Journal of
Chemistry & Applied Biochemistry

Open Science Publications

Volume 2, Issue 1 - 2015

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Schiff's Bases Derived from Amino Acids-Imidazole Conjugates as Promising Antioxidant and Antimicrobial Agents

Research Article

BJ Ullas[1], PG Chandrashekar[1], R Suhas[2], KP Rakesh[2], P Avinash[2] and D Channe Gowda[2*]

[1]*Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore-570 008, Karnataka, India*

[2]*Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India*

***Corresponding author:** D. Channe Gowda, Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India, Tel.: +91 821 2419664; E-mail: dchannegowda@yahoo.co.in

Article Information: **Submission:** 29/09/2015; **Accepted:** 02/11/2015; **Published:** 10/11/2015

Abstract

A series of amino acids conjugated imidazole derivatives were synthesized and characterized by standard spectroscopical techniques. The title compounds were evaluated for their in vitro antimicrobial activity against bacteria and fungi by zone of inhibition method. The results showed that this skeletal framework exhibited interesting potency as antimicrobial agents. Amongst, compounds 10,11,13,14,16,17 and 18 showed most potent gram negative and gram positive antibacterial activity whereas compounds 11,12,14,15,17 and 26 displayed most potent antifungal activity against A. niger and compounds 16,17,18, 21,22 and 24 exhibited good antifungal activity against F. oxysporum species. On the other hand, conjugates 11,12,13,14,15,16,17 and 18 showed very good antioxidant activity compared to commercial standard drugs. The results highlight the amino acids conjugated imidazole derivatives as potential leads for designing new future antimicrobial drug candidates possessing good antioxidant properties.

Keywords: Imidazole; Amino acids; Conjugation; Antimicrobial activity.

Introduction

Heterocyclic compounds of nitrogen containing five membered ring systems have been described for their biological activity against various microorganisms [1]. Besides this, the chemistry of imidazoles has also been reviewed in literature and a number of derivatives of imidazoles serve as valuable therapeutic agents [2]. Considerable interest has been created in the chemistry of imidazoles due to their versatile therapeutic activities like antibacterial [3,4], antimalarial [5], antihypertensive [6], antidepressant [7], antitubecular [8], antiviral [9], antiepileptic [10], antirheumatoid arthritis [11], anti-inflammatory [12,13], anticancer activities [14,15] etc. The emergence of powerful and elegant imidazole has stimulated major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy. Besides this, it is also reported that imidazole compounds are one of the effective antifungal agents [16]. Considering the importance of imidazole, we planned to incorporate this crucial moiety in the design of our project.

On the other hand, earlier reports have shown that conjugation of different amino acids/ peptides to various biologically active scaffolds has fetched remarkable results which are very promising and even enthusiastic [17-19]. Further, amino acid/ peptide-based drugs have low toxicity, ample bioavailability and permeability, modest potency and good metabolic and pharmacokinetic properties [20]. Prompted by all these observations and with a further interest to develop more biologically active compounds, the present work encompasses the synthesis of novel imidazole-based amino acids analogues as promising antimicrobial and antioxidant agents.

Material and Methods

ISSN: 2394-3106

General

Imidazole 1 was gifted from Jubilant Life Sciences Ltd, all other chemicals and reagents were obtained from Merck (India) and Avra Synthesis (India) which were used directly. Melting point was determined on a Superfit melting point apparatus (India) and is uncorrected. FT-IR was performed using a Jasco spectrometer (Japan) using nujol media. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Agilent Technologies spectrometer (USA) using DMSO (d_6) as solvent. High resolution mass spectroscopic analysis was performed on a Bruker MicroTOF QII mass spectrometer in positive mode. Progress of the reaction was monitored by TLC using silica gel coated on glass plates with the solvent system comprising chloroform/ methanol/ acetic acid in the ratio 98:02:03 (R_f^a) and 95:05:03 (R_f^b) and the compounds on TLC plates were detected by iodine vapors. Chemicals and reagents used for antimicrobial studies were of bacteriological grade.

General procedure for *N*-alkylation

Compound 1 (2.0 g, 0.008 mol) was dissolved in acetone and added base K_2CO_3 (2.3 g, 2 mol) followed by slow addition of 4-chlorobenzyl chloride (1.33 g, 0.008 mol). Reaction was maintained for 10 h at reflux (monitored by TLC), filtered K_2CO_3, evaporated solvent, cooled and recrystallized *N*-alkylated product 2 from ethanol.

General procedure for hydrolysis

Compound 2 (2.0 g, 0.0054 mol) was dissolved in methanol, added 0.1 N NaOH solution (0.43 g, 0.011 mol) and the reaction was maintained for 5 h at 50 °C. Completion of reaction was monitored by TLC, cooled and pH was adjusted to 1-2 using dil. HCl solution. Compound was extracted into DCM, washed with water, evaporated solvent to obtain compound 3.

General procedure for conjugation of 3 with different amino acids (HCl.NH_2-Xaa-COOMe) where Xaa = Phe, Tyr, Trp, Pro, Met and Lys

To compound **3** (0.002 mol) and HOBt (0.305 g, 0.002 mol) dissolved in DMF (10 mL/g of compound) cooled to 0 °C was added NMM (0.55 mL, 0.002 mol). EDCI (0.383 g, 0.005 mol) was added under stirring while maintaining the temperature at 0 °C. Reaction mixture was stirred for an additional 10 min and a pre-cooled solution of HCl.NH_2-Xaa-COOMe (0.631 g, 0.002 mol) and NMM (0.25 mL, 0.002 mol) in DMF (10 mL) was added slowly. After 20 min, pH of the solution was adjusted to 8 by the addition of NMM and the reaction mixture was stirred over night at room temperature. DMF was removed under reduced pressure and the residue was poured into about 200 mL of ice-cold 90% saturated $KHCO_3$ solution and stirred for 30 min. The precipitated product was taken into $CHCl_3$ and washed with 5% $NaHCO_3$ solution (2×100 mL), water (1×100 mL), HCl (2×100 mL) and brine (1×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The products so obtained were recrystalized from ether/petroleum ether to get conjugates 4 (Phe), 5 (Tyr), 6 (Trp), 7 (Pro), 8 (Met) and 9 (Lys).

General procedure for the synthesis of hydrazides

Compound 4, 5, 6, 7, 8 and 9 (0.3mmol) was dissolved separately in ethanol (2 mL) and hydrazine hydrate (0.03 mL, 2 mol) was added slowly and the reaction was maintained at reflux for 12 h. Completion of the reaction was monitored by TLC, evaporated solvent, cooled and poured into ice cold water. Solid separated was filtered and dried to obtain 4a, 5a, 6a, 7a, 8a and 9a respectively.

General procedure for the condensation of aldehydes to 4a, 5a, 6a, 7a, 8a and 9a

To compound 4a, 5a, 6a, 7a, 8a and 9a (0.3 mmol) and benzladehyde (0.3 mmol) dissolved in ethanol (10 mL/g) was added few drops of acetic acid as a catalyst which was maintained at reflux for 15 h. Completion of the reaction was monitored by TLC, solvent was evaporated, cooled and poured into ice cold water precipitate is obtained and then filtered, washed with cold water to obtain compound (10-27).

Antibacterial activity

In vitro antibacterial activity was evaluated against human pathogens of both gram positive organisms namely *X. oryzae* and gram negative organisms namely *E. coli* by agar well diffusion method [21].

The microorganisms were inoculated in to the sterilized nutrient broth and maintained at 37 °C for 24 h. On the day of testing, bacteria were subcultured separately into 25 mL of sterilized nutrient broth. Inoculated subcultured broths were kept at room temperature for the growth of inoculums. Each test compound (10-27) and standard drug of 10 mg was dissolved in 10 mL of DMSO to get a concentration of 1 µg/mL and further diluted to get a final concentration of 50 µg/mL. About 15-20 mL of molten nutrient agar was poured into each of the sterile plates. With the help of cork borer of 6mm diameter, the cups were punched and scooped out of the set agar and the plates were inoculated with the suspension of particular organism by spread plate technique. The cups of inoculated plates were then filled with 0.1 mL of the test solution, Chloromphenicol solution and DMSO (negative control). The plates were allowed to stay for 24 h at 37 °C and zone of inhibition (mm) was then measured.

Antifungal activity

In vitro antifungal activity was evaluated against two fungal species namely *A.niger,* and *F. oxysporum* by agar well diffusion method [22].

The fungal strains were subcultured separately into 25 mL of sterilized nutrient broth and compounds and standard drug (bavistin) of 10 mg was dissolved in 10 mL of DMSO to get a concentration of 1 mg/ml and further diluted to get a final concentration of 50 µg/mL. Molten media of sabouraud agar of 10-15 mL was poured into the petri plates and allowed to solidify. Fungal subculture was inoculated on the solidified media. With the help of 6 mm cork borer, the cups were punched and scooped out of the set agar. The cups of inoculated plates were then filled with 0.1 mL of the test solution, bavistin solution and DMSO (negative control). The plates were allowed to stay for 3 days at room temperature and zone of inhibition (mm) was then measured.

Antioxidant activities

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DPPH (1,1-diphenyl-2-picryl-hydrazyl) assay

The radical scavenging activity of DPPH free radicals by synthesized compounds were determined according to the reported method [23]. Briefly, 50 µL of test compounds was mixed at different concentrations (25, 50, 100, 200 and 300 µg/mL) with 1 mL of 0.1 mM DPPH in methanol solution and 450 µL of 50 mM Tris HCl buffer (pH 7.4). Methanol (50 µL) only was used as the experimental control. After 30 min of incubation at room temperature, reduction in the number of DPPH free radicals was measured by reading absorbance at 517 nm. BHT (butylatedhydroxytoluene) was used as control similar to test concentrations. Percent inhibition was calculated from the following equation:

$$\% \text{ Inhibition} = \left[\frac{\text{Absorbance of control - Absorbance of test sample}}{\text{Absorbance of control}}\right] \times 100$$

ABTS (2,2-azinobis-(3-ethylbenzothiazoline-6-sufonic acid) assay

The ability of the test sample to scavenge $ABTS^{\cdot+}$ radical cation was determined according to the literature method [24] with slight modification. The $ABTS^{\cdot+}$ radical cation was pregenerated by mixing 7 mM $ABTS^{\cdot+}$ stock solution with 2.45 mM potassium persulfate (final concentration) and incubating for 12-16 h in dark at room temperature until the reaction was complete and absorbance was stable. Absorbance of the $ABTS^{\cdot+}$ solution was equilibrated to 0.70 (± 0.02) by diluting with distilled water at room temperature, then 2 mL was mixed with different concentration of the test sample (25, 50, 100, 200, and 300 µg/mL) and the absorbance was measured at 734 nm after 6 min. The scavenging capability of $ABTS^{\cdot+}$ radical was calculated using the following equation:

$ABTS^{\cdot+}$ scavenging effect (%) = $[(A_c\text{-}A_s)/A_c] \times 100$

Where, A_c is the initial concentration of the $ABTS^{\cdot+}$ and A_s is the absorbance of the remaining concentration of $ABTS^{\cdot+}$ in the presence of compounds.

DMPD (*N, N*-dimethyl-*p*-phenylenediamine) assay

The DMPD radical scavenging ability of synthesized compounds was determined by the Fogliano et al., method [25] with slight modifications by Gulcin [26]. This assay is based on the capacity of the extract to inhibit $DMPD^{\cdot+}$ cation radical formation. Briefly, 105 mg of DMPD was dissolved in 5 mL of distilled water. Then, 1 mL of this solution was added to 100 mL of 0.1 M acetate buffer (pH 5.3). $DMPD^{\cdot+}$ was produced by adding 0.3 mL ferric chloride (0.05 M) to this solution. Different concentrations of standard antioxidants or synthesized compounds (25-300 µg/mL) were added, and the total volume was adjusted to 1 mL with distilled water. One millilitre of the $DMPD^{\cdot+}$ solution was directly added to the reaction mixture. The reaction mixtures were incubated in the dark for 15 min. The absorbance was measured at 505 nm and percent inhibition was calculated according to the formula:

$$\% \text{ Inhibition} = \left[\frac{\text{Absorbance of control - Absorbance of test sample}}{\text{Absorbance of control}}\right] \times 100$$

Results and Discussion

Chemistry

Starting material 1 was subjected to *N*-alkylation using benzyl chloride that resulted in 2 which was ascertained by the absence of NH proton peak. Product 2 on saponification yielded 3 which exhibited carboxylic acid peak in its PMR spectrum. This compound was conjugated with different amino acids to obtain 4-9 which did not have COOH peak and showed –NH peak at δ ~8.00 (1H, s) in ^{1}H NMR spectra. Compounds 4-9 was separately reacted with hydrazine hydrate to get 4a-9a which was confirmed by disappearance of $-OCH_3$ peak. The final imines 10-27 were synthesized by condensation of 4a-9a with substituted aldehydes (Scheme). Synthesis were confirmed by the presence of all requisite peaks and absence of extraneous peaks in ^{1}H NMR and ^{13}C NMR spectra and also mass values were in accordance with the mol. wt. calculated. The analytical and spectroscopic data of the synthesized compounds are given in Table 1.

Biological evaluation

Antimicrobial activity

The Schiff bases of imidazole-amino acid conjugates were evaluated for their antibacterial studies against both gram-positive and gram-negative bacteria namely *X. oryzae* and *E. coli* respectively and antifungal studies against *A. niger* and *F. oxysporum*. Synthesized compounds exhibited a significant broad spectrum inhibitory effect against all the tested microorganisms. The result obtained as zone of inhibition (mm) is presented in Table 2**.** The standard drugs chloromphenicol and bavistin were used as standards for antibacterial and antifungal activities respectively.

Previous reports have shown that there is no significant activity with just imidazoles linked amino acids [27,28]. Further, derivatives of amino acids-heterocycle conjugates have exhibited promising results and in continuation it was decided to introduce different aldehydes *viz.* dihydroxy, trihydroxy and trimethoxy benzaldehyde in the present study to obtain imines 10-27. Among the twenty naturally occurring amino acids, selective moieties like Phe, Trp and Tyr (aromatics); Pro (an imine); Met (thio) and Lys (basic) were used in the current investigation. Amongst, compounds 10-18, 21 and 27 appeared to be more active than the standards which may be due to the presence of aromatic side chains in Phe, Trp and Tyr and also could be due to more hydrophobicity of these amino acids along with the presence of more electron donating groups like OH and OCH_3 present on the other end of the molecules. Together these parameters would have contributed to the superior activity. And also it is observed that compounds with trihydroxy benzaldehyde derivatives have shown enhanced activity compared to rest of the analogues which imparts that these hydroxyl functions play a key role in enhancing the activity. On the other hand, compounds containing thio group (22-24) have shown slightly decreased activity than Pro (19-21) which are further less active than Lys (25-27) analogues and

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Table 1: Physical and analytical data of the conjugated compounds **(10-27)**

Entry	R_f value	Yield (%)	M.P. (°C)	Theoretical Mol. Wt.	Actual MS	IR (v cm^{-1}) and NMR ($CDCl_3$, δ ppm)
10	0.61	89	103-105	617.10	618.3	IR: 3250 (NH), 1690 (CO), 1590 (-HC=N-) ^{1}H NMR: 0.90 (3H,t,-CH_3 of propyl), 1.57 (6H,s,-CH_3), 1.68 (2H,m,-CH_2 of propyl), 2.45 (2H,t,-CH_2 of propyl), 2.92 (2H,t,β–CH_2), 4.92 (1H,t,α-CH), 4.97 (2H,s,-CH_2 of benzyl), 5.0 (2H, s,-OH), 6.66-7.22 (12H,m,Ar-H), 8.1 (1H,s,-HC=N-), 8.8 (2H,d,-NH) ^{13}C NMR:13.6, 24.4, 28.5, 31.1, 37.8, 40.1, 55.2, 69.7, 115.8, 115.8., 116.2, 117.5, 123.2, 126.4, 128.2, 128.7, 130.9, 131.2, 133.9, 138.7, 143.1, 147.2, 148.6, 150.1, 155.6, 156.5, 160.6, 177.2
11	0.59	91	101	633.30	634.5	IR: 3260 (NH), 1695 (CO), 1620 (-HC=N-) ^{1}H NMR: 0.93 (3H,t,-CH_3 of propyl), 1.54 (6H,s,-CH_3), 1.70 (2H,m,-CH_2 of propyl), 2.48 (2H,t,-CH_2 of propyl), 2.89 (2H,t,β–CH_2), 4.88 (1H,t,α-CH), 4.90 (2H,s,-CH_2 of benzyl), 5.6 (3H, s,-OH), 6.70-7.30 (11H,m,Ar-H), 8.1 (1H,s,-HC=N-), 8.6 (2H,d,-NH). ^{13}C NMR:14.2, 26.2, 27.6, 33.1, 38.4, 41.2, 55.8, 66.6, 116.4, 117.5, 118.8, 119.2, 121.6, 128.6, 128.9, 130.5, 131.4, 131.9, 133.2, 138.4, 140.9, 146.0, 149.5, 151.4, 154.1, 156.0, 161.4, 175.8
12	0.62	92	113-114	675.0	676.1	IR: 3258 (NH), 1680 (CO), 1640 (-HC=N-) ^{1}H NMR: 1.0 (3H,t,-CH_3 of propyl), 1.55 (6H, s, -CH_3), 1.69 (2H,m,-CH_2 of propyl), 2.31 (2H,t,-CH_2), 2.42 (2H,t,-CH_2 of propyl), 3.09 (1H,m,β-CH_2), 3.53 (9H,s,-OMe), 4.95 (1H,α,-CH), 4.92 (2H,s,-$CH_2$of benzyl), 6.6-7.22 (11H,m,Ar-H), 8.2 (2H,d,NH), 8.2 (1H,s,-HC=N-) ^{13}C NMR: 14.5, 26.0, 27.9, 30.1, 38.4, 41.2, 53.7, 56.2, 63.6, 105.1, 114.8, 126.1, 126.6, 129.1, 132.2, 133.8, 134.0, 134.4, 136.9, 140.2, 143.2, 150.5, 150.8, 151.8, 156.0, 156.4, 176.6
13	0.55	85	120-122	633.5	634.5	IR: 3264 (NH), 1691 (CO), 1640 (-HC=N-) ^{1}H NMR: 0.92 (3H,t,-CH_3 of propyl), 1.60 (6H,s,-CH_3), 1.64 (2H,m,-CH_2 of propyl), 2.41 (2H,t,-CH_2 of propyl), 2.92 (2H,t,β –CH_2), 4.92 (1H,t,α-CH), 4.99 (2H,s,-CH_2 of benzyl), 5.2 (3H, s,-OH), 6.66-7.18 (11H,m,-Ar-H), 8.0 (1H,s,-HC=N-), 8.3 (2H,d,-NH) ^{13}C NMR: 13.7, 24.2, 28.3, 31.0, 37.9, 40.2, 55.3, 69.8, 115.7, 115.8., 116.4, 117.4, 123.2, 128.8, 129.2, 130.5, 131.3, 132.1, 134.4, 138.6, 143.0, 147.4, 149.6, 150.7, 155.7, 156.4, 160.8, 177.0
14	0.58	92	Gum	649.10	650.5	IR: 3245 (NH), 1698 (CO), 1630 (-HC=N-) ^{1}H NMR: 0.93 (3H,t,-CH_3 of propyl), 1.54 (6H,s,-CH_3), 1.70 (2H,m,-CH_2 of propyl) ,2.48 (2H,t,-CH_2 of propyl), 2.89 (2H,t,β –CH_2), 4.88 (1H,t,α-CH) 4.93 (2H,s,-CH_2 of benzyl), 5.6 (4H, s,-OH), 6.70-7.30 (10H,m,-Ar-H), 8.1 (1H,s,-HC=N-) 8.6 (2H,d,-NH) ^{13}C NMR: 13.9, 24.8, 28.7, 32.0, 37.7, 40.3, 54.9, 69.8, 115.4, 115.5, 115.9, 117.2, 122.8, 128.6, 129.1, 130.6, 131.4, 131.9, 134.3, 138.5, 139.9, 147.2, 149.5, 150.6, 155.7, 156.2, 160.6, 177.2
15	0.70	88	122	691.20	692.2	IR: 3246 (NH), 1686 (CO), 1595 (-HC=N-) ^{1}H NMR: 1.0 (3H,t,-CH_3 of propyl), 1.55 (6H, s, -CH_3), 1.69 (2H,m,-CH_2 of propyl), 2.31 (2H,t,-CH_2), 2.42 (2H,t,-CH_2 of propyl), 3.09 (1H,m, β-CH_2), 3.53 (9H,s,-OMe), 4.95 (1H,α,-CH), 4.98 (2H,s,-CH_2 of benzyl), 5.40 (1H,s,-OH), 6.6-7.22 (11H,m,Ar-H), 8.2 (2H,d,NH), 8.2 (1H,s,-HC=N-) ^{13}C NMR: 13.5, 24.3, 28.5, 31.3, 37.8, 40.1, 55.4, 56.2, 64.8, 106.5, 115.8, 128.0, 128.6, 129.2, 130.4, 131.5, 132.0, 134.4, 138.6, 141.5, 143.0, 150.7, 150.9, 150.9, 155.7, 156.4, 177.5
16	0.66	96	Gum	657.14	658.5	IR: 3266(NH),1670 (CO), 1590 (-HC=N-) ^{1}H NMR: 0.82 (3H,t,-CH_3 of propyl), 1.37 (6H,s,-CH_3), 1.68 (2H,m,-CH_2 of propyl), 2.45 (2H,t,-CH_2 of propyl), 3.06 (2H,d,β-CH_2), 4.92 (1H, t,δ -CH), 5.40 (2H,s, -OH), 4.99 (2H,s,- CH_2 of benzyl), 6.6-7.18 (11H,m,Ar-H), 8.4 (1H,s,-HC=N-), 10.1 (2H,t,-NH) ^{13}C NMR: 12.9, 22.2, 28.6, 32.0, 31.6, 40.4, 56.4, 69.8, 110.9, 111.1, 116.4, 116.9, 118.2, 120.6, 121.1, 122.2, 123.1, 127.6, 127.9, 128.6, 130.4, 131.3, 134.4, 136.4, 138.6, 143.0, 147.3, 149.6, 150.4, 156.4, 160.4, 178.0
17	0.57	86	89-90	672.2	673.5	IR: 3261 (NH), 1675 (CO), 1625 (-HC=N-) ^{1}H NMR: 0.88 (3H,t,-CH_3 of propyl), 1.34 (6H,s,-CH_3), 1.64 (2H,m,-CH_2 of propyl), 2.45 (2H,t,-CH_2 of propyl), 3.16 (2H,d,β-CH_2), 4.90 (1H, t,δ -CH), 5.39 (3H,s,-OH), 4.99 (2H,s,-CH_2 of benzyl), 6.6-7.18 (10H,m,Ar-H), 8.1 (1H,s,-HC=N-), 10.1 (2H,t,-NH) ^{13}C NMR: 11.7, 23.1, 27.5, 31.6, 31.9, 40.1, 54.2, 66.5, 109.0, 116.4, 118.2, 120.6, 121.1, 122.2, 127.6, 127.9, 128.6, 129.2, 130.4, 131.3, 134.4, 136.4, 143.0, 143.1, 146.7, 148.5, 151.2, 155.1, 159.0, 176.2

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18	0.60	90	96	714.29	715.4	IR: 3258 (NH),1660 (CO), 1605 (-HC=N-) ^{1}H NMR: 0.82 (3H,t,-CH_3 of propyl), 1.42 (6H,s,-CH_3), 1.55 (2H,m,-CH_2 of propyl), 2.51(2H,t,-CH_2 of propyl), 3.16 (2H,d,β-CH_2), 3.23 (2H,d,β-CH_2), 3.77 (9H,s,-OCH_3), 4.88 (1H,t,α-CH), 5.0 (2H,s,-$CH_2$of benzyl), 6.3-7.02 (10H,m,Ar-H), 8.2(1H,s,-HC=N-), 9.36 (2H,d,-NH) ^{13}C NMR:13.8,23.6,29.0,30.5,31.3,39.8,56.0,69.8, 106.7,110.9,111.1,120.0,122.2,122.9,127.5,128.1,128.8,130.5,131.3,134.4,136.5,138.6,141.5,143.0,150.7,150.9160.8,173.0
19	0.55	92	102	567.10	568.4	IR: 3244 (NH), 1685(CO), 1650 (-HC=N-) ^{1}H NMR: 0.86 (3H,t,-CH_3 of propyl), 1.54 (2H,m,β –CH_2), 1.65 (6H,s,-CH_3), 1.70 (2H,m,α-CH_2), 1.72 (2H,m,-CH_2 of propyl), 2.56 (2H,t,-CH_2 of propyl), 3.29 (2H,t,α –CH_2), 4.29 (1H,t,δ-CH_2), 5.2 (2H,s,- CH_2 of benzyl), 5.40 (2H,s, -OH), 6.66-7.18 (7H,m,Ar-H), 8.1 (1H,s,-HC=N-) 8.6 (1H,d,-NH) ^{13}C NMR: 12.7, 24.1, 26.0, 31.0, 32.1, 37.0, 55.0, 65.4, 108.6, 110.9, 116.2, 116.8, 119.0, 122.0, 122.3, 122.8, 123.0, 126.5, 127.0, 128.8, 130.4, 131.0, 133.8, 135.5, 137.5, 142.0, 148.2, 149.1, 150.7, 160.6, 169.0
20	0.60	90	109-110	583.20	584.5	IR : 3256 (NH),1669 (CO), 1635 (-HC=N-) ^{1}H NMR : 1.02 (3H,t,-CH_3 of propyl), 1.52 (2H,m,β-CH_2), 1.56 (6H,s,-CH_3), 1.68 (2H,m,-CH_2 of propyl), 1.71 (2H,m,γ-CH_2), 2.32 (2H,t,-CH_2 of propyl), 3.30 (2H,s,-CH_2 of propyl), 4.29 (1H,t,δ-CH), 5.03 (3H,s,-OH), 6.5-7.15 (6H,s,Ar-H), 8.0 (1H,s,-NH), 8.3 (1H,s,-HC=N-) ^{13}C NMR: 15.1, 20.4, 24.2, 25.1, 28.3, 39.6, 55.0, 64.1, 106.3, 110.4, 115.8, 118.5, 121.3, 126.4, 128.3, 129.4, 130.1, 132.1, 134.1, 138.3, 138.6, 140.4, 148.8, 152.2, 154.3, 164.8, 172.7
21	0.68	93	Gm	625.27	626.2	IR: 3244 (NH),1692 (CO), 1625 (-HC=N-) ^{1}H NMR: 0.99 (3H,t,-CH_3 of propyl), 1.49 (2H,m,β-CH_2), 1.57 (6H,s,-CH_3), 1.62 (2H,m,-CH_2 of propyl), 1.72 (2H,m,γ-CH_2), 2.30 (2H,t,-CH_2 of propyl), 3.30 (2H,s,-CH_2 of propyl), 4.31 (1H,t,δ-CH), 5.13 (9H,s,-OMe), 6.5-7.15 (6H,s,Ar-H), 8.1 (1H,s,-NH), 8.4 (1H,s,-HC=N-) ^{13}C NMR: 15.0, 20.2, 30.3, 30.6, 31.2, 39.3, 54.2, 55.0, 68.0, 106.7, 110.8, 113.0, 118.0, 119.1, 122.2, 122.9, 128.8, 128.1, 131.3, 134.4, 138.4, 141.5, 143.0, 150.9, 150.9, 160.8, 168.0
22	0.55	94	Gum	587.2	588.6	IR: 3267 (NH),1700 (CO), 1610 (-HC=N-) ^{1}H NMR: 0.99 (3H,t,-CH_3 of propyl), 1.39 (6H,s,-CH_3), 1.62 (2H,m,-CH_2 of propyl), 2.09 (3H,s,δ-CH3), 2.53 (2H,t,-CH_2 of propyl), 2.92 (2H,d,β-CH_2), 4.92 (1H,t,α-CH), 4.99 (2H,s,-CH_2 of benzyl)), 5.13 (2H,s,-OH), 6.6-7.10 (7H,m,Ar-H), 8.15 (1H,s,-HC=N-) 8.21 (1H,s,-NH) ^{13}C NMR: 14.8, 17.1, 24.7, 27.3, 30.1, 36.5, 40.0, 50.6, 69.8, 114.4, 115.2, 116.4, 121.1, 123.2, 126.8, 127.8, 128.9, 130.3, 131.0, 134.4, 138.6, 147.4, 149.6, 150.7, 156.4, 166.9
23	0.56	88	Gum	603.19	604.3	IR : 3270 (NH),1695 (CO), 1595 (-HC=N-) ^{1}H NMR: 1.1 (3H,t,-CH_3 of propyl), 1.35 (6H,s,-CH_3), 1.58 (2H,m,-CH_2 of propyl), 2.16 (3H,s,δ-CH3), 2.54 (2H,t,-CH_2 of propyl), 2.88 (2H,d,β-CH_2), 4.88 (1H,t,α-CH), 4.96 (2H,s,-CH_2 of benzyl),5.11 (3H,s,-OH), 6.6-7.10 (6H,m,Ar-H), 8.15 (1H,s,-HC=N-), 8.20 (1H,s,-NH) ^{13}C NMR: 14.5, 21.2, 29.3, 32.2, 32.6, 47.9, 51.9, 71.2, 109.0, 115.2, 118.1, 119.4, 128.8, 130.5, 138.2, 143.0, 147.6, 148.5, 150.1, 151.2, 154.1, 160.8, 171.6
24	0.60	92	108	645.24	646.3	IR: 3240 (NH),1689 (CO), 1645 (-HC=N-) ^{1}H NMR: 0.90 (3H,t,-CH_3 of propyl), 1.35 (6H,s,-CH_3), 1.58 (2H,m,-CH_2 of propyl), 2.16 (3H,s,δ-CH3), 2.54 (2H,t,-CH_2 of propyl),3.07 (2H,d,β-CH_2), 4.88 (1H,t,α-CH), 4.96 (2H,s,-CH_2 of benzyl), 5.20 (9H,s,-OCH_3), 6.6-7.10 (6H,m,Ar-H), 8.0 (1H,s,-HC=N-), 8.10 (1H,s,-NH) ^{13}C NMR: 11.6, 17.2, 24.2, 26.1, 31.1, 31.4, 52.8, 56.2, 67.2, 106.7, 114.1, 116.7, 128.1, 131.3, 134.4, 141.0, 144.8, 147.7, 146.0, 149.6, 150.9, 154.0, 161.5, 169.5
25	0.56	91	118	686.27	687.3	IR: 3243 (NH),1695 (CO), 1630 (-HC=N-) ^{1}H NMR: 0.88 (3H,t,-CH_3 of propyl), 1.29 (2H,m,γ-CH_2), 1.36 (6H,s,-CH_3), 1.37 (2H,m,-CH_2 of propyl), 1.41 (2H,m,δ-CH_2), 1.96 (2H,t,-CH2 of propyl), 2.55 (2H,t,ω-CH_2), 2.46 (2H,s,-CH_2 of benzyl), 3.81 (2H,d,-CH_2 of benzyl), 4.51 (1H,t,-CH), 5.12 (2H,s,-OH), 6.6-7.22 (12H,m,Ar-H), 8.0 (3H,s,-NH), 8.1 (1H,s,-HC=N-) ^{13}C NMR: 13.6, 23.1, 26.3, 32.2, 32.6, 37.0, 51.9, 52.8, 56.2, 69.8, 116.3, 117.0, 118.4, 126.0, 127.8, 128.7, 134.3, 138.6, 139.5, 148,7, 149.0, 150.7, 156.4, 162.4, 170.3

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26	0.59	86	Gum	702.32	703.3	IR: 3260 (NH),1698 (CO), 1620 (-HC=N-) ^{1}H NMR: 0.96 (3H,t,-CH_3 of propyl), 1.30 (2H,m,γ-CH_2), 1.33 (6H,s,-CH_3), 1.27 (2H,m,-CH_2 of propyl), 1.42 (2H,m,δ-CH_2), 1.88 (2H,t,-CH_2 pf propyl), 2.45 (2H,t,ω,-CH_2), 2.54 (2H,s,-CH_2 of benzyl), 3.80 (2H,d,-CH_2 of benzyl), 4.49 (1H,t,-CH), 5.10 (3H,s,-OH), 6.6-7.22 (12H,m,Ar-H), 8.2 (3H,s,-NH), 8.3 (1H,s,-HC=N-) ^{13}C NMR: 13.7, 22.6, 24.2, 28.3, 28.9, 31.0, 32.6, 45.7, 56.2, 58.7, 68.5, 69.8, 116.3, 117.3, 118.5, 127.2, 127.7, 129.0, 134.3, 138.6, 141.2, 148.7, 149.0, 150.7, 156.4, 165.4, 171.6
27	0.60	90	128	744.37	745.5	IR: 3256 (NH),1696 (CO), 1610 (-HC=N-) ^{1}H NMR: 0.90 (3H,t,-CH_3 of propyl), 1.33 (2H,m,γ-CH_2), 1.35 (6H,s,-CH_3), 1.38 (2H,m,-CH_2 of propyl), 1.41 (2H,m,δ-CH_2), 1.96 (2H,t,-CH_2 of propyl), 2.55 (2H,t,ω,-CH_2), 2.46 (2H,s,-CH_2 of benzyl), 3.81 (2H,d,-CH_2 of benzyl), 4.51 (1H,t,-CH), 5.05 (9H,s,-CH_3), 6.6-7.22 (12H,m,Ar-H), 8.0 (3H,s,-NH), 8.1 (1H,s,-HC=N-) ^{13}C NMR: 12.5, 24.1, 27.3, 31.8, 33.4, 37.0, 51.9, 52.8, 54.3, 68.6, 115.8, 116.1, 118.2, 118.5, 129.2, 132.1, 135.3, 138.4, 148.7, 149.6, 151.6, 155.7, 156.2, 160.8, 171.2

Table 2: Antimicrobial and Antioxidant activity of synthesized derivatives

Entry	Antibacterial activity		Antifungal activity		Antioxidant activity		
	Zone of inhibition (mm) ± SD (n=3)				IC_{50} µg/Ml		
	E. coli	*X. oryzae*	*A. niger*	*F. oxysporum*	DPPH	ABTS	DMPD
1	3±0.12	2±0.63	4±0.42	3±0.40	220±2.01	175±2.15	180±1.45
10	16±0.52	14±0.20	15±0.12	5±0.20	40±0.98	40±0.46	45±0.47
11	18±0.20	12±0.52	18±0.22	7±0.52	25±0.66	35±0.79	35±0.52
12	15±0.50	14±0.35	16±0.52	8±0.2	35±1.02	40±0.64	40±0.95
13	17±0.50	14±0.41	14±0.44	5±0.10	35±0.89	35±0.43	40±0.15
14	20±0.41	16±0.50	20±0.36	6±0.40	20±0.49	30±0.63	30±0.65
15	16±0.46	10±0.15	18±0.10	6±0.25	35±0.65	40±0.14	35±0.24
16	20±0.45	14±0.15	15±0.40	10±0.33	30±0.78	35±0.57	35±0.65
17	22±0.47	16±0.25	16±0.25	12±0.40	20±0.61	25±0.69	20±0.54
18	19±0.41	15±0.26	10±0.33	11±0.25	30±0.43	35±0.52	40±0.26
19	12±0.50	10±0.30	14±0.40	9±0.31	60±0.55	45±0.48	40±0.54
20	14±0.20	14±0.20	16±0.25	9±0.10	55±1.04	35±0.33	35±0.25
21	11±0.40	11±0.10	10±0.33	10±0.40	70±1.22	45±0.49	40±0.45
22	10±0.45	8±0.20	9±0.12	11±0.25	95±1.69	50±0.49	80±0.59
23	10±0.36	7±0.10	12±0.22	10±0.33	75±1.64	45±0.43	65±0.65
24	9±0.30	6±0.20	11±0.30	8±0.40	80±1.69	50±0.58	90±0.45
25	13±0.35	9±0.20	13±0.33	9±0.25	65±0.98	60±0.55	80±0.26
26	14±0.30	12±0.20	15±0.35	7±0.32	60±0.24	75±1.02	85±0.47
27	12±0.35	10±0.26	16±0.44	9±0.21	70±0.66	85±1.54	95±1.23
Chloromphenicol	14±0.65	10±0.24	-	-	-	-	-
Bavistin	-	-	13±0.94	8±0.15	-	-	-
BHA	-	-	-	-	55±0.52	45±0.54	50±0.56
AA	-	-	-	-	55±0.69	50±0.66	60±0.42
GA	-	-	-	-	60±0.48	50±0.49	55±0.26

this trend in activity reveals that presence of basic moiety is more helpful in obtaining good results. Further these compounds are found to be more selective in arresting the growth of *A. niger* fungus than *F. oxysporum*.

In vitro antioxidant activities of all the synthesized compounds were evaluated by (i) 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay, an convenient technique for screening the antioxidant activities of the antioxidants; (ii) 2,2-azinobis-3-ethylbenzothiazoline-6-sufonic acid (ABTS) cation radical assay which is a conventional and excellent model for assessing the antioxidant activities of hydrogen donating and chain breaking antioxidants [29]; and (iii) *N,N*-dimethyl-*p*-phenylenediamine dihydrochloride (DMPD) cation radical assay which is similar to the DPPH radical scavenging assay. The IC_{50} values is the effective concentration at which 50% of the

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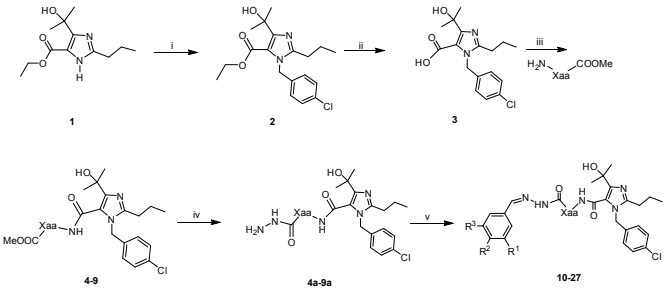
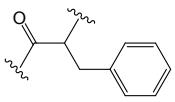
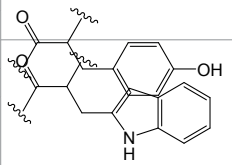
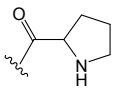
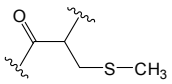
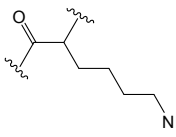
Scheme: Schematic for target compounds



Reagents and Conditions: (i) 4-Chloro benzyl chloride, K_2CO_3, acetone, reflux, 12 h (ii) 0.1 N NaOH, MeOH, 50-55 °C, 5 h (iii) EDCI, HOBt, NMM, 0-5 °C, 15 h (iv) Hydrazine hydrate, EtOH, reflux, 10 h (v) Substituted aldehydes, EtOH, AcOH, reflux, 14 h

Comp. No.	Xaa	R^1	R^2	R^3
10		OH	OH	H
11		OH	OH	OH
12		OCH_3	OCH_3	OCH_3
13		OH	OH	H
14		OH	OH	OH
15		OCH_3	OCH_3	OCH_3
16		OH	OH	H
17		OH	OH	OH
18		OCH_3	OCH_3	OCH_3
19		OH	OH	H
20		OH	OH	OH
21		OCH_3	OCH_3	OCH_3
22		OH	OH	H
23		OH	OH	OH
24		OCH_3	OCH_3	OCH_3
25		OH	OH	H
26		OH	OH	OH
27		OCH_3	OCH_3	OCH_3

radicals were scavenged, were calculated to evaluate the antioxidant activities. A lower IC_{50} value indicate greater antioxidant activity. IC_{50} values of lower than 10 mg/mL usually implied effective activities in antioxidant properties [30]. The IC_{50} of butylatedhydroxylanisole (BHA), ascorbic acid (AA) and gallic acid (GA) was also determined for comparison. The results are presented in Table 2.

Most of the synthesized analogues showed potent antioxidant activities especially 11, 12, 13, 14, 15, 16, 17 and 18 showed excellent radical scavenging activities with IC_{50} values 25, 35, 35, 20, 35, 30, 20 and 30 µg/mL respectively in DPPH assay much better than the standard BHA (IC_{50} = 55 µg/mL). In $ABTS^+$ radical scavenging assay, the compounds 11, 12, 13, 14, 15, 16, 17 and 18 showed potent antioxidant activity with IC_{50} values 35, 40, 35, 30, 40, 35, 25 and 35 µg/mL respectively which is much better than the commercial standards AA (IC_{50}= 55 µg/mL). The compounds 11, 12, 13, 14, 15, 16, 17 and 18 also exhibited striking antioxidant activity with IC_{50} values 35, 40, 40, 30, 35, 35, 20 and 40 µg/mL respectively which is better than the standards BHA (IC_{50} = 50 µg/mL), AA (IC_{50}= 60 µg/mL) and GA (IC_{50} = 55 µg/mL) in DMPD assay. In all the three assays performed, compounds 11, 12, 13, 14, 15, 16, 17 and 18 showed excellent antioxidant activities with IC_{50} values much lower than the standards. The IC_{50} values of these compounds have antioxidant activities lower than 10 mg/mL demonstrating greater capacity in all the three assays. On the basis of the above observation, compounds having –OH (phenolic), –indole and phenyl ring (11, 12, 13, 14, 15, 16, 17 and 18) were found to be the most potent antioxidants. Conjugates with alkyl, imino and thio group showed least antioxidant activity.

Conclusion

A novel series of Schiff base analogues of amino acids-imidazole conjugates has been presented in this work. These compounds were evaluated for antibacterial and antifungal activities by agar well diffusion method. Activity profile revealed that compounds containing aromatic amino acids have shown profound results along with the beneficiary electron loving hydroxyl groups. Presence of thio (Met) and imino (Pro) amino acids have shown moderate activity compared to Lys, a basic amino acid. These target molecules have exhibited selective activity against *A. niger* fungal species and hence these could be used to treat fungal infections. In case of antioxidant activity compounds containing phenyl ring, indole ring and –OH (phenolic) group showed remarkable activity which may be due to electron donating activity and resonating property of phenyl ring. Compounds like 22, 23, 24, 25, 26, and 27 showed least activity which could be be due to long alkyl group and also may be due to thio group in methionine.

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