Synthesis of Putrescine Bisamides as Antimicrobial and Anti-Inflammatory Agents

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Abstract

A new naturally occurring N6, N6-dihydrocinnamyl putrescine bisamide, JBIR-94, along with nine structural analogs and a series of substituted phenyl and alkyl putrescine bisamides have been synthesized from putrescine and appropriately substituted carboxylic acids, through carboxylic acid chlorides. Antimicrobial, 5-Lipooxygenase enzyme inhibitory and antioxidant studies were performed for all synthesized compounds. Dihydrocinnamyl series of putrescine bisamides (4a-4i) showed good bioactivities compared to substituted phenyl (6a-6g) and diaryl (6h-6j) series of compounds. Among all compounds, 4h (methyleneedioxy analog) and 4a (JBIR-94) showed good antimicrobial, anti-inflammatory and antioxidant activities.

Keywords: JBIR-94; Putrescine bisamide; Antimicrobial; Antioxidant; 5-LOX; Docking

Introduction

Putrescine bisamides are one of the subclasses of naturally occurring polyamides [1]. During the last two decades several symmetrical and unsymmetrical putrescine bisamides have been isolated from Aglaia [2-4], Liberica [5], and Carydalis [6], species. These compounds have been reported to possess various biological activities including cytotoxicity [7], anti-inflammatory [8], antioxidant [9,10], insecticidal [11,12], and antiviral activity. Putrescine derivatives have been hypothesized to be one of the precursors in bio-synthesis of rocaglamides, which have displayed pronounced anti proliferative activity against Human cancer cell [10,13], and exhibit strong insecticidal activity against Spodoptera littoralis [13]. The insecticidal activity of rocaglamides is comparable to the potency of azadirachtin [13]. Synthesis of these compounds is usually based on the condensation of putrescine with carboxylic acid chlorides in the presence of bases, or with carboxylic acids in the presence of coupling reagents such as 1-Ethyl-3-(3-dimethylaminopropyl) carboxiamide (EDC), N,N-Dicyclohexylcarbodiimide (DCC) and (Benzotriazol-1-yl)oxy(tri)dimethylamino) phosphonium hexafluorophosphate (BOP). Recently, a new N6, N6-dihydrocinnamyl putrescine bisamide, JBIR-94, has been isolated from broth culture of Streptomyces (strain R56-07), and reported to have antioxidant activities [9].

Experimental Section

General

Melting points were recorded on a Met-Temp melting point apparatus, in open capillaries and are uncorrected. 1H NMR (400 MHz), 13C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer using TMS as internal standard and the values for chemical shifts (δ) being given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were recorded on an Agilent 1100 LC/MSD. Acme silica gel G and silica gel (100-200 mesh) were used for analytical TLC and column chromatography, respectively. Other chemicals were purchased from Sigma Aldrich and used without further purification.

General experimental procedure for synthesis of 3: A mixture of carboxylic acid (6.58 mmol) and thionyl chloride (13.1 mmol) was refluxed at 80°C for 1 h. After 1 h excess of SOCl2 was removed under reduced pressure. Triethylamine (14.3 mmol) and putrescine (3.3 mmol) dissolved in DCM was added to the above reaction mixture at 0°C and warm to room temperature for 1h. Then the solution was diluted with CHCl3 and washed consequently with 2N HCl, saturated aq NaHCO3, and brine solution. The organic phase was dried over Na2SO4 and the solvent was removed under vacuum. The residue was suspended in ethyl acetate filtered off and washed with cold ethyl acetate and dried to obtain the pure product. It was directly used in the next step.

General experimental procedure for synthesis of 4: The compound (0.5 gm) (3) was dissolved in THF, and 10% palladium on carbon (5 mg, 10%) was added. The mixture was stirred under hydrogen balloon pressure at ambient temperature for 2 h. The reaction mixture was filtered through celite bed and washed with methanol. Methanol was evaporated under reduced pressure and the resultant solid was recrystallized in cold ethyl acetate to afford title compound.

General experimental procedure for synthesis of 6: Putrescine (3.3 mmol) and triethylamine (14.3 mmol) were added to the solution of acid chloride (7.6 mmol) in CH2Cl2 at 0°C. The reaction mixture was then allowed to stir at room temperature for 0.5 h. After the completion of the reaction mixture was basificed with saturated aq NaHCO3 solution and extracted with CH2Cl2. The organic layer was dried over anhydrous Na2SO4, and concentrated under reduced pressure to afford 6. This was purified by recrystallization with hexane.

Antimicrobial assay

Antimicrobial assay performed on human pathogenic bacteria and fungi. Salmonella typhi, Vibrio cholerae, Shigella dysenteriae, Enterococcus faecalis are gastrointestinal pathogenic bacteria, which

Received February 14, 2014; Accepted March 22, 2014; Published March 24, 2014


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are clinical isolates collected from King Gerorge Govt. Hospital, Visakhapatnam, India. *Staphylococcus aureus* (NCIM 3021) culture was purchased at NCL, Pune, India. *Candida albicans* is a dermatophytic fungus collected from K. Ramamurthy memorial hospital, Ravivalsa, India. Zone of inhibitions were determined using agar well diffusion method and minimum inhibitory concentration (MIC) was done by broth dilution assay. Microbial broth cultures (Mueller Hinton broth for bacteria, Sabouraud Dextrose broth for fungi) were adjusted to an absorbance of 0.6 (Optical Density at 620 nm) in Spectrophotometer according to CLSI guidelines. These cultures were used as Inoculums for antimicrobial study. The agar plates were prepared by pour plate method using 20 ml of sterilized agar medium (MH agar for bacteria, SD agar for fungi). The sterile agar medium was cooled to 45°C and mixed thoroughly with 1ml of growth culture of concerned test organism (inoculum) and then poured into the sterile petri dishes and allowed to solidify. Wells of 6 mm size were made with sterile cork borer and test compounds were added. The agar plates were incubated at for 4 days at 28°C for fungi wire 24 hours at 37°C for bacteria. Zone of inhibitions were measured by Himedia milli meter zone reader. Minimum Inhibitory Concentration (MIC) was performed on broth media (10 ml) containing 1000-1 µg/ml of test compound prepared by 10 fold dilution. 0.1 ml of culture inoculums was added. The MIC was determined at the concentration of compound that causes nil absorbance (no growth) in the spectrophotometer at 620 nm. All the experiments were conducted according to Clinical Laboratory Standard Institute. Ciprofloxacin (for bacteria) and Griseofulvin (for fungi) were used as positive control. DMSO used as negative control [14-18].

### 5-Lipoxygenase (5-LOX) inhibitory assay

5-LOX from potato tubers was purified and assayed as per the method described by Reddanna et al. [18] The assay mixture contained 80 mM linoleic acid and sufficient amount of potato 5-Lipoxygenase enzyme in 50 mM phosphate buffer (pH 6.3). The reaction was initiated by the addition of enzyme buffer mix to substrate (linoleic acid) and the enzyme activity was monitored by an increase in absorbance at 234 nm for 120 seconds using UV Kinetic mode on Varian Cary-50 UV-VIS spectrophotometer. In the inhibition studies the activities were measured by incubating various concentration of compound with enzyme buffer mix for two minutes before adding the substrate. The assay was performed in triplicate. Percentage of inhibition was calculated by change in absorbance of test with that of control enzyme activity. Nordihydroguaiaretic acid (NDGA) was used as positive control [19-21].

### Molecular docking studies

5-Lipoxygenase (PDB ID 308Y) X-Ray crystal structure was obtained from Protein Data Bank and used in docking studies. Co-crystallized ligands and water molecules are removed from target protein using Argus lab. Ligands are prepared using Chemoffice (Cambridge). Energy minimization was done using molecular mechanics. The minimized was executed until root mean square value reached smaller than 0.001 Kcal/mol. Such energy minimized ligands and receptor used for docking studies using GEMDOCK (Generic Evolutionary Method for molecular DOCKing) is a generic evolutionary method with an empirical scoring function for the protein–ligand docking, which is a problem of paramount importance in structure-based drug design, combines both continuous and discrete search mechanisms. A population size of 300 with 70 generations and 3 solutions were used in docking accuracy setting. PyMol is used for better visualization of interactions [22-24].

### DPPH radical scavenging activity

DPPH (1, 1-diphenyl -2-picryl -hydrazyl) radical scavenging activity of the compounds was determined by the method of Lamaison et al. [19] which depends on scavenging of coloured free radical (DPPH) in methanol solution by test compound. The reaction mixture contains DPPH and compound in a final concentration in 3ml. Absorption of DPPH at its absorption maximum 516 nm is inversely proportional to scavenging activity of compound. The activity was expressed as inhibition concentration 50 (IC₅₀) i.e. the concentration of test compound required to give 50% reduction in absorbance of test solution compared to that of blank solution [25].

### Superoxide scavenging activity

Superoxide scavenging activity of the synthesized compounds was determined by the method of Mc Cord & Fridovich [20] (1969), modified by Ruby et al. [21], which depends on the light induced superoxide generation by riboflavin and the corresponding reduction of NBT. The assay mixture contained different concentrations of the test substances and EDTA (6mM containing 3 µg NaCN), NBT (5 µM) and phosphate buffer 58 mM, pH 7.8) in a total vol. of 300 µl. The wells received uniform illumination for 15 min and thereafter optical density was measured at 560 nm [26,27].

In conclusion, a new naturally occurring 

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\text{N}_1 \text{N'}-(\text{Butane-1,4-diy))bis(3-(4-hydroxy-3-methoxyphenyl)} \ \text{propanamide (4a). Gray solid, yield 90%, mp 140-148°C; } ^{1}H \text{ NMR (400 MHz, MeOD) } \delta 6.67 (d, J = 1.6 \text{ Hz, 2H}), 6.59 (d, J = 8 \text{ Hz, 2H}), 6.52 (d, J = 1.6, 8 \text{ Hz, 2H}), 3.72 (s, 6H), 2.93 (brs, 4H), 2.71 (t, J = 7.6 \text{ Hz, 4H}), 2.32 (t, J = 7.6 \text{ Hz, 4H}), 1.18 (m, 4H); ^{13}C \text{NMR (100 MHz, MeOD) } \delta 175.4, 148.9, 145.9, 133.8, 121.9, 116.3, 113.4, 56.5, 39.9, 39.4, 32.6, 27.6; \text{LC-MS: } m/z: 443.3 (M+H)+; \text{ Anal. Calcd. for } C_{24}H_{32}N_{2}O_{4}: C, 64.85; H, 7.26, N, 6.30. \]

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\text{N}_1 \text{N'}-(\text{Butane-1,4-diy))bis (3-(3-hydroxy-3-methoxyphenyl)} \ \text{propanamide (4b). White solid, yield 92%, mp 160-166°C; } ^{1}H \text{ NMR (400 MHz, MeOD) } \delta 7.05 (d, J = 8 \text{ Hz, 2H}), 6.67 (m, 4H), 6.62 (dd, J = 1.2, 8.0 \text{ Hz, 2H}), 3.65 (s, 6H), 2.98 (t, J = 6.4 \text{ Hz, 4H}), 2.76 (t, J = 7.6 \text{ Hz, 4H}), 2.35 (t, J = 7.6 \text{ Hz, 4H}), 1.22 (brs, 4H); ^{13}C \text{NMR (100 MHz, MeOD) } \delta 175.1, 161.3, 143.7, 130.4, 113.8, 112.1, 115.2, 55.6, 39.9, 39.4, 32.6, 27.6; \text{LC-MS: } m/z: 411.3 (M+H)+; \text{ Anal. Calcd. for } C_{24}H_{32}N_{2}O_{4}: C, 69.32; H, 7.26, N, 6.30. \]

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\text{N}_1 \text{N'}-(\text{Butane-1,4-diy))bis (3-(3-methoxyphenyl)} \ \text{propanamide (4c). White solid, yield 92%, mp 150-156°C; } ^{1}H \text{ NMR (400 MHz, DMSO-d}_6 \delta 7.73 (t, J = 4.8 \text{ Hz, 4H}), 7.17 (t, J = 7.6 \text{ Hz, 4H}), 7.12 (d, J = 7.2 \text{ Hz, 2H}), 6.93 (d, J = 8.0 \text{ Hz, 2H}), 6.84 (t, J = 7.2 \text{ Hz, 2H}), 3.78 (s, 6H), 3.01 (d, J = 4.8 \text{ Hz, 4H}), 2.76 (t, J = 7.6 \text{ Hz, 4H}), 2.30 (t, J = 8.0 \text{ Hz, 4H}), 1.33 (brs, 4H); ^{13}C \text{NMR (100 MHz DMSO-d}_6 \delta 171.3, 156.9, 129.3, 129.1, 127.2, 120.2, 110.5, 55.2, 38.1, 35.4, 26.6, 25.7; \text{LC-MS: } m/z: 368.3.} \]
2.36 (t, 6): δ 171.1, 147.1, 145.2, 135.2, 120.9, 108.6, 107.9, 419.2 (M-H)-. Anal. Calcd for.

N, 6.40. LC-MS: m/z 254.5 (M+H)+. 413.5 (M+Na)+. Anal. Calcd for. C12H12N2O4, C, 63.44; H, 6.75; N, 5.26. Found: C, 63.40; H, 6.82; N, 5.78.

N,N’-(Butane-1,4-diyl)bis(3-(3,4-dimethoxyphenyl)propanamide) (4d). White solid, yield 90%, mp 176-178ºC, 1H NMR (400 MHz, DMSO-d6) δ 7.82 (t, J = 5.2 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 3.84 (s, 6H), 3.82 (s, 6H), 3.79 (s, 6H), 3.07 (d, J = 5.2 Hz, 4H), 2.77 (t, J = 7.6 Hz, 4H), 2.34 (t, J = 7.6 Hz, 4H), 1.39 (t, J = 7.6 Hz, 4H), 1.36 (t, J = 7.6 Hz, 4H), 2.05 (q, J = 7.6 Hz, 4H), 1.51 (brs, 4H). 13C-NMR (100 MHz, DMSO-d6) δ 171.2, 150.1, 149.1, 135.3, 121.8, 113.9, 113.5, 56.7, 39.9, 39.2, 32.5, 27.6; LC-MS: m/z 495 (M+Na)+. Anal. Calcd for. C24H32N2O4, C, 69.83; H, 7.87; N, 6.83.

N,N’-(Butane-1,4-diyl)bis(3-(3,4-dimethoxyphenyl)propanamide) (4e). White solid, yield 90%, mp 150-154ºC, 1H NMR (400 MHz, MeOD) δ 6.74 (d, J = 8.4 Hz, 2H), 6.71 (s, 2H), 6.64 (d, J = 8.0 Hz, 2H), 3.70 (s, 6H), 3.68 (s, 6H), 2.97 (t, J = 6.0 Hz, 4H), 2.74 (t, J = 7.6 Hz, 4H), 2.34 (t, J = 7.6 Hz, 4H), 1.20 (t, brs, 4H); 13C-NMR (100 MHz, MeOD) δ 175.0, 152.5, 149.1, 135.3, 121.8, 113.9, 113.5, 56.7, 39.9, 39.2, 32.5, 27.6; LC-MS: m/z 555 (M+Na)+. Anal. Calcd for. C32H36N2O4, C, 66.18; H, 7.68; N, 5.93; Found: C, 66.03; H, 7.73; N, 5.98.

N,N’-(Butane-1,4-diyl)bis(3-(2,3,4-trimethoxyphenyl)propanamide) (4f). White solid, yield 90%, mp 150-154ºC, 1H NMR (400 MHz, MeOD) δ 7.82 (t, J = 5.2 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 3.84 (s, 6H), 3.82 (s, 6H), 3.79 (s, 6H), 3.07 (d, J = 5.2 Hz, 4H), 2.77 (t, J = 7.6 Hz, 4H), 2.34 (t, J = 7.6 Hz, 4H), 1.39 (t, J = 7.6 Hz, 4H), 1.36 (t, J = 7.6 Hz, 4H), 2.05 (q, J = 7.6 Hz, 4H), 1.51 (brs, 4H). 13C-NMR (100 MHz, DMSO-d6) δ 171.2, 150.1, 149.1, 135.3, 121.8, 113.9, 113.5, 56.7, 39.9, 39.2, 32.5, 27.6; LC-MS: m/z 495 (M+Na)+. Anal. Calcd for. C24H32N2O4, C, 69.83; H, 7.87; N, 6.83.
N,N'-[Butane-1,4-diyldi]hexanamide (6j). Pale yellow solid, mp154-160°C. 1H NMR (400 MHz, DMSO-d6) δ 7.77 (brs, 2H), 3.06 (q, J = 5.2 Hz, 4H), 2.08 (t, J = 7.2 Hz, 4H), 1.53 (m, 4H), 1.41 (brs, 4H), 1.33-1.24 (m, 8H), 0.91 (t, J = 7.2 Hz, 6H). 13C-NMR (100 MHz, DMSO-d6) δ 171.9, 71.6, 71.8, 66.9, 62.5, 38.1, 35.4, 30.9, 26.7, 24.9, 21.8, 13.8. LC-MS: m/z 307 (M+Na)+. Anal. Calcd for. C16H32N2O2, C, 67.56; H, 11.34; N, 9.85,

Results and Discussion

In this study, we have synthesized JBIR-94 along with nine structural analogs and a series of substituted phenyl and dialkyl putrescine bisamides for the first time. We have also screened these compounds for antimicrobial, 5-lipoxygenase enzyme inhibitory and antioxidant activities.

Chemistry

Benzyl protected ferulic acid was coupled with putrescine via acid chloride which leads to the formation of N1,N6-diferulic putrescine bisamide. Subsequently it was reduced and deprotected with Pd/CaCO3 to afford the desired product JBIR-94 in good yields (Scheme 1). All the spectral data of the synthesized compound is in good agreement with advanced spectroscopic techniques like 1H NMR, 13C NMR and Mass (Tables 1 and 2).

Similarly, we have synthesized a series of N1,N6-substituted phenyl and N1,N6-alkyl putrescine bisamides with putrescine by varying aromatic/aliphatic acid chlorides Scheme 2. All the compounds were well characterized by advanced spectroscopic techniques like 1H NMR, 13C NMR and Mass (Tables 1 and 2).

Bioactivity

Antimicrobial activity: Antimicrobial studies were carried out on clinical isolates of human pathogenic bacteria (Salmonella typhi, Vibrio cholerae, Shigella dysenteriae, Enterococcus faecalis and Staphylococcus aureus) and dermatophytic fungi. (Candida albicans). As shown in Table 3, newly synthesized putrescine bisamides showed significant antibacterial activity but poor anti-fungal activity. Compounds inhibitory zones were found to be in the range between 2-14 mm while 1-1000 µg/ml was the MIC range of compounds. In N1,N6-dihydrocinnamyl putrescine bisamides series (4a-4i), 4h (JBIR-94) and 4f showed potent antimicrobial activity but compounds, 4c, 4b, 4d, 4e, 4g, and 4i showed moderate activity. Substituted phenyl (6a-6g) and dialkyl (6h-6j) series of putrescine bisamides showed poor antimicrobial activity. Among all the tested compounds, 4h showed highest (14 mm) inhibitory zone and lowest MIC value (1 µg/ml) on St. typhi. Moreover it showed comparable potency with Ciprofloxacin which is an antibiotic used as positive control.

5-Lipoxygenase inhibitory activity: All synthesized putrescine bisamides were evaluated for 5-Lipoxygenase assay and found to have significant 5-LOX inhibitory activity with IC50 range from 9.2 to 29.2 µg/ml (Table 4). Dihydrocinnamyl series of compounds (4a-4i), and substituted phenyl (6a-6g) series of compounds showed effective enzyme inhibitory activity with IC50 range from 9.2 to 14.6 µg/ml.
dialkyl series of compounds 6h, 6i and 6j showed dose dependent inhibition with an IC50 of 21, 26.5 and 29.2 µg/ml respectively. These results demonstrated that with the increase in aliphatic carbon chain in dialkyl series causes the decreasing inhibitory activity. Among all the tested compounds 4a (JIBR-94) and 4h (methyleneedioxy analog) showed potent inhibitory activity with IC50 of 9.7 and 9.2 µg/ml respectively. Nordihydroguaiaretic acid (positive control) inhibited 5-LOX with IC50 of 4.40 µg/ml.

Further molecular docking studies of all synthesized putrescine bisamides were performed on 5-Lipoxygenase crystal protein (PDB ID 308Y) using iGEM dock programme and found the docking scores (binding energies) range between -98.92 − -141.23 Kcal/mol (Table 4). Among all compounds, 4a and 4h showed good docking efficiency, which was comparable with Nordihydroguaiaretic acid (Positive control). Docking of 5-LOX with 4a (JIBR-94) showed the binding energy of −138.67 (kcal/mol) and binds the vicinity of amino acid residues present at active site were Leu188, Ala561, Asn187 and Ser 562. 4h binds the vicinity of Leu188, Asp368, Ser562, Asn187 amino acid residues of 5-LOX crystal protein with the binding energy of -141.23 kcal/mol (Figure 1).

Among all synthesized putrescine bisamides, 4a and 4h showed good in vitro 5-LOX inhibition activities and also possess good binding capability with catalytic amino acids of 5-LOX in molecular docking studies (Figure 1).

**Antioxidant activity**

![Antioxidant activity](image_url)

**Table 4:** Anti-inflammatory and antioxidant activities of newly synthesized putrescine bisamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>5-LOX inhibitory activity (Anti-inflammatory activity)</th>
<th>Antioxidant activity (Radical scavenging activity)</th>
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<tr>
<td></td>
<td>in vitro studies IC50 (µg/ml)</td>
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*Nordihydroguaiaretic acid for 5-LOX, Ascorbic acid for antioxidant activity, ND; Not Determined*
Antioxidant activities of putrescine bisamides were performed through radical scavenging assay using DPPH and Superoxide radicals. Dihydrocinnamyl (4a-4i), substituted phenyl (6a-6g) and dialkyl (6h-6j) series of putrescine bisamides showed good free radical scavenging activity. Among all the tested compounds, 4h (methylenedioxy analog) series of putrescine bisamides showed good free radical scavenging activities.

In conclusion, a new naturally occurring N$_1$, N$_2$-dihydrocinnamyl putrescine bisamide, JBIR-94, along with nine structural analogs and a series of substituted phenyl and alkyl putrescine bisamides have been synthesized from putrescine and appropriately substituted carboxylic acids. Antimicrobial, 5-LOX enzyme inhibitory and antioxidant studies were performed for all synthesized compounds. Dihydrocinnamyl series of putrescine bisamides (4a-4i) showed efficient bioactivities compared to substituted phenyl (6a-6g) and dialkyl (6h-6j) series of compounds. Among the tested compounds, 4h and 4a (JBIR-94) showed good antimicrobial, anti-inflammatory and antioxidant activities.

Acknowledgement

The authors thank to the University Grants Commission (UGC/MRP F.No37-1/2009/AP(SR), New Delhi for financial assistance (Through a project No 37-1/2009(AP)(SR)). The authors are thankful to Laila Impex R&D center, Vijayawada 1/2009(AP)(SR), New Delhi for financial assistance (Through a project No 37-1/2009(AP)(SR)). The authors are thankful to Laila Impex R&D center, Vijayawada 1/2009(AP)(SR), New Delhi for financial assistance (Through a project No 37-1/2009(AP)(SR)). The authors are thankful to Laila Impex R&D center, Vijayawada 1/2009(AP)(SR), New Delhi for financial assistance (Through a project No 37-1/2009(AP)(SR)). The authors are thankful to Laila Impex R&D center, Vijayawada 1/2009(AP)(SR), New Delhi for financial assistance (Through a project No 37-1/2009(AP)(SR)).

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