Synthesis and characterization of new quinazolines as potential antimicrobial agents

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Ethyl 4-[2-(2-chlorophenyl)-4-oxo-3-hydroquinazolin-3yl]-benzoate 1 which reacts with hydrazine hydrate in presence of methanol resulted into N-amino{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)phenyl]carboxamide 2. Compound 2 on treatment with aryl isothiocyanates in presence of acetone is converted into aryl-N-[{({4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carbonylamino)amino]thioxo methyl}amides 3. Compound 3, in presence of sulphuric acid has yielded aryl-N-{5-{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}(1,3,4,thiadiazol-2-yl)}amides 4a-l. Newly synthesized compounds 4a-l have been screened for their antibacterial and antifungal activities on *Eschericia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *C. albicans*, *A. niger* and *A. clavatus*.

Keywords: Quinazoline, antibacterial activity, antifungal activity

IPC: Int.Cl.8

Quinazolines are nitrogen containing compounds having broad spectrum of medicinal values such as antifungal1 anticancer2, anti-HIV3, antiinflammatory4, analgesic5, antiviral6, antitubercular7, antimicrobial8, anticonvulsant9, anticoagulant10, anti-fibrillatory11, cardiac stimulant12, diuretic13, antibacterial14-19, etc.

Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes. And therefore, it is an ongoing effort to synthesize new antimicrobial agents. Over and above there is no permanent structure and activity relationship. In continuation to this, we have selected medicinally important quinazolines by modifying the third position, for the preparation of newer antimicrobial agents.

The present paper describes the synthesis of aryl-N-{5-{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}(1,3,4,thiadiazol-2-yl)}amides 4a-l (Scheme I). These compounds were screened for antibacterial and antifungal activities by broth dilution method. Compound 4 was prepared by the reaction of H2SO4 with aryl-N-{[{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carbonylamino]thioxomethyl}amides 3. Compound 3 was obtained by the condensation of 2 and aryl isothiocyanates in presence of anhydrous acetone. Compound 2 was synthesized by the reaction between ethyl 4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3yl)benzoate and hydrazine hydrate. Compound 4a was characterized with the help of elemental analysis, IR, 1H NMR and mass spectral analysis. IR spectra of this compound exhibited absorption bands at 1660 and 1690 cm⁻¹, which indicated the presence of carbonyl group. The 1H NMR of compound 4a showed signals at δ 6.8-7.9 for aromatic protons and due to the cyclization of 3, one signal at δ 12.90 of –CONH-proton was obtained. In the mass spectrum of the compound, base peak appeared at m/z 105 and molecular ion peak was observed at m/z 535.5. Details of the characterized data of compound 4 are reported in (Table I).

Biological activity

**Antibacterial activity.** Antibacterial activity was carried out by broth dilution method25,26. The strains used for the activity were procured from Institute of Microbial Technology, Chandigarh. The compounds 4a-l were screened for their antibacterial activity against *Eschericia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Staphylococcus pyogenes* at concentrations of 1000, 500, 200, and 100 µg/mL respectively (Table II). The results are recorded in the form of primary and secondary screening. Each synthesized drug was diluted obtaining 1000 µg/mL concentration, as a stock solution.

The synthesized drugs found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. Secondary screening: The drugs found active in primary screening were similarly diluted to obtain 100, 50,
25 μg/mL concentrations, 10 μL suspension from each well was further inoculated on appropriate media and growth was noted after 24 and 48 hr. The lowest concentration, which showed no growth after spot subculture was considered as MBC/MFC for each drug. The highest dilution showing at least 99% inhibition is taken as MBC/MFC. The result of this test is affected by the size of the inoculum. The test mixture should contain 10^8 organisms/mL. The standard drug used in the present study was gentamycin for evaluating antibacterial activity which showed (0.25, 0.05, 0.5 and 1 μg/mL MBC against S. aureus, S. pyogenes and P. aeruginosa respectively. Knystatin was used as the standard drug for antifungal activity, which showed 100 μg/mL MFC against fungi, used for the antifungal activity.

Compounds 4e and 4i are considered to be active against S. pyogenes. The antibacterial activity of both compounds were enhanced due to the introduction of chloro and methyl group in the heterocyclic frame work. Compounds 4e was active against C. albicans and A. clavatus. Due to the presence of nitro group consequently 4k is active against C. albicans and A. clavatus. The enhancement of the activity of this compound is due to the presence of chlorine atom in the frame work. From the activity data, it was observed that minor change in molecular configuration of these compounds profoundly influences the activity.

**Experimental Section**

Melting points for resultant compounds were determined in open capillary tubes using a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a FT IR 9201 VC spectrophotometer; 1H NMR spectra in CDCl$_3$ on DRX (200 MHz) and DRX (300 MHz) spectrometer using TMS as internal standard. Mass spectra was recorded on Q-TOF Micro Mass. Purity of these compounds were checked by TLC. Compounds ethyl
Aryl-N-{(5-[4-{2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}[1,3,4-thiadiazol-2-yl)} amides 4a-l. Compound 3 (0.01 mole) was added to cold conc. sulphuric acid (25 mL). The mixture was stirred at room temp for 2 hr. The resultant solid mass was poured onto crushed ice (100 g) with stirring. The product was filtered, washed with water and dried. The characterization data of compound 4a prepared according to this procedure was given in Table I, m.p. 145°C, yield : 70%. Anal. Found: C 64.87, H 3.20, N 12.80. Calcd. for C_{29}H_{47}ClN_{5}O_{3}S: C 64.98, H 3.38, N 12.24. IR(KBr): 3156 (>N-H); 1H NMR: δ 7.0-7.9 (m, 12H, ArH), 12.80 (s, 1H, -CONH). MS: [M'] at m/z 535.5 and other prominent peaks are appeared at 531.40, 437.3, 336.08, 256.31, 228.28, 202.19, 105, 81.03.
Table II — Antimicrobial activity of compounds 4a-l

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<th>S. aureus MTCC 96</th>
<th>S. pyogenus MTCC 442</th>
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For antibacterial activity, in present protocol 100 µg/mL is considered as moderately active, 50 µg/mL is considered as good activity and 25 µg/mL is considered as active as compared to the standard drug gentamycin. For antifungal activity, 200 µg/mL is considered as moderately active, 100 µg/mL is considered as active as compared to standard drug K nystatin.

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**References**