

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF QUINAZOLINONE PEPTIDE DERIVATIVES

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ABSTRACT

Objective: The increased microbial resistance against commercially available drugs initiated the development of novel and safe antimicrobial agents in last few decades. In this view, a series of amino acid/dipeptide derivatives of quinazolin-3(4H)-one was synthesized and was evaluated for their antimicrobial potential.

Method: Synthesis of amino acid/peptide derivatives were carried out by coupling 5-(2-(2-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxy benzoic acid with amino acid/dipeptide methyl esters in the presence of dicyclohexylcarbodiimide and *N*-methylmorpholine. The chemical structures of synthesized compounds were characterized by ¹H nuclear magnetic resonance and infrared spectroscopy and were screened for antibacterial activity by disc diffusion method.

Results: All the synthesized derivatives exhibited moderate to significant antibacterial activity against both Gram-positive and Gram-negative bacteria. The potency of compound 5d was comparable to standard drug ciprofloxacin in all the strains of bacteria used. The compound 5a was found to be more active against *Streptococcus pyogenes* and *Staphylococcus aureus* while compound 5c against *Pseudomonas aeruginosa* and *Escherichia coli*.

Conclusion: Peptide derivatives of quinazolinone are promising antimicrobial agent and can be used for the synthesis of other novel compounds.

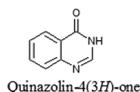
Keywords: Quinazolinone, Peptide, Antimicrobial agents.

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INTRODUCTION

Infectious diseases have become a major cause of mortality worldwide, especially in immunocompromised patients such as patients suffering from tuberculosis, acquired immune deficiency syndrome, and cancer [1,2]. Although a number of antibiotics are commercially available for various infections but the development of microbial resistance is another challenge which is due to overuse of antibiotics and poor infection control practices [3-6].

Heterocyclic systems comprising quinazolinones have been explored to a major extent in last few decades due to its chemotherapeutic and antimicrobial potential. Quinazolinone (1) is a bicyclic compound containing benzene ring fused with pyrimidine ring. This heterocyclic molecule occupies a distinct place in the field of medicinal chemistry due to its wide spectrum of biological activities such as analgesic [7-11], antioxidant [12,13], antimicrobial [14,15], anticancer [16,17], anti-inflammatory [18,19], antitubercular [20], antihyperlipidemic [21], antihistamine [22], antiviral [23], anticonvulsant [24], and antiparkinsonian [25].



Peptides are heteropolymers and function as hormones, neurotransmitter, enzymes, substrate, and immunomodulators; hence considered as an important molecule in the field of health science [26-29]. Thus keeping in mind the therapeutic potential of quinazolinone as well as biodegradability and bioavailability profile of amino acids/peptide, an attempt has been made to synthesize amino acid/peptide derivatives of quinazolinone so as to increase its therapeutic potential and minimize adverse effects [30-33].

METHODS

Chemistry

All the chemicals such as *tert*-butoxycarbonyl protected amino acids (valine, tryptophan), amino acids (L-phenylalanine, L-leucine, L-serine, and L-arginine), dicyclohexylcarbodiimide (DCC), anthranilic acid, benzoyl chloride, *N*-methylmorpholine (NMM), and trifluoroacetic acid (TFA) were purchased from Spectrochem Pvt. Ltd., (Mumbai, India). All the solvents were of commercial grade and distilled before use. Melting point of synthesized derivatives was determined by an open capillary method using digital melting point apparatus (Popular, India). The progress of reactions was monitored by thin layer chromatography (TLC) on silica gel F₂₅₄ plates with visualization by ultraviolet or iodine vapors. The molecular structures of all the synthesized derivatives were confirmed by elemental analysis, infrared (IR), and ¹H nuclear magnetic resonance (NMR). The IR spectra (in KBr pellet) were recorded on FTIR-8400S (Shimadzu) spectrophotometer. Bruker Avance II (400 MHz) spectrometer was used to record ¹H NMR, and chemical shifts were given in δ (ppm) scale.

General scheme for synthesis of quinazolinone-amino acid/peptide derivatives

The general scheme for the synthesis of quinazolinone nucleus and its amino acid/peptide derivatives has been provided in Figs. 1 and 2.

Experimental

Synthesis of quinazolinone nucleus: (5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3-(4H)-yl)-2-hydroxy benzoic acid (5)

Synthesis of 2-(2-Chlorobenzamido) benzoic acid (3)
To a stirred solution of anthranilic acid (10 mmol) in pyridine (12 ml), 2-chlorobenzoyl chloride (10 mmol) was added dropwise. The mixture obtained was further stirred at room temperature for 5 hrs. The resulting reaction mixture was filtered, washed with water and dried; followed by crystallization with ethanol to get pure compound.

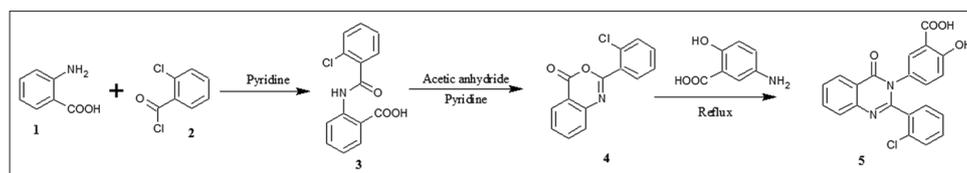


Fig. 1: Synthesis of quinazolinone nucleus

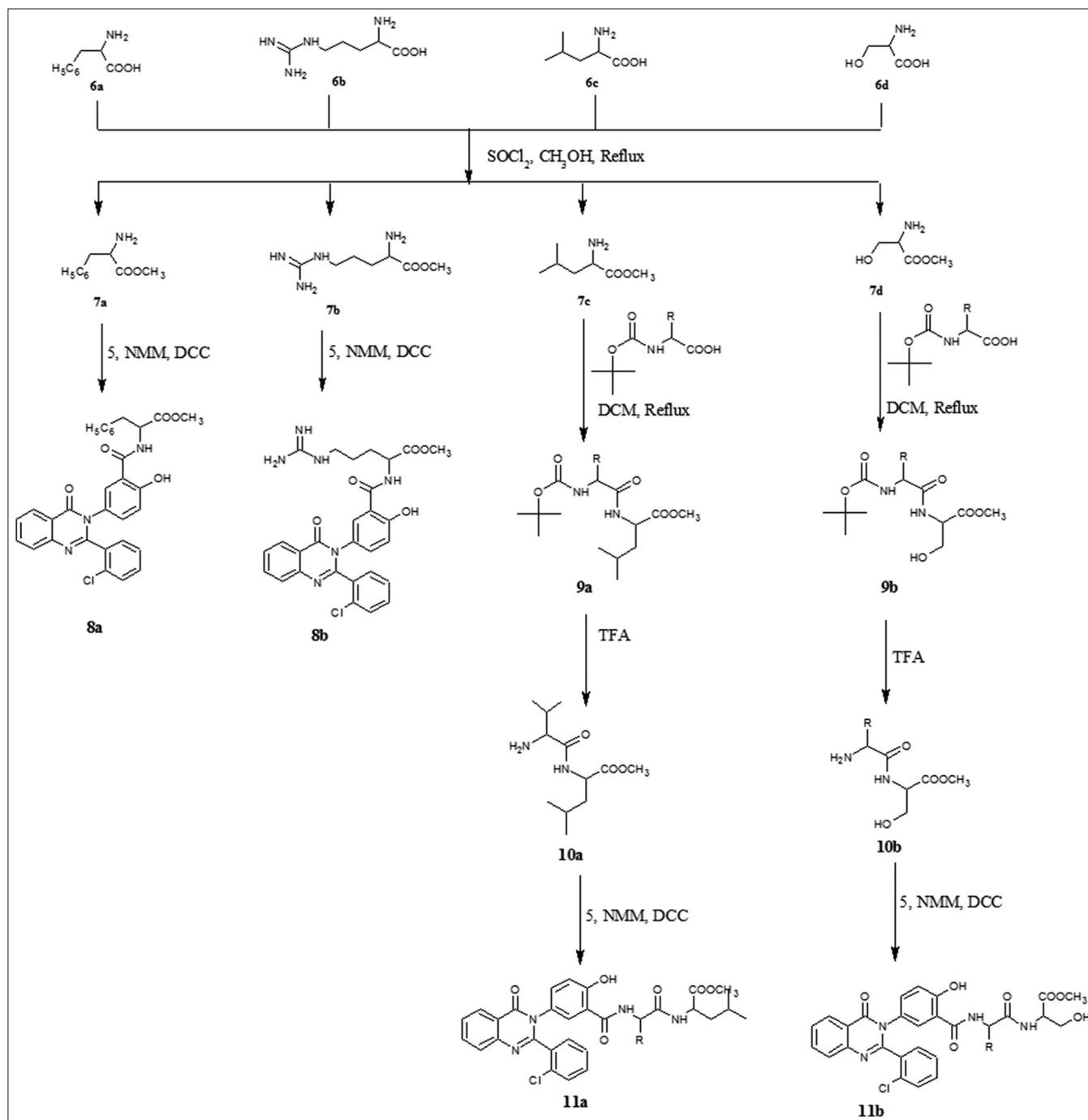


Fig. 2: Coupling of Boc-amino acid/peptides with quinazolinone nucleus

Synthesis of 2-(2-Chlorophenyl)-4H-benzo[d][1,3]oxazin-4-one (4)
The solution of compound 3 (20 mmol) in acetic anhydride (34 ml) was refluxed for 6 hrs or till the completion of reaction. The solvent was removed under reduced pressure; the precipitate was washed with petroleum ether and purified by crystallization with ethanol.

Synthesis of 5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxy benzoic acid (5)

Equimolar amount of compound 4 (16.4 mmol) and 5-aminosalicylic acid was heated on a water bath at 200°C for 2 hrs. The separated solid was crystallized with ethanol to get pure compound.

Preparation of L-amino acid methyl ester hydrochloride (7a-d)

Esterification of amino acids 6a-d (10 mmol) was carried out by conversion into acid chloride using thionyl chloride (10 mmol), followed by addition of methanol at 0°C. The reaction mixture was refluxed on a water bath for 12 hrs at a temperature of 110°C. The progress of the reaction was monitored by TLC. After the completion of the reaction, methanol was removed under reduced pressure and the treated with ether to remove dimethyl sulfite. The purification of the product was carried out by recrystallization with methanol [34,35].

Preparation of Boc-dipeptide methyl ester (9a-b)

To the solution of amino acid methyl ester hydrochloride 7c and 7d (20 mmol) in chloroform (40 ml), NMM (42 mmol) was added at 0°C, and the mixture was stirred for 15 minutes. Then, Boc-amino acid (20 mmol) in chloroform (40 ml) and DCC (20 mmol) was added while stirring the reaction mixture. After stirring for 48 hrs, the reaction mixture was filtered, and residue was washed with chloroform (30 ml) and added to the filtrate. The combined filtrate was further extracted with 25 ml of 5% sodium hydrogen carbonate and then with 25 ml saturated sodium chloride solution. After drying of the organic layer, the solvent was removed under vacuum by rotary evaporator. The crude product obtained was purified by crystallization using a mixture of chloroform and petroleum ether [26,36].

Deprotection of dipeptide methyl ester at amino end (10a-b)

Deprotection of Boc group was carried out by dissolving Boc-dipeptide methyl ester (10 mmol) in chloroform (15 ml) followed by addition of TFA (20 mmol). The resulting solution was stirred for 30 minutes. Then, the reaction mixture was concentrated, dried and washed with a mixture of chloroform and petroleum ether [37-39].

Synthesis of amino acid/peptide derivatives of 5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxy benzoic acid (8a-b, 11a-b)

Amino acid methyl ester/deprotected dipeptide methyl ester (1 mmol) was dissolved in THF; NMM (0.01 mmol) was added at 0°C, and the reaction mixture was stirred for 15 minutes. In another beaker, a solution of compound 5 (1 mmol) in THF (7.4 ml) and DCC (0.01 mmol) was prepared and added to reaction mixture with stirring. After stirring for 36 hrs, the reaction mixture was filtered, and the residue was washed with THF (5 ml), followed by washing with 5% sodium hydrogen carbonate and saturated sodium chloride solutions (15 ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated by rotary evaporator. The purification of the crude product was carried out by recrystallization with a mixture of chloroform and n-hexane (Table 1).

Spectral analysis of synthesized compounds**5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxy benzoic acid (5)**

FTIR (KBr, cm⁻¹): 3356-3285 (O-H, str.), 3076 (C-H str. aromatic), 1725 (C=O str. acid), 1665 (C=O str. amide), 775 (C-Cl str.), 750 (ortho substitution oop); ¹H NMR (400 MHz, DMSO, δ ppm): 12.1 (s, COOH, 1H), 8.18 (s, Ar-H, 1H, benzoic acid), 8.13-7.64 (m, Ar-H, 4H, quinazoline), 7.51-7.42 (m, Ar-H, 4H, chlorobenzene), 7.39-7.36 (m, Ar-H, 2H, benzoic acid), 3.8 (s, OH, 1H).

L-Phenylalanine methyl ester hydrochloride (7a)

FTIR (KBr, cm⁻¹): 3423 and 3368 (primary N-H str.), 2926 (C-H str. aromatic), 2852 (C-H str. aliphatic), 1745 (C=O str. ester), 1238 (C-O str.), 762 and 695 (mono substitution oop); ¹H NMR (400MHz, DMSO, δ ppm): 8.71 (d, NH₂, 2H), 7.19-7.14 (m, Ar-H, 5H), 3.66 (s, OCH₃, 3H), 3.54 (m, CH₂ benzyl, 2H), 3.32 (m, CH, 1H).

L-Arginine methyl ester hydrochloride (7b)

FTIR (KBr, cm⁻¹): 3456 and 3370 (primary N-H str.), 2955 (C-H str. aliphatic), 1743 (C=O, ester), 1200 (C-O str.); ¹H NMR (400MHz, DMSO,

δ ppm): 8.76 (d, NH₂, 2H), 7.84 (s, terminal NH of guanidine group, 1H), 6.63 (m, terminal NH₂ of guanidine group, 2H), 3.69 (s, OCH₃, 3H), 3.36 (m, CH-NH₂, 1H), 3.28 (m, CH-NH, 2H), 1.8-1.6 (m, CH₂, 4H).

L-Leucine methyl ester hydrochloride (7c)

FTIR (KBr, cm⁻¹): 3462 and 3390 (primary N-H str.), 2872 (C-H str. aliphatic), 1739 (C=O, ester) 1240 (C-O str.); ¹H NMR (400 MHz, DMSO, δ ppm): 8.63 (d, NH₂, 2H), 3.61 (s, OCH₃, 3H), 3.36 (m, CH-NH₂, 1H), 1.87 (m, CH₂, 2H), 1.49 (m, CH, 1H), 0.90-0.96 (m, CH₃, 6H).

L-Serine methyl ester hydrochloride (7d)

FTIR (KBr, cm⁻¹): 3550 (O-H str.), 2996 (C-H str. aliphatic), 1760 (C=O, ester), 1249 (C-O str.); ¹H NMR (400 MHz, DMSO, δ ppm): 8.96 (d, NH₂, 2H), 4.94 (t, OH, 1H), 4.26 (t, CH₂, 2H), 3.66 (s, OCH₃, 3H), 3.46 (m, CH-NH₂, 1H).

tert-Butyloxycarbonyl-valine-leucine methyl ester (9a)

FTIR (KBr, cm⁻¹): 3350 (secondary N-H str.), 2978 (C-H str. aliphatic), 1756 (C=O str. ester), 1680 (C=O str. amide), 1210 (C-O str.); ¹H NMR (400 MHz, DMSO, δ ppm): 8.32 (d, NH, 1H), 7.39 (d, NH, 1H), 4.51 (m, CH, 1H), 4.34 (m, CH, 1H), 3.68 (s, OCH₃, 3H), 2.73 (m, CH, 1H), 1.81 (m, CH₂, 2H), 1.42 (m, CH, 10H), 0.96-0.90 (m, CH₃, 12 H).

tert-Butyloxycarbonyl-tryptophenyl-serine methyl ester (9b)

FTIR (KBr, cm⁻¹): 3590 (O-H str.), 3235 (secondary N-H str.), 3090 (C-H str. aromatic), 2985 (C-H str. aliphatic), 1758 (C=O str. ester), 1692 (C=O str. amide), 1270 (C-O str.); ¹H NMR (400MHz, DMSO, δ ppm): 11.6 (d, NH of tryptophan ring, 1H), 8.3-8.1 (d, NH, 2H), 7.41-7.10 (m, Ar-H tryptophan ring, 5H), 5.82 (d, CH, 1H), 4.94 (t, OH, 1H), 4.26 (t, CH₂, 2H), 4.02 (m, CH, 1H), 3.58 (s, OCH₃, 3H), 1.46 (m, CH₃, 9H).

Valine-leucine methyl ester (10a)

FTIR (KBr, cm⁻¹): 3420 & 3350 (primary N-H str.), 2954 (C-H str. aliphatic), 1762 (C=O str. ester), 1674 (C=O str. amide), 1219 (C-O str.); ¹H NMR (400MHz, DMSO, δ ppm): 8.32 (d, NH, 1H), 6.5 (d, NH₂, 2H), 4.54 (m, CH, 1H), 3.61 (s, OCH₃, 3H), 3.37 (m, CH, 1H), 2.06 (m, CH, 1H), 1.81 (m, CH₂, 2H), 1.42 (m, CH, 10H), 0.96-0.90 (m, CH₃, 12 H).

Tryptophan-serine methyl ester (10b)

FTIR (KBr, cm⁻¹): 3598 (O-H str.), 3224 (secondary N-H str.), 3082 (C-H str. aromatic), 2973 (C-H str. aliphatic), 1767 (C=O str. ester), 1696 (C=O str. amide), 1296 (C-O str.); ¹H NMR (400MHz, DMSO, δ ppm): 11.24 (d, NH of tryptophan ring, 1H), 8.32 (d, NH, 1H), 7.46-7.19 (m, Ar-H tryptophan ring, 5H), 6.7 (s, NH₂, 2H) 4.86 (t, OH, 1H), 4.6 (t, CH, 1H), 4.26 (m, CH₂, 2H), 4.02 (m, CH, 1H), 3.63 (s, OCH₃, 3H).

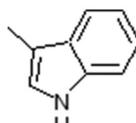
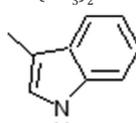
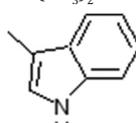
5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxybenzoyl-phenylalanine methyl ester (8a)

FTIR (KBr, cm⁻¹): 3486-3452 (O-H str.), 3054 (C-H str. aromatic), 2958 (C-H str. aliphatic), 1743 (C=O str. ester), 1670 (C=O str. amide), 1608 and 1458 (C=C str. aromatic), 1338 (C-O str.), 1219 (C-N str.), 782 (C-Cl str.); ¹H NMR (400 MHz, DMSO, δ ppm): 9.87 (d, NH, 1H, amide), 8.18 (s, Ar-H, 1H, benzoic acid), 8.13-7.64 (m, Ar-H, 4H, quinazoline), 7.51-7.42 (m, Ar-H, 4H, chlorobenzene), 7.19-7.14 (m, Ar-H, 5H), 4.84 (d, CH, 1H), 3.96 (s, OH, 1H), 3.66 (s, CH₃, 3H), 3.27 (d, CH₂, 2H).

5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxybenzoyl-arginine methyl ester (8b)

FTIR (KBr, cm⁻¹): 3469-3427 (O-H str.), 3244 and 3212 (N-H str.), 3076 (C-H str. aromatic), 2972 (C-H str. aliphatic), 1756 (C=O str. ester), 1689 (C=O str. amide), 1624 and 1470 (C=C str. aromatic), 1342 (C-O str.), 1235 (C-N str.), 756 (C-Cl str.); ¹H NMR (400 MHz, DMSO, δ ppm): 8.87 (d, NH, 1H, amide), 8.20 (s, Ar-H, 1H, benzoic acid), 8.09-7.72 (m, Ar-H, 4H, quinazoline), 7.81 (s, terminal NH of guanidine group, 1H), 7.53-7.49 (m, Ar-H, 4H, chlorobenzene), 6.52 (m, terminal NH₂ of guanidine group,

Table 1: Physicochemical properties of synthesized compounds

Compounds	Molecular formula	Molecular weight	R	Yield (%)	M.p (°C)	R _f value ^a
5	C ₁₂ H ₁₃ ClN ₂ O ₄	392.79	-	71	127-130	0.81
7a	C ₁₀ H ₁₄ ClNO ₂	215.67	-	92	161-164	0.79
7b	C ₇ H ₁₇ ClN ₄ O ₂	224.68	-	88	155-162	0.64
7c	C ₇ H ₁₆ ClNO ₂	181.66	-	72	155-159	0.62
7d	C ₄ H ₁₀ ClNO ₃	155.58	-	-	-	-
9a	C ₁₇ H ₃₂ N ₂ O ₅	344.44	-CH(CH ₃) ₂	70	143-145	0.86
9b	C ₂₀ H ₂₇ N ₃ O ₆	405.44		78	160-162	0.91
10a	C ₁₂ H ₂₄ N ₂ O ₃	244.33	-CH(CH ₃) ₂	89	172-177	0.85
10b	C ₁₅ H ₁₉ N ₃ O ₄	305.32		66	169-171	0.77
8a	C ₃₁ H ₂₄ ClN ₃ O ₅	553.99	-	76	159-161	0.76
8b	C ₂₈ H ₂₇ ClN ₆ O ₅	563.00	-	69	145-151	0.64
11a	C ₃₃ H ₃₅ ClN ₄ O ₆	619.10	-CH(CH ₃) ₂	73	132-134	0.67
11b	C ₃₆ H ₃₀ ClN ₅ O ₇	680.10		65	161-164	0.71

^aTLC mobile phase: n-butanol:acetic acid:water (3:1:1)

Table 2: Antimicrobial activity of quinazolinone peptide derivatives

S.No.	Compounds	Zone of inhibition (mm)			
		<i>S. pyogenes</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>
1	8a	18±0.56	19±0.13	16±0.7	14±0.45
2	8b	6±0.87	13±0.3	10±0.55	11±0.7
3	11a	15±0.9	16±0.1	19±0.2	18±0.48
4	11b	19±0.2	22±0.11	20±0.32	18±0.5
5	Ciprofloxacin	23±0.12	25±0.19	27±0.78	22±0.43

Zone of inhibition is expressed as mean±standard deviation of triplicates.

S. pyogenes: *Streptococcus pyogenes*, *S. aureus*: *Staphylococcus aureus*,

Pseudomonas aeruginosa: *P. aeruginosa*, *E. coli*: *Escherichia coli*

2H), 4.51 (d, CH, 1H), 4.02 (s, OH, 1H), 3.74 (s, CH₃, 3H), 3.34 (d, CH₂, 2H), 2.5 (m, NH of guanidine group, 1H), 1.92 (m, CH₂, 2H), 1.51 (m, CH₂, 2H).

5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxybenzoyl-valine-leucine methyl ester (11a)

FTIR (KBr, cm⁻¹): 3456-3399 (O-H str.), 3050 (C-H str. aromatic), 2947 (C-H str. aliphatic), 1765 (C=O str. ester), 1660 (C=O str. amide), 1635 and 1475 (C=C str. aromatic), 1290 (C-O str.), 1260 (C-N str.), 742 (C-Cl str.); ¹H NMR (400 MHz, DMSO, δ ppm): 8.88 and 8.65 (d, NH, 2H, amide), 8.24 (s, Ar-H, 1H, aromatic), 8.13-7.68 (m, Ar-H, 4H, quinazolinone), 7.51-7.42 (m, Ar-H, 4H, chlorobenzene), 4.84 (d, CH, 1H), 4.51 (m, CH, 1H), 4.24 (s, OH, 1H), 3.74 (s, CH₃, 3H), 1.87 (m, CH₂, 2H), 1.49 (m, CH, 1H), 0.96-0.9 (m, CH₃, 12 H).

5-(2-(2-Chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxybenzoyl-tryptophan-serine methyl ester (11b)

FTIR (KBr, cm⁻¹): 3468-3412 (O-H str.), 3069 (C-H str. aromatic), 2960 (C-H str. aliphatic), 1772(C=O str. ester), 1675(C=O str. amide), 1638 and 1482(C=C str. aromatic), 1286(C-O str.), 1254(C-N str.), 764(C-Cl str.); ¹H NMR (400 MHz, DMSO, δ ppm): 10.79 (d, NH of tryptophan ring, 1H), 8.78&8.32 (m, NH, 2H, amide), 8.01 (s, Ar-H, 1H, aromatic), 8.11-

7.69 (m, Ar-H, 4H, quinazolinone), 7.51-7.42 (m, Ar-H, 4H, chlorobenzene), 7.25-7.09 (m, Ar-H, 2H), 5.82 (d, CH, 1H), 4.94 (m, OH, 1H), 4.26 (t, CH₂, 2H), 3.71 (s, CH₃, 3H).

In vitro antimicrobial activity

Newly synthesized amino acid and peptide derivatives of quinazolinone 8a-b and 11a-b were screened for their antimicrobial potential by disc diffusion method against Gram-positive bacteria such as *Streptococcus pyogenes*, *Staphylococcus aureus*, and Gram-negative bacteria like *Pseudomonas aeruginosa*, *Escherichia coli* at a concentration of 100 µgml⁻¹. The test compounds were dissolved in an appropriate solvent and were incubated at 37°C for 24 hrs. After incubation, the zone of inhibition was measured in mm and was compared with standard drug ciprofloxacin (10 µg/ml). The results have been summarized in Table 2.

RESULTS AND DISCUSSION

Chemistry

Four novel amino acid and peptide derivatives of quinazolinone-4(3H)-one were synthesized by condensation of 5-(2-(2-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxy benzoic acid with different amino acid/dipeptide methyl ester in the presence of NMM and DCC as a coupling agent. The temperature of reaction mixture was maintained at 0°C for 36 hrs with continuous stirring. The yield of all synthesized compounds was in the range of 65-76%. The purification of all compounds was carried out by recrystallization in a suitable solvent and structures of synthesized compounds were confirmed by spectral techniques including IR and ¹H NMR.

The formation of quinazolinone-4(3H)-one scaffold was confirmed by appearance of characteristic IR absorption bands at 3356-3285 cm⁻¹ (O-H), 1665 cm⁻¹ (C=O amide), and 1725 cm⁻¹ (C=O ester). In ¹H NMR, peaks at δ 12.1 ppm indicated carboxyl proton, 8.13-7.64 ppm due aromatic protons of quinazolinone ring, 7.39-7.36 ppm corresponding to benzene ring protons, and at 3.8 ppm due to hydroxyl proton. The coupling of quinazolinone nucleus with amino acids/peptides was

confirmed by disappearance of NH₂ and COOH signals and appearance of CONH signals in both IR and NMR spectra.

Biological activity

All the synthesized compounds 8a-b and 11a-b were evaluated for their *in vitro* antimicrobial potential against both Gram-positive and Gram-negative bacteria such as *S. pyogenes*, *S. aureus*, *P. aeruginosa*, and *E. coli*. Both amino acid and peptide derivatives exhibited excellent to moderate antimicrobial activity as compared to the test drug ciprofloxacin. The compound 11b was found to be most potent against all test microorganisms. It is expected due to the presence of indole moiety. The ester functionality present in designed peptide chain might undergo hydrolysis to give carboxylic group which form zwitterion by proton transfer to basic indole moiety, thereby exhibited broad spectrum antibacterial activity similar to most of quinolones. The moderate biological activity of other synthesized derivatives was expected to be due to the presence of nitrogen containing six membered fused heterocyclic ring of quinazolinone. The introduction of amino acid/peptide chain substitutions at 3-position of quinazolinone ring gives polar character to the molecule which helps in permeation through bacterial cell membrane via densely charged porin channels [40]. The compound 11a has shown maximum activity against *P. aeruginosa* while 8a against *S. aureus* bacteria. All the synthesized compounds were found to be least active against *S. pyogenes*.

CONCLUSION

In summary, a series of amino acid and peptide derivatives of 5-(2-(2-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-hydroxy benzoic acid were synthesized by coupling reaction and screened for their antimicrobial potential against *S. pyogenes*, *S. aureus*, *P. aeruginosa*, and *E. coli*. All the derivatives have shown promising antimicrobial activity; compound 11b has shown maximum antimicrobial activity against both Gram-positive and Gram-negative bacteria whereas compound 11a was more active against Gram-negative bacteria and 8a against Gram-positive bacteria.

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