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Synthesis of Novel Daclatasvir amino acid analogues for NS5A hepatitis-c virus inhibitor

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Abstract: *The present invention relates to synthesize the novel Daclatasvir amino acid substituted analogue compounds (7a-7e). Their pharmaceutically acceptable salts and their isomers, hydrate and solvates. Which invention further relates to use of the above mentioned analogue compounds for the preparation of medicament for use as pharmaceuticals.*

Keywords: *Medicament, amino acid analogues, non-structural proteins NS5A, antiviral.*

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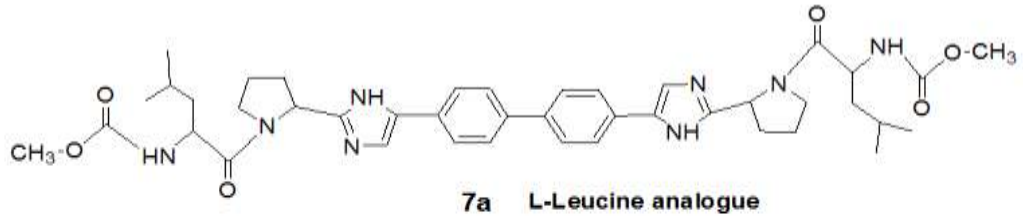
I. Introduction

The world health organisation (WHO) 2014 guidelines for the screening care and treatment persons with hepatitis C infection state that worldwide more than 185 million people are infected with hepatitis C virus (HCV). An estimated one third of these who become chronically infected (or) hepatocelullar carcinoma. Nearly 350000 to 500000 die each year (HCV affected people). HCV is member of the faviviridae, with seven major genotypes and major number of sub types. Hepatitis C virus is a serious global medical problem. Acton of HCV on proteins can be divided into two groups those are structural proteins (C, E1 and E2) and non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B).

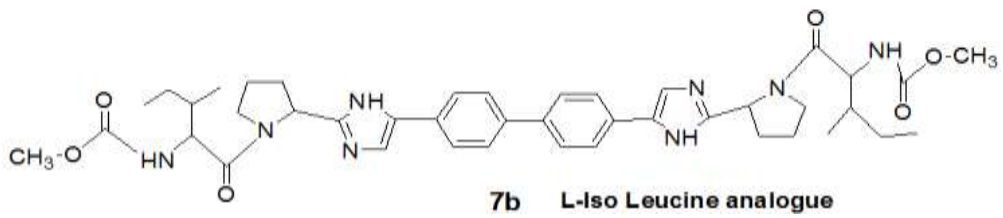
Dalatasvir belongs to a class of new directly acting antiviral that inhibit non-structural proteins NS5A. It has been tested in combination regements with pegylated interferon and ribavirin as well as with other direct-acting antiviral agents including asunaprevir and sofosbuvir. Daclatasvir stops HCV viral RNA replication and protein translation by directly inhibiting HCV protein NS5A. Daclatasvir reaches steady state in human subjects after about 4 days of once-daily 60 mg oral administration.

Daclatasvir is hepatitis-c virus NS5A inhibitor. It stops HCV viral replication and protein translation by directly inhibiting HCV protein NS5A. It was discovered by scientists of Bristol- Myers Squibb. In the present study, we efficiently synthesized a series of five novel amino acid substituted Daclatasvir analogues (**7a-7e**) as potential prodrug. Amino acid analogues of Daclatasvir (**7a-7e**) shown in Figure-**1**.

Bristol-Meyers Squibb discovered the drug and get approval from the United States Food and Drug Administration (FDA) in 2014 for the treatment of genotype 1b chronic HCV. The European medicines agency approved in august 2014 in combination with other drugs for use across genotype for the treatment of chronic hepatitis C virus in adults. The chemical name for Daclatasvir is methyl N-[(2S)-1-[(2S)-2-[5-[4-[4-[2-[(2S)-1-[(2S)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate.



7a L-Leucine analogue



7b L-Iso Leucine analogue

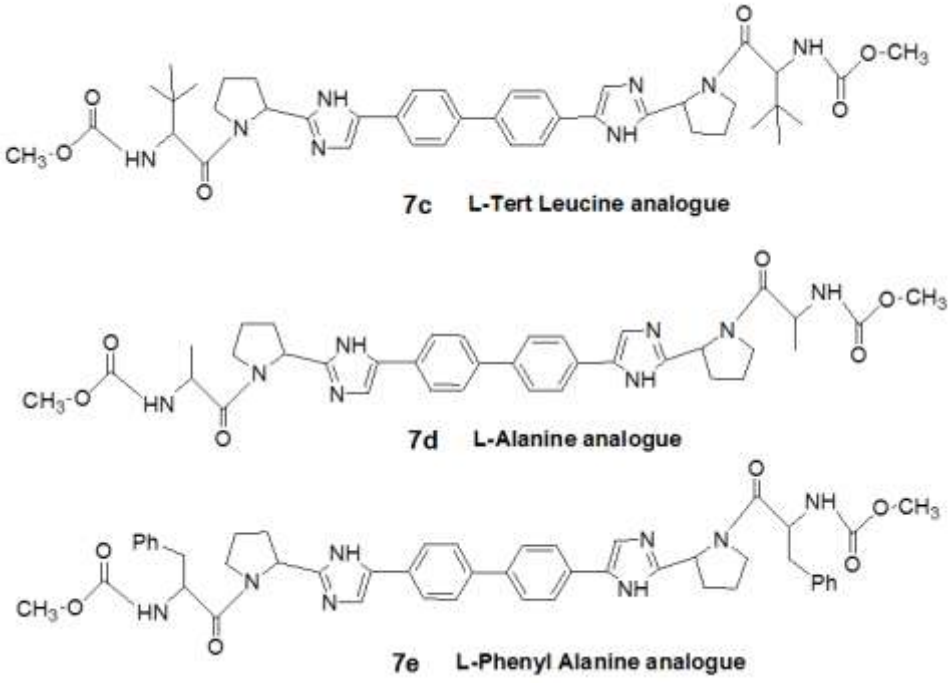
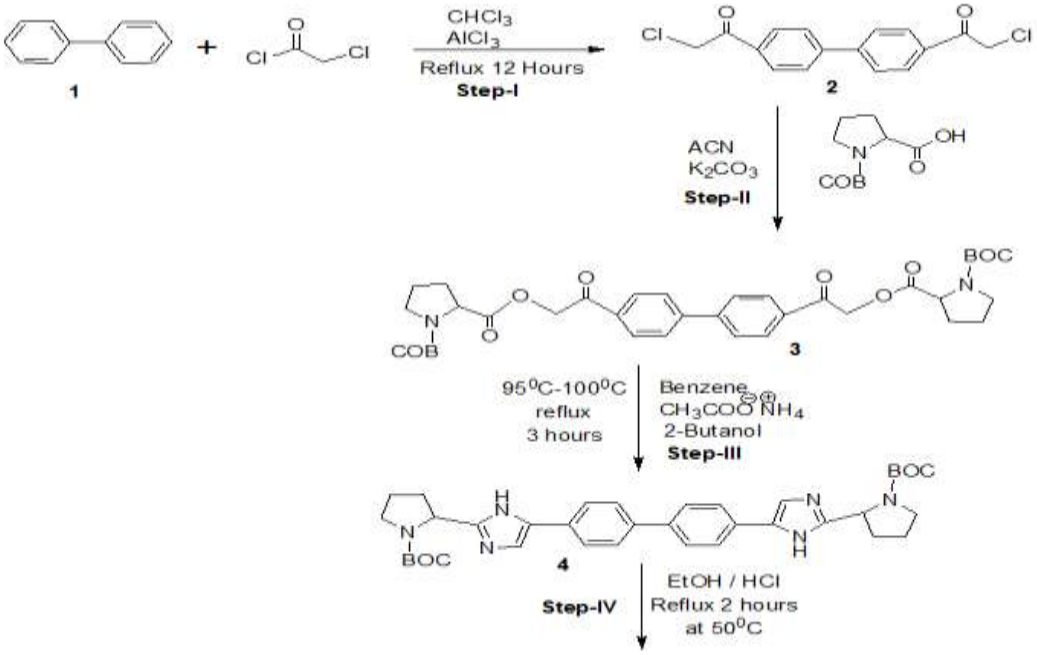


Figure-1

II. Results And Discussion

The synthesized Daclatasvir amino acid analogues were characterized by ^{1}H NMR, IR and HPLC. ^{1}H NMR was recorded in DMSO and $CDCl_3$. The chemical shifts were reported in ppm. The IR spectrum was recorded using as such solid on FTIR. With an objective of developing a viable and efficient method would give high yields and easy handling procedure under aerobic conditions. The target symmetrical structure compounds were synthesized from biphenyl (1) on Friedal-Craft acylation with two equivalent chloro acetyl chlorides in presence of anhydrous $AlCl_3$ in $CHCl_3$ converted to di substituted chloro acetyl biphenyl (2). This was coupled with N-BOC proline in presence of ACN and K_2CO_3 to form (3). The compound 3 treated with ammonium acetate ($CH_3COO^-NH_4^+$) in Benzene refluxing for 3hours to form (4). After the deprotection of N-BOC group with Conc. HCl in Ethyl alcohol to gave (5). The resulting amine coupled with N-MOC amino acids (6a-6e) gave (7a-7e) amino acid analogues. All the target compounds were new chemical entities and are shown in figure-1.

Scheme:



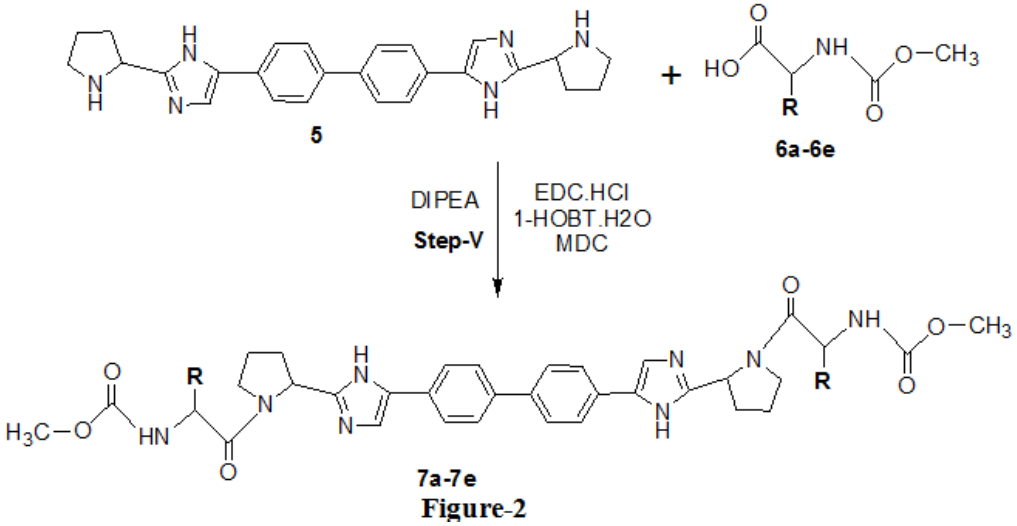
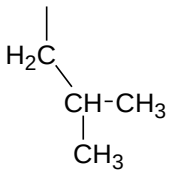
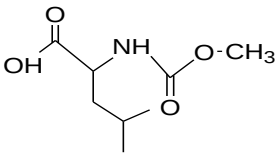
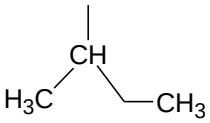
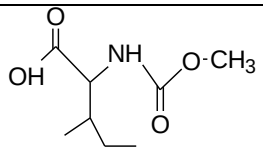
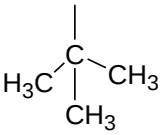
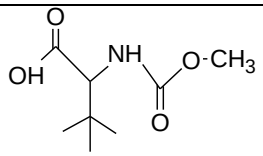
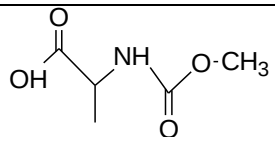
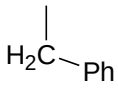
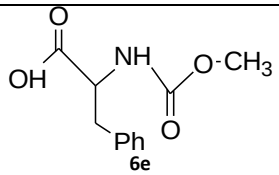


Figure-2

Table 1:

Amino acid Analogues	R	N-MOC Amino acid
L-Leucine analogue **7a**		 **6a**
L-Iso Leucine analogue **7b**		 **6b**
L-Tert Leucine analogue **7c**		 **6c**
L-Alanine analogue **7d**		 **6d**
L-Phenyl Alanine analogue **7e**		 **6e**

III. Experimental Section

General: All starting materials and other reagents were purchased from commercial suppliers and were used without further purification. Nuclear Magnetic Resonance (NMR) spectra were recorded on bruker instrument operating at 300 and 500 MHz and ^{1}H NMR spectra are obtained with TMS as internal standard in DMSO solvent. ^{13}C NMR spectra are also obtained in DMSO instrument operating at 75 and 125 MHz IR and Mass spectra were recorded. The reactions were assayed by thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. When peak multiplicities are reported.

Step-I: Syntesis of 2-Chloro-1-[4'-(2-chloro-acetyl)-biphenyl-4-yl]-ethanone

Anhydrous AlCl3 (1.33 g, 10 mmol) and chloro acetyl chloride (1.12g, 10 mmol) suspended in 5 ml of $CHCl_3$. And then added the biphenyl (771 mg, 5 mmol). The contents refluxed for 12 hours. The reaction was monitored by TLC. The reaction mixture was extracted with 6 ml of water 10 ml of acetone added and separate the layers. The organic layer was dried results the solid. The crude was used for step-II process.

Step-II: Synthesis of (2S)-′2, 2-2, 2′-(Biphenyl-4,4′-diyl)bis(2-oxoethane-2,1-diyl)1-tert-butyl dipyrrolidine-1,2-dicarboxylate

N-BOC proline (1.07 g, 5 mmol) and K_2CO_3 (691 mg, 5 mmol) were added to a suspension of 1, 1′-(Biphenyl-4, 4′-diyl) bis (2-Chloroethanone) **2** (768 mg, 2.5 mmol) in acetonitrile (10 ml). The solution was stirred for 30 min and reflux 18 hours at room temperature. The reaction was monitored by TLC. 25 ml of toluene was added and separate the layers. Organic layer concentrated under reduced pressure. The crude solid was dried and used for step-III process.

Step-III: Synthesis of (2S,2′S)-tert-Butyl 2,2′-(5,5′-(biphenyl-4,4′-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

(2S)-′2, 2-2, 2′-(Biphenyl-4, 4′-diyl) bis (2-oxoethane-2,1-diyl)1-tert-butyl dipyrrolidine-1,2-dicarboxylate **3** (1.32 g, 2 mmol) dissolved in 9 ml of Benzene and added ammonium acetate (3.36 g, 43.6 mmol). The contents were stirred and refluxing for 3 hours at 95-100^{0}C. The reaction was monitored by TLC. The combined EtOAc extracts were concentrated under reduced pressure. Separate the solid and dried. The crude was analysed by NMR, Mass and FTIR spectra.

^{1}H NMR (300 MHz, in DMSO) δ:7.77-7.67 (d, 4H J = 8.25), 7.61-7.47 (d,4H J = 8.25), 7.21 (s, 2H), 4.88 (d, 2H), 3.62-3.38 (m, 4H), 2.34-1.19 (m, 8H), 1.39 (s, 9H), 1.19 (d, 9H); **^{13}C NMR (75 MHz, DMSO+$CDCl_3$, δ)**:153.82, 153.36, 150.61, 149.88, 137.35, 132.64, 126.09, 124.49, 55.19, 54.49, 46.16, 46.44, 33.24, 31.41, 27.78, 23.77, 23.07; **FT-IR (neat)λmax:**3423.14, 3218.48, 2974.70,2877.13, 1670.88, 1409.75; **ESI-MS:** m/z = 625 $[M + H]^+$, Molecular Weight: 624.677

Step-IV:

(2S, 2′S)-tert-Butyl 2,2′-(5,5′-(biphenyl-4,4′-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate **4** (1 g, 1.6 mmol) suspended in 2.6 ml of Ethyl alcohol and added 1.68 ml of Conc. HCl. The solution refluxed for 3 hours at 50^{0}C. The reaction was monitored by TLC. And add 10 ml of iso propyl alcohol at 50^{0}C cooled to 0-5^{0}C. Filter the solid and dried. The crude was analysed by NMR, Mass and FTIR spectra.

^{1}H NMR (300 MHz, in DMSO) δ: 7.92 (d, 4H), 8.07 (d, 4H), 8.31 (s, 2H), 10.32 (bs, 2H), 5.15 (t, 2H), 3.50 (q, 4H), 2.53 (q, 4H), 2.01 (m, 4H), 2.22 (s, 2H); **^{13}C NMR (75 MHz, DMSO+$CDCl_3$, δ)**:141.81, 139.32, 133.51, 127.19, 126.69, 126.01, 116.46, 52.30, 45.52, 39.52, 29.42, 24.02; **FT-IR (neat) λmax: 3425.24**, 2974.70, 1409.75, 1080.54, 810.5; **ESI-MS:** m/z = 425 $[M + H]^+$, Molecular Weight: 423.1.

Step-V: Synthesis of Daclatasvir Amino acid analogues (**7a-7e**)

1-hydroxy benzotrizole hydrate (382 mg, 2.5 mmol) in 10 ml of MDC. Added different N-MOC amino acid (2 mmol) and EDC HCl (460 mg, 2.4 mmol) stirred the contents for 1 hour at room temperature and cooled to 0-5^{0}C. Add Di amine compound **5** (424 mg, 1 mmol) and Di iso propyl ethyl amine (516 mg, 4 mmol) mixture stands at 0-5^{0}C for 30 min. Allowed to raise the temp to room temp , stirred for 12 hours at room temp. The reaction was monitored by TLC. Add ten times water and separate the organic layer washed with aqueous NaOH and water. Concentrated the organic layer results the solid. The solid was analysed by NMR, Mass and FTIR spectra.

7a. (1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-4-methyl-pentanoyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-3-methyl-butyl)-carbamic acid methyl ester

^{1}H NMR (300 MHz, in DMSO) δ: 7.84-7.70 (d, 4H J = 8.25), 7.58-7.47 (d, 6H), 6.34 (d, 2H), 5.31 (t, 2H), 4.46-4.37 (m, 2H), 4.18-4.08 (m, 2H), 3.84-3.76 (m, 2H), 3.54 (s 6H), 2.42-2.19 (m, 6H), 2.08-1.97 (m, 2H), 1.81-1.71(m, 2H), 1.67-1.57(m, 2H), 1.41-1.33 (m, 2H), 0.91 (d, 6H), 0.85 (d, 6H); **^{13}C NMR (75 MHz, DMSO+$CDCl_3$, δ)**:171.99, 156.61, 148.80, 139.50, 131.85, 126.85, 125.71, 114.10, 56.76, 52.80, 51.32, 50.80, 46.76, 31.69, 24.71, 24.05, 23.04, 20.97; **FT-IR (neat) λ max:** 3320.71, 2956.28, 1712.63, 1640.40, **ESI-MS:** m/z = 767 $[M + H]^+$, Molecular Weight: 766.93

7b: (1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-pentanoyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-butyl)-carbamic acid methyl ester

^{1}H NMR (300 MHz, in DMSO) δ: 7.75 (d, 4H J = 8.25), 7.49-7.36 (d, 6H), 5.99 (s, 2H), 5.28 (t, 2H), 15.05 (bs, 2H), 4.31-4.18 (m, 4H), 3.95-3.84 (m, 4H), 3.56 (s, 6H), 2.46-2.24 (m, 6H), 2.01-1.90 (m, 2H), 1.86-1.77 (m, 2H), 1.33-1.21 (m, 2H), 0.96-0.88 (m, 2H), 0.76 (t, 12H); **^{13}C NMR (75 MHz, DMSO+$CDCl_3$, δ):** 171.22, 156.62, 148.46, 139.58, 131.94, 126.77, 125.72, 113.89, 56.76, 52.65, 51.43, 47.12, 35.59, 30.92, 24.92, 23.48, 15.37, 10.48. **FT-IR (neat) λ max:** 3417.64, 2960.58, 2696.64, 1709.66, 1638.27, 1524.81; **ESI -MS:** m/z = 767 $[M + H]^+$, Molecular Weight: 766.93

7C: (1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3,3-dimethyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2,2-dimethyl-propyl)-carbamic acid methyl ester

^{1}H NMR (300 MHz, in DMSO) δ: 7.83-7.79 (d, 4H J = 8.25), 7.57-7.55 (d, 2H), 7.53-7.52 (d, 4H), 5.99 (d, 2H), 5.28 (t, 2H), 15.06 (bs, 2H), 4.28-4.22 (m, 4H), 4.15-4.08 (m, 2H), 3.97-3.90 (m, 4H), 3.58 (s, 6H), 2.44-2.26 (m, 6H), 1.99-1.92 (m, 2H), 0.88 (t, 18H); **^{13}C NMR (75MHz, in DMSO+CDCL3 δ):** 170.87, 156.60, 148.17, 139.67, 131.95, 126.83, 125.77, 113.90, 58.84, 53.37, 52,54, 51.62, 47.97, 41.69, 34.52, 30.84, 26.04, 25.01, 17.97, 16.63; **FT-IR (neat) λ max:** 3404.34, 2962.40, 2874.95, 2658.02, 1762.41, 1646.74, 1516.57. **ESI -MS:** m/z = 767 $[M + H]^+$, Molecular Weight: 766.93

7d: (2-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-propionyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid methyl ester

^{1}H NMR (300 MHz, in DMSO) δ: 7.35-7.86 (d, 8H), 7.24 (s 2H), 11.74-12.07 (bs, 2H), 4.39 (q, 2H), 3.55 (s, 6H), 3.70 (t, 4H), 6.74-6.93 (bs, 2H), 5.16 (t, 2H), 2.28 (q, 4H), 2.0 (m, 4H) 1.24 (d, 6H); **^{13}C NMR (75 MHz, DMSO+CDCl$_3$, δ):**171.14, 156.26, 148.98, 139.12, 137.23, 126.22, 124.69, 112.51, 55.01, 54.82, 54.62, 51.38, 48.34, 48.10, 46.40, 32.90, 30.96, 24.24, 21.64, 17.50, 16.94: **FT-IR (neat) λ max:** 3325.68, 2949.38, 1717.83, 1645.15, **ESI-MS:** m/z = 683 $[M + H]^+$, Molecular Weight:683.3.

7e: (1-Benzyl-2-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-phenyl-propionyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidin-1-yl}-2-oxo-ethyl)-carbamic acid methyl ester

^{1}H NMR (300 MHz, in DMSO) δ: 7.81-7.77 (d, 2H), 7.54-7.53 (d, 6H), 7.53-7.49 (d, 4H), 7.18-7.14 (d, 4H), 7.13-7.05 (m, 6H), 6.47- (d, 2H), 5.33 (t, 2H), 14.92 (bs, 2H), 4.63-4.55 (m, 2H), 4.30-4.21 (m, 2H), 3.89-3.80 (m, 2H), 3.48 (s, 6H), 3.41-3.35 (m, 4H), 2.76-2.69 (m, 2H), 2.40-2.24 (m, 6H), 2.03-1.97 (m, 2H), 3.46 (t, 4H), 8.0 (bs, 2H), 3.67 (s, 6H)., 4.92 (s, 2H),3.05 (d, 4H),7.21 (d, 4H), 7.12(d, 4H). **^{13}C NMR (500MHz, in DMSO+CDCL3 δ):** 171.17, 156.22, 148.12, 139.52, 136.70, 132.09, 128.86, 127.61, 126.70, 125.92, 125.68, 113.57, 53.67, 52.76, 51.46, 47,13, 36.38, 30.94, 24.70; **FT-IR (neat) λ max:** 3402.29, 2879.25, 2676.43, 1708.71, 1639.30, 1528.31 **ESI-MS:** m/z = 835 $[M + H]^+$, Molecular Weight: 834.96

IV. Conclusion

The invention research work to be continuing for further research of Therapeutic/ Pharmacokinetic.

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