SYNTHESIS OF NOVEL 1,5-DIARYL-1*H*-PYRROLE-2,3-DIONES

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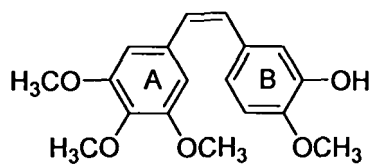
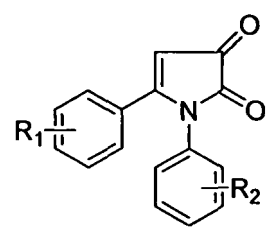
Abstract: A two-step synthesis of nine novel 1,5-diaryl-1*H*-pyrrole-2,3-diones from commercially available acetophenones and anilines is reported.

Introduction

1*H*-Pyrrole-2,3-diones have been utilized as synthons for preparation of other nitrogen-heterocycles and as Diels-Alder reactants with olefins and dienes (1-3). Despite this utility there are only a limited number of reports of the synthesis of 1,5-diaryl-1*H*-pyrrole-2,3-diones (3-5). A large number of vicinal diaryl heterocycles have been studied as analogues of the potent antitumor drug Combretastatin A4 (CA-4) (6-15). CA-4 strongly inhibits the polymerization of tubulin by binding to the colchicine binding site (11). SAR studies showed that the *cis* orientation of the two aryl rings is required and 3,4,5-trimethoxy substituents on the A-ring of CA-4 are essential for potent cytotoxicity (11,13). Consequently, considerable effort has been focused on the design of analogues by altering the spacer between the two aryl rings, including use of numerous heterocyclic systems, and alteration of the B-ring of the CA-4 with the goal of enhancing efficacy and pharmacokinetic profiles of these tubulin interacting molecules (6-15). Herein, we report an efficient procedure for the preparation of 1,5-diaryl pyrrole-2,3-diones analogues of CA-4. In addition to using the pyrrole-2,3-dione unit as the cisoid linker, we have also synthesized various analogues with variation in both the A and B-ring substitution.



Combretastatin A4



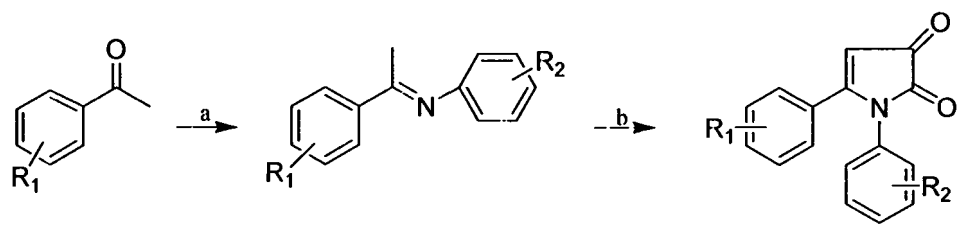
1,5-diaryl-1*H*-pyrrole-2,3-diones

Results and Discussion

The synthetic route employed to make 2,5-diary-1*H*-pyrrole-2,3-diones (**3a-3i**) is outlined in Scheme 1. The key intermediates (*E*)-*N*-(1-phenylethylidene)benzenamines (**2a-2i**) were obtained in good yield by the molecular sieves facilitated reaction between commercially available acetophenones and anilines using well described literature methodology (16-21). Reaction of the ketimine intermediates with oxalyl chloride in the presence of pyridine furnished the corresponding target compounds, 1*H*-pyrrole-2,3-diones (**3a-3i**), as red prisms in good yield, employing the approach reported by Cogas *et al* (4). The ^{1}H-, ^{13}C-NMR and elemental analyses data are consistent with the structures assigned to these compounds. The 2,5-diaryl-1*H*-pyrrole-2,3-diones (**3a-3f**) were evaluated for cytotoxicity against the CEM cell line. The IC_{50} value found for **3a** was 6.14 M and the values for the others tested were greater than 25 M. The IC_{50} value for the control compound CA-4 was 1.63 nM (11). Further evaluation of these compounds was not pursued in view of their marginal activity.

In conclusion, an efficient two-step sequence to the 1*H*-pyrrole-2,3-diones starting from the commercially available acetophenones and anilines was developed. Nine novel 1,5-diaryl-1*H*-pyrrole-2,3-diones (**3a-3i**) have been obtained in satisfactory yields, suitable for multigram preparation.

Scheme 1. Synthesis of 1,5-diaryl-1*H*-pyrrole-2,3-diones



2a	R_1=3,4-$(OMe)_2$,	R_2=H	3a R_1=3,4-$(OMe)_2$, R_2=H
2b	R_1=2,6-$(OMe)_2$,	R_2=4'-OMe	3b R_1=2,6-$(OMe)_2$, R_2=4'-OMe
2c	R_1=3,4,5-$(OMe)_3$,	R_2=4'-OMe	3c R_1=3,4,5-$(OMe)_3$, R_2=4'-OMe
2d	R_1=4-OMe,	R_2=3',4',5'-$(OMe)_3$	3d R_1=4-OMe, R_2=3',4',5'-$(OMe)_3$
2e	R_1=3,4,5-$(OMe)_3$,	R_2=2',4'-$(OMe)_2$	3e R_1=3,4,5-$(OMe)_3$, R_2=2',4'-$(OMe)_2$
2f	R_1=3,4-$(OMe)_2$,	R_2=4'-OMe	3f R_1=3,4-$(OMe)_2$, R_2=4'-OMe
2g	R_1=3,4-$(OMe)_2$,	R_2=3,4-$(OMe)_2$	3g R_1=3,4-$(OMe)_2$, R_2=3,4-$(OMe)_2$
2h	R_1=3,4-$(OMe)_2$,	R_2=3'-Cl-4'-OMe	3h R_1=3,4-$(OMe)_2$, R_2=3'-Cl-4'-OMe
2i	R_1=4-OMe,	R_2=3'-Cl-4'-OMe	3i R_1=4-OMe, R_2=3'-Cl-4'-OMe

Reagents and conditions: a) Ar-NH_2, molecular sieves (4Å), $NaHCO_3$, toluene, reflux overnight. b) $(COCl)_2$, pyridine, CCl_4, 40 , 1 h.

Experimental

Metlting points were recorded using a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded employing a Bruker 400 ultrashield^{TM} instrument and chemical shifts (δ) are in ppm relative to TMS used as internal standard. Mass spectra were recorded on a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab, Inc. (Norcross, GA).

General procedure for the preparation of 1,5-diaryl-1*H*-pyrrole-2,3-diones 3a-i. A mixture of $NaHCO_3$ (50 mmol), aniline (10 mmol), acetophenone (10 mmol) and activated molecular 4Å sieves (8.0 g) in anhydrous toluene (10 ml) was heated at reflux overnight under a nitrogen atmosphere, cooled to room temperature and filtered through celite. The filtrate was concentrated in vacuo. The crude product was crystallized once from acetone/hexane to give **2a-i** and was used in the next step without further purification. Oxalyl chloride (5 mmol) in dry CCl_4 (3.0 ml) was added dropwise to a solution of **2a-i** (5 mmol) and pyridine (10 mmol) in dry CCl_4 (9.0 ml) cooled at 0 [illegible]. The temperature was raised to 40 [illegible], and the mixture was stirred for 5 min. The thick oil which formed was dispersed by additional 5.0 ml of CCl_4 and stirred at 40 [illegible] for 1 h. The red precipitate was collected by filtration and chromatographed (silica gel, 3:1 hexane: ethyl acetate) to afford the title compounds **3a-i** in good yield.

5-(3,4-Dimethoxyphenyl)-1-phenyl-1*H*-pyrrole-2,3-dione (3a): Red solid , 70% yield, m.p. 215-216 [illegible], ^1H NMR ($CDCl_3$) δ 3.54 (s, 3H), 3.91 (s, 3H), 5.81 (s, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 7.11 (m, 3H), 7.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.1, 100.3, 111.0, 111.2, 120.7, 123.3, 127.2, 128.0, 129.3, 134.6, 148.7, 152.9, 159.5, 171.1, 181.7. *Anal.* Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.72; H, 4.85; N, 4.55.

5-(2,6-Dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,3-dione (3b): Red solid , 63% yield, m.p. 167-168 [illegible], ^1H NMR ($CDCl_3$) δ 3.70 (s, 6H), 3.76 (s, 3H), 5.59 (s, 1H), 6.48 (d, J = 8.4 Hz, 2H), 6.76(dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H), 6.96 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H), 7.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 55.4, 55.8, 103.6, 103.7, 107.3, 113.6, 126.8, 127.3, 133.1, 157.5, 158.0, 158.7, 168.6, 183.3. *Anal.* Calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.17; H, 5.00; N, 4.19.

1-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-2,3-dione (3c): Red solid, 68% yield, m.p. 170-172 [illegible], ^1H NMR ($CDCl_3$) δ 3.66 (s, 6H), 3.82 (s, 3H), 3.90 (s, 3H), 5.79 (s, 1H), 6.56 (s, 2H), 6.92 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H), 7.06 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.1, 61.1, 100.3, 106.4, 114.6, 123.3, 127.1, 128.5, 141.7, 153.0, 159.2, 159.5, 171.1, 182.2. *Anal.* Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.75; H, 5.21; N, 3.88.

5-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-2,3-dione (3d): Red solid, 50% yield, m.p. 192-194 [illegible], ^1H NMR ($CDCl_3$) δ 3.75 (s, 6H), 3.86 (s, 3H), 3.87 (s, 3H), 5.80 (s, 1H), 6.32 (s, 2H), 6.89 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H), 7.35 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.3, 61.0, 100.1, 104.9, 114.4, 120.6, 129.9, 130.7, 137.7, 153.5, 159.7, 163.3, 171.1, 181.7. *Anal.* Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.77; H, 5.17; N, 3.78.

1-(2,4-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-2,3-dione (3e): Red solid, 65% yield, m.p. 163-165 □, ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 3.69 (s, 6H), 3.83 (s, 3H), 3.89 (s, 3H), 5.75 (s, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.56 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.62 (s, 2H), 7.18 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.1, 56.1, 56.4, 61.0, 99.5, 99.7, 105.0, 105.4, 116.4, 124.2, 130.2, 141.4, 152.9, 156.0, 160.4, 161.4, 172.3, 182.4. *Anal.* Calcd. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.06; H, 5.32; N, 3.56.

5-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,3-dione (3f): Red solid, 63% yield, m.p. 215-216 □, ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 5.79 (s, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.86(d, J = 8.4 Hz, 1H), 6.92 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H), 7.06 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H), 7.11 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H); MS: 340.6 (M + H); ^{13}C NMR ($CDCl_3$) δ 55.5, 55.7, 56.1, 99.8, 111.0, 111.3, 114.6, 120.8, 123.4, 127.2, 128.5, 148.7, 152.8, 159.2, 160.0, 171.2, 181.9. *Anal.* Calcd. for $C_{19}H_{17}NO_5$ + 0.25H_2O: C, 66.37; H, 5.13; N, 4.07. Found: C, 66.23; H, 4.97; N, 4.02.

1,5-Bis(3,4-dimethoxyphenyl)-1*H*-pyrrole-2,3-dione (3g): Red solid, 72% yield, m.p. 187-188 □, ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 5.80 (s, 1H), 6.68 (m, 2H), 6.79 (d, J = 2.0 Hz, 1H), 6.86 (m, 2H), 7.09 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.8, 56.1, 56.2, 99.8, 110.9, 110.9, 111.1, 111.2, 119.9, 120.8, 123.3, 127.3, 148.7, 148.9, 149.4, 152.8, 159.9, 171.1, 181.9; *Anal.* Calcd. for $C_{19}H_{17}NO_5$: C , 65.03; H, 5.18; N, 3.79. Found: C, 64.85; H, 5.19; N, 3.76.

1-(3-Chloro-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2,3-dione (3h): Red solid, 69% yield, m.p. 173-174 □, ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 5.81 (s, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.99 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.05 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.22 (d, J_1 = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 56.1, 56.4, 100.4, 111.0, 111.1, 112.0, 120.4, 123.1, 123.3, 126.7, 127.5, 129.1, 148.9, 153.0, 154.8, 159.7, 170.7, 181.5. *Anal.* Calcd. for $C_{20}H_{19}NO_6$: C, 61.05; H, 4.31; N, 3.75. Found: C, 61.17; H, 4.44; N, 3.72.

1-(3-Chloro-4-methoxyphenyl)-5-(4-methoxyphenyl)-1*H*-pyrrole-2,3-dione (3i): Red solid, 62% yield, m.p. 143-145 □, ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.93 (s, 3H), 5.78 (s, 1H), 6.89 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H), 6.92 (d, J_1 = 8.8 Hz, 1H), 6.98 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.16 (d, J_1 = 2.4 Hz, 1H), 7.32 (dd, J_1 = 2.0 Hz, J_2 = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 56.4, 100.3, 112.0, 114.5, 120.2, 123.0, 126.6, 127.3, 129.0, 130.9, 154.7, 159.8, 163.3, 170.8, 181.5. *Anal.* Calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.07. Found: C, 62.99; H, 4.16; N, 4.05.

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