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ORIGINAL ARTICLE

Antimicrobial activities of heterocycles derived from thienylchalcones

Ofentse Mazimba *

Department of Chemistry, University of Botswana, Private Bag 00704, Gaborone, Botswana

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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

* Tel.: +267 3552494; fax: +267 2638.
E-mail address: mazimbaof@yahoo.com.
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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*,