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Synthesis and characterization of novel amide derivatives of substituted 2-aminothiohenes and ferulic acid

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Abstract

Ferulic acid converted into acetyl ferulic acid by treating with acetic anhydride in pyridine and subsequently acetyl feruloyl chloride was prepared using thionyl chloride. Substituted 2-aminothiophenes **(1-12)** were condensed with acetyl feruloyl chloride to get novel 4-acetoxy-3-methoxy phenyl acrylamide derivatives containing substituted 2-aminothiophenes. All the resulted compounds were deprotected using pyrrolidine to get another set of novel 4-hydroxy-3-methoxy phenyl acrylamide derivatives containing substituted 2-aminothiophenes **(1A–12A)**. The structures of the title compounds were confirmed based on functional groups, number of protons, number of carbons and molecular weight from FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra respectively.

Keywords: Substituted 2-aminothiophene, Ferulic acid, Feruloyl chloride.

Introduction

Ferulic acid, also known as 4-hydroxy-3-methoxycinnamic acid, is a phenolic chemical that exists naturally in plant cell walls. It is found in large quantities in the bran of grasses including rice, wheat, and oats, as well as in coffee, apples, and peanuts [1]. Ferulic acid is renowned for its antioxidant properties [2,3], which arise from its ability to neutralize free radicals and enhance the stability and efficacy of other antioxidants such as vitamins C and E. Its biological properties include antimicrobial and anti-inflammatory [4], anticancer actions [5], rendering it as a substance of considerable interest in the domains of nutrition, cosmetics, and medicines.

Ferulic acid derivatives were developed with the aim of enhancing its biological activity, improving its solubility, and increasing its stability for diverse uses [6]. These derivatives can be classified according to the alterations introduced to the structure of ferulic acid, including esterification, amidation, and glycosylation. Ferulic acid amides are a distinct

set of derivatives in which the carboxylic acid group of ferulic acid is transformed into an amide. These compounds are generating interest because of their improved biological activity and stability in comparison to the original molecule. Ferulic acid amides possess strong antioxidant [7], anti-inflammatory [8], anti-diabetic [9,10] and anticancer characteristics [11]. For example, the synthesis of feruloyl amides using different amines has demonstrated enhanced solubility in lipids and more potent abilities to scavenge radicals. Some ferulic acid amides not only possess antioxidant capabilities but also exhibit inhibitory effects on enzymes that play a role in inflammatory processes. This makes them potential candidates for treating inflammatory illnesses.

2-Aminothiophenes are a class of five membered heterocyclic compounds characterized by the presence of amino group at 2nd position on thiophene ring. The incorporation of an amino group significantly influences the chemical reactivity and biological activity of these compounds. 2-Aminothiophenes exhibit a wide range of biological activities, making them valuable in medicinal chemistry and drug development. Their biological significance is attributed to their ability to interact with different biological targets, such as enzymes, receptors, and nucleic acids. Various notable biological activities associated with 2-aminothiophenes are anti-inflammatory [12], antioxidant and antibacterial [13], antimicrobial [14], antiproliferative [15], anti-leishmanial [16], anticonvulsant [17], and antitumor activities [18]. Many medicinally important drugs like Tinoridine, Tiaprofenic acid, and Tenidap contain the thiophene ring in their structural frame work and they were used as anti-inflammatory medications [19]. Based on the above observations in the present work new chemical entities were designed to synthesize using molecular hybridization technique. Two biologically active moieties ferulic acid and substituted 2-aminothiophenes are coupled to get novel amide derivatives. The present study aimed to characterize all the novel amide derivatives by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra.

Experimental

Material and Methods

All the chemicals (reagents and solvents) were purchased from commercial suppliers (Merck and Avra chemicals) and they were used as received without further purification. The progress of the reactions was monitored by thin layer chromatography on TLC Silica gel 60 F_{254} plates. Spots were visualized by ultraviolet light. Melting points were determined by an electrical melting point apparatus (Temp-SM1056) and were uncorrected. FT-IR spectra for all the compounds were recorded on Bruker analyzer FT-IR spectrophotometer (KBr pressed pellet

technique). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-400 MHz and 100 MHz spectrometers (chemical shifts in ppm) using tetramethylsilane as an internal standard. The mass spectra of the compounds were recorded on Agilent 6120 single quadrupole LC-MS with ES-APCI.

Synthesis of substituted 2-aminothiophenes

Ketones like 2-butanone, cyclopentanone, cyclohexanone and cycloheptanone (0.01 mol), activated nitriles like ethyl cyanoacetate, cyanoacetamide and malononitrile (0.01 mol) and sulfur (0.01 mol, 0.32 g) in 20 mL of ethanol were stirred at 50°C. To this mixture morpholine (0.025 mol, 2.16 mL) was added dropwise and stirring was continued for another 3 h at ambient temperature. Further, the resultant solution was left overnight in refrigerator and the obtained crude compound was filtered, dried and recrystallized from absolute ethanol. Synthesized substituted 2-aminothiophenes (**1-12**) were characterized by reported reference melting points [20-21].

Synthesis of acetyl feruloyl chloride from ferulic acid [22]

Ferulic acid (0.005 mol, 0.97 g), pyridine (0.045 mol, 3.64 ml) and acetic anhydride (0.014 mol, 1.32 ml) mixture was stirred at room temperature for half an hour. Cold water was added into the reaction product until the formation of white precipitate. The precipitate was filtered, washed with water, dried and recrystallized from hot methanol. Acetyl ferulic acid (0.005 mol, 1.18 g) in 20 mL of benzene and thionyl chloride (0.029 mol, 2.10 ml) were refluxed for 4 hours, the resultant solution was distilled to remove unreacted thionyl chloride to give acetyl feruloyl chloride. The solid was used in further procedure without purification.

General procedure for the synthesis of novel acetyl feruloyl amide derivatives containing substituted 2-aminothiophenes [22]

To the mixture of acetyl feruloyl chloride (0.005 mol) in 20 mL of dichloromethane, pyridine (0.004 mol, 0.32 mL), triethyl amine (0.004 mol, 0.56 mL) and substituted 2-aminothiophenes (0.005 mol) **(1-12)** were added. The reaction mixture was stirred at room temperature for 4 h until the completion of reaction, monitored by TLC. Further the reaction mixture was washed with 20 mL of 1N HCl, the organic layer was washed again with 20 mL of saturated ammonium chloride solution and dried with anhydrous Na_2SO_4. The resultant mixture was filtered, evaporated to get solid and recrystallized from absolute ethanol.

General procedure for the deprotection of novel acetyl feruloyl amide derivatives containing substituted 2-aminothiophenes to get title compounds (1A-12A) [22]

To acetyl feruloyl amide (0.005 mol), 1 mL of pyrrolidine and 25 mL of ethyl acetate were added then the reaction mixture was stirred at room temperature for 4 h. The resultant solution

was washed with 20 mL of 1M H_2SO_4 the organic layer was washed again with 20 mL of saturated ammonium chloride, dried with anhydrous Na_2SO_4 and evaporated. The formed solid was recrystallized from ethanol. Further, all the synthesized compounds were characterized by IR, ^{1}H-NMR and ^{13}C-NMR and mass spectra.

Ethyl 2-((*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamido)-4,5-dimethylthiophene-3-carboxylate (1A)

$C_{19}H_{21}NO_5S$, IR [KBr film] cm^{-1}: 3405 (OH, str), 3201 (NH, str), 2940 (CH, str), 1773 & 1684 (C=O, str), 1267 (asymmetric C-O-C, str), 1029 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, $CDCl_3$] δ: 1.42-1.45 (t, 3H, O-CH_2<u>CH_3</u>), 1.62 (s, 3H, <u>CH_3</u>), 2.29 (s, 3H, <u>CH_3</u>), 3.90 (s, 3H, <u>OCH_3</u>), 4.37-4.42 (q, 2H, O-<u>CH_2</u>CH_3), 6.62-6.65 (d, 1H, Ar-H), 6.86-6.88 (d, 1H, CO-<u>CH</u>=CH), 7.120-7.124 (d, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.77-7.81 (d, 1H, CO-CH=<u>CH</u>), 9.68 (s, 1H, O<u>H</u>), 11.56 (s, 1H, N<u>H</u>). ^{13}C-NMR [100 MHz, $CDCl_3$] δ: 12.7, 14.1, 14.6, 55.9, 60.7, 111.8, 114.8, 118.3, 118.5, 121.9, 123.3, 129.3, 130.7, 143.2, 146.0, 146.2, 148.2, 162.2, 166.9. ES+APCI MS: m/z 376 $(M+H)^+$.

2-((*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamido)-4,5-dimethylthiophene-3-carboxamide (2A)

$C_{17}H_{18}N_2O_4S$, IR [KBr film] cm^{-1}: 3316 (OH, str), 3159 (NH, str), 2967 (CH, str), 1660 (C=O, str), 1209 (asymmetric C-O-C, str), 1025 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, $CDCl_3$] δ: 1.61 (s, 3H, <u>CH_3</u>), 2.30 (s, 3H, <u>CH_3</u>), 3.89 (s, 3H, <u>OCH_3</u>), 6.62-6.66 (d, 1H, Ar-H), 6.87-6.89 (d, 1H, CO-<u>CH</u>=CH), 7.115-7.119 (d, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.78-7.82 (d, 1H, CO-CH=<u>CH</u>), 9.68 (s, 1H, O<u>H</u>), 11.58 (s, 1H, N<u>H</u>). ^{13}C-NMR [100 MHz, $CDCl_3$] δ: 12.6, 14.5, 56.0, 112.0, 114.6, 117.9, 118.2, 123.0, 123.1, 129.2, 130.9, 143.1, 146.1, 146.4, 160.0, 162.0, 166.3. ES+APCI MS: m/z 347 $(M+H)^+$.

(*E*)-N-(3-cyano-4,5-dimethylthiophen-2-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (3A)

$C_{17}H_{16}N_2O_3S$, IR [KBr film] cm^{-1}: 3420 (OH, str), 3196 (NH, str), 2879 (CH, str), 2165 (CN, str), 1647 (C=O, str), 1216 (asymmetric C-O-C, str), 1070 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, $CDCl_3$] δ: 1.63 (s, 3H, <u>CH_3</u>), 2.31 (s, 3H, <u>CH_3</u>), 3.91 (s, 3H, <u>OCH_3</u>), 6.63-6.67 (d, 1H, Ar-H), 6.87-6.89 (d, 1H, CO-<u>CH</u>=CH), 7.11-7.12 (d, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.78-7.82 (d, 1H, CO-CH=<u>CH</u>), 9.69 (s, 1H, O<u>H</u>), 11.57 (s, 1H, N<u>H</u>). ^{13}C-NMR [100 MHz, $CDCl_3$] δ: 12.7, 14.7, 56.1, 112.2, 114.5, 115.3, 118.0, 119.0, 122.1, 123.5, 129.4, 130.4, 143.5, 146.0, 146.3, 162.3, 167.1. ES+APCI MS: m/z 329 $(M+H)^+$.

Ethyl 2-((*E*)-3-(4-hydroxy-3-methoxyphenylacrylamido)-5,6-dihydro-4*H*-cyclopenta[*b*] thiophene-3-carboxylate (4A)

$C_{20}H_{21}NO_5S$, IR [KBr film] cm^{-1}: 3401 (OH, str), 3275 (NH, str), 2800 (CH, str), 1775 & 1658 (C=O, str), 1231 (asymmetric C-O-C, str), 1015 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, DMSO-d_6] δ: 1.41-1.44 (t, 3H, O-CH_2<u>CH_3</u>), 2.31-2.38 (m, 2H, <u>CH_2</u>), 2.71-2.74 (t, 2H, <u>CH_2</u>), 2.81-2.85 (t, 2H, <u>CH_2</u>), 3.83 (s, 3H, <u>OCH_3</u>), 4.36-4.41 (q, 2H, O-<u>CH_2</u>CH_3), 6.83-6.85 (d, 1H, Ar-H), 6.93-6.97 (d, 1H, CO-<u>CH</u>=CH), 7.03 (s, 1H, Ar-H), 7.220-7.224 (d, 1H, Ar-H), 7.54-7.58 (d, 1H, CO-CH=<u>CH</u>), 9.61 (s, 1H, O<u>H</u>), 11.50 (s, 1H, N<u>H</u>). ^{13}C-NMR [100 MHz, DMSO-d_6] δ: 17.3, 26.4, 27.6, 28.5, 55.7, 60.3, 98.5, 115.4, 119.0, 120.2, 124.2, 126.3, 126.5, 129.5, 143.1, 144.1, 148.3, 161.0, 167.1, 176.2. ES+APCI MS: m/z 388 $(M+H)^+$.

2-((*E*)-3-(4-hydroxy-3-methoxyphenylacrylamido)-5,6-dihydro-4*H*-cyclopenta[*b*] thiophene-3-carboxamide (5A)

$C_{18}H_{18}N_2O_4S$, IR [KBr film] cm^{-1}: 3476 (OH, str), 3293 (NH, str), 2909 (CH, str), 1646 (C=O, str), 1257 (asymmetric C-O-C, str), 1069 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, DMSO-d_6] δ: 2.32-2.39 (m, 2H, <u>CH_2</u>), 2.71-2.74 (t, 2H, <u>CH_2</u>), 2.81-2.84 (t, 2H, <u>CH_2</u>), 3.81 (s, 3H, <u>OCH_3</u>), 6.79-6.81 (d, 1H, Ar-H), 6.89-6.93 (d, 1H, CO-<u>CH</u>=CH), 6.99 (s, 1H, Ar-H), 7.193-7.197 (d, 1H, Ar-H), 7.53-7.57 (d, 1H, CO-CH=<u>CH</u>), 9.54 (s, 1H, O<u>H</u>), 11.52 (s, 1H, N<u>H</u>). ^{13}C-NMR [100 MHz, DMSO-d_6] δ: 24.5, 25.7, 26.2, 55.0, 111.4, 115.0, 118.2, 120.1, 124.3, 125.9, 126.1, 128.4, 143.4, 144.3, 148.5, 165.1, 166.3, 179.4. ES+APCI MS: m/z 359 $(M+H)^+$.

(*E*)-*N*-(3-cyano-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-2-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (6A)

$C_{18}H_{16}N_2O_3S$, IR [KBr film] cm^{-1}: 3458 (OH, str), 3373 (NH, str), 2869 (CH, str), 2208 (CN, str), 1621 (C=O, str), 1275 (asymmetric C-O-C, str), 1036 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, DMSO-d_6] δ: 2.33-2.40 (m, 2H, <u>CH_2</u>), 2.72-2.75 (t, 2H, <u>CH_2</u>), 2.82-2.86 (t, 2H, <u>CH_2</u>), 3.84 (s, 3H, <u>OCH_3</u>), 6.83-6.85 (d, 1H, Ar-H), 6.91-6.95 (d, 1H, CO-<u>CH</u>=CH), 7.02 (s, 1H, Ar-H), 7.19-7.20 (d, 1H, Ar-H), 7.55-7.59 (d, 1H, CO-CH=<u>CH</u>), 9.63 (s, 1H, O<u>H</u>), 11.61 (s, 1H, N<u>H</u>). ^{13}C-NMR [100 MHz, DMSO-d_6] δ: 26.7, 27.9, 28.8, 55.5, 87.9, 114.6, 115.7, 116.0, 121.3, 122.6, 125.9, 133.8, 141.0, 143.0, 147.9, 149.2, 151.9, 168.5. ES+APCI MS: m/z 341 $(M+H)^+$.

(*E*)-ethyl 2-(3-(4-hydroxy-3-methoxyphenyl)acrylamido)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxylate (7A)

$C_{21}H_{23}NO_5S$, IR [KBr film] cm^{-1}: 3453 (OH, str), 3244 (NH, str), 2919 (CH, str), 1742 & 1620 (C=O, str), 1205 (asymmetric C-O-C, str), 1025 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, DMSO-d_6] δ: 1.32-1.35 (t, 3H, C<u>H</u>$_3$CH$_2$), 1.70-1.73 (d, 4H, <u>CH_2-CH_2</u>), 2.40-2.43 (t, 2H, (<u>CH_2</u>), 2.54-2.59 (t, 2H, C<u>H</u>$_2$), 3.85 (s, 3H, OC<u>H</u>$_3$), 4.29-4.34 (q, 2H, <u>CH_2</u>-CH_3), 6.80-6.82 (d, 1H, Ar

H), 6.97-7.01 (d, 1H, CO-CH=CH), 7.13-7.15 (d, 1H, Ar H), 7.39 (s, 1H, Ar H), 7.54-7.57 (d, 1H, CO-CH=CH), 9.59 (s, 1H, OH), 11.19 (s, 1H, NH). ^{13}C-NMR [100 MHz, DMSO-d_6] δ: 14.1, 24.4, 24.6, 25.8, 27.1, 58.7, 61.5, 112.7, 117.4, 118.9, 119.2, 125.0, 128.1, 128.3, 130.5, 143.1, 143.4, 149.9, 159.0, 164.3, 169.1. ES+APCI MS: m/z 402 $(M+H)^+$.

(*E*) 2-(3-(4-hydroxy-3-methoxyphenyl)acrylamido)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxamide (8A)

$C_{19}H_{20}N_2O_4S$, IR [KBr film] cm^{-1}: 3505 (OH, str), 3120 (NH, str), 2819 (CH, str), 1672 (C=O, str), 1276 (asymmetric C-O-C, str), 1073 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, DMSO-d_6] δ: 1.74-1.75 (d, 4H, CH_2-CH_2), 2.62-2.71 (m, 4H, CH_2-CH_2), 3.84 (s, 3H, OCH_3), 6.79-6.81 (d, 1H, Ar H), 6.85-6.89 (d, 1H, d, 1H, CO-CH=CH), 7.10-7.12 (d, 1H, Ar H), 7.36 (s, 1H, Ar H), 7.48-7.52 (d, 1H, d, 1H, CO-CH=CH), 9.55 (s, 1H, OH), 11.59 (s, 1H, NH). ^{13}C-NMR [100 MHz, DMSO-d_6] δ: 22.3, 22.5, 23.7, 25.0, 55.7, 110.9, 115.5, 116.4, 117.1, 123.0, 126.0, 126.2, 128.9, 142.0, 142.3, 147.9, 162.3, 167.2, 181.0. ES+APCI MS: m/z 373 (M+H).

(*E*)-N-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-3-(4-hydroxy-3-methoxy phenyl)acrylamide (9A)

$C_{19}H_{18}N_2O_3S$, IR [KBr film] cm^{-1}: 3477 (OH, str), 3294 (NH), 2839 (CH, str), 2165 (CN, str), 1647 (C=O, str), 1216 (asymmetric C-O-C, str), 1070 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, DMSO-d_6] δ: 1.78-1.79 (d, 4H, CH_2-CH_2), 2.67-2.77 (m, 4H, CH_2-CH_2), 3.89 (s, 3H, OCH_3), 6.91-6.95 (d, 1H, Ar H), 6.99-7.00 (d, 1H, d, 1H, CO-CH=CH), 7.21-7.28 (d, 1H, Ar H), 7.50 (s, 1H, Ar H), 7.64-7.67 (d, 1H, CO-CH=CH), 9.56 (s, 1H, OH), 11.48 (s, 1H, NH). ^{13}C-NMR [100 MHz, DMSO-d_6] δ: 19.5, 22.3, 23.0, 24.5, 56.2, 67.6, 112.1, 115.5, 116.8, 118.9, 120.1, 128.8, 128.9, 139.9, 144.0, 144.9, 146.8, 151.3, 166.7. ESI-MS: m/z 355 $(M+H)^+$.

Ethyl 2-((*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamido)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxylate (10A)

$C_{22}H_{25}NO_5S$, IR [KBr film] cm^{-1}: 3341 (OH, str), 3114 (NH, str), 2926 (CH, str), 1724 & 1649 (C=O, str), 1220 (asymmetric C-O-C, str), 1027 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, $CDCl_3$] δ: 1.42-1.45 (t, 3H, O-CH_2CH_3), 1.63-1.72 (m, 4H, CH_2-CH_2), 1.84-1.90 (qu, 2H, CH_2), 2.75-2.78 (m, 4H, CH_2-CH_2), 3.98 (s, 3H, OCH_3), 4.37-4.42 (q, 2H, O-CH_2CH_3), 6.45-6.49 (d, 1H, Ar-H), 6.94-6.96 (d, 1H, CO-CH=CH), 7.113-7.117 (d, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.69-7.73 (d, 1H, CO-CH=CH), 9.61 (s, 1H, OH), 11.42 (s, 1H, NH). ^{13}C-NMR [100 MHz, $CDCl_3$] δ: 14.2, 26.9, 27.8, 28.3, 28.6, 32.2, 56.0, 60.6, 109.1, 112.8, 114.7, 116.9, 123.3, 127.1, 131.4, 136.4, 143.3, 146.1, 146.8, 147.9, 162.7, 167.0. ES+APCI MS: m/z 416 $(M+H)^+$.

2-((*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamido)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxamide (11A)

$C_{20}H_{22}N_2O_4S$, IR [KBr film] cm^{-1}: 3444 (OH, str), 3295 (NH, str), 2944 (CH, str), 1608 (C=O, str), 1268 (asymmetric C-O-C, str), 1033 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, $CDCl_3$] δ: 1.62-1.71 (m, 4H, CH_2-CH_2), 1.83-1.89 (qu, 2H, CH_2), 2.79-2.82 (m, 4H, CH_2-CH_2), 3.97 (s, 3H, OCH_3), 6.45-6.49 (d, 1H, Ar-H), 6.93-6.95 (d, 1H, CO-CH=CH), 7.10-7.11 (d, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.68-7.72 (d, 1H, CO-CH=CH), 9.69 (s, 1H, OH), 11.40 (s, 1H, NH). ^{13}C-NMR [100 MHz, $CDCl_3$] δ: 26.8, 27.7, 28.1, 28.4, 32.0, 56.2, 108.9, 112.7, 114.6, 116.7, 123.1, 127.6, 130.9, 136.3, 143.2, 146.8, 147.3, 160.9, 162.6, 166.8. ES+APCI MS: m/z 387 $(M+H)^+$.

(*E*)-N-(3-cyano-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-2-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (12A)

$C_{20}H_{20}N_2O_3S$, IR [KBr film] cm^{-1}: 3473 (OH, str), 3209 (NH, str), 2925 (CH, str), 2212 (CN, str), 1601 (C=O, str), 1228 (asymmetric C-O-C, str), 1036 (symmetric C-O-C, str). ^{1}H-NMR [400 MHz, $CDCl_3$] δ: 1.63-1.72 (m, 4H, CH_2-CH_2), 1.84-1.90 (qu, 2H, CH_2), 2.78-2.81 (m, 4H, CH_2-CH_2), 3.96 (s, 3H, OCH_3), 6.45-6.49 (d, 1H, Ar-H), 6.94-6.96 (d, 1H, CO-CH=CH), 7.105-7.109 (d, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.69-7.72 (d, 1H, CO-CH=CH), 9.67 (s, 1H, OH), 11.41 (s, 1H, NH). ^{13}C-NMR [100 MHz, $CDCl_3$] δ: 26.7, 27.6, 28.0, 28.5, 31.9, 56.1, 99.9, 112.6, 114.6, 115.7, 116.8, 123.3, 127.5, 130.6, 136.2, 143.2, 146.4, 147.1, 162.5, 166.9. ES+APCI MS: m/z 369 $(M+H)^+$.

Results and Discussion

Chemistry

In the present work ferulic acid was converted into acetyl ferulic acid using acetic anhydride and pyridine in order to protect phenolic hydroxy group. The formation of acetyl ferulic acid was confirmed by the reference melting point and by the presence of carbonyl stretching in FT-IR spectrum. The carboxylic group of acetyl ferulic acid was treated with thionyl chloride to get acetyl feruloyl chloride. In sequence acetyl feruloyl chloride was condensed with substituted 2-aminothiophenes **(1-12)** in the presence of dichloromethane, triethylamine and pyridine to get acetyl feruloyl amide derivatives. Further deprotection of phenolic hydroxy group (deacetylation) was carried out by using pyrrolidine and ethyl acetate to get various novel amide derivatives containing substituted 2-aminothiophenes and ferulic acid **(1A-12A)** in good yield. The steps involved in the synthesis of title compounds illustrated in **Scheme-I**.

The FT-IR spectra of compounds revealed the absence of amine and carboxylic acid peaks. Appearance of amide peak confirms the formation of the amide compounds. The absorption bands due to NH stretching and carbonyl stretching of amide functional group appeared in the

range of 3373-3114 cm^{-1} and 1684-1601 cm^{-1} respectively. The absorption band at 1775-1724 cm^{-1} in compounds **1A**, **4A**, **7A**, and **10A** confirmed the presence of carbonyl carbon of ester functional group. A sharp band at 2212-2165 cm^{-1} in compounds **3A**, **6A**, **9A**, and **12A** confirmed the presence of nitrile functional group. In ^{1}H-NMR spectra, protons of 4-hydroxy-3-methoxy phenyl acrylamido group appears in the following ranges, NH protons appeared as singlet at δ 11.19-11.61 and protons of CH=CH of acryloyl groups showed doublet at δ 6.85-7.01 and δ 7.48-7.82. Two aromatic hydrogens appeared as two doublets at δ 6.45-6.95 & 7.10-7.28 and one aromatic hydrogen showed singlet at δ 6.99-7.50. Protons of methoxy group appeared as singlet at δ 3.81-3.98. The protons of substituted thiophene ring appears in the following ranges, singlet in the region of δ 1.61-2.31 indicates the methyl group protons of compounds **1A**, **2A** and **3A**. The methylene protons of fused cyclic rings in compounds **4A-12A** appeared between δ 1.62 and 2.86. Splitting pattern of these signals was observed according to the nature of fused cyclic ring. Methyl groups of ethyl ester in compounds **1A**, **4A**, **7A** and **10A** showed triplet at δ 1.32-1.45 and the adjacent CH_2 appeared as quartet at δ 4.29-4.42.

In ^{13}C-NMR spectra, amide carbonyl carbon signal appears between δ 160.0 and 168.5, acryloyl carbon signal appears at δ 116.7-144.0 and aromatic carbons were appeared in the range of δ 111.8-151.9. Methoxy group carbons appears between δ 55.0 and 58.7. Thiophene ring carbons appear in the range of δ 67.6-181.0, whereas ester carbonyl carbon shows the signal at δ 147.9-161.0 and nitrile carbon signal varies between δ 115.3 and 115.7. Aliphatic carbon signals appeared in the range of δ 12.7-61.5. Mass spectra of all the synthesized compounds revealing their molecular weight.

Conclusion

In order to develop new drug molecules, the synthesis of hybrid molecules of biologically active compounds has emerged as an expanding approach. Ferulic acid is an essential natural lead molecule in the design of compounds of biological interest. By structural modification with a variety of substituted 2-aminothiophenes, we were able to synthesize a range of amide derivatives of ferulic acid in good yields. Further, there is a scope for the evaluation of these compounds for possible biochemical and pharmacological activities.

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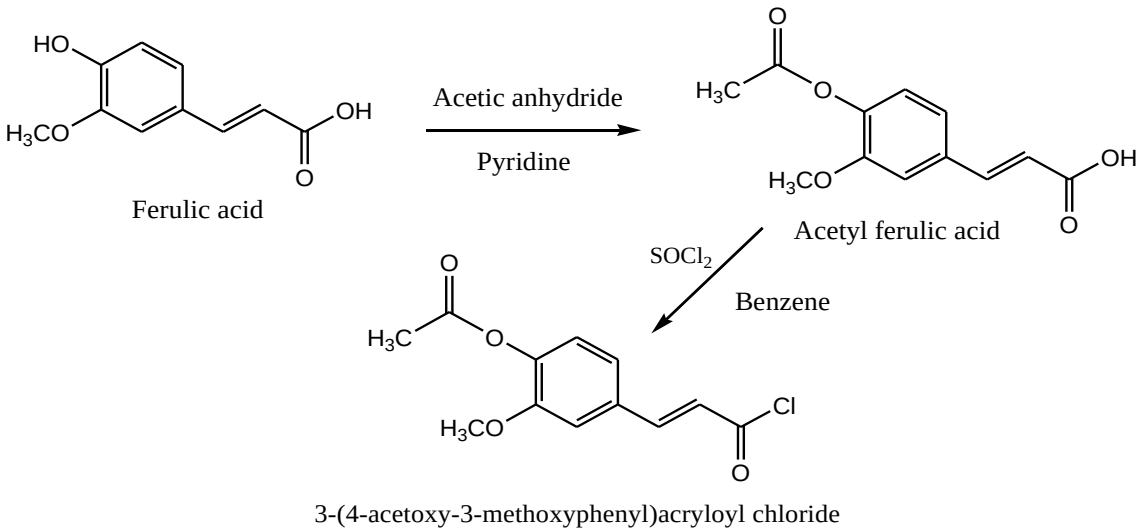

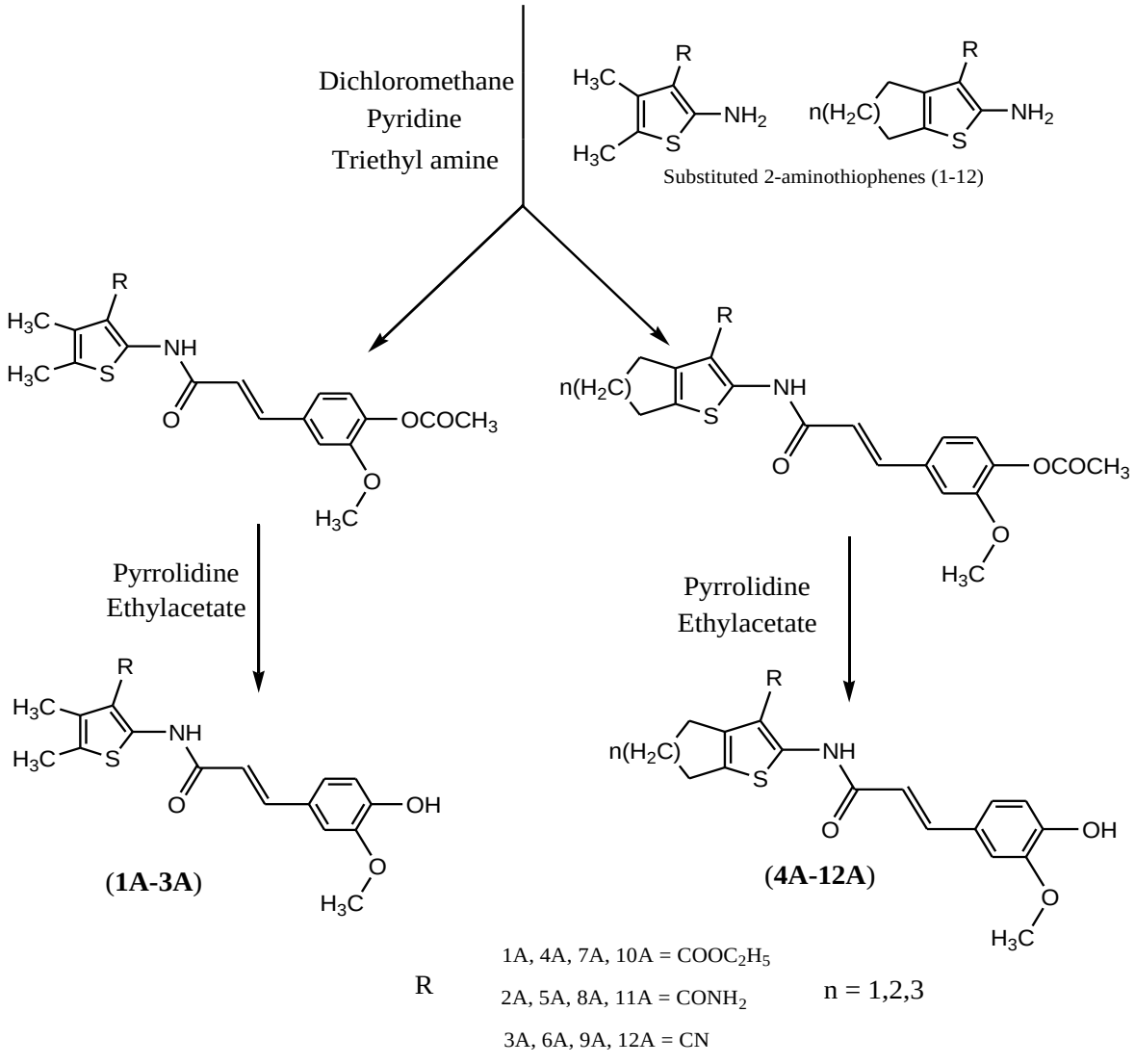

Scheme 1. Synthesis of novel amide derivatives of substituted 2-aminothiophenes and ferulic acid (**1A-12A**)

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