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Research Article

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Synthesis, characterization and biological evaluation of iodoquinazolinone derivatives

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ABSTRACT

A novel series of 6-Iodoquinazolin-4-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. Streptomycin 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, Benzimidazole, Antibacterial activity, Antifungal activity.

INTRODUCTION

Heterocyclic chemistry is a chemistry involving the heterocyclic compounds which contain atoms of at least two different elements as number of ring. The heterocyclic may be inorganic, though the compound has carbon atoms in the ring, the word hetero means different from carbon and hydrogen. Nitrogen containing heterocyclic compounds plays an important role in medicinal chemistry. Quinazolinone consists of two fused benzene and pyrimidinone ring. Quinazolinones are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans. 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 quinazoline 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 benzimidazole 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 SECTION

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.

2-Amino-3-(4-chlorophenyl)-6-iodoquinazolin-4(3H)-one (IQZN-1):
A solution of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (2.07 g, 0.005 mol) in formamide (20 ml) was heated under reflux for 20 h. On cooling, the obtained precipitate was filtered (Fig 1), washed with water and crystallized from ethanol (Table 1, 2). ^{1}H NMR (DMSO-d_6): δ 5.92 (brs, 2H, NH2), 7.41 (d, 1H, J = 7.5 Hz, Quin-11), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.67 (d, 2H, J = 8.5 Hz, Ar-H), 8.04-8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-11), 8.31 (d, 1H, J = 2 Hz, Quin-H).

2-(2-Oxopropylthio)-3-(4-chlorophenyl)-6-iodoquinazolin-4(3H)-one (IQZN-2):
To a solution of IQZN (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 chloroacetone (0.015 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot and the filtrate was concentrated in *vacuo* (Fig 1). The separated crude product was filtered, dried and crystallized from ethanol (Table 1, 2). ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3CO), 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).

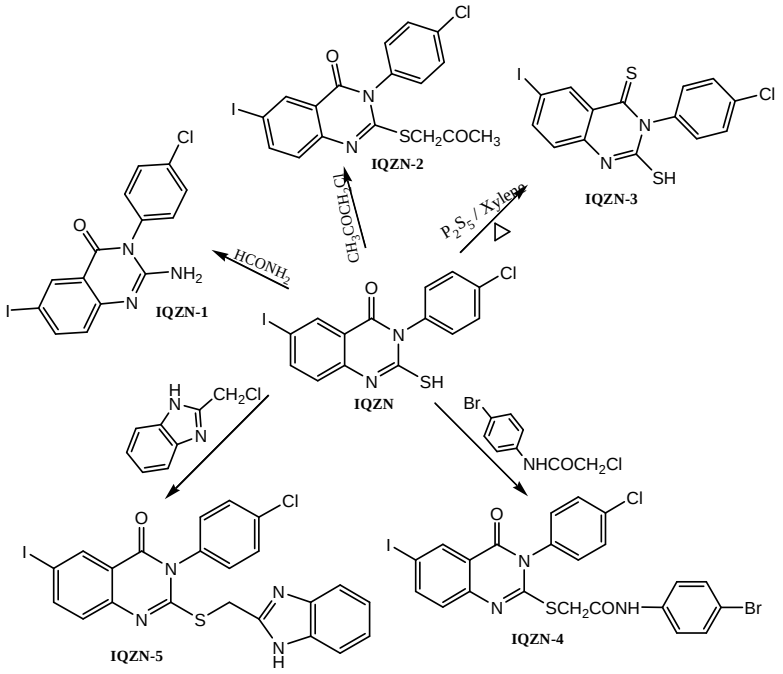
3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-thione (IQZN-3):
To a solution of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (4.145 g in 0.01 mol) in dry xylene (40 ml) phosphorous pentasulfide (2.3 g, 0.01 mol) was added. The reaction mixture was refluxed for 18 hr, cooled and solvent was evaporated under *vacuo*. The obtained solid was treated with acidulated cold water (100 ml) with stirring for 15 min (Fig 1). The obtained solid was filtered, washed with water, dried and crystallized from ethanol (Table 1, 2). 1H NMR (DMSO-d_6): δ 7.38 (d, 1H, J = 7.5 Hz, Quin-H), 7.52 (d, 2H, J = 8.5 Hz, Ar-H), 7.66 (d, 2H, J = 8.5 Hz, Ar-H), 8.06-8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J = 2 Hz, Quin-H), 12.3 (brs,^{1}H, NH).

3-(4-Chlorophenyl)-6-iodo-2[N-4-bromophenyl)carbamoylthio]-4-(3H)-quinzolin-4-one (IQZN-4):
To a solution of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (4.14 g, 0.01 mol) in acetone (60 ml), anhydrous K_2CO_3 (2.0 g) was added, followed by the appropriate *N*-(4-bromophenyl)-2-chloroacetamide (0.012 mol). The reaction mixture was heated under reflux for 20 h, then filtered while hot and the filtrate was concentrated in *vacuo* (Fig 1). The separated solid was filtered, washed with water, dried and crystallized from the suitable solvent (Table 1). ^{1}H NMR (DMSO-d_6): 4.28 (s, 2H, S-CH_2CO), 7.08-7.81 (m, 9H, Ar-H and Quin-H), 3.03-8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.31 (d, 1H, J = 2 Hz, Quin-H), 11.86 (brs, 1H, NH).

2-(2-Benzimidazolylmethylthio)-3-(4-chlorophenyl)-6-iodo-(3*H*)-quinazolin-4-one (IQZN-5):
To a solution of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) (2.07 g, 0.005 mol) in acetone (40 ml), anhydrous potassium carbonate (2.0 g) was added, followed by 2-chloromethylbenzimidazole (1 g, 0.0065 mol). The reaction mixture was heated under reflux for 20 h (Fig 1). The solvent was removed in *vacuo* and the obtained solid was crystallized from ethanol (Table 1, 2). ^{1}H NMR (DMSO-d_6), δ 3.91 (s, 2H, S-CH2-Hetero), 7.26-7.72 (m, 10H, Ar-H, benzimidazole-H, NH and Quin-H), 8.05-8.19 (dd, 1H, J = 2, 7.5 Hz, Quin-H), 8.29 (d, 1H, J =2Hz, Quin-H).

Figure 1: Synthesis of Iodoquinazolinone derivatives

Synthesis of Iodoquinazolinone derivatives



RESULTS AND DISCUSSION

Chemistry:

The synthetic strategy to obtain the target compounds **IQZN-1 – IQZN-5** is depicted in Schemes 1. The starting material IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) was treated with formamide to get 2-Amino-3-(4-chlorophenyl)-6-iodoquinazolin-4(3H)-one **(IQZN-1)**. Alkylation of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) with chloroacetone gave the 2-oxopropylthio analog 2-(2-Oxopropylthio)-3-(4-chlorophenyl)-6-iodoquinazolin-4(3H)-one **(IQZN-2)**. 3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one was treated with phosphorous pentasulphide in boiling xylene to afford the 4-thioxo derivative 3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazoline-4(3H)-thione **(IQZN-3)** in high yield. Treatment of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one) with *N*-(4-bromophenyl)-2-chloroacetamide (0.012 mol) afforded 3-(4-Chlorophenyl)-6-iodo-2[N-4-bromophenyl)carbamoylthio]-4-(3H)-quinzoline-4-one **(IQZN-4)**. Treatment of IQZN (3-(4-Chlorophenyl)-6-iodo-2-mercaptoquinazolin-4(3H)-one)with 2-chloromethyl benzimidazole afforded 2-(2-Benzimidazolylmethylthio)-3-(4-chlorophenyl)-6-iodo-(3*H*)-quinazoline-4-one **(IQZN-5)**.

Table 1: The physiochemical properties of the synthesized compounds

Compd	Solvent	M.P.^{0}C	Yield	Molecular formula
IQZN-1	Ethanol	240-242	41	$C_{14}H_9ClIN_3O$
IQZN-2	Ethanol	195-197	68	$C_{17}H_{12}ClIN_2O_2S$
IQZN-3	Ethanol	290-292	70	$C_{14}H_8ClIN_2S_2$
IQZN-4	Ethanol, dioxane	245-247	66	$C_{22}H_{14}BrClIN_3O_2S$
IQZN-5	Ethanol	260-262	40	$C_{22}H_{14}ClIN_4OS$

Table 2: Mass spectral data of some compounds

Compd	MS (Relative Intensity)
IQZN-1	m/z 397 (M+, 91.96), 399 (M + 2, 30.23), 258.3 (38.20), 244 (63.61).
IQZN-3	m/z 430 (M+, 32.82), 432 (M + 2, 11.40); 319 (1.81), 287 (37.69), 144 (70.59).
IQZN-4	m/z 625 (M+, 0.71), 627 (M + 2, 0.23), 514 (14.31), 455 (6.47), 427 (9.31), 413 (3.61), 381 (2.12).
IQZN-5	m/z 544 (M+, 2.93), 427 (1.23), 413 (2.13), 381 (0.8).

Antimicrobial Activity:

All the tested compounds along with standard streptomycin 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 3: Antimicrobial screening results for the tested compounds at 1 mg/ml concentration

Comp	*E. coli*	*S. aureus*	*B. subtilis*	*S. cerevisiae*	*C. albicans*
IQZN-1	++	++	++	--	--
IQZN-2	+	+	+	--	--
IQZN-3	--	--	+	++	++
IQZN-4	++	++	--	+	--
IQZN-5	+++	+++	+++	+++	+++
Streptomycin	+++	+++	++	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 Streptomycin and Nystatin as positive controls. Compound IQZN-5 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 IQZN-1 and IQZN-5. Compound IQZN-5 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 IQZN-5 proved to be the most active broad spectrum antimicrobial agents in this study.

In conclusion, the present study revealed that attachment of benzimidazole to the 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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