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An efficient and convenient microwave-assisted chemical synthesis of (thio)xanthones with additional in vitro and in silico characterization

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Keywords: xanthones, microwave synthesis, Lewis acid, antibacterial, cytotoxicity

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ABSTRACT

Xanthones and their thio-derivatives are a class of pleiotropic compounds with various reported pharmacological and biological activities. Although these activities are mainly determined in laboratory conditions, the class itself has a great potential to be utilized as promising chemical scaffold for the synthesis of new drug candidates. One of the main obstacles in utilization of these compounds was related to the difficulties in their chemical synthesis. Most of the known methods require two steps, and are limited to specific reagents not applicable to a large number of starting materials. In this paper a new and improved method for chemical synthesis of xanthones is presented. By applying a new procedure, we have successfully obtained these compounds with the desired regioselectivity in a shorter reaction time (50 s) and with better yield (> 80%). Finally, the preliminary in vitro screening on different bacterial species and cytotoxicity assessment, as well as in silico activity evaluation were performed. The obtained results are in line with potential pharmacological use of this class of molecules.
Keywords: xanthones, microwave synthesis, Lewis acid, antibacterial, cytotoxicity

Abbreviations: MW - microwave
1. INTRODUCTION

Many plants are known to have pharmacological properties and have been used in traditional medicine for the treatment of numerous ailments and diseases since ancient times. Various plants have been used for religious purposes and some of them in mystical rituals.\textsuperscript{1} Although these plants have exhibited healing effects in some populations and in many conditions, the clear pharmacological bases of these actions still remain to be fully elucidated. Since pharmaceutical companies are on a continual quest for new active compounds, in recent years many attempts have been focused on the utilization of natural biodiversity of traditional medicinal plants’ constituents by applying virtual and biological screening approaches to detect their therapeutic potentials.\textsuperscript{2}

The main objective of this paper is to present the synthesis optimization of the naturally occurring compounds. Synthetic variants can be further optimized to enhance their biological activity and improve their selectivity and safety. The obtained compounds can be considered as new promising hits for subsequent research and development of novel pharmacophores.\textsuperscript{3}

Xanthones are a group of heterocyclic compounds containing a dibenzo-\(\gamma\)-pyrone skeleton (\textbf{Fig. 1}).

These secondary metabolites are found in higher plant families such as \textit{Guttiferae} and \textit{Gentianaceae}\textsuperscript{4,5} and they also occur in fungi, lichens and ferns.\textsuperscript{6} The growing interest in the natural and synthetic xanthones is due to their pharmacological and biological activities,\textsuperscript{7-10} like antibacterial, anti-inflammatory and modulators of glucose
metabolism,\textsuperscript{11} anticancer\textsuperscript{12} and antiviral.\textsuperscript{9} Their antioxidant potential makes them feasible for utilization as nutritional supplements in order to prevent premature ageing and ameliorate conditions in chronic inflammatory diseases.\textsuperscript{9}

Thioxanthones, their synthetic analogues that are not found in nature, have also been found to exhibit pharmacologic characteristics\textsuperscript{13-21} such as antihistaminic, antiparasitic, neuroleptic, and antiproliferative properties.\textsuperscript{22} Hydroxyl thioxanthones are particularly useful as heat and ultraviolet stabilizers for polyolefins.\textsuperscript{19} Acetylation of hydroxy xanthones and thioxanthones can further enhance their biological activities.\textsuperscript{23, 24}

Monohydroxyxanthones, such as 1-hydroxyxanthone, are reported in the literature as monoamine oxidase inhibitors,\textsuperscript{25, 26} α-glucosidase inhibitors\textsuperscript{27, 28} and exhibit antioxidant properties.\textsuperscript{29} Of the dihydroxyxanthones, 1,3-dihydroxyxanthone possesses antimalarial activity,\textsuperscript{30} antihypertensive activity\textsuperscript{31} and can inhibit α-glucosidase.\textsuperscript{27, 28} The same has been reported for 1,3-diaceotoxyxanthone and in addition, this compound can inhibit Na/K-ATPase.\textsuperscript{32} Likewise, its analogue, 1,6-dihydroxyxanthone, possesses antihypertensive activity\textsuperscript{31} and can inhibit α-glucosidase.\textsuperscript{27, 28} Trihydroxyxanthones, like 1,3,5-trihydroxyxanthone, has shown anticancer\textsuperscript{33} and antimalarial activity.\textsuperscript{30} The same compound tested \textit{in vitro} exhibited antiviral activity on HIV-1-infected MT-4 cells and MDCK cells infected with influenza virus.\textsuperscript{34} Trihydroxyxanthones have also been shown to be monoamine oxidase\textsuperscript{25, 26} and Na/K-ATPase inhibitors.\textsuperscript{32} Finally, 1,3,7-trihydroxyxanthone also shows anticancer activity\textsuperscript{33} and possesses monoamine oxidase,\textsuperscript{25, 26} α-glucosidase\textsuperscript{27, 28} and fatty acid synthase inhibitory activity.\textsuperscript{35}
Synthetically, xanthones are usually obtained by chemical synthesis from benzophenones or diaryl ethers under harsh reaction conditions and/or in the presence of strong acids or toxic metals.\(^{36}\)

In the literature, different methods have been reported\(^{37-42}\) so far for the synthesis of xanthones, with varying yields. Base catalyzed cyclisation of a substituted benzophenone precursor to obtain some polymethoxyxanthones has also been reported, but the yields were low.\(^{38}\) However, when the same precursor was heated for 72 h in the presence of tetramethylammonium hydroxide/pyridine/H\(_2\)O, the yield improved.\(^{43}\) This reaction was also carried out applying microwave (MW) irradiation\(^ {44}\) during 13 minutes. Finally, the synthesis of thioxanthones and substituted thioxanthones has also been carried out using different methods.\(^ {13,15-20}\)

The above mentioned methods suffer from one or another disadvantage such as low yields, long reaction times, the use of large amounts of concentrated sulfuric acid, and lack of regiochemical control in the ring closure step. Moreover, most of these methods require two steps, are limited to specific benzoic acids or benzene derivatives having electron-withdrawing groups and are not applicable to a large number of starting materials.

Bearing all this in mind and taking into consideration the pharmacological importance of xanthones, thioxanthones and their acetyl derivatives, we have developed and report here a simple methodology to obtain hydroxyxanthones and hydroxythioxanthones in a short time using MW irradiation. Moreover, this paper also includes the \textit{in vitro} screening on different bacterial species and cytotoxicity assessment as well as preliminary \textit{in silico} evaluation of their potential biological targets.
2. Results and discussion

2.1. Synthesis

Herein we report the modified microwave synthesis of hydroxy xanthones and thioxanthones (Scheme 1).

In the modified synthesis, a homogenous mixture of resorcinol/phloroglucinol, substituted salicylic acids and a Lewis acid AlCl3/ZnCl2/TiCl4/SnCl2, was subjected to microwave irradiation using CEM Discover Model 908010 at a power of 200W, with continuous stirring to obtain the required xanthone(s) with good yield (Table 1) without the formation of any side products, which was confirmed by TLC and HPTLC. The use of a Lewis acid under microwave irradiation reduces the reaction time from 13 min to just 50 s. Of all the Lewis acids, SnCl2 was found to be the most efficient with xanthone yields of 80-84%. Compounds 1a-h were then acetylated separately using acetic anhydride in DMAP under dry conditions to obtain acetyl derivatives 2a-h in quantitative yield. The method has also been extended to the synthesis of thioxanthones.

2.2. In vitro biological screening

Experimentally, the synthesized compounds have been assessed in terms of their antibacterial potency as well as cytotoxicity, the two major concerns associated with potential preventive or curative drugs that are intended for prolonged use.
The determined antibacterial and cytotoxic activities are presented in the Table 2. The majority of compounds showed no effects on the growth of the microorganisms tested. However, several compounds exhibited weak antibacterial activity on *M. catarrhalis*, *S. aureus* and *H. influenzae*. In order to improve antibacterial activity of these few compounds, the exact mode of action should be clarified and the compounds have to be further derivatised.

The cytotoxic activity was assessed on a HepG2 (hepatocytes) and Jurkat (T lymphocytes) cell lines that are used to determine potential inhibitory effects on cell metabolism. The test measures cellular metabolic activity by assessing NADH levels, thus indicating whether the compounds impair any of the key metabolic pathways. An encouraging result was obtained in that none of the compounds tested exhibited any significant inhibition on the HepG2 or Jurkat within 24 h, suggesting that the compounds could be used as potential hits for further derivatisation in order to further optimize their biological activities.

### 2.3. *In silico* analysis

All compounds were additionally subjected to a similarity search for potential biological activity in order to identify their additional “hidden” values and to create conditions for further exploration of their pharmacological effects. Such an approach is currently widely accepted by the pharmaceutical industry.\(^{45}\)

By combining computational and biological methods, positive and reliable hits could be detected in a very short time-frame by using small amounts of reagents. In this way, the
whole early stage drug discovery process known as “hit generation” can be performed utilizing minimal resources and any duplication work can be avoided.\textsuperscript{46} Considering simple structural characteristics and lipophilicity, the synthesized hydroxy xanthones/thioxanthones are drug-like molecules satisfying the Rule of Five.\textsuperscript{47} According to the calculated lipophilicity clogP coefficients, all molecules have moderate lipophilicity. In addition, all considered polyphenolic derivatives are weakly acidic compounds (ACD (Advanced Chemistry Development, www.acdlabs.com) with $pK_a$ values $\sim 7$ as calculated using ChEMBL (www.ebi.ac.uk/chembl/). This can affect their ADME properties like binding to plasma protein human serum albumin.\textsuperscript{48} Regarding anti-infective activities, only antihelmintic activity ($Pa > 0.6$) of studied thioxanthones were predicted by PASS in accordance with reported experimental observations (\textit{Tables 3 and 4}).\textsuperscript{49} According to PASS predictions the most plausible human biological targets of hydroxylated xanthones are oxidoreductases, particularly CYP450 isoforms ($Pa > 0.9$), similar to other planar polyphenols such as quercetin. Other targets pointed out by program PASS may be involved in glucose and lipids metabolism and homeostasis, e.g. chlordecone reductase and UDP-glucuronosyltransferase. All molecules have been predicted to be membrane integrity agonists and permeability inhibitors ($Pa > 0.9$). The predicted membrane activity is in accordance with already experimentally detected activities on the membrane localized targets lysosomal $\alpha$-glucosidase\textsuperscript{50} and mitochondrial monoamine oxidases.\textsuperscript{25} In addition to metabolic targets, PASS predictions ($Pa > 0.8$) indicate that these compounds could bind to kinases such as protein kinase C zeta and PI3-kinase subunit gamma.
By PASS, fewer activities for hydroxy thioxanthone derivatives have been predicted in comparison with the xanthone analogues. This is due to their lower structural similarity with the compounds with known activities used in the PASS training set.\textsuperscript{51} In that respect, the studied thioxanthones can be considered the “newest” chemical entities. They were not predicted to have CYP450 activities but they do also target enzymes related to xenobiotic metabolism. Thioxantones have been suggested as chemopreventive agents (predicted with Pa = 0.500, Pi = 0.019).\textsuperscript{22} According to the Molinspiration predictions, acetyl derivatives appeared to be potential nuclear receptor ligands.

3. CONCLUSIONS

A series of (poly)hydroxylyxanthones and their acetyl derivatives have been successfully synthesized in moderate to high yields by using the microwave approach along with Lewis acids AlCl$_3$, ZnCl$_2$, TiCl$_4$ or SnCl$_2$ during just 50 s. Out of the four explored Lewis acids, SnCl$_2$ was found to be most efficient with xanthone yields of 80-84\%.

The (poly)hydroxyl-xanthones and their thio-analogs shown no significant HepG2 or Jurkat cytotoxicity and majority have no anti-bacterial activities on 6 bacterial strains tested.

The \textit{in silico} predictions based on the program PASS indicate that these xanthone derivatives possess the potential to target membrane associated proteins, particularly those with redox activity. Therefore, structural modification of the synthesized xanthones is a good and feasible approach to increase their activities towards specific targets.
4. Materials and methods

4.1. General Procedures for the Synthesis of Hydroxyxanthones

To an equimolar mixture of phenolic acids and phenol derivatives, anhydrous AlCl₃, ZnCl₂, TiCl₄ or SnCl₂ was added. The reaction mixture was heated at 140°C for 50 s in CEM microwave. The contents were poured into ice and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The product thus obtained was purified by silica gel column chromatography.

4.2. General Procedures for the Synthesis of Acetoxyxanthones

To a solution of hydroxyxanthone/thioxanthones (0.2 mmol) in acetic anhydride (5–8 mL), DMAP was added in catalytic amount. The mixture was stirred at 60°C for 4–5 h. The contents were then poured into ice and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to obtain the desired acetoxy xanthones. Since this is a simple acetylation reaction and all the hydroxyl groups present in the molecule get acetylated under these conditions, there are no issues regarding regioselectivity of this reaction.

All the above compounds were characterized by comparing their melting points as well as their ¹H NMR data with those already reported in the literature.²⁸,⁵²,⁵³

4.3. Antibacterial activity

Bacterial strains, *Staphylococcus aureus* (ATCC 29213), *Streptococcus pneumoniae* (ATCC 49619), *Streptococcus pyogenes* (ATCC 700294), *Moraxella catarrhalis* (ATCC
were purchased from ATCC and used for evaluation of antibacterial activity of the compounds.

Antibacterial activity was determined by the standard broth microdilution method with azithromycin as comparator. Minimum inhibitory concentrations (MICs) were established according to guidelines of the Clinical Laboratory Standards Institute, except that for Streptococcus medium, lysed blood was substituted with 5% horse serum. Double dilutions of tested compounds in 96-well microtitre plates were prepared in a 128-0.5 µg/mL concentration range. Bacteria were grown on appropriate agar plates (Becton Dickinson, USA) - Columbia agar with 5% sheep blood for streptococci, Mueller-Hinton chocolate agar for H. influenzae and Mueller-Hinton agar for staphylococci. Inocula were prepared by direct colony suspension method and plates inoculated with 5x104 CFU/well. Results were determined by visual inspection after 20-22h incubation at 37°C in ambient air.

4.4. Cytotoxic activity

A HepG2 human hepatocellular carcinoma cell line (ATCC HB-8065) and Jurkat human leukemic T cell lymphoblast cell line (ATCC TIB-152) were purchased from ATCC and maintained in complete RPMI 1640 medium (Sigma, R7388) supplemented with 10% Fetal Bovine Serum (Sigma, R7524) at 37°C in 5% CO₂ atmosphere.

A cytotoxicity assay was performed using MTS CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega, G3580).45 Double dilutions of tested compounds in 96-well microtiter plates were prepared in 100-0.2 µM concentration range. 5x10⁴ cells were
added per well and incubated overnight at 37°C in 5% CO₂ atmosphere. 15 µL of MTS reagent was dispensed per well. Plates were incubated for 1 hour at 37°C in 5% CO₂ atmosphere and absorbance recorded at 490 nm using a 96-well Wallac Victor2 plate reader. Results were analyzed in GraphPad Prism software.

4.5. *In silico* analysis

Simple structural characteristics and physicochemical properties were calculated using the Internet servers of Molinspiration [http://www.molinspiration.com/] and the ChEMBL database [https://www.ebi.ac.uk/chembl/].

Tentative predictions of biological targets and activities were made by web-services using methods based on the identification of substructure features typical for active molecules which are available publicly at the Molinspiration [www.molinspiration.com/] and PASS [www.pharmaexpert.ru/PASSOnline/services.php] web pages.

**Conflict of interest**

The authors declare there are no conflicts of interest.

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Authors are grateful to Jennifer Parish for editing the manuscript.
REFERENCES:

Reference List


Figure captions

Figure 1. Xanthones as heterocyclic compounds with dibenzo-γ-pyrone scaffold.
Scheme 1. Xanthone synthesis.

20
Table 1.

Microwave assisted synthesis of xanthones/thioxanthones using different Lewis acids.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Reagents</th>
<th>Yield (%)</th>
<th>Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Hydroxyxanthone (1a)</td>
<td>AlCl₃</td>
<td>64</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>ZnCl₂</td>
<td>77</td>
<td>50</td>
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<td></td>
<td>TiCl₄</td>
<td>79</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>SnCl₂</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>1,3-Dihydroxyxanthone (1b)</td>
<td>AlCl₃</td>
<td>68</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>ZnCl₂</td>
<td>76</td>
<td>50</td>
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<td>77</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>SnCl₂</td>
<td>82</td>
<td>50</td>
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<tr>
<td>1,6-Dihydroxyxanthone (1c)</td>
<td>AlCl₃</td>
<td>63</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>ZnCl₂</td>
<td>71</td>
<td>50</td>
</tr>
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<td></td>
<td>TiCl₄</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>SnCl₂</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>1,3,5-Trihydroxyxanthone (1d)</td>
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<td>50</td>
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<tr>
<td></td>
<td>ZnCl₂</td>
<td>75</td>
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</tr>
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<td></td>
<td>SnCl₂</td>
<td>83</td>
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<td>TiCl₄</td>
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<td>81</td>
<td>50</td>
</tr>
<tr>
<td>1,3,7-Trihydroxyxanthone (1f)</td>
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<td>50</td>
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<tr>
<td>Compounds</td>
<td>Reagents</td>
<td>Yield (%)</td>
<td>Time (s)</td>
</tr>
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<td>-----------</td>
<td>----------</td>
<td>-----------</td>
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</tr>
<tr>
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<td>TiCl$_4$</td>
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<td>SnCl$_2$</td>
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<td>82</td>
<td>50</td>
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</table>
Table 2.

The results of compound antibacterial screening are shown as follows and are expressed as minimum inhibitory concentrations (MICs) in µg/mL. The compound cytotoxicity results are expressed as IC\textsubscript{50} values in µM.

<table>
<thead>
<tr>
<th>Compound #</th>
<th>Antibacterial activity MIC (µg/mL)</th>
<th>Cytotoxicity IC\textsubscript{50} (µM)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>S. aureus \textsuperscript{*} ATCC 29213</td>
<td>S. pneumoniae \textsuperscript{*} ATCC 49619</td>
</tr>
<tr>
<td>1a</td>
<td>&gt;128</td>
<td>&gt;128</td>
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<tr>
<td>2a</td>
<td>&gt;128</td>
<td>&gt;128</td>
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<tr>
<td>1b</td>
<td>64</td>
<td>&gt;128</td>
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<td>128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>1c</td>
<td>32</td>
<td>&gt;128</td>
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<td>2c</td>
<td>64</td>
<td>&gt;128</td>
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<td>1d</td>
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<tr>
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<tr>
<td>2f</td>
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<tr>
<td>1g</td>
<td>8</td>
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<td>1h</td>
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<td>&gt;128</td>
</tr>
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<td>2h</td>
<td>&gt;128</td>
<td>&gt;128</td>
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<tr>
<td>Azithromycin (standard)</td>
<td>1</td>
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</tbody>
</table>

* Gram-positive bacterial species.

** Gram-negative bacterial species.
Supplementary data

$^1$H NMR DATA OF HYDROXY/ACETOXY XANTHONES

1-Hydroxyxanthone (1a)
$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 12.65 (s, 1H), 8.28 (d, $J$ = 8.0 Hz, 1H), 7.76 (t, 1H), 7.60 (t, 1H), 7.48 (d, $J$ = 8.4 Hz, 1H), 7.40 (t, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 6.80 (d, $J$ = 8.4 Hz, 1H)

1-Acetoxyxanthone (2a)
$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 8.25 (d, $J$ = 7.6 Hz, 1H), 7.69 (m, 2H), 7.46 (d, $J$ = 8.6 Hz, 1H), 7.42 (d, $J$ = 8.6 Hz, 1H), 7.36 (t, 1H), 7.00 (d, $J$ = 7.6 Hz, 1H), 2.50 (s, 3H)

1,3-Dihydroxyxanthone (1b)
$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 12.80 (s, 1H), 8.16 (d, $J$ = 7.7 Hz, 1H), 8.04 (s, 1H), 7.75 (t, 1H), 7.49 (d, $J$ = 8.4 Hz, 1H), 7.41 (t, 1H), 6.37 (s, 1H), 6.20 (s, 1H)

1,3-Diacetoxyxanthone (2b)
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.24 (d, $J$ = 7.8 Hz, 1H), 7.71 (t, 1H), 7.45 (d, $J$ = 8.4 Hz, 1H), 7.37 (t, 1H), 7.26 (s, 1H), 6.83 (s, 1H), 2.49 (s, 3H), 2.35 (s, 3H)

1,6-Dihydroxyxanthone (1c)
$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 11.29 (s, 1H), 9.93 (s, 1H), 7.44 (t, 1H), 6.47 (s, 1H), 6.44 (d, $J$ = 9.0 Hz, 1H), 6.41 (d, $J$ = 8.8 Hz, 2H), 6.40 (d, $J$ = 9.0 Hz, 1H)

1,6-Diacetoxyxanthone (2c)
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.26 (d, $J$ = 8.4 Hz, 1H), 7.70 (t, 1H), 7.41 (d, $J$ = 8.0 Hz, 1H), 7.28 (s, 1H), 7.11 (d, $J$ = 7.4 Hz, 1H), 7.01 (d, $J$ = 7.4 Hz, 1H), 2.49 (s, 3H), 2.36 (s, 3H)

1,3,5-Trihydroxyxanthone (1d)
$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 12.89 (s, 1H), 10.89 (brs, 1H), 7.88 (brs, 1H), 7.59 (d, $J$ = 8.0 Hz, 1H), 7.27 (d, $J$ = 8.0 Hz, 1H), 7.17 (t, 1H), 6.45 (s, 1H), 6.21 (s, 1H)
1,3,5-Triacetoxyxanthone (2d)
\[^1\text{H}\text{ NMR (300 MHz, CDCl}_3\]: } \delta 8.11 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.34 (t, 1H), 7.27 (s, 1H), 6.84 (s, 1H), 2.48 (s, 3H), 2.45 (s, 3H), 2.34 (s, 3H)

1,3,6-Trihydroxyxanthone (1e)
\[^1\text{H NMR (300 MHz, DMSO-d}_6\): } \delta 13.03 (s, 1H), 11.90 (s, 1H), 8.12 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.79 (s, 1H), 6.32 (s, 1H), 6.15 (s, 1H)

1,3,6-Triacetoxyxanthone (2e)
\[^1\text{H NMR (300 MHz, CDCl}_3\): } \delta 8.24 (d, J = 8.7 Hz, 1H), 7.26 (s, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.84 (s, 1H), 2.48 (s, 3H), 2.35 (s, 6H)

1,3,7-Trihydroxyxanthone (1f)
\[^1\text{H NMR (400 MHz, DMSO-d}_6\)ppm (TMS): } \delta 12.84 (s, 1H), 10.24 (s, 1H), 9.33 (s, 1H), 7.50 (s, 1H), 7.22 (m, 2H), 6.24 (s, 1H), 6.12 (s, 1H)

1,3,7-Triacetoxyxanthone (2f)
\[^1\text{H NMR (400 MHz, CDCl}_3\)ppm (TMS): } \delta 7.92 (s, 1H), 7.46 (m, 2H), 7.27 (s, 1H), 6.85 (s, 1H), 2.47 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H)

1,3,8-Trihydroxyxanthone (1g)
\[^1\text{H-NMR (400 MHz, DMSO-d}_6\): } \delta 11.83 (s, 1H), 11.75 (s, 1H), 7.79 (s, 1H), 7.49 (t, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.27 (s, 1H), 6.13 (s, 1H)

1,3,8-Triacetoxyxanthone (2g)
\[^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 7.65 (t, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.22 (s, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 2.43 (s, 6H), 2.34 (s, 3H)

1,3-Dihydroxythioxanthone (1h)
\[^1\text{H-NMR (400 MHz, DMSO-d}_6\): } \delta 14.37 (s, 1H), 8.49 (s, 1H), 7.80 (t, 1H), 7.63 (d, J = 6.9 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.48 (t, 1H), 6.54 (s, 1H), 6.32 (s, 1H)

1,3-Diacetoxythioxanthone (2h)
\[^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 8.46 (d, J = 7.3 Hz, 1H), 7.59 (t, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.45 (t, 1H), 7.33 (s, 1H), 6.91 (s, 1H), 2.49 (s, 3H), 2.34 (s, 3H)