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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF MERCAPTOQUINAZOLIN-4(3H)-ONE DERIVATIVES

Gollapalli NagaRaju[2], Karumudi Bhavya Sai[1]*, Alavala Sandhya Rani[1], Gudivaka Janaki[1], Palaparthi Supriya[2], Nallamothu Sucharitha[2] and Rama Rao Nadendla[2]

[1]Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Guntur, India.

[2]Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Guntur, India.

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***Correspondence for Author**
Karumudi Bhavya Sai
Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Guntur, India.

ABSTRACT

A novel series of 3-(4-chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one derivatives were synthesized and evaluated for their antibacterial and antifungal activities against gram negative viz *Escherichia coli*, *P.aeruginosa* and gram positive bacteria viz *staphylococcus aures*, *Bacillus subtilis and Bacillus cereus and pathogenic fungi* viz *Candida albicans* and *Saccharomyces cerevisiae*. Ampicillin and Nystatin used as standard drugs. All the compounds were characterized by physical and spectral data. All the compounds showed potent to moderately potent antimicrobial activity. These compounds can be further exploited to get the potent lead compound. The detailed synthesis and the antimicrobial screening of the new compounds are reported.

KEYWORDS: Quinazolinone, Pyridazine, 2-Mercaptoquinazolin-4(3H)-one, Antibacterial activity, Antifungal activity.

INTRODUCTION

Quinazolinone is one of the most important and prosperous structures in medicinal chemistry. Quinazolinone is a compound made up of two fused six member simple aromatic benzene ring and a number of substituted quinazolinone are known for their biological importance like anticancer, anti-biotic, anti-microbial, anti-HIV, anti-oxidant, anti-tubercular, anti-malarial, anti-viral, anti-psychotics and anti-inflammatory activity. The spread of antibiotic resistance

among pathogenic bacteria has become a serious problem for the clinical management of infectious diseases and has resulted in need for novel antibacterial agents other than existing antibiotics. Literature studies on quinazolinones have shown that these derivatives possess a wide variety of biological activities such as antioxidant[1], antifungal[2], antibacterial[3], anticonvulsant[4], anti-inflammatory[5], antihyperlipidemic[6], anticancer[7], antimalarial[8], antispasmodial[9], analgesic[10] , antiviral[11], antitubercular[12] and antimicrobial[13-18] activities.

In recent years much attention has been focused on the synthesis of some Quinazolinone compounds as potential antimicrobial agents. In the present investigation, the quinazolinone analogs were designed to contain a proper side chain bearing sulphur group which are believed to contribute to the antimicrobial activity, in addition, some heterocyclic rings that known to have antimicrobial activity such as pyridazine has been incorporated into the quinazolinone nucleus. The newly synthesized compounds were screened for their activity against a panel of gram-positive and gram-negative bacteria and pathogenic fungi.

EXPERIMENTAL

MATERIAL AND METHODS

The melting point of the compounds was determined in open capillary tube and values are uncorrected. Microanalyses were conducted on a Heraeus instrument; results are within ± 0.4% of the theoretical values. TLC was carried out on a precoated plate (silica gel 60F-254, Merck) and spots were visualized with Iodine (or) UV light. IR spectra were recorded in KBr discs on a Brooker FTIR Spectrophotometer. The purity of the newly synthesized compounds was evidenced by HPLC (Agilent) and their elemental analysis was generally found to be in agreement with the structure. 1H-NMR spectra were recorded on a JOEL-JNM EX-90 FT-NMR, (90 MHZ) Spectrometer in $CDCl_3$/DMSO-d6 as a solvent, the chemical shifts(δ) are expressed in ppm using TMS as internal standard. All the solvents used were of analytical grade.

Ethyl 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetate (MQZN- 1)

To a solution of MQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (4.15 g, 0.01 mol) in dry acetone (50 ml), anhydrous potassium carbonate (2.0 g) was added, followed by chloromethyl propionate (0.015 mol). The reaction mixture was heated under

reflux for 20 h, filtered while hot and the filtrate was concentrated in *vacuo*. The separated crude product was filtered, dried and crystallized from ethanol.

^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, C_2H_5CO), 4.32 (s, 2H, CH_2CO), 7.41 (d, 1H, J = 7.5 Hz, Quin-H), 7.53 (d, 2H, J = 8.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.02-8.18 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H).

3-(4-chlorophenyl)-6-iodoquinazoline-2,4(1H,3H)-dione (MQZN-2)

To a solution of MQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (4.15 g, 0.01 mol) in polyphosphoric acid (20 ml) were heated under reflux on an oil bath at 120°C for 4 hr. On cooling, the mixture was neutralized with 10% sodium hydrogen carbonate solution and separated product was filtered, washed with water, dried and crystallized from acetic acid.

^{1}H NMR (DMSO-d_6): δ 7.39 (d, 1H, J = 7.5 Hz, Quin-H, 7.51 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 8.05-8.21 (dd, 1H, J = 2, 7.5 Hz, Quin-H, 8.33 (d, 1H, J = 2 Hz, Quin-H), 12.67 (brs, 1H, NH).

2-Methyl benzo[d]oxazolo-3-(4-chlorophenyl)-6-iodoquinazoline-4(3H)-dione (MQZN-3)

To a solution of MQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (4.15 g, 0.01 mol) and 2-aminophenol (0.0075 mol) were heated under reflux on an oil bath at 120°C for 4 hr. On cooling, the mixture was neutralized with 10% sodium hydrogen carbonate solution and separated product was filtered, washed with water, dried and crystallized from acetic acid.

2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (MQZN-4)

To a solution of MQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (4.15 g, 0.01 mol) with hydrazine in ethanol were heated under reflux on an oil bath at 120°C for 4 hr. then filtered while hot and the filtrate was concentrated in *vacuo*. The separated crude product was filtered, dried.

5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-quinazolin-2-yl)thio]-pyridazin-6-one (MQZN-5):

An equimolar amount 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (MQZN-4) of (4.86 g, 0.01 mol), aldehyde (1.52 g, 0.01 mol) and sodium ethoxide (0.068 g, 0.01 mol) in ethanol (50 ml) was heated under reflux for 20 h. The

reaction mixture was cooled and acidified with dilute HCl. The separated solid was filtered, washed with cold water and crystallized from ethanol.

^{1}H NMR (DMSO-d_6): 2.31 (d, 1H, J = 10 Hz, CH2), 4.92 (t,1H, J = 10 Hz, CH), 7.24 (d, 1H, J = 7.5 Hz, Quin-H), 7.41 (t, 1H, J = 10 Hz, N=CH), 7.53 (d, 2H, J = 8.5 Hz, Ar-H0, 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.03-8.17 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H).

5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]pyridazine-3,4,6-trione (MQZN-6)

An equimolar mixture of 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (MQZN-4) (4.86 g, 0.01 mol), diethyl oxalate (1.4 6 g, 0.01 mol) and sodium metal (0.23 g) in ethanol (30 ml) was heated under reflux for 12 hr. On cooling, the mixture was acidified with dil. HCl and the separated solid was filtered, dried and crystallized from ethanol.

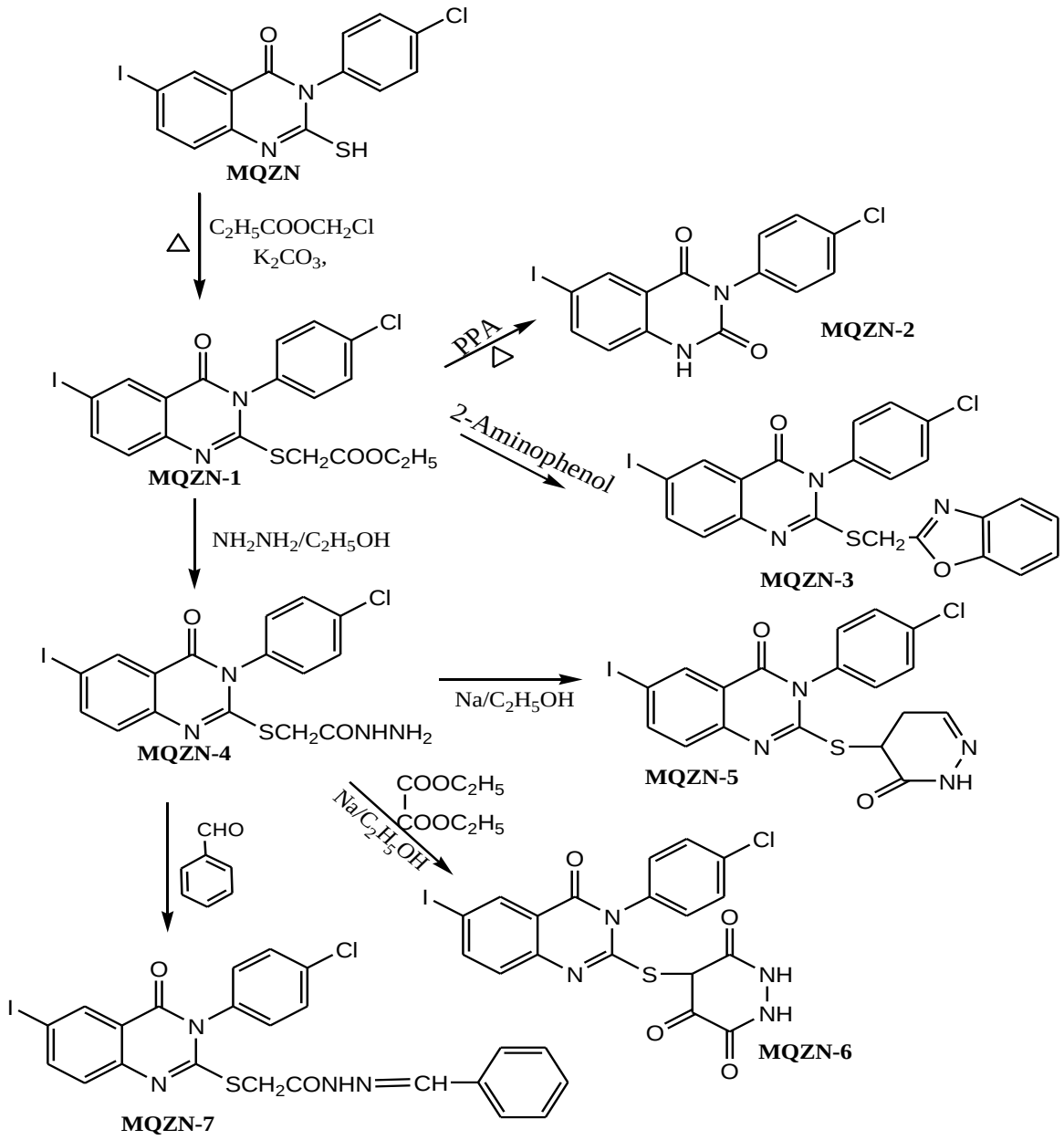
^{1}H NMR (DMSO-d_6): δ 7.03 (brs, 1H, NHCO), 7.24 (d, 1H, J = 7.5 Hz, Quin-H), 7.35 (d, 2H, J = 8.5 Hz, Ar-H), 7.69 (d, 2H, J = 8.5 Hz, Ar-H), 7.81 (s, 1H, OH), 8.03-8.16 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 10.11 (s, 1H, OH).

N-(benzylidene)-N-[2-(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*quinazolin-2-yl)thioacetyl] hydrazine (MQZN-7)

A mixture of 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio) acetohydrazide (MQZN-4) (4.86 g, 0.01 mol) and benzaldehyde (0.015 mol) in acetic acid (20 ml) was heated under reflux for 12 h.

The reaction mixture was cooled, and the separated solid was filtered, washed with petroleum ether, dried and recrystallized from acetic acid.

^{1}H NMR (DMSO-d6) δ 4.14 (s, 2H, S-CH2CONH), 7.21-7.69 (m, 10, Ar-H and Quin-H), 8.03-8.18 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 9.59 (s, 1H, CH=N), 10.31 (brs, 1H, NH).



Scheme 1: Synthesis of Mercaptoquinazolin-4(3H)-one derivatives MQZN-1 to MQZN-7

RESULTS AND DISCUSSION

Chemistry

The synthetic strategy to obtain the target compounds **MQZN-1 – MQZN-7** is depicted in Schemes 1. The starting material MQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) was treated with chloromethyl propionate to get Ethyl 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetate **(MQZN-1)**. MQZN-1 treated with polyposphoric acid to get 3-(4-chlorophenyl)-6-iodoquinazoline-2,4(1H,3H)-dione **(MQZN-2)**. Reaction of MQZN-1 with o-aminophenol to give compound 2-Methyl benzo[d]oxazolo-3-(4-chlorophenyl)-6-iodoquinazoline-4(3H)-dione **(MQZN-3)**. Reaction of MQZN-1 with

hydrazine in presence of alcohol to give the compound 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide **(MQZN-4)**. Interaction of the acid hydrazide 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (MQZN-4) with chloroacetaldehyde diethylacetal and/or diethyloxalate yielded the corresponding heterocycles 5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-quinazolin-2-yl)thio]-pyridazin-6-one **(MQZN-5)** and 5-[3-(4-Chlorophenyl)-4-oxo-6-iodo-3*H*-quinazolin-2-yl)thio]pyridazine-3,4,6-trione **(MQZN-6)** respectively. Condensation of the hydrazide 2-(3-(4-chlorophenyl)-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (MQZN-4) with benzaldehyde in acetic acid afforded the hydrazone N-(benzylidene)-N-[2-(3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*quinazolin-2-yl)thioacetyl] hydrazine **(MQZN-7)**.

Antimicrobial Activity

All the tested compounds along with standard Ampicillin and Nystatin were screened *in-vitro* for antimicrobial activity against gram positive bacteria *Staphylococcus aureus* (ATCC 06538), *Bacillus subtilis* (RTCC 6633), *Escherichia coli* (ATCC 10536) and pathogenic fungi *Candida albicans* (ATCC 1023) and *Saccharomyces cerevisiae* (ATCC 9763).

Nutrient agar plates were seeded using 0.1 ml of overnight cultures. Cylindrical plugs were removed from agar plate using a sterile cork borer and 100 µg of the tested compounds (1 mg/ml, DMSO) were added to the well in triplicates. Blank solvent was used as control. Plates inoculated with tested bacteria were incubated at 37^0C, while those of fungi were incubated at 30^0C. Results were taken after 24 h of incubation and were recorded as average diameter of the inhibition zone in mm.

Table 1: Antimicrobial screening results for the tested compounds at 1 mg/ml concentration.

Comp	*E. coli*	*S. aureus*	*B. subtilis*	*S. cerevisiae*	*C. albicans*
MQZN-1	++	++	++	--	--
MQZN-2	+	+	+	+	+
MQZN-3	--	--	+	++	++
MQZN-4	++	++	--	+	--
MQZN-5	+++	+++	+++	+++	+++
MQZN-6	+++	++	+++	+++	+++
MQZN-7	++	++	--	++	++
Ampicillin	+++	+++	++	NT	NT
Nystatin	NT	NT	NT	++	+++

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

CONCLUSION

All of the newly synthesized compounds were subjected to antimicrobial screening by the *in vitro* cup-plate technique using Ampicillin and Nystatin as positive controls. Compound **MQZN-6** showed remarkable activity toward the Gram negative bacteria *E. coli*. The Gram positive bacteria *S. aureus* and *B. subtilis* proved to be sensitive toward compounds, **MQZN-5** and **MQZN-6**. Compounds **MQZN-5** and **MQZN-6** showed remarkable activity towards the used fungi *S. cerevisiae* and *C. albicans*. All of the aforementioned compounds showed antimicrobial activity comparable to the used positive control drug. In addition compounds **MQZN-5** and **MQZN-6** proved to be the most active broad spectrum antimicrobial agents in this study. In conclusion, the present study revealed that attachment pyridazine quinazolinone nucleus could be useful as a template for further development through modification or derivatization to design more potent antimicrobial agents.

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