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ORIGINAL ARTICLE

Antimicrobial activities of heterocycles derived from thienylchalcones

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2-Thienylchalcones;
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Abstract Thiophene analogues of chalcones were synthesized in good yields by condensation of 2-acetylthiophene and salicylaldehydes. Solvent-free Michael addition of cyclohexanone to 2-thienylchalcones devoid of hydroxyl groups yielded 1,5-diketones. The chalcones and 1,5-diketones were utilised as synthons for flavans, 6*H*-benzo[*c*]chromen-6-ones, tetrahydro-2*H*-chromens, tetrahydroquinolines and diazepines. The methods utilised were short and efficient in good yields and operational simplicity. The synthesized heterocyclic compounds were characterised by IR, NMR and HR-MS spectral data and screened for their antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Candida albicans*. The compounds demonstrated moderate to good antibacterial and antifungal activities. The synthesis of new heterocyclic compounds with an antimicrobial activity argument this study.

1. Introduction

Chalcones are an important group of natural products that consist of two aromatic rings joined by an α,β-unsaturated carbonyl system. The α,β-unsaturated carbonyl system enables chalcones and their heteroanalogs to undergo conjugated addition reactions in the presence of Lewis acid and basic catalysts (Al-Jaber et al., 2012; Samshuddin et al., 2012). Literature has indicated that this reaction has been exploited to obtain heterocyclic compounds of biological significance, such as pyridines, pyrazoles, pyrimidines, isoxazoles (Azab et al., 2013; Samshuddin et al., 2012), 1,5-benzodiazepines (Al-Jaber et al., 2012), flavonoids (Bano et al., 2013), thiazines (Konstantinova et al., 2007) and cyclohexenones (Sreevidya et al., 2010; Roman, 2004).

The appreciation of chalcone derived heterocyclic compounds' diverse biological applications and the continuous application of chalcone derivatives as synthons in organic synthesis, has led to the synthesis of thiophene analogues of chalcone and their subsequent heterocyclics. The thiophene heteroaryl ring is important owing to elemental sulphur having antifungal properties, while chalcones bearing sulphur either as a thiophene or as a side chain (thiomethyl group) have been reported to exhibit biological activities such as antimicrobial, antibacterial, antifungal (Tran et al., 2012; Ranganathan et al., 2012) and anti-tumour (Rizvi et al., 2012).

Herein, the synthesis of 2-thienylchalcones as intermediates towards flavans, 6*H*-benzo[c]chromen-6-ones, tetrahydro-2*H*-chromens, tetrahydroquinolines and diazepines is reported. The new heterocyclic compounds' chemical structures were

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assigned based on IR, NMR and HR-MS spectral data and were screened for antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Candida albicans*.

2. Material and methods

2.1. General methods

Melting points were determined on a Stuart melting point apparatus SMP1 (UK) and are uncorrected. Infrared spectra were recorded neat on a Perkin Elmer FT-IR spectrophotometer 1000. ^{1}H, ^{13}C and 2D-NMR spectra were recorded on a Bruker Avance DPX 300 MHz NMR spectrometer in $CDCl_3$ (or acetone-d_6) with TMS as an internal standard at room temperature. Electron impact (EI) High resolution mass spectra (HR-MS) were carried out on GCT Premier Mass Spectrometer (Waters) ionisation energy 70 eV, at the Chemistry Department, University of Botswana. All reactions were monitored by TLC, which was carried out on 0.25 mm layer of Merck silica gel 60 F254 pre-coated on aluminium sheets. Laboratory grade chemicals and solvents available commercially in high purity were used. All the prepared compounds were identified by physical properties, IR, HRMS and NMR data. Yields reported are isolated yields unless indicated otherwise.

2.1.1. General procedure for the synthesis of thiophen-2-yl-chalcones (**1a**–**d**)

Chalcones, **1a** and **1b** were prepared using the solvent-free green protocol of hand grinding (Dev and Dhaneshwar, 2013; ZiXing et al., 2010), while conventional base-catalysed Claisen–Schmidt condensation was used for the synthesis of chalcones **1c** and **1d** (Mazimba et al., 2011).

*2.1.1.1. (E)-3-(2-Hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**1a**).* Yellow solid; m.p.; 156–158 °C; Yield 87%; IR (neat, cm^{-1}): 3326 (OH), 3095 (=C—H), 1692 (C=O), 1666 (C=O), 2922 (C—H), 1233, 1176 (C—O), 1558, 1456, 750 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.98 (3H, *m*, H-3, 4 & 5), 7.23 (1H, *dd*, J = 1.2, 3.6 Hz, H-4′), 7.61 (1H, *d*, J = 15.6 Hz, H_α), 7.63 (1H, *dd*, J = 1.5, 8.1 Hz, H-6), 7.72 (1H, *dd*, J = 1.2, 4.5 Hz, H-5′), 7.93 (1H, *dd*, J = 0.9, 3.6 Hz, H-3′), 8.29 (1H, *d*, J = 15.6 Hz, H_β); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 116.1 (C-3), 119.9 (C-5), 121.2 (C_α), 121.8 (C-1), 128.4 (C-6), 128.9 (C-4′), 131.8 (C-4), 132.0 (C-3′), 134.0 (C-5′), 138.7 (C_β), 146.2 (C-1′), 156.9 (C-2), 181.7 (C=O); HRMS (EI, 70 eV): found *m*/*z* 230.0402 [M+], mol. formula $C_{13}H_{10}O_2S$, needing 230.0402.

*2.1.1.2. (E)-3-(2-Hydroxy-3-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**1b**).* White solid; m.p.; 156–158 °C; yield 85%; IR (neat, cm^{-1}): 3325 (OH), 3096 (=C—H), 2922 (C—H), 1664 (C=O), 1224, 1088 (C—O—C), 1558, 1457, 755 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.54 (3H, *s*, 3-OCH_3), 6.68 (1H, *t*, J = 8.1 Hz, H-4), 7.07 (1H, *dd*, J = 1.2, 7.8 Hz, H-5), 7.29 (1H, *dd*, J = 0.9, 3.9 Hz, H-4′), 7.41 (1H, *dd*, J = 1.2, 7.8 Hz, H-6), 7.79 (1H, *d*, J = 15.6 Hz, H_α), 7.93 (1H, *dd*, J = 1.2, 4.8 Hz, H-4′), 8.12 (1H, *dd*, J = 0.9, 3.6 Hz, H-3′), 8.19 (1H, *d*, J = 15.6 Hz, H_β); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 55.9 (3-OCH_3). 112.9 (C-4), 119.3 (C-6), 120.2 (C-5), 121.3 (C-1), 121.5 (C_α), 128.4 (C-4′), 132.0 (C-3′), 134.0 (C-5′), 138.4 (C_β), 146.2 (C-1′), 146.7 (C-2), 147.8 (C-3), 181.7 (C=O); HRMS (EI, 70 eV): found *m*/*z* 260.0507 [M+], mol. formula $C_{14}H_{12}O_3S$, needing 260.0507.

*2.1.1.3. (E)-3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one (**1c**).* White solid; m.p.; 90–92 °C; yield 87%; IR (neat, cm^{-1}): 3082 (=C—H), 2948, 2863 (C—H), 1660 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.23 (1H, *t*, J = 5.4 Hz, H-4′), 7.44 (1H, *m*, H-4), 7.46 (2H, *m*, H-3 & 5), 7.47 (1H, *d*, J = 15.0 Hz, H_α), 7.69 (2H, *m*, H-2 & 6), 7.73 (1H, *dd*, J = 0.9, 4.8 Hz, H-5′), 7.88 (1H, *d*, J = 15.0 Hz, H_β), 7.93 (1H, *dd*, J = 3.3, 4.2 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 121.6 (C_α), 128.2 (C-4), 128.5 (C-3 & 5), 129.0 (C-2 & 6), 134.7 (C-1), 130.6 (C-4′), 131.9 (C-5′), 133.9 (C-3′), 144.1 (C_β), 145.5 (C-1′), 182.0 (C=O); HRMS (EI, 70 eV): found *m*/*z* 214.0452 [M+], mol. formula $C_{13}H_{10}OS$, needing 214.0452.

*2.1.1.4. (E)-3-(4-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**1d**).* Yellow solid; m.p.; 108–110 °C; yield 84%; IR (neat, cm^{-1}): 3088 (=C—H), 2945, 2860 (C—H), 1659 (C=O), 1245, 1031 (C—O), 1510, 1416, 755 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.91 (3H, *s*, 4-OCH_3), 7.03 (2H, *dd*, J = 8.4 Hz, H-3 & 5), 7.44 (2H, *d*, J = 8.4 Hz, H-2 & 6), 7.62 (1H, *t*, J = 5.0 Hz, H-4′), 7.71 (1H, *dd*, J = 0.9, 4.3 Hz, H-5′), 7.82 (1H, *dd*, J = 3.3, 4.5 Hz, H-3′), 7.90 (1H, *d*, J = 15.9 Hz, H_α), 8.23 (1H, *d*, J = 15.9 Hz, H_β); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 54.8 (4-OCH_3), 116.2 (C-3 & 5), 121.6 (C_α), 122.0 (C-1), 128.9 (C-2 & 6), 129.7 (C-3′), 131.7 (C-5′), 133.4 (C-4′), 140.0 (C_β), 157.0 (C-1′), 160.0 (C-4), 189.2 (C=O); HRMS (EI, 70 eV): found *m*/*z* 244.0558 [M+], mol. formula $C_{14}H_{12}O_2S$, needing 244.0558.

2.1.2. General procedure for the synthesis of flavans (**2a**,**b**)

To a methanolic solution of chalcone (10 mmol) at 20 °C sodium borohydride powder (50 mmol) was introduced slowly over 20 min. The reaction was quenched with 2 M HCl in an ice bath. The organic layer was extracted with ethyl acetate, dried over magnesium sulphate and concentrated to a residue. To this residue glacial acetic acid (15 ml) was added and refluxed for 20 min. The organic layer was treated as above and after purification using flash column chromatography using *n*-hexane–ethylacetate (5:1, v/v) a pure product was obtained.

*2.1.2.1. 2-(Thiophen-2-yl)chroman (**2a**).* Brown gum; yield 70%; IR (neat, cm^{-1}): 3179 (=C—H), 2931, 2880 (C—H), 1239, 1167 (C—O—C), 1595, 1456, 755 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.31 & 2.40 (each 1H, *m*, H-3a & 3b), 2.95 & 3.04 (each 1H, *m*, H-4a & 4b), 5.40 (1H, *dd*, J = 2.4, 9.6 Hz, H-2), 6.98 (2H, *m*, H-6 & 8), 7.09 (1H, *dd*, J = 1.5, 4.8 Hz, H-5′), 7.17 (2H, *m*, H-5 & 7), 7.23 (1H, *dd*, J = 1.2, 4.2 Hz, H-4′), 7.37 (1H, *dd*, J = 0.9, 5.1 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.8 (C-4), 29.8 (C-3), 73.7 (C-2), 117.1 (C-8), 120.6 (C-6), 121.6 (C-4a), 124.5 (C-3′), 125.1 (C-5′), 126.7 (C-4′), 127.4 (C-7), 129.6 (C-5), 144.8 (C-1′), 154.6 (C-8a); HRMS (EI, 70 eV): found *m*/*z* 216.0604 [M+], mol. formula $C_{13}H_{12}OS$, needing 216.0604.

*2.1.2.2. 8-Methoxy-2-(thiophen-2-yl)chroman (**2b**).* Brown gum; yield 65%; IR (neat, cm^{-1}): 3108 (=C—H), 2951, 2850 (C—H), 1230, 1182, 1110 (C—O—C), 1581, 1487, 749 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.53 (3H, *s*,

8-OCH_3) 2.75 & 2.82 (each 1H, *m*, H-3a & 3b), 2.99 & 3.01 (each 1H, *m*, H-4a & 4b), 4.90 (1H, *dd*, *J* = 3.9, 9.3 Hz, H-2), 6.90–6.98 (3H, *m*, H-5, 6 & 7), 7.13–7.18 (2H, *m*, H-4′ & 5′), 7.28 (1H, *dd*, *J* = 0.9, 3.6 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 29.9 (C-4), 39.4 (C-3), 45.6 (8-OCH_3), 68.7 (C-2), 116.1 (C-7), 120.9 (C-5), 124.1 (C-6), 124.8 (C-3′), 126.7 (C-5′), 127.7 (C-4′), 130.6 (C-4a), 147.6 (C-8a), 144.7 (C-1′), 154.3 (C-7); HRMS (EI, 70 eV): found *m*/*z* 246.0708 [M+], mol. formula $C_{14}H_{14}O_2S$, needing 246.0715.

2.1.3. General procedure for synthesis of 6H-benzo[c]chromen-6-one (**4a**,**b**)

Thiophen-2-yl-chalcones (**1a** or **1b**) (2 mmol), potassium carbonate powder (20 mol%) and ethylacetoacetate (2 mmol) were taken in ethanol and stirred at 60 °C for 30 min. Then the reaction mixture was cooled and poured into cold water. The precipitated solid was collected by filtration and recrystallized in ethanol.

*2.1.3.1. 7-Hydroxy-9-(thiophen-2-yl)-6H-benzo[c]chromen-6-one (**4a**).* White solid; m.p.; 163–165 °C; yield 60%; IR (neat, cm^{-1}): 3105 (=C—H), 2974, 2860 (C—H), 1676 (C=O), 1276, 1208, 1108 (C—O—C), 1564, 1410, 851 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 7.22 (1H, *dd*, *J* = 1.5, 3.6 Hz, H-4′), 7.35 (1H, *d*, *J* = 1.5 Hz, H-8), 7.41 (1H, *dd*, *J* = 1.2, 8.1 Hz, H-4), 7.46 (1H, *dd*, *J* = 1.2, 8.1 Hz, H-2), 7.51 (1H, *dd*, *J* = 1.2, 5.1 Hz, H-3′), 7.54 (1H, *dd*, *J* = 1.8, 7.5 Hz, H-3), 7.59 (1H, *dd*, *J* = 1.2, 3.6 Hz, H-5′), 7.81 (1H, *d*, *J* = 1.5 Hz, H-10), 8.14 (1H, *dd*, *J* = 1.8, 7.8 Hz, H-1), 11.4 (1H, *s*, 7-OH); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 104.8 (C-6a), 109.4 (C-8), 113.0 (C-10), 117.0 (C-4), 118.1 (C-10b), 123.3 (C-2), 125.2 (C-3′), 125.8 (C-5′), 127.6 (C-4′), 128.5 (C-3), 130.8 (C-1), 135.7 (C-10a), 142.3 (C-1′), 142.9 (C-9), 150.8 (C-4a), 162.7 (C-6), 165.1 (C-7); HRMS (EI, 70 eV): found *m*/*z* 294.0351 [M+], mol. formula $C_{17}H_{10}O_3S$, needing 294.0351.

*2.1.3.2. 7-Hydroxy-4-methoxy-9-(thiophen-2-yl)-6H-benzo[c]chromen-6-one (**4b**).* White solid; m.p.; 148–150 °C; yield 52%; IR (neat, cm^{-1}): 3130 (=C—H), 2952, 2850 (C—H), 1678 (C=O), 1271, 1268 (C—O—C), 1556, 1407, 817 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 3.57 (3H, *s*, 4-OCH_3), 6.84 (1H, *dd*, *J* = 0.9, 7.8 Hz, H-3), 7.14 (1H, *dd*, *J* = 1.5, 3.6 Hz, H-4′), 7.27 (1H, *dd*, *J* = 1.2, 7.8 Hz, H-2), 7.33 (1H, *d*, *J* = 1.5 Hz, H-8), 7.42 (1H, *dd*, *J* = 1.5, 3.6 Hz, H-3′), 7.92 (1H, *dd*, *J* = 1.2, 3.6 Hz, H-3), 7.99 (1H, *dd*, *J* = 1.2, 7.8 Hz, H-1), 8.12 (1H, *d*, *J* = 1.5 Hz, H-10), 12.6 (1H, *s*, 7-OH); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 55.7 (4-OMe), 105.7 (C-6a), 108.4 (C-8), 111.3 (C-10), 113.0 (C-3), 119.4 (C-1), 121.2 (C-10b), 121.9 (C-2), 127.5 (C-5′), 127.9 (C-3′), 128.0 (C-4′), 134.4 (C-10a), 140.0 (C-1′), 140.3 (C-9), 148.1 (C-4a), 150.0 (C-4), 161.9 (C-6), 165.2 (C-7); HRMS (EI, 70 eV): found *m*/*z* 324.0456 [M+], mol. formula $C_{18}H_{12}O_4S$, needing 324.0456.

2.1.4. General procedure for synthesis of tetrahydroquinolines (**7a**,**b**)

A mixture of chalcones (**1c** or **1d**) (1 mmol), cyclohexanone (2 mmol) and NaOH (2 mmol) were ground with an agate mortar and a pestle for 25 min until the reaction mixture became a solid. The solid was dissolved in acetone (10 mL) and cold water was added (20 mL). The separated solid was collected by filtration, washed with water and ethanol. The 1,5-diketone (1 mmol) and ammonium acetate (5 mmol) in glacial acetic acid (20 mL) were heated to reflux (30 min). The crude product was precipitated out of solution by the addition of cold water (10 mL), collected and washed with water and ethanol.

*2.1.4.1. 5,6,7,8-Tetrahydro-4-phenyl-2-(thiophen-2-yl)quinoline (**7a**).* Brown solid; m.p.; 175–177 °C; yield 90%; IR (neat, cm^{-1}): 3057 (=C—H), 2928, 2854 (C—H), 1655, 1544 (pyridine ring), 1584, 1453, 853 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 1.66 (2H, *m*, H-6), 1.82 (2H, *m*, H-7), 2.52 (2H, *m*, H-5), 2.94 (2H, *t*, *J* = 4.5 Hz, H-8), 6.96 (1H, *m*, H-4′), 6.98 (1H, *m*, H-4″), 7.22 (2H, *m*, H-2″ & 6″), 7.25 (1H, *s*, H-3), 7.31 (1H, *m*, H-5′), 7.34 (2H, *m*, H-3″ & 5″), 7.45 (1H, *dd*, *J* = 0.9, 3.6 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 23.0 (C-7), 27.3 (C-6), 29.7 (C-5), 33.1 (C-8), 117.6 (C-3), 124.1 (C-3′), 127.6 (C-4′), 127.8 (C-4a), 128.0 (C-5′), 128.4 (C-2″ & 6″), 128.5 (C-3″ & 5″), 128.6 (C-4″), 139.5 (C-1″), 145.1 (C-1′), 149.3 (C-4), 150.3 (C-2), 157.2 (C-8a); HRMS (EI, 70 eV): found *m*/*z* 291.1080 [M+], mol. formula $C_{19}H_{17}NS$, needing 291.1082.

*2.1.4.2. 5,6,7,8-Tetrahydro-4-(4-methoxyphenyl)-2-(thiophen-2-yl)quinoline (**7b**).* Brown solid, m.p.; 212–214 °C; yield 90%; IR (neat, cm^{-1}): 3025 (=C—H), 2931, 2860 (C—H), 1658, 1537 (pyridine ring), 1515, 1450, 834 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 1.82 (2H, *m*, H-7), 1.93 (2H, *m*, H-6), 2.68 (2H, *m*, H-5), 3.07 (2H, *t*, *J* = 6.6 Hz, H-8), 3.91 (3H, *s*, 4″-OCH_3), 7.04 (2H, *d*, *J* = 8.4 Hz, H-3″ & 5″), 7.12 (2H, *dd*, *J* = 1.2, 3.6 Hz, H-4′ & 5′), 7.33 (2H, *d*, *J* = 8.4 Hz, H-2″ & 6″), 7.37 (1H, *s*, H-3), 7.56 (1H, *d*, *J* = 3.6 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) *δ*: 23.1 (C-7), 27.4 (C-6), 29.7 (C-5), 33.1 (C-8), 55.3 (4″-OCH_3), 113.8 (C-3″ & 5″), 117.7 (C-3), 124.0 (C-3′), 127.8 (C-3′ & 4′), 129.0 (C-2″ & 6″), 129.1 (C-4), 131.7 (C-4a), 145.2 (C-1′), 149.3 (C-2), 149.9 (C-4), 157.6 (C-8a), 159.3 (C-4′); HRMS (EI, 70 eV): found *m*/*z* 321.1185 [M+], mol. formula $C_{20}H_{19}NOS$, needing 321.1187.

2.1.5. General procedure for synthesis of 5-oxotetrahydro-2H-chromenes

To a methanolic solution of the 1,5-diketone (1 mmol) sodium borohydride powder (5 mol) was added over 10 min. Then cold 2 M HCl was added. The organic layer was extracted with chloroform, dried over magnesium sulphate and concentrated to a residue. The residue was taken in glacial acetic acid (10 ml) and refluxed for 30 min. The organic layer was extracted using ethyl acetate and dried over magnesium sulphate. After being concentrated it was purified using flash column chromatography eluted by petroleum ether-ethylacetate (v/v, 4:1) to obtain a pure product.

*2.1.5.1. Octahydro-4-phenyl-2-(thiophen-2-yl)-2H-chromene (**9a**).* White gum; yield 85%; IR (neat, cm^{-1}): 3059 (=C—H), 2923, 2856 (C—H), 1598, 1450, 757 (Aromatic), 1239, 1077 (C—O); ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 1.17–1.87 (8H, *m*, H-5, 6, 7 & 8), 2.05 (1H, *dt*, *J* = 2.4, 9.0 Hz, H-4a), 2.17 (2H, *m*, H-3), 3.09 (1H, *dt*, *J* = 3.3, 12.3 Hz, H-4), 4.06 (1H, *q*, *J* = 2.4, 12.3 Hz, H-8a), 5.05 (1H, *dd*, *J* = 2.8, 8.4 Hz, H-2), 6.83 (1H, *m*, H-4′) 6.86 (1H, *m*, H-3′), 7.10 (1H, *m*,

H-5′), 7.14 (2H, *m*, H-2″ & 6″), 7.19 (1H, *m*, H-4″), 7.20 (2H, *m*, H-3″ & 5″); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.3 (C-7), 25.4 (C-5), 25.5 (C-6), 26.8 (C-8), 39.3 (C-4), 40.4 (C-3), 42.8 (C-4a), 68.4 (C-2), 76.5 (C-8a), 123.2 (C-3′), 124.3 (C-5′), 126.4 (C-4″), 126.5 (C-4′), 127.5 (C-2″ & 6″), 128.6 (C-3″ & 5″), 143.9 (C-1″), 146.4 (C-1′); HRMS (EI, 70 eV): found *m*/*z* 298.1391 [M+], mol. formula $C_{19}H_{22}OS$, needing 298.1391.

*2.1.5.2. Octahydro-4-(4-methoxyphenyl)-2-(thiophen-2-yl)-2H-chromene (**9b**).* Brown gum; yield 86%; IR (neat, cm^{-1}): 3025 (=C—H), 2923, 2857 (C—H), 1510, 1444 (Aromatic), 1240, 1171 (C—O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.19–1.99 (8H, *m*, H-5, 6, 7 & 8), 2.04 (1H, *dt*, *J* = 3.9, 11.4 Hz, H-4a), 2.17 (2H, *m*, H-3), 3.05 (1H, *dt*, *J* = 3.3, 7.5 Hz, H-4), 3.68 (3H, *s*, 4″-OCH_3), 4.05 (1H, *q*, *J* = 3.9, 7.5 Hz, H-8a), 5.01 (1H, *dd*, *J* = 2.1, 11.4 Hz, H-2), 6.78 (2H, *d*, *J* = 8.4 Hz, H-3″ & 5″), 6.85 (2H, *brs*, H-4′ & 5′), 7.06 (2H, *d*, *J* = 8.4 Hz, H-2″ & 6″), 7.11 (1H, *dd*, *J* = 1.8, 4.8 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.3 (C-7), 25.4 (C-5), 26.8 (C-6), 29.7 (C-8), 38.4 (C-4), 40.7 (C-3), 43.1 (C-4a), 55.2 (4″-OCH_3), 68.4 (C-2), 76.5 (C-8a), 114.0 (C-3″ & 5″), 123.2 (C-3′), 124.3 (C-5′), 126.4 (C-4′), 128.3 (C-2″ & 6″), 135.8 (C-1″), 146.8 (C-1′), 158.2 (C-4″); HRMS (EI, 70 eV): found *m*/*z* 328.1500 [M+], mol. formula $C_{20}H_{24}O_2S$, needing 328.1497.

*2.1.6. General procedure for the preparation of diazepine (**10a,b**)*

A mixture of 1,5-diketone (10 mmol) and hydrazine hydrate (10 mmol) in glacial acetic acid (20 mL) was refluxed for 3 h. The reaction mixture was cooled and poured into ice-cold water. The precipitate formed was collected by filtration and recrystallized from ethanol.

*2.1.6.1. 5-Phenyl-3-(thiophen-2-yl)-5,5a,6,7,8,9-hexahydro-4H-benzo[c][1,2]diazepine (**10a**).* White solid; m.p.; 126–128 °C; yield 66 %; IR (neat, cm^{-1}): 2931, 2854, (CH), 1607 (C=N), 1510, 1450 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.14–1.78 (8H, *m*, H-6, 7, 8 & 9), 2.05–2.17 (2H, *m*, H-4), 2.24 (1H, *m*, H-5a), 2.34 (1H, *m*, H-5), 6.72–6.84 (5H, *m*, H-2″, 3″, 4″, 5″ & 6″), 6.98 (1H, *t*, *J* = 3.1 H-4′), 7.12 (1H, *dd*, *J* = 2.4, 3.8 Hz, H-5′), 7.15 (1H, *dd*, *J* = 1.5, 6.0 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.9 (C-7), 26.0 (C-8), 28.9 (C-6), 33.7 (C-9), 43.8 (C-4), 42.1 (C-5), 46.9 (C-5a), 125.0 (C-3′), 126.0 (C-4″), 126.6 (C-4′), 126.9 (C-5′), 127.6 (C-1′), 135.0 (C-1″), 128.8 (C-2″ & 6″), 129.2 (C-3″ & 5″), 157.9 (C-3), 158.0 (C-9a); HRMS (EI, 70 eV): found *m*/*z* 308.1350 [M+], mol. formula $C_{19}H_{20}N_2S$, needing 308.1347.

*2.1.6.2. 5-(4-Methoxyphenyl)-3-(thiophen-2-yl)-5,5a,6,7,8,9-hexahydro-4H-benzo[c] [1,2]diazepine (**10b**).* White solid, m.p; 126–128 °C; yield 68 %; IR (neat, cm^{-1}): 2930, 2856 (CH), 1610 (C=N), 1570, 1458 (Aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.16–1.82 (8H, *m*, H-6, 7, 8 & 9), 2.29 (2H, *m*, H-4), 2.54 (1H, *t*, *J* = 6.6 Hz, H-5a), 2.99 (1H, *t*, *J* = 6.0 Hz, H-5), 3.54 (3H, s, 4″-OCH_3), 6.94 (2H, *d*, *J* = 8.4 Hz, H-3″ & 5″), 7.09 (1H, *t*, *J* = 2.4 Hz, H-4′), 7.13 (1H, *dd*, *J* = 1.2, 2.4 Hz, H-5′), 7.22 (2H, *d*, *J* = 8.4 Hz, H-2″ & 6″), 7.31 (1H, *dd*, *J* = 1.5, 5.4 Hz, H-3′); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.9 (C-7), 23.0 (C-8), 29.1 (C-6), 33.4 (C-9), 39.1 (C-4), 42.3 (C-5), 43.1 (C-5a), 60.0 (4″-OCH_3), 118.0 (C-3″ & 5″), 124.1 (C-1′), 125.6 (C-3′), 127.8 (C-4′), 127.9 (C-5′), 128.4 (C-2″ & 6″), 134.9 (C-1″), 159.8 (C-4″), 168.7 (C-9a & C-3); HRMS (EI, 70 eV): found *m*/*z* 338.1461 [M+], mol. formula $C_{20}H_{22}N_2OS$, needing 338.1453.

2.2. Antimicrobial activity

The synthesized compounds were tested *in vitro* for their antibacterial and antifungal profile using Dilution Method (Ragavan et al., 2010; Danielle, 2006) against *S. aureus* (ATCC 9144), *E. coli* (ATCC 11229), *B. subtilis* (ATCC 6633), *P. aeruginosa* (NCTC 10332) and *C. albicans* (ATCC 10231). The test microorganisms were obtained from the Department of Biological Sciences, University of Botswana. Ciprofloxacin and Fluconazole were used as standards for bacteria and fungi respectively. The tested solutions were serially diluted to give concentrations of 5, 2.5, 1.25, 0.625 and 0.313 mg/mL. All tests were done in triplicate. The antimicrobial activity was expressed as minimum inhibitory concentration (MIC) of sample that prevented the visible growth of a microorganism.

3. Result and discussions

Initially, the synthesis of *trans*-2-thienylchalcones was attempted using the efficient, economical and a green protocol of grinding the reactants together in the presence of catalytic amount of sodium hydroxide. This method worked only for chalcones devoid of hydroxyl groups (**1c**–**d**, 90% yield) while grinding 2-hydroxybenzaldehydes did not afford chalcones. The presence of hydroxyl groups on aryl aldehydes or ketones is a limiting factor for the green protocol of chalcone synthesis. Literature survey shows solvent-free synthesis of chalcones and heterocyclic analogous of chalcones that excludes hydroxyl groups as substituents (Dev and Dhaneshwar, 2013; ZiXing et al., 2010; Rateb and Hussein, 2009). Hence, the conventional base-catalysed Claisen–Schmidt condensation reaction was adopted (Mazimba et al., 2011) and the thiophene chalcone analogues (**1a**–**d**) were obtained in 84–87% yields. The thienyl chalcones have been previously reported in good yields (81–90%) using the base catalysed condensation method (Roman, 2004; Tran et al., 2012; Yin et al., 2012), the literature spectroscopic data were also used to confirm the identity of reported chalcones. Next, the chalcones (Fig. 1) were used for the synthesis of the desired heterocyclic compounds.

3.1. Synthesis of flavans

Flavans (2-(thiophen-2-yl)chroman, **2a**,**b**) were derived by the reduction of the α,β-unsaturated ketone function of the chalcones (**1a**,**b**) using $NaBH_4$. The ring closure to form a chroman

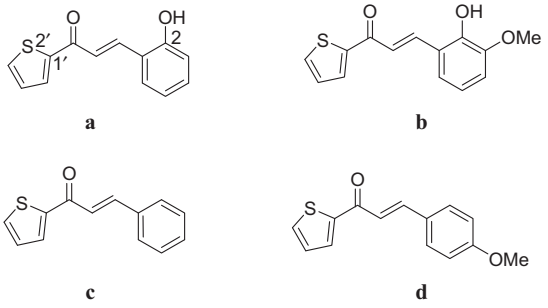


Figure 1 Structures of thienylchalcones.

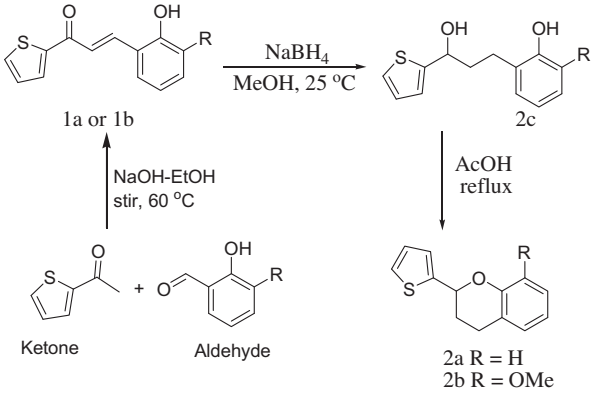
ring was achieved by refluxing the resulting 2-(3-hydroxy-3-(thiophen-2-yl)propyl)phenol (**2c**) in glacial acetic acid (Scheme 1) as previously described (Mazimba et al., 2011). The substitution of the chalcone benzene ring with the electron rich thiophene ring did not affect the reaction path but resulted in reduced yields. The 2-phenylchroman yield was 88% (Mazimba et al., 2011) while the yield for 2-thiophenylchroman (**2a**) was found to be 70%. The electron donating MeO-group led to the corresponding flavan (**2b**) in 65% yields.

3.2. Synthesis of 7-hydroxy-9-(thiophen-2-yl)-6H-benzo[c]chromen-6-ones

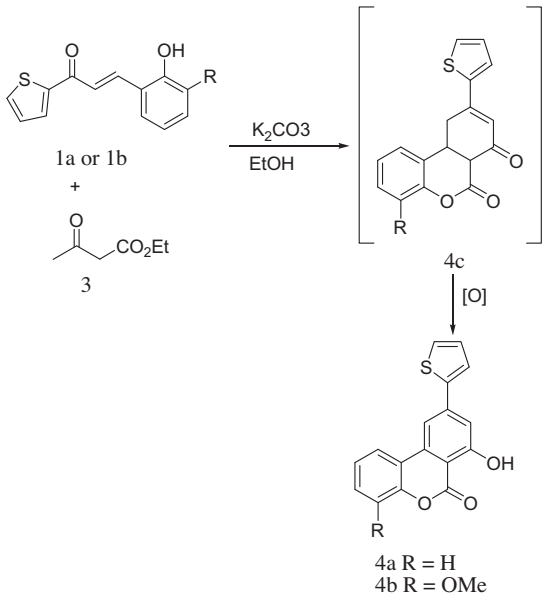
It is well reported that the reaction of chalcones with ethylacetoacetate affords cyclohexanones (Samshuddin et al., 2012; Roman, 2004), while the Knoevenagel reaction affords coumarins from the condensation of ethylacetoacetate with 2-hydroxybenzaldehydes (Sashidhara et al., 2010). Therefore, it was expected that 2-hydroxy-2′-thienylchalcones would react with ethylacetoacetate to furnish a 6*H*-benzo[*c*]chromene-6,7(6a*H*)-dione (**4c**) ring system. But the product of the reaction that was assisted by K_2CO_3, was identified to be 6*H*-benzo[*c*]chromen-6-ones (**4a**,**b**) instead of the expected 9-(thiophen-2-yl)-10,10a-dihydro-6*H*-benzo[*c*]chromene-6,7(6a*H*)-dione (**4c**), Scheme 2. The reaction is thought to proceed by the Michael addition of ethylacetoacetate to chalcone, followed by the ring forming intramolecular Aldol condensation of the ester methyl group with the chalcone keto-group to form cyclohexenones (Roman, 2004). The presence of 2′-OH enables a *trans*-esterification reaction to form intermediate **4c**, which undergoes oxidative aromatization to form 6*H*-benzo[*c*]chromen-6-ones (**4a**,**b**).

3.3. Synthesis of tetrahydroquinolines

2,4-Diaryltetrahydroquinolines were targeted owing to their pharmacological activities (Chabert et al., 2006) and ease of the availability of 1,5-diketones from chalcones. The required 1,5-diketones (**6a**–**b**) were obtained *via* the green protocol involving the Michael addition of cyclohexanone (**5**) to chalcones (**1c**,**d**) under solventless conditions. The reaction exclusively affords a single Michael addition product due to the unfavourable intramolecular self-condensation of the 1,5-diketones (ZiXing et al., 2010). Treatment of 1,5-diketones with ammonium acetate in acetic acid (Scheme 3) yielded



Scheme 1 Synthesis of thienylchalcones and flavans.

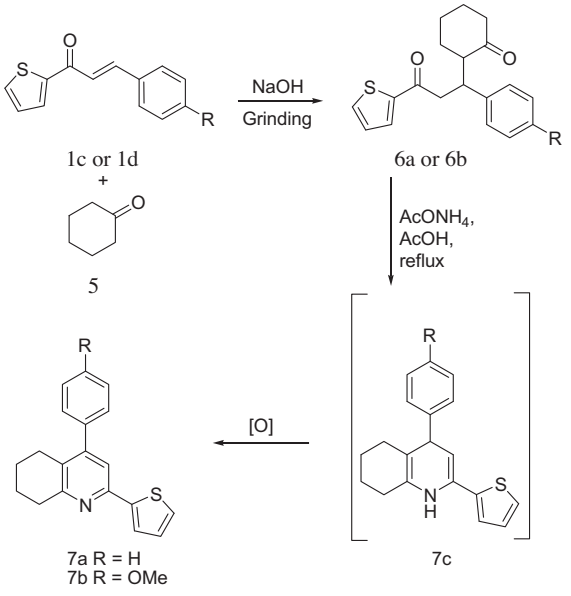


Scheme 2 Synthesis of thiophen-2-yl-6*H*-benzo[c]chromen-6-one.

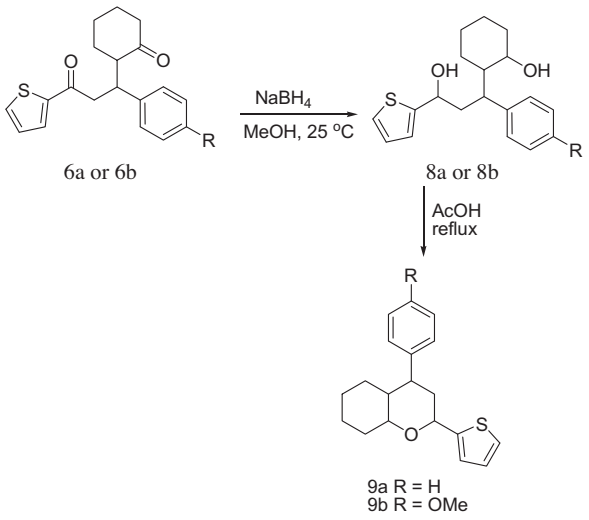
tetrahydroquinolines (**7a**,**b**) in good yields, 90%. This green protocol is an efficient '1 + 5' strategy that involves double condensation of an amino group with 1,5-diketones to afford six membered ring 1,4-dihydropyridine (4-phenyl-2-(thiophen-2-yl)-1,4,5,6,7,8-hexahydroquinoline, **7c**). The 1,4-dihydropyridine is subsequently oxidised to 4-phenyl-2-(thiophen-2-yl)-5,6,7,8-tetrahydroquinoline, Scheme 3 (Gezegen et al., 2010). The quinolyl ring singlet proton NMR signal (7.25 ppm) was diagnostic.

3.4. Synthesis of 5-oxotetrahydro-2H-chromenes

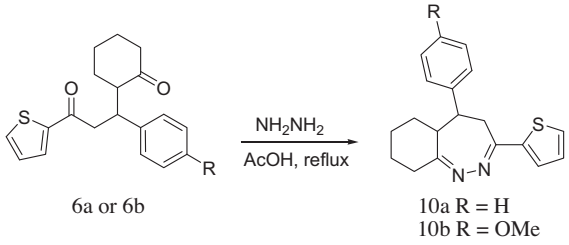
The strategy towards 2*H*-chromene involved the reduction of 1,5-diketones (**6a**,**b**) using $NaBH_4$ followed by the cyclization



Scheme 3 Synthesis of tetrahydroquinolines.



Scheme 4 Synthesis of 5-oxotetrahydro-2*H*-chromenes.



Scheme 5 Synthesis of diazepines.

of the resulting 1,5-diols (**8a**,**8b**) in glacial acetic acid which afforded 5-oxotetrahydro-2*H*-chromenes (**9a**,**b**) (Scheme 4). The heterocyclization of 1,5-diketones has been reported under $CF_3CO_2H/PtCl_2$–H_2 at 200 °C, Rh/C-H_2, Raney Nickel–AcOH at 150 °C (Kharchenko et al., 2000) and $TiCl_4$–Et_3N (Sergeeva et al., 2010). The reported reactions were carried out at elevated temperatures and suffered from low yields (34–50%), but the current protocol offers higher yields (85–86%) and operational simplicity.

3.5. Synthesis of diazepines

The condensation reaction between amines and ketones is known to yield imines or Schiff bases (Shaikh et al., 2013). Thus, 1,5-diketones bears a good synthon for heterocyclization reactions with *N*-nucleophiles to form six or seven membered rings. This conventional reaction was applied to obtain diazepines (**10a**,**b**, Scheme 5) from the reaction of hydrazine hydrate with 1,5-diketones (**6a**,**b**) derived from 2-thienylchalcone. The reaction was found to be simple and short affording moderate yields (66–68%) and a single product. The synthesis and pharmacological importance of diazepines are widely reported (Samshuddin et al., 2012; Luszczki, 2009; Rodriguez et al., 2004).

4. Antimicrobial studies

The synthesized new heterocyclic compounds were tested *in vitro* for their antimicrobial profile using the dilution method (Ragavan et al., 2010; Danielle, 2006) against *S. aureus*, *E. coli*, *B. subtilis*, *P. aeruginosa* and *C. albicans*. The tested compounds showed moderate to good antibacterial and antifungal activities. 6*H*-benzo[*c*]chromen-6-ones (**4a**,**b**) show good activities (0.625 mg/mL) against both bacteria and fungi, and the conjugation of hydroxy and ester groups may favour the uptake of these compounds by microbial cells. Tetrahydroquinolines (**7a,b**) and diazepines' (**10a**,**b**) excellent (0.313 mg/mL) results show the importance of the carbon–nitrogen bond in biological systems (Yadav and Purohit, 2013). The presence of the MeO-group does not seem to have a significant effect on the activities of compounds **7a,b** and **10a,b**, Table 1. These activities are in comparison with other reports which show antimicrobial activities for these N-containing compounds (Samshuddin et al., 2012; Dodiya et al., 2011). Flavans (**2a,b**) and 5-oxotetrahydro-2*H*-chromenes (**9a**,**b**) indicate moderate (1.25 mg/mL) activities. The data on antimicrobial activities of the target compounds are given in Table 1.

5. Conclusion

Thiophene analogues of chalcone (**1a**–**d**) were synthesized in good yields. 1,5-diketones were obtained utilising green

Table 1 Antimicrobial activity of thiophen-2-yl-chalcone derived heterocyclic compounds.

Compound	Minimum inhibitory concentration (MIC; mg/mL)				
	S. aureus	*E. coli*	*B. subtilis*	*P. aeruginosa*	*C. albicans*
2a	1.25	1.25	1.25	1.25	0.625
2b	1.25	1.25	1.25	1.25	1.25
4a	0.625	0.625	0.625	0.625	0.625
4b	0.625	0.625	0.625	0.625	0.625
7a	0.625	0.625	0.625	0.313	0.625
7b	0.625	0.625	0.625	0.313	0.625
9a	1.25	2.5	1.25	1.25	2.5
9b	1.25	1.25	1.25	1.25	1.25
10a	0.313	0.625	0.625	0.313	0.313
10b	0.313	0.625	0.625	0.313	0.313
Ciprofloxacin	0.625	0.625	0.625	0.625	–
Fluconazole	–	–	–	–	0.625

Michael addition of cyclohexanone to 2-thienylchalcones devoid of hydroxyl groups. The chalcones and 1,5-diketones were a good synthon for the synthesis of heterocyclic compounds, shown here by the synthesis of new flavans, 6*H*-benzo[*c*]chromen-6-ones, tetrahydro-2*H*-chromens, tetrahydroquinolines, and diazepines. The methods utilised were short and efficient in good yields and operational simplicity. The heterocyclic compounds were screened for their antimicrobial activity against *S. aureus*, *E. coli*, *B. subtilis*, *P. aeruginosa* and *C. albicans*, showing moderate to good antibacterial and antifungal activities. Diazepines (**10a**,**b**) exhibited excellent antibacterial (*S. aureus* and *P. aeruginosa*) and antifungal (*C. albicans*) activities. The preliminary data on the antimicrobial activities of the new scaffolds should serve as an indicator for structural modulation to improve activities and explain the structure activity relationships. The exhibition of chalcone synthon potential and the antimicrobial activity of the target heterocyclic compounds validates the significance of this study.

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