial Technology, Chandigarh (India). Chemicals and reagents were obtained from Aldrich (USA), CDH Delhi and SD Fine Mumbai (India) was used without further purification.

Experimental:

Synthesis of 3-(4-substituted-phenyl)-2-thioxo-2, 3-dihydroquinazolin-4(1H)one (IIa-c): A solution of substituted aniline (0.1 mol) in dimethyl sulphoxide (50 mL) was stirred vigorously. To this was added carbon disulphide (8 mL) and aqueous sodium hydroxide 6 mL (20 mol solution) drop wise during 30 min with stirring. Dimethyl sulphate (0.1 mol) was added gradually keeping the reaction mixture stirring in freezing mixture for 2 h. The reaction mixture was then poured into ice water. The solid (Ia-c) obtained was filtered, washed with water, dried and recrystallized from ethanol. Methyl anthranilate (0.05 mol) and the above prepared compound (Ia-c) (0.05 mol), were dissolved in ethanol (100 mL).

To this anhydrous potassium carbonate (500 mg) was added and refluxed for 21 h. The reaction mixture was cooled in ice and the solid separated was filtered and purified by dissolving in 10% alcoholic sodium hydroxide solution and reprecipitated by treating with dilute hydrochloric acid. The solid obtained of compound (IIa-c) was filtered, washed with water, dried under high vacuum and recrystallized from ethanol. The physical properties of synthesized compounds II_{a-c} mentioned in **table 1** and spectral data in **table 2**.

Synthesis of 3-(4-substituted-phenyl)-2-(methylthio) quinazolin-4(3H)-one (IIIa-c): The compound (IIa-c) (0.02mol) was dissolved in 80 mL of 3% alcoholic sodium hydroxide solution. To this dimethyl sulphate (0.02 mol) was added drop wise with stirring. The stirring was continued for 1 h, the reaction mixture was then poured into ice water. The solid obtained of compound (IIIa-c) was filtered, washed with water, dried under high vacuum and recrystallized from ethanol chloroform (75:25) mixture. The physical properties of synthesized compounds III_{a-c} mentioned in **table 1** and spectral data in **table 2**.

Synthesis of 3-(4-substituted-phenyl)-2-hydrazinyl quinazolin-4(3H)-one (IVa-c): The compound (IIIa-c) (0.01 mol) was dissolved in ethanol (25 ml). To this hydrazine hydrate (99%) (0.1 mol) and anhydrous potassium carbonate (100 mg) was added and refluxed for 30 h. The reaction mixture was cooled and poured into ice water. The solid so obtained of compound (IVa-c) was filtered, washed with water, dried under high vacuum and recrystallized from chloroform benzene (25:75) mixture. The physical properties of synthesized compounds IV_{a-c} mentioned in **table 1** and spectral data in **table 2.**

TABLE 1: PHYSICOCHEMICAL DATA OF SYNTHESIZED COMPOUNDS

Compound code	R	Molecular formula	M Wt*	%yield	M.P. (^{0}c)	Color
IIa	Cl	$C_{14}H_9ClN_2OS$	288	80%	306-308	White
IIb	Br	$C_{14}H_9BrN_2OS$	333	72%	300-302	White
IIc	NO_2	$C_{14}H_9N_3O_3S$	299	70%	154-156	Yellow
IIIa	Cl	$C_{15}H_{11}ClN_2OS$	303	82%	176-178	White
IIIb	Br	$C_{15}H_{11}BrN_2OS$	346	85%	129-131	White
IIIc	NO_2	$C_{15}H_{11}N_3O_3S$	313	65%	166-168	Yellow
IVa	Cl	$C_{14}H_{11}N_4OCl$	286	78%	192-194	White
IVb	Br	$C_{14}H_{11}N_4OBr$	330	75%	166-168	White
IVc	NO_2	$C_{14}H_{11}N_5O_3$	297	57%	170-172	Yellow

* Molecular weight determinate by mass spectra

TABLE 2: SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

Compound code	IR (cm^{-1}) (KBr)					^{1}H NMR ($CDCl_3$) δ ppm
	NH	C=O	C=S	CH-Ar	CH-Ali	
IIa	3248#	1687	1200	3069	-	3.9629(s, 1H, -NH), 6.99-7.972(m, 8H, Ar-H)
IIb	3263#	1694	1234	3078	-	3.9721(s, 1H, -NH), 7.013-8.786(m, 8H, Ar-H)
IIc	3449#	1629	1258	3024	-	3.786(s, 1H, -NH), 7.113-8.77(m, 8H, Ar-H)
IIIa	-	1682	-	3064	2932	2.530(s, 3H, SCH_3), 7.842-8.09(m, 8H, Ar-H)
IIIb	-	1675	-	3065	2956	2.528(s, 3H, SCH_3), 7.426-8.094(m, 8H, Ar-H)
IIIc	-	1624	-	3063	2951	2.493(s, 3H, -SCH_3), 7.421-8.102(m, 8H, Ar-H)
IVa	3324#*,3219#	1677	-	3062	-	5.162-2.211(s, 2H, NH_2), 7.227-8.024(m, 8H, Ar-H), 8.969-9.091(s, 1H, -NH)
IVb	3331#*,3215#	1676	-	3089	-	5.189-5.231(s, 2H, NH_2), 7.235-7.822(m, 8H, Ar-H), 9.013-9.278(s, 1H, -NH)
IVc	3321#*,3227#	1641	-	2962	-	5.211-5.213(s, 2H, NH_2), 7.351-7.788(m, 8H, Ar-H), 8.740-9.691(s, 1H, -NH)

#* Primary amine stretching vibration frequency (cm^{-1}); # Secondary amine stretching vibration frequency (cm^{-1})

Determination of Antimicrobial Activity: All the synthesized compounds were reported in table 1 were screened for their antibacterial and anti-fungal activity in vitro against gram positive bacteria (*Bacillus subtilis, Staphyllococcus aureus*), gram negative bacteria (Escherichia coli) and fungi (*Aspergillus niger, Candida albicans*) using disc diffusion technique [10-14] at 100ug/ml concentration. The activity was compared with known standard streptomycin for antibacterial and fluconazole for antifungal activity. Dimethylformamide (DMF) was taken as solvent for all synthesized compounds. In order to account for the effect due DMF a blank was also performed. Observations of anti-microbial study are mentioned in **table 3**.

RESULT AND DISCUSSION: The structures of the all synthesized compounds (IIa-c-IVa-c) were elucidated on the basis of, IR, ^{1}H-NMR and mass spectroscopy. All the final synthesized compounds have strong absorption band around 1694-1624 cm^{-1}, which is evidence for the presence of >C=O bond in all synthesized compounds. Presence of aromatic ring was confirmed by absorption band around 3078-2962 cm^{-1}. IR data of all final synthesized compounds confirms the presence of specific functional groups present in the synthesized compounds. The mass and 1H-NMR spectra of were in conformity with assigned structures.

As per usual of the table 3, the antimicrobial activity of synthesized compounds as compared to standard drugs, all the synthesized compounds possessed anti-bacterial activity against all the five strains. Compound IIa, IIb and IIIa showed moderate activity against *B. subtilis*, *E. coli* and *A. niger* as compared to standard drug. Compound IIIb and Iva exhibited good activity against *A. niger.* Compound IIIc and IVc was found to be most active compound against *E. coli* and moderately active against *B. subtilis* and *A. niger*, of the prepared series.

ACKNOWLEDGEMENT:I am very thankful to University Grant commission, India for provide me financial support during my project work.

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How to cite this article:
Singh O, Namdeo KP and Sindhia VR: Synthesis of Quinazolinone Derivatives and their Antimicrobial Evaluation. *Int J Pharm Sci Res*. 3(11); 4408-4411.