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Research Article

In-vitro Antimicrobial Activity of Novel Quinazoline Derivatives: One-Pot Synthesis and Characterization

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ABSTRACT

Designing an efficient class of novel antimicrobial agents becomes an enormous task in pharmaceuticals research and development. Current research work comprised of finding a novel series of various substituted quinazoline derivatives. The synthetic scheme involves single-step, one-pot synthesis involving the condensation of highly activated aromatic amide starting materials with weakly nucleophilic alkyl nitriles to directly provide the corresponding quinazoline derivatives employing trifluoromethanesulfonic anhydride catalyst. All the synthesized compounds were characterized by IR, proton nuclear magnetic resonance (^{1}HNMR) and message, audience, situation, significance (MASS) spectral methods and screened for antimicrobial activity against four bacterial strains *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and two fungal strains *Aspergillus niger* and *Candida albicans*. All the compounds displayed decent antimicrobial profile when compared with the standard drugs neomycin and nystatin. Among the synthesized compounds (3a1-3a5&3b1-3b5) evaluated, compounds 3a1, 3a2, 3a3, 3b1and 3b2 have demonstrated decent antimicrobial activity against selected strains of bacteria and fungi.

INTRODUCTION

Antibiotic resistance in bacterial pathogens has currently reached extremely high and alarming levels. Indeed, according to a number of international bodies, this "antibiotic resistance crisis" could possibly bring us back to a "pre-antibiotic era" soon, if no effective actions are promptly undertaken.[1,2] Unfortunately, the low success rate in antibiotic discovery and development observed during the last decades has led to a limited availability of new compounds for clinical use, thus exacerbating the burden of antibiotic resistance on morbidity and mortality rates. In this scenario, also many modern clinical practices associated with an increased risk of infection and in which antibiotics are essential (e.g., anti-cancer treatments, solid organ and stem cell transplantations, or implantation of prosthetic devices) are seriously at risk of success.[3]

Quinazoline (1,3-diazanaphthalene) is a nitrogen containing heterocyclic compound illustrated by a double-ring structure that contains a benzene ring system fused to pyrimidine at two adjacent carbon atoms.[4] Quinazoline and quinazolinone scaffolds role can be objectivised in pharmaceutical industry by their presence in the structure of marketed drugs such as doxazosin[5] and terazosin[6] (Fig. 1).

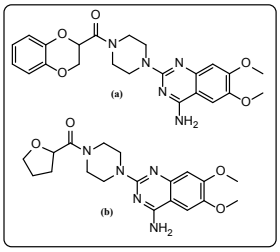

Fig.1: Structures of quinazoline scaffold containing drugs (a) Doxazosin (b) Terazosin

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Quinazolines and its derivatives exemplify one of the most prominent classes of compounds, which possess a wide range of pharmacological activities like analgesic,[7] antioxidant,[8] anti-inflammatory,[9] anti-hypertensive,[10] antitubercular,[11] anti-microbial,[12,13] anti-viral[14,15] and anticancer[16,17] activities. Owing to the enormous scope of the quinazoline nucleus in microbial infections, an effort was made to develop novel organic molecules with quinazoline ring system as a central part and evaluated their invitro antimicrobial activity against selected bacterial and fungal strains. Pharmaceutically, the investigation of these quinazoline derivatives might be advantageous for the drug discovery concerning with the novel antimicrobial agent that can serve as lead compounds.

Material and Methods

Synthesis

All chemicals and solvents used in this work were of synthetic grade purchased from Sigma-Aldrich, local vendors and used without purification. Merck-precoated aluminum TLC plates of silica gel 60 F254 were employed for the reaction monitoring and the spots visualized with iodine vapors and in UV chamber. Melting points were determined by Remi electronic melting point apparatus. IR spectra were recorded on Agilent fourier transform infrared spectroscopy (FTIR) by KBr pellet method. ^{1}H NMR recorded on BRUKER DRX – 500 MHz. Chemical shift values (δ) articulated in ppm with reference to internal standard tetra methyl silane (TMS). The splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. MASS recorded on BRUKER ESI-IT MS.

General Procedure for Synthesis of Quinazoline Derivatives 3a1-3a5 & 3b1-3b5

The scheme of synthesis for the quinazoline derivatives was depicted in Fig. 2. To the mixture of 0.38 mmol of amides (1a or 1b, 1 equiv), 0.38 mmol of different nitriles (2, 1equiv) and 0.41 mmol of 2-chloropyridine (1.2 equiv), 0.38 mmol of trifluoromethanesulfonic anhydride (1.1 equiv) was added via syringe over 1 minute in carbon tetrachloride (1.0 mL) at -78°C (with the help of dry ice and acetone mixture).[18] After 10 minutes, the reaction mixture was placed in an ice-water bath for 5 minutes and warmed to 0°C. The resulting solution was allowed to warm to ambient temperature. After 1-hour of reflux, aqueous sodium hydroxide solution (1 mL, 1N) was introduced to neutralize the trifluoro methane sulfonate salts. 5 mL of carbon tetrachloride was added to dilute the mixture and the layers were separated. The organic layer was washed with brine, was dried over anhydrous sodium sulfate, and was filtered. The volatiles were removed under reduced pressure and the residue was purified by column chromatography with 10% EtOAc in hexane on neutralized silica gel to give the final quinazoline products (3a1-3a5 & 3b1-3b5).[19]

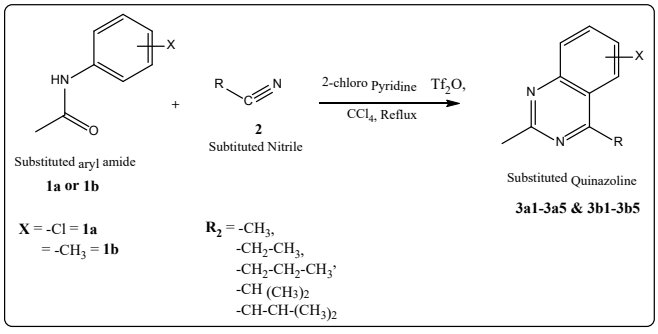

Fig. 2: Scheme of synthesis of quinazoline derivatives

Antimicrobial Activity

Antibacterial Activity

Antibacterial activity was screened for the titled compounds (1–10) at a dose 60 µg/mL by agar plate method by using standard protocols.[20] Various gram-positive (*B. subtilis* and *S. aureus*) and gram-negative bacteria (*P. aureus* and *E. coli*) were selected for the antibacterial screening. Standard Neomycin sulfate and dimethylsulfoxide (DMSO) were served as positive and negative control, respectively. The experiment was done in triplicates and the zone of inhibition measured in mm was taken for the evaluation of antibacterial activity of the test compounds.

Peptone, meat extract and sodium chloride were dissolved in distilled water and PH of the medium was adjusted to 7.2. agar was dissolved and distributed in 40 mL quantities into 100 mL flasks and were sterilized in an autoclave at 121°C (15 lbs /sq.in) for 20 minutes. The medium was inoculated at 1% level with 18 hours of old cultures of the above-mentioned test organism and transferred into sterile 15 cm diameter petri dishes. The medium in the plates were set at room temperature for 30 minutes. For the preparation of cup agar plates 6mm diameter holes were made with the help of a sterile borer at the corner of the plate at equal distance. Solution of test compounds was placed in the cups by means of sterile pipettes. In each plate one cup was used for control with 2 drops (0.05 mL) of DMSO Neomycin sulphate in 10 µg/mL concentration was used as standard. The plates were incubated at room temperature for 1-hour to diffuse. Then, the plates were incubated for 24 hours at 37°C and zone of inhibition was recorded. The experiments ran in duplicate and the average diameter of the zones of inhibition was recorded.

Antifungal Activity

The prepared compounds were also screened for their antifungal activity at 60 µg/mL by agar plate method using the above protocols. The experiment was done in triplicates and the compounds were evaluated for its antifungal activity on *A. niger* and *C. albicans*. Standard Nystatin and DMSO were served as positive and negative control, respectively. The inhibition zone measured in mm was taken for the evaluation of antifungal activity.

Peeled potatoes are cut into small chips and boiled with 200 mL of water for 30 minutes. The chips were crushed during boiling and pulp was removed after cooling by filtration through muslin. Dextrose and agar were added slowly by stirring and the volume was made up to 1000 mL. Nystatin in 10 µg/mL concentration and DMSO was taken as standard and control, respectively. All the plates were incubated at room temperature (30°C) after 48 hours the plates were examined, and the diameter of the zones were recorded.

Results and Discussion

Chemistry

All the synthesized compounds 3a1-3a5 & 3b1-3b5 were resulted in competitive yield as reported in Table 1. Synthesis was achieved by the condensation of highly activated amide starting materials with weakly nucleophilic alkyl and aryl nitriles to directly provide the corresponding quinazoline derivatives. The structures of the newly synthesised compounds were in good agreement with their IR, MS, and 1H-NMR, analyses data.

Structural and physical data of the synthesized compounds was enumerated below in the Table 1 and general structure of the quinazoline derivatives displayed in Fig. 3.

Compound 3a1: *6-chloro-2,4-dimethylquinazoline*

Pale yellow solid, IR (KBr): ν_{max} in cm^{-1}: 1610 (C=N), 3070 (=C–H), 1286.0 (C-N); ^{1}H NMR: δ 2.57 (3H, s), 2.73 (3H, s), 7.81-7.90 (2H, 7.84 (dd, J = 8.4, 1.7 Hz), 7.87 (dd, J = 8.4, 0.4 Hz)), 7.96 (1H, dd, J = 1.7, 0.4 Hz). ESI-MS: m/z Anal. Calcd. For $C_{10}H_9ClN_2$ ([M + H]$^+$): 192.65, found 193.50.

Compound 3a2: *6-chloro-4-ethyl-2-methylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1604.5 (C=N), 3063.9 (=C–H); ^{1}H NMR: δ 1.17 (3H, t, J = 7.2 Hz), 2.57 (3H, s), 2.91 (2H, q, J = 7.2 Hz), 7.79 (1H, dd, J = 1.7, 0.4 Hz), 7.81-7.90 (2H, 7.84 (dd, J = 8.2, 1.7 Hz), 7.87 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{11}H_{11}ClN_2$ ([M + H]$^+$): 206.65, found 207.55.

Compound 3a3: *6-chloro-2-methyl-4-propylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1613.5 (C=N), 3049.2 (=C–H), 1273.1 (C-N); ^{1}H NMR: δ 1.04 (3H, t, J = 6.7 Hz), 1.80 (2H, tq, J = 7.5, 6.7 Hz), 2.57 (3H, s), 2.72 (2H, t, J = 7.5 Hz), 7.79 (1H, dd, J = 1.7, 0.4 Hz), 7.81-7.90 (2H, 7.84 (dd, J = 8.2, 1.7 Hz), 7.88 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{12}H_{13}ClN_2$ ([M + H]$^+$): 220.70, found 221.55.

Compound 3a4: *6-chloro-4-isopropyl-2-methylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1615 (C=N), 3062.2 (=C–H), 1284.5 (C-N), 675.5 (C-Cl); ^{1}H NMR: δ 1.29 (6H, d, J = 6.7 Hz), 2.59 (3H, s), 3.25 (1H, sept, J = 6.7 Hz), 7.79 (1H, dd, J = 1.7, 0.4 Hz), 7.81-7.90 (2H, 7.84 (dd, J = 8.2, 1.7 Hz), 7.88 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{12}H_{13}ClN_2$ ([M + H]$^+$): 220.70, found 221.55.

Compound 3a5: *6-chloro-4-isopentyl-2-methylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1609.3 (C=N), 3062.7 (=C–H), 1282.5 (C-N); ^{1}H NMR: δ 0.78 (6H, d, J = 6.6 Hz), 1.47 (1H, tsept, J = 6.8, 6.6 Hz), 1.58 (2H, td, J = 7.5, 6.8 Hz), 2.57 (3H, s), 2.73 (2H, t, J = 7.5 Hz), 7.79 (1H, dd, J = 1.7, 0.4 Hz), 7.81-7.90 (2H, 7.84 (dd, J = 8.2, 1.7 Hz), 7.88 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{14}H_{17}ClN_2$ ([M + H]$^+$): 248.75, found 249.60.

Compound 3b1: *2,4,6-trimethylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1606.5 (C=N), 3045.8 (=C–H), 1286.3 (C-N); ^{1}H NMR: δ 2.36 (3H, s), 2.57 (3H, s), 2.70 (3H, s), 7.60 (1H, dd, J = 8.2, 1.9 Hz), 7.82-7.88 (2H, 7.87 (dd, J = 1.9, 0.4 Hz), 7.85 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{11}H_{12}N_2$ ([M + H]$^+$): 172.25, found 173.20.

Compound 3b2: *4-ethyl-2,6-dimethylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1601.5 (C=N), 3055.6 (=C–H), 1280.5 (C-N); ^{1}H NMR: δ 1.20 (3H, t, J = 7.2 Hz), 2.36 (3H, s), 2.58 (3H, s), 2.90 (2H, q, J = 7.2 Hz), 7.60 (1H, dd, J = 8.2, 1.9 Hz), 7.82-7.88 (2H, 7.87 (dd, J = 1.9, 0.4 Hz), 7.85 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{12}H_{14}N_2$ ([M + H]$^+$): 186.25, found 187.15.

Table 1: Molecular formula, melting point and yield of compounds 3a1-3a5 & 3b1-3b5.

Compound	*X*	*R*	*Mol. form.*	*M.p in °C*	*% Yield*
3a1	-Cl	$-CH_3$	$C_{10}H_9ClN_2$	103–105	91
3a2	-Cl	$-CH_2CH_3$	$C_{11}H_{11}ClN_2$	107–108	89
3a3	-Cl	$-CH_2CH_2CH_3$	$C_{12}H_{13}ClN_2$	112–113	89
3a4	-Cl	$-CH(CH_3)_2$	$C_{12}H_{13}ClN_2$	99–100	81
3a5	-Cl	$-CH-CH(CH_3)_2$	$C_{14}H_{17}ClN_2$	94–96	74
3b1	$-CH_3$	$-CH_3$	$C_{11}H_{12}N_2$	83–85	81
3b2	$-CH_3$	$-CH_2CH_3$	$C_{12}H_{14}N_2$	89–91	78
3b3	$-CH_3$	$-CH_2CH_2CH_3$	$C_{13}H_{16}N_2$	99-101	73
3b4	$-CH_3$	$-CH(CH_3)_2$	$C_{13}H_{16}N_2$	95–96	68
3b5	$-CH_3$	$-CH-CH(CH_3)_2$	$C_{15}H_{20}N_2$	91–92	63

Compound 3b3: *2,6-dimethyl-4-propylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1615.5 (C=N), 3054.3 (=C–H), 1282.5 (C-N); 1H NMR: δ 1.04 (3H, t, J = 6.7 Hz), 1.80 (2H, tq, J = 7.5, 6.7 Hz), 2.36 (3H, s), 2.58 (3H, s), 2.71 (2H, t, J = 7.5 Hz), 7.60 (1H, dd, J = 8.2, 1.9 Hz), 7.83-7.88 (2H, 7.87 (dd, J = 1.9, 0.4 Hz), 7.85 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{13}H_{16}N_2$ ([M + H]$^+$): 200.30, found 201.25.

Compound 3b4: *4-isopropyl-2,6-dimethylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1611.4 (C=N), 3051.9 (=C–H), 1280.3 (C-N); ^{1}H NMR: δ 1.27 (6H, d, J = 6.7 Hz), 2.36 (3H, s), 2.59 (3H, s), 3.25 (1H, sept, J = 6.7 Hz), 7.60 (1H, dd, J = 8.2, 1.9 Hz), 7.83-7.89 (2H, 7.88 (dd, J = 1.9, 0.4 Hz), 7.86 (dd, J = 8.2, 0.4 Hz)). ESI-MS: m/z Anal. Calcd. For $C_{13}H_{16}N_2$ ([M + H]$^+$): 200.30, found 201.25.

Compound 3b5: *4-isopentyl-2,6-dimethylquinazoline*

Pale yellow solid, IR (KBr):ν_{max} in cm^{-1}: 1603.7 (C=N), 3062.5 (=C–H), 1286.5 (C-N); ^{1}H NMR: δ 0.85 (6H, d, J = 6.6 Hz), 1.47 (1H, sept, J = 6.9, 6.6 Hz), 1.61 (2H, td, J = 7.5, 6.9 Hz), 2.36 (3H, s), 2.58 (3H, s), 2.73 (2H, t, J = 7.5 Hz), 7.60 (1H, dd, J = 8.2, 1.9 Hz), 7.83-7.88 (2H, 7.87 (dd, J = 1.9, 0.4 Hz), 7.86 (dd, J = 8.2, 0.4 Hz)).ESI-MS: m/z Anal. Calcd. For $C_{15}H_{20}N_2$ ([M + H]$^+$): 228.35, found 229.20.

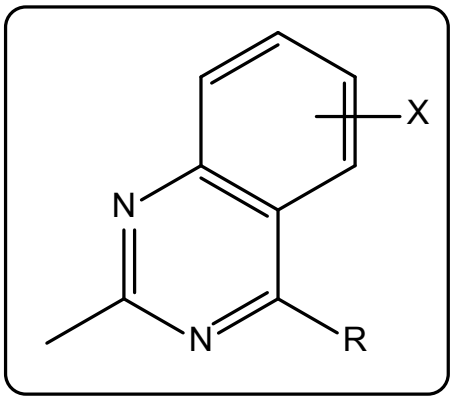

Fig. 3: General structure of quinazoline derivatives

Antimicrobial Activity

The antibacterial screening of the compounds (3a1-3a5 & 3b1-3b5) were screened against two gram-positive namely, *B. subtilis* and *S. aureus*, two gram-negative namely, *E. coli* and *P. aeruginosa* by using agar plate method. The results depicted in Table 2. All the synthesized compounds display considerable antibacterial properties. Interestingly, compounds possessing alkyl and phenyl substitutions at the 6th position of quinazoline ring are showing comparatively higher inhibition to both gram-positive and gram-negative bacteria especially compounds 3a1, 3a2, 3a3, 3b1 and 3b2.

Since, the quinazoline moiety is already reported to possess antifungal properties, the prepared compounds are also screened for their potency to inhibit the growth of fungi. The activity results are illustrated in the Table 3. It indicates that all the substituted quinazoline derivatives are antifungal in nature. They are specific against *Aspergillus niger* and *Candida albicans*. Compounds 3a1 and 3b2 displayed good inhibition of growth against *Aspergillus niger* and *Candida albicans.*

From the above results the quinazoline derivatives are antimicrobial in nature. The alkyl and aryl substitutions on the quinazoline ring enhance the sensitivity to the microorganism and inhibiting the growth. This experiment is clearly disclosed that the synthesized quinazoline derivatives can control the population of pathological microorganism. Interestingly, the compounds 3a1, 3a2, 3a3, 3b1 and 3b2 displayed good antimicrobial potential.

Compounds with higher alkyl substitutions such as isopropyl (3b4) and iso butyl (3b5) substitutions on the quinazoline rings displayed marked decrease in both antibacterial and antifungal activity. This suggests that the

Table 2: Antibacterial activity of the compounds against gram-positive and gram-negative bacteria

Bacterial strain	*Zone of inhibition of the compounds (60 µg/mL) in mm*[a]										*Solvent control DMSO*	*Neomycin sulphate 10µg/mL*
	3a1	*3a2*	*3a3*	*3a4*	*3a5*	*3b1*	*3b2*	*3b3*	*3b4*	*3b5*		
B. subtilis	18	17	14	11	09	17	15	12	10	11	4	19
S. aureus	16	16	13	10	10	15	15	12	11	08	3	18
E. coli	18	17	15	11	08	18	17	13	09	07	4	20
P. aeruginosa	17	15	15	09	10	16	13	12	10	10	3	20

[a] Values including diameter of the disc (6.0 mm), are averages of triplicates.

Table 3: Antifungal activity of the compounds

Fungus	*Zone of inhibition of the Compounds (60 µg/mL) in mm*[a]										*Solvent control DMSO*	*Nystatin 10 µg/mL*
	3a1	*3a2*	*3a3*	*3a4*	*3a5*	*3b1*	*3b2*	*3b3*	*3b4*	*3b5*		
A. niger	16	13	12	10	08	15	10	11	13	10	4	20
C. albicans	19	11	12	11	10	17	11	09	10	06	2	21

[a] Values including diameter of the disc (6.0 mm), are averages of triplicates.

branching of the side chain on 6th position in quinazoline ring can be the factor for the decrease in activity. This further suggests potential importance of the 6th position in quinazoline ring of the synthesized derivatives. The above findings can clear that these quinazoline derivatives can serve as lead molecules to the development of potent antimicrobial agents.

Conclusion

A novel series of quinazoline derivatives were synthesized through a feasible single-step one-pot synthetic route employing trifluoro methane sulfonic anhydride catalyst and this method provided a good yield for all the designed compounds. Synthesized compounds were characterized and screened for antimicrobial activity against four bacterial strains and two fungal strains. Comparatively most compounds displayed good to moderate antimicrobial potential relative to the standard drugs neomycin and nystatin. The compound 3a1, 3a2, 3a3, 3b1, and 3b2 displayed good antimicrobial potential against selected strains of bacteria and fungi. Further investigations are needed to establish the detailed mechanism of action of the developed novel quinazoline derivatives.

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