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Dedicated to the memory of
Professor Mircea D. Banciu (1941–2005)

2-(α-ARYLOXYACETYL)-PHENOXATHIIN DERIVATIVES. SYNTHESIS AND PROPERTIES

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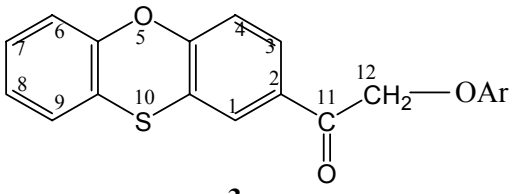
Solid sodium (or potassium) aroxides with various substituents derived from phenols (**1a** = phenol, **1b** = guaiacol, **1c** = 2,6-dimethoxyphenol, **1d** = eugenol, **1e** = (*cis*+*trans*) isoeugenol, **1f** = 4-(3-oxobutyl)-phenol) and **g** = Etoposide cytostatic) were reacted with 2-(α-bromoacetyl)-phenoxathiin (**2**) in the presence of crown ethers (15C5 or 18C6, respectively). The resulting fluorescent title compounds **3a**–**g** were characterized by ^{1}H-NMR and ^{13}C-NMR. The chromatographic behavior of compounds **3a**–**g** was investigated by TLC and reverse-phase-TLC. Calculations for the hydrophobicity of the new compounds are reported.

INTRODUCTION

Phenoxathiin derivatives exhibit interesting biological activities[1-7] and fluorescent properties.[8-15] We present the synthesis and some physico-chemical properties of seven new ethers **3a**–**g** (Tab. 1) with 2-(α-aryloxyacetyl)-phenoxathiin structure. Compounds **3a**–**g** were obtained from solid aroxides of the phenols **1a**–**g** (Tab. 2) with 2-(α-bromoacetyl)-phenoxathiin **2,** in presence of crown ethers suitable for the cation in the aroxide anion. All phenols **1a**–**g** are biologically active compounds, being either natural compounds or drug substructures: compound **1f** is an important component for flavors ("raspberry ketone") and **1g** is the cytostatic Etoposide.[16]

Table 1

The new compounds **3a**–**g**



3a-g

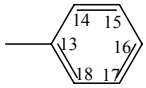
Compound	–Ar in the compound
3a	

Table 1 (continues)

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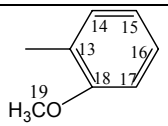
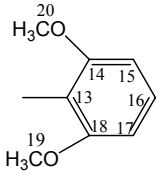
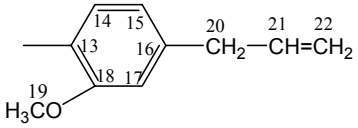
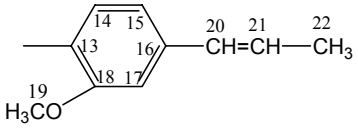
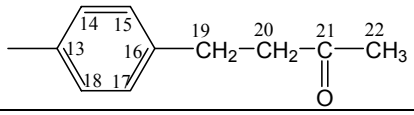
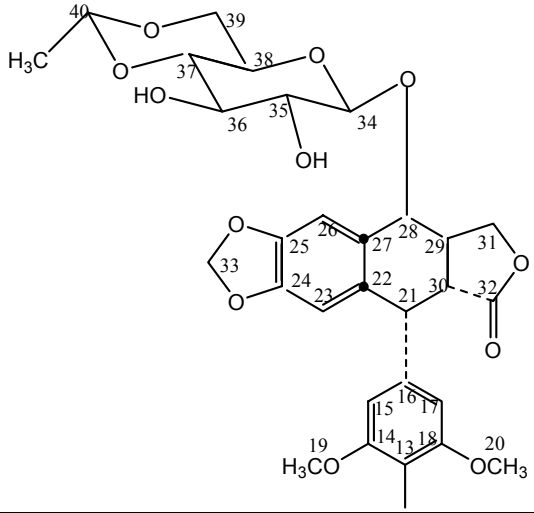
Table 1 (continued)

3b	
3c	
3d	
3e	
3f	
3g	

RESULTS AND DISCUSSION

Synthesis of compounds 3a–g

The starting materials were phenols **1a**–**g** (Table 2) and the bromo-ketone **2**.

For the synthesis of the compounds **3a**–**g** (Tab. 1) we used a two-step procedure described by eqs. 1 and 2.

(i) Phenols **1a, 1c, 1g** (Tab. 2) were converted into the corresponding sodium aroxides,[17] and the phenols **1b, 1d-f** (Tab. 2) into the corresponding potassium aroxides, which were dissolved in methylene chloride, using a crown ether (CE) specific for the cation (15C5 for Na^+, 18C6 for K^+ respectively). The corresponding supramolecular hydrophobic complex $[CE\ldots M]^+ArO^-$ was formed (eq. 1), where the anion ArO^- becomes a very reactive nucleophilic partner.[18,19]

(ii) Then, the addition, at room temperature, of the halide derivative **2** (PT-CO-CH_2Br, where PT means 2-phenoxathiinyl) leads to the fluorescent ethers **3a**–**g** (PT-CO-CH_2OAr, eq. 2) via an S_N2 process. The reaction was monitored for 24 to 96 hours, from case to case, by thin layer chromatography (TLC) and by fluorescence at 366 nm.

(iii) Then the reaction mixture was processed through liquid/liquid extractions, after which the compounds were isolated and purified by preparative TLC on silica gel.

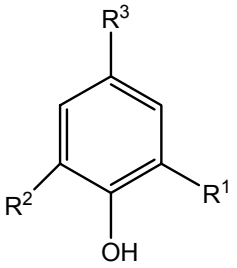
$$ArO^-M^+_{(s)} + CE_{(o)} \rightleftharpoons [CE.....M]^+ArO^-_{(o)} \quad \text{eq. 1}$$

$$[CE.....M]^+ArO^-_{(o)} + PT{-}CO{-}CH_2Br_{(o)} \longrightarrow PT{-}CO{-}CH_2{-}OAr_{(o)} + [CE.....M]^+Br^-_{(o)} \quad \text{eq. 2}$$

Subscripts *s* and *o* indicate solid and organic phases, respectively.

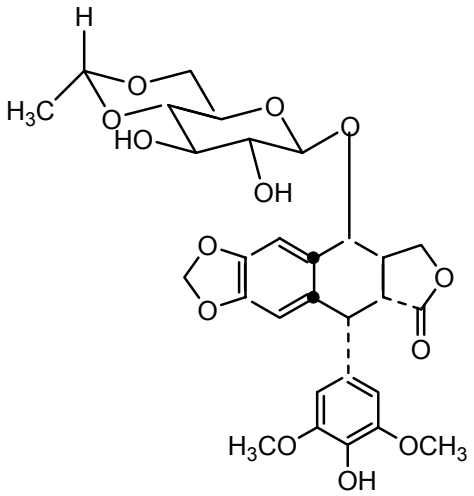
Table 2

The phenols **1a-f** used in synthesis



1a-f

Compound	R^1	R^2	R^3
Phenol, **1a**	H	H	H
Guaiacol, **1b**	OCH_3	H	H
2,6-Dimethoxyphenol, **1c**	OCH_3	OCH_3	H
Eugenol, **1d**	OCH_3	H	CH_2-CH=CH_2
Isoeugenol, **1e**	OCH_3	H	HC=CH-CH_3 (*E* + *Z*)
4-(3-Oxobutyl)-phenol, **1f**	H	H	H_2C-CH_2-CO-CH_3



1g

NMR Spectra of compounds 3a–g

The NMR data confirmed the structures of the new compounds **3a**–**g** by identifying: (i) the presence of the phenoxathiin moiety; (ii) the presence of the phenyl ring and of the substituents (MeO groups for **3b**–**e** and **3g** in C-14, C-18 positions; allyl in C-16 position for **3d,** propenyl for **3e**, butanone for **3f**, and the groups of cytostatic Etoposide moiety for **3g**); (iii) the presence of the methylene (C-12) and carbonyl (C-11) groups in the fragment –O–CH_2–CO– from the bromo-ketone **2**. In the ^{13}C-NMR spectra the signal of the C-12 carbon atom of the methylene group is shifted to higher chemical shift values, depending of the number and position of MeO groups (C-14 and C-18) on the phenyl ring (probably due to steric hindrance): δ (C-12) **3a, 3f**< δ (C-12) **3b, 3d, 3e**< δ (C-12) **3c, 3g**.

Table 3

^{1}H-NMR and ^{13}C-NMR data of compounds **3a**–**g**

Compound	NMR-spectra in $CDCl_3$ [a,b] (δ, ppm, *J* Hz)
3a	**^{1}H-NMR**: 5.16 (s, 2H, H-12); 6.94 (dd, 2H, H-14,18, 1.0, 8.8); 6.92-7.08 (m, 5H, H-4,6,8,9,16); 7.13 (ddd, 1H, H-7, 2.3, 6.6, 8.0); 7.29 (dd, 2H, H-15,17, 7.4, 8.8); 7.77 (dd, 1H, H-3, 2.1, 8.4); 7.74 (d, 1H, H-1, 2.1). **^{13}C-NMR**: 192.72 (C-11); 157.93 (Cq); 156.05 (Cq); 150.88 (Cq); 131.17 (Cq); 120.90 (Cq); 118.63 (Cq); 129.62 (CH); 128.43 (CH); 128.05 (CH); 127.16 (CH); 126.79 (CH); 125.23 (CH); 121.76 (CH); 117.87 (CH); 117.83 (CH); 114.82 (CH); 70.84 (C-12).
3b	**^{1}H-NMR**: 3.88 (s, 3H, H-19); 5.21 (s, 2H, H-12); 6.85 (m, 2H, H-15,18); 7.08- 6.88 (m, 6H, H-4,6,8,9,16,17); 7.13 (ddd, 1H, H-7, 2.3, 6.7, 8.0); 7.79 (dd, 1H, H-3, 2.1, 7.6); 7.81 (d, 1H, H-1, 2.1); **^{13}C-NMR**: 192.91 (C-11); 155.93 (Cq); 150.92 (Cq); 149.89 (Cq); 147.43 (Cq); 131.27 (Cq); 120.71 (Cq); 118.70 (Cq); 128.48 (CH); 128.00 (CH); 127.32 (CH); 126.77 (CH); 125.18 (CH); 122.66 (CH); 120.84 (CH); 117.86 (CH); 117.76 (CH); 115.13 (CH); 112.29 (CH); 72.40 (C-12); 55.91 (C-19).
3c	**^{1}H-NMR:** 3.82 (s, 6H, H-19,20); 5.06 (s, 2H, H-12); 6.56 (d, 2H, H-15,17, 8.4); 7.09-6.95 (m, 5H, H-4,6,8,9,16); 7.09-6.96 (m, 5H, H-4,6,8,9,16); 7.13 (ddd, 1H, H-7, 2.1, 6.8, 8.0); 7.86 (dd, 1H, H-3, 2.0, 8.5); 7.93 (d, 1H, H-1, 2.0). **^{13}C-NMR**: 193.46 (Cq); 155.61 (Cq); 153.22 (C-14-18); 151.06 (Cq); 131.86 (Cq); 120.22 (Cq); 118.94 (Cq); 128.76 (CH); 127.93 (CH); 127.81 (CH); 126.75 (CH); 125.07 (CH); 124.23 (CH); 117.85 (CH); 117.60 (CH); 105.33 (CH); 75.55 (C-12); 56.05 (C-19-20).
3d	**^{1}H-NMR**: 3.32 (dt, 2H, H-20, 6.7, 1.7); 3.87 (s, 3H, H-19); 5.07 (dq, 1H, H-22-*trans*, 18.8, 1.7); 5.08 (dq, 1H, H-22-*cis*, 8.6, 1.7); 5.18 (s, 2H, H-12); 5.94 (tdd, 1H, H-21, 6.7, 8.6, 18.8); 6.66 (dd, 1H, H-17, 2.0, 8.1); 6.73 (d, 1H, H-15, 2.0); 6.77 (d, 1H, H-18, 8.1); 7.13 (ddd, 1H, H-7, 2.1, 6.8, 8.0); 7.09- 6.96 (m, 4H, H-4,6,8,9); 7.79 (dd, 1H, H-3, 2.1, 8.6); 7.81 (d, 1H, H-1, 2.1). **^{13}C-NMR**: 193.09 (C-11); 155.92 (Cq); 150.92 (Cq); 149.74 (Cq); 145.74 (Cq); 137.42 (Cq); 134.65 (Cq); 131.30 (Cq); 120.68 (Cq); 128.49 (CH); 128.00 (CH); 127.34 (CH); 126.77 (CH); 125.17 (CH); 120.52 (CH); 117.86 (CH); 117.75 (CH); 115.20 (C-21); 115.09 (C-21); 115.20 (CH); 112.70 (CH); 72.61 (C-12); 55.88 (C-19); 39.83 (C-16).
3e	**^{1}H-NMR**: 7.80 (d, 1H, H-1, 2.1); 7.79 (dd, 1H, H-3, 2.1, 7.9); 7.13 (ddd, 1H, H-7, 2.3, 6.9, 7.9); 7.08-6.96 (m, 4H, H-4,6,8,9); 6.89 (d, 1H, H-15, 1.9); 6.79 (dd, 1H, H-17, 1.9, 8.3); 6.74 (d, 1H, H-18, 8.3); 6.31 (dq, 1H, H-20, 15.7, 1.6); 6.10 (dq, 1H, H-21, 15.7, 6.6); 5.19 (s, 2H, H-12); 3.89 (s, 3H, H-19); 1.85 (dd, 3H, H-22, 1.6, 6.6). **^{13}C-NMR**: 193.14 (C-11); 155.96 (Cq); 151.12 (Cq); 150.21 (Cq); 146.88 (Cq); 146.81 (Cq); 133.36 (Cq); 131.70 (Cq); 120.74 (Cq); 130.67 (CH); 128.65 (CH); 127.99 (CH); 127.53 (CH); 126.80 (CH); 125.16 (CH); 124.61 (CH); 118.80 (CH); 117.89 (CH); 117.72 (CH); 115.88 (CH); 110.26 (CH); 73.08 (C-12); 56.10 (C-19); 18.16 (C-22).
3f	**^{1}H-NMR**: 8.04 (dd, 1H, H-3, 8.3, 2.1); 8.01 (d, 1H, H-1, 2.1); 7.41 (ddd, 1H, H-7, 2.2, 6.7, 7.9); 7.37-7.24 (m, 4H, H-4,6,8,9); 7.30 (d, 2H, H-15,17, 8.6); 7.12 (d, 2H, H-14,18, 8.6); 5.40 (s, 2H, H-12); 3.09 (m, 2H, H-20, A_2B_2 system); 2.98 (m, 2H, H-19, A_2B_2 system); 2.39 (s, 3H, H-22). **^{13}C-NMR**: 205.45 (C-21); 192.84 (C-11); 156.41 (Cq); 156.37 (Cq); 156.05 (Cq); 137.29 (Cq-16); 131.23 (Cq); 120.90 (Cq); 118.64 (Cq); 129.39 (CH); 128.44 (CH); 128.06 (CH); 127.17 (CH); 126.79 (CH); 125.23 (CH); 117.89 (CH); 117.82 (CH); 114.93 (CH); 114.89 (CH); 71.07 (C-12); 45.29 (C-19); 30.04 (C-22); 28.91 (C-20).

Table 3 (continues)

Table 3 (continued)

3g	**[1]H-NMR**: 7.88 (d, 1H, H-1, 2.1); 7.82 (dd, 1H, H-3, 2.1, 8.4); 7.30-6.96 (m, 5H, H-4,6,7,8,9); 6.83 (s, 1H, H-23 or H-26); 6.54 (s, 1H, H-26 or H-23); 6.24 (s, 2H, H-33); 6.00 (d, 1H, H-15 or H-17, 1.3); 5.98 (d, 1H, H-17 or H-15, 1.3); 5.01 (s, 2H, H-12); 4.92 (d, 1H, H-34, 3.4); 4.75 (q, 1H, H-40, 5.1); 4.63 (d, 1H, H-29, 7.6); 4.60 (d, 1H, H-36, 5.2); 4.41 (dd, 1H, H-31A, AB system, 8.9, 10.7); 4.24-4.17 (m, 2H, H-31B, H-35); 3.68-3.23 (m, 5H, H-21-37-38-39); 3.69 (s, 3H, H-19 or H-20); 3.68 (s, 3H, H-20 or H-19); 2.90 (m, 1H, H-29); 1.39 (d, 3H, H-41, 5.1). **[13]C-NMR**: 193.50 (C-11); 174.55 (C-32); 155.65 (Cq); 153.47 (Cq); 152.49 (Cq); 151.25 (Cq); 148.98 (Cq); 147.39 (Cq); 135.69 (Cq); 132.81 (Cq); 132.23 (Cq); 128.59 (Cq); 120.29 (Cq); 119.14 (Cq); 128.91 (CH); 127.92 (Cq); 126.78 (Cq); 125.05 (Cq); 117.86 (Cq); 117.54 (Cq); 110.76 (Cq); 109.75 (Cq); 109.15 (Cq); 109.00 (Cq); 102.24 (Cq); 101.62 (C-33); 99.89 (C-40); 80.01 (C-34); 75.73 (C-12); 75.44 (CH); 74.78 (CH); 73.97 (CH); 73.45 (CH); 68.12 (CH2); 67.83 (CH2); 66.69 (C-28); 55.47 (C-19-20); 44.06 (C-21); 41.27 (C-30); 37.81 (C-29); 20.27 (C-41).

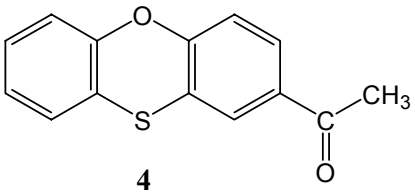
[a] At about 295K and with TMS as internal standard.
[b] The numbering of compounds **3a**-**g** as in Tab. 1.

Hydrophobicity/hydrophilicity of compounds 3a–g

The hydrophobicity/hydrophilicity balance of compounds **3a–g** is very important for their biomedical applications: the hydrophobicity/hydrophilicity determines how substances interact with biomembranes and receptors, influencing their bioavailability and biospecificity. The octanol-water partition coefficient (*P*) and its logarithm (log *P*) are the usual parameters for estimating quantitatively these characteristics,[20] and they can be measured or computed. In our case, this property for compounds **3a–g** was studied experimentally by reversed phase TLC (RP-TLC) and compared with phenols **1a–g** and compounds **2, 4** (2-acetylphenoxathiin), and **5** (phenoxathiin). Thus, R_f values were measured, using precoated C_{18}-chain layers as stationary phases and different ethanol-water mixtures as mobile phases (Tab. 4). The hydrophobicity was appreciated as a result of experimental data depending on R_{M0} values calculated[21-24] with eqs. 3 and 4 were: R_{M0} (the molecular hydrophobicity) is the R_M value extrapolated to zero concentration of organic component in the alcohol-water mixture; *b* is the change in the R_M value caused by increasing the concentration (*K*) of the organic component in the mobile phase. Statistical analysis involved the correlation coefficient (*r*), the Fisher parameter[25-27] (*F*), and the standard deviation (*SD*) (Tab. 4).

$$R_M = \log(1/R_f - 1) \quad \text{eq. 3}$$

$$R_M = R_{M0} + bK \quad \text{eq. 4}$$



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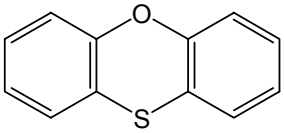

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Table 4

R_f values and hydrophobic characteristics (R_{M0} and *b*) of compounds **1a–g, 2, 3a–g, 4** and **5**. RP-TLC results for five ethanol-water mixtures (A–E) [a,b]

Compound	R_f					Hydrophobic Characteristics		Statistical parameters		
	A	B	C	D	E	R_{M0}	*b*	*r*	*F*	*SD*
1a	0.944	0.891	0.861	0.819	0.777	1.948	-0.032	-0.973	54.650	0.069
1b	0.930	0.891	0.847	0.805	0.763	1.821	-0.030	-0.990	156.727	0.038
1c	0.916	0.851	0.833	0.791	0.736	1.623	-0.027	-0.970	49.204	0.061
1d	0.888	0.810	0.777	0.736	0.680	1.653	-0.026	-0.973	53.996	0.056

Table 4 (continues)

Table 4 (continues)

1e	0.861	0.783	0.75	0.694	0.555	2.255	-0.031	-0.982	81.120	0.056
1f	0.680	0.638	0.625	0.567	0.527	0.981	-0.013	-0.988	125.798	0.019
1g	0.944	0.918	0.888	0.847	0.805	1.683	-0.030	-0.997	700.129	0.018
2	0.722	0.608	0.555	0.430	0.388	2.536	-0.030	-0.987	117.330	0.044
3a	0.675	0.636	0.5	0.378	0.297	3.137	-0.036	-0.990	148.771	0.047
3b	0.689	0.666	0.542	0.418	0.337	2.871	-0.034	-0.984	96.652	0.055
3c	0.689	0.666	0.528	0.418	0.351	2.779	-0.033	-0.984	91.678	0.055
3d	0.648	0.606	0.385	0.297	0.216	3.895	-0.044	-0.982	85.007	0.075
3e	0.635	0.575	0.357	0.256	0.189	4.174	-0.046	-0.986	107.087	0.071
3f	0.714	0.638	0.555	0.416	0.277	3.397	-0.040	-0.990	151.600	0.051
3g	0.891	0.848	0.728	0.675	0.594	2.756	-0.038	-0.986	104.918	0.059
4	0.666	0.567	0.513	0.416	0.388	2.119	-0.025	-0.985	104.814	0.038
5	0.638	0.5	0.430	0.333	0.277	2.884	-0.032	-0.991	168.387	0.039

[a] Five determinations on silica gel RP-18F_{254S} (Merck), with percent of ethanol in mixture ethanol-water: A = 95, B = 90, C = 85, D =80, E = 75%.
[b] R_{M0}, b, r, F, and SD are defined by the preceding text and eqs. 3 and 4.

In attempting to calculate log P values using fragmental constants,[20] a fair correlation (r =0.846) with experimental data for R_{M0} was obtained for the series **3a**–**g** (Fig. 1).

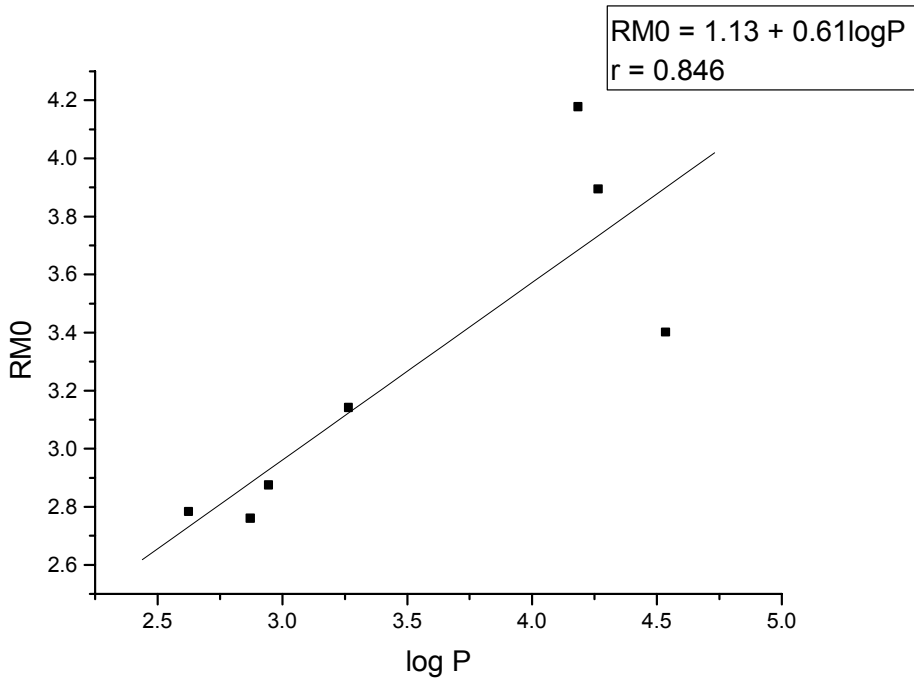


Fig. 1 – R_{M0} *vs* logP for compounds **3a-g**.

The 2-acetylphenoxathiin moiety is relatively hydrophobic, with log P = 1.08, conferring hydrophobicity to compounds **3a**–**g**. The experimental results concerning the hydrophobic/hydrophilic character (R_{M0} values, Tab. 4) allowed the following observations: (i) compared with phenols **1a**–**g**, the ethers **3a**–**g** are more hydrophobic (due to the acetylphenoxathiin moiety); (ii) the hydrophobicity of compounds **3a**–**g** decreases in order R_{M0} **3e**> R_{M0} **3d**> R_{M0} **3f**> R_{M0} **3a**> R_{M0} **3b**> R_{M0} **3c**> R_{M0} **3g** depending on the groups present in the molecule; (iii) the hydrophobicity depends on the number of methoxy groups (R_{M0} **3a**> R_{M0} **3b**> R_{M0} **3c**, with the hydrophilicity increasing obviously in reverse order); (iv) allyl and propenyl moieties increase hydrophobicity (R_{M0} **3e**> R_{M0} **3d**>R_{M0} **3b**); (v) the butanone moiety increases hydrophobicity (R_{M0} **3f**> R_{M0} **3a**) and (vi) the hydrophobicity of compound **3g** is the smallest (the hydrophilicity is highest), due to the glycoside moiety.

The thin-layer chromatographic behavior of compounds 3a–g

The TLC behavior was investigated because this characteristic has practical and theoretical importance. For this purpose we have chosen pure solvents with different values of the $E_T(30)$ (Dimroth-Reichardt`s) parameter,[28] as well as a mixture chloroform/toluene/methanol which allows the evaluation of compound **3g** (Tab. 5).

Table 5

TLC behavior (R_f) [a] of compounds **3a**–**g** on silica gel 60 GF_{254} plates (Merck) with five mobile phases (solvents with different $E_T(30)$ values)[28]

Comp.	1,2-Dichloroethane $E_T(30)$ = 41.9	Dichloromethane $E_T(30)$ = 41.1	Chloroform $E_T(30)$ = 39.1	Toluene $E_T(30)$ = 33.9	Chloroform: toluene: methanol=6.5:3:0.5 v/v
3a	0.933	0.915	0.901	0.417	0.986
3b	0.760	0.603	0.524	0.095	0.959
3c	0.605	0.377	0.205	0.041	0.932
3d	0.802	0.650	0.573	0.109	0.973
3e	0.818	0.698	0.590	0.109	0.979
3f	0.760	0.509	0.418	0.054	0.905
3g	0.040	0.014	0	0	0.310

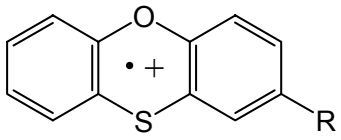
[a] For five determinations.

The experimental results for compounds **3a**–**g** with pure solvents (Tab. 5) can be interpreted as follows: (i) in chlorinated solvents the R_f values depend on the solvent polarity ($E_T(30)$ values) and decrease in the following order: 1,2-dichloroethane> dichloromethane> chloroform; (ii) the groups present in the molecule modify the R_f values (R_f **3a**> R_f **3e**≥ R_f **3d**> R_f **3b**≥ R_f **3f**> R_f **3c**> R_f **3g**) and (iii) the R_f value for compound **3g** is relatively high (R_f = 0.310) only in the mixed solvent which contains methanol, because of its numerous hydroxyl groups.

Other properties. Qualitative experiments

The newly synthesized compounds **3a**–**g** have yellow to blue fluorescence (excited at 366 nm) in solution and in solid state (TLC detection). The compounds **3a**–**g** with Fe^{3+} salts are not colored, but the phenols **1a**–**g** are colored (TLC detection spraying with ethanolic solution of Fe^{3+} salts).

In the presence of concentrated sulfuric acid, compounds **3a**–**g** have blue-purple colors, unlike compounds **2** (purple), **4** (red), and **5** (blue); this behavior indicates a structural dependence of the electronic absorption spectra of the free cation-radicals **6** formed in sulfuric acid,[13,14,29,30] depending on the substituent R.



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Fluorescent and color characteristics, in presence of sulfuric acid, will be discussed in more detail in a separate paper.

CONCLUSIONS

New keto-ethers 2-(α-aryloxyacetyl)-phenoxathiin **3a**–**g** were prepared starting from the aroxides corresponding to phenolic compounds **1a**–**g** and the halogenated derivative **2**, involving a S_N2 type mechanism mediated by a crown ether in methylene chloride. The cation of the aroxide corresponded to the size of the crown ether. The structures of the compounds **3a**–**g** were confirmed by ^1H- and ^{13}C-NMR spectra. The hydrophobicity/

hydrophilicity properties were investigated through reverse phase thin-layer chromatography (RP-TLC), and a fair correlation with calculated log *P* values was found. The TLC behavior was also investigated.

EXPERIMENTAL PART

Starting compounds for synthesis, **1a–d, 1e** (*cis-trans*), and crown ethers (15C5 and 18C6) were from Merck, Darmstadt. Compounds **1f** and **5** were Aldrich products. Compound **1g** was supplied by the Romanian pharmaceutical company, Sindan. Aroxides of the phenols **1a–g** were prepared according to literature data.[17] Compounds **2**[8,9,31,32] and **4**[33] were obtained as previously described. Silica gel plates 60 GF_{254} (for TLC) and silica gel RP-18 F_{254S} (for RP-TLC) were from Merck, Darmstadt.

^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian Gemini 300 BB spectrometer (300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR).

Synthesis of compounds 3a–g. General procedure.

The molar ratio of the reactants, aroxides[17] corresponding to the phenols **1a-g**: **2**: CE was 1.5: 1: 1.5 The solid aroxides were dissolved under stirring in methylene chloride (50mL for 1g solid aroxides) by addition of crown ether 15C5 (for sodium aroxides of phenols **1a, 1c**, **1g**) and 18C6 (for potassium aroxides of phenols **1b, 1d–f**). Then the halogen derivative **2** was added and the mixture was stirred at room temperature: 24h for **3a** and **3c**; 72h for **3d** and **3e**; 96h for **3b**, **3f** and **3g**. The reaction mixture was washed twice with hydrochloric acid (1N) and the twice with sodium hydroxide (1N). The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was removed using a rotary evaporator. The crude compound was dissolved in methylene chloride and then was purified by preparative TLC on silica gel GF_{254} plates using as mobile phases: (i) a mixture of methylene chloride/n-hexane 1/1 v/v one time for **3a**; (ii) methylene chloride one time for **3b, 3d**, **3e** and three times for **3f**; (iii) a mixture of methylene chloride/n-hexane 7/3 v/v one time for **3c** and (iv) mixture of chloroform/toluene/methanol 6.5/3/0.5 v/v six times for **3g**. The extraction (Soxhlet apparatus) of the major fluorescent zone from the silica gel strip was performed with a methylene chloride/methanol mixture (9/1 v/v).

3a, *2-(α-Phenyloxyacetyl)-phenoxathiin*, 73.3% yield; yellow solid, m.p. 110-111°C; Anal.: Calcd.% for $C_{20}H_{14}O_3S$: C 71.84; H 4.22; found% C 71.64; H 4.19.

3b, *2-(α-2-Methoxyphenyloxyacetyl-)phenoxathiin*, 58.4% yield; yellow solid, m.p. 103-104°C; Anal.: Calcd.% for $C_{21}H_{16}O_4S$: C 69.21; H 4.43; found% C 69.15; H 4.38.

3c, *2-(α-2,6-Dimethoxyphenyloxyacetyl)-phenoxathiin*, 53.4% yield; white solid, m.p. 140.5-141.5°C; Anal.: Calcd.% for $C_{22}H_{18}O_5S$: C 66.99; H 4.60; found% C 66.90; H 4.56.

3d, *2-(α-4-Allyl-2-methoxyphenyloxyacetyl)-phenoxathiin*, 52.3% yield; dark-yellow semi-solid material; Anal.: Calcd.% for $C_{24}H_{20}O_4S$: C 71.27; H 4.98; found% C 71.20; H 4.91.

3e, *2-(α-2-Methoxy-4-(E+Z)-propenylphenyloxyacetyl)-phenoxathiin*, 84.4% yield; yellow solid, m.p. 95.5-96.5°C; Anal.: Calcd.% for $C_{24}H_{20}O_4S$: C 71.27; H 4.98; found% C 71.18; H 4.88.

3f, *2-(α-4-(3-oxobutyl)-phenyloxyacetyl)-phenoxathiin*, 79.1% yield; white solid, m.p. 113.5-114.5°C; Anal.: Calcd.% for $C_{24}H_{20}O_4S$: C 71.27; H 4.98; found% C 71.20; H 4.93

3g *Etoposide-yl 2-(α-acetylphenoxathiin) ether*, 21.8% yield; white solid, m.p. 150-154°C; Anal.: Calcd.% for $C_{43}H_{40}O_{15}S$: C 62.31; H 4.86; found% C 62.26; H 4.79.

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