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TETRAHEDRON

Synthesis and UV Studies of A Small Library of 6-Aryl-4-hydroxy-2-pyrones. A Relevant Structural Feature for the Inhibitory Property of Arisugacin Against Acetylcholinesterase.

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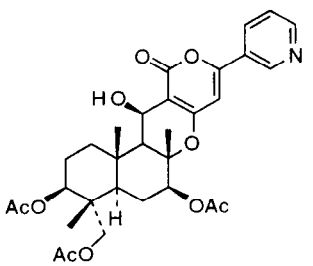
ABSTRACT: 4-Hydroxypyrones belong to an important class of compounds not only because of their medicinal significance, but also because they represent a common structural feature among natural products that are biologically relevant. We describe here preparations of a small library of 6-aryl-4-hydroxy-pyrones which represent structural analogs of the DE-ring of arisugacin, a potent and selective inhibitor against acetylcholinesterase. Given the structural significance of the DE-ring in the inhibitory activity of arisugacin, chemical shifts of relevant protons on the pyrone ring are compared, and distinct features in UV absorptions of these 6-aryl-4-hydroxy-pyrones are described.

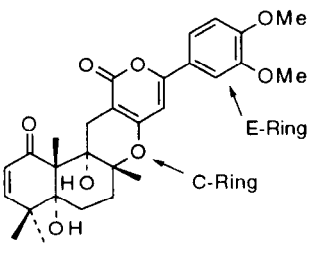
Keywords: Pyrones, NMR, Electronic Spectra, Electronic Effects.

INTRODUCTION

4-Hydroxypyrones are important structural moieties found in a variety of medicinally significant compounds. Specifically, a series of 4-hydroxy-pyrones with various substitutions at the C-6 position were reported to possess anti-HIV or anti-viral properties.[4,5] In addition, several recently isolated natural products such as pyripyropene A (**1**)[6-8] and arisugacin (**2**)[9] are found to possess the 6-aryl-4-hydroxypyrone structural feature. The 6-aryl-4-hydroxypyrone moieties in these two natural products are shown to be very critical to the biological activity of pyripyropene A (**1**) as an inhibitor of acyl-CoA: cholesterol acyltransferase (ACAT),[6-8] and of arisugacin (**2**) as a potent and selective inhibitor of acetylcholinesterase (AChE).[10]



1: pyripyropene-A



2: arisugacin

We are specifically interested in arisugacin (**2**) because of its tremendous potential in the therapeutic treatment of Alzheimer's and other dementia diseases.[8,11-15] Synthetically, we have been developing methods that are targeted towards the ABC-ring[16] and pyranyl C-ring uniquely fused to the 6-aryl-4-hydroxypyrone

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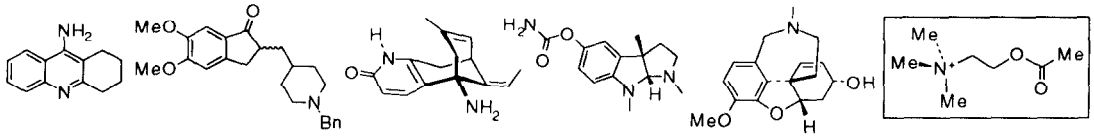
moiety (the DE-ring),[17] and medicinally, we are intrigued by the DE-ring which is a significant structural feature for the inhibitory activity of **2**.[10] Arisugacin (**2**) demonstrates an impressive potency against AChE with an IC_{50} value of 1 nM. This *in vitro* potency is greater than the existing anti-dementia therapeutics such as tacrine[18] (**3**), aricept[19] (**4**), and huperzine A[20] (**5**), and other known cholinesterase inhibitors such as physostigmines (**6**)[21] and galanthamine (**7**).[22] The compound **2** is also highly selective against AChE since an IC_{50} value of >18,000 nM is required to achieve inhibition of butyrylcholinesterase (BuChE).[23]



3: tacrine **4**: aricept **5**: huperzine A **6**: physostigmine **7**: galanthamine **8**: acetylcholine

Effective inhibitors should contain a nitrogen atom because it could mimic the binding action of the quaternary nitrogen atom in acetylcholine (**8**), a neurotransmitter responsible for memory and other cognitive functions. This quaternizable nitrogen atom is believed to interact electrostatically with the tryptophan (Trp 84) residue situated near the "anionic gorge" of the active site.[13] Intriguingly, despite demonstrating the superior potency and selectivity against AChE, arisugacin (**2**) does not contain a single nitrogen atom. Arisugacin (**2**) could inhibit AChE by binding at an allosteric site or may have other modes of actions since the enone A-ring also has been reported to be structurally significant.[9,10] However, Ōmura's modeling study[9] provides an excellent assumption that the compound **2** can effectively bind to AChE at the same active site. Given Ōmura's model and the known structural significance of the DE-ring,[9,10] we postulate that the DE-ring could exert an electronic effect in the binding to AChE because it essentially consists of an electron donor (the methoxy groups) and an acceptor (the 2-pyrone moiety). This postulation led us to prepare a small library of 6-aryl-4-hydroxy-2-pyrones which are DE-ring analogs of **2**. We report here synthesis and UV studies of these 6-aryl-4-hydroxy-2-pyrones.

RESULTS AND DISCUSSIONS.

1. Preparations of Pyrones and ^1H NMR Comparisons.

All 6-aryl-4-hydroxy-2-pyrones (**15-19**) were synthesized in a two-step sequence analogous to a related procedure[15] (**Scheme 1**). The diketoesters (**10-14** except **12e**) were prepared by an addition of the dianion intermediate, generated from 2.5 eq of LDA, 1.0 eq ethyl acetoacetate, and 1.0 eq of TMEDA, to the ester **9** in THF. This Claisen condensation was relatively slow and usually required 1-2 d to achieve synthetically useful yields (see **Table 1**). Furthermore, the reaction produced numerous keto and enol tautomers that were either difficult to separate via silica gel column chromatography, or equilibrated rapidly to provide new isomeric mixtures. This severely hindered our ability to characterize these diketoesters. These mixtures of tautomers were simply flashed or filtered through silica gel and used for the pyrone formation without further purification. The diketoester **12e** could only be prepared in useful yields by addition of the dianion intermediate to the corresponding benzoyl chloride.

Pyrones **15-19** were obtained by heating the oily diketoester tautomeric mixture in a 150 °C sand bath at a pressure of 0.5–3.0 mmHg for 20 min to 1 h. A yellow solid immediately formed along with a dark red oil, and the solid was isolated by vacuum filtration and rinsed with 5% CH_2Cl_2 in ether or 100% CH_2Cl_2. This simple filtration method provided spectroscopically pure pyrones. The structures of all the pyrones **15-19** are illustrated in the **Product Chart**. These pyrones are highly colored, ranging from yellow to red. Attempts were made to further purify these pyrones via recrystallization but were not successful because they are extremely polar compounds. Yields for the first cycle range from 21% to 73% (**Table 1**). The filtrate could be concentrated under reduced pressure and resubjected to the same reaction condition to afford more pyrone. The second cycle usually provided an additional 10-15 % yield of the product. We found some minor tautomers in the diketoester mixture will not cyclize properly to form pyrones.

Scheme 1

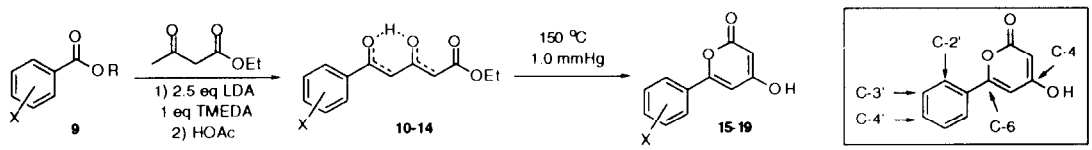


Table 1: Isolated Yields.

entry	substituents	diketoesters	yield	pyrones	yield
1	6-phenyl	**10**	44 %	**15**	48 %
	mono-methoxy				
2	4'-methoxy	**11a**	48	**16a**	59
3	3'-methoxy	**11b**	65	**16b**	35
4	2'-methoxy	**11c**	63	**16c**	52
	di-methoxy				
5	3',5'-dimethoxy	**12a**	41	**17a**	45
6	3',4'-dimethoxy	**12b**	42	**17b**	45
7	2',4'-dimethoxy	**12c**	50	**17c**	40
8	2',3'-dimethoxy	**12d**	47	**17d**	33
9	2',6'-dimethoxy	**12e**	30	**17e**	56
	trimethoxy				
10	3',4',5'-trimethoxy	**13a**	49	**18a**	53
11	2',3',4'-trimethoxy	**13b**	51	**18b**	32
12	2',4',5'-trimethoxy	**13c**	48	**18c**	73
	fluorinated				
13	4'-fluoro	**14a**	45	**19a**	45
14	3'-fluoro	**14b**	46	**19b**	21
15	2'-fluoro	**14c**	53	**19c**	58

Product Chart

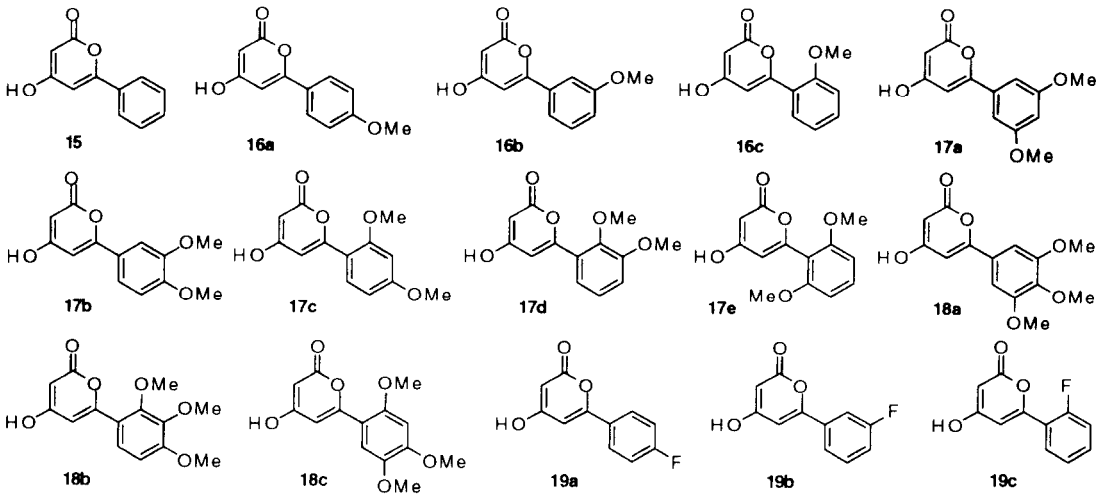
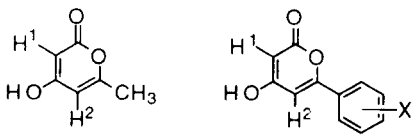


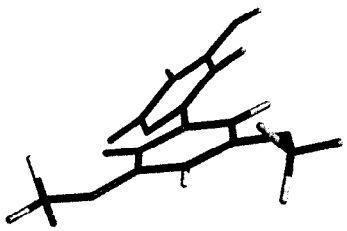
Table 2: ^{1}H NMR Comparisons (3% DMSO-d_6 in $CDCl_3$).



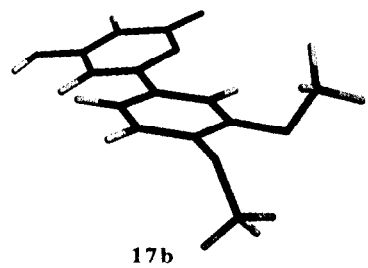
entry	pyrones		H^1 (δ)	H^2 (δ)
1	6-methyl:	**20**	5.41	5.82
2	6-phenyl:	**15**	5.57	6.41
3	4'-methoxy:	**16a**	5.51	6.38
4	3'-methoxy:	**16b**	5.57	6.48
5	2'-methoxy:	**16c**	5.55	6.94
6	4'-fluoro:	**19a**	5.56	6.44
7	3'-fluoro:	**19b**	5.59	6.49
8	2'-fluoro:	**19c**	5.58	6.73
9	3',5'-dimethoxy:	**17a**	5.57	6.40
10	3',4'-dimethoxy:	**17b**	5.53	6.45
11	2',4'-dimethoxy:	**17c**	5.49	6.87
12	2',3'-dimethoxy:	**17d**	5.56	6.89
13	2',6'-dimethoxy:	**17e**	5.53	6.07
14	3',4',5'-trimethoxy:	**18a**	5.44	6.30
15	2',3',4'-trimethoxy:	**18b**	5.52	6.85
16	2',4',5'-trimethoxy:	**18c**	5.51	6.94

Several intriguing patterns were observed in the chemical shifts of protons H-1 and H-2 (**Table 2**). These ^{1}H NMR data were taken by using the same solvent system (3% DMSO-d_6 in $CDCl_3$) with TMS as an internal standard. Since chemical shifts of both protons H-1 and H-2 of 6-aryl-4-hydroxy-2-pyrones **15-19** are all higher than those in **20**, in which there is a methyl group at the C-6 position (entry 1), the pyrone **15** containing a phenyl group at C-6 serves as a reference point for the following comparisons (entry 2). The phenyl group at C-6 of pyrones **15-19** evidently provides a deshielding effect towards H-1 and H-2.

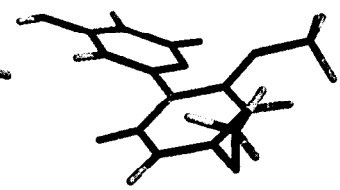
Figure 1



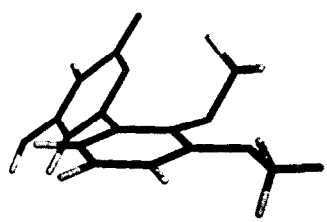
17a
[dihedral angle = 23.2 °]



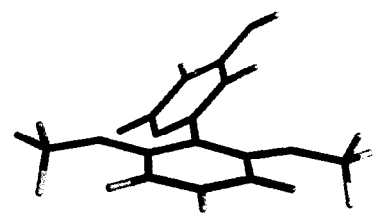
17b
[dihedral angle = 16.8 °]



17c
[dihedral angle = 34.0 °]



17d
[dihedral angle = 45.3 °]



17e
[dihedral angle = 41.4 °]

For all pyrones, the proton H-1 is slightly affected by substitution patterns on the phenyl ring. Substitutions such as electron donating (entries 3-4, 9-10, and 14 versus entry 2) or withdrawing groups (entries 6 and 7 versus entry 2) on the phenyl ring do not appear to exert a significant effect on the chemical shift of H-2. However, when there is one *ortho* substituent on the phenyl ring (entries 5, 8, 11-12, and 15-16), chemical shifts of H-2 are much higher than those without substitutions at the *ortho*-positions (entries 2-4, 6-7, 9-10, and 13-14), giving a $\Delta\delta$ range of 0.24 to 0.64 ppm. More intriguingly, when there are methoxy groups occupying both *ortho*-positions (entry 13) in compound **17e**, the chemical shift of H-2 is the lowest among all 6-aryl-4-hydroxy-2-pyrones. From computational modeling (Spartan^{TM} *Ab inito* - HF 6-31G**), compound **17e** appears to be the less planar relative to other dimethoxy-substituted pyrones except **17d** (**Figure 1**). This structural difference could diminish the anisotropic deshielding effect of the phenyl ring on H-2 in **17e**, although such a correlation does not fit well with the pyrone **17d**. The minimized structure of **17d** possess the highest dihedral angle between the planes of the pyrone and phenyl rings, while **17b**, containing the same substitution pattern on the phenyl ring as that of arisugacin (**2**), possesses the best co-planarity.

2. UV Studies.

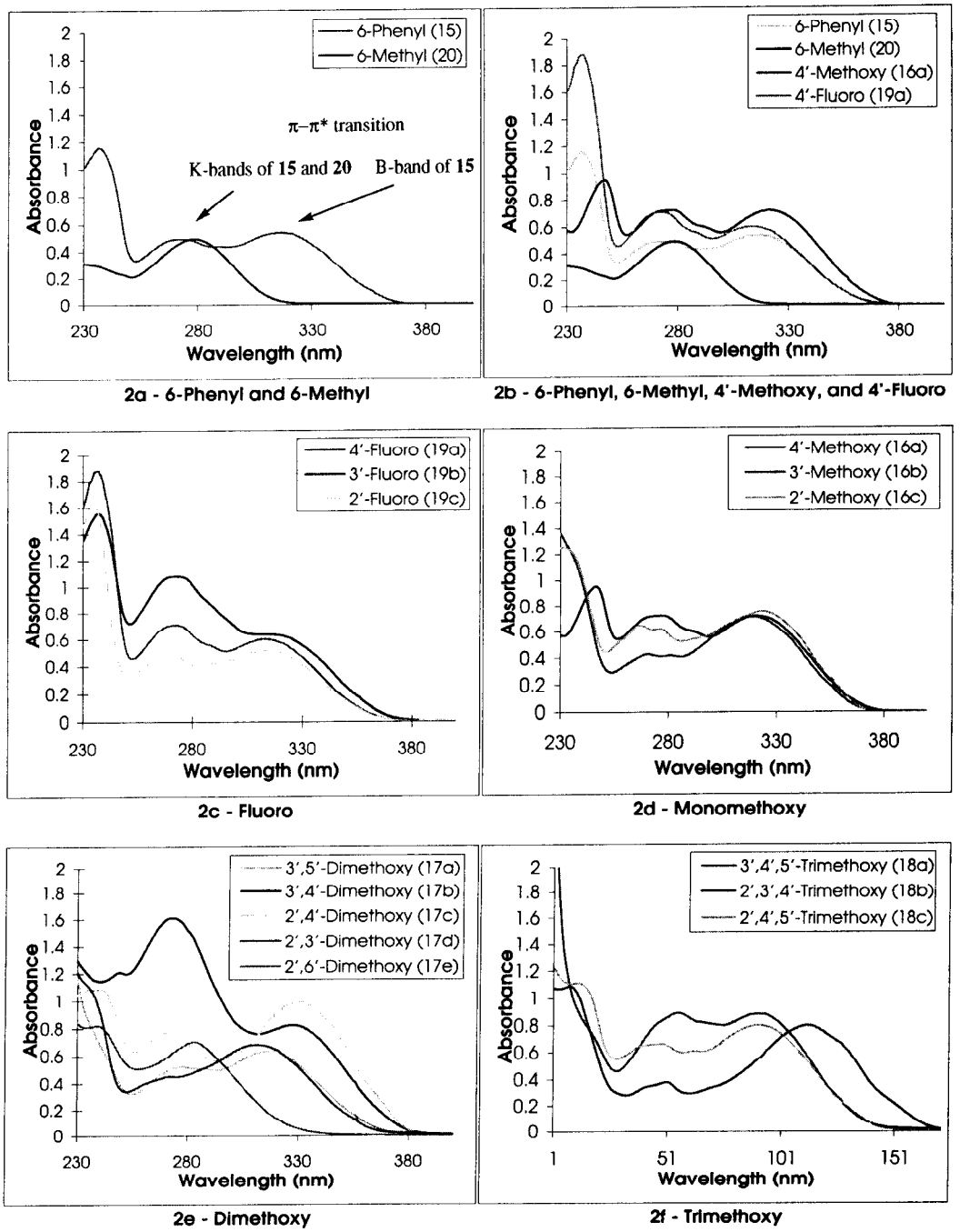
UV studies also revealed several unique characteristics among these 6-aryl-4-hydroxy-2-pyrones. The λ_{max} and molar absorptivities for K- and B-bands of π-π^* transitions of these pyrones are tabulated in **Table 3**. These UV spectra are obtained in 95% EtOH using the same concentration for all pyrones (**Figure 2**). As shown in **Figure 2a**, 6-methyl-4-hydroxy-2-pyrone (**20**) displays a K-band (π-π^* transition) at 278 nm due to the pyrone chromophore, while 6-phenyl-4-hydroxy-2-pyrone (**15**) displays bathochromic shifts in all π-π^* transitions of the phenyl chromophore due to extended conjugation. Thus, the K-band (the phenyl absorption) of **15** would overlap with the absorption due to the pyrone chromophore at 274 nm (but two maxima can be found in this region for some 6-aryl-4-hydroxy-2-pyrones), and the B-band can be seen at 316 nm.

Table 3: UV Absorptions (in 95% Ethanol).

entry	pyrones		K - band λ_1 [nm]	K - band ε_1	B - band λ_2 [nm]	B - band ε_2
1	6-methyl:	**20**	278	7239	-	-
2	6-phenyl:	**15**	274	7736	316	8470
3	4'-methoxy:	**16a**	277	11406	321	11353
4	4'-fluoro:	**19a**	273	10738	313	9115
5	3'-methoxy:	**16b**	281	6613	319	11210
6	3'-fluoro:	**19b**	272	17458	314	10301
7	2'-methoxy:	**16c**	276	9104	323	11111
8	2'-fluoro	**19c**	273	7788	315	8454
9	3',5'-dimethoxy:	**17a**	277	8321	317	10066
10	3',4'-dimethoxy:	**17b**	274	28145	328	14382
11	2',4'-dimethoxy:	**17c**	270	11981	331	15600
12	2',3'-dimethoxy:	**17d**	272	7008	311	10559
13	2',6'-dimethoxy:	**17e**	283	11488	-	-
14	3',4',5'-trimethoxy:	**18a**	284	14066	318	13965
15	2',3',4'-trimethoxy:	**18b**	279	5994	341	12685
16	2',4',5'-trimethoxy:	**18c**	277	10468	319	12670

Substitutions at the C-4' position of the phenyl ring with a methoxy or fluoro group (the pyrone **16a** or **19a**) provide no dramatic shifts, although the B-band of **16a** (4'-methoxy-substituted) is red-shifted, giving a maximum at 321 nm (**Figure 2b**). For fluoro-substituted compounds **19a** and **19b**, there is a clear increase in intensity at the K-band region (**Figure 2c**), while mono-methoxy-substituted compounds (**16a-c**) provide no real difference in the maxima. Overall, compounds **16a-c** provide higher maxima for the B-band than those of fluoro-substituted compounds **19a-c** ($\Delta\lambda_{max}$ = 5 - 8 nm, see entries 3-8 in **Table 3**).

Figure 2: UV Spectra of 4-hydroxy-2-pyrones



2a - 6-Phenyl and 6-Methyl

2b - 6-Phenyl, 6-Methyl, 4'-Methoxy, and 4'-Fluoro

2c - Fluoro

2d - Monomethoxy

2e - Dimethoxy

2f - Trimethoxy

UV spectra that would provide the most distinct contrast would be those of di- and trimethoxy-substituted compounds (**17a-e** and **18a-c** in **Figure 2e-f**). Pyrones **17b** and **17c** (3',4'-dimethoxy- and 2',4'-dimethoxy-substituted) provide a distinct bathochromic shift at the B-band, leading to λ_{max} of 328 and 331 nm, respectively. In addition, the pyrone **17b**, which has the same substitution pattern on the phenyl ring as that of arisugacin (**2**), also displays a great increase in intensity of the K-band. These distinct features are similar to those of known aromatic systems containing electron donors and acceptors.[24]

On the other hand, the pyrone **17e** (2',6'-dimethoxy-substituted) exhibits a hypsochromic shift in the B-band in which it overlaps with the K-band from 4-hydroxy-2-pyrone absorption. The UV spectrum of **17e** resembles that of 6-methyl-4-hydroxy-2-pyrone (**20**), suggesting a lack of conjugation of the phenyl ring with the pyrone moiety. Finally, the pyrone **18b** (2',3',4'-trimethoxy-substituted) displays the highest bathochromic shift, giving a λ_{max} at 341 nm, while its intensity for the K-band is much smaller than those of **18a** and **18c**.

There exists a clear diversity in the UV absorption properties of 6-aryl-4-hydroxy-2-pyrones. These UV studies suggest differences in the electronic properties of these pyrones, and could provide valuable correlations to the biological activity of arisugacin. We are currently using these different pyrones to prepare various structural analogs of arisugacin via the methodologies that we are developing.[17]

We have described here the preparation of a series of 6-aryl-4-hydroxy-pyrones analogous to those found in biologically relevant natural products such as arisugacin. Given the structural significance of the DE-ring in the inhibitory activity of arisugacin, we have also compared chemical shifts of relevant protons on the pyrone ring, and described distinct features in UV absorptions of these 6-aryl-4-hydroxy-pyrones. Although syntheses of arisugacin and its analogs have not been achieved at this point to incorporate these various 6-aryl-4-hydroxy-pyrones, these compounds and the properties described here could be useful for future studies involving structure-activity relationships of arisugacin or other compounds containing the 6-aryl-4-hydroxy-pyrone moiety.

EXPERIMENTAL SECTION

All reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Tetrahydrofuran (THF) was distilled from benzophenone ketyl under nitrogen. The thin-layer chromatography (TLC) analysis was done using EM Science silica gel-60 plates (0.25 mm in thickness) with F254 as the fluorescence indicator. The eluted plates were developed under UV detector and/or stained with either an aqueous solution of potassium permanganate ($KMnO_4$) or an alcoholic solution of phosphomolybdic acid (PMA). Chromatographic purifications were performed on EM Science silica gel (230-400 mesh) by flash technique.[25] ^1H NMR data (δ, ppm) were obtained either on a Varian - 300 MHz or 500 MHz instrument using chloroform-*d* as solvent with DMSO-d_6 added in cases of pyrones to enhance solubility, and tetramethylsilane as an internal standard set at 0.00 ppm. The multiplicities of the NMR spectra absorptions were indicated by: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; sextet; septet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; m, multiplet. ^{13}C NMR data (δ, ppm) were obtained on the Varian instrument at 75 MHz or 125 MHz using chloroform-*d* as solvent with DMSO-d_6 added

in cases of pyrones to enhance solubility. Infrared spectra (cm^{-1}) were taken on a Perkin-Elmer 1600 Series FTIR and intensities of absorptions were described qualitatively as: s, strong; m, medium; w, weak. Low resolution mass spectra and high resolution mass analysis were recorded on a Finnigan MAT 95 mass spectrometer. UV spetra were taken on a Beckmann DU-650 Spectrometer. All reactions were carried out under either argon or nitrogen in oven (150 °C) dried or flame dried glassware.

General Procedure for Preparations of 6-Aryl-4-hydroxy-2-pyrones.

The starting benzoic esters (methyl or ethyl) could be either obtained from commercial sources or prepared from corresponding benzoic acids using the following procedure specifically for methyl 3,4-dimethoxybenzoate. 3,4-Dimethoxybenzoic acid (91.0 g, 0.5 mol) was refluxed with $SOCl_2$ (5.0 eq) in 300 mL of benzene for 24 h. After refluxing, the excess $SOCl_2$ was removed under reduced pressure and azeotroped with benzene (2 x 100 mL). The resulting crude solid was dissolved in 150 mL of benzene and 100 mL of MeOH (or EtOH) and refluxed for 24 h. After the solvents were evaporated under reduced pressure, the crude solid was dissolved in a minimum amount of CH_2Cl_2 and filtered through a small bed of silica gel. More CH_2Cl_2 was used to complete the filtration. After removal of CH_2Cl_2 under reduced pressure and drying on a high vacuum pump, an off-white solid was obtained as the pure ester in nearly quantitative yield.

Preparation of Diketoesters. To a solution of diisopropylamine (8.9 mL, 63.7 mmol, 2.5 eq) in 100 mL of THF at -10 °C (ice in acetone) was added n-BuLi (2.5 *M* in hexane) (25.5 mL, 63.7 mmol, 2.5 eq) via a syringe. This solution was stirred at -10 °C for 45 min. In a separate flask, a solution of ethyl acetoacetate (3.32 g, 25.5 mmol) in 50 mL of THF was cooled to -78 °C, and the LDA solution was carefully transferred to the ethyl acetoacetate solution dropwise via a cannula. A yellow cloudy solution formed initially but quickly turned homogeneous. After completing the addition of the LDA solution, freshly distilled (from CaH_2 under N_2) TMEDA (3.84 mL, 25.5 mmol, 1.0 eq) was added in one shot via a syringe. The reaction mixture was then stirred for 2 h at -78 °C.

The reaction mixture turned orange when a solution of methyl *p*-methoxy benzoate (4.24 g, 25.5 mmol) was added via cannulation, and then yellow precipitate was observed. The reaction mixture was warmed to rt and stirred at 24–48 h. The progress of the reaction could be observed by TLC analysis (25-50% EtOAc in hexane) or ^1H NMR. When the reaction was deemed complete by TLC or ^1H NMR, 4 mL of acetic acid was added to the reaction mixture which was subsequently concentrated under reduced pressure.

The resulting crude residue was filtered through a small bed of silica gel eluted with ample CH_2Cl_2. After removal of the solvent, the crude diketoester was purified using silica gel column chromatography and a gradient eluent system involving EtOAc in hexane (0-50% EtOAc in hexane). In each case, numerous keto and enol tautomers could be found in many fractions. These tautomers also frequently equilibrated upon isolation. Hence, it was difficult to isolate one pure isomer and characterization was difficult. These mixtures of tautomers from different fractions were simply used for the pyrone formation without further charcterization and purifications.

Preparation of Pyrones. The oily diketoester tautomeric mixture prepared above (2.40 g, 8.2 mmol) was heated in a 150 °C sand bath under 0.5–3.0 mmHg pressure for 20 min to 1 h. A crude yellow solid immediately formed along with a dark red oil. The crude mixture was cooled and immersed in ~20 mL 5%

CH_2Cl_2 in ether. This heterogenous mixture was then filtered, and the solid was washed with 5% CH_2Cl_2 in ether to provide 0.91 g of an orange solid as the pure and desired pyrone (45 %). The filtrate could be concentrated under reduced pressure and resubjected to the same reaction conditions to afford more pyrone. The yields for the first cycle ranged from 21 to 59%, and the second cycle usually provided an additional 10-15 % yield of the product. These pyrones are highly colored, ranging from yellow to red, and are extremely polar. They appeared to be unstable to silica gel column chromatography, and recrystallization in various solvents were not fruitful. However, the simple filtration using 5% CH_2Cl_2 in ether provided spectrocopically pure pyrones.

Characterizations of 6-Aryl-4-hydroxy-2-pyrones 15-19.

For the Pyrone **15**:

Rf = 0.36 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 234 - 248 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 5.57 (d, 1H, J = 2.3 Hz), 6.49 (d, 1H, J = 2.3 Hz), 7.44 (m, 3H), 7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 88.9, 97.2, 124.3, 127.7, 129.6, 130.1, 159.1, 162.8, 169.5; IR (neat) cm^{-1} 3422w, 1640s, 1532m, 856m; mass spectrum (EI): m/e (%relative intensity) 188 (82) M^+, 160 (94), 105 (100), 77 (57), 51 (17); m/e calcd for $C_{11}H_8O_3$ 188.0473, measd 188.0488.

For the Pyrone **16a**:

Rf = 0.46 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 180 - 181 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.86 (s, 3H), 5.52 (d, 1H, J = 2.0 Hz), 6.38 (d, 1H, J = 2.0 Hz), 6.94 (dt, 2H, J = 3.0, 10.0 Hz), 7.75 (dt, 2H, J = 3.0, 10.0 Hz); ^{13}C NMR (75 MHz, methanol-d_4) δ 54.6, 88.4, 96.7, 114.1, 123.4, 127.1, 161.5, 162.3, 166.6, 172.4; IR (neat) cm^{-1} 3330s, 1654s, 1619m, 1605m, 1584m, 1549s, 1516s, 1369m; mass spectrum (EI): m/e (%relative intensity) 220 (58) M^+, 129 (35), 218 (6.44), 192 (32), 191 (18), 135 (100); m/e calcd for $C_{12}H_{10}O_4$ 218.0579, measd 218.0583.

For the Pyrone **16b**:

Rf = 0.35 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 199 - 200 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.86 (s, 3H), 5.57 (d, 1H, J = 1.8 Hz), 6.48 (d, 1H, J = 1.8 Hz), 6.99 (dt, 1H, J = 2.0, 8.0 Hz), 7.34 (t, 1H, J = 2.0 Hz), 7.37 (dd, 1H, J = 8.0, 10.0 Hz), 7.38 (dt, 1H, J = 2.0, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 55.4, 90.4, 98.6, 110.7, 116.4, 117.8, 129.7, 132.5, 159.7, 160.2, 160.6, 170.6; IR (neat) cm^{-1} 3452s, 1645s, 1540m, 1458m, 863m; mass spectrum (EI): m/e (%relative intensity) 218 (100) M^+, 190 (63), 176 (15), 135 (90), 107 (16), 77 (16); m/e calcd for $C_{12}H_{10}O_4$ 218.0579, measd 218.0577.

For the Pyrone **16c**:

Rf = 0.46 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 195 - 196 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.93 (s, 3H), 5.55 (d, 1H, J = 1.8 Hz), 6.94 (d, 1H, J = 1.8 Hz), 7.00 (brd, 1H, J = 8.3 Hz), 7.04 (dt, 1H, J = 0.5, 8.3 Hz), 7.40 (ddd, 1H, J = 1.5, 7.5, 10.0 Hz), 7.93 (dd, 1H, J = 1.5, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 55.5, 90.4, 103.3, 111.5, 120.0, 120.6, 128.8, 131.5, 157.3, 164.9, 170.8; IR (neat) cm^{-1} 3583brd, 1780w, 1718s, 1625w, 1558s, 1493m,

1457m, 1372m, 1251s, 1186m, 1060w, 860m; mass spectrum (EI): m/e (%relative intensity) 218 (80) M^+, 190(26), 187 (35), 135 (100), 77 (26); m/e calcd for $C_{12}H_{10}O_4$ 218.0579, measd 218.0579.

For the Pyrone **17a**:

Rf = 0.32 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 200 - 210 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.84 (s, 6H), 5.58 (d, 1H, J = 1.8 Hz), 6.45 (d, 1H, J = 1.8 Hz), 6.55 (t, 1H, J = 2.0 Hz), 6.93 (d, 2H, J = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$/DMSO-d_6) δ 55.7, 90.9, 98.9, 103.6, 104.9, 133.4, 160.5, 161.0, 165.0, 170.6; IR (neat) cm^{-1} 3416s, 1649s, 1454m, 1422m, 1354m, 1241m, 1205m, 1161m; mass spectrum (EI): m/e (%relative intensity) 248 (89) M^+, 220 (18), 206 (46), 165 (100), 124 (6), 92 (5), 77 (6), 32 (13), 28 (46); m/e calculated $C_{13}H_{12}O_5$ 248.0684, measd 248.0682.

For the Pyrone **17b**:

Rf = 0.39 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 183 - 188 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.94 (s, 3H), 3.95 (s, 3H), 5.53 (d, 1H, J = 1.7 Hz), 6.40 (d, 1H, J = 1.7 Hz), 6.88 (d, 1H, J = 8.7 Hz), 7.33 (d, 1H, J = 1.8 Hz), 7.38 (dd, 1H, J = 1.8, 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$/DMSO-d_6) δ 55.7, 55.8, 89.3, 91.0, 108.2, 110.9, 118.8, 123.9, 148.7, 150.9, 160.4, 164.4, 170.7; IR (neat) cm^{-1} 3043s, 2986s, 1648m, 1606m, 1540m, 1421s, 1218m, 1157m, 896s, 754s; mass spectrum (EI): m/e (%relative intensity) 248 (100) M^+, 220 (18), 206 (46), 165 (91), 124 (6), 92 (5), 77 (6), 32 (13), 28 (46); m/e calculated $C_{13}H_{12}O_5$ 248.0684, measd 248.0680.

For the Pyrone **17c**:

Rf = 0.39 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 246 - 265 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.86 (s, 3H), 3.91 (s, 3H), 5.49 (d, 1H, J = 2.0 Hz), 6.52 (d, 1H, J = 2.0 Hz), 6.56 (dd, 1H, J = 2.5, 8.8 Hz), 6.87 (d, 1H, J = 2.5 Hz), 7.90 (d, 1H, 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 55.4, 55.5, 89.6, 98.7, 101.5, 104.9, 112.8, 129.9, 157.4, 158.8, 162.4, 164.9, 171.1; IR (neat) cm^{-1} 3423s, 2950s, 1718s, 1607s, 1542s, 1508m, 1457m, 1260s, 1213m, 1166m, 1024m, 837m; mass spectrum (EI): m/e (%relative intensity) 248 (93) M^+, 220 (27), 165 (100); m/e calculated $C_{13}H_{12}O_5$ 248.0684, measd 248.0679.

For the Pyrone **17d**:

Rf = 0.39 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 164 - 168 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.86 (s, 3H), 3.92 (s, 3H), 5.56 (d, 1H, J = 2.0 Hz), 6.89 (d, 1H, J = 2.0 Hz), 7.01 (dd, 1H, J = 1.5, 8.0 Hz), 7.13 (t, 1H, J = 8.0 Hz), 7.42 (dd, 1H, J = 1.5, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 56.0, 60.6, 91.0, 103.2, 114.3, 120.5, 124.2, 125.7, 147.5, 153.2, 157.7, 165.2, 170.9; IR (neat) cm^{-1} 3378s, 2975s, 2928m, 2898m, 1662m, 1048s; mass spectrum (EI): m/e (%relative intensity) 248 (80) M^+, 220 (18), 206 (40), 165 (90), 124 (6), 92 (5); m/e calculated $C_{13}H_{12}O_5$ 248.0684, measd 248.0688.

For the Pyrone **17e**:

Rf = 0.47 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 218 - 222 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.78 (s, 6H), 5.53 (d, 1H, J = 2.0 Hz), 6.07 (d, 1H, J = 2.0 Hz), 6.58 (d, 2H, J = 9.0 Hz), 7.33 (t, 1H, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 55.9, 55.94, 90.5, 103.8, 105.3, 111.3, 131.6, 157.1, 158.5, 166.2, 170.4; IR (neat) cm^{-1} 3438s, 1654s, 1637s, 1254m, 1129m; mass spectrum (EI): m/e (%relative intensity) 248 (45) M$^+$, 217 (63), 165 (100), 107 (18); m/e calculated $C_{13}H_{12}O_5$ 248.0684, measd 248.2356.

For the Pyrone **18a:**

Rf = 0.14 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 180 - 185 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.77 (s, 3H), 3.80 (s, 6H), 5.44 (d, 1H, J = 2.0 Hz), 6.30 (d, 1H, J = 2.0 Hz), 6.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 56.2, 60.8, 90.3, 98.2, 102.9, 126.8, 140.2, 153.3, 160.5, 165.0, 170.8; IR (neat) cm^{-1} 3423s, 1637s, 1508m, 1130m; mass spectrum (EI): m/e (%relative intensity) 278 (100) M+, 236 (12), 195 (10), 181 (10); m/e calculated $C_{14}H_{14}O_6$ 278.0790, measd 278.0787.

For the Pyrone **18b**:

Rf = 0.36 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 259 - 262 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.88 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.52 (d, 1H, J = 2.3 Hz), 6.75 (d, 1H, J = 9.0 Hz), 6.85 (d, 1H, J = 2.3 Hz), 7.61 (d, 1H, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 56.5, 61.0, 61.3, 89.7, 101.4, 108.7, 118.1, 123.7, 143.0, 152.4, 156.0, 158.0, 163.7, 171.1; IR (neat) cm^{-1} 3412s, 1622s, 1500m, 1295m, 1114m; mass spectrum (EI): m/e (%relative intensity) 278 (100) M+, 236 (22), 195 (23), 181 (15); m/e calculated $C_{14}H_{14}O_6$ 278.278.0790, measd 278.0788.

For the Pyrone **18c**:

Rf = 0.17 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 220 - 226 °C;

^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 3.90 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 5.51 (d, 1H, J = 2.3 Hz), 6.58 (s, 1H), 6.94 (d, 1H, J = 2.3 Hz), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 56.0, 56.2, 56.5, 89.8, 97.0, 102.1, 111.2, 111.6, 143.0, 151.5, 152.9, 157.4, 165.2, 171.2; IR (neat) cm^{-1} 3431s, 1645s, 1553m, 1543m, 1524m, 1351m, 1276m, 1224m; mass spectrum (EI): m/e (%relative intensity) 278 (100) M+, 236 (42), 195 (63), 181 (16); m/e calculated $C_{14}H_{14}O_6$ 278.0790, measd 278.0781.

For the Pyrone **19a:**

Rf = 0.47 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 225 - 229 °C;

^{1}H NMR (500 MHz, 33% DMSO-d_6, $CDCl_3$) δ 5.56 (d, 1H, J = 2.0 Hz), 6.44 (d, 1H, J = 2.0 Hz), 7.14 (m, 2H), 7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 90.4, 98.2, 102.9, 115.8 (d, J = 21.0 Hz), 127.7 (d, J = 8.4 Hz), 159.7, 164.1 (d, J = 250.0 Hz), 164.7, 170.7; IR (neat) cm-1 3417s, 1615s, 1513m, 1219m; mass spectrum (EI): m/e (%relative intensity) 206 (23) M+, 178 (67), 149 (19), 123 (100), 95 (40), 75 (30); m/e caled for $C_{11}H_7O_3F$ 206.0379, measd 206.0382.

For the Pyrone **19b**:

Rf = 0.41 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 214 - 216 °C;
^{1}H NMR (500 MHz, 3% DMSO-d_6, $CDCl_3$) δ 5.59 (d, 1H, J = 2.0 Hz), 6.49 (d, 1H, J = 2.0 Hz), 7.17 (m, 1H), 7.43 (m, 1H), 7.52 (m, 1H), 7.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 91.1, 99.2, 112.6 (d, J = 23.7 Hz), 117.6 (d, J = 21.3 Hz), 121.2 (d, J = 2.9 Hz), 130.4 (d, J = 8.1 Hz), 133.6, 141.6, 160.2 (d, J = 152.0 Hz), 164.5, 170.4; IR (neat) cm^{-1} 3377w, 3019m, 2975s, 2933s, 2916s, 2893s, 1661s, 1450m, 1381s, 1327m, 1243m, 1087s, 1069m; mass spectrum (EI): m/e (%relative intensity) 206 (60) M$^+$, 178 (71), 149 (10), 123 (100), 95 (50), 75 (25); m/e calcd for $C_{11}H_7O_3F$ 206.0379, measd 206.0382.

For the Pyrone **19c**:

Rf = 0.50 (methanol : ethyl acetate : ether 5 : 45 : 50); mp 191 - 195 °C;
^{1}H NMR (500 MHz, 33% DMSO-d_6, $CDCl_3$) δ 5.58 (d, 1H, J = 2.0 Hz), 6.73 (d, 1H, J = 2.0 Hz), 7.16 (m, 1H), 7.26 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 91.2, 103.5 (d, 15.2 Hz), 116.3 (d, J = 22.6 Hz), 119.5 (d, J = 9.5 Hz), 124.5 (d, J = 3.7 Hz), 128.7, 131.9 (d, 9.2 Hz), 156.7 (d, J = 249.0 Hz), 161.7, 164.5, 170.5; IR (neat) cm-1 3386w, 1660s, 1638s, 1627s, 1370m, 835m; mass spectrum (EI): m/e (%relative intensity) 206 (30) M$^+$, 178 (79), 149 (10), 123 (100), 95 (40), 75 (15); m/e calcd for $C_{11}H_7O_3F$ 206.0379, measd 206.0386.

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