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Synthesis and antibacterial screening of some novel cinnamic acid derivatives

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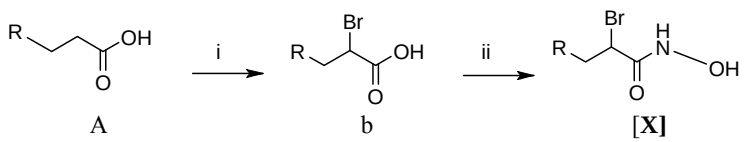
Abstract
A series of cinnamic acid derivatives (TA1–TA12) were synthesized and tested for their *in vitro* antibacterial activity against different strains of bacteria. Ampicillin anitibiotic is taken as standard for antibacterial activity. This study found that out of 12 synthesized compounds 6 compounds namely TA1, TA4, TA5, TA7, TA8, TA11 showed good activity against different microorganism strains as compared to standard drug. Amongst the six compounds, it is further found that compounds TA5, TA8 and TA11 having 4-hydroxy group in their structure showed best antibacterial activity as compared to standard.

Keywords: Cinnamic acid, Anti-bacterial

1. Introduction
In nineteenth century, scientists discovered that microorganisms were the leading cause of several infections. In search of curing these infections, antibacterial drugs and then antibiotics were discovered. They saved many patients suffering from infections/diseases like pneumonia, rheumatic fever, bacterial meningitis etc. Despite saving many lives each year, their overuse and misuse reduced efficacy of these antibiotics, leading to development of bacterial resistance. The need to invent more and more antibiotics arose due to the development of resistance. Further search led to the advent of antibiotics to provide efficacious and safe therapy to the patients. The newer antibiotics were developed to broaden antimicrobial spectrum with better potency and minimal associated side effects. The present study was undertaken to synthesize novel antibacterial compounds against different strains of bacteria [1-3].

2. Experimental
2.1 General
All reagents were obtained from Sigma Aldrich and Loba Chem Ltd. [India]. All the solvents used in this study were dried and distilled before use. Sineo, Microwave Chemistry Instrument, (Shanghai Sineo Microwave Chemistry Tech. Co. Ltd., China) was used to perform the microwave assisted reaction. Melting point [m.p.]: was determined using Veego VMP-PM digital melting point apparatus. Thin layer chromatography (TLC) was used for monitoring the progress of the reactions and purity was checked by TLC single spot study on uniform silica gel (silica gel-G) layer. KBr pellet method was used for recording infrared (IR) spectra on Shimadzu FTIR spectrophotometer. Bruker Avance II 300 MHz NMR Spectrophotometer was used for recording of ^{1}H-NMR spectra using appropriate deuterated DMSO (Dimethyl sulfoxide) as solvent and reported as chemical shift in Parts per million (δ, ppm).

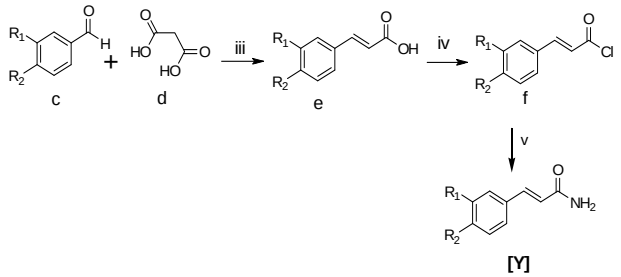
2.2 Synthesis
The cinnamic acid derivatives were synthesized by a multistep synthetic route as presented in Scheme 1, 2 and 3.



A b [X]

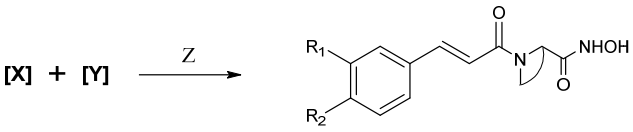
Scheme 1: Synthesis of aliphatic carboxylic acid derivatives.

Reagents and conditions
(i) Br_2, PCl_3, 4 hours.
(ii) NH_2OH, 30 min.
R= -Br (A-1), $-CH_2Br$ (A-2), $-CH_2CH_2Br$ (A-3)



Scheme 2: Synthesis of caffeoyl amides.

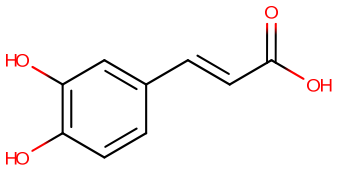
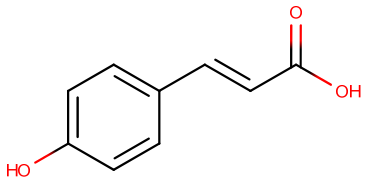
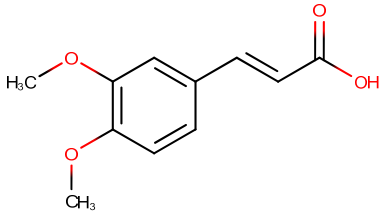
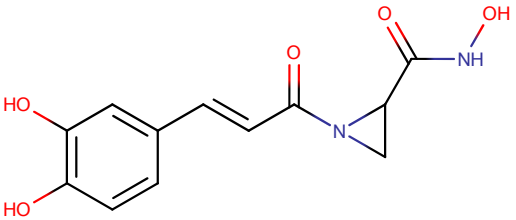
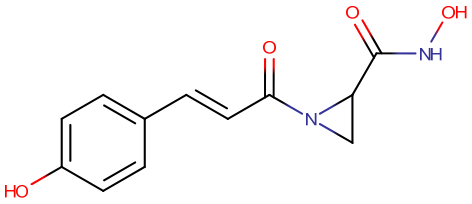
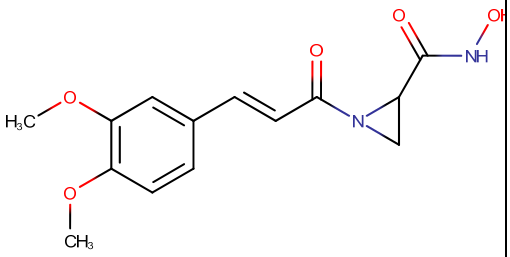
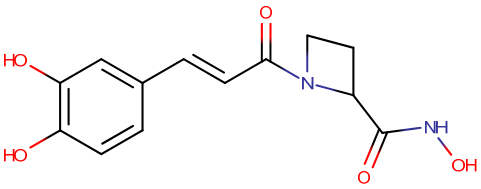
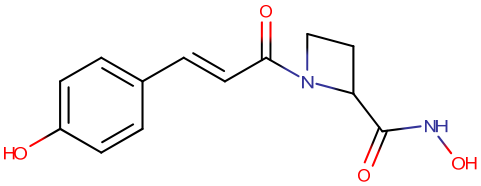
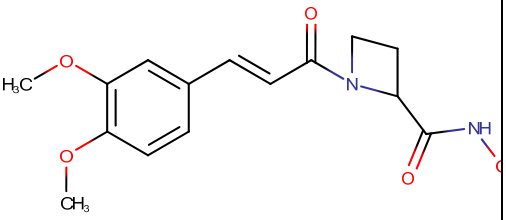
Reagents and conditions
(iii) Pyridine, aniline, 55 ^{0}C, 3 hours.
(iv) $SOCl_2$, 4 hours
(v) NH_3, 3 hours.
R_1= -OH, R_2= -OH (C-1), R_1= -H, R_2= -OH (C-2), R1= -OCH_3, R_2= -OCH_3 (C-3).

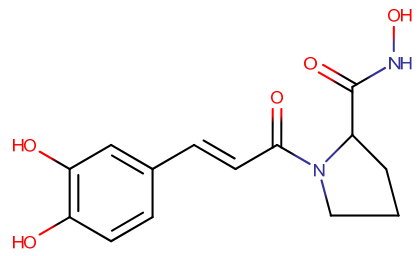
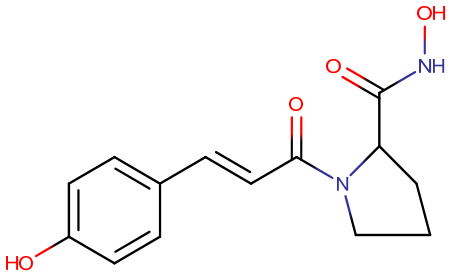
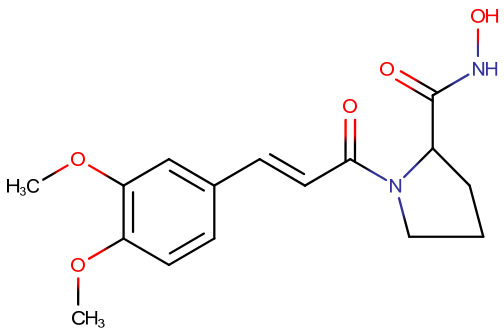


Scheme 3: Synthesis of caffeic acid derivatives.

Reagents and conditions: (z) 120 ^{0}C, K_3CO_3, 90 Watts, Microwave, 20 min.

2.3 Compouds Synthesised

Compound	Structure & IUPAC Name
TA1.	 (2E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid
TA2.	 (2E)-3-(4-hydroxyphenyl)prop-2-enoic acid
TA3.	 (2E)-3-(3,4-dimethoxyphenyl)prop-2-enoic acid
TA4.	 N-hydroxy-1-[(2E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]aziridine-2-carboxamide
TA5.	 N-hydroxy-1-[(2E)-3-(4-hydroxyphenyl)prop-2-enoyl]aziridine-2-carboxamide
TA6.	 N-hydroxy-1-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]aziridine-2-carboxamide
TA7.	 N-hydroxy-1-[(2E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]azetidine-2-carboxamide
TA8.	 N-hydroxy-1-[(2E)-3-(4-hydroxyphenyl)prop-2-enoyl]azetidine-2-carboxamide
TA9.	 N-hydroxy-1-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]azetidine-2-carboxamide

TA10.	 N-hydroxy-1-[(2E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]pyrrolidine-2-carboxamide
TA11.	 N-hydroxy-1-[(2E)-3-(4-hydroxyphenyl)prop-2-enoyl]pyrrolidine-2-carboxamide
TA12.	 N-hydroxy-1-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]pyrrolidine-2-carboxamide

2.4 General procedure for synthesis of phenyl butyric acid derivatives

Different acids were (0.01mol) kept in flask with molecular bromine (0.011mol) and when temperature reached at 65 ^{0}C, phosphorous trichloride (catalyst) was added. Then temperature was raised to 100 ^{0}C and mixture was refluxed for 4 hours to get (b). Then hydroxylamine (0.03mol) was added, toluene was used as solvent and system was refluxed for 30 minutes. In the end, toluene was evaporated using Schott Biotec Rotary evaporator and respective [X] was collected [4].

2.5 General procedure for preparation of caffeoyl amide derivatives

3, 4-dihydroxybenzaldehyde**(c)** (0.1mol) and malonic acid **(d)** (0.22mol) was added to 50 ml of dry pyridine, containing 1.4g of aniline, to form a solution. This solution was allowed to stand overnight, followed by heating for 3 hours at 55 ^{0}C in order to remove carbon dioxide. Reaction mixture was then poured into the mixture of 60 ml of concentrated hydrochloric acid and 100g of chopped ice. The acid precipitated immediately which was allowed to stand for few minutes for complete separation. The filtration was done. The product was washed using 10 ml of 5% hydrochloric acid and then with two portions of 10 ml water. At the end, drying of residue was carried out at room temperature. Substituted cinnamic acid (e) (0.1 mol) was refluxed with $SOCl_2$ (0.11 mol) for 4 hours. Thereafter, ammonia (1.0 mol) was added to the mixture containing (f) and system was further refluxed for 3 hours. The collection of caffeoyl amide derivatives was carried out. [5]

2.6 General procedure to synthesize final products

Respective [X] (1.1mmol) was mixed with [Y] (1.0 mmol). Potassium carbonate (1.1 mmol) was added as a catalyst. This step was performed by using microwave. The temperature was set at 120 ^{0}C, power was maintained at 90 watts and duration of reaction was set as 20 minutes. At the end, solvent was removed using Schott Biotec Rotary evaporator [6]

2.7 Physicochemical and Spectral Characterization

TA1)

Yield: 62%; mp: 211-213 °C; IR ν cm^{-1}: 3433, 3420, 3232, 3026, 2954, 2864, 1695, 1654. ^{1}HNMR (δppm, DMSO):7.55 (1 H, d, CH), 7.07 (1 H, d, ArH), 6.95 (1 H, dd, ArH), 6.81 (1 H, d, ArH), 6.24 (1 H, d, CH), 5.35 (2H, s, OH), 11 (1H, s, OH).

TA2)

Yield: 67%; mp: 213-215 °C; IR ν cm^{-1}: 3436, 3239, 30267 2944, 2872, 1672, 1634.
^{1}HNMR (δppm, DMSO):7.45 (1 H, d, CH), 7.56 (2H, d, ArH), 6.65 (2 H, d, J = 8.2, 2.0 Hz, ArH), 6.33 (1 H, d, J = 15.9 Hz, CH), 5.42 (1H, s, OH), 11.06 (1H, s, OH).

TA3)

Yield:65%; mp:181-183°C; IR ν cm^{-1}: 3439, 3242, 3022, 2964, 2853, 1690, 1647^{1}HNMR (δppm, DMSO):7.63 (1 H, s, CH), 7.22 (1 H, d, ArH), 6.89 (1 H, dd, ArH), 7.18 (1 H, d, ArH), 6.45 (1 H, d, CH), 3.83 (6H, s, CH_3), 10.94 (1H, s, OH).

TA4)

Yield: 56%;mp: 164-166 °C;IR ν cm^{-1}: 3432, 3422, 3234, 3028, 2956, 2862, 1693, 1656, ^{1}HNMR (δppm, DMSO):7.32 (1 H, s, CH), 7.17 (1 H, d, ArH), 6.93 (1 H, dd, ArH), 6.79 (1 H, d, ArH), 7.03 (1 H, d, CH), 5.32 (2H, s, OH), 1.98-1.73 (2H, d, CH_2), 3.15 (1H, m, CH), 8.13 (1H, s, NH), 2.1 (1H, s, OH).

TA5)

Yield: 62%; mp: 156-158°C;IR ν cm^{-1}: 3431, 3418, 3230, 3028, 2952, 2866, 1697, 1659, ^{1}HNMR (δppm, DMSO):7.28 (1 H, d, CH), 7.61 (2 H, d, ArH), 6.73 (2 H, dd, ArH), 7.11 (1 H, d, CH), 5.45 (1H, s, OH), 1.78-1.88 (2H, d, CH_2), 3.23 (1H, m, CH), 8.06 (1H, s, NH), 1.98 (1H, s, OH).

TA6)

Yield: 45%;mp:161-163 °C;IR ν cm^{-1}: 3439, 3426, 3238, 3032, 2960, 2871, 1701, 1655^{1}HNMR (δppm, DMSO):7.28 (1 H, d, CH), 7.25 (1 H, s, ArH), 6.97 (1 H, d, ArH), 7.16 (1 H, d, ArH), 7.08 (1 H, d, CH), 2.02,1.81 (2H, s, CH_2) 3.22 (1H, m, CH), 3.82 (6H, s, CH_3), 8.04 (1H, s, NH), 2.06 (1H, s, OH).

TA7)

Yield: 61%;mp: 155-157 °C;IR ν cm^{-1}: 3427, 3414, 3226, 3020, 2948, 2858, 1689, 1648^{1}HNMR (δppm, DMSO):: 7.29 (1 H, d, CH), 7.15 (1 H, s, ArH), 6.88 (1 H, d, ArH), 6.76(1 H, d, ArH), 7.08 (1 H, d, CH), 5.35 (2H, s, OH), 3.59,3.49

(2H, m, CH_2), 2.60,2.35 (2H, m, CH_2) 5.08 (1H, m, CH), 8.11 (1H, s, NH), 2.1 (1H, s, OH).

TA8)
Yield: 68%; mp: 165-167 °C;IR ν cm^{-1}: 3433, 3420, 3232, 3026, 2954, 2864, 1695, 1654^{1}HNMR (δppm, DMSO):7.36 (1 H, d, CH), 7.61 (2 H, d, ArH), 6.78 (2 H, dd, ArH), 7.05 (1 H, d, CH), 5.40 (1H, s, OH), 3.57,3.46 (2H, m, CH_2), 2.57,2.33 (2H, m, CH_2) 5.23 (1H, m, CH), 8.03 (1H, s, NH), 2.4 (1H, s, OH).

TA9)
Yield: 52%; mp: 145-147 °C;IR ν cm^{-1}: 3443, 3430, 3242, 3036, 2964, 2874, 1685, 1664^{1}HNMR (δppm, DMSO):7.37 (1 H, d, CH), 7.22 (1 H, s, ArH), 6.94 (1 H, d, ArH), 7.18 (1 H, d, ArH), 7.04 (1 H, d, CH), 3.52,3.46 (2H, m, CH_2), 2.61,2.30 (2H, m, CH_2) 5.12 (1H, m, CH),3.83 (6H, s, CH_3), 8.16 (1H, s, NH), 2.13 (1H, s, OH).

TA10)
Yield: 54%;mp: 153-155 °C;IR ν cm^{-1}: 3438, 3425, 3237, 3031, 2959, 2868, 1699, 1651^{1}HNMR (δppm, DMSO):7.42(1 H, d, CH), 7.18 (1 H,s, ArH), 6.94 (1 H, d, ArH), 6.80 (1 H, d, ArH), 7.04 (1 H, d, CH), 3.41,3.32 (2H, m, CH_2), 1.99,1.68 (2H, m, CH_2), 1.60, 1.55 (2H, m, CH_2), 4.31 (1H, m, CH), 5.29 (2H, s, OH), 8.12 (1H, s, NH), 2.02 (1H, s, OH).

TA11)
Yield: 59%;mp: 157-159 °C; IR ν cm^{-1}: 3434, 3424, 3235, 3029, 2961, 2852, 1688, 1633^{1}HNMR (δppm, DMSO):7.32(1 H, d, CH), 7.56 (2 H,d, ArH), 6.67 (2 H, d, ArH), 7.03 (1 H, d, CH), 3.38,3.30 (2H, m, CH_2), 1.95,1.75 (2H, m, CH_2), 1.66, 1.52 (2H, m, CH_2), 4.35 (1H, m, CH),5.27 (1H, s, OH), 8.01 (1H, s, NH), 2.11 (1H, s, OH).

TA12)
Yield: 64%; mp: 149-151 °C;IR ν cm^{-1}: ×3456, 3411, 3250, 3091, 2918, 2832, 1681, 1643^{1}HNMR (δppm, DMSO):738(1 H, d, CH), 7.19 (1 H,s, ArH), 6.97 (1 H, d, ArH), 7.20 (1 H, d, ArH), 7.07 (1 H, d, CH), 3.40,3.30 (2H, m, CH_2), 1.96,1.71 (2H, m, CH_2), 1.64, 1.54 (2H, m, CH_2), 4.29 (1H, m, CH),3.72 (6H, s, CH_3), 8.12 (1H, s, NH), 2.01 (1H, s, OH).

2.9 Antibacterial Activity
For detecting the antibacterial activity, the nutrient agar media was prepared using peptone (0.5%), beef extract (0.3%), agar (1.5%), sodium chloride (0.5%) and distilled water. The pH of the prepared agar media was adjusted to neutral (7.4) at 25 °C. This nutrient agar media was sterilized in autoclave. Suspensions of different microorganisms [inoculums] were prepared in different tubes in sterile distilled water.
When the temperature of the sterile molten media reached to 40-45 ^{0}C, 0.5 ml of the inoculum was added to agar media, mixed and poured immediately into the sterile petri plates [10 cm diameter] and labeled accordingly. The agar was then allowed to solidify. The wells were prepared in plates using sterilized borer of 6 mm diameter [3 wells/plate]. About 50 µL of the control [Ethanol], sample solutions [TA1-TA12, 300µg/ml] and the standard drug [ampicillin 300µg/ml] were transferred into the wells in each plate using micropipettes. The plates were then refrigerated to allow prediffusion for 1 hour and then the plates were transferred to the incubator (37 ^{0}C), and were kept in incubator for 24 hrs. The zones of inhibition were measured as average of 3 readings [see table 1] [7, 8].

Table 1: Antimicrobial screening result [zone of inhibition in mm] of synthesized compounds

M.O.*	zone of inhibition(MM)														
	Std.	Control	1	2	3	4	5		6	7	8	9	10	11	12
E.coli	++	+	+++	+	++	++	++		+	+++	++	++	+	++	++
P. aeruginosa	++	+	+	+	++	++	+	+	+	++	+	+	++	+	++
S. pyrogene	++	+	++	++	+	++	++		++	++	++	++	+	+++	++
S. aureus	++	+	++	++	+	+	+++		+	+	+++	+	+	++	+
K. pneumoniae	++	+	++	++	+	++	+++		+	+	++	+	+	+++	++
A. baumannii	++	+	+	+	++	+++	++		+	+	+	++	+	+	++

- < [6], + [6-12], ++ [12-18],+++> [18] *

M.O. – Microorganisms
E. coli- Escherichia coli
P. aeruginosa- Psudomonas aeruginosa
S. pyrogene- Streptococcus pyogenes
S. aureus- Staphylococcus aureus.
K. pneumoniae- Klebsiella pneumoniae
A. baumannii- Acinetobacter baumannii

3. Result and Discussion
All the synthesized compounds [TA1-TA12] were screened for antibacterial activity against different strains of bacteria. The results are presented in Table 1 and the discussion is given below.

- ***E. coli:*** It is found that compound 1 and 7 showed better activities, wherever compound 3, 4, 5, 8, 9, 11 and 12 gave equal activity as compared to standard drug against *E. coli*.
- ***P. aeruginosa:*** It is found that compound 3, 4, 7, 10 and 12 gave equal activity as compared to standard drug against *P. aeruginosa*.
- ***S. pyrogene:*** It is found that compound 11 showed better activities, wherever compound 1, 2, 4, 5, 6, 7, 8, 9 and 12 gave equal activity as compared to standard drug against *S. pyrogene*.
- ***S. aureus:*** It is found that compound 5 and 8 showed better activities, wherever compound 1, 2, 4 and 11 gave equal activity as compared to standard drug against *S. aureus*.
- ***K. pneumoniae:*** It is found that compound 5 and 11 showed better activities, wherever compound 1, 2, 4, 8 and 12 gave equal activity as compared to standard drug against *K. pneumoniae*.
- ***A. baumannii:*** It is found that compound 4 showed better activities, wherever compound 3, 5, 9, and 12 gave equal activity as compared to standard drug against *A. baumannii*.

4. Conclusion
Overall, out of 12 synthesized compounds 6 compounds namely TA1, TA4, TA5, TA7, TA8, TA11 showed good

activity against different microorganism strains as compared to standard drug ampicillin. Compound 12 gave equal activity as that of the standard against most of the strains.

The authors tried to correlate the activity with the structures of compounds and the probable correlation is described below.

Amongst the six compounds (TA1, TA4, TA5, TA7, TA8, TA11) showing better activity, it is found that compounds TA5, TA8 and TA11 showed best antibacterial activity as compared to standard drug ampicillin, probably due to presence of 4-hydroxy group in their structure. On other hand compounds 1, 4 and 7 showed better activity as compared to standard drug and they all have 3, 4-dihydroxy group in their structure. The study shows that cinnamic acid derivatives are good antibacterial targets. Further studies on cinnamic acid derivatives can yield potential antibacterial drug molecules.

5. Reference

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