Synthesis and Preliminary Pharmacological Evaluation of Aryl Dithiolethiones with Cyclooxygenase-2 Selective Inhibitory Activity and Hydrogen-Sulfide-Releasing Properties

Shannon D. Zanatta, a,b Bevyn Jarrott, a,c Spencer J. Williams* b

a School of Chemistry and Bio21 Institute of Molecular Science and Biotechnology, University of Melbourne, Parkville, Victoria 3010, Australia

b Howard Florey Institute, Parkville, Victoria 3010, Australia

c Department of Pharmacology, University of Melbourne, Parkville, Victoria 3010, Australia
Representative procedure for the MOM protection of phenols

Acetyl chloride (5.00 mmol) was added dropwise to a solution of dimethoxymethane (5 mmol), and ZnCl₂ (0.02 mmol) in toluene (6 mL). The reaction was stirred at rt for 4 h, and then the phenol (1.00 mmol) was added followed by N-ethyl-N,N-diisopropylamine (1.50 mmol). The reaction was then stirred at rt overnight. Water was added and the mixture was stirred for 15 min. The aqueous layer was extracted with EtOAc (× 2) and the combined organic extracts washed with 1 M NaOH (× 3), sat. NaHCO₃ (× 1), water (× 2), brine (× 1), dried (Na₂SO₄) and concentrated.

\[ 1\text{-}[4\text{-}(\text{Methoxymethoxy})-3,5\text{-dimethylphenyl}]\text{ethanone \(5b\)} \]

The title compound was prepared by the representative procedure starting from 1-(4-hydroxy-3,5-dimethylphenyl)ethanone\(^{[1]}\) (4b). Flash chromatography (10% EtOAc/petrol) afforded \(5b\) as a yellow oil (427 mg, 68%). \(\delta_H\) (500 MHz, CDCl₃) 2.25 (s, 6H, ArCH₃ × 2), 2.46 (s, 3H, COCH₃), 3.52 (s, 3H, CH₃), 4.92 (s, 2H, CH₂), 7.56 ppm (s, 2H, Ar); \(\delta_C\) (100 MHz, CDCl₃) 16.7 (ArCH₃), 26.1 (COCH₃), 57.1 (OCH₃), 98.8 (CH₂), 129.1, 131.1, 133.0, 158.9 (6C, Ar), 197.0 ppm (CO); IR \(\nu\) 2925, 1677, 1596, 1155, 959, 769 cm\(^{-1}\); HRMS-ESI\(^+\) \(m/z\) [M+Na]\(^+\) Calc. for C₁₂H₁₇O₃: 209.1172, found: 209.1170.

\[ 1\text{-}[3,5\text{-Diethyl-4\text{-}(methoxymethoxy)phenyl}]\text{ethanone \(5c\)} \]

The title compound was prepared the representative procedure starting from 1-(3,5-diethyl-4-hydroxyphenyl)ethanone\(^{[2]}\) (4c). Flash chromatography (5% EtOAc/petrol) afforded \(5c\) as a yellow oil (691 mg, 46%). \(\delta_H\) (400 MHz, CDCl₃) 1.25 (t, \(J = 7.5\) Hz, 6H, CH₂CH₃ × 2), 2.56 (s, 3H, COCH₃), 2.71 (q, \(J = 7.5\) Hz, 4H, CH₂CH₃ × 2), 3.60 (s, 3H, OCH₃), 4.97 (s, 2H, OCH₂O), 7.68 ppm (s, 2H, Ar); \(\delta_C\) (100 MHz, CDCl₃) 14.5 (CH₂CH₃), 23.3 (CH₂CH₃), 26.5 (COCH₃), 57.3 (OCH₃), 99.7 (OCH₂O), 127.5, 133.5, 137.4, 158.3 (6C, Ar), 197.6 ppm (CO); IR \(\nu\) 2968, 1679, 1357, 1288, 1155, 1072, 882 cm\(^{-1}\); HRMS-ESI\(^+\) \(m/z\) [M+H]\(^+\) Calc. for C₁₄H₂₁O₃: 237.1485, found: 237.1485.

\[ 1\text{-}[3,5\text{-Diisopropyl-4\text{-}(methoxymethoxy)phenyl}]\text{ethanone \(5d\)} \]

The title compound was prepared by the representative procedure starting from 1-[4-hydroxy-3,5-diisopropyl)phenyl]ethanone\(^{[3]}\) (4d). Flash chromatography (5% EtOAc/petrol) afforded \(5d\) as a yellow oil (206 mg, 37%). \(\delta_H\) (500 MHz, CDCl₃) 2.59 (s, 3H, COCH₃), 3.36 (septet, \(J = 7.0\) Hz, 2H, (CH₃)₂CH × 2) 3.62 (s, 3H, OCH₃),
4.96 (s, 2H, CH₂), 7.73 ppm (s, 2H, Ar); δ C (100 MHz, CDCl₃) 23.8 (CH(CH₃)₂) 26.5 (COCH₃), 26.6 (CH(CH₃)₂), 62.1 (OCH₃), 99.1 (CH₂), 124.7, 133.6, 142.0, 158.9 (6C, Ar), 197.5 ppm (CO); IR ν 2963, 1680, 1300, 1192, 1006, 798 cm⁻¹; HRMS-ESI⁺ m/z [M+H]⁺
Calc. for C₁₆H₂₅O₃: 256.1798, found 265.1798.

1-[3,5-di-(tert-Butyl)-4-(methoxymethoxy)phenyl]ethanone 5e

The title compound was prepared by the representative procedure starting from 1-[3,5-di-(tert-butyl)-4-hydroxyphenyl]ethanone [4] (4e). Flash chromatography (10% EtOAc/petrol) and recrystallisation from EtOH/water afforded 5e as a colourless solid (1.67 g, 71%). mp 60-61 °C; δH (500 MHz, CDCl₃) 0.88 (s, 18H, (C(CH₃)₃)× 2), 1.98 (s, 3H, COCH₃), 3.06 (s, 3H, OCH₃), 4.33 (s, 2H, CH₂), 7.32 ppm (s, 2H, Ar); δC (100 MHz, CDCl₃) 26.4 (CO(CH₃)₃), 31.8 ((C(CH₃)₃), 35.8 (C(CH₃)₃), 57.4 (CH₃), 100.7 (CH₂), 127.0, 132.1, 144.7, 159.0 (6C, Ar), 197.8 ppm (CO); IR ν 2956, 2873, 1762, 1676, 1589, 1227, 881 cm⁻¹; HRMS-ESI⁺ m/z [M+Na]⁺ Calc. for C₁₈H₂₈NaO₃: 315.1931, found 315.1931; Anal. Calc. for C₁₈H₂₈O₃: C 73.93, H 9.65. Found: C 73.92, H 9.70%.

Representative procedure for the etherification of phenols

Iodoalkane (2.50 mmol) was added to a mixture of anhydrous potassium carbonate (1.70 mmol) and the phenol (1.00 mmol). The mixture was heated at reflux for 18 h. Diethyl ether was then added to the cooled solution and the organic phase washed with water (× 2), brine (× 1), dried (Na₂SO₄) and concentrated.

1-(4-Methoxy-3,5-dimethylphenyl)ethanone 9b2

The title compound was prepared by the representative procedure starting from 1-(4-hydroxy-3,5-dimethylphenyl)ethanone [1] (4b) and iodomethane. After flash chromatography (5% EtOAc/petrol), 9b2 was obtained as a yellow oil (1.19 g, 70%). δH (400 MHz, CDCl₃) 2.21 (s, 6H, ArCH₃ × 2), 2.44 (s, 3H, COCH₃), 3.65 (s, 3H, OCH₃), 7.53 ppm (s, 2H, Ar); δC (100 MHz, CDCl₃) 15.9 (ArCH₃), 26.1 (COCH₃), 59.2 (OCH₃), 129.0, 130.7, 132.5, 160.9 (6C, Ar), 197.1 ppm (CO); IR ν 2940, 1674, 1591, 1482, 1092, 874 cm⁻¹; HRMS-ESI⁺ m/z [M+H]⁺
Calc. for C₁₈H₁₆O₂: 179.1067, found 179.1066.
The title compound was prepared by the representative procedure starting from 1-(4-hydroxy-3,5-dimethylphenyl)ethanone\(^{[1]}\) (4b) and iodoethane. After flash chromatography (5% EtOAc/petrol), 9b\(^3\) was obtained as a yellow oil (94% 1.08 g). \(\delta_H (400 MHz, CDCl_3) 1.30 (t, J = 6.4 Hz, 3H, CH_2CH_3), 2.27 (s, 6H, ArCH_3 × 2), 2.50 (s, 3H, COCH_3), 3.84 (q, J = 6.4 Hz, 2H, CH_2), 7.59 ppm (s, 2H, Ar); \(\delta_C (100 MHz, CDCl_3) 15.6, 16.3 (ArCH_3,CH_2CH_3), 26.3 (COCH_3), 67.8 (CH_2), 129.1, 131.0, 132.5, 160.3 (6C, Ar), 197.4 ppm (CO); IR \(\nu 2980, 2929, 1677, 1306, 1030, 900, 777 \text{ cm}^{-1}; \) HRMS-ESI\(^+ m/z [M+H]^+\) Calc. for C\(_{12}\)H\(_{17}\)O\(_2\): 193.1223, found 193.1223.

**1-(3,5-Diethyl-4-methoxyphenyl)ethanone 9c\(^2\)**

The title compound was prepared by the representative procedure starting from 1-(3,5-diethyl-4-hydroxyphenyl)ethanone\(^{[2]}\) (4c) and iodomethane. After flash chromatography (5% EtOAc/petrol), 9c\(^2\) was obtained as a yellow oil (59%, 505 mg). \(\delta_H (500 MHz, CDCl_3) 1.25 (t, J = 7.5 Hz, 6H, CH_2CH_3), 2.56 (s, 3H, COCH_3), 2.70 (q, J = 7.5 Hz, 4H, CH_2), 3.76 (s, 3H, OCH_3), 7.62 ppm (s, 2H, Ar); \(\delta_C (125 MHz, CDCl_3) 14.7 (CH_2CH_3), 22.8 (CH_2), 26.4 (COCH_3), 61.0 (OCH_3), 127.6, 133.3, 137.2, 160.5 (6C, Ar), 197.6 ppm (CO); IR \(\nu 2968, 1679, 1595, 1356, 1191, 1164 \text{ cm}^{-1}; \) HRMS-ESI\(^+ m/z [M+Na]^+\) Calc. for C\(_{13}\)H\(_{19}\)NaO\(_2\): 229.1199, found 229.1199.

**1-[3,5-Diisopropyl-4-methoxyphenyl]ethanone 9d\(^2\)**

The title compound was prepared by the representative procedure starting from 1-(4-hydroxy-3,5-diisopropylphenyl)ethanone\(^{[3]}\) (4d) and iodomethane. After flash chromatography (5% EtOAc/petrol), 9d\(^2\) was obtained as a yellow oil (46%, 836 mg). \(\delta_H (500 MHz, CDCl_3) 1.30 (d, J = 6.5 Hz, 12H, (CH_3)_2CH × 2), 2.57 (s, 3H, COCH_3), 3.33 (septet, J = 6.5 Hz, 2H, (CH_3)_2CH × 2), 3.75 (s, 3H, OCH_3), 7.72 ppm (s, 2H, Ar); \(\delta_C (125 MHz, CDCl_3) 23.8 (CH(CH_3)_2), 26.4 (COCH_3), 26.5 (CH(CH_3)_2), 62.1 (OCH_3), 124.7, 133.6, 142.0, 158.9 (6C, Ar), 197.5 ppm (CO); IR \(\nu 2963, 1680, 1300, 1192, 1006, 798 \text{ cm}^{-1}; \) HRMS-ESI\(^+ m/z [M+H]^+\) Calc. for C\(_{15}\)H\(_{23}\)O\(_2\): 235.1693, found 235.1693.

**1-[4-Ethoxy-3,5-diisopropylphenyl]ethanone 9d\(^3\)**

The title compound was prepared by the representative procedure starting from 1-(4-hydroxy-3,5-diisopropylphenyl)ethanone (4d) and iodoethane. After flash chromatography (5% EtOAc/petrol) and recrystallisation from EtOH/water, 9d\(^3\) was obtained as a yellow oil (72%,
772 mg. mp 81-82 °C; δH (500 MHz, CDCl3) 1.26 (d, J = 7 Hz, 12H, CH(CH3)2× 2), 1.47 (t, J = 7 Hz, CH2CH3), 2.59 (s, 3H, COCH3), 3.34 (septet, J = 7 Hz, CH(CH3)2× 2), 3.84 (q, J = 7 Hz, 2H, CH2), 7.73 ppm (s, 2H, Ar); δC (125 MHz, CDCl3) 15.8 (CH2 C6H5), 24.0 (CH(CH3)2), 26.5 (COCH3), 70.6 (CH2), 133.6, 142.3, 144.7, 158.0 (6C, Ar), 197.8 ppm (CO); IR ν 2963, 1680, 1462, 1192, 1007, 973, 816, 730 cm⁻¹; HRMS-ESI⁺ m/z [M+H]⁺ Calc. for C16H25O2: 249.1849, found 249.1850.

1-[3,5-di-(tert-Butyl)-4-methoxyphenyl]ethanone 9e2

The title compound was prepared by the representative procedure starting from 1-[3,5-di-(tert-butyl)-4-hydroxyphenyl]ethanone⁴ (4e) and iodomethane. After flash chromatography (10% EtOAc/petrol) and recrystallisation from EtOH/water, 9e2 was obtained as a colourless solid (2.68 g, 82%). mp 52-53 °C (lit.[⁷] mp 49-50 °C). δH (400 MHz, CDCl3) 1.45 (s, 18H, C(CH3)3× 2), 2.57 (s, 3H, COCH3), 3.71 (s, 1H, OCH3), 7.88 ppm (s, 2H, Ar).

1-[3,5-di-(tert-Butyl)-4-ethoxyphenyl]ethanone 9e3

The title compound was prepared by the representative procedure starting from 1-[3,5-di-(tert-butyl)-4-hydroxyphenyl]ethanone (4e) and iodoethane. After flash chromatography (5% EtOAc/petrol), 9e3 was obtained as a yellow oil (171 mg, 65%). δH (400 MHz, CDCl3) 1.43 (t, 3H, J = 7 Hz, CH2CH3), 1.44 (s, 18H, C(CH3)3× 2), 2.57 (s, 3H, COCH3), 3.77 (t, 2H, J = 7 Hz, CH2), 7.78 ppm (s, 2H, Ar); δC (100 MHz, CDCl3) 14.8 (CH2 CH3), 31.8 (C(CH3)3), 35.9 (C(CH3)3), 72.0 (CH2), 127.1, 131.7, 144.0, 162.6 (6C, Ar), 197.8 ppm (CO); IR ν 2963, 1682, 1590, 1298, 1105, 971, 887 cm⁻¹; HRMS-ESI⁺ m/z [M+H]⁺ Calc. for C18H29O2: 277.2162, found 277.2162; Anal. Calc. for C18H28O2: C 78.21, H 10.21. Found C 78.24, H 10.20%.

References

$^1$H NMR spectrum of compound (5b)

$^{13}$C NMR spectrum
$^1$H NMR spectrum of compound (5c)

$^{13}$C NMR spectrum
$^1$H NMR spectrum of compound (5d)

**STANDARD PROTON PARAMETERS**

- solvent: 
- temp: 25°C / 298.1 K
- instrument: "Chester"
- pulse 45.0 degrees
- acc. time 2.995 sec
- td 1024, 200
- spectral width 6000.0000 Hz
- OBSERVED: 400.1003763 MHz
- Peak Processing
- Total time 8 min, 4 sec

![NMR Spectrum](Image)
$^1$H NMR spectrum of compound (6a)

$^{13}$C NMR spectrum
$^1$H NMR spectrum of compound (6b)

13C NMR spectrum
$^1$H NMR spectrum of compound (6c)

$^{13}$C NMR spectrum
$^1$H NMR spectrum of compound (7b1)

![1H NMR spectrum image]

$^{13}$C NMR spectrum

![$^{13}$C NMR spectrum image]
$^1$H NMR spectrum of compound (7c1)

- **File**: Proton
- **Pulse Sequence**: 42pul
- **Solvent**: DMSO
- **Sample temp**: 80°C / 0.1 ppm
- **Parameter**: 200 MHz
- **SNR**: 665

- **Pulse 45.6 degrees**
- **Data Time**: 6 min 10 sec
- **NMR Times**: 27384

**Note**: The spectrum shows a series of peaks at various ppm values.

$^{13}$C NMR spectrum

- **File**: Carbon
- **Pulse Sequence**: nups
- **Solvent**: DMSO
- **Sample temp**: 80°C / 0.1 ppm
- **Parameter**: 200 MHz

- **Pulse 45.6 degrees**
- **Data Time**: 6 min 10 sec
- **NMR Times**: 27384

**Note**: The spectrum shows a series of peaks at various ppm values.
$^1$H NMR spectrum of compound (7c2)

Carbon Standard Parameters

Pulse sequence: 4p9ps

Pulse sequence: 4p9ps

$^{13}$C NMR spectrum

Carbon Standard Parameters

Pulse sequence: 4p9ps

Pulse sequence: 4p9ps
$^1$H NMR spectrum of compound (7e3)

$^{13}$C NMR spectrum
$^1$H NMR spectrum of compound (9c2)

Proton Standard Parameters

Field: Proton
Pulse Sequence: ZBUR
Solvent: CDCl$_3$
Freq.: 300.1 MHz
Sweep: 3.56 ppm / 259.1 kHz

$^{13}$C NMR spectrum

Carbon Standard Parameters

Field: Carbon
Pulse Sequence: ZBUR
Solvent: CDCl$_3$
Freq.: 75.4 MHz
Sweep: 150.6 ppm / 3.2 kHz

Freq.: 300.1 MHz
Sweep: 3.56 ppm / 259.1 kHz

Magnetic Field: 7.0 T
Spectral Width: 16.0 kHz

Total time: 6 min; 30 sec
1H NMR spectrum of compound (9d2)

**Spectrum Parameters**
- **Solvent:** DMSO-d6
- **Temperature:** 25.0 ± 0.1 °C
- **Operator:** BFM
- **INCFAR-100 INSTRUMENT**
- **Pulse:** 45.6 degrees
- **Width:** 1.0 min, 18 sec
- **Number of pulses:** 256
- **Line Broadening:** 8.0 Hz
- **Total time:** 1 min, 16 sec

---

13C NMR spectrum

**Spectrum Parameters**
- **Solvent:** DMSO-d6
- **Temperature:** 25.0 ± 0.1 °C
- **Operator:** BFM
- **INCFAR-100 INSTRUMENT**
- **Pulse:** 45.6 degrees
- **Width:** 1.0 min, 18 sec
- **Number of pulses:** 256
- **Line Broadening:** 8.0 Hz
- **Total time:** 1 min, 16 sec
1H NMR spectrum of compound (9d3)

13C NMR spectrum
$^1$H NMR spectrum of compound (10b2)

13C NMR spectrum
$^1$H NMR spectrum of compound (10b3)

Sample: DI-Chloroacetone
Solvent: CDCl$_3$
Temp: 25.0 °C / 300.1 K
Sweep: 0.025 ppm

$^{13}$C NMR spectrum

Sample: DI-Chloroacetone
Solvent: CDCl$_3$
Temp: 25.0 °C / 300.1 K
Sweep: 50.0 ppm

$^1$H NMR spectrum of compound (10c3)

File: Proton
Pulse Sequence: sipy1
Solvent: cdcl3
Temperature: 293 K / 99.5 °C
Operator: sje

Pulse 45.9 degree
Acq. Time 2.009 sec
Vfield 5.005 MHz
Gain 7063

Frequency 400.00 MHz
Spectrum 89.564060 MHz
Zero Frequencies
IT 100510400
Total Time 2 min, 0 sec

$^{13}$C NMR spectrum

File: Carbon
Pulse Sequence: sibt1
Solvent: cdcl3
Temperature: 293 K
Gain 7063

Pulse 45.9 degree
Acq. Time 2.009 sec
Vfield 5.005 MHz
Gain 7063

Frequency 100.6 MHz
Spectrum 1.327000 MHz
Zero Frequencies
IT 100544800
Total Time 2 min, 0 sec
$^1$H NMR spectrum of compound (10d2)

13C NMR spectrum

std proton
$^1$H NMR spectrum of compound (10d3)
$^{1}H$ NMR spectrum of compound (10e2)

13C NMR spectrum
$^1$H NMR spectrum of compound (10e3)

$^{13}$C NMR spectrum
\textbf{\textsuperscript{1}H NMR spectrum of compound (11)}

\textbf{\textsuperscript{13}C NMR spectrum}
1H NMR spectrum of compound (12e2)

13C NMR spectrum
$^1$H NMR spectrum of compound (12e2)

$^{13}$C NMR spectrum
$^{1}H$ NMR spectrum of compound (12e3)

$^{13}C$ NMR spectrum
$^1$H NMR spectrum of compound (14e2)

File: proton
Pulse Sequence: 626ul
Solvent: DMSO
Temp.: 25 ± 2°C
Operator: TC
Instrument: Varian 400 G206
Helix: delay 1.900 sec
Pulse Δl. 8.000 sec
Resonator: 5 mm
Width: 49.200 Hz

$^{13}$C NMR spectrum

File: proton
Pulse Sequence: 626ul
Solvent: DMSO
Temp.: 25 ± 2°C
Operator: TC
Instrument: Varian 400 G206
Helix: delay 1.900 sec
Pulse Δl. 8.000 sec
Resonator: 5 mm
Width: 49.200 Hz
$^{1}H$ NMR spectrum of compound (15e2)

Std proton
Pulse Sequence: xiirad
Valance: decy7
Temp: 30.0 C / 86.3 K
Operator: 20g

Pulse delay 1.000 sec
Pulse 50.0 deg
Acc. Time 1.000 sec
Width 6000.0 Hz
Spw 128 channels
Norm 100000 0.0
FM 10.0806
Total time 6 min. 03 sec

$^{13}C$ NMR spectrum
Std carbon
Pulse Sequence: xiirad
Valance: decy7
Temp: 30.0 C / 86.3 K
Operator: 20g

Pulse delay 1.000 sec
Pulse 50.0 deg
Acc. Time 1.000 sec
Width 6000.0 Hz
Spw 128 channels
Norm 100000 0.0
FM 10.0806
Total time 6 min. 03 sec
$^1$H NMR spectrum of compound (15e3)

**13C NMR spectrum**