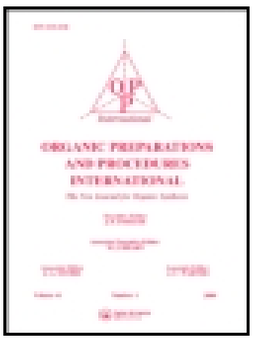

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A Facile Synthesis of Hydroxamic Acids of N^{α}-Protected Amino Acids Employing BDMS, a Study of Their Molecular Docking and Their Antibacterial Activities

K. Uma,[1] H. S. Lalithamba,[1] V. Chandramohan,[2] and K. Lingaraju[3]

[1]Department of Chemistry, Siddaganga Institute of Technology, B.H. Road, Tumakuru-572 103, Karnataka, India
[2]Department of Biotechnology, Siddaganga Institute of Technology, B.H. Road, Tumakuru-572 103, Karnataka, India
[3]Department of Biotechnology, Tumkur University, B.H. Road, Tumakuru-572 103, Karnataka, India

Hydroxamic acids have received much attention as biologically active compounds. Synthetic hydroxamic acids enhance the growth of plant sources and improve the soil quality, act as antibiotics, cell division agents or tumor inhibitors.[1] Hydroxamic acids were found to be histone deacetylase (HDAC) inhibitors[2] and the functionality of hydroxamic acid is an important structural component in bioactive agents such as antibacterial, antifungal and anticancer agents.[3] The one-pot oxidative transformation of aldehydes into hydroxamic acids using an aqueous solution of hydroxylamine[4] has been reported. Acylation of carboxylic acids with hydroxylamine using coupling reagents like cyanuric chloride,[5] propylphosphonic anhydride[6] and *N,N′*-carbonyldiimidazole[7] can be found in the literature. Economical ways to obtain hydroxamic acid derivatives by the reaction of hydroxylamine salt with acid chlorides and esters[8] have been described. The reported methods for the preparation of hydroxamic acids include the reaction of activated carboxylic acids with *O/N*- protected hydroxylamines[9] and MgO mediated preparation of Fmoc-protected amino acid hydroxamates from acid chlorides.[10] Suresh Babu *et al.,* achieved the synthesis of N^{α}-protected amino/peptide hydroxamic acids mediated by (1-cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate (COMU)[11] and 1-propanephosphonic acid cyclic anhydride (T3P) as proficient promoters for the Lossen rearrangement (LR).[12] These hydroxamic acids are vital precursors for the LR to obtain ureas, carbamates and thiocarbamates.

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Address correspondence to H. S. Lalithamba, Department of Chemistry, Siddaganga Institute of Technology, B.H. Road, Tumakuru-572 103, Karnataka, India. E-mail: lalithambasit@yahoo.co.in

This article is dedicated to Dr. Sree Sree Sree Shivakumara Mahaswamiji, Siddaganga Math, Tumakuru, Karnataka, India.

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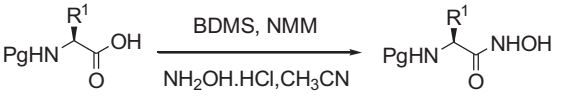
In this study, we report the application of bromodimethylsulfonium bromide (BDMS) for the synthesis of hydroxamic acids. The reagent BDMS is readily available and has numerous applications in synthetic chemistry. According to a literature survey, this reagent acts as a catalyst for numerous organic transformations and even as a brominating reagent.[13] The one-pot synthesis of α-aminophosphonates from aldehyde, amine and phosphite was established from the catalytic activity of BDMS.[14] Nitration of phenols with tetrabutylammonium nitrite in the presence of BDMS was reported.[15] BDMS was also employed for the synthesis of α-bromo-*β*-keto esters and α-bromoenones, from their corresponding keto esters and enones respectively.[16] One-pot multicomponent synthesis of functionalized piperidines using BDMS was reported.[17] BDMS was employed as an efficient and regioselective reagent for aromatic and heteroaromatic thiocyanation of ketones and *β*-dicarbonyl compounds in the presence of ammonium thiocyanate.[18] BDMS accelerated the synthesis of a xanthine,[19] acted as a brominating reagent for the conversion of anthracene into 9,10-dibromoanthracene[20] and promoted the ring opening reactions of epoxides and aziridines at room temperature.[21] Khan and others have developed the synthesis of 2,3-unsaturated *O*-glycosides using BDMS as pre-catalyst.[22] BDMS catalyzed the three-component synthesis of α-amino amidines from aldehydes, amines and isocyanides.[23] BDMS was used as a reagent for the synthesis of unsymmetrical ureas.[24] Further, it was found to be a useful reagent for the conversion of primary amides and aldoximes into nitriles.[25]

However, there are no reports for the synthesis of N^{α}-protected hydroxamic acids employing BDMS in peptide chemistry. In the present study BDMS was used for the synthesis of ureas and carbamates in one pot through LR by the transformation of the hydroxamic acid into its isocyanate[26] and then coupling with an amine or alcohol. Isocyanates can be obtained *via* the Hofmann rearrangement but the rearrangement is not well-suited with amino acid chemistry due to epimerization problems.[27] The LR of hydroxamic acids to isocyantes is also well known. Reagents such as N,N^{1}-dicyclohexyl carbodiimide,[28] N,N^{1}-carbonyldiimidazole[29] and cyanuric chloride[30] have been employed for the formation of isocyanates *via* LR. Thalluri and others reported the ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino) acetate-mediated LR for the synthesis of hydroxamic acids and ureas from carboxylic acids.[31] Some of the protocols mentioned here suffer due to reagent instability, longer reaction times, low yields or multiple steps; some could not be extended to *N*-Boc/Cbz-protected amino acids. The disadvantage of these reported protocols is mainly the accumulation of isocyanate before the complete activation of hydroxamic acid leading to the formation of by-product. Such a problem can be solved by the use of an efficient promoter for LR.

Herein, we report an efficient protocol for the synthesis of hydroxamic acids from N^{α}-Fmoc/Cbz/Boc amino acids using BDMS as an activating agent. BDMS was utilized for the formation of intermediate isocyanates and conversion of the latter into ureas and carbamates in one pot. The prepared hydroxamic acids were subjected to *in silico* molecular docking studies[32] and *in vitro* antibacterial activities.

For the synthesis of N^{α}-protected hydroxamic acids (**2,** *Scheme 1*), a protected amino acid was dissolved in acetonitrile. *N*-methylmorpholine (NMM) and BDMS were added at 0°C and the solution was stirred for about 15 min. Then was added hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) (neutralized by the NMM). The reaction mixture was stirred until the completion of the reaction as indicated by TLC. After a simple work up, the desired products were obtained in good yield. In this way several hydroxamic acids **(2a-2o)** were synthesized from N^{α}-protected Fmoc/Cbz/Boc amino acids



1 2

Pg = Fmoc/Boc or Cbz protecting group; R^1 = CH_3, $CH(CH_3)_2$, C_6H_5.

Scheme 1. Synthesis of N^{α}-protected hydroxamic acids.

Table 1
List of N^{α}-Protected Hydroxamic Acids Prepared following *Scheme 1*

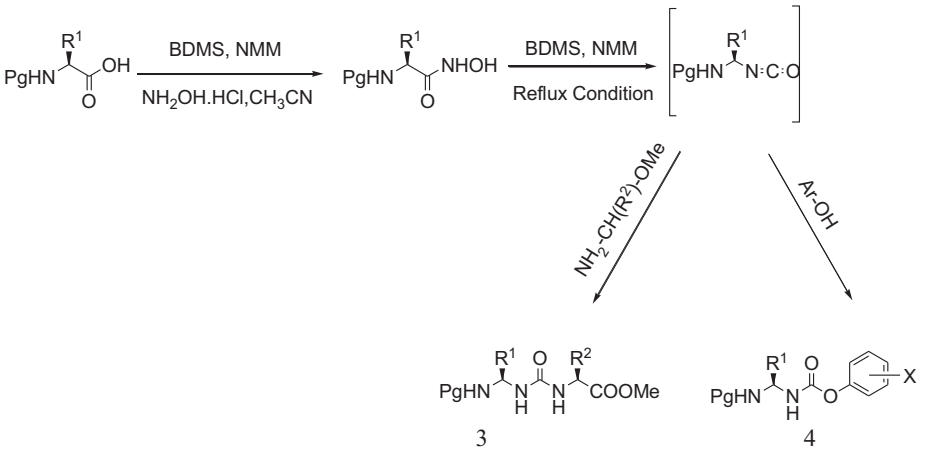
Entry	Hydroxamic acids	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$ in degrees
2a	N^{α}-Fmoc-Phe-NHOH	90	156	−0.012
2b	*N^{α}-Fmoc-Ala-NHOH	88	Gum	−0.043
2c	N^{α}-Fmoc-Tyr-NHOH	80	163	−0.008
2d	N^{α}-Fmoc-Pro-NHOH	82	141	−0.025
2e	N^{α}-Fmoc-Val-NHOH	87	Gum	−0.023
2f	N^{α}-Fmoc-Leu-NHOH	85	Gum	−0.021
2g	N^{α}-Fmoc-Ile-NHOH	84	118	−0.029
2h	N^{α}-Fmoc-Asp-NHOH	80	Gum	−0.028
2i	N^{α}-Fmoc-Glu-NHOH	86	Gum	−0.018
2j	N^{α}-Fmoc-Trp-NHOH	89	Gum	−0.006
2k	N^{α}-Cbz-Phe-NHOH	87	Gum	−0.020
2l	N^{α}-Cbz-Asp-NHOH	84	Gum	−0.014
2m	N^{α}-Cbz-Trp-NHOH	86	Gum	−0.079
2n	N^{α}-Boc-Phe-NHOH	80	128	−0.005
2o	N^{α}-Boc-Tyr-NHOH	81	146	−0.015

*ee for the product = 97.67%.

(*Table 1*). The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis.

The method was further extended for inserting the hydroxamic acid moiety into the side chains of Asp/Glu. The key intermediates, *N*-protected Asp/Glu-5-oxazolidinones, were prepared by treating *N*- protected amino acids with paraformaldehyde and a catalytic amount of *p*-toluene sulfonic acid in toluene under reflux conditions. This reaction was complete in 45 min as monitored by TLC. After the reaction, the mixture was diluted with ethyl acetate and washed with water and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and finally concentrated. The resulting residue was recrystallized using ethyl acetate and hexane. *N*-Protected Asp/Glu-5-oxazolidinones were treated with NMM and BDMS at 0°C. Then hydroxylamine hydrochloride was added. In the next step, the oxazolidinone ring was selectively saponified with 1 N LiOH to obtain the free α-COOH of Asp/Glu bearing hydroxamic acids in the side chains.

During the synthesis of the hydroxamates, the *O*-activation of hydroxamic acids takes a longer time than that required for carboxy activation, so that an excess of BDMS is required to drive the reaction towards completion. After the formation of the isocyanates, we aimed to trap these isocyanates with nucleophiles such as amines and alcohols. Ureas and carbamates were prepared starting from *N*-protected amino acids

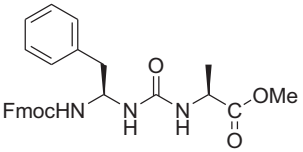
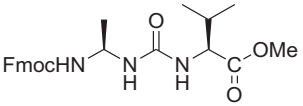
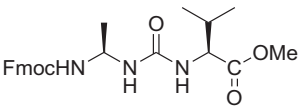
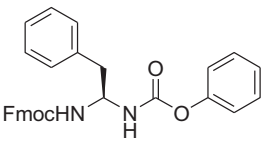
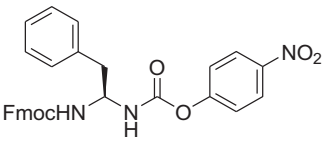
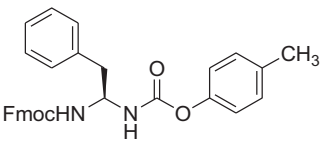


Pg = Fmoc/Boc or Cbz group;

R^1, R^2 = CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH_2(C_6H_5)$; X=CH_3, NO_2.

Scheme 2. Synthesis of N^{α}-protected ureas and carbamates.

Table 2
List of N^{α}-Protected Ureas and Carbamates Prepared following *Scheme 2*

Entry	N^{α}-protected Ureas and Carbamates	Yield (%)	Mp (°C)
3a		85	184
3b		90	180
3c		88	158
4a		90	Gum
4b		88	170
4c		86	Gum

along with BDMS and NMM in acetonitrile at 0°C for 15 minutes, then $NH_2OH{\cdot}HCl$ was added. The reaction mixture was stirred until the reaction was completed. BDMS and NMM were added again to the reaction mixture and it was subjected to reflux for an hour. Then, the intermediate isocyanate was treated with the amino acid ester to give the related ureidopeptide in good yields. The protocol was further extended to the synthesis of carbamates, in which the intermediate isocyanate was trapped with an alcohol/phenol and a simple workup led to isolation of pure ureas and carbamates (*Scheme 2*).

During this study, we also synthesized the set of enantiomeric *N*-Fmoc-L-Ala-NHOH (a) and *N*-Fmoc-D-Ala-NHOH (b). The synthesis of hydroxamic acids employing BDMS was found to be racemization-free as indicated by the chiral-HPLC. A single peak was observed at R_t 6.55 min for compound (a) and for its epimer (b) the R_t value was at 7.38 min. This confirms that the BDMS mediated synthesis of N^{α}-protected hydroxamic acids is a racemization free protocol. Results are summarized in *Table 2*.

In silico Studies

To evaluate the binding efficacy and inhibitory effects of the synthesized compounds, two protein targets from two different organisms, namely *Escherichia coli* in *Figure 1a* and *Staphylococcus aureus* in *Figure 1b*, were selected for the study. The X-ray crystallographic structure of enoyl-ACP reductase (1C14) *E. coli*[33] and X-ray crystallographic structure of dehydrosqualene synthase (2ZCP) *S. aureus* [34] respectively were obtained from the Protein Data Bank (PDB). The prepared targets were then used for a molecular docking study which predicts possible ligand interactions with the active site residues that can inhibit protein activity.

To perform the docking, the FlexX module of LeadIT software was used[35] and the LeadIT scores obtained after the docking were considered to obtain the free binding energy (ΔG). Based on the very low binding energy and maximum possible intermolecular interactions, the best lead compounds with strong binding efficacy were determined. Two dimensional structures of all the ligands were drawn in ChemDraw Ultra 8.0 and were exported as mol files for further processing in DS 3.5. The generated conformers were optimized using the CHARMm force field[36] and then minimized. The selected conformers were grouped into one library file and were subjected to docking. The FlexX docking score correlates with the binding affinity of the molecules with the target. The docking scores of hydroxamic acids with *E. coli* and *S. aureus* are tabulated in *Table 3 (a)* and *Table 3 (b)*.

The ligand Fmoc-Tyr-NHOH showed a minimum binding energy of −14.78 kcal/mol with *E. coli* and the ligand Fmoc-Trp-NHOH showed a minimum binding energy of −15.07 kcal/mol with *S. aureus*. *Figure 2* shows the pictorial representation of the binding modes of the synthesized molecules with the target proteins. All the listed molecules in *Table 3 (a)* and *Table 3 (b)* were evaluated for *in vitro* studies. The compounds Fmoc-Tyr-NHOH and Fmoc-Trp-NHOH showed significant antibacterial activities, in accordance with the *in silico* results.

In vitro Antibacterial Activity

The antibacterial activities of the synthetic compounds was screened by an agar well diffusion[37] assay against the pathogenic bacterial strains *E. coli* [NCIM-5051] gram negative and *S. aureus* [NCIM-5022] gram positive. Preliminary screening was done to check antibacterial activities of synthesized compounds over Mueller-Hinton agar plates.

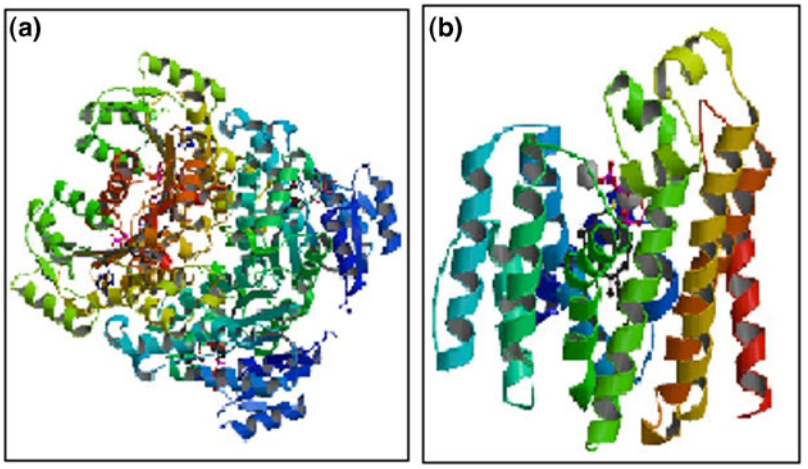


Figure 1. a. Crystal structure of *E. coli*. **b.** Crystal structure of *S aureus*.

Table 3
(a) Docking Results of Hydroxamic Acids with *E. coli (4V49)*

Entry	Compound name	*E. coli* Docking score (kcal/mol)
1.	Fmoc-Tyr-NHOH	−14.78
2.	Fmoc-Ala-NHOH	−14.42
3.	Fmoc-Phe-NHOH	−13.38
4.	Cbz-Trp-NHOH	−8.630
5.	Boc-Phe-NHOH	−8.016

Table 3
(b) Docking Results of Hydroxamic Acids with *S. aureus (1T2W)*

Entry	Compound name	*S. aureus* Docking score (kcal/mol)
1.	Fmoc-Trp-NHOH	−15.07
2.	Fmoc-Asp-NHOH	−14.88
3.	Fmoc-Val-NHOH	−14.81
4.	Cbz-Asp-NHOH	−14.18
5.	Fmoc-Pro-NHOH	−9.990

In case of *E. coli*, the synthesized hydroxamic acids Fmoc-Tyr-NHOH and Fmoc-Ala-NHOH showed a moderate zone of inhibition. The smallest zones of inhibition were for Fmoc-Phe-NHOH, Cbz-Trp-NHOH and Boc-Phe-NHOH. *S. aureus* strains exhibited significant inhibition for Fmoc-Trp-NHOH, Fmoc-Asp-NHOH, Fmoc-Val-NHOH and the least inhibition for Cbz-Asp-NHOH and Fmoc-Pro-NHOH.

In sum, an efficient conversion of *N*-protected amino acids into hydroxamates under reflux conditions using BDMS as carboxyl group activator was described. The BDMS was employed to mediate the LR. The *in situ* generated isocyanates were

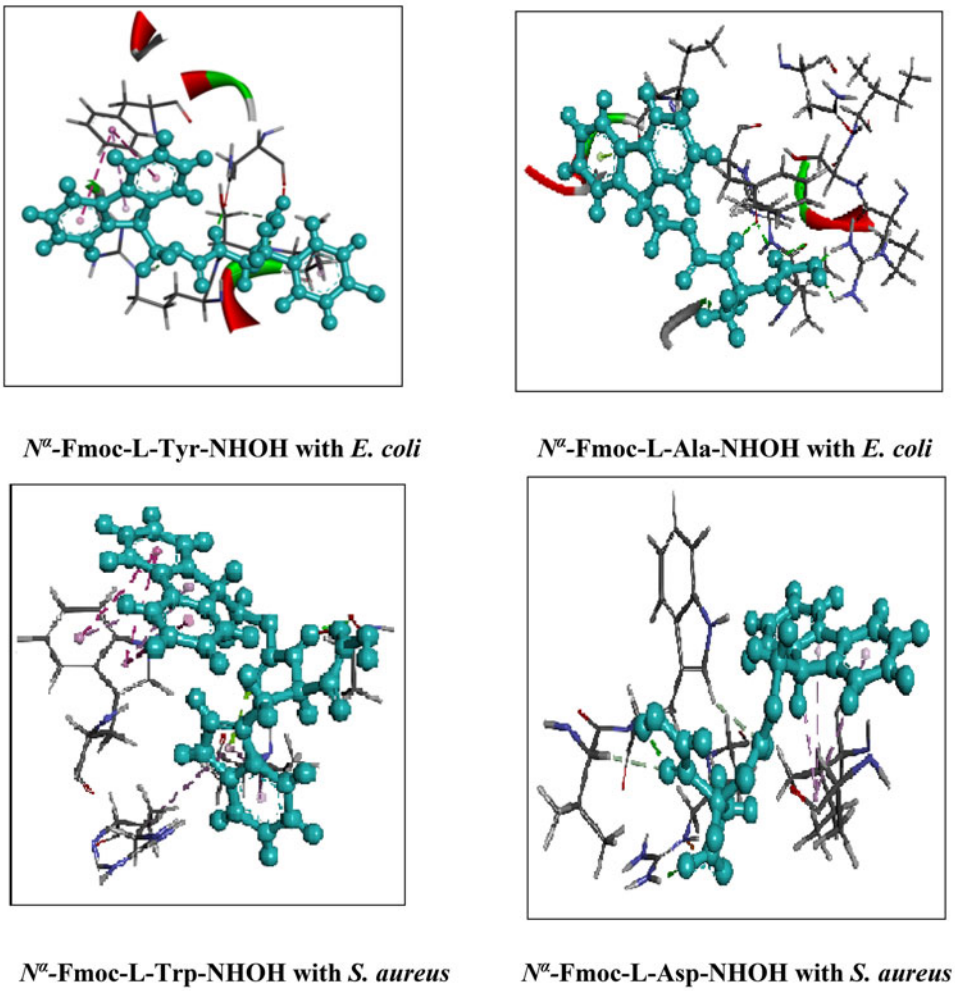


Figure 2. Pictorial representations of the binding modes of synthesized molecules with target proteins.

utilized to synthesize urea and carbamate derivatives in one pot. Docking and antibacterial studies were reported.

Experimental Section

General

All reactants were purchased from Sigma-Aldrich and Merck and used without purification. The solvents were distilled prior to use. Melting points were taken in open capillaries and are uncorrected. TLC analysis was carried out using precoated silica gel F_{254} plates. IR spectra were recorded on Bruker Alpha-T FT-IR spectrometer (KBr windows, $2\,cm^{-1}$ resolution). ^{1}H NMR and ^{13}C NMR spectra were done on a Bruker AMX 400 MHz spectrometer using Me_4Si as an internal standard and $CDCl_3$ as a solvent. Mass spectra were recorded on a Micromass Q-ToF Micro Mass Spectrometer. Optical

rotations were measured at 25°C using Rudolf research analytical, Autopol-II, Automatic Polarimeter. (Sodium-D-line 589 nm and C = 1). The Pathogenic bacterial strains were purchased from National Chemical Laboratory (NCL) Pune, India. We have prepared 21 new compounds as noted below.

Synthesis of Hydroxamic Acids (2a-2o)

To a solution of *N*-protected amino acid (1 mmol) in acetonitrile (10 mL), at 0°C, NMM (1.5 mmol) and BDMS (1.2 mmol) were added. The reaction mixture was stirred at the same temperature for 15 min, followed by the addition of $NH_2OH{\cdot}HCl$ (1.2 mmol) neutralized with NMM prior to the addition. The reaction mixture was stirred until the reaction was complete. The mixture was diluted with EtOAc (15 mL), washed with H_2O (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, the solvent was evaporated under reduced pressure to yield the product.

Ureidopeptide and Carbamate Synthesis (3a-3c and 4a-4c)

To a chilled (0°C) solution of *N*-protected amino acid (1 mmol) in acetonitrile (10 mL), NMM (1.5 mmol) and BDMS (1.2 mmol) were added. The reaction mixture was stirred at the same temperature for 15 min, followed by the addition of $NH_2OH{\cdot}HCl$ (1.2 mmol) neutralized with NMM prior to the addition. The reaction mixture was stirred for 60 minutes. BDMS (1.2 mmol) and NMM (1.5 mmol) were added to the reaction mixture and subjected to reflux for an hour. Then an amine or alcohol were added (1.2 mmol) to give urea or carbamate product respectively. Then, the solvent was removed under reduced pressure, the residue was diluted with EtOAc (15 mL) and the organic layer was washed with 10% HCl (10 mL), Na_2CO_3 (10 mL), H_2O (10 mL) and brine (10 mL), then dried over anhydrous Na_2SO_4. The solvent was evaporated to afford the product.

N*$^{\alpha}$*-Fmoc-Phe-NHOH: (2a) Yield 90%; Solid; Melting Point 156°C; IR: (KBr, cm^{-1}) 1640; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.08 (s, 1H), 2.91–3.12 (m, 2H), 4.40 (t, *J* 8.0 Hz, 1H), 4.75 (d, *J* 4.0 Hz, 2H), 4.98 (t, *J* 8.0 Hz, 1H), 5.05 (s, 2H), 7.10–7.77 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 37.0, 46.5, 51.25, 66.55, 126.0, 126.80, 127.80, 128.20, 128.40, 128.70, 128.80, 139.5, 141.0, 143.6, 156.0, 169.5. MS: Cald. for $C_{24}H_{22}N_2O_4$ *m/z*: 402.1578 (M^+ +Na), Found: 402.1576.

Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.45; N, 6.89.

N*$^{\alpha}$*-Fmoc-Ala-NHOH: (2b) Yield 84%, Gum. IR (KBr): 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (d, *J* 8.0 Hz, 3H), 1.99 (s, 1H), 4.22 (m, 1H), 4.41 (t, *J* 8.0 Hz, 2H), 5.0 (s, 2H), 5.36 (s, 1H), 7.26-7.77 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.73, 47.13, 47.20, 67.04, 120.01, 125.10, 127.09, 127.73, 141.35, 141.82, 156.0, 169.50. MS: Cald. for $C_{18}H_{18}N_20_4$ *m/z*: 326.1267 (M^+ +Na), Found: 326.1265.

Anal. Calcd for $C_{18}H_{18}N_20_{4:}$ C, 66.25; H, 5.56; N, 8.58. Found: C, 66.32; H, 5.51; N, 8.63.

N*$^{\alpha}$*-Fmoc-Tyr-NHOH: (2c) Yield 80%, Solid, Melting Point 163°C. IR (KBr): 1651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.75 (s, 2H), 2.81 (m, 2H), 4.27 (t, *J*

8.0 Hz, 1H), 4.85 (s, 2H), 6.0 (s, 1H), 6.10 (s, 2H), 6.80–7.10 (m, 4H), 7.30–7.85 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.52, 47.0, 51.25, 67.85, 119.82, 126.80, 128.20, 128.45, 128.69, 129.20, 141.0, 143.60, 155.70, 156.68, 169.50. MS: Cald. for $C_{24}H_{22}N_2O_5$ *m/z*: 418.1529 (M^+ +Na), Found: 418.1531.

Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.78; H, 5.27; N, 6.53.

N$^{\alpha}$-Fmoc-Pro-NHOH: (2d) Yield 82%, Solid, Melting Point 141°C. IR (KBr): 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.9 (m, 2H), 1.30 (m, 2H), 1.92 (s, 1H), 2.75 (m, 2H), 4.27 (t, *J* 4.0 Hz, 1H), 4.50 (br, 1H), 4.70 (d, *J* 8.0 Hz, 2H), 5.05 (s, 1H), 7.30–7.79 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 28.56, 47.0, 48.15, 48.66, 66.90, MS: Cald. for $C_{20}H_{20}N_2O_4$ *m/z*: 352.1423 (M^++Na), Found: 352.1420.

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.09; H, 5.61; N, 7.83.

N$^{\alpha}$-Fmoc-Val-NHOH: (2e) Yield 87%, Gum. IR (KBr): 1635 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.97-0.99 (d, *J* 8.0 Hz, 6H), 2.0 (s, 1H), 2.16 (m, 1H), 4.28 (m, 1H), 4.35 (m, 1H), 4.43 (d, *J* 4.0 Hz, 2H), 5.30 (br, 2H), 7.26–7.77 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.63, 31.31, 47.22, 59.04, 67.04, 115.98, 125.0, 127.06, 127.70, 141.32, 143.79, 156.0, 168.58. MS: Cald. for $C_{20}H_{22}N_2O_4$ *m/z*: 354.1580 (M^++Na), Found: 354.1582.

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.22; N, 8.02.

N$^{\alpha}$-Fmoc-Leu-NHOH: (2f) Yield 85%, Gum. IR (KBr): 1642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.94 (d, *J* 4.0 Hz, 6H), 1.1–1.40 (m, 3H), 1.51–1.80 (m, 1H), 2.03 (s, 1H), 4.10–4.20 (m, 1H), 4.23-4.39 (t, *J* 8.0 Hz, 1H), 4.58 (d, *J* 4.0 Hz, 2H), 5.98–6.0 (t, *J* 8.0 Hz, 1H), 7.24–7.75 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.83, 22.78, 41.69, 47.16, 52.44, 66.92, 120.07, 126.46, 127.64, 130.01, 141.40, 143.76, 155.97, 173.67. MS: Cald. for $C_{21}H_{24}N_2O_4$ *m/z*: 368.1736 (M^++Na), Found: 368.1732.

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.37; H, 6.51; N, 7.51.

N$^{\alpha}$-Fmoc-Ile-NHOH: (2g) Yield 84%, Solid, Melting Point 118°C. IR (KBr): 1638 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.92 (br, 3H), 1.25 (s, 3H), 1.61 (br, 2H), 1.92 (s, 1H), 2.04 (m, 1H), 4.32 (m, 1H), 4.40 (m, 1H), 4.60 (s, 2H), 5.28 (br, 2H), 7.29–7.77 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 10.90, 14.65, 24.70, 36.84, 47.75, 53.86, 67.40, 127.11, 128.20, 128.35, 128.86, 141.0, 143.66, 156.0, 168.69. MS: Cald. for $C_{21}H_{24}N_2O_4$ *m/z*: 368.1736 (M^+ +Na), Found: 368.1730.

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.40; H, 6.49; N, 7.64.

N$^{\alpha}$-Fmoc-Asp-NHOH: (2h) Yield 80%, Gum. IR (KBr): 1648 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.98 (s, 1H), 4.43 (t, *J* 12.0 Hz, 1H), 4.48 (d, *J* 8.0 Hz, 2H), 5.0 (s, 1H), 5.65 (s, 2H), 6.0 (s, 1H), 7.28–7.8 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.6, 66.7, 68.5, 77.2, 126.4, 128.0, 128.4, 128.6, 140.0, 142.8, 152.8, 166.0, 170.9. MS: Cald. for $C_{19}H_{16}N_2O_6$ *m/z*: 391.100 (M^++Na), Found: 391.1002.

Anal. Calcd for $C_{19}H_{16}N_2O_6$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.90; H, 4.29; N, 7.54.

N^{α}-Fmoc-Glu-NHOH: (2i) Yield 86%, Gum. IR (KBr): 1690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.85 (s, 1H), 2.60 (d, *J* 8.0 Hz, 2H), 4.4 (t, *J* 12.0 Hz, 1H), 4.6 (t, *J* 12.0 Hz, 1H), 4.7 (d, *J* 8.0 Hz, 2H), 5.67 (s, 2H), 6.0 (s, 1H), 7.2–7.75 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 26.5, 46.8, 53.7, 66.9, 77.4, 126.0, 127.9, 128.2, 128.8, 141.0, 143.4, 154.7, 170.6, 174.5. MS: Cald. for $C_{20}H_{18}N_2O_6$ *m/z*: 405.12 (M^++Na), Found: 405.1180.

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.73; H, 4.68; N, 7.44.

N^{α}-Fmoc-Trp-NHOH: (2j) Yield 89%, Gum. IR (KBr): 1656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 1H), 3.25 (d, *J* 8.0 Hz, 2H), 4.35 (s, 1H), 4.42 (d, 2H), 4.90 (t, 1H), 5.00 (s, 3H), 6.09 (s, 1H), 7.26–7.71 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.24, 47.65, 52.15, 67.46, 110.9, 111.35, 118.86, 120.28, 122.20, 122.76, 126.80, 127.45, 128.20, 128.45, 128.80, 136.50, 141.0, 143.68, 156.0, 168.78. MS: Cald. for $C_{26}H_{23}N_3O_4$ *m/z*: 441.1689 (M^++Na), Found: 441.1688.

Anal. Calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H, 5.25; N, 9.52. Found: C, 70.68; H, 5.16; N, 9.45.

N^{α}-Cbz-Phe-NHOH: (2k) Yield 82%, Gum. IR (KBr): 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.78 (s, 1H), 3.24 (m, 2H), 4.38 (m, 1H), 5.24 (s, 2H), 5.50 (br, 2H), 7.24–7.51 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.89, 52.36, 67.03, 127.17, 128.22, 128.65, 129.30, 135.80, 136.29, 155.78, 159.37, 172.73, 173.40. MS: Cald. for $C_{17}H_{18}N_2O_4$ *m/z*: 314.1267 (M^++Na), Found: 314.1269.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.03; H, 5.64; N, 8.82.

N^{α}-Cbz-Asp-NHOH: (2l) Yield 84%, Gum. IR (KBr): 1655 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.0 (s, 1H), 5.3 (s, 2H), 5.38 (s, 1H), 5.64 (s, 2H), 6.0 (s, 1H), 7.18 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 65.6, 68.4, 77.2, 127.4, 127.6, 128.9, 154.4, 166.0, 170.8. MS: Cald. for $C_{12}H_{12}N_2O_6$ *m/z*: 303.07 (M^++Na), Found: 303.0670.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.32; H, 4.24; N, 10.08.

N^{α}-Cbz-Trp-NHOH: (2m) Yield 86%, Gum. IR (KBr): 1658 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.14 (s, 1H), 3.04 (s, 2H), 4.26 (s, 1H), 4.89 (m, 2H), 4.99 (s, 3H), 6.82–7.93 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.20, 50.27, 65.90, 110.86, 111.08, 119.26, 120.0, 122.15, 122.90, 127.25, 127.56, 127.80, 129.05, 136.43, 141.28, 156.98, 168.70. MS: Cald. for $C_{19}H_{19}N_3O_4$ *m/z*: 353.2176 (M^++Na), Found: 353.2174.

Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.46; H, 5.37; N, 11.77.

N^{α}-Boc-Phe-NHOH: (2n) Yield 80%, Solid, Melting Point 128°C. IR (KBr): 1639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.39 (s, 9H), 2.27 (s, 1H), 3.09 (m, 2H), 4.33 (m, 1H), 4.95 (br, 2H), 7.18–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.25, 37.50, 51.17, 72.55, 126.0, 127.85, 128.69, 139.44, 156.0, 169.48. MS: Cald. for $C_{14}H_{20}N_2O_4$ *m/z*: 280.1423 (M^++Na), Found: 280.1422.

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.87; H, 7.11; N, 9.87.

N$^{\alpha}$-Boc-Tyr-NHOH: (2o) Yield 81%, Solid, Melting Point 146°C. IR (KBr): 1643 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.41-1.60 (m, 9H), 1.76 (m, 2H), 3.14 (d, *J* 4.0 Hz, 2H), 4.34 (m, 1H), 5.00 (s, 2H), 6.75–6.81 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.27, 37.56, 64.91, 79.50, 115.51, 121.33, 130.42, 155.0, 155.68, 169.43. MS: Cald. for $C_{14}H_{20}N_2O_5$ *m/z*: 296.1372 (M^++Na), Found: 296.1368.

Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.67; H, 6.73; N, 9.34.

N$^{\alpha}$-Fmoc-Phe-ψ[NHCONH]-Ala-OMe: (3a) Yield 83%; Solid; Melting Point 185°C; IR: (KBr, cm^{-1}) 3355; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.83 (s, 3H), 3.40 (m, 2H,), 3.39 (s, 3H), 4.32 (m, 1H), 4.58 (d, *J* 6.6 Hz, 1H), 4.75 (d, *J* 10.0 Hz, 2H, 5.02 (br, 3H), 5.82 (t, *J* 8.0 Hz,1H), 7.20–7.85 (m, 13H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.05, 38.0, 46.54, 48.9, 51.86, 62.12, 66.30, 120.55, 125.54, 126.90, 127.51, 128.2, 128.81,129.53, 138.42, 141.56, 144.51, 156.8, 157.40,174.0. MS: Cald. for $C_{28}H_{29}N_3O_5$ *m/z*: 510.2005 ($M + Na^+$), found 510.2005.

Anal. Calcd for $C_{28}H_{29}N_3O_5$: C, 68.98; H, 6.00; N, 8.62. Found: C, 68.90; H, 5.93; N, 8.56.

N$^{\alpha}$-Fmoc-Ala-ψ[NHCONH]-Val-OMe: (3b) Yield 90%; Solid; Melting Point 182°C; IR: (KBr, cm^{-1}) 3288; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.01 (br, 6H), 1.16-1.94 (br, 3H), 3.05 (m. 1H), 3.55 (s, 3H), 4.0 (d, *J* 12.0 Hz, 1H), 4.15–4.24 (br, 1H), 4.51–4.82 (br, 2H), 5.13 (br, 1H), 6.31-6.37 (br, 3H), 7.22-7.94 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 18.34, 20.75, 31.28, 45.18, 51.35, 53.82, 59.74, 66.15, 126.53, 126.81, 127.12, 128.39, 141.12, 144.23, 156.02, 157.23, 174.12. MS: Cald. for $C_{24}H_{29}N_3O_5$ *m/z*: 462.2005 ($M + Na^+$), found 462.2008.

Anal. Calcd for $C_{24}H_{29}N_3O_5$: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.50; H, 6.76; N, 9.63.

N$^{\alpha}$-Fmoc-Leu-ψ[NHCONH]-Ala-OMe: (3c) Yield 86%; Solid, Melting Point 161°C; IR: (KBr, cm^{-1}) 3271; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.96 (t, *J* 10.0 Hz, 3H), 1.10 (d, *J* 6.0 Hz, 6H), 1.22 (d, *J* 10.0 Hz, 3H), 1.38 (m, 2H), 2.90 (m, 1H), 3.14 (m, 1H), 3.65 (s, 3H), 4.09 (t, *J* 8.0 Hz, 1H), 4.45 (t, *J* 12.0 Hz, 1H), 4.80 (d, *J* 8.0 Hz, 2H), 5.66 (m, 1H), 6.0 (br, 3H), 7.25–7.85 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.65, 12.35, 17.20, 22.48, 30.13, 38.8, 47.3, 51.7, 57.6, 65.9, 67.8, 126.8, 128.4, 128.6, 128.8, 140.9, 143.8, 156.2, 157.9, 170.8. MS: Calc. for $C_{27}H_{35}N_3O_5$ *m/z*: 504.25 ($M + Na^+$), found 504.2214.

Anal. Calcd for $C_{27}H_{35}N_3O_5$: C, 67.34; H, 7.33; N, 8.73. Found: C, 67.46; H, 7.14; N, 8.67.

N$^{\alpha}$-Fmoc-Phe-ψ[NHCO]-OC$_6$H$_5$: (4a) Yield 90%, Gum, IR (KBr): 1638 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.8 (t, *J* 8.0 Hz, 2H), 4.45 (m, 1H), 4.59 (d, *J* 6.0 Hz, 2H), 6.0 (s, 3H), 7.03–7.8 (m, 18H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 42.2, 45.0, 63.23, 67.38, 121.4, 125.6, 126.0, 126.65, 127.46, 128.2, 128.38, 128.7, 128.85, 129.2, 139.0, 141.0, 143.7, 151.5, 155.8. MS: Cald. for $C_{30}H_{26}N_2O_4$ *m/z*: 501.19 (M^++Na), Found: 501.1890.

Anal. Calcd for $C_{30}H_{26}N_2O_4$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.40; H, 5.59; N, 5.76.

N$^{\alpha}$-Fmoc-Phe-ψ[NHCO]-OC$_6$H$_5$NO$_2$: (4b) Yield 88%, Solid, Melting Point 170°C IR (KBr): 1656 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.95 (t, *J* 8.0 Hz, 2H), 4.38 (t, *J* 12.0 Hz, 1H), 4.79 (d, *J* 6.0 Hz, 2H), 6.0 (s, 5H), 7.1–7.84 (m, 15H). ^{13}C

Table 4
Antibacterial Test for Protected Hydroxamic Acids with *E. coli* & *S. aureus*

Sample	Treatment (Concentration in μg/μL)	*E. coli* (Mean ± SE)	Sample	Treatment (Concentration in μg/μL)	*S. aureus* (Mean ± SE)
Ciprofloxacin	5	10.13 ± 0.06	Ciprofloxacin	5	11.13 ± 0.03
Fmoc-Tyr-NHOH	500	1.53 ± 0.03	Fmoc-Trp-	500	3.17 ± 0.03
	1000	3.37 ± 0.07	NHOH	1000	5.90 ± 0.06
Fmoc-Ala-NHOH	500	1.03 ± 0.03	Fmoc-Asp-	500	2.00 ± 0.03
	1000	2.40 ± 0.06	NHOH	1000	3.60 ± 0.06
Fmoc-Phe-NHOH	500	1.07 ± 0.03	Fmoc-Val-	500	1.40 ± 0.06
	1000	2.03 ± 0.03	NHOH	1000	3.13 ± 0.03
Cbz-Trp-NHOH	500	0.53 ± 0.03	Cbz-Asp-	500	Inactive
	1000	1.23 ± 0.03	NHOH	1000	2.17 ± 0.09
Boc-Phe-NHOH	500	In active	Fmoc-Pro-	500	1.23 ± 0.12
	1000	1.10 ± 0.06	NHOH	1000	2.13 ± 0.09

NMR (100 MHz, DMSO-d_6): δ (ppm) 41.5, 47.0, 63.4, 66.8, 121.5, 122.8, 126.0, 126.5 126.8, 127.4, 128.2, 128.4, 128.8, 129.0, 139.5, 141.0, 143.4, 145.2, 154.6, 156.0, 157.5. MS: Cald. for $C_{30}H_{25}N_3O_6$ *m/z*: 546.17 (M^++Na), Found: 546.1681

C, H, N

Anal. Calcd for $C_{30}H_{25}N_3O_6$: C, 68.82; H, 4.81; N, 8.03. Found: C, 68.93; H, 4.90; N, 7.94.

N^{α}-Fmoc-Phe-ψ[NHCO]-$OC_6H_5CH_3$: (4c) Yield 86%, Gum, IR (KBr): 1660 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.36 (d, *J* 6.0 Hz, 3H), 2.9 (d, *J* 6.0 Hz, 2H), 4.38 (t, *J* 8.0 Hz, 1H) 4.66 (d, *J* 6.0 Hz, 2H), 6.0 (s, 3H), 6.95–7.84 (m, 17H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 24.5, 42.2, 46.8, 63.4, 67.6, 121.5, 126.0, 126.5, 127.8, 128.0, 128.2, 128.6, 128.8, 129.5, 135.0, 139.8 141.1, 143.5, 148.2, 154.6, 155.8. MS: Cald. for $C_{31}H_{28}N_2O_4$ *m/z*: 515.2 (M^++Na), Found: 515.2001.

Anal. Calcd for $C_{31}H_{28}N_2O_4$: C, 75.59; H, 5.73; N, 5.69. Found: C, 75.64; H, 5.85; N, 5.60.

In silico Studies

The purpose of the study was to analyze the inhibitory action of the synthesized hydroxamic acids by computational docking. Such *in silico* methods are extremely useful to find out potential binding sites and also to discover new molecules that could bind to a known site. In this study, the target protein and hydroxamic acid molecule were optimized by drug discovery studio version 3.5 software available from Accelrys Discovery Studio.

In vitro Antibacterial Activity

Agar plates were inoculated with a standardized inoculum of the test microorganism. Then, the test compound at a desired concentration was placed on the agar surface and petri dishes were incubated under appropriate conditions. Generally, the antimicrobial

agent diffuses into the agar and inhibits the growth of test microorganism and then the diameters of inhibition growth zones are measured.

The nutrient medium was prepared by dissolving 37.0 g of nutrient agar medium in 1000 ml of distilled water and adjusting pH to 7.3 (±0.1), subjecting it to sterilization in an autoclave at 121°C for 15–30 min. Nutrient agar plates were prepared and 20–25 ml of sterile nutrient agar medium was poured into sterile petri-dishes and allowed to solidify. Then, 100 µl of mature broth culture of individual pathogenic bacterial strains was spread all over the surface of agar plates using sterilized L-shaped glass rod. About 6 mm well are made in each nutrient agar plate using sterile cork borer. Different concentrations of synthetic compounds were used to assess the dose dependent activity of the product. Antibacterial activity for listed molecules in *Table 3 (a)* and *Table 3 (b)* were carried out. At two different concentrations 500 µg/µL and 1000 µg/µL of synthesized molecules, the inhibition zones were measured using vernier callipers in mm and its values were depicted in *Table 4*. Simultaneously the standard antibiotic (Ciprofloxacin used as a positive control) was tested against the pathogenic bacterial strains. Then, the plates were incubated at 37°C for 36 h. After incubation, the zone of inhibition of each well was measured and the values were recorded. The experiments were carried out in triplicates with each compound and the average values were calculated for determining the antibacterial activity.

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