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Synthesis, Characterization and Biological Screening of Ferulic Acid Derivatives

T. Naga Ravi Kiran[1*], Ch. Sri Alekhya[1], B. V. S. Lokesh[1], A. V. S. Madhu Latha[2], Y. Rajendra Prasad[1], T. Naga Mounika[1]

[1]Department of Pharmaceutical Chemistry, Andhra University, Visakhapatnam, India
[2]Nalanda Institute of Pharmaceutical Sciences, Sattenapalli, Guntur, India
Email: [*]ravikirannaga58@gmail.com

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Abstract

According to WHO, cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012. Among several factors involved in the pathogenesis of cancer, free radical formation followed by damage to DNA and cell protein is one of the causes. Natural plant products have gained enormous interest in the prevention or treatment of chronic diseases. Ferulic acid, like other phenolic acids (caffeic acid, sinapic acid) possess anti cancer activity. A series of ferulic esters (FE1 - FE11) and ferulic amides (FA1 - FA10) were synthesized and evaluated for their cytotoxic activity.

Keywords

Ferulic Acid, Cytotoxicity, Hela (Cervical Cancer Cell Lines), A549 (Lung Cancer Cell Lines), HT-29 (Colorectal Cancer Cell Lines), Synthesis

1. Introduction

Natural plant products have gained enormous interest in the prevention or treatment of chronic diseases [1]. From the evolution to till date, whether on an empirical or rational basis, natural based molecules have long been used as drugs or drug leads. Several small molecules available worldwide on the drug market can be traced back to or were inspired by natural products. In the ongoing search for new therapeutic compounds, phenolic acids, which are widely distributed in plants [2], are usually available in cell wall as glycosidic conjugates or esters or amides, therefore they can be released from nature by alkaline hydrolysis [3]. Phenolic acids are widely

[*]Corresponding author.

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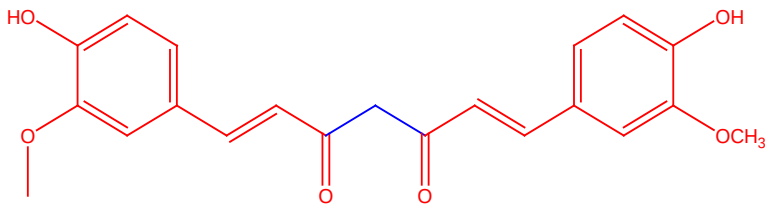
used as anti oxidants in various food products and cosmetics. Other applications of phenolic acids includes anti tumor, hypoglycemic, antihypertensive, anti inflammatory, anti oxidant etc. [4].

According to WHO, cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012. The number of new cases is expected to rise by about 70% over the next 2 decades. More than half of cancers occurring worldwide are in less developed regions. Among several factors involved in the pathogenesis of cancer, free radical formation followed by damage to DNA and cell protein is one of the causes. Ferulic acid, like other phenolic acids (caffeic acid, sinapic acid) possess anti cancer activity. FA scavenges the free radical, regulates cell growth and proliferation and stimulates cytoprotective enzymes and inhibits cytotoxic systems in both *in vitro* and *in vivo* experimental models [3].

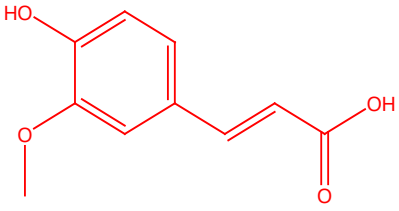
Ferulic acid (4-hydroxy-3-methoxy cinnamic acid) is a phenolic acid found in seeds and leaves of most plants. It is biosynthesized from aminoacid phenylalanine through shikmic acid pathway. FA was first isolated from a commercial resin in 1866. Hlasiwetz Barth, an Austrian, isolated 3-methoxy-4-hydroxycinnamic acid from the genus *Ferula foetida* for structure determination [4]. FA serves to cross link the polysaccharides and proteins during lignin cell wall synthesis [5]. The synthesis of Ferulic acid was established by Dutt in 1935 [4], more over its chemical structure resembles that of curcumin. Ferulic acid [6], was used as a precursor in the manufacturing of vanillin and malonic acid. Numerous studies have shown that ferulic acid is a potent antioxidant, antitumor, hypoglycemic, UV-absorber, anti atherogenic, neuroprotective, anti inflammatory, anti-hyperlipidemic, anti platelet [7] etc. (**Figure 1**, **Figure 2**).

Ferulic acid exhibits antioxidant property through Free radical scavenging property via donating one hydrogen atom from its phenolic hydroxyl group [8] [9]. Ferulic acid and Ferulic acid ethyl ester (FAEE) have shown to regulate the key enzymes which were being responsible for free radical induced cell damage, such as heme oxygenase/biliverdin reductase (HO/BVR) system, superoxide dismutase (SOD), catalase (CAT) as well as the chaperone heat shock protein (Hsp)-70 [3] [10]. Fu-Hsiung Linl *et al*., have proved that addition of 0.5% of ferulic acid to 15% L-ascorbic acid and 1% α-tocopherol stabilizes the solution and doubled photo protection effect [5] [11].

FA has a structural resemblance to curcumin. A number of preclinical studies showed that curcumin, a component of the Indian spice (tumeric), has antioxidant and anti cancer properties [1].



Curcumin



Ferulic acid

Anurag Khatkar *et al*., have synthesized various series of esters and amides of ferulic acid, and tested them for antimicrobial activity [12].

Owing to its diversified therapeutic application, our research work focused on synthesis and anti cancer evaluation of various ferulic esters and amides.

2. Materials and Reagents

Ferulic acid, Thionyl chloride, conc. H_2SO_4. R'-OH (R' as given in **Table 1**), R-NH_2 (R as given in **Table 3**).

Potable water, Ethyl acetate, n-hexane, TLC plates (Merck pre-coated silica gel F plates), P-Anisaldehyde, ninhydrin (TLC visualizing agent).

Derivatives of ferulic acid (corresponding esters and amides) were synthesized using the following method.

2.1. Scheme of Synthesis of Ferulic Esters

Ferulic esters (FE1-FE11) were synthesized as outlined in **Scheme 1**. Ferulic acid (0.0102 moles) is added with appropriate alcohol (5 volumes), it was heated under reflux in presence of sulfuric acid for 4 hrs. The reaction

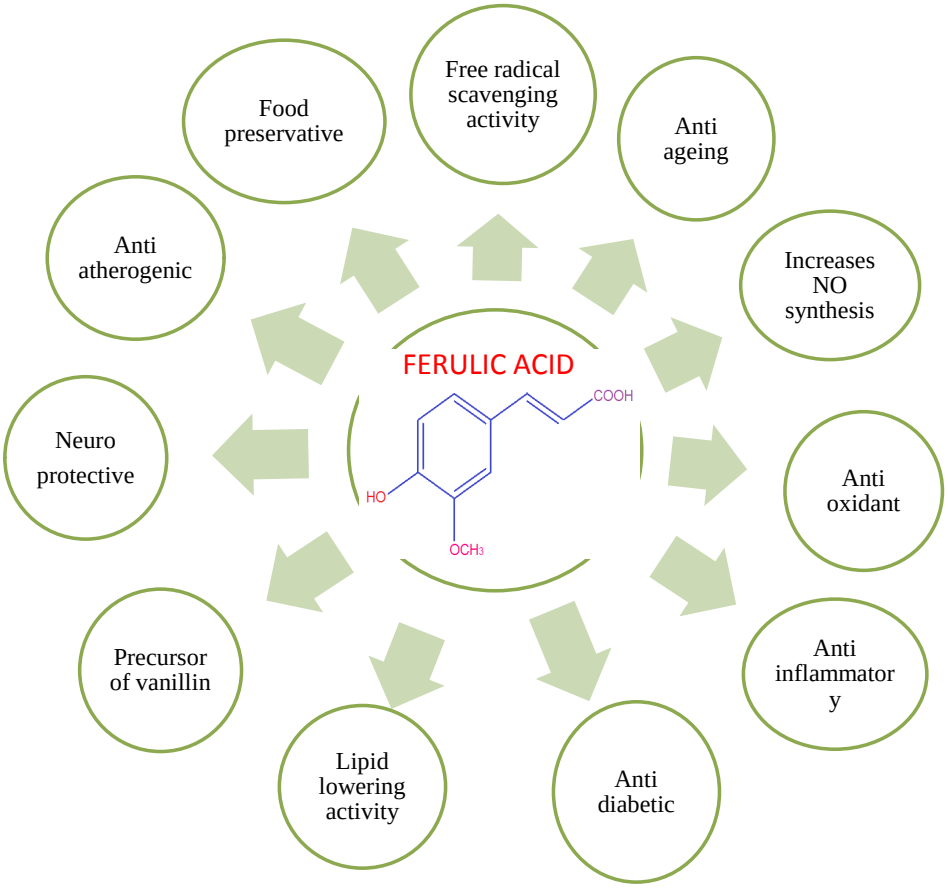
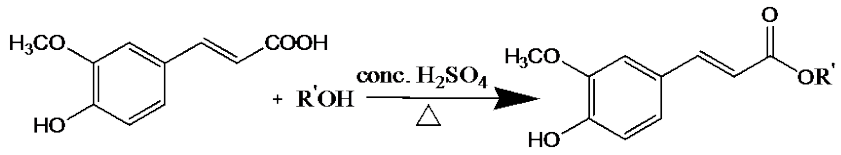


Figure 1. Potential applications of ferulic acid.

Figure 2. Various marketed formulations of ferulic acid.



Scheme 1. Synthesis of ferulic esters.

was monitored by TLC (Merck grade), the reaction mixture was purified through column chromatography (silica gel mesh 100/200) with 20% ethyl acetate in hexane. The physicochemical properties were presented in **Table 1**. The structures of the all the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy.

Compound FE1:

IR absorption bands (cm^{-1}) 3630 (Ar-OH), 1635(C=O str., ester), 3010 (C-H str., aromatic), 1596 (C=C skeletal str., phenyl), 1699 (C=C str., alkene), 2860 (C-H str., Ar-OCH_3); ^{1}H NMR spectrum (400 MHz,$CDCl_3$,) showed the characteristic signals of: 5.00 of Ar-OH (s, 1H), 3.91 of-OCH_3 (s, 1H), 3.78 of Ar-OCH_3 (s, 3H), 7.630 (d, 1H, C_1 of acrylate, j = 1.2 Hz), 6.90 (d, 1H, C_2 of acrylate, j = 8 Hz), ^{13}C NMR (δ ppm) spectrum of compound FE1 exhibited the characteristic signals at: 52.50 (-OCH_3), 56.2 (Ar-OCH_3), 118.1 ($C_2$of acrylate), 143.7 (C_1 of acrylate).

Compound FE2:

IR absorption bands (cm^{-1}) 3600 (Ar-OH), 1685 (C=Ostr., ester), 3004 (C-H str., aromatic), 1592 (C=C skeletal str., phenyl), 1689 (C=C str., alkene), 1080 (C-O str. Ester), 2842 (C–H str., Ar–OCH3); ^{1}H NMRspectrum (400 MHz, $CDCl_3$) 5.00 Ar-OH (s, 1H), 3.91-OCH_3 (s, 1H), 3.78-ArOCH_3 (s, 3H), 7.630 (d, 1H, C_1 of acrylate, j = 1.2 Hz), 6.90 (d, 1H, C_2 of acrylate, j = 8 Hz) 6.37 Ar-H (d, 1H, j = 1.6 Hz) 6.925 Ar-H (d, 1H, j = 1.6 Hz).

Compound FE3:

IR absorption bands cm^{-1} 3620 (Ar-OH), 1675 (C=Ostr., ester), 3006 (C-H str., aromatic), 1589 (C=C skeletal str., phenyl), 1685 (C=C str., alkene), 1095 (C-O str. Ester), 2946 (C–H str., Ar–OCH3) 710.94 (long chain band); 5.890 (1H s Ar-OH), 3.924 (1H, s, OCH_3), ^{1}H NMRspectrum 3.88-ArOCH_3 (s, 3H), 7.059 (d, 1H, C_1 of acrylate, j = 3.6 Hz), 6.275 (s, 1H, C_2 of acrylate) 6.904 Ar-H (d, 1H j = 1.2 Hz) 7.036 Ar-H (d, 1H j = 4.4 Hz) 1.012 CH_3 of propyl chain, (m3H) 1.682 CH_2 of propyl chain, (m, 2H) 4.174 CH_2 of n-propyl chain, (m, 2H).

2.1.1. Cytotoxicity Studies by MTT Assay Method

Maintainence of cell lines:

HT-29 and A-549 cells were grown as adherent in DMEM media, whereas Hela cells were grown in MEM media supplemented with 10% fetal bovine serum the culture was maintained in a humidified atmosphere with 5% CO_2.

MTT assay method:

The cells (HT29, Hela, A549) were seeded in 96 well plate at a density of $1*10^4$ (counted by tryphan blue exclusion dye method) per wall and were incubated for 24 hrs to recover. After incubation, the medium was replaced with fresh media containing different dilutions of test compounds. Then the plates were incubated for additional 48 hr at 37˚ in DMEM (Dulbeccos Eagles medium), /MEM (Minimum essential media eagle) with 10% FBS (fetal bovine serum) medium. Following incubation, the medium was removed and replated with 90 µl of fresh DMEM without FBS. To the above wells, 10 µl of MTT [3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazoliun bromide] reagent was added and incubated at 37˚ for 10 min. The absorbance at 570 nm was measured on a UV spectrophotometer [13] [14].

Methotrexate was used as reference drug for comparison. Assay was performed in triplicate for three independent determinations. The cytotoxicity was expressed as IC_{50} (µg/ml) which is the concentration of the compound that inhibited proliferation rate of the tumor cells by 50% as compared to the control untreated cells. IC_{50} values were determined from the plot *i.e.*, % inhibition versus concentration (**Table 2**) (**Supplementary Data**).

$$\%\ \text{Inhibition of the given concentration} = \frac{1-\left(\text{Absorbance average}\right)}{\text{control absorbance average}} * 100$$

2.1.2. Results and Discussion

In a nutshell, it is evident that all the synthesized esters of Ferulic acid are having good cytotoxic activity with different IC_{50} values against three cell lines (Hela, HT-29, A-549). Methotrexate was used as standard. Of all the compounds tested against HT-29 cell lines, FE10 having a chloroethyl group showed maximum cytotoxicity with a IC_{50} value of 19 µg/mL. Down the order, FE11-having bromine group (IC_{50} = 50 µg/mL) FE5-having n-butyl chain (IC_{50} = 74 µg/mL). FE3 having n-propyl chain (IC_{50} = 75 µg/mL) follows. The other compounds were also moderately potent but with higher IC_{50} values. The potency indicated the importance of halogen in enhancing the cytotoxicity; and as the chain length increases cytoxicity increases. Neverthless, branching of the

Table 1. Physical characterization of esters (FE1 - FE11).

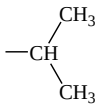
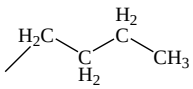
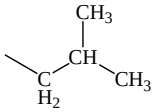
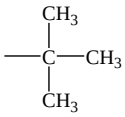
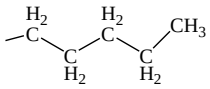
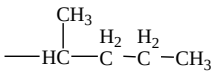
Compound	R'	Molecular formula	Relative Molecular mass (RMM)	Melting point (˚C)	Yield %
FE1	-CH_3	$C_{11}H_{12}O_4$	208.21	266 - 268	89
FE2	-C_2H_5	$C_{12}H_{14}O_4$	222.23	224 - 226	85
FE3	-C_3H_7	$C_{13}H_{16}O_4$	236.26	246 - 248	75
FE4		$C_{13}H_{16}O_4$	236.26	112 - 114	80
FE5		$C_{14}H_{18}O_4$	250.29	203 - 205	70
FE6		$C_{14}H_{18}O_4$	250.29	180 - 182	78
FE7		$C_{14}H_{18}O_4$	250.29	162 - 164	85
FE8		$C_{15}H_{20}O_4$	264.31	139 - 141	79
FE9		$C_{15}H_{20}O_4$	264.31	126 - 128	90
FE10	-CH_2-CH_2-Cl	$C_{12}H_{13}ClO_4$	256.38	239 - 241	85
FE11	-CH_2-CH_2-Br	$C_{12}H_{13}BrO_4$	301.18	244 - 246	82

Table 2. Cytotoxicity of ferulic esters.

Compound	R'	Cell lines		
		HT-29	HELA	A-549
FE1	Methyl	126 ± 1	92 ± 2	101 ± 2
FE2	Ethyl	94 ± 2	70 ± 2	92 ± 1
FE3	n-propyl	75 ± 2	64 ± 2	60 ± 1
FE4	Isopropyl	92 ± 2	138 ± 2	NA
FE5	n-butyl	74 ± 1	61 ± 2	83 ± 2
FE6	Isobutyl	96 ± 1	105 ± 2	NA
FE7	t-butyl	NA	127 ± 2	108 ± 1
FE8	n-pentyl	77 ± 1	69 ± 1	95 ± 1
FE9	2-pentyl	92 ± 2	89 ± 2	98 ± 2
FE10	Chloro ethyl	19 ± 2	32 ± 1	43 ± 2
FE11	Bromo ethyl	50 ± 2	55 ± 2	20 ± 1
Methotrexate		12 ± 1	9 ± 1	5 ± 1

chain diminish the activity.

Among the compounds tested against HeLa cell lines, FE10 having a chlorine group exhibited maximum cytotoxicity with a IC_{50} value of 32 µg/mL. This is followed by compounds, FE11-having bromine group (IC_{50} = 55 µg/mL), FE5-having n-butyl chain (IC_{50} = 61 µg/mL), FE3-having npropyl chain (IC_{50} = 64 µg/mL). The other compounds were also moderately potent, but with higher IC_{50} values. The potency may be due to the presence of halogen, which enhances the cytotoxicity. As the chain length increases, cytoxicity increases. However branching of the chain hinders the activity.

Among the compounds tested against A-549 cell lines, FE11 having a bromine group showed maximal cytotoxicity with a IC_{50} value of 20 µg/mL. This is followed by compounds, FE10, having chlorine group (IC_{50} = 43 µg/mL), FE5-having n-propyl chain (IC_{50} = 60 µg/mL), FE3, having n-butyl chain (IC_{50} = 83 µg/mL). The other compounds also showed the activity but at a higher IC_{50} values. The results indicated the importance of presence of a halogen in enhancing the cytotoxicity. As the chain length increases cytoxicity increases. But branching of the chain reduces the activity.

2.2. Scheme of Synthesis of Ferulic Amides

Ferulic amides (FA1-FA11) were synthesized as outlined in **Scheme 2**. Ferulic acid (0.0102 moles) is added with Thionyl chloride (0.0102 moles) and heated to 60˚C for 1 hr. A pale yellow residue was observed. The acid chloride was then treated with amines in THF (R-NH_2, 10 ml) and stirred at 0˚C - 10˚C using a guard tube (made of $Cacl_2$). The reaction is monitored using TLC, the reaction mixture was purified through column chromatography (silica gel mesh 100/200) with 30% ethyl acetate in hexane as mobile phase. The physicochemical properties were presented in **Table 3**. The structures of the all the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy.

Compound FA1:

The IR (cm^{-1}) spectrum, showed the characteristic absorption bands at 3598.78 (Ar-OH), 3089.74 (C-H str. Alkenes), 3398.78 (NH str.). 1699.44 (C=O str. Amides); The ^{1}H NMR spectrum (400 MHz, $CDCl_3$,) showed the characteristic signals of 5.20 Ar-OH (s, 1H), 3.91-OCH_3 (s, 1H), 3.88 Ar-OCH_3 (s, 3H), 7.09 (d, 1H, C_1 of acrylate, j = 16 Hz), 6.290 (s, 1H, C_2 of acrylate) 6.67 Ar-H (d, 1H j = 15.2 Hz), 6.825 Ar-H (d, 1H j = 8.4 Hz), 6.005 (s, 2H, NH_2).

Compound FA2:

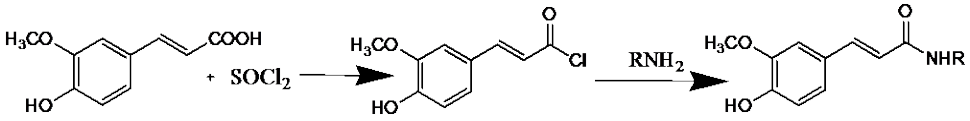
IR absorption bands (cm^{-1}) 3630 (Ar-OH), 3119 (NH_2), 1653 (C=O str., amide) 3018 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1689 (C=C str., alkene), 2865 (C–H str., Ar–OCH3) 2855 (CH_3 str.,). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) 5.88 Ar-OH (s, 1H), 3.79-OCH_3 (s, 1H), 3.45 Ar-OCH_3 (s, 3H), 7.29 (d, 1H, C_1 of acrylate, j = 12 Hz), 6.390 (d, 1H, C_2 of acrylate, j = 2 Hz), 6.77 Ar-H (d, 1H j = 8 Hz), 6.925 Ar-H (d, 1H j = 26 Hz), 8.005 (s, 2H, NH_2), 2.75 (s, 3H, CH_3).

2.2.1. Cytotoxicity Studies by MTT Assay Method

The Method followed was same as that of ferulic esters$_{(FE1\text{-}11)}$ (**Table 4**).

2.2.2. Results and Discussion

In a nutshell, it is evident that all the synthesized amides of Ferulic acid are having good cytotoxic activity with different IC_{50} values against three cell lines (Hela, HT-29, A-549), Methotrexate was used as standard drug. Of all the compounds tested against HT-29 cell lines, FA10 having a morpholine showed maximum cytotoxicity with a IC_{50} value of 18 µg/mL. This is followed by compounds, FA6 with p-amino benztrifluroide (IC_{50} = 19 µg/mL) FA1-a simple amide (IC_{50} = 20 µg/mL), FA9-having p-fluoro benzyl (IC_{50} = 30 µg/mL), FA4-with benzyl moiety (IC_{50} = 38 µg/mL). The other compounds were also moderately potent but with higher IC_{50} values. The potency indicated the importance of halogen in enhancing the cytotoxicity.



FA1-FA10

Scheme 2. Synthesis of ferulic amides.

Table 3. Physical characterization of amides (FA1 - FA10).

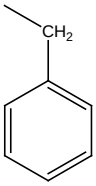
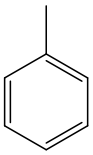
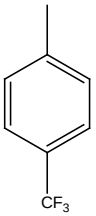
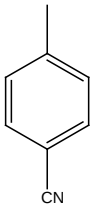
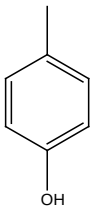
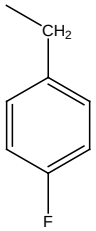
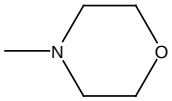
Compound	R	Molecular formula	Relative Molecular mass (RMM)	Melting point (˚C)	Yield %
FA1	-H	$C_{10}H_{11}NO_3$	193.19	206 - 208	80
FA2	$-CH_3$	$C_{11}H_{13}NO_3$	207.23	224 - 226	82
FA3	$-C_2H_5$	$C_{12}H_{15}NO_3$	221.25	230 - 232	75
FA4		$C_{17}H_{17}NO_3$	283.32	146 - 148	79
FA5		$C_{16}H_{15}NO_3$	269.29	150 - 152	75
FA6		$C_{17}H_{14}F_3NO_3$	337.29	145 - 147	87
FA7		$C_{17}H_{14}N_2O_3$	294.304	200 - 202	70
FA8		$C_{16}H_{15}NO_4$	285.29	230 - 232	75
FA9		$C_{17}H_{16}FNO_3$	319.75	228 - 230	80
FA10		$C_{14}H_{17}NO_4$	263.28	250 - 252	75

Table 4. Cytotoxicity of ferulic amides.

Compound	R	Cell line		
		HT-29	HELA	A-549
FA1	H	20 ± 2	35 ± 2	18 ± 1
FA2	Methyl	55 ± 2	45 ± 1	40 ± 1
FA3	Ethyl	50 ± 1	NA	70 ± 2
FA4	Benzyl	38 ± 1	65 ± 2	50 ± 2
FA5	Aniline	90 ± 1	120 ± 2	NA
FA6	4-amino benztrifluoride	19 ± 2	38 ± 2	66 ± 1
FA7	Amino benz nitrile	NA	80 ± 2	72 ± 1
FA8	p-hydroxy aniline	50 ± 2	90 ± 1	40 ± 2
FA9	p-fluoro benzyl	30 ± 1	25 ± 2	55 ± 2
FA10	Morpholine	18 ± 2	23 ± 1	30 ± 1
Methotrexate		12 ± 1	9 ± 1	5 ± 1

Among the compounds tested against Hela cell lines, FA10 having a morpholine group showed maximum cytotoxicity with a IC_{50} value of 23 µg/mL. This is followed by compounds, FA9 with p-fluoro benzyl (IC_{50} = 25 µg/mL), FA1, a simple amide (IC_{50} = 35 µg/mL). FA6 having p-amino benztrifluroide (IC_{50} = 38 µg/mL). The other compounds were also moderately potent but with a higher IC_{50} values. The potency indicated the importance of halogen in enhancing the cytotoxicity.

Among the compounds tested against A-549 cell lines, FA1 simple amide showed maximum cytotoxicity with a IC_{50} value of 18 µg/mL. This is followed by compounds, FA2, having methyl (IC_{50} = 40 µg/mL), FA8, having p-hydroxyl moiety (IC_{50} = 40). FA10, having morpholine moiety (IC_{50} = 42 µg/mL). The other compounds were also moderately potent but with a higher IC_{50} values. The potency indicated the importance of halogen in enhancing the cytotoxicity.

3. Conclusions

Ferulic acid, a multi-faceted phenolic acid was found to possess wide spectrum of biological activities till date. In light of its therapeutic applications, it's derivatives (esters and amides), were designed to synthesize and evaluate for their anti cancer activity.

3.1. Safety Concern

Ferulic acid is a free carboxylic acid with gastric irritation as inevitable adverse effect when consumed orally and this is our rationale for selecting its simple derivatives (esters and amides), lacking free carboxylic acids and thereby preventing G.I. problems and increasing its lipophilicity and membrane penetration. Till date, no such adverse effects were reported. Additional work is under progress with respect to its drug profile.

3.2. Significance

Ferulic acid solely possess very low anti cancer activity and its potency increases manifold only when used in combination with other anti neopastics [15]. Our current work aimed at synthesizing its derivatives (circumventing its commonly found side effect *i.e.*, G. I. problems) and evaluating those derivatives for anticancer activity.

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Abbreviations

IR: infrared spectroscopy;
str: stretch;
s: singlet,
d: doublet;
m: mutiplet;
MTT: [3-(4,5-di methyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide;
TLC: thin layer chromatography;
Ar: aromatic;
DMEM: dubelcoccous eagles medium;
MEM: minimum essential media eagle;
UV spectroscopy: ultraviolet spectroscopy;
IC_{50}: 50% inhibitory concentration;
µl: micro liters;
µg/mL: microgram per ml;
NMR: nuclear magnetic resonance spectroscopy;
THF: tetrahydrofuran;
$CaCl_2$: calicium chloride.

Supplementary Data

Compound	Ir spectral data Position of absorption band (cm^{-1})	^{1}H NMR Chemical shift (δ) in ppm	^{13}C NMR Chemical shift (δ) in ppm	Mass spectral data
FE1	3630 (Ar-OH), 1695 (C=Ostr., ester), 3010 (C-H str., aromatic), 1596 (C=C skeletal str., phenyl), 1699 (C=C str., alkene), 1123 (C-O str. Ester), 2860 (C-H str., Ar-OCH_3)	5.00 Ar-OH(s.1H), 3.91-OCH_3 (s, 1H), 3.78-ArOCH_3 (s, 3H), 7.630 (d, 1H, C_1 of acrylate, j = 1.2 Hz), 6.90 (d, 1H, C_2 of acrylate, j = 8 Hz) 6.37 Ar-H (d, 1H, j = 1.6 Hz) 6.925 Ar-H (d, 1H, j= 1.6 Hz)	144.9(C1), 151.3(C2), 112.0(C3), 143.7(C1') 118.1(C2') 166.5(C3') 56.2(C4')	Molecular ion peak at 209
FE2	3600 (Ar-OH), 1685 (C=Ostr., ester), 3004 (C-H str., aromatic), 1592 (C=C skeletal str., phenyl), 1689 (C=C str., alkene), 1080 (C-O str. Ester), 2842 (C-H str., Ar-OCH_3)	5.27 Ar-OH (s.1H), 3.88 OCH_3 (s, 1H), 3.88-ArOCH_3 (s, 3H), 7.010 (d, 1H, C_1 of acrylate, j = 4 Hz), 6.890 (s, 1H, C_2 of acrylate) 6.256Ar-H (d, 1H j = Hz) 6.890 Ar-H (d, 1H j = 0.8 Hz)	144.9(C1), 151.3(C2), 112.0(C3), 145.7(C1') 116.1(C2') 166.5(C3') 61.4(C4') 14.2(C5') 56.2(C4')	Molecular ion peak at 223
FE3	3620 (Ar-OH), 1675 (C=Ostr., ester), 3006 (C-H str., aromatic), 1589 (C=C skeletal str., phenyl), 1685 (C=C str., alkene), 1095 (C-O str. Ester), 2946 (C-H str., Ar-OCH_3) 710.94 (long chain band)	5.890 (1H s Ar-OH), 3.924 (1H , s, OCH_3), 3.88-ArOCH_3 (s, 3H), 7.059 (d, 1H, C_1 of acrylate, j = 3.6 Hz), 6.275 (s, 1H, C_2 of acrylate) 6.904 Ar-H (d, 1H j = 1.2 Hz) 7.036 Ar-H (d, 1H j = 4.4 Hz) 1.012 CH_3 of propyl chain, (m3H) 1.682 $CH_2$of propyl chain, (m, 2H) 4.174 $CH_2$of propyl chain, (m , 2H)	144.9(C1), 152.3(C2), 116.3(C3), 56.2(C4') 148.7(C1') 118.1(C2') 169.5(C3') 67.6(C4') 22.2(C5') 10.2(C6')	Molecular ion peak at 237
FE4	3625 (Ar-OH), 1679 (C=O str., ester), 3010 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1695 (C=C str., alkene), 1099 (C-O str. Ester), 2846 (C-H str., Ar-OCH_3) 750.94 (long chain band)	5.813 (1H s Ar-OH), 3.907 (1H , s, OCH_3), 3.907-ArOCH_3 (s, 3H), 7.044 (d, 1H, C_1ofacrylate, j = 16 Hz), 7.570 (s, 1H, C_2 of acrylate) 6.246 Ar-H (d, 1H j = 2.4 Hz) 6.896 Ar-H (d, 1H j = 8 Hz) 1.312 CH_3 of propyl chain, (m, 6H) 5.084 - 5.162 $CH_2$of propyl chain, (m)	147.9(C1), 155.3(C2), 119.3(C3), 56.2(C4') 152.7(C1') 122.1(C2') 168.5(C3') 69.6(C5') 24.2(C6'.C7')	Molecular ion peak at 237
FE5	3629 (Ar-OH), 1685 (C=Ostr., ester), 3003 (C-H str., aromatic), 1575 (C=C skeletal str., phenyl), 1687 (C=C str., alkene), 1095 (C-O str. Ester), 2946 (C-H str., Ar-OCH_3) 718.94 (long chain band)	5.890 (1H s Ar-OH), 3.923-ArOCH_3 (s, 3H), 7.056 (d, 1H, $C_1$of acrylate, j = 2 Hz), 7.584 (d, 1H, C_2 of acrylate, j = 16 Hz) 6.307Ar-H (d, 1H j = 16 Hz) 6.922 Ar-H (d, 1H j = 6 Hz) 0.98 CH_3 of butyl chain, (m 3H) 1.465 - 1.409 (m) CH_2 of butyl chain, 1.720 - 1.625 (m) CH_2 of butyl chain,	147.9(C1), 155.3(C2), 119.3(C3), 152.7(C1') 122.1(C2') 168.5(C3') 56.2(C4') 65.1(C5') 31.3(C6'). 19.0(C7') 13.8(C8')	Molecular ion peak at 251
FE6	3625 (Ar-OH), 1689 (C=Ostr., ester), 3009 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1697 (C=C str., alkene), 1085 (C-O str. Ester), 2956 (C-H str., Ar-OCH_3) 613.94 (long chain band)	5.180 (1H s Ar-OH), 3.943-ArOCH_3 (s, 3H), 7.086 (d, 1H, $C_1$of acrylate, j = 9.6 Hz), 7.594 (d, 1H, C_2 of acrylate, j = 12 Hz) 6.207Ar-H (d, 1H j = 5.6 Hz) 6.944 Ar-H (d, 1H j = 3.2 Hz) 4.11 CH of butyl chain, (d, 2H j = 20.8 Hz) 1.012 (d, 6 H, j = 39.2 Hz $CH_3$of butyl chain, 2.400 - 2.475 (m, 2H) CH of iso butyl chain.	149.9(C1), 150.3(C2), 117.3(C3), 155.7(C1') 120.1(C2') 167.5(C3') 74.9(C4') 27.8(C5'). 19.4(C6') 19.4(C7')	Molecular ion peak at 251

Continued

FE7	3630 (Ar-OH), 1669 (C=Ostr., ester), 3019 (C-H str., aromatic), 1569 (C=C skeletal str., phenyl), 1699 (C=C str., alkene), 1198 (C-O str. Ester), 2856 (C-H str., Ar-OCH_3) 608.94 (long chain band)	5.28 (1H s Ar-OH), 3.73-ArOCH_3(s, 3H), 7.69 (d, 1H, $C_1$of acrylate, j = 12 Hz), 6.49 (d, 1H, C_2 of acrylate, , j = 12 Hz), 6.59 Ar-H (d, 1H j = 8 Hz) 6.84 Ar-H (d, 1H j = 20 Hz) 1.40 CH_3 protons of t-butyl group (9H, s)	149.9(C1), 150.3(C2), 117.3(C3), 155.7(C1') 120.1(C2') 167.5(C3') 82.2(C4') 28.9(C5', C6', C7')	Molecular ion peak at 251
FE8	3625 (Ar-OH), 1689 (C=Ostr., ester), 3009 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1697 (C=C str., alkene), 1085 (C-O str. Ester), 2956 (C-H str., Ar-OCH_3) 613.94 (long chain band)	5.280 (1H s Ar-OH), 3.943-ArOCH_3(s, 3H), 7.086 (d, 1H, $C_1$of acrylate, j = 3.6 Hz), 7.594 (d, 1H, C_2 of acrylate, j = 1.6 Hz) 6.207 Ar-H(d, 1H j = 2 Hz) 6.944 Ar-H(d, 1H j = 2.4 Hz) 1.33 CH_2 protons of pentyl chain(2H, m) 1.29 CH_2 protons of pentyl chain (2H, m) 1.59 CH_2 protons of pentyl chain (2H, m) 4.29 CH_2 protons of pentyl chain (2H, m) 0.98 CH_3protons of pentyl chain (3H, m).	149.9(C1), 150.3(C2), 117.3(C3), 155.7(C1') 120.1(C2') 167.5(C3') 65.4(C4') 28.8(C5'). 28.1(C6') 22.5(C7') 14.1(C8')	Molecular ion peak at 265
FE9	3625 (Ar-OH), 1689 (C=Ostr., ester), 3009 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1697 (C=C str., alkene), 1085 (C-O str. Ester), 2956 (C-H str., Ar-OCH_3) 613.94 (long chain band)	5.880 (1H s Ar-OH), 3.943-ArOCH_3 (s, 3H), 6.086 (d, 1H, $C_1$of acrylate, j = 25.6 Hz), 7.694 (s, 1H, C_2 of acrylate) 6.207 Ar-H (d, 1H j = 2 Hz) 6.944 Ar-H (d, 1H j = 18 Hz) 1.40 CH_2 of pentyl chain, (m 3H) 4.13 (m, 1 H) CH of pentyl chain, 1.53 (m, 2H) CH_2 of pentyl chain. 1.33 (m, 2H) CH_2 of pentyl chain. 0.96 (t, 3H) CH_3 of pentyl chain.	149.9(C1), 150.3(C2), 117.3(C3), 155.7(C1') 120.1(C2') 167.5(C3') 71.9(C4') 21.8(C5'). 39.4(C6') 16.4(C7') 14.1(C8')	Molecular ion peak at 265
FE10	3630 (Ar-OH), 1669 (C=Ostr., ester), 3019 (C-H str., aromatic), 1569 (C=C skeletal str., phenyl), 1687 (C=C str., alkene), 1152 (C-O str. Ester), 2966 (C-H str., Ar-OCH_3) 570.94 (chlorine)	5.880 (1H s Ar-OH), 3.943-ArOCH_3(s, 3H), 7.486 (d, 1H, $C_1$of acrylate, j = 13.6 Hz), 7.524 (d, 1H, C_2 of acrylate, j = 2 Hz) 6.507 Ar-H (d, 1H j = 4.4 Hz) 6.844 Ar-H (d, 1H j = 2.4 Hz) 4.41-CH_2 (d, 2H, j = 3.6 Hz) 3.66-CH_2 (d, 2H, j = 24 Hz)	149.9(C1) 155.3(C2) 127.3(C3) 151.9(C1') 118.5(C2') 173.5(C3') 69.6(C4') 42.4(C5')	Molecular ion peak at 257
FE11	3615 (Ar-OH), 1699 (C=Ostr., ester), 3019 (C-H str., aromatic), 1569 (C=C skeletal str., phenyl), 1677 (C=C str., alkene), 1255 (C-O str. Ester), 2956 (C-H str., Ar-OCH_3) 613.94 (bromine)	5.680 (s, 1H, Ar-OH), 3.743-ArOCH_3 (s, 3H), 6.41 (d, 1H, $C_1$of acrylate, j = 16 Hz), 7.641 (d, 1H, C_2 of acrylate, j = 20 Hz) 6.69 Ar-H (d, 1H, j = 3.2 Hz) 6.84 Ar-H (d, 1H, j = 20 Hz) 4.65 (d, 2H, CH_2, j = 28 Hz) 3.58 (d, 2H, CH_2, j = 32 Hz)	150.9(C1) 155.3(C2) 119.3(C3) 159.7(C1') 119.1(C2') 169.5(C3') 70.6(C4') 20.4(C5')	Molecular ion peak at 302

Elemental Analysis Data of Ferulic Esters

Compound	%Calculated			% Found		
	C	H	O	C	H	O
FE1	63.45	5.81	30.74	63.43	5.79	30.71
FE2	64.85	6.35	28.80	64.81	6.33	28.79
FE3	66.09	6.83	27.09	66.06	6.81	27.06
FE4	66.09	6.83	27.09	66.05	6.80	27.04
FE5	67.18	7.25	25.57	67.15	7.23	25.54
FE6	67.18	7.25	25.57	67.12	7.20	25.50
FE7	67.18	7.25	25.57	67.11	7.22	25.51

Continued

FE8	68.16	7.63	24.21	68.14	7.62	24.22
FE9	68.16	7.63	24.21	68.19	7.59	24.10
FE10	56.15	5.10	24.93	56.10	5.15	24.99
FE11	47.86	4.35	21.25	47.90	4.30	47.85

Elemental Analysis Data of Ferulic Amides

Compound	%Calculated				% Found			
	C	H	O	N	C	H	O	N
FA1	62.17	5.74	24.84	7.25	62.19	5.77	24.87	7.29
FA2	63.36	6.32	23.16	6.76	63.39	6.39	23.18	6.78
FA3	65.14	6.83	21.69	6.33	65.10	6.85	21.72	6.30
FA4	72.07	6.05	16.94	4.94	72.10	6.08	16.99	4.89
FA5	71.36	5.61	17.82	5.20	71.30	5.69	17.89	5.29
FA6	60.54	4.18	14.23	4.25	60.50	4.11	14.22	4.20
FA7	69.38	4.79	16.31	9.52	69.30	4.70	16.30	9.58
FA8	67.36	5.30	22.43	4.91	67.39	5.35	22.49	4.85
FA9	67.76	5.35	15.93	4.65	67.69	5.30	15.90	4.69
FA10	63.87	6.51	24.31	5.32	63.79	6.50	24.39	5.38

Compound	Ir spectral data Position of absorption band (cm^{-1})	^{1}H NMR Chemical shift (δ) in ppm	^{13}C NMR Chemical shift (δ) in ppm	Mass spectral data
FA1	3620 (Ar-OH), 3109 (NH_2), 1635 (C=Ostr., amide) 3, 012 (C-H str., aromatic), 1586 (C=C skeletal str., phenyl), 1, 689 (C=C str., alkene), , 2860 (C-H str., Ar-OCH_3)	5.20 Ar-OH (s.1H), 3.91-OCH_3 (s, 1H), 3.88-ArOCH_3 (s, 3H), 7.09 (d, 1H, $C_1$of acrylate, j = 12 Hz), 6.290 (d, 1H, C_2 of acrylate, , j = 2 Hz) 6.67 Ar-H (d, 1H, j = 28 Hz) 6.825 Ar-H (d, 1H j = 24 Hz) 6.005 (s, 2H, NH_2)	144.9(C1) 151.3(C2) 112.0(C3) 128.1(C4) 120.1(C5) 116.2(C6) 144.9(C1') 116.1(C2') 169.5(C3') 56.8(C4')	Molecular ion peak-194
FA2	3630 (Ar-OH), 3119 (NH_2), 1653 (C=Ostr., amide) 3018 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1689 (C=C str., alkene), 2865 (C-H str., Ar-OCH_3) 2855 (CH_3 str.,)	5.88 Ar-OH (s.1H), 3.79-OCH_3 (s, 1H), 3.45-ArOCH_3 (s, 3H), 7.29 (d, 1H, $C_1$of acrylate, j = 12 Hz), 6.390 (d, 1H, C_2 of acrylate, j = 2 Hz) 6.77 Ar-H (d, 1H j = 8 Hz) 6.925 Ar-H (d, 1H j = 26 Hz) 8.005 (s, 2H, NH_2) 2.75 (s, 3H, CH_3)	147.9(C1) 155.8(C2) 111.9(C3) 127.7(C4) 122.2(C5) 118.5(C6) 145.4(C1') 118.9(C2') 167.5(C3') 57.4(C4')	Molecular ion peak-208
FA3	3635 (Ar-OH), 3109 (NH_2), 1683 (C=Ostr., amide) 3002 (C-H str., aromatic), 1565 (C=C skeletal str., phenyl), 1699 (C=C str., alkene), 2868 (C-H str., Ar-OCH_3) 2855 (CH_3 str.,) 2745 (CH_3 str.,)	5.25Ar-OH (s.1H), 3.59-OCH_3 (s, 1H), 3.04-ArOCH_3 (s, 3H), 7.55 (d, 1H, $C_1$of acrylate, j = 12 Hz), 6.84 (d, 1H, C_2 of acrylate, j = 20 Hz) 6.75 Ar-H (d, 1H j = 16 Hz) 6.89 Ar-H (d, 1H, j = 24 Hz) 8.102 (s, 2H, NH_2) 3.50 (d, 2H, CH_2) 1.35 (d, 3H, CH_3)	144.9(C1), 153.8(C2), 112.8(C3), 129.9(C4) 124.4(C5) 116.5(C6) 149.4(C1') 116.9(C2') 169.3(C3') 57.4(C4') 34.2 (C4") 15.2(C5")	Molecular ion peak-222

Continued

FA4	3630 (Ar-OH), 3398 (NH_2), 1665 (C=Ostr., amide) 3069 (C-H str., aromatic), 1582 (C=C skeletal str., phenyl), 1685 (C=C str., alkene), 2899 (C-H str., Ar-OCH_3) 1436 (CH_2 bend.) 1609, 1473 (stret. C=C aromatic)	5.35Ar-OH(s.1H), 3.79-OCH_3(s, 1H), 3.25-ArOCH_3(s, 3H), 7.58(d, 1H, $C_1$of acrylate, j = 16 Hz), 6.95(s, 1H, C_2 of acrylate) 6.65 Ar-H(d, 1H j = 12 Hz) 6.94 Ar-H(d, 1H j = 20 Hz) 8.102(s, 2H, NH_2) 4.25(d, 2H, CH_2) 7.063(d, 2H, Ar-CH, j = 23.6 Hz) 7.142(t, 2H, Ar-CH)	144.9(C1), 153.8(C2), 112.8(C3), 129.9(C4) 124.4(C5) 116.5(C6) 149.4(C1') 116.9(C2') 169.3(C3') 44.1(C4') 141.7(C1") 127.58(C2, 6") 126.25(C4") 128.32(C3, 5")	Molecular ion peak-284
FA5	3625 (Ar-OH), 3389 (NH_2), 1679 (C=Ostr., amide) 3104 (C-H str., aromatic), 1375 (C=C skeletal str., phenyl), 1665(C=C str., alkene), 2885 (C-H str., Ar-OCH_3) 1604, 1475 (str., C=C aromatic)	5.35Ar-OH(s.1H), 3.79-OCH_3(s, 1H), 3.25-ArOCH_3(s, 3H), 7.58(d, 1H, $C_1$of acrylate, j = 16 Hz), 6.95(d, 1H, C_2 of acrylate, j = 24 Hz) 6.65 Ar-H(d, 1H, j = 4 Hz) 6.94 Ar-H(d, 1H, j = 20 Hz) 8.102(s, 2H, NH_2) 7.64(d, 2H, Ar-CH_2, j = 18 Hz) 7.45(t, 2H, Ar-CH) 7.09 (t, 2H, Ar-CH)	142.7(C1), 155.2(C2), 116.1(C3), 128.0(C4) 123.4(C5) 118.5(C6) 145.4(C1') 118.9(C2') 166.3(C3') 56.9(C4') 135.9(C1") 121.6(C2, 6") 124.4(C4") 129.3(C3, 5")	Molecular ion peak- 270
FA6	3630 (Ar-OH), 3399 (NH_2), 1679 (C=Ostr., amide) 3107 (C-H str., aromatic), 1379 (C=C skeletal str., phenyl), 1678 (C=C str., alkene), 2895 (C-H str., Ar-OCH_3) 1604, 1475 (str., C=C aromatic) 1324 (str., C-F)	5.75Ar-OH(s.1H), 3.79-OCH_3(s, 1H), 3.25-ArOCH_3(s, 3H), 7.58(d, 1H, $C_1$of acrylate, j = 24 Hz), 6.55(d, 1H, C_2 of acrylate, j = 16 Hz) 6.45 Ar-H(d, 1H, j = 16 Hz) 6.64 Ar-H(d, 1H , j = 20 Hz) 8.202(s, 2H, NH_2) 7.57(d, 2H, Ar-CH, j = 20 Hz) 7.43 (d, 2H, Ar-CH, j = 24 Hz)	142.7(C1), 155.2(C2), 116.1(C3), 128.0(C4) 123.4(C5) 118.5(C6) 145.4(C1') 118.9(C2') 166.3(C3') 139.8(C1") 121.8.6(C2, 6") 126.6(C4") 125.4(C3, 5") 124.2(C in CF_3)	Molecular ion peak- 338
FA7	3146 (Ar-OH), 3334 (NH_2), 1633 (C=Ostr., amide) 3106 (C-H str., aromatic), 1325 (C=C skeletal str., phenyl), 1633, (C=C str., alkene), 2375 (C-H str., Ar-OCH_3) 1588, 1465 (str., C=C aromatic) 2231 (stret.-CN)	5.55Ar-OH(s.1H), 3.79-OCH_3(s, 1H), 3.45-ArOCH_3(s, 3H), 7.57(d, 1H, $C_1$of acrylate, j = 28 Hz), 6.45(d, 1H, C_2 of acrylate, j = 20 Hz) 6.39 Ar-H(d, 1H, j = 16 Hz) 6.69 Ar-H(d, 1H, j = 24 Hz) 8.352(s, 2H, NH_2) 7.82(d, 2H, Ar-CH, j = 28 Hz) 7.49 (d, 2H, Ar-CH, j = 15 Hz)	144.7(C1), 157.2(C2), 118.1(C3), 122.0(C4) 125.4(C5) 116.5(C6) 145.4(C1') 118.9(C2') 166.3(C3') 56.2(C4') 140.8(C1") 122.3(C2, 6") 108.2(C4") 132.4(C3, 5") 115.8(C in CN)	Molecular ion peak-295

Continued

FA8	3572 (Ar-OH), 3146 (NH_2), 1643 (C=Ostr., amide) 3105(C-H str., aromatic), 1325 (C=C skeletal str., phenyl), 1636, (C=C str., alkene), 2345 (C-H str., Ar-OCH_3) 1510, 1435 (str., C=C aromatic)	5.60Ar-OH(s.2H), 3.68-OCH_3(s, 1H), 3.38-ArOCH_3(s, 3H), 7.59(d, 1H, $C_1$of acrylate, j = 12 Hz), 6.28(d, 1H, C_2 of acrylate, j = 12 Hz) 6.45Ar-H(d, 1H, j = 8 Hz) 6.78Ar-H(d, 1H, j = 16 Hz) 8.012(s, 2H, NH_2) 7.47(d, 2H, Ar-CH, j = 20 Hz) 6.71(d, 2H, Ar-CH, j = 16 Hz)	142.7(C1), 155.2(C2), 116.1(C3), 128.0(C4) 123.4(C5) 118.5(C6) 145.4(C1') 118.9(C2') 166.3(C3') 128.5(C1") 123.5(C2, 6") 154.1(C4") 116.2(C3, 5")	Molecular ion peak-286
FA9	3572 (Ar-OH), 3146 (NH_2), 1643 (C=Ostr., amide) 3105 (C-H str., aromatic), 1325 (C=C skeletal str., phenyl), 1636, (C=C str., alkene), , 2345 (C-H str., Ar-OCH_3) 1510, 1435 (str., C=C aromatic) 1377 (str., C-F)	5.50Ar-OH(s.2H), 3.78-OCH_3(s, 1H), 3.58-ArOCH_3(s, 3H), 7.54(d, 1H, $C_1$of acrylate, j = 20 Hz), 6.25(d, 1H, C_2 of acrylate, j = 16 Hz) 6.49Ar-H(d, 1H, j = 24 Hz) 6.82Ar-H(d, 1H, j = 28 Hz) 8.312(s, 1H, NH) 4.22(s, 2H, CH_2) 7.07(d, 2H, Ar-CH, j = 16 Hz) 6.81(d, 2H, Ar-CH, j = 12 Hz)	142.7(C1), 155.2(C2), 116.1(C3), 128.0(C4) 123.4(C5) 118.5(C6) 145.4(C1') 118.9(C2') 166.3(C3') 44.1(-CH_2) 137.3.5(C1") 128.6(C2, 6") 160.9(C4") 115.3(C3, 5")	Molecular ion peak-320
FA10	3650 (Ar-OH), 350 (NH), 1635 (C=Ostr., amide) 3089 (C-H str., aromatic), 1377 (C=C skeletal str., phenyl), 1655, (C=C str., alkene), , 2345 (C-H str., sAr-OCH_3) 1324 (str., C-N)	5.52Ar-OH(s.2H), 3.68-OCH_3(s, 1H), 3.29-ArOCH_3(s, 3H), 7.51(d, 1H, $C_1$of acrylate, j = 16 Hz), 6.61(d, 1H, C_2 of acrylate, j = 12 Hz) 6.43Ar-H(d, 1H, j = 28 Hz) 6.99Ar-H(d, 1H, j = 15 Hz) 8.110(s, 1H, NH) 3.47(d, 2H, Ar-CH, j = 20 Hz) 3.67(d, 2H, Ar-CH, j = 16 Hz)	140.7(C1), 159.2(C2), 118.1(C3), 127.0(C4) 125.4(C5) 119.5(C6) 142.4(C1') 116.9(C2') 167.3(C3') 45.6(C1"C4") 66.8(C2"C3")	molecular ion peak-264