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Synthesis and characterization of novel mono, bis and tris heteroaryl chalcone derivatives of 1,3,5-trimethoxybenzene

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Abstract: In this study, a new series consisting of 12 heteroaryl chalcone derivatives of 1,3,5-trimethoxybenzene were synthesised. Chalcones were synthesised in high purity and efficiency, via condensation of mono, bis and tris 2,4,6-trimethoxy acetophenones with hetero-2-carbaldehyde derivatives based on Claisen Schdmit condensation. The reactions feature a good scope for the all products, mild reaction conditions and good yields. The synthesized compounds were characterized by using FT-IR, NMR and elemental analysis spectroscopic techniques.

Keywords: Heteroaryl; chalcone; synthesis; characterization.

1. Introduction

Chalcones, a member of the flavonoid family, are one of the natural product classes with a skeleton of 1,3-diaryl-2-propen-1-one.[1] Recently, a widespread study of synthetic and biological applications of chalcone derivatives has revealed a large number of pharmacological activities thereof.[2] The addition of a heterocyclic system around three carbon units of α,β-unsaturated system of chalcones, which are associated in the literature with many biological activities, also expands this activity range.[3] Heteroaryl chalcone analogues were found to exhibit biological activities in a wide spectrum, such as anticancer, antifungal, antimalarial, anti-HIV, anthelmintic, antibacterial, anti-inflammatory, antiangiogenic, antileishmanial and MAO inhibition activities.[4] Studies which separately studied the synthesis hetero, biological activity, cyclisation reactions and cytotoxic properties of heterocyclic derivatives of chalcones are known.[5]

Several synthesis for chalcone derivatives containing heterocyclic aromatic rings such as furan, thiophene, pyrrole, pyridine and indole have been reported.[6] It is proved that the conjugation of heteroaryl, which bonds to the α,β-unsaturated ketone group, is responsible for the aforementioned activities.[7,8] Despite the fact that in most commonly used anticancer drugs, genotoxic effects occur as a result of the interaction of nucleic acids with amino groups; no such undesirable situations are observed with aryl and heteroaryl chalcones.[9,10]

Another aspect is that important heterocyclic compounds are achieved by breaking out structures that have a chalcone skeleton.[11] Achieving these structures through cyclisation of chalcones emerge as a developing area of heterocyclic chemistry.[12,13]

In the literature, the synthesis and activity studies of chalcone derivatives with trimethoxy group in 2, 4 and 6 positions in the aryl units of chalcones are frequently encountered.[14] Particularly, various examples of heteroaryl analogues of these structures exhibit strong activity against certain cell lines.[15]

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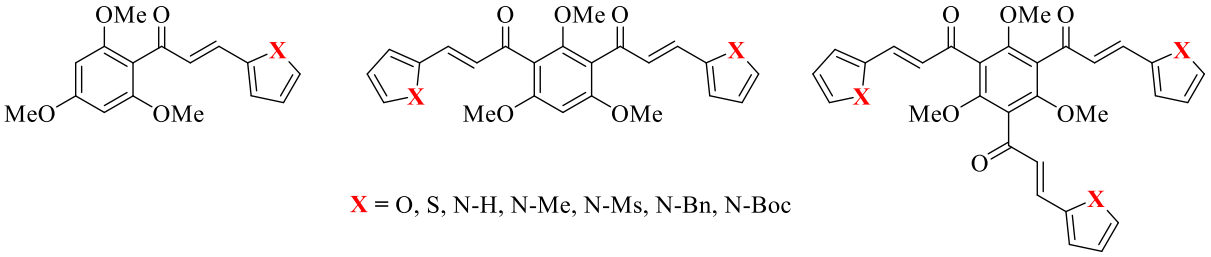


Scheme 1. Synthesized mono, bis and tris heteroaryl chalcone structures

In this study, we aimed to achieve new heteroaryl chalcone derivatives, which take the trimethoxy motif to the centre that can play an important role in the development of active compounds that are unknown to the literature. Starting from 2,4,6-trimethoxy acetophenone in the presence of alkali, a series of reactions were planned to achieve new analogues of heteroaryl chalcones that may be important for the literature through Claisen Schmidt condensation reaction of heteroaryl aldehydes (Scheme 1).

2. Experimental

2.1. Chemistry

All synthesized chalcone structures were verified using spectral techniques such as FT-IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. The ^{1}H-NMR and ^{13}C-NMR spectra of chalcone compounds were measured using Varian 400 MHz and Bruker 400 MHz spectrometry in chloroform-d at ambient temperature. Fourier transformed infrared spectroscopy (FT-IR) spectra were recorded in the wavenumber range of 400-4000 cm^{-1} using Perkin Elmer Spectrum One FT-IR spectrometer. The melting points were measured using a Gallenkamp melting point apparatus. The elemental analysis results were confirmed using a Leco CHNS-932 device. Commercially purchased solvents and chemicals were used.

2.2. Chemistry Experimental Procedure

The starting material **1**,**7** and **8** were synthesized according to the procedure given in the literature.[16]

*2.2.1. General Procedure for Preparation of Mono Condensation Products (**5**, **6**, **9**, **10**)*

To a solution of 1-(2,4,6-trimethoxyphenyl)ethan-1-one, (1 mmole) in MeOH (10 mL) furan, thiophene and 1*H*-pyrrole-2-carbaldehyde derivatives (1.6 mmole) and 50 % KOH solution (5 mmole) was added and resultant mixture was sequentially stirred overnight at room temperature. The solvent was evaporated in vacuum. Crude material was extracted with NH_4Cl solution (10 mL) and dichloromethane (DCM) (15 mL x 3). The combined extracts were dried over Na_2SO_4. The solvent was removed in vacuum.

*2.2.2. General Procedure for Preparation of Bis Condensation Products (**11-14**)*

To a solution of 1,1'-(2,4,6-trimethoxy-1,3-phenylene)bis(ethan-1-one), (1 mmole) in MeOH (10 mL) furan, thiophene and 1*H*-pyrrole-2-carbaldehyde derivatives (3.2 mmole) and 50 % KOH solution (10 mmole) was added and resultant mixture was sequentially stirred overnight at room temperature. The solvent was evaporated in vacuum. Crude material was extracted with NH_4Cl solution (10 mL) and dichloromethane (DCM) (15 mL x 3). The combined extracts were dried over Na_2SO_4. The solvent was removed in vacuum.

*2.2.3. General Procedure for Preparation of Tris Condensation Products (**15-18**)*

To a solution of 1,1',1''-(2,4,6-trimethoxybenzene-1,3,5-triyl)tris(ethan-1-one), (1 mmole) in MeOH (10 mL) furan, thiophene and 1*H*-pyrrole-2-carbaldehyde derivatives (4.8 mmole) and 50 % KOH solution (15 mmole) was added and resultant mixture was sequentially stirred overnight at room temperature. The solvent was evaporated in vacuum. Crude material was extracted with NH_4Cl solution (10 mL) and dichloromethane (DCM) (15 mL x 3). The combined extracts were dried over Na_2SO_4. The solvent was removed in vacuum.

*(E)-3-(1-methyl-1H-pyrrol-2-yl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (**5**):* The above procedure was followed with N-methyl-2-pyrrolecarboxaldehyde to yield **5** as a yellow solid (83 % yield). Rf (EtOAc/n-Hexane 1:1) = 0.36; mp = 124-126 °C; IR (KBr, cm^{-1}): Vmax 2940, 1605, 1126; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 15.7 Hz, 1H), 6.77 – 6.74 (m, 1H), 6.71 (d, *J* = 16 Hz, 1H), 6.67 (dd, *J* = 3.9, 1.5 Hz, 1H), 6.18 – 6.15 (m, 1H), 6.14 (s, 2H), 3.85 (s, OMe), 3.77 (s, 2×OMe), 3.66 (s, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7 (C=O), 162.4 (C-4'), 158.9 (C-2', C-6'), 131.9 (C-2''), 130.1 (C-3), 127.8 (C-5''), 124.4 (C-2), 113.1 (C-1'), 112.7 (C-3''), 109.7 (C-4''), 90.9 (C-3', C-5'), 56.2 (2×OCH_3), 55.7 (OCH_3), 34.8 (N-Me); Anal. calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; Found: C, 67.66; H, 6.32; N, 4.60.

*(E)-3-(1-benzyl-1H-pyrrol-2-yl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (**6**):* The above procedure was followed with N-benzyl-2-pyrrolecarboxaldehyde to yield **6** as a yellow solid (40 % yield). Rf (EtOAc/n-Hexane 3:7) = 0.4; mp = 151-153 °C; IR (KBr, cm^{-1}): Vmax 2938, 1605, 1126; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.18 (m, 4H), 6.96 – 6.91 (m, 2H), 6.87 – 6.85 (m, 1H), 6.79 – 6.75 (m, 1H), 6.66 (d, *J* = 15.7 Hz, 1H), 6.27 – 6.23 (m, 1H), 6.08 (s, 2H), 5.07 (s, 2H), 3.85 (s, OMe), 3.63 (s, 2×OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.2 (C=O), 162.3 (C-4'), 158.8 (C-2', C-6'), 137.5 (C-Bn), 132.7 (C-2''), 129.7 (C-3), 129.1 (2×C-Bn), 127.9 (2×C-Bn), 127.2 (C-Bn), 126.7 (C-5''), 125.0 (C-2), 112.9 (C-1'), 112.0 (C-3''), 110.3 (C-4''), 90.8 (C-3', C-5'), 55.9 (2×OCH_3), 55.7 (OCH_3), 51.0 (CH_2-Bn); Anal. calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71; Found: C,73.24; H, 6.30; N, 3.83.

*(E)-3-(furan-2-yl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (**9**):* The above procedure was followed with furfural to yield **9** as a yellow solid (79 % yield). Rf (EtOAc/n-Hexane 3:7) = 0.43; mp = 99-101 °C; IR (KBr, cm^{-1}): Vmax 2939, 1603, 1126; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (bs, 1H), 7.13 (d, *J* = 16 Hz, 1H), 6.83 (d, *J* = 16 Hz, 1H), 6.59 (d, *J* = 3.2 Hz, 1H), 6.45 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.14 (s, 2H), 3.84 (s, OMe), 3.75 (s, 2×OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9 (C=O), 162.6 (C-4'), 159.1 (C-2', C-6'), 151.7 (C-2''), 145.0 (C-5''), 130.5 (C-3), 126.9 (C-2), 115.4 (C-1'), 112.7 (C-3''), 111.9 (C-4''), 90.9 (C-3',C-5'), 56.1 (2×C-OCH_3), 55.7 (C-OCH_3); Anal. calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59; Found: C, 66.52; H, 5.45.

*(E)-3-(thiophen-2-yl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (**10**):* The above procedure was followed with 2-thiophenecarboxaldehyde to yield **10** as a yellow solid (77 % yield). Rf (EtOAc/n-Hexane 3:7) = 0.4; mp = 102-104 °C; IR (KBr, cm^{-1}): Vmax 2939, 1605, 1127; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 15.6 Hz, 1H), 7.36 (d, *J* = 5.2 Hz, 1H), 7.21 (d, *J* = 3.6, Hz, 1H), 7.02 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.75 (d, *J* = 15.6 Hz, 1H), 6.14 (s, 2H), 3.84 (s, OMe), 3.76 (s, 2×OMe) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9 (C=O), 162.7 (C-4'), 159.1 (C-2', C-6'), 140.6 (C-2''), 136.7 (C-3), 131.4 (C-5''), 128.9 (C-4''), 128.4 (C-3''), 128.3 8 (C-2), 111.8 (C-1'), 90.9 (C-3', C-5') 56.1 (2×OCH_3), 55.7 (OCH_3); Anal. calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; Found: C, 63.00; H, 5.30.

*(2E,2'E)-1,1'-(2,4,6-trimethoxy-1,3-phenylene)bis(3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one) (**11**):* The above procedure was followed with N-methyl-2-pyrrolecarboxaldehyde to yield **11** as a yellow solid (85 % yield). Rf (EtOAc/n-Hexane 4:1) = 0.36; mp = 171-173 °C; IR (KBr, cm^{-1}): Vmax 2941, 1593, 1277; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 15.7 Hz, 2H), 6.86 – 6.66 (m, 6H), 6.34 (s, 1H), 6.20 (s, 2H), 3.86 (s, 2×OMe), 3.71 (s, OMe), 3.68 (s, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8 (2×C=O), 159.2 (C-2'), 156.9 (C-4', C-6'), 132.6 (2×C-2''), 129.6 (2×C-3), 128.1 (2×C-5''), 123.4 (2×C-2), 116.8 (C-3', C-1'), 113.5 (2×C-3''), 109.8 (2×C-4''), 91.2 (C-5'), 63.2 (OCH_3), 56.1 (2×OCH_3),

34.6 (2×N-Me); Anal. calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45; Found: C, 69.20; H, 6.30; N, 6.25.

(2E,2'E)-1,1'-(2,4,6-trimethoxy-1,3-phenylene)bis(3-(1-benzyl-1H-pyrrol-2-yl)prop-2-en-1-one) ***(12)****:* The above procedure was followed with N-benzyl-2-pyrrolecarboxaldehyde to yield **12** as a yellow solid (25 % yield). Rf (EtOAc/n-Hexane 1:1) = 0.26; mp = 169-171 °C; IR (KBr, cm^{-1}): Vmax 2941, 1593, 1111; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.19 (m, 8H), 7.00 – 6.95 (m, 4H), 6.90 (s, 2H), 6.80 (d, *J* = 2.6 Hz, 2H), 6.70 (d, *J* = 15.6 Hz, 2H), 6.30 – 6.26 (m, 2H), 6.16 (s, 1H), 5.12 (s, 4H), 3.71 (s, 2×OMe), 3.45 (s, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0 (2×C=O), 158.9 (C-2'), 156.7 (C-4', C-6'), 137.2 (2×C-Bn), 133.0 (2×C-2"), 129.3 (2×C-3), 128.9 (4×C-Bn), 127.7 (4×C-Bn), 127.5 (2×C-Bn), 126.5 (2×C-5"), 124.2 (2×C-2), 116.2 (C-3', C-1') 113.2 (2×C-3"), 110.2 (2×C-4"), 90.8 (C-5'), 62.8 (OCH_3), 55.9 (2×OCH_3), 50.9 (2×CH_2-Bn); Anal. calcd for $C_{37}H_{34}N_2O_5$: C, 75.75; H, 5.84; N, 4.77; Found: C,75.70; H, 5.80; N, 4.71.

(2E,2'E)-1,1'-(2,4,6-trimethoxy-1,3-phenylene)bis(3-(furan-2-yl)prop-2-en-1-one) ***(13)****:* The above procedure was followed with furfural to yield **13** as a orange solid (68 % yield). Rf (EtOAc/n-Hexane 2:3) = 0.43; mp = 126-128 °C; IR (KBr, cm^{-1}): Vmax 2942, 1596, 111; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (bs, 2H), 7.20 (d, *J* = 16 Hz, 2H), 6.90 (d, *J* = 16 Hz, 2H), 6.67 (d, *J* = 3.2 Hz, 2H), 6.52 – 6.49 (m, 2H), 6.34 (s, 1H), 3.87 (s, 2×OMe), 3.70 (s, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1 (2×C=O), 159.5 (2×C-2"), 156.9 (C-4', C-6'), 151.2 (2×C-2"), 145.2 (2×C-5"), 131.2 (C-3), 126.2 (C-2), 116.1 (C-3', C-1'), 115.9 (2×C-3"), 112.6 (2×C-4"), 91.1 (C-5'), 63.3 (C-OCH_3), 56.1 (2×C-OCH_3); Anal. calcd for $C_{23}H_{20}O_7$: C, 67.64; H, 4.94; Found: C, 67.50; H, 4.69.

(2E,2'E)-1,1'-(2,4,6-trimethoxy-1,3-phenylene)bis(3-(thiophen-2-yl)prop-2-en-1-one) ***(14)****:* The above procedure was followed with 2-thiophenecarboxaldehyde to yield **14** as a orange solid (65 % yield). Rf (EtOAc/n-Hexane 1:1) = 0.43; mp = 152-154 °C; IR (KBr, cm^{-1}): Vmax 2936, 1592, 1110; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 15.6 Hz, 2H), 7.43 (d, *J* = 4.9 Hz, 2H), 7.29 (s, 2H), 7.10 – 7.03 (m, 2H), 6.83 (d, *J* = 15.6 Hz, 2H), 6.35 (s, 1H), 3.87 (s,2×OMe), 3.71 (s, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9 (2×C=O), 159.5 (C-2'), 157.0 (C-4', C-6'), 139.9 (2×C-2"), 137.5 (C-3), 131.7 (2×C-5"), 129.2 (2×C-4"), 128.3 (2×C-3"), 127.5 (C-2), 116.1 (C-1', C-3'), 91.2 (C-5'), 63.3 (OCH_3), 56.1(2×OCH_3); Anal. calcd for $C_{23}H_{20}O_5S_2$: C, 62.71; H, 4.58; Found: C, 62.55; H, 4.25.

(2E,2'E,2"E)-1,1',1"-(2,4,6-trimethoxybenzene-1,3,5-triyl)tris(3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one) ***(15)****:* The above procedure was followed with N-methyl-2-pyrrolecarboxaldehyde to yield **15** as a brown solid (75 % yield). Rf (EtOAc/n-Hexane 4:1) = 0.6; mp = 194-196 °C; IR (KBr, cm^{-1}): Vmax 2939, 1573, 1267; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 15.7 Hz, 3H), 6.87 – 6.72 (m, 9H), 6.21 (s, 3H), 3.76 (s, 3×OMe), 3.72 (s, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, (3×C=O), 156.9 (C-2', C-4', C-5'), 132.9 (3×C-2"), 129.5 (3×C-3), 128.7 (3×C-5"), 124.9 (3×C-2), 122.4 (C-3', C-1'. C-5'), 114.1 (3×C-3"), 110.1 (3×C-4"), 63.5 (3×OCH_3), 34.6 (3×N-Me); Anal. calcd for $C_{33}H_{33}N_3O_6$: C, 69.83; H, 5.86; N, 7.40; Found: C, 69.73; H, 5.77; N, 7.32.

(2E,2'E,2"E)-1,1',1"-(2,4,6-trimethoxybenzene-1,3,5-triyl)tris(3-(1-benzyl-1H-pyrrol-2-yl)prop-2-en-1-one) ***(16)****:* The above procedure was followed with N-benzyl-2-pyrrolecarboxaldehyde to yield **16** as a yellow solid (25 % yield). Rf (EtOAc/n-Hexane 3:7) = 0.6; mp = 137-139 °C; IR (KBr, cm^{-1}): Vmax 2941, 1574, 1229; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.17 (m, 9H), 7.05 – 6.91 (m, 6H), 6.83 (d, *J* = 2.9 Hz, 3H), 6.72 (d, *J* = 15.6 Hz, 3H), 6.30 (s, 3H), 5.14 (s, 3×CH_2Ph), 3.49 (s, 3×OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9 (3×C=O), 156.6 (C-2', C-4', C-6'), 136.9 (3×C-Bn), 133.5 (3×C-2"), 129.1 (3×C-3), 128.9 (6×C-Bn), 128.0 (6×C-Bn), 127.9 (3×C-Bn), 126.5 (3×C-5"), 124.1 (3×C-2), 123.2 (C-3', C-5', C-1'), 113.8 (3×C-3"), 110.4 (3×C-4"), 63.0 (3×OCH_3), 51.1 (3×CH_2-Bn); Anal. calcd for $C_{51}H_{45}N_3O_6$: C, 76.96; H, 5.70; N, 5.28; Found: C,76.82; H, 5.62; N, 5.17.

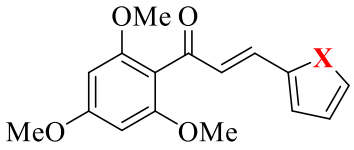
(2E,2'E,2"E)-1,1',1"-(2,4,6-trimethoxybenzene-1,3,5-triyl)tris(3-(furan-2-yl)prop-2-en-1-one) ***(17)****:* The above procedure was followed with furfural to yield **17** as a orange solid (55 % yield). Rf (EtOAc/n-Hexane 3:7) = 0.46; mp = 162-164 °C; IR (KBr, cm^{-1}): Vmax 2939, 1598, 1235; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (bs, 3H), 7.26 (d, *J* = 16 Hz, 3H), 6.95 (d, *J* = 16 Hz, 3H), 6.75 (s, 3H), 6.53 (s, 3H),

3.75 (s, 3×OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7 (3×C=O), 157.3 (C-2',C-4', C-6'), 151.0 (3×C-2"), 145.8 (3×C-5"), 132.3 (3×C-3), 125.6 (3×C-2), 124.0 (C-1', C-3', C-5'), 117.2 (3×C-3"), 113.1 (3×C-4"), 63.8 (3×OCH_3); Anal. calcd for $C_{30}H_{24}O_9$: C, 68.18; H, 4.58; Found: C, 68.45; H, 4.70.

(2E,2'E,2"E)-1,1',1"-(2,4,6-trimethoxybenzene-1,3,5-triyl)tris(3-(thiophen-2-yl)prop-2-en-1-one) ***(18)****:* The above procedure was followed with 2-thiophenecarboxaldehyde to yield **18** as a yellow solid (85 % yield). Rf (EtOAc/n-Hexane 3:7) = 0.56; mp = 218-220 °C; IR (KBr, cm^{-1}): Vmax 2939, 1580, 1236; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 3H), 7.48 (d, *J* = 4.8 Hz, 3H), 7.36 (d, *J* = 3.2 Hz, 3H), 7.14 – 7.07 (m, 3H), 6.89 (d, *J* = 15.6 Hz, 3H), 3.77 (s, 3×OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3 (3×C=O), 157.1 (C-2', C-4', C-6'), 139.6 (3×C-2"), 138.5 (3×C-3), 132.4 (3×C-5"), 129.9 (3×C-4"), 128.5 (3×C-3"), 126.6 (3×C-2), 123.9 (C-3', C-5', C-1'), 63.6 (3×OCH_3); Anal. calcd for $C_{30}H_{24}O_6S_3$: C, 62.48; H, 4.19; Found: C, 62.47; H, 4.22.

3. Results and Discussion

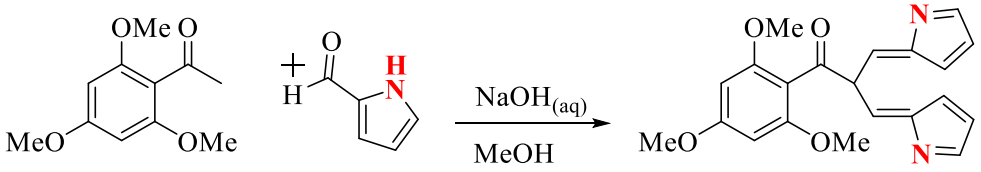
When different modifications of heteroaryl chalcone templates are examined, there are a lot of studies on the design, chemistry and synthesis of these analogues. Especially the studies on chalcones comprising a heterocyclic nucleus, such as furan, thiophene and pyrrole, in this field are frequently seen.[17] Thanks to the synthesis of the derivatives comprising a wide range of substituents in the aromatic benzene ring of this chalcone structure, a fairly large number of biologically important compounds are achieved. Especially, the derivatives comprising methoxy (-OMe) substituent are one primary example of these.[18] Synthesis of these derivatives is made easily using common chalcone synthesis methods. It was concluded that furan, thiophene and pyrrole groups are adjacent to the double bond of the chalcone; however, the reactions of their derivatives comprising trimethoxy substituent at 2,4,6 positions in the aryl ring are not known to the literature (Scheme 2).



X = O. S, N-H, N-Me, N-Ms, N-Bn, N-Boc

Scheme 2. Mono hetereoaryl chalcone structure

Tsukerman *et al*. synthesized a series of 1-aryl-3-pyrrole and 1-pyrrole-3-aryl chalcones via Claisen Schmidt condensation. However, they reported that any chalcone from condensation of 2,4,6-trimethoxy acetophenone and pyrrole-2-carboxaldehyde did not obtained. Instead an interesting compound, 2*H*-pyrrol-2-ylidene)methyl)-3-(2*H*-pyrrol-2-ylidene)-1-(2,4,6-trimethoxyphenyl)propan-1-one, including two pyrrole ring was formed (Scheme 3).[19]

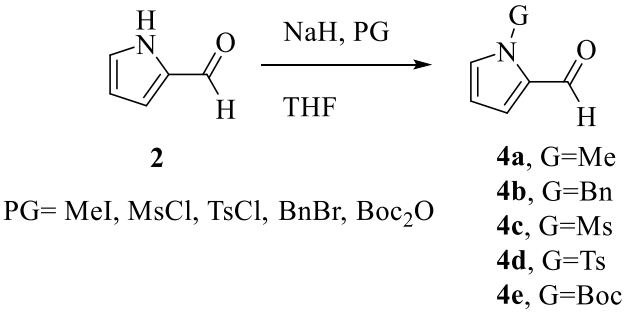


1 **2** **3**

Scheme 3. The synthesis of 2*H*-pyrrol-2-ylidene)methyl)-3-(2*H*-pyrrol-2-ylidene)-1-(2,4,6-trimethoxyphenyl)propan-1-one

Indeed our attempts to synthesize (*E*)-3-(1*H*-pyrrol-3-yl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one via condensation of 2,4,6-trimethoxy acetophenone and pyrrole-2-carboxaldehyde was

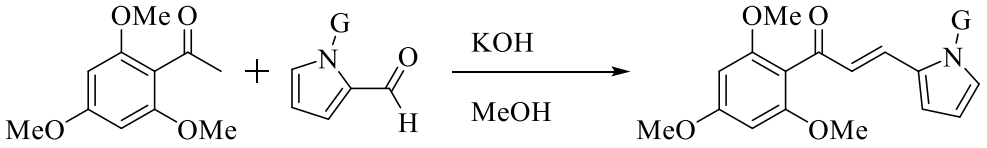
unsuccessful. Therefore, we decided the use of N-H protected derivatives (-Me, -Bn, -Ms, -Ts and -Boc) of pyrrole aldehyde in the condensation reaction (Scheme 4).



Scheme 4. The synthesis of 1-substituted-1*H*-pyrrole-2-carbaldehyde derivatives

It was decided to easily achieve other chalcone compounds that was targeted through Claisen condensation reaction after achieving the substituted Pyrrole-2-carboxaldehyde derivatives (**4a-4e**), which will be achieved by the protection of the amino group. As seen in Table 1 among the protected pyrrole derivatives **4a-4e**, the most effective to afford the desired chalcones was benzyl (Bn) protected one. Therefore, we decided to prepare the other mono, bis and tris derivatives were readily obtained. In particularly, important biological activity studies of compounds similar to these structures are presented in the literature.[20–22]

Table 1. Optimization of the reaction conditions for the formation of chalcone 3-(1-substituted-1*H*-pyrrol-2-yl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one. [a]

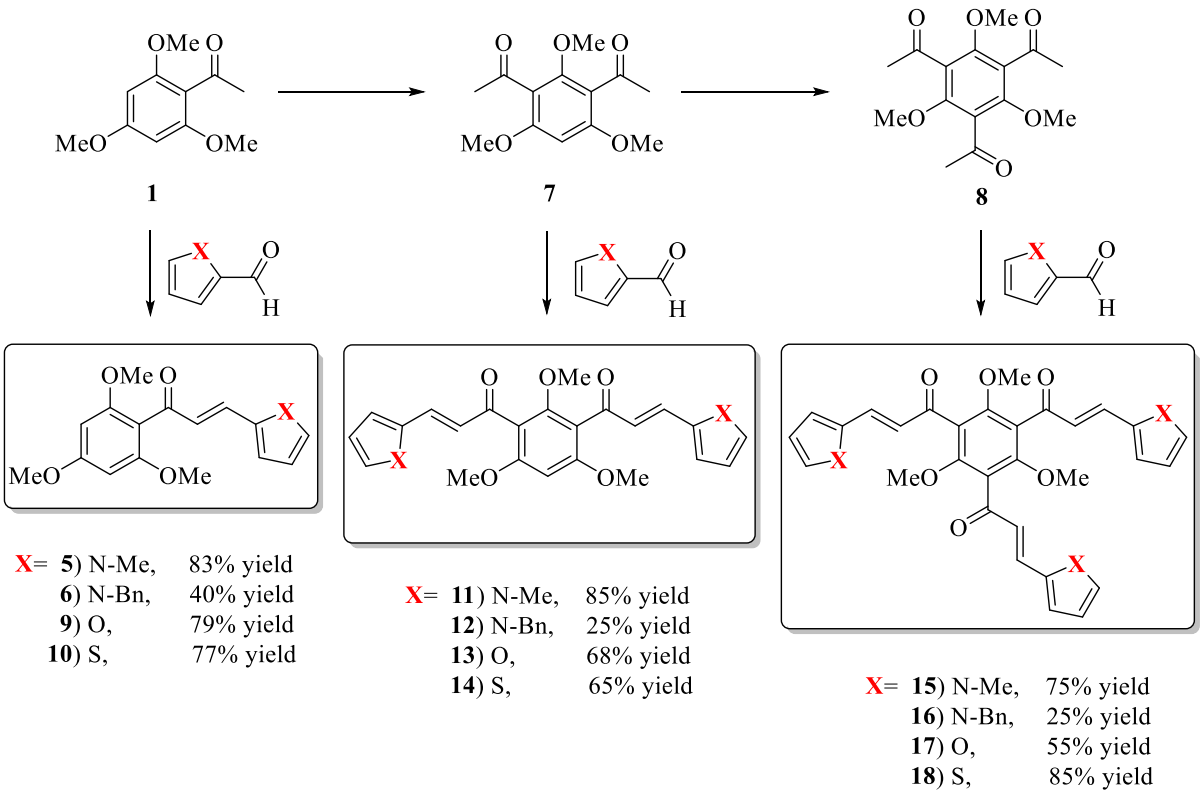


Entry	Pyrrole derivatives	Group	Product	Yield(%)[b]
1	2	H	-	-
2	4a	Ms	-	-
3	4b	Ts	-	-
4	4c	Boc	-	-
5	4d	Me	5	83
6	4e	Bn	6	40

[a] A solution of **1** (1 molar mmole.), pyrrole aldehydes **2, 4a-4e** (1.6 molar mmole.), and KOH (1 mmole.) in solvent (1 mL) was stirred overnight at room temperature. After full conversion of acetophenone 1, the reaction was quenched with NH_4Cl(aq). [b] Isolated yield.

After these studies were performed with pyrrole aldehyde, trials were made on the results of the Claisen Schmidt reaction with five-member heterocyclic aromatic derivatives. Therefore, bis and tris derivatives of chalcones were evaluated in the present study. In conclusion, after mono-substituted

derivatives of heteroaryl chalcones (**5**, **6**, **9**, **10**), the synthesis of their bis and tris derivatives (**11-18**) was also performed with high purity and efficiency (Scheme 5).



Scheme 5. General synthesis method

To best our knowledge, any synthetic procedure and physical or spectral data for mono derivatives of furan and thiophene chalcones of 1,3,5-trimethoxy benzene are not recorded in the literature. Thus the synthesis of heteroaryl chalcone analogs in mono, bis and tris structure was also carried out by the reaction of trimethoxy acetophenones with heterocyclic aromatic benzaldehydes.

4. Conclusion

Trimethoxy chalcone derivatives carrying a five-membered heteroaryl unit (**5**, **6**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16**, **17**, **18**) were synthesised with good efficiency and structures of these compounds were determined using NMR, IR and elemental analysis. In addition to the preparation of the first examples of bis and tris chalcones based on 1,3,5-trimethoxybenzene, we showed the new examples of fully substitued benzene via 2,4,6-trimethoxy acetophenone. We suppose that the synthesized compounds may exhibit severe important biological activities and may be used for further chemical and biological purposes.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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