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RESEARCH ARTICLE

SYNTHETIC STUDIES ON NOVEL NITROQUINAZOLINONE ANALOGS WITH ANTIMICROBIAL POTENTIAL

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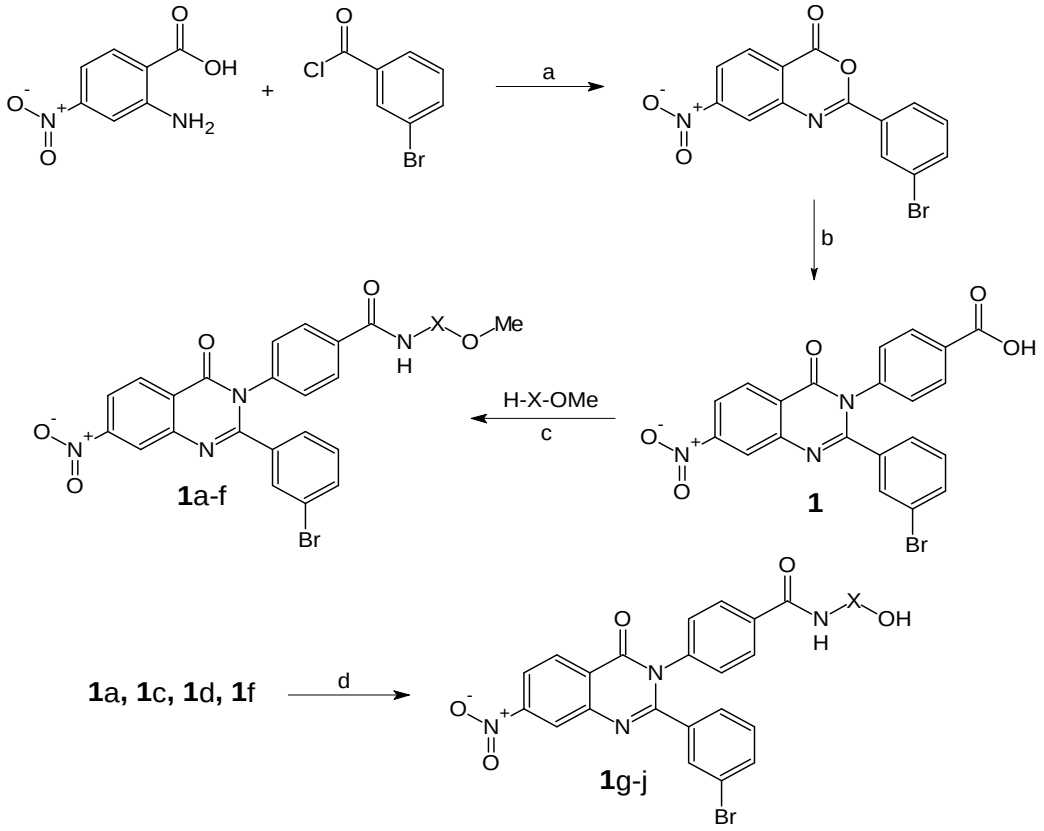
A novel series of 4-[2-(3-bromophenyl)-7-nitro-4-oxo-3,4-dihydro-3-quinazolinyl]benzoyl amino acids and di/tripeptides was synthesized using diisopropylcarbodiimide (DIPC) as the coupling agent and *N*-methylmorpholine (NMM) as the base. Structures of all the newly synthesized peptide analogs were elucidated using IR, $^{1}H/^{13}C$ NMR, MS spectral data and evaluated for antimicrobial potential against pathogenic microbes. Most of the compounds exhibited potent antifungal activity against pathogenic *Candida albicans* and dermatophytes, in comparison to reference compound. Good bioactivity was also seen against gram-negative bacteria for synthesized compounds.

Key words: Quinazolinones, 4-Nitroanthranilic acid, Peptide analogs, Coupling, Antifungal activity.

INTRODUCTION

Literature is enriched with several works on synthesis of potent quinazolinone and benzoic acid derivatives with diverse biological activities (de Moura *et al* 2004; Trusheva *et al* 2010; Wu *et al* 2010; Sharma *et al* 2011; Wu *et al* 2011) but very few reports have been yet received regarding peptide coupling of quinazolinones, although potent peptide analogs of aroylbenzoic acid, furoic acid, aryloxyacetic acid, coumarin, quinoxaline, benzothiophene, benzimidazole and imidazole are already reported (Poojary *et al* 2001; 2003; Himaja *et al* 2002; 2003; Dahiya and Pathak, 2006a; 2006b; 2006c; Dahiya *et al* 2006a; 2006b; Dahiya and Pathak, 2007; Dahiya and Kaur, 2007a; 2007b; 2008; Dahiya, 2008a, 2008b; Dahiya *et al* 2008a; 2008b; Dahiya and Kumar, 2008; Dahiya and Bansal, 2008; Dahiya *et al* 2010). Keeping in view the pharmacological potential of quinazolinone and benzoic acid derivatives, both moieties were coupled in single nucleus and further, in continuation of our work on synthesizing potent antimicrobial peptide analogs (Dahiya and Mourya, 2012), a novel series of 4-[2-(3-bromophenyl)-7-nitro-4-oxo-3,4-dihydro-3-quinazolinyl]benzoyl amino acids and peptides was synthesized to get bioactive agents with biological interest. 4-[2-(3-bromo phenyl)-7-nitro-4-oxo-3,4-dihydro-3-quinazolin--nyl]benzoic acid (**1**) was prepared by interaction of *p*-aminobenzoic acid and 2-(3-bromophenyl)-7-nitro-4*H*-3,1-benzoxazin-4-one, which was in turn prepared from the 4-nitro anthranilic acid and 3-bromobenzoyl chloride at 0-5 °C in presence of pyridine (Gao *et al* 2007). Dipeptides Boc-Pro-Pro-OMe, Boc-Try-His-OMe, Boc-His-Phe-OMe, were prepared from the corresponding Boc-amino acids and amino acid methyl ester hydrochlorides using the dicyclohexylcarbodiimide (DCC) and tri-ethylamine (TEA) in dichloromethane (DCM). Similarly, Boc-Phe-Ile-Pro-OMe and Boc-His-Tyr-His-OMe was prepared by coupling Boc-Phe/ Boc-His with Ile-Pro-OMe/Tyr-His-OMe in alkaline conditions. For coupling, di/tripeptide units were selected from pharmacologically active natural as well as synthetic cyclic polypeptides (Dahiya and Pathak, 2006d; Dahiya and Gautam, 2011).

The free acid **1** was coupled with various L-amino acid methyl ester hydrochlorides using diisopropylcarbodiimide (DIPC) as the coupling agent to get newly synthesized 4-[2-(3-bromo phenyl)-7-nitro-4-oxo-3,4-dihydro-3-quinazolin-yl]benzoyl amino acid methyl ester (**1**a). Similarly, dipeptide and tripeptide coupling was done to get dipeptide (**1**b-d) and tripeptide (**1**e, **1**f) methyl ester derivatives. Finally, selected compounds were hydrolyzed with lithium hydroxide to get (**1**g-j), corresponding acid derivatives (**Scheme 1**).



X = Try (**1**a, **1**g), Pro-Pro (**1**b) , Try-His (**1**c, **1**h), His-Phe (**1**d, **1**i), Phe-Ile-Pro (**1**e), His-Tyr-His (**1**f, **1**j)

a = pyridine, 0 ^{o}C; b = PABA, 170 ^{o}C, 2h; c = DIPC, NMM, DCM, RT, 24 h; d = LiOH, THF:H_2O (1:1), RT, 1 h

Scheme 1. Synthetic pathway for novel quinazolinopeptide analogs (**1**a-j)

All the compounds were synthesized in good yields and their structures were confirmed by FTIR, $^{1}H/^{13}C$ NMR and Mass spectra. In addition, elemental analysis of the newly synthesized compounds was performed for carbon, hydrogen and nitrogen content (**Table 1**).

Table 1. Physical data of newly synthesized quinazolinopeptide analogs

Compd	X	M.P. (°C)	Yield (%)	C (%) Calcd./Found	H (%) Calcd./Found	N (%) Calcd./Found
1a	L-Try	122	78	59.47/59.49	3.63/3.59	10.51/10.52
1b	L-Pro-L-Pro	–	89	56.98/56.99	4.18/4.15	10.38/10.40
1c	L-Try-L-His	188	79	58.29/58.27	3.89/3.92	13.94/13.95
1d	L-His-L-Phe	207	80	58.12/58.09	3.95/3.96	12.82/12.85
1e	L-Phe-L-Ile-L-Pro	166	95	60.22/60.19	4.93/4.95	10.03/10.05
1f	L-His-L-Tyr-L-His	223	92	56.28/56.25	4.06/4.08	15.26/15.25
1g	L-Try	159	70	58.91/58.89	3.40/3.43	10.73/10.75
1h	L-Try-L-His	145	67	57.80/57.78	3.70/3.73	14.19/14.20
1i	L-His-L-Phe	192	71	57.61/57.59	3.76/3.75	13.06/13.09
1j	L-His-L-Tyr-L-His	179	89	55.82/55.79	3.90/3.92	8.84/8.85

EXPERIMENTAL

Materials and Methods

Melting points were determined by open capillary method and are uncorrected. L-Amino acids, di-*tert*-butylpyrocarbonate (Boc_2O), diisopropylcarbodiimide (DIPC), trifluoroacetic acid (TFA), *N*-methylmorpholine (NMM) and triethylamine (TEA) were obtained from Spectrochem Limited, Mumbai, India. IR spectra were recorded on fourier transform infrared spectrophotometer (Jasco, Japan) using KBr pellets/$CHCl_3$ for all the synthesized compounds. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on Bruker spectrospin spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II triple quadrupole mass spectrometer at 70 eV. Elemental analysis of all compounds were performed on CHN Analyzer (Elementar, Germany). Purity of all the compounds was checked by TLC on precoated silica gel G plates.

Preparation of peptides

Peptide units were prepared by stirring a mixture of amino acid methyl ester hydrochloride and Boc-amino acid/dipeptide (0.01 mol each) with DCC (0.01 mol), TEA (0.021 mol), and DCM (50 ml) for 24 h. Then, reaction mixture was filtered and the residue was washed with DCM (25 ml). After washing the filtrate with 5% $NaHCO_3$ and saturated NaCl solutions, organic layer was dried over anhyd. Na_2SO_4 and evaporated in vacuum after filtration. The crude product was recrystallized from a mixture of chloroform and petroleum ether followed by cooling at 0 °C. Resulting Boc-di/tripeptide methyl ester (0.01 mol) was dissolved in $CHCl_3$ (25 ml) and treated with trifluoroacetic acid (0.02 mol). The mixture was stirred at RT for 1 h and washed with saturated $NaHCO_3$ solution. The resulting organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, crude product was purified by recrystallization with $CHCl_3$ and petroleum ether to get the deprotected di/tripeptide methyl ester. For protecting L-amino acids at amino end, Boc_2O was used whereas the carboxyl group of L-amino acids was protected by esterification with methanol using thionyl chloride. Peptides were prepared by Bodanszky method with certain modifications (Bodanzsky and Bodanzsky, 1984). Furthermore, trifluoroacetic acid was used for the removal of Boc group and ester group was removed by alkaline hydrolysis with lithium hydroxide.

Preparation of 4-[2-(3-bromophenyl)-7-nitro-4-oxo-3,4-dihydro-3-quinazolinyl]-benzoic acid (1)

To a cold solution of 4-nitroanthranilic acid (0.01 mol) in pyridine (30 ml) maintained at 0°C, another solution of 3-bromobenzoyl chloride (0.02 mol) in pyridine (30 ml) was added slowly with constant stirring. The reaction mixture was further stirred for 30 min at RT and set aside for 1 h. The pasty mass obtained was diluted with water (50 ml) and treated with aqueous sodium bicarbonate solution. The precipitate obtained was filtered off, washed with water and finally dried. Equimolar amounts (0.025 mol) of precipitate and *p*-aminobenzoic acid (PABA) were heated at 170-180 °C for 2 h in an oil bath. The separated jelly like mass solidified upon cooling. The crude product was finally recrystallized from ethanol to give a good yield of title compound as pale yellow solid; yield 78%; M.P. 193 °C; IR (KBr): 3298-2509 (O–H str, COOH), 3078-3069, 3054-3049 (C–H str, rings), 1706 (C=O str, COOH), 1667 (C=O str, ring), 1596 (C=N str, ring), 1584-1575, 1422-1414 (C=C str, rings), 1515, 1350 (NO_2 str, asym and sym), 1402 (O–H def, COOH), 863 (C–N str, Ar-NO_2), 779, 735, 721, 702, 698, 663 (C–H def, oop, rings), 685, 622 (C–Br str) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 10.76 (1H, s, O<u>H</u>, COOH), 10.76 (1H, s, H-8, quinazolinone ring [qze]), 8.34 (1H, d, J = 7.4 Hz, H-6, qze), 8.28 (1H, d, J = 7.6 Hz, H-5, qze), 8.15 (1H, s, H-2, bromobenzene moiety [bbz]), 7.91-7.89 (1H, d, J = 6.9 Hz, H-2, bbz), 7.85-7.83 (2H, dd, J = 6.95 Hz, 7.2 Hz, m-H's, benzoic acid moiety [bza]), 7.42-7.38 (3H, m, o-H's, bza and H-4, bbz), 7.42-7.38 (1H, t, J = 6.6 Hz, H-5, bbz) ppm; ^{13}C NMR ($CDCl_3$, 70 MHz): δ 171.5 (C=O, -COOH), 168.2 (C-2, qze), 157.9 (C-4, qze), 154.6 (C-7, qze), 149.2 (C-2′, qze), 138.6 (C-1, bza), 133.7 (C-1, bbz), 133.2 (2C, m-C's, bza), 132.6 (2C, o-C's, bza), 130.4 (C-4, bbz), 129.9 (p-C, bza), 129.2 (C-2, bbz), 128.8 (C-5, bbz), 128.2 (C-5, bbz), 127.7 (C-5, qze), 125.1 (C-3′, qze), 123.4 (C-3, bbz), 118.8 (C-6, qze), 116.5 (C-8, qze) ppm.

General procedure for preparation of 4-[2-(3-bromophenyl)-7-nitro-4-oxo-3,4-dihydro-3-quinazolinyl]benzoyl amino acid and peptide derivatives (1a-j)

Title compounds **1**a-j were prepared by the coupling of 4-[2-(3-bromophenyl)-7-nitro-4-

oxo-3,4-dihydro-3-quinazolinyl]benzoic acid (**1**) with amino acid methyl ester hydrochlorides/ peptide methyl esters by using DIPC and NMM in DCM by following the same procedure as that adopted for peptide synthesis to get the amino acid and peptide derivatives (**1**a-j). Amino acid (**1**a), dipeptide (**1**c, **1**d) and tripeptide (**1**f) derivatives were further hydrolyzed with LiOH to get the corresponding free acids (**1**g-j).

For removal of the ester group, peptide ester derivative (0.01 mol) was dissolved in THF:H_2O (1:1) and LiOH (0.015 mol) was added to the solution at 0 °C. The resulting mixture was stirred at RT for 1 h and then acidified to pH 3.5 with 1 N H_2SO_4. The aqueous layer was extracted with Et_2O (2 × 20 ml) and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to get the desired hydrolyzed compound.

1a ($C_{33}H_{24}BrN_5O_6$): ^{13}C NMR ($CDCl_3$, 70 MHz): δ 172.3 (C=O, ester), 169.0 (C-2, qze), 168.6 (C=O, bza), 158.3 (C-4, qze), 154.1 (C-7, qze), 148.9 (C-2′, qze), 139.7 (C-1, bza), 137.8 (C-2′, indole ring [idr]), 134.2 (C-1, bbz), 131.9 (C-4, bbz), 130.8 (C-2, bbz), 129.2 (C-5, bbz), 128.7 (C-6, bbz), 128.0 (C-5, qze), 127.5 (2C, m-C's, bza), 127.0 (2C, o-C's, bza), 126.8 (C-3′, idr), 125.6 (p-C, bza), 124.8 (C-3′, qze), 123.1 (C-3, bbz), 122.6 (C-2, idr), 121.7 (C-6, idr), 119.5 (C-5, idr), 118.7 (C-4, idr), 117.9 (C-6, qze), 116.6 (C-8, qze), 114.4 (C-3, idr), 112.9 (C-7, idr), 55.6 (C-α, Trp), 51.7 (O*C*H$_3$), 19.9 (C-β, Trp) ppm.

1b ($C_{32}H_{28}BrN_5O_7$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.64 (1H, s, H-8, qze), 8.44-8.39 (2H, m, m-H's, bza), 8.31-8.26 (2H, m, H-5 and H-6, qze), 8.11 (1H, s, H-2, bbz), 7.92-7.89 (1H, t, J = 6.5 Hz, H-6, bbz), 7.62-7.58 (2H, m, o-H's, bza), 7.40-7.38 (1H, d, J = 6.85 Hz, H-4, bbz), 7.29-7.26 (1H, t, J = 6.7 Hz, H-5, bbz), 4.41-4.38 (1H, t, J = 6.9 Hz, H-α, Pro-1), 4.26-4.23 (1H, t, J = 6.85 Hz, H-α, Pro-2), 3.72-3.69 (2H, t, J = 7.15 Hz, H-δ, Pro-2), 3.62 (3H, s, OC<u>H</u>$_3$), 3.45-3.42 (2H, t, J = 7.2 Hz, H-δ, Pro-1), 2.69-2.64 (2H, m, H-β, Pro-1), 2.05-2.01 (2H, m, H-β, Pro-2), 1.97-1.92 (4H, m, H-γ, Pro-1 and Pro-2) ppm.

1c ($C_{39}H_{31}BrN_8O_7$): IR (KBr): 3486-3479 (N–H str, heterocyclic rings), 3129, 3122 (N–H str, amide), 3085-3069, 3055, 3047-3042 (C–H str, rings), 2925 (C–H str, asym, CH_2), 2844 (C–H str, sym, CH_2), 1745 (C=O str, ester), 1664 (C=O str, ring), 1639-1634 (C=O str, 2° amide), 1599-1595 (C=N str, rings), 1594-1573, 1438-1423 (C=C str, rings), 1537, 1532 (N–H bend, 2° amide), 1515, 1357 (NO_2 str, asym and sym), 1274 (C–O str, ester), 864 (C–N str, Ar-NO_2), 854-843, 775, 729-714, 692, 657-653 (C–H def, oop, rings), 681, 622 (C–Br str) cm^{-1}.

1d ($C_{37}H_{34}BrN_5O_7$): ^{13}C NMR ($CDCl_3$, 70 MHz): δ 171.6 (C=O, His), 170.3 (C=O, ester), 169.4 (C-2, qze), 167.7 (C=O, bza), 158.0 (C-4, qze), 152.3 (C-7, qze), 149.1 (C-2′, qze), 142.8 (C-2, imidazole ring [imz]),140.2 (C-1, bza), 137.3 (C-γ, Phe), 134.7 (C-1, bbz), 133.5 (C-4, bbz), 132.4 (C-2, bbz), 130.2 (C-5, bbz), 129.4 (2C, o-C's, Phe), 128.9 (C-6, bbz), 128.3 (2C, m-C's, Phe), 128.1 (2C, o-C's, bza), 127.9 (C-5, qze), 127.5 (2C, m-C's, bza), 126.7 (p-C, Phe), 125.6 (C-4, imz), 125.0 (p-C, bza), 124.5 (C-3′, qze), 123.6 (C-3, bbz), 120.5 (C-6, qze), 118.8 (C-8, qze), 116.6 (C-5, imz), 59.2 (C-α, His), 55.8 (C-α, Phe), 52.7 (O*C*H$_3$), 38.6 (C-β, Phe), 18.8 (C-β, His) ppm.

1e ($C_{42}H_{41}BrN_6O_8$): MS *m/z* (rel. int.): 14 (4.7), 15 (14.2), 29 (9.8), 31 (9.6), 59 (12.4), 70 (11.5), 77 (16.4), 86 (17.1), 91 (21.5), 120 (13.9), 145 (11.8), 156 (11.4), 190 (16.9), 345 (24.5), 421 (32.6), 449 (68.2), 568 (10.7), 596 (100), 681 (24.7), 709 (74.7), 778 (16.6), 806 (24.2), 822 (19.4), 837 (M^+, 2.9), 838 (M^+, 0.6).

1f ($C_{43}H_{37}BrN_{10}O_9$): MS *m/z* (rel. int.): 14 (3.9), 15 (3.6), 17 (4.7), 31 (9.9), 59 (13.3), 67 (15.7), 81 (22.9), 93 (9.4), 107 (11.8), 110 (19.5), 136 (14.8), 145 (12.6), 156 (10.9), 190 (16.9), 345 (21.2), 421 (29.4), 449 (65.6), 558 (14.3), 586 (100), 721 (14.6), 749 (70.2), 858 (15.9), 886 (33.7), 902 (17.2), 917 (M^+, 2.6), 918 (M^+, 0.8).

1g ($C_{32}H_{22}BrN_5O_6$): ^{13}C NMR ($CDCl_3$, 70 MHz): δ 175.8 (C=O, -<u>CO</u>OH), 169.1 (C=O, bza), 168.6 (C-2, qze), 157.8 (C-4, qze), 152.9 (C-7, qze), 148.0 (C-2′, qze), 140.5 (C-1, bza), 136.9 (C-2′, idr), 133.7 (C-1, bbz), 132.3 (C-4, bbz), 130.4 (C-2, bbz), 130.1 (C-6, bbz), 129.6 (C-5, bbz), 128.4 (C-5, qze), 128.0 (2C, m-C's, bza), 127.6 (2C, o-C's, bza), 127.1 (C-3′, idr), 125.4 (C-3′, qze), 124.5 (p-C, bza), 123.5 (C-2, idr), 123.0 (C-3, bbz), 122.2 (C-6, idr), 119.2 (C-5, idr), 118.2 (C-6, qze), 117.7 (C-4, idr), 117.2 (C-8, qze), 115.4 (C-3, idr), 111.5 (C-7, idr), 54.9 (C-α, Trp), 19.4 (C-β, Trp) ppm.

1h ($C_{38}H_{29}BrN_8O_7$): IR (KBr): 3488-3481 (N–H str, heterocyclic rings), **:** 3298-2487 (O–H str, -COOH), 3127, 3120 (N–H str, amide), 3087-

3072, 3058, 3044-3036 (C–H str, rings), 2928 (C–H str, asym, CH_2), 2845 (C–H str, sym, CH_2), 1716 (C=O str, COOH), 1668 (C=O str, ring), 1639-1632 (C=O str, 2° amide), 1596-1592 (C=N str, rings), 1597-1577, 1439-1425 (C=C str, rings), 1535, 1530 (N–H bend, 2° amide), 1516, 1359 (NO_2 str, asym and sym), 868 (C–N str, Ar-NO_2), 856-842, 777, 726-717, 698, 655-649 (C–H def, oop, rings), 685, 626 (C–Br str) cm^{-1}.

1i ($C_{36}H_{28}BrN_7O_7$): ^{13}C NMR ($CDCl_3$, 70 MHz): δ 173.5 (C=O, COOH), 171.4 (C=O, His), 169.2 (C-2, qze), 168.3 (C=O, bza), 158.6 (C-4, qze), 152.0 (C-7, qze), 148.8 (C-2′, qze), 141.9 (C-2, imz), 138.1 (C-γ, Phe), 137.7 (C-1, bza), 134.2 (C-1, bbz), 133.9 (C-4, bbz), 132.0 (C-2, bbz), 130.6 (C-5, bbz), 129.7 (2C, o-C's, Phe), 128.8 (C-5, qze), 128.5 (2C, o-C's, bza), 128.3 (C-6, bbz), 127.9 (2C, m-C's, bza), 127.5 (2C, m-C's, Phe), 126.3 (C-4, imz), 125.2 (p-C, bza), 124.8 (C-3′, qze), 124.5 (p-C, Phe), 124.0 (C-3, bbz), 120.9 (C-6, qze), 119.0 (C-8, qze), 115.8 (C-5, imz), 58.9 (C-α, His), 54.5 (C-α, Phe), 37.8 (C-β, Phe), 18.9 (C-β, His) ppm.

1j ($C_{42}H_{35}BrN_{10}O_9$): MS *m/z* (rel. int.): 14 (3.5), 17 (8.2), 45 (10.8), 67 (15.4), 81 (22.2), 93 (9.8), 107 (12.5), 110 (20.2), 136 (14.5), 145 (12.9), 156 (11.4), 190 (16.2), 345 (20.6), 421 (27.9), 449 (65.2), 558 (14.2), 586 (100), 721 (14.9), 749 (69.7), 858 (15.5), 886 (32.9), 903 (M^+, 3.8), 904 (M^+, 0.5).

Antimicrobial activity

Modified Kirby-Bauer disc diffusion method (Bauer *et al* 1966) was utilized for the testing antibacterial activity against four pathogenic bacteria *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. MIC values of test compounds were determined by tube dilution technique. Ciprofloxacin was used as a reference compound and solvent (DMF) as negative control. Test sample and reference drug were tested at the concentration of 12.5-6 μg/ml. Serial plate dilution method (Khan, 1997) was employed for the evaluation of antifungal activity against three fungal strains, including dermatophytes *Microsporum audouinii*, *Trichophyton mentagrophytes* and diamorphic fungi *Candida albicans*. MIC values of test compounds were determined by employing the same technique as used for antibacterial studies using DMSO instead of DMF. During antifungal evaluation, test sample and reference drug – Griseofulvin were tested at the concentration of 6 μg/ml. The results of antibacterial and antifungal activity studies are compiled in **Table 2**. The detailed procedure for antimicrobial evaluation is reported in our previously published report (Dahiya and Pathak, 2007).

Table 2. Antimicrobial activity data of newly synthesized quinazolinopeptide analogs

Compound	Zone of inhibition (in mm)						
	B.sub.	***E.coli***	***S.aur.***	***P.aeru.***	***M.audo.***	***T.menta.***	***C.alb.***
1a	11	16	11	22	15	15	14
1b	14	–	13	20	–	16	16
1c	10	13	10	19	18	18	19
1d	10	13	10	19	15	17	16
1e	–	11	–	21	13	17	–
1f	9	13	11	19	17	19	19
1g	12	18	14	24	16	17	16
1h	11	14	11	21	20	20	21
1i	12	15	12	22	16	18	17
1j	11	14	14	21	18	21	22
Control	–	–	–	–	–	–	–
Ciprofloxacin	20	19	20	25	–	–	–
Griseofulvin	–	–	–	–	17	18	18

RESULTS AND DISCUSSION

All novel quinazoliopeptide analogs were synthesized successfully with good yield. All the synthesized compounds were found to exhibit good antimicrobial activity against pathogenic dermatophytes, *Candida albicans* and gram-negative bacterium *Pseudomonas aeruginosa*. DIPC was found to be a good coupling agent both

economically as well as yield wise. IR spectra of synthesized compounds showed characteristic amide I and amide II bands of the –CO-NH– moiety and mass spectra showed molecular ion peak (M^+) at *m/z* values which were in consistent with the molecular formulas. Comparison of the antimicrobial activity data suggested that greater activity is observed in compounds with heterocyclic amino acid residues in their chain.

CONCLUSION

Almost, all the synthesized compounds were found to exhibit potent antifungal activity and moderate to good antibacterial activity against gram-negative bacteria. No significant bioactivity was observed against gram-positive bacteria for newly synthesized peptide analogs. Compounds (**1**c, **1**f) and their hydrolyzed derivatives (**1**h, **1**j) were found to be more active than standard drug against pathogenic fungus *C. albicans* and dermatophytes whereas compounds (**1**a, **1**g) displayed good activity against bacteria *E. coli* and *P. aeruginosa.* Comparison of antimicrobial data has suggested that amino acid and peptide derivatives (**1**g-j) were more potent antifungal and antibacterial agents than corresponding methyl ester derivatives (**1**a, **1**c, **1**d and **1**f). On passing toxicity tests, these peptide derivatives may prove good candidate for clinical studies and can be new antifungal agents of tomorrow.

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