Solvent-free synthesis of novel spirocyclic oxindole derivatives *via* a Michael-aldol cascade by grinding

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A simple and novel synthesis of spirocyclic oxindole derivatives by the reaction of (*E*)-3-arylideneindole-2-ones and 1,4-dithiane-2,5-diol *via* a Michael-aldol cascade under solvent-free reaction conditions is reported. This method provides a new practical and facile approach to 4′-hydroxy-2′-aryl-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones in moderate to good yields. The structures of all the products were characterised by NMR, infrared spectroscopy and HRMS.

Keywords: oxindole, spirocycle, Michael-aldol cascade, solvent free synthesis

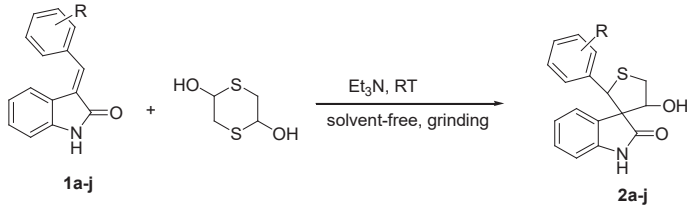
The oxindole moiety is an important structure responsible for the biological activity of alkaloids and pharmaceutically active compounds, such as pteropodine,[1] paraherquamide A,[2] tryprostatins B[3] and sunitinib.[4] Compounds with an oxindole unit have aroused great interest because of their broad spectrum of biological activities, such as antitumour,[5] anti-inflammatory, analgesic,[6] cyclooxygenase[7] and myosin inhibition[8] activity.

Spiroheterocycles are important structures found in many biologically active natural products[9] and their biological properties make them good targets for drug candidates and clinical pharmaceuticals.[10,11]

It is well known that there are pronounced advantages to solvent-free synthetic approaches, including easy work-up procedures, short reaction times and simple apparatus requirements, which has attracted considerable attention in recent years.[12–14] Here we report a facile synthesis of spirocyclic oxindole derivatives by the Michael-aldol cascade reaction of 1,4-dithiane-2,5-diol with (*E*)-3-arylideneindole-2-ones under solvent-free conditions (Scheme 1).

Results and discussion

The 4′-hydroxy-2′-aryl-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thio-phen]-2-ones **2** were synthesised in moderate to good yields by the Michael-aldol cascade reaction of (*E*)-3-arylideneindole-2-ones with 1,4-dithiane-2,5-diol in the presence of triethylamine under solvent-free conditions at room temperature. The reaction can be scaled up to 5 mmol with similar yields, for example, 5 mmol of **1a** gives 1.17 g of **2a** (79.0% yield) under the reaction conditions. The intermediate product (*E*)-3-arylideneindole-2-ones **1** were obtained by condensation of oxindole and various substituted benzaldehydes in the presence of triethylamine at room temperature.



1a-j **2a-j**

2a: R = H, 2b: R = *o*-Cl, 2c: R = *m*-Cl, 2d: R = *p*-Cl, 2e: R = *p*-CH_3, 2f: R = *m*-CH_3, 2g: R = *p*-CH_3O, 2h: R = *o*-Br, 2i: R = *o*-F, 2j: R = *p*-F

Scheme 1 Synthesis of spiro oxindole-tetrahydrothiophenes.

The structures of all compounds **2a–j** were established by different spectroscopic techniques (NMR, IR) and HRMS. The high-resolution mass spectrum of **2d** gave the molecular ion peak at *m/z* 332.0515, which indicates the addition of one molecule of 1,4-dithiane-2,5-diol to **1d**. The IR spectrum of **2d** displayed $\nu_{C=O}$ at 1689.4 cm^{-1}. The ^1H NMR spectrum of **2d** revealed a doublet at δ 5.58 ppm (*J* = 6.0 Hz, OH), two singlets — a singlet at δ 10.40 ppm for –NH and another singlet at δ 4.94 resulting from –HCPh — a multiplet at δ 4.70–4.65 ppm for –CH–OH, a doublet of doublets at δ 3.32 ppm (J_1 = 10.0 Hz, *J2* = 6.0 Hz) and a triplet at δ 3.20 ppm (*J* = 10.0 Hz) resulting from H_2C5', The presence of signals at δ 6.62–7.58 ppm corresponded to the aromatic protons.

The ^{13}C NMR spectrum of the product **2d** exhibited the presence of carbonyl carbons at δ 176.79 (C2). The signal at δ 79.45 represented the spiro carbon of C3. Furthermore, the structure of the product was confirmed by X-ray diffraction analysis of **2d** (Fig. 1).

There are three diastereoisomeric carbon atoms in the products **2a–j**; therefore, two diastereoisomers might exist in the obtained products. TLC and the ^1H NMR spectra of the reaction mixtures only showed one set of typical absorptions for the characteristic groups in the molecules, which indicated that the products **2a–j** existed as only one diastereoisomer with the structure being established *via* the single-crystal structure determination.

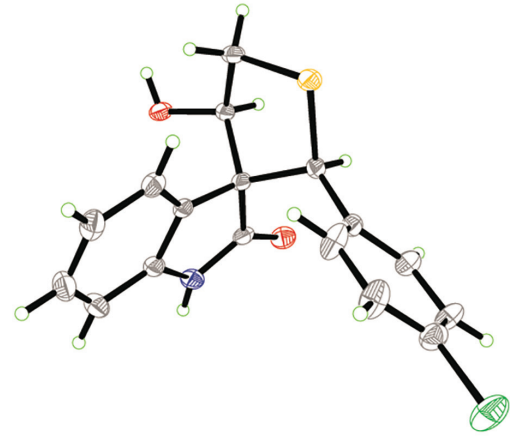


Fig. 1 ORTEP diagram of **2d** with 50% probability.

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Conclusion

A facile and green synthesis of spiro compounds was accomplished by the Michael-aldol cascade of (*E*)-3-arylideneindole-2-one and 1,4-dithiane-2,5-diol under solvent-free reaction conditions. Simplicity of operation, high yields and easy work-up are the key advantages of this method.

Experimental

Compound **1** ((*E*)-3-arylideneindole-2-ones) was prepared according to the literature method.[15] All of the reagents were from commercial suppliers and used without further purification. All of the solvents were freshly distilled from the appropriate drying agents before use. The analytical TLCs were performed with silica gel 60 F254 plates. Column chromatography was carried out by using silica gel 60 (200–300 mesh). All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C. TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts and $CDCl_3$ was used as solvent. Mass spectra were collected on a Waters Xevo Q-TOF HRMS instrument. IR spectra were recorded on a PerkinElmer spectrometer (Spectrum One). Melting points were measured with a Yanaco MP500 melting point apparatus and are uncorrected. X-ray analysis was performed on a Bruker Apex-II CCD diffractometer. A single crystal of **2d** was obtained by slow evaporation of a CH_2Cl_2/CH_3OH solution of **2d**. Crystal data for **2d**: $C_{17}H_{14}ClNO_2S$, M_r = 331.80 g mol^{-1}, triclinic space group $P2_1/c$, a = 13.6768(16) Å, b = 12.4921(15)Å, c = 8.9120(11) Å, β = 104.395(4), V = 1474.8(3) Å^3, T = 296(2) K, Z = 4, D_c = 1.494 g m^{-3}, μ = 0.407 mm^{-1}, $F(000)$ = 688, R_{int} = 0.0467, 9048 reflections, 2588 with $I > 2\sigma(I)$ for 200 parameters, GOF = 1.068, R_1 = 0.0338, wR_2 = 0.0908 [$I > 2\sigma(I)$] and R_1 =0.0387, wR_2 = 0.0960 (all data). CCDC 1814629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

*Synthesis of 4′-hydroxy-2′-aryl-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2**)*; general procedure*

(*E*)-3-arylideneindole-2-ones **1** (1.0 mmol) and 1,4-dithiane-2,5-diol (1.0 mmol) was added into a mortar containing the triethylamine (3 mmol). The resulting reaction mixture was ground at room temperature. After completion of the reaction as monitored by TLC, the mixture was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (3:1, V/V) as eluent and recrystallised from ethyl alcohol to afford the corresponding product **2**.

*4′-Hydroxy-2′-phenyl-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2a**): White powder; yield 82.3%; m.p. 181–182 °C; IR (KBr) (ν cm^{-1}): 3458, 3183, 3060, 2939, 2888, 1687, 1621, 1469, 1404, 1345, 1188, 1089; ^{1}H NMR (500 MHz, DMSO): δ 10.38 (s, 1H, NH), 7.60 (d, *J* = 7.5 Hz, 1H, ArH), 7.15–7.13 (m, 2H, ArH), 7.08–7.06 (m, 4H, ArH), 6.96 (t, *J* = 7.5 Hz, 1H, ArH), 6.60 (d, *J* = 7.5 Hz, 1H, ArH), 5.58 (d, *J* = 5.0 Hz, 1H, OH), 4.96 (s, 1H, CH), 4.71–4.67 (m, 1H, CH–OH), 3.32 (dd, *J* = 10.5, 7.5 Hz, 1H, CH_2), 3.20 (t, *J* = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.96, 142.32, 135.68, 128.11, 127.93, 127.68, 127.57, 126.46, 125.53, 120.99, 109.08, 79.54, 65.14, 52.69, 34.08. HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{16}NO_2S]^+$ (M + H)$^+$: 298.0896; found: 298.0905.

*4′-Hydroxy-2′-(2-chlorophenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2b**): White powder; yield 85.6%; m.p. 182–183 °C; IR (KBr) (ν cm^{-1}): 3379, 3229, 3012, 2934, 1713, 1621, 1468, 1402, 1353, 1322, 1240, 1080; ^{1}H NMR (500 MHz, DMSO): δ 10.34 (s, 1H, NH), 8.05 (d, *J* = 8.0 Hz, 1H, ArH), 7.40 (t, *J* = 7.5 Hz, 1H, ArH), 7.25–7.16 (m, 2H, ArH), 7.02 (t, *J* = 7.5 Hz, 1H, ArH), 6.69 (d, *J* = 7.5 Hz, 1H, ArH), 6.52 (t, *J* = 7.5 Hz, 1H, ArH), 6.00 (d, *J* = 7.5 Hz, 1H, ArH), 5.61 (d, *J* = 5.0 Hz, 1H, OH), 5.13 (s, 1H, CH), 4.51–4.47 (m, 1H, CH–OH), 3.48 (t, *J* = 10.0 Hz, 1H, CH_2), 3.15 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 178.09, 143.30, 136.90, 134.21, 131.42, 129.10, 128.83, 128.24, 127.79, 126.80, 124.00, 120.40, 108.69, 80.76, 61.53, 48.50, 33.37. HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{15}ClNO_2S]^+$ (M + H)$^+$: 332.0507; found: 332.0512.

*4′-Hydroxy-2′-(3-chlorophenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2c**): White powder; yield 71.7%; m.p. 176–177 °C; IR (KBr) (ν cm^{-1}): 3434, 3292, 3014, 2920, 1699, 1618, 1469, 1398, 1087; ^{1}H NMR (500 MHz, DMSO): δ 10.45 (s, 1H, NH), 7.57 (d, *J* = 7.5 Hz, 1H, ArH), 7.15–7.07 (m, 5H, ArH), 6.97 (t, *J* = 7.5 Hz, 1H, ArH), 6.63 (d, *J* = 7.5 Hz, 1H, ArH), 5.61 (d, *J* = 6.0 Hz, 1H, OH), 4.94 (s, 1H, CH), 4.70–4.66 (m, 1H, CH–OH), 3.32 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2), 3.21 (t, *J* = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.77, 142.28, 138.33, 132.32, 129.56, 128.16, 127.88, 127.60, 126.81, 126.42, 125.16, 121.06, 109.24, 79.40, 65.14, 52.02, 34.22. HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{15}ClNO_2S]^+$ (M + H)$^+$: 332.0507; found: 332.0502.

*4′-Hydroxy-2′-(4-chlorophenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2d**): White powder; yield 81.3%; m.p. 176–177 °C; IR (KBr) (ν cm^{-1}): 3294, 3019, 2926, 1689, 1619, 1467, 1399, 1326, 1171, 1082, 1017; ^{1}H NMR (500 MHz, DMSO): δ 10.40 (s, 1H, NH), 7.57 (d, *J* = 7.0 Hz, 1H, ArH), 7.17–7.13 (m, 4H, ArH), 7.09 (t, *J* = 7.5 Hz, 1H, ArH), 6.96 (t, *J* = 7.5 Hz, 1H, ArH), 6.62 (d, *J* = 8.0 Hz, 1H, ArH), 5.58 (d, *J* = 6.0 Hz, 1H, OH), 4.94 (s, 1H, CH), 4.70–4.65 (m, 1H, CH–OH), 3.32 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2), 3.20 (t, *J* = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.79, 142.30, 134.81, 132.09, 129.84, 128.10, 127.70, 126.40, 125.24, 121.09, 109.19, 79.45, 65.15, 52.00, 34.20. HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{15}ClNO_2S]^+$ (M + H)$^+$: 332.0507; found: 332.0515.

*4′-Hydroxy-2′-(4-methylphenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2e**): White powder; yield 89.5%; m.p. 185–186 °C; IR (KBr) (ν cm^{-1}): 3294, 3012, 2930, 1691, 1619, 1469, 1395, 1329, 1174, 1078; ^{1}H NMR (500 MHz, DMSO): δ 10.33 (s, 1H, NH), 7.60 (d, *J* = 7.0 Hz, 1H, ArH), 7.08 (t, *J* = 7.5 Hz, 1H, ArH), 7.01 (d, *J* = 8.0 Hz, 2H, ArH), 6.96 (t, *J* = 7.5 Hz, 1H, ArH), 6.87 (d, *J* = 8.0 Hz, 2H, ArH), 6.61 (d, *J* = 7.5 Hz, 1H, ArH), 5.53 (d, *J* = 5.5 Hz, 1H, OH), 4.91 (s, 1H, CH), 4.69–4.64 (m, 1H, CH–OH), 3.30 (dd, *J* = 10.0, 7.5 Hz, 1H, CH_2), 3.17 (t, *J* = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.98, 142.37, 136.71, 132.63, 128.29, 128.04, 127.90, 126.46, 125.63, 120.97, 109.09, 79.54, 65.12, 52.50, 34.04, 20.47. HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{18}NO_2S]^+$ (M + H)$^+$: 312.1053; found: 312.1055.

4′-Hydroxy-2′-(3-methylphenyl)-4′,5′-dihydro-2′H-spiro[oxindole-3,3′-thiophen]-2-ones (**2f**): White powder; yield 87.8%; m.p. 174–175 °C; IR (KBr) (ν cm^{-1}): 3422, 3221, 2929, 3015, 1704, 1617, 1466, 1402, 1328, 1094; ^{1}H NMR (500 MHz, DMSO): δ 10.37 (s, 1H, NH), 7.60 (d, *J* = 7.5 Hz, 1H, ArH), 7.08 (t, *J* = 7.5 Hz, 1H, ArH), 6.98–6.87 (m, 5H, ArH), 6.61 (d, *J* = 7.5 Hz, 1H, ArH), 5.56 (d, *J* = 6.0 Hz, 1H, OH), 4.90 (s, 1H, CH), 4.69–4.65 (m, 1H, CH-OH), 3.31 (dd, *J* = 10.0, 7.5 Hz, 1H, CH_2), 3.18 (t, *J* = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.99, 142.35, 136.61, 135.62, 128.88, 128.22, 127.90, 127.52, 126.52, 125.61, 125.26, 120.88, 109.09, 79.55, 65.09, 52.66, 34.06, 20.84. HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{18}NO_2S]^+$ (M + H)$^+$: 312.1053; found: 312.1062.

*4′-Hydroxy-2′-(4-methoxyphenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2g**): Yellow powder; yield 61.3%; m.p. 196–197 °C; IR (KBr) (ν cm^{-1}): 3391, 3225, 3016, 2932, 1704, 1510, 1401, 1248, 1176, 1060, 1028; ^{1}H NMR (500 MHz, DMSO): δ 10.33 (s, 1H, NH), 7.61 (d, *J* = 7.5 Hz, 1H, ArH), 7.09 (t, *J* = 7.0 Hz, 1H, ArH), 7.04 (d, *J* = 8.5 Hz, 2H, ArH), 6.97 (t, *J* = 7.5 Hz, 1H, ArH), 6.64–6.62 (m, 3H, ArH), 5.52 (d, *J* = 6.0 Hz, 1H, OH), 4.89 (s, 1H, CH), 4.68–4.63 (m, 1H, CH–OH), 3.60 (s, 3H, CH_3), 3.30 (dd, *J* = 10.5, 7.5 Hz, 1H, CH_2), 3.17 (t, *J* = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.98, 158.52, 142.40, 129.30, 127.90, 127.36, 126.48, 125.66, 120.98, 113.03, 109.10, 79.42, 65.16, 54.84, 52.29, 34.09. HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{18}NO_3S]^+$ (M + H)$^+$: 328.1002; found: 328.1008.

*4′-Hydroxy-2′-(2-bromophenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2h**): White powder; yield 70.1%; m.p. 175–176 °C; IR (KBr) (ν cm^{-1}): 3354, 3227, 3029, 2934, 1712, 1620, 1466, 1433, 1403, 1352, 1238, 1080; ^{1}H NMR (500 MHz, DMSO): δ 10.34 (s, 1H, NH), 8.08 (d, *J* = 8.0 Hz, 1H, ArH), 7.45 (t, *J* = 7.5 Hz, 1H, ArH), 7.35 (d, *J* = 8.0 Hz, 1H, ArH), 7.16 (t, *J* = 7.5 Hz, 1H, ArH), 7.02

(t, J = 7.5 Hz, 1H, ArH), 6.68 (d, J = 8.0 Hz, 1H, ArH), 6.50 (t, J = 7.5 Hz, 1H, ArH), 5.91 (d, J = 7.5 Hz, 1H, ArH), 5.60 (d, J = 5.0 Hz, 1H, OH), 5.07 (s, 1H, CH), 4.53–4.49 (m, 1H, CH–OH), 3.48 (t, J = 10.0 Hz, 1H, CH_2), 3.15 (dd, J = 10.0, 6.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 177.97, 143.46, 138.67, 132.10, 131.90, 129.42, 128.15, 127.77, 127.36, 125.84, 123.99, 120.36, 108.69, 80.45, 61.54, 50.81, 33.12. HRMS (ESI) m/z calcd for $[C_{17}H_{15}BrNO_2S]^+$ $(M+H)^+$: 376.0001; found: 376.0009.

*4′-Hydroxy-2′-(2-fluorophenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2i**): White powder; yield 82.4%; m.p. 171–172 °C; IR (KBr) (ν cm^{-1}): 3266, 3011, 2930, 1696, 1618, 1470, 1400, 1330, 1225, 1178, 1089; ^{1}H NMR (500 MHz, DMSO): δ 10.35 (s, 1H, NH), 7.51 (d, J = 7.0 Hz, 1H, ArH), 7.45–7.42 (m, 1H, ArH), 7.10–7.07 (m, 2H, ArH), 6.98–6.92 (m, 2H, ArH), 6.87 (t, J = 7.5 Hz, 1H, ArH), 6.63 (d, J = 7.0 Hz, 1H, ArH), 5.62 (d, J = 5.5 Hz, 1H, OH), 5.24 (s, 1H, CH), 4.72–4.68 (m, 1H, CH–OH), 3.34 (dd, J = 10.0, 7.5 Hz, 1H, CH_2), 3.25 (t, J = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.48, 159.86 (d, J = 245.0 Hz), 142.52, 130.89 (d, J = 2.5 Hz), 129.36 (d, J = 8.8 Hz), 128.08, 126.66, 125.43, 123.40 (d, J = 3.8 Hz), 123.02 (d, J = 13.8 Hz), 120.85, 114.68 (d, J = 22.5 Hz), 109.09, 79.86, 63.85, 44.49, 34.40. HRMS (ESI) m/z calcd for $[C_{17}H_{15}FNO_2S]^+$ $(M + H)^+$: 316.0802; found: 316.0810.

*4′-Hydroxy-2′-(4-fluorophenyl)-4′,5′-dihydro-2′*H*-spiro[oxindole-3,3′-thiophen]-2-ones* (**2j**): Grey powder; yield 72.2%; m.p. 175–176 °C; IR (KBr) (ν cm^{-1}): 3304, 3012, 2916, 1691, 1619, 1508, 1468, 1397, 1225, 1168, 1080; ^{1}H NMR (500 MHz, DMSO): δ 10.39 (s, 1H, NH), 7.59 (d, J = 7.0 Hz, 1H, ArH), 7.17–7.14 (m, 2H, ArH), 7.09 (t, J = 7.0 Hz, 1H, ArH), 6.97 (t, J = 7.5 Hz, 1H, ArH), 6.92 (t, J = 8.5 Hz, 2H, ArH), 6.62 (d, J = 7.5 Hz, 1H, ArH), 5.58 (d, J = 5.5 Hz, 1H, OH), 4.94 (s, 1H, CH), 4.70–4.66 (m, 1H, CH–OH), 3.32 (dd, J = 10.0, 7.5 Hz, 1H, CH_2), 3.20 (t, J = 10.0 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, DMSO): δ 176.84, 161.34 (d, J = 242.5 Hz), 142.33, 131.84 (d, J = 2.5 Hz), 129.99 (d, J = 8.8 Hz), 128.04, 126.44, 125.34, 121.05, 114.50 (d, J = 21.2 Hz), 109.15, 79.39, 65.20, 52.00, 34.22. HRMS (ESI) m/z calcd for $[C_{17}H_{15}FNO_2S]^+$ $(M + H)^+$: 316.0802; found: 316.0809.

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