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The synthesis of xanthones, xanthenediones, and spirobenzofurans: Their antibacterial and antifungal activity

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ABSTRACT

Exposure of the phenol, (5-bromo-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone **18** to ceric ammonium nitrate (CAN) resulted in the formation of 7-bromo-3,4*a*-dimethoxy-2*H*-xanthene-2,9(4*aH*)-dione **19** and 5-bromo-2′,5′-dimethoxy-3*H*-spiro[benzofuran-2,1′-cyclohexa[2,5]diene]-3,4′-dione **20**. The brominated spirobenzofuran **20** was then subjected to Suzuki–Miyaura reactions to give six derivatives **22a**–**f**. These compounds, related diones and xanthones displayed mostly noteworthy antimicrobial activity, particularly towards the yeasts *Cryptococcus neoformans* and *Candida albicans*. Diones **15** and **30** displayed significant activity (7.8 μg/mL) against *C. albicans* and *C. neoformans*, respectively. Furthermore, dione **10** displayed the most significant activity (3.6 μg/mL) against both yeasts.

Xanthones often display biological activities that allow them to be classed as useful antibacterial and antifungal agents.[1] For example, laurentixanthone A **1** (Fig. 1) isolated from the roots of *Vismia laurentii* shows an MIC value of 2.44 μM against *Candida glabrata*,[2] while cudraxanthone S **2** shows good antifungal activity against *Cryptococcus neoformans* (MIC 3 μM).[3]

Meanwhile a simple structurally related compound, 6-deoxyjacareubin **3** showed an MIC of 4.6 μM against *Bacillus subtilis*.

During the course of our work on the use of novel methodology for the synthesis of xanthones and related compounds, we discovered that oxidation of **5** with cerium(IV) ammonium nitrate (CAN) resulted in the formation of three products (Scheme 1). The major products were the dione **7** and xanthone **6**, both produced in a similar yield. In addition, we were also able to isolate a third product, spirobenzofuran **8**.[5] Using other phenol substrates we were able to generalize this reaction, however, all three products were not formed in each case.[5]

Closer examination of the third product **8** showed that the skeleton resembled griseofulvin, **4** (Fig. 1) a commercial antifungal agent that has mainly been used for the treatment of dermatomycoses.[6a–c] Griseofulvin has also been shown to exhibit an inhibitory activity against the yeast *Candida albicans* over a large range of between 20 and 500 μg/mL.[7a–c] Therefore, we decided to explore this reaction further, and test all these products for antibacterial and antifungal activity.

Hence, we planned to take advantage of the methodology we had developed to make griseofulvin-like spirobenzofurans, such as **8**, (albeit in poor yields) and make derivatives of these compounds. By attempting the CAN-mediated reaction on a bromine substituted equivalent of **5**, we hoped that this would provide spirobenzofurans with a handle that could be utilized in Suzuki–Miyaura reactions.[8] Finally, we wished to ascertain if the xanthenediones such as **7** could be converted into xanthones.

As described previously,[5] phenol **9** was exposed to CAN resulting in the formation of dione **10** exclusively, in good yield. In an

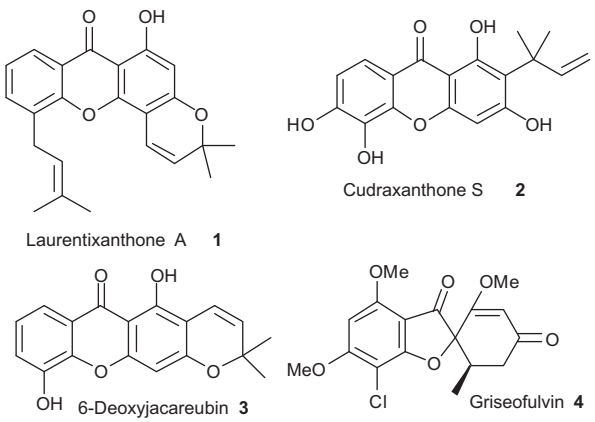

Figure 1. Biologically active xanthones and related compounds.[4]

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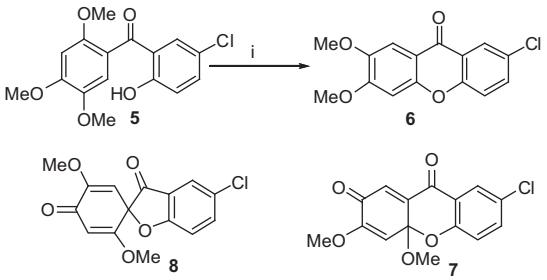
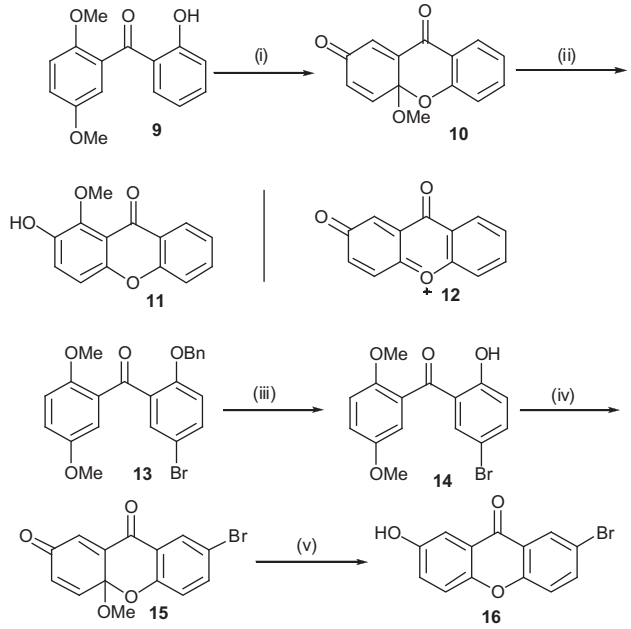
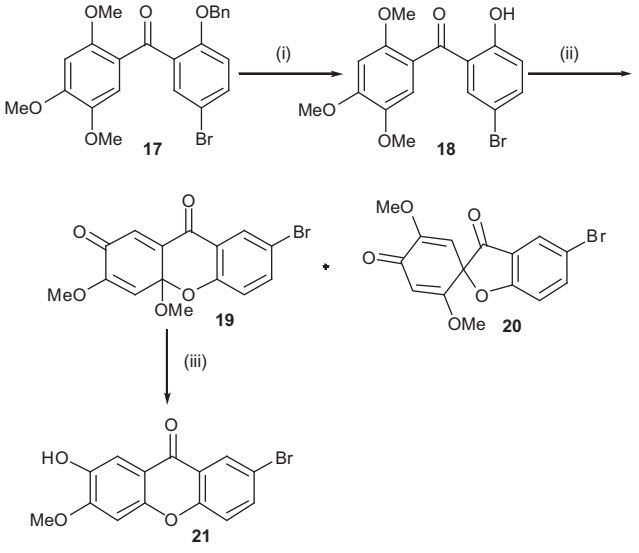


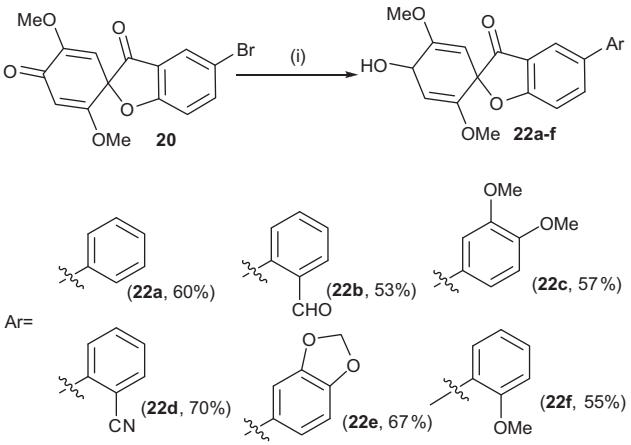
Scheme 1. *Reagents and conditions:* (i) CAN, H_2O/MeCN/$CHCl_3$, rt, **6**, 21%, **7**, 29%, **8**, 9%.



Scheme 2. *Reagents and conditions:* (i) CAN, H_2O/MeCN/$CHCl_3$, rt, 10 min 72%; (ii) DME, microwave, 10 min, 150 °C, 120 W, 50%; (iii) 5% Pd/C, EtOAc, H_2, 24 h, 1 atm, 72%; (iv) CAN, H_2O/MeCN/$CHCl_3$, rt, 10 min, 45%; (v) DME, microwave, 10 min, 150 °C, 120 W, 10%.



Scheme 3. *Reagents and conditions:* (i) 5% Pd/C, EtOAc, H_2, 24 h, 1 atm, 70%; (ii) CAN, H_2O/MeCN/$CHCl_3$, rt, 10 min **19** 18%, and **20**, 22%; (iii) DME, microwave, 10 min, 150 °C, 120 W, 33%.



Scheme 4. *Reagents and conditions:* (i) 5% $Pd(PPh_3)_4$, $ArB(OH)_2$, DME, CsF, microwave, 10 min, 150 °C, 120 W, yields see scheme.

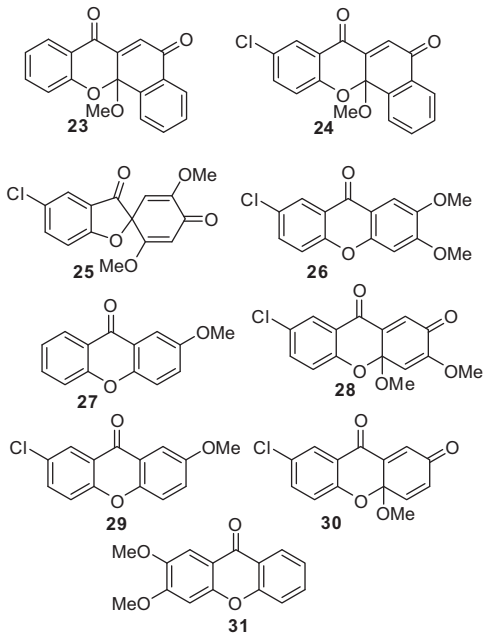


Figure 2. Structures of compounds previously synthesized tested for antibacterial and antifungal activity.

attempt to convert the dione into a xanthone, dione **10** was placed in DME in a Discovery microwave and heated for 10 min. The xanthone **11** was formed in a 50% yield presumably by means of an intermediate Michael acceptor **12** as shown in Scheme 2. In order to assemble xanthones or the related diones containing an aromatic bromine atom for possible Suzuki–Miyaura reactions, we attempted the same reaction on phenol **14**, which was easily prepared from the *O*-benzylated precursor **13** by exposure to hydrogen gas and a palladium on carbon catalyst. Subjecting **14** to CAN resulted in the formation of only the dione **15** but in a disappointing yield of 45%. Dione **15** was then subjected to the microwave conditions developed previously to give xanthone **16** in a poor yield of 10%.

Undeterred by this result, we wished to use substrates in the CAN-mediated reaction that would also lead to the formation of spirobenzofuran type compounds as we believed that these would show, in particular, good antifungal activity. Hence, as a result of our previous experience with the CAN reaction,[5] we prepared the

Table 1
Antimicrobial and antifungal activity of selected compounds

Compound	*Bacillus cereus* ATCC 11778	*Staphylococcus aureus* ATCC 2587	*Escherichia coli* ATCC 8739	*Moraxella catarrhalis* ATCC 232446	*Cryptococcus neoformans* ATCC 90112	*Candida albicans* ATCC 10231
Pathogen (MIC μg/mL)						
10	31.3	93.7	125.0	125.0	**3.6**	**3.6**
11	31.3	125.0	125.0	125.0	15.6	31.3
15	31.3	62.5	62.5	125.0	15.6	**7.8**
16	31.3	250.0	125.0	>250	11.7	31.3
19	31.3	62.5	187.5	125.0	15.6	31.3
20	31.3	62.5	62.5	125.0	15.6	31.3
21	31.3	62.5	125.0	125.0	15.6	31.3
22a	46.9	62.5	125.0	>250	23.4	31.3
22b	15.6	15.6	62.5	125.0	15.6	31.3
22c	31.3	62.5	62.5	125.0	15.6	62.5
22d	31.3	62.5	62.5	125.0	15.6	23.4
22e	31.3	62.5	62.5	125.0	15.6	62.5
22f	31.3	62.5	62.5	125.0	15.6	23.4
23	19.5	78.1	156.2	78.1	19.5	78.1
24	78.1	19.5	468.7	312.5	29.2	468.7
25	156.2	156.2	312.5	312.5	39.0	156.2
26	312.5	117.1	312.5	625.0	78.1	156.2
27	312.5	156.2	312.5	625.0	78.1	156.2
28	39.0	39.0	156.2	156.2	15.6	20.8
29	625.0	234.3	625.0	1250.0	156.2	234.3
30	156.2	156.2	312.0	156.2	**7.8**	156.2
31	46.9	62.5	125.0	125.0	31.3	31.3
Ciprofloxacin	0.08	1.25	0.12	1.25	NA	NA
Amphotericin B	NA	NA	NA	NA	2.5	3.0

NA = Not appropriate control; media control (not presented) demonstrated sterility and solvent control (not presented) had no additional antimicrobial effects.

trimethoxy derivative **17**. Removal of the *O*-benzyl substituent afforded the phenol **18** in good yield. Treatment of **18** with CAN yielded the dione **19** as well as the expected spirobenzofuran **20**.[9] Subsequently, the dione **19** was subjected to microwave conditions developed previously to yield the desired xanthone **21** in a mediocre yield of 33% (Scheme 3).

As we had prepared the spirobenzofuran **20** with a aromatic bromine substituent in place, we were now in a position to attempt Suzuki–Miyaura reactions on this substrate. Treatment of **20** with a range of boronic acids under Suzuki–Miyaura microwave conditions, as shown in Scheme 4, resulted in the formation of compounds **22a–f** in fair to good yields.[10]

The collection of xanthones, xanthenediones, and spirobenzofurans both from the work reported in this Letter, as well as that published previously,[5] (Fig. 2) were subjected to antibacterial and antifungal testing. Two pathogenically important yeasts (*C. albicans* and *C. neoformans*) were selected for representation of the fungal group. The in vitro antimicrobial MIC screening results for selected compounds are given in Table 1. Compounds with antimicrobial activities of 64–100 μg/mL were accepted as having clinical relevance[11] and compounds with activities 10 μg/mL or less were considered significant.[12] All compounds showing significant antimicrobial activity are highlighted in bold (Table 1).[13]

Examination of these biological results shows that a sizable number of the spirobenzofurans **19**–**21** and **22b**–**f** showed very good activity against the yeast, *C. neoformans*. In addition, xanthone **11** was also very active against *C. neoformans*. The same order of activity was noted with diones **15**, **16**, **23**, **28**, and **30**. Slightly less activity was generally observed against *C. albicans*, however, the majority of compounds tested still presented with activities being clinically significant. Dione **10** displayed the most significant activity against both yeasts having mean MIC values of 3.6 μg/mL. This noteworthy activity observed has potential for further development as an antifungal, as activities expressed are close to that of the commercial antifungal controls (2.5–3.0 μg/mL). As griseofulvin **4** is particularly active against filamentous fungi, this will be the focus of future biological testing.

Acknowledgments

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9. Synthesis of 7-bromo-3,4*a*-dimethoxy-2*H*-xanthene-2,9(4a*H*)-dione **19** and 5-bromo-2′,5′-dimethoxy-3*H*-spiro[benzofuran-2,1′-cyclohexa[2,5]diene]-3,4′-dione **20**.
Ceric ammonium nitrate (1.2880 g, 2.35 mmol) in water (20 mL) was added dropwise to a stirring mixture of (5-bromo-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone **18** (200 mg, 0.55 mmol) in acetonitrile (25 mL) and chloroform (5 mL). The mixture was stirred at room temperature for 10 min. The reaction mixture was filtered through celite and washed with EtOAc (3 × 25 mL). The organic layer was washed consecutively with a

saturated aqueous $NaHCO_3$ solution (25 mL), brine (25 mL), and water (25 mL). The organic layer was dried over magnesium sulfate. The solvent was removed in vacuo and silica column chromatography (20% EtOAc/hexane) afforded two products as yellow grains **19** (35 mg, 18%) and **20** (42 mg, 22%). **19**: Mp: 119–125 °C; IR (solid): ν_{max} (cm^{-1}): 1728, 1690, 1678, 1664, 1653, 1601, 1534, 1426; ^1H NMR (300 MHz; $CDCl_3$): δ 8.09 (1H, d, J = 2.4), 7.66 (1H, dd, J = 2.4, 8.7), 6.98 (1H, d, J = 8.7), 6.85 (1H, s), 5.95 (1H, s), 3.81 (3H, s), 3.32 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$): δ 180.2, 179.8, 156.4, 152.4, 144.1, 139.4, 129.9, 128.0, 122.9, 120.4, 115.9, 106.7, 98.1, 55.7, 51.2; HRMS (m/z): calcd for $C_{15}H_{11}BrO_5$ [M^++H] 350.9790 found: 350.9668. **20**: Mp 208–215 °C; IR (solid): ν_{max} (cm^{-1}): 1729, 1632, 1593, 1492, 1433, 1422; ^1H NMR (300 MHz; $CDCl_3$): δ 7.82–7.77 (2H, m), 7.14 (1H, d, J = 8.7), 5.75 (1H, s), 5.10 (1H, s), 3.68 (3H, s), 3.67 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$): δ 194.1, 181.1, 171.2, 167.5, 153.3, 141.5, 127.9, 121.5, 115.5, 115.2, 104.0, 102.3, 86.8, 56.6, 55.6; HRMS (m/z): calcd for $C_{15}H_{11}BrO_5$ [M^++H] 350.9790 found: 350.9855.

10. Synthesis of 4′-hydroxy-2′,5′-dimethoxy-5-phenyl-3*H*-spiro[benzofuran-2,1′-cyclohexa[2,5]diene]-3-one **22a**
5-Bromo-2′,5′-dimethoxy-3*H*-spiro[benzofuran-2,1′-cyclohexa[2,5]diene]-3,4′-dione **20** (30 mg, 0.08 mmol) was dissolved in 2 mL of dimethoxyethane (DME). Cesium fluoride (38 mg, 0.25 mmol); phenylboronic acid (14.6 mg, 0.12 mmol); and $Pd(PPh_3)_4$ (1.16 mg, 0.01 mmol) were added and the solution was heated in the microwave (at 150 °C, 120 W) for 10 min. The reaction mixture was filtered through filter paper and cotton wool. The solvent was removed in vacuo and silica gel column chromatography (20% EtOAc/hexane) afforded a yellow compound **22a** (0.018 g, 60%). Mp: 158–160 °C; IR (solid): ν_{max} (cm^{-1}): 1690, 1642, 1596, 1488, 1462, 1418; ^1H NMR (300 MHz; $CDCl_3$): δ 12.16 (1H, s, OH), 7.71 (1H, dd, J = 2.1, 8.4), 7.65 (1H. d, J = 2.4), 7.43–7.29 (4H, m), 7.10 (1H, d, J = 8.7), 6.93 (1H, s), 6.67 (1H, s), 5.99 (1H, s), 3.87 (3H, s), 3.71 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$): δ 200.9, 162.1, 152.5, 149.3, 140.5, 140.0, 134.8, 132.1, 131.7, 128.8 (2), 126.9, 126.4 (2), 120.4, 118.5, 118.4, 112.1, 99.3, 56.6, 56.2; HRMS (m/z): calcd for $C_{21}H_{16}O_5$, [M^++H] 351.1154 found: 351.1247.
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13. Positive controls (ciprofloxacin for bacteria and amphotericin B for yeasts) were included to monitor susceptibility of test organisms. Negative controls (media and solvent only) were included to monitor sterility and possible antimicrobial efficacy of diluents (Table 1).