INTRODUCTION

Chalcone or (E)-1,3-diphenyl-2-propene-1-one, is an imperative chemotype that has fascinated enormous research interest for decades due to the elevated natural abundance of chalcone compounds, their easy synthesis and most prominently their varied biological activities. A number of chalcone compounds have been marketed or clinically tested for a variety of health conditions e.g., (i) diuretic-metochalcone/choleretic, (ii) antiulcer-sofalcone/mucoprotective (iii) hesperidin methyl-chalcone-vascular protective [1]. They are significant as structural motifs among biologically active molecules and also for combinatorial assembly of heterocyclic scaffolds [2-4]. Chalcones containing several functional groups showed a wide spectrum of biological activities such as antileishmanial [5,6], antimalarial [5,7], anticancer [8,9], anti-HIV [10], antioxidant [11], inflammatory [12] antiprotozoal [13], antiulcer [14] and antimicrobial [15,16] activities.

In view of the various biological and pharmacological activities associated with chalcones, we report the synthesis, characterization and anti-inflammatory activities of some new chalcone derivatives (9A-9K), prepared by furfural and apocynin.

EXPERIMENTAL

The solvents were purified according to standard procedures prior to use and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F254) were used and spots were visualized under UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point determinations were performed by using Mel-temp apparatus and are uncorrected. 1H NMR spectra were recorded in Varian MR-400 MHz instrument. The mass spectra were recorded on Agilent ion trap MS and infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer.

5-Nitrofurfural diacetate (2): A premixed solution of concentrated nitric acid (8.6 mL, 12.2 g, 193.62 mmol) and concentrated sulphuric acid (0.06 mL, 1.1 g, 11.2 mmol) was added drop-wise into acetic anhydride (90 mL) at 0 °C with stirring. To the above reaction mixture, furfural (1) (freshly distilled, 10.4 mL, 12.06 g, 125.5 mmol) was added drop-wise over a period of 45 min and stirred for 1 h at 0 °C. After cooling to room temperature, the white precipitate formed was filtered, washed with water, recrystallized from anhydrous ethanol and dried to obtain diacetate compound 2. Yield: 24.84 g, 82 %.

5-Nitrofurfural (3): A mixture of 5-nitrofurfural diacetate (2) (10 g, 41.12 mmol) and 50 % aqueous sulphuric acid (100 mL) was heated to 100 °C for 10 min. After completion of the
reaction, checked by TLC, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2 x 100 mL) and the organic layer was washed with water, brine solution and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain 5-nitrofurural (3). Yield: 5.10 g, 88 %; m.p.: 35-36 °C.

(5-Nitrofurural-2-yl)methanol (4): To a stirred solution of 5-nitrofurural (3) (5 g, 35.44 mmol) in methanol (100 mL), cooled to 0 °C, was added sodium borohydride (1.47 g, 38.98 mmol) portion-wise and continued to stirred for additional 30 min. After completion of the reaction, checked by TLC, the solvent was concentrated under reduced pressure and the residue was quenched with water (2 mL) and extracted with cyclopentyl methyl ether (4 x 25 mL). The organic layer was washed with water (2 x 30 mL), dried over 

Hydroxide (0.3 mmol) was thoroughly ground with a pestle in an open mortar [17,18] at room temperature for 5-10 min. After completion of the reaction, checked by TLC, the precipitated solid was washed with water (4 mL) and further recrystallized from ethanol (2 mL) to give the corresponding chalcone derivatives (9A-K). Yields of the compounds varied between 86-96 %.

3-(4-Bromo-phenyl)-1-[3-methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]propiophene (9A): Pale yellow solid; Yield: 94 %; m.p.: 97-98 °C; IR (KBr, νmax, cm⁻¹): 3110 (-C-H stretch, aromatic), 2942 (-C-H stretch, aliphatic), 1655 (-C=O, conjugated with -C=C and benzene ring), 1603, 1575(-C=C of enone moiety), 1513 and 1340 (-NO₂ stretch), 1069 (C-O stretch); ¹H NMR (400 MHz, DMSO-d₆); δ 3.95 (s, 3H), 5.20 (s, 2H), 6.58 (s, 1H), 6.80 (s, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.58-7.50 (m, 5H), 7.68 (d, J = 5.8 Hz, 2H), 7.80 (d, J = 12.4 Hz, 1H); ESI-MS: m/z, 458.1 (M+1).

3-(4-Chloro-phenyl)-1-[3-methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]propiophene (9B): Yellow solid; Yield: 89 %; m.p.: 107-108 °C; IR (KBr, νmax, cm⁻¹): 3112 (-C-H stretch, aromatic), 2938 (-C-H stretch, aliphatic), 1654 (-C=O, conjugated with -C=C and benzene ring), 1602, 1567 (-C=C of enone moiety), 1513 and 1349 (-NO₂ stretch), 1072 (C-O stretch); ¹H NMR (400 MHz, DMSO-d₆); δ 3.85 (s, 3H), 5.29 (2H), 6.67 (s, 1H), 7.28 (d, J = 9.5 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 15.0 Hz, 1H), 7.65 (d, J = 18.0 Hz, 1H), 7.83 (d, J = 6.0 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H); ESI-MS: m/z, 414.2 (M+1).

3-(4-Fluoro-phenyl)-1-[3-methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]propiophene (9C): Off white solid; Yield: 88 %; m.p.: 123-124 °C; IR (KBr, νmax, cm⁻¹): 2943 (-C-H stretch, aromatic), 1655 (-C=O, conjugated with -C=C and benzene ring), 1574 (-C=C of enone moiety), 1508 and 1350 (-NO₂ stretch), 1024 (C-O stretch); ¹H NMR (400 MHz, DMSO-d₆); δ 3.96 (s, 3H), 5.20 (2H), 6.54 (d, J = 2.5 Hz, 1H), 6.78 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 15.5 Hz, 1H), 7.65 (d, J = 2.0 Hz, 2H), 7.64 (d, J = 3.0 Hz, 2H), 7.78 (d, J = 15.5 Hz, 1H); ESI-MS: m/z, 398.3 (M+1).

1-[3-Methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]-3-(4-trifluoromethoxyphenyl)propiophene (9D): Pale yellow solid; Yield: 90 %; m.p.: 76-77 °C; IR (KBr, νmax, cm⁻¹): 3111 (-C-H stretch, aromatic), 1656 (-C=O, conjugated with -C=C and benzene ring), 1603, 1574 (-C=C of enone moiety), 1507 and 1351 (-NO₂ stretch), 1106 (-C-O stretch); ¹H NMR (400 MHz, DMSO-d₆); δ 3.97 (s, 3H), 5.20 (2H), 6.54 (d, J = 3.5 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 15.5 Hz, 1H), 7.67 (d, J = 16.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 3H), 7.78 (d, J = 15.5 Hz, 1H); ESI-MS: m/z, 464.1 (M+1).

1-[3-Methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]-3-(4-nitrophenyl)propiophene (9E): Yellow solid; Yield: 89 %; m.p.: 68-69 °C; IR (KBr, νmax, cm⁻¹): 3120 (-C-H stretch, aromatic), 2944 (-C-H stretch, aliphatic), 1655 (-C=O, conjugated with -C=C and benzene ring), 1574 (-C=C of enone moiety), 1517 and 1341 (-NO₂ stretch), 1169 (C-O stretch); ¹H NMR (400 MHz, DMSO-d₆); δ 3.90 (s, 3H), 5.30 (2s, 2H), 6.83 (s, 1H), 7.28 (s, 1H), 7.30 (d, J = 15.2 Hz, 1H), 7.65 (s, 1H), 7.67

General experimental preparation of chalcones derivatives (9A-K): A mixture of compound 7 (100 mg, 0.343 mmol), aromatic aldehydes (8A-K) (0.346 mmol) and sodium hydroxide (0.3 mmol) was thoroughly ground with a pestle in an open mortar [17,18] at room temperature for 5-10 min. After completion of the reaction, checked by TLC, the precipitated solid was washed with water (4 mL) and further recrystallized from ethanol (2 mL) to give the corresponding chalcone derivatives (9A-K). Yields of the compounds varied between 86-96 %.
Results and Discussion

The synthesis of chalcone derivatives (9A-K) is illustrated in Scheme 1. Nitration of furfural (1) in presence of conc. HNO₃ and catalytic quantity of H₂SO₄ in acetic anhydride at 0 °C for 1 h gave the 5-nitrofurfural diacetate (2). Hydrolysis of diacetate 2 in presence of 20 %aq. H₂SO₄ at 100 °C for 10 min produced the intermediate 5-nitrofurural (3) [18]. Reduction of 5-nitrofurural (3) in presence of NaBH₄ in methanol at 0 °C for 30 min gave the desired (5-nitrofuran-2-yl)methanol (4). Treatment of alcohol 4 with triphenylphosphine and tribromoisuocyanuric acid [19] in dichloromethane at room temperature for 4 h produced the desired bromide intermediate (5). Coupling of bromide 5 with apocynin (6) in presence of potassium carbonate in 2-methyltetrahydrofuran at reflux for 1 h gave the desired product 1-(4-(5-nitrofuran-2-yl)methoxy)-3-methoxyphenylethanone (7). Chaisen-Schmidt reaction of ethanone 7 with aromatic aldehydes 8A-K was carried out under solvent free conditions using solid NaOH as catalyst at room temperature [20,21] for 5-10 min to afford chalcones 9A-9K in 86-96 % yield.

Structural elucidation of the synthesized chalcones derivatives 9A-K was determined by various spectroscopic techniques like ¹H NMR, mass and IR spectral data. As a representative example, the ¹H NMR of 3-(3,4,5-trimethoxy-phenyl)-1-(3-
methoxy-4-(5-nitro-furan-2-ylmethoxy)-phenyl]-propenone 9K is described here, protons resonating at 7.20 ppm as singlet is assigned to the 3,4,5-trimethoxy phenyl ring while the protons resonating at 7.28 ppm, 7.60 ppm as doublet and singlet respectively is assigned to the vanillin ring. The singlet signals with one proton integration resonating at 6.80 and 7.88 ppm corresponds to the furan ring. The characteristic olefin protons resonating at 7.70 ppm and 7.99 ppm as doublets with $J = 15.5$ Hz indicates the ‘$E$’ isomeric form of chalcone. Similarly, the $^1$H NMR spectra of the remaining chalcone derivatives are in agreement with the desired structures.

The mass spectra of the compounds showed (M+1) peaks and are in agreement with their molecular formulae. The IR spectra of the compounds 9A-K represented the characteristic peaks that comply with the desired functional group in the structure. The characteristic $\alpha,\beta$-unsaturated carbonyl stretching bands appeared in the regions 1606-1570 cm$^{-1}$ (-C=C of enone moiety) and 1664-1648 cm$^{-1}$ (-C=O, conjugated with -C=C and benzene ring).

**Anti-inflammatory activity:** The results of the anti-inflammatory activity (dosage: 10 mg/Kg po) of the synthesized chalcone derivatives 9A-K is presented in Table-1. Compounds 9D, 9C, 9F, 9K and 9E bearing R = -4-trifluoromethoxy-phenyl, -4-flouro-phenyl, 4-sulphonyl methyl phenyl, 3,4,5-trimethoxy phenyl and 4-nitro-phenyl exhibited significant anti-inflammatory activity while the compounds 9G, 9H, 9I and 9J bearing 4-methoxy-phenyl, 2,4-dimethoxy phenyl, 2,5-dimethoxy phenyl and 2,6-dimethoxy phenyl displayed moderate anti-inflammatory activity. Furthermore, chalcones, 9A and 9B bearing 4-bromo-phenyl and 4-chloro-phenyl group was found to be inactive.

<table>
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<th>Treatments</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
</thead>
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<tr>
<td>Carrageenan control</td>
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<td>2.55 ± 0.12</td>
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<tr>
<td>9A</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9B</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>0.88 ± 0.44</td>
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<tr>
<td>9E</td>
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<td>0.72 ± 1.58</td>
<td>0.78 ± 0.86</td>
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<tr>
<td>9F</td>
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<td>0.82 ± 0.34</td>
<td>0.88 ± 0.22</td>
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<tr>
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<td>0.95 ± 0.12</td>
<td>1.16 ± 0.11</td>
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</table>

**Scheme-I: Synthesis of novel chalcone derivatives 9A-9K, embedded with apocynin and furan ring:**

**Reaction conditions:** a) conc. HNO$_3$, cat.conc:H$_2$SO$_4$, Ac$_2$O, O °C, 1h, 82 %; b) 50 % aq. H$_2$SO$_4$, 100 °C, 10 min, 88 %; c) NaBH$_4$, MeOH, 0 °C, 30 min, 56 %; d) triphenylphosphine, tribromoisocyanuric acid, room temperature, 4 h, 84 %; e) Apocynin, potassium carbonate, 2-methyltetrahydrofuran, reflux, 1h, 94 %; f) aromatic aldehydes 8A-K, sodium hydroxide, grinding, room temperature, 5-10 min, 86-96 %

**Table 1: Results of anti-inflammatory activity of hydrazide-hydrazone derivatives (9A-9K)***
Conclusion

In conclusion, we have described the synthesis and characterization of chalcone derivatives 1-[3-methoxy-4-(5-nitrofuran-2-ylmethoxy)-phenyl]-3-(substituted phenyl)-propenone derivatives 9A-9K utilizing commercially available furfural and apocynin. The results of the anti-inflammatory activity of these compounds revealed that, compounds 9D, 9C, 9F, 9K and 9E bearing R = -4-trifluoromethoxy-phenyl, -4-fluoro-phenyl, 4-sulphonyl methyl phenyl, 3,4,5-trimethoxy phenyl and 4-nitro-phenyl exhibited significant anti-inflammatory activity.

REFERENCES