# Design, Synthesis and Biological Evaluation of Caffeic Acid Analogue for Peptide Deformylase Based Antimicrobial Activity

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**ABSTRACT :**

A new series of cinnamic acid amide and cinnamaldehyde Schiff base were synthesized by coupling cinnamic acid to different amino acids. The synthesized compounds were characterized and compared by reported NMR spectroscopy and analytical data. All the synthesized compounds were evaluated for in vitro antimicrobial activities. Among the tested compounds 6c and 6e showed potential antimicrobial activities. Further antimicrobial results were supported by in silico molecular docking study. Compounds 6c and 6e were found to be more selective toward HpPDF(PDB ID: 4E9A). Among all these synthesized compounds, 2-(cinnamamido)-3-(1H-imidazol-4-yl)propanoic acid (6e) emerged as most potent active molecule with antimicrobial activity for Klebbsiella pneumoniae.

**Keyword:** PDF, CAPE, Cinnamic acid amide derivatives, Schiff base.

## INTRODUCTION:

Bacterial metalloenzyme peptide deformylase (PDF) has emerged as an attractive target for the design of novel antibacterial drugs as broad spectrum [1, 2]. Peptide deformylase(PDF) catalyzes the hydrolytic removal of the N-terminal formyl group from nascent proteins [3,4]. This is an essential step in bacterial protein synthesis not for mammalian cell [5, 6, 7], making PDF an attractive target for antibacterial drug development [8, 9]. Generally, the majority of reported PDIs are pseudopeptide, including hydroxamic acids (e.g. Actinonin, VRC-3375[10], VRC-4307), N-formyl hydroxylamine (e.g. LBM-415, BB-3497[11] BB-83698 and GSK-1322322) and thiol peptides [12-15,]. LBM-415, BB-83698 and GSK1322322 [16] have entered clinical trials. NVP-PDF-713 is a PDI that has emerged as a candidate for treating Gram-positive infections and selected Gram-negative species that commonly cause community-acquired respiratory tract infections[17] (**Figure 1**).

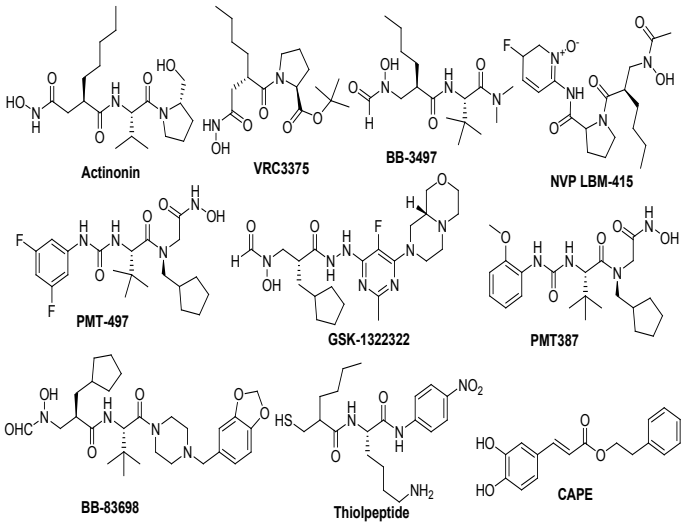


**Figure 1: Structure of pseudopeptide and non-peptide active as PDF inhibitors.**

Caffeic acid phenethyl ester (CAPE), a component of propolis obtained from honeybee hive was reported to have antimicrobial activity [18]. Naturally occurring antibacterial drugs, both Actinonin and CAPE

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are inhibit the activity of the PDF enzyme. Actinonin represent the majority of known PDF inhibitor's which chelate the active site metal ion by hydroxamic or hydroxylamine part. However, there is no chelation between CAPE and the active site metal ion which is different from most known PDF Inhibitor's. The main reason for the inhibition on *Hp*PDF is CAPE blocks the substrate entrance, preventing substrate from approaching the active site [19]. This show that the binding mode of CAPE was different from most PDF inhibitor's which may lead to less adverse effects which caused by interactions with other metallo-enzymes in human bodies.

## BASIS OF WORK:

Cinnamic acid is a key intermediate in shikimate and phenyl propanoid paths [20]. A large number of natural and synthetic cinnamic acid derivatives or analogues, which may act as a precursor for ester or amide function group such as Caffeic acid, CAPE, Ferulic acid, Curcumin, Chlorogenic acid, N-trans-caffeoyltyramine, etc. with various biological properties such as antimicrobial, antifungal, anti-inflammatory, antioxidant etc. were studied by many groups [21,22]. The Cinnamic acid compound served as the mimic core and aromatic rings were suitably aligned in the desired molecular geometry as to mimic CAPE. The presence of hydroxyl, methoxy on benzene enhance potency of activity and α, β- unsaturated acid group in cinnamic acid found to be responsible for their biological activity (**Figure 2**).

In this view cinnamoyl precursor with amide or ester functional group and having terminal aromatic ring show peptide deformylase inhibitor. By this literature survey, we design and synthesized, cinnamic acid derivatives with amide functional group and terminal aromatic or aliphatic group [23, 24, 25]. Cinnamaldehyde Schiff base with aromatic ring can open a new broad spectrum as antimicrobial agent. Amide bond with aromatic or aliphatic group was introduce by simply reaction with various amino acids (i.e. glycine, asparagine, tyrosine, tryptophan, histidine and phenylalanine).[26,27]

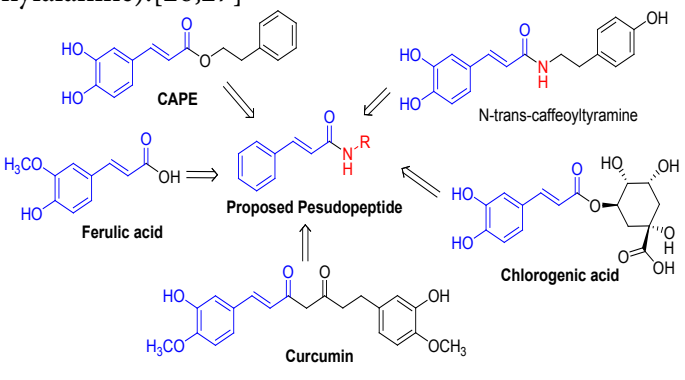
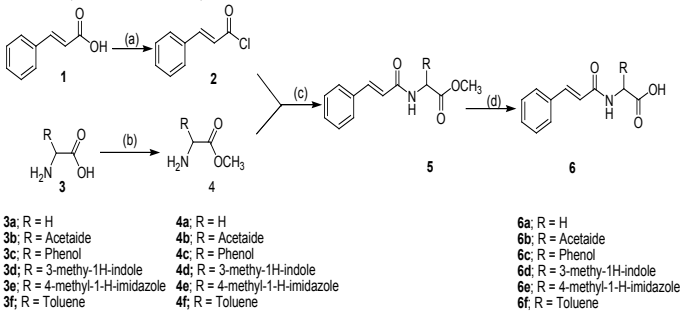



**Figure 2**: Chemical structural identical similarities between other natural obtaining compounds

## RESULT AND DISCUSSION:

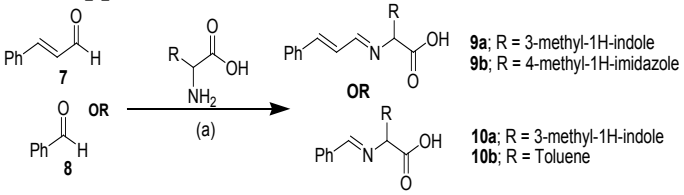
### Chemistry

Cinnamic acid (**1**), cinnamaldehyde (**7**) and benzaldehyde (**8**) were used as main compound and their different derivatives were prepared with various amino acids by amidation and Schiff base reaction. Reaction between cinnamic acid (**1**) and various substituted 2-aminoacetic acid (**3a-f**) was carried out by the cinnamoyl chloride (**2**), cinnamoyl chloride (**2**) was simply synthesized by reaction of cinnamic acid (**1**) with thionyl chloride ($SOCl_2$) in $N_2$ atmosphere at room temperature. Meanwhile, esters of amino acids (**4a-f**) were synthesized by Fischer esterification. Finally desired cinnamic acid amide derivatives (**6a-f**) were obtained by reaction of cinnamoyl chloride (**2**) with various esters of amino acids (**4a-f**) in tetrahydrofuran (THF) at 0 °C under nitrogen atmosphere with catalytic amount of potassium phosphate ($K_3PO_4$) as base and deprotection of ester group furnish desired compound **6a-f**. All synthesized compounds (**6a-f**) were confirmed and compared with reported analysis data (**Scheme 1**).




**Scheme 1** Reaction and Regents for the synthesis of **6a-f** (a) $SOCl_2$, reflux (b) $CH_3OH/H^+$; (c) $K_3PO_4$, THF , 12 h, rt; (d) Hydrolysis

Schiff bases, 2-(3-phenylallylidene amino) acetic acid derivatives (**9a-b**) and 2-(benzlideneamino)acetic acid derivatives (**10a-b**) were synthesized by condensation of cinnamaldehyde (**7**) or benzaldehyde (**8**) with substituted 2-amino acetic acid (**3d & 3e**) assisted by microwave (Raga's Scientific) at power level 3(240W, 35% irradiation) till the completion of reaction (approx.20-25min)**(Scheme 2).**




**Scheme 2 Reaction** and regents for the synthesis of **9a-b** and **10a-b** :( a) Ethanol/NaOH assisted with microwave level 3, for 20 min

### Biological Activities:

For determination of antimicrobial activity of the synthesized compounds were done on Gram-positive and Gram-negative bacterias (i.e. *Staphylococcus aureus(MSSA),Methicillin resistant Staphylococ-*

*cus aureus(MRSA), Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia*) in references of Amoxicillin sodium inj. IP(Ranbaxy lab.) and Doxycycline hydrochloride cap. IP(NuLife Pharmaceuticals) by the radial diffusion agar microbiological assay (bioassay). The radial diffusion agar microbiological assay is also known as the "Zone of inhibition" (ZOI) assay as it depend on a dose-dependent inhibition of microbial growth made visible in a bacterial lawn [28]. The following micro-organisms were tested by zone inhibition with Mueller Hinton media (without blood addition except for *Enterococcus faecalis* gm +ve bacteria). Ethanol is used as co-solvent for enhance solubility of compound in sterile water. Instruments were Yorco Incubator Bacteriological IS: 3118 and Denver Instrument SI-234 used. The evaluated data of tested compounds on different microbial were shown in **Table 1**.

Order of antimicrobial activity evaluated after screening on Gram-negative bacteria (**6e > 6b > 9b> 6c > 10b)** and Gram-positive (**6c > 6b > 9a > 6e > 6d)** respectively. Among the tested synthesized compounds, **6c** show broad spectrum activity and **6e** was found to be the most active with compare to standard Doxycycline and Amoxicillin on *Klebbsiella pneumoniae*. However, compound **6e**, characterized by having imidazole ring and saturated ethyl group at N-terminal and unsaturated ethyl group at C-terminal of amide function group form a chain between phenyl and imidazole ring. This six carbon chain which contains

**Table no.1**: Determination of antimicrobial activity

| S. No. | Compounds | MIC (µg/ml) | Organism with their inhibition zone(mm) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ***MSSA*** | ***MRSA*** | ***Enterococcus faecalis*** | ***E. coli*** | ***Pseudomonas aeruginosa*** | ***Klebbsiella pneumonia*** |
| **1.** | Amoxycillin | 10 | 4 | 4 | 5 | - | - | 3 |
| **2.** | Doxycycline | 10 | 3 | - | - | - | 4 | 1 |
| **3.** | 6a | 530 | - | - | - | - | - | - |
| **4.** | 6b | 530 | - | 6 | - | - | 5 | - |
| **5.** | **6c** | **300** | **6** | **4** | **-** | **1** | **3** | **2** |
| **6.** | 6d | 200 | 2 | - | - | - | - | - |
| **7.** | **6e** | **450** | **-** | **3** | **-** | **-** | **2** | **10** |
| **8.** | 6f | 530 | - | - | - | - | - | - |
| **9.** | 9a | 375 | 5 | 1 | - | 2 | - | - |
| **10.** | 9b | 250 | - | - | - | - | 3 | - |
| **11.** | 10a | 400 | - | - | - | - | - | - |
| **12.** | 10b | 400 | - | - | - | - | - | 2 |
| **13.** | Ethanol (99.0%) | _ | - | - | - | - | - | - |

amide group and unsaturated ethyl at one side might have a role of entrapping the specific inhibiting cavity of *Hp*PDF for all synthesized compounds. The results of the microbiology screening suggested that the synthesized Cinnamic acid amide derivative with the exhibit a promising antibacterial activity (**Figure 3**).

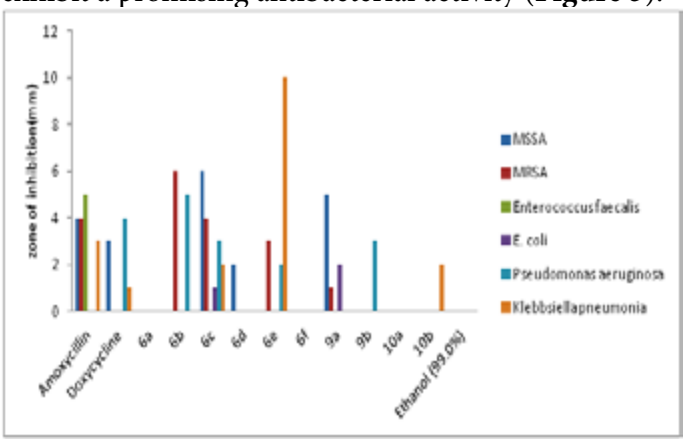



**Figure 3**: Comparison of the Antimicrobial activity through zone of inhibition of synthesized compounds and reference market available drugs

**Molecular Docking:**

Piecewise Linear Pairwise Potential (PLP) (i.e GRIP) used to minimize the interaction energy between ligand – receptor. PLP docking is a rigid docking method that includes ligand-receptor interactions of hydrogen bonding (donor-acceptor), repulsions (donor-donor, acceptor-acceptor) and dispersion (involving non-polar group interactions) types. All sketched 2D structures were converted into 3D and then all structures minimized and optimized with Merck Molecular Force Field (MMFF) method taking the root mean square gradient (RMS) of 0.01kcal/mol Å. Furthermore conformers were generated for each by Monte carlo method and least energy conformer was selected after docked in generated grid (As the co-crystal structure of 4E9A showed nine cavities, the selection of cavity for docking studies of the designed ligands was made on the basis of presence of the inhibitor CAPE(i.e.QAP202A) in the cavity#1) of *Helicobacter pylori* metalloenzyme peptide deformylase

(*Hp*PDF, Polypeptide deformylase 11; EC:3.5.1.88 obtained from Protein Data Bank, (http://www.rcsb.org/pdb/home) which were evaluated by least score and compared interaction of reference ligand QAP202A surrounding residues(i.e.SER42A, ILE45A, GLU94A, CYS96A, PRO100, GLY101, TYR103) interaction all of docking done by GRIP method on VLife MDS 3.0 software. After the docking was accomplished and the best docked complex was chosen for a given ligand, the entire docked complex was optimized by using MMFF and the net GRIP binding energy (kcal/ mol) of the given ligand to the receptor(**Table 2**) was determined from the following equation.

GRIP energy = Optimized docked complex energy – (energy of optimized apo receptor without ligand + energy of optimized ligand)

**Table 2:** Docked score and energy of designed ligands with calculated Lipinski's rule of five

| Sr. No. | Compd | Mol. formula | M.Wt | $H_{acp}$ | $H_{dor}$ | LogP | G R I P score | GRIP energy | H-bond | Lip |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 6a | $C_{11}H_{11}NO_3$ | 235.28 | 3 | 2 | 1.67 | -53.54 | -114.39 | 2 | - |
| 2 | 6b | $C_{13}H_{14}N_2O_4$ | 262.26 | 5 | 3 | -6.15 | -65.21 | -99.35 | 3 | 1 |
| 3 | 6c | $C_{17}H_{15}NO_4$ | 297.31 | 5 | 3 | 2.28 | -75.01 | -100.74 | 2 | 4 |
| 4 | 6d | $C_{20}H_{18}N_2O_3$ | 334.13 | 5 | 3 | 2.49 | -75.70 | -113.81 | - | 2 |
| 5 | 6e | $C_{15}H_{15}N_3O_3$ | 295.12 | 6 | 3 | 2.95 | -68.16 | -147.91 | 4 | 2 |
| 6 | 6f | $C_{18}H_{17}NO_3$ | 285.11 | 4 | 2 | 0.5 | -67.46 | -58.09 | 2 | 2 |
| 7 | 9a | $C_{20}H_{18}N_2O_2$ | 318.14 | 4 | 2 | 3.1 | -74.91 | -70.08 | 1 | 2 |
| 8 | 9b | $C_{15}H_{15}N_3O_2$ | 269.12 | 5 | 2 | 1.11 | -72.31 | -137.78 | 3 | 3 |
| 9 | 10a | $C_{18}H_{16}N_2O_2$ | 292.12 | 4 | 2 | 3.21 | -75.02 | -125.77 | 2 | 3 |
| 10 | 10b | $C_{16}H_{15}NO_2$ | 253.11 | 3 | 1 | 3.67 | -68.32 | -127.63 | 2 | 2 |
| 11. | CAPE | $C_{17}H_{16}O_4$ | 284.31 | 4 | 2 | 3.43 | -63.56 | -74.71 | 3 | 2 |

*M.Wt _Molecular weight (≤500 Da)
*$H_{acp}$ _Hydrogen bond acceptors (≤10)
*$H_{dor}$ _Hydrogen bond donors (≤5)
*LogP _An octanol-water partition coefficient (≤5)
*H-bond_Hydrogen bond
*Lip_Hydrophobic bond

**GRIP-score:**

The Dock score as it is called compute binding affinity of a given protein ligand complex with known 3-D structure. Dock scoring function include terms for van der Walls interaction, hydrogen bonding, deformation penalty, hydrophobic effects. The results of the docking studies were generated in the form of GRIP-score. The more negative value of GRIP-score indicated that the compound may be more potent and indicated the good binding potential of the compound. The GRIP-score of the standard ligand i.e. CAPE (QAP202A), in case of docking with 4E9A was found as -63.566 and GRIP energy was -74.71Kcal. The GRIP-score of compounds **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **9a**, **9b**, **10a** and **10b** were also found as -53.54, -65.21, -75.01, -75.70, -68.16, -67.46, -74.91, -72.31, -75.02 and -68.32 respectively. Close analysis of these result suggest that design compounds were comparable with standard PDF inhibitor, CAPE. Beside the GRIP-score, other parameter energy of compounds **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **9a**, **9b**, **10a** and **10b** were also taken into consideration for the evaluation of the docking results i.e. -114.39, -99.35, -100.74, -113.81, -147.91, -58.09, -70.08, -137.78, -125.77 and -127.63 Kcal respectively. The value of energy was significantly below to the value of standard CAPE. Compound **6e** was shown best binding energy as compared with other compounds because of binding environment residues were most common with reference ligand (**Figure 4**).

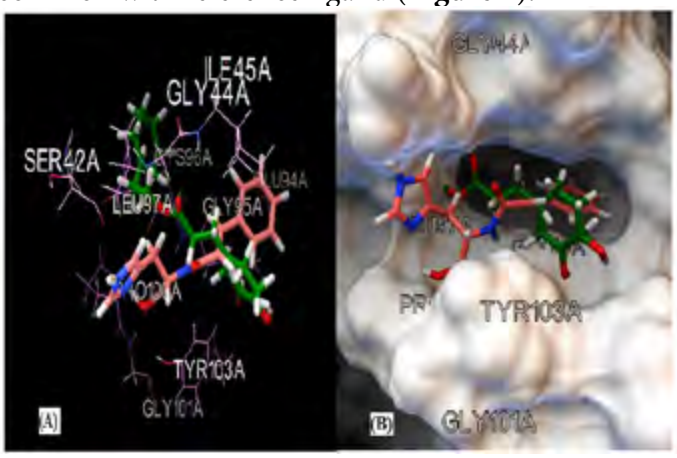



**Figure 4**: Evaluation of Docking result (A) Binding environment of **6e** (pink color) and CAPE (green color) in *Hp*PDF (B) Docked **6e** (pink) and CAPE (green) in PDF represented by surface

Not only compound **6e** and other also docked in specific generated grid cavity. Docked score and binding energy depend on interactions between ligand and residues as represented in **figure 5** for ligand **6e** and reference ligand. In the structure HpPDF-CAPE complex, the head of Cape (phenyl group) fits in the hydrophobic pocket and the tail expands to the pocket entrance. The carbonyl oxygen atom forms one hydro-

gen bond to hydrogen atom of ILE 45A and two more hydrogen bonds are also formed between the oxygen atom of hydroxyl and the main chain nitrogen atom of GLY 101A and hydrogen atom of active oxygen of phenol group of TYR 103A. Hydrophobic interaction formed between phenyl ring and GLU 94A and ILE 45A while other residues SER 42A, GLY 44A, LYS 93A, GLU 94A, GLY 95A,CYS 96A, PRO100A, GLY 101A, TYR 103A make vdW interaction with CAPE (**Figure 5A**).

Compound **6e** in complex, the tail contain imidazole ring fitted in one pocket of cavity and head contain phenyl ring enter in cavity by this fully fill the cavity. However, the carbonyl oxygen atom forms three hydrogen bonds to hydrogen at atoms of CYC 96A, GLY 101A and TYR 103A respectively. Hydrogen bond was also formed between hydrogen atom secondary nitrogen of imidazole ring and the carbonyl oxygen atom of SER 42A. The two rings make hydrophobic interaction with LEU 97A, GLY 95A and vdW interaction with SER 42A, GLY44A, ILE45A, LYS 93A, GLU94A, GLY95A, CYS 96A, PRO 100A, GLY101A, TYR 103A, LEU131A (**Figure 5 B**).

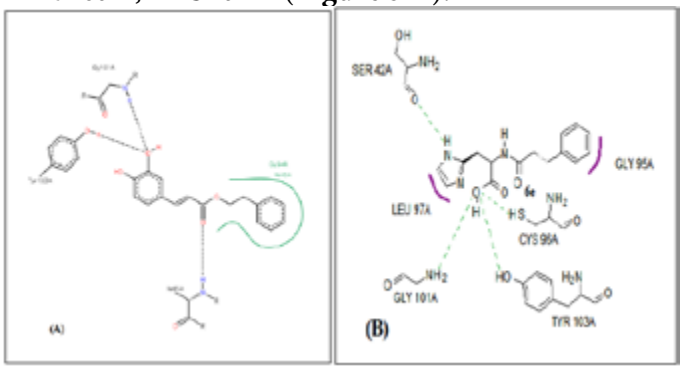



**Figure 5**: Diagrammatic representation of Hydrogen bonds (dot line) and hydrophobic interaction (curve) formed between CAPE (i.e. QAP) and **6e** shown in (A) & (B).

## CONCLUSION:

Natural obtain cinnamic acid ester derivative (i.e. Caffeic acid phenethyl ester (CAPE)) show more potency as PDF inhibitor as compare to pseudopeptide Actinonin without chelating with present metal in enyzme. By this mode of binding of CAPE with PDF as inhibitor will greatly facilitate to design and synthesis of cinnamic acid amide derivatives with improved PDF inhibitor with broad spectrum antimicrobial. Ten compounds have been designed, synthesized and subjected to Gram-negative and Gram-positive pathogens including multidrug- resistant strain for bacterial screening and found in order to Gram-negative bacteria ( **6e > 6b > 9b> 6c > 10b)** and Gram-positive ( **6c > 6b > 9a > 6e > 6d)** respectively. Among the tested compounds, **6c** and **6e** showed potential inhibitor effect on bacterial stains while compound **6e** was found to be more active on *Klebbsiella pneumoniae* as compared to other synthesized compounds and reference drugs. Molecular docking studies also favor for anti-microbial activity of all designed compounds, the binding energy has been obtained in order of **6e > 9b > 10b > 10a > 6a > 6d > 6c > 6b > CAPE > 9a > 6f** respectively.

**General Synthetic procedures for compounds (6a-f)** [26]

A reaction mixture of Cinnamic acid (**1**) (1.78 g, 0.012 mol) and $SOCl_2$ (10 ml) was refluxed for 4h. The resulting solution was distilled in under vacuum to give cinnamoyl chloride (**2**) as a pale yellow liquid (mp. 35-37 °C). Simultaneously esters of compound **3a-f** (0.012mol) were synthesized by refluxing of acid **3a-f** in in methanol (15 mL) with catalytic amount of conc HCl for 30 min stirring. The reaction mixture was distilled to get desired ester **4a-f** as white solid in good yield. The synthesized cinnamoyl chloride (**2**) (0.012mol) was soluble in THF (5mL) and cooled to 0°C under $N_2$ atmosphere. Potassium phosphate ($K_3PO_4$) (4.18gm, 0.023 mol) was added in one portion followed by the addition of compound **4a-f** (0.012mol). The mixture was allowed to increase temperature 0oC to rt and stirred for 12h. Reaction progress was monitored by TLC, after complete, reaction mixture was quenched with water (8 mL). Organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with saturated brine solution and dried over anhydrous $Na_2SO_4$. The organic layer was evaporated under vacuum. The crude product was purified to get compounds **5a-f** by either crystallization or by silica gel column chromatography and confirmed by IR and NMR spectroscopy methods. Finally desired **6a-f** compounds were synthesized by acid hydrolysis of **5a-f**.

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