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ROOSENILSON DIAS MUNIZ

SÍNTESE “VERDE” DE TETRACETONAS FUNCIONALIZADAS, CATALISADAS POR $Al(OH)_3$, COM EFEITO BACTERICIDA

Macapá-AP

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Federal do Amapá, como parte dos requisitos para obtenção do título de Mestre em Ciências Farmacêuticas.

Orientador: Prof. Dr. Irlon Maciel Ferreira

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SÍNTESE “VERDE” DE TETRACETONAS SUBSTITUÍDAS COM EFEITO BACTERICIDA

Dissertação apresentada ao Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Federal do Amapá, como parte dos requisitos para obtenção do título de Mestre em Ciências Farmacêuticas.

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Dedico este trabalho à minha esposa Michelly Muniz, que sempre acreditou em mim e esteve ao meu lado, mesmo nos momentos mais difíceis. Às minhas filhas Camilly Sofia Muniz e Rute Louisy Muniz, que alegram nosso dia. Vocês são minha maior motivação e inspiração.

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“A imaginação é mais importante que a ciência, porque a ciência é limitada, ao passo que a imaginação abrange o mundo inteiro”

Albert Einstein

RESUMO

Xanteno e seus derivados é uma classe importante de compostos orgânicos por causa de suas atividades farmacêuticas, biológicas e médicas como anti-inflamatório, antibacteriano, antiviral, antidepressivo e agente antimalárico. São antagonistas da ação paralisante da Zoxazolamina e utilizados na terapia fotodinâmica, assim, vários métodos sintéticos já foram relatados para a preparação de derivados de xanteno. Diante disso, o objetivo deste estudo foi realizar a síntese de tetracetonas (xantenodiona) catalisada $Al(OH)_3$ e avaliar seus efeitos bacteriológicos frente a cepas de *Staphylococcus aureus* (ATCC-6538P) e *Pseudomonas aeruginosa* (ATCC-9027). Uma mistura a partir de aldeído (1 mmol), dimedona (2,5 mmol), $Al(OH)_3$ (0,1 mmol) foi aquecida a 80ºC por 60 min. Após a conclusão da reação, a mistura foi lavada com água (15 mL). O produto bruto foi purificado por recristalização de EtOH resultando em cristais brancos de **3a-k** puro. Os espectros de RMN de ^1H e RMN de ^{13}C foram registrados em um espectrômetro Agilent Technologies 500/54, com $CDCl_3$ como solvente. A reutilização de $Al(OH)_3$ como um catalisador para síntese de tetracetona foi investigado. A novidade dessa metodologia se deu pela aplicação do catalisador $Al(OH)_3$ para a reação em cascata de Knoevenagel-Michael de aldeídos aromáticos e dicetonas 1,3-cíclicas em água. O processo foi quimiosseletivo e proporciona alto rendimento de tetracetonas sob condições benignas. O catalisador manteve 80% da atividade inicial em quatro ciclos. O método proposto pode ser considerado uma alternativa às sínteses existentes de tetracetonas biologicamente ativas que utilizam catalisadores heterogêneos homogêneos e caros.

Palavras-chave: Tetracetona, síntese ecológica, hidróxido de alumínio, efeito bactericida, tetracetonas, solventes apróticos.

Agradecimentos: CAPES, FAPEAP e PROPESPG/UNIFAP.

They are antagonists of the paralyzing action of Zoxazolamine and used in photodynamic therapy, so several synthetic methods have been reported for the preparation of xanthene derivatives. Therefore, the objective of this study was to perform the synthesis of catalyzed $Al(OH)_3$ tetraketones (xanthenedione) and to evaluate their bacteriological effects against strains of *Staphylococcus aureus* (ATCC-6538P) and *Pseudomonas aeruginosa* (ATCC-9027). A mixture of aldehyde (1 mmol), dimedione (2.5 mmol), $Al(OH)_3$ (0.1 mmol) was heated to 80ºC for 60 min. After the reaction was complete, the mixture was washed with water (15 mL). The raw product was purified by recrystallization of EtOH resulting in pure **3a-k** white crystals. The ^1H NMR and ^{13}C NMR spectra were recorded in an Agilent Technologies 500/54 Premium Shielded spectrometer, with $CDCl_3$ as the solvent. The reuse of $Al(OH)_3$ as a catalyst for tetraketone synthesis was investigated. The novelty of this methodology was due to the application of the $Al(OH)_3$ catalyst for the Knoevenagel-Michael cascade reaction of aromatic aldehydes and 1,3-cyclic diketones in water. The process was chemoselective and provides high yield of tetraketones under benign conditions. The catalyst maintained 80% of the initial activity in four cycles. The proposed method can be considered an alternative to the existing syntheses of biologically active tetraketones that use homogeneous and expensive heterogeneous catalysts.

Keywords: Tetraketone, eco-friendly synthesis, aluminum hydroxide, bactericide effect, tetraketones, aprotic solvents.

Acknowledgements: CAPES, FAPEAP e PROPESPG/UNIFAP.

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LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

ºC	Grau Celsos
MSNBA	Nanopartículas de sílica mesoporosa dispersas em água
mmol	Mili mol
HI	Ácido iodídrico
H_2O	Água
CH_3OH	Metanol
Zn	Zinco metálico
I_2	Iodo molecular
$Al(OH)_3$	Hidróxido de alumínio
$KAl(SO_4)_2 \cdot 12H_2O$	Sulfato de potássio de alumínio
$Zr(KPO_4)_2$	Fosfato dipotássico de zircônio
$CaCl_2$	Cloreto de cálcio
DMSO	dimetilsulfóxido
THF	Tretrahidrofurano
CH_3CN	acetonitrila
EtOAc	Acetato de etila
MetOH	Metanol
MIC	Concentração Inibitória Mínima
MBC	Concentração Bactericida Mínima
FTIR	Fourier Transform Infrared Spectroscopy
ppm	Parte por milhão
J	Constante de acoplamento

SUMÁRIO

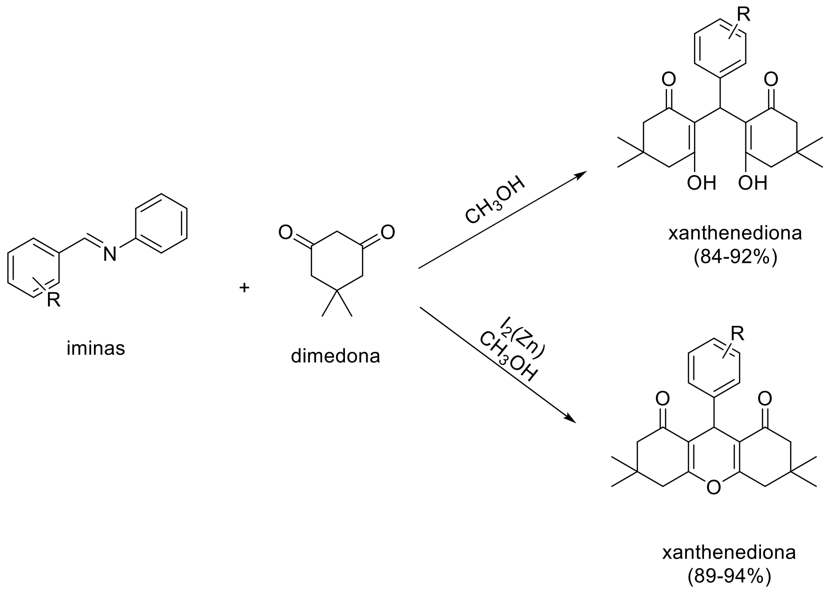
1 INTRODUÇÃO

Xanteno e seus derivados é uma classe importante de compostos orgânicos por causa de suas atividades farmacêuticas, biológicas e médicas como anti-inflamatório, antibacteriano, antiviral, antidepressivo e agente antimalárico (CHUNG et al., 2015). São antagonistas da ação paralisante da Zoxazolamina e utilizados na terapia fotodinâmica. Além disso, estão sendo usados como precursores sintéticos valiosos para muitos compostos orgânicos, corantes, materiais fluorescentes sensíveis ao pH para a visualização de conjuntos biomoleculares, e em tecnologias a laser (BIGDELI; HERAVI; HOSSEIN MAHDAVINIA, 2007).

Vários métodos sintéticos já foram relatados para a preparação de derivados de xanteno. Entre esses métodos, a utilização de iminas (1 mmol), 5,5-dimetil-1,3-ciclo hexandiona 2 (2 mmol) em metanol à 70ºC, sem nenhum catalisador, foi utilizado por RONG et al., (2006) para obter derivados de xantenodionas abertas em altos rendimentos (Esquema 1). No entanto, sob condições de reação semelhantes, quando iodo molecular e quantidade catalítica de pó de zinco foram utilizados foi formado xantenodionas fechadas em excelente rendimento (Esquema 1).

A síntese de xantenodionas precisou do catalisador de iodo molecular; no entanto, foi observado que uma quantidade catalítica de pó de zinco é necessária, e isso poderia promover a reação. No processo de reação, as ligações duplas (“ligação σ” e “ligação π”) de carbono e nitrogênio em iminas foram rompidas; segundo os autores esse fenômeno raramente ocorre. Com base na literatura, segundo os autores, o possível mecanismo foi descrito, a molécula iodo atua como um catalisador ácido de Lewis fraco e participa da reação. A princípio, influenciada pelo poder do zinco, a molécula iodo ocorre polarização e então forma HI pela interação do iodo com um hidroxi. HI combina outro hidroxi e perde uma molécula de H_2O e finalmente, os derivados de xantenodionas podem ser obtidos. Acreditamos que o HI tem um efeito importante durante a reação.

Esquema 1. Síntese de xantenodiona abertos na presença de MetOH e ciclizados na presença I_2/MetOH.

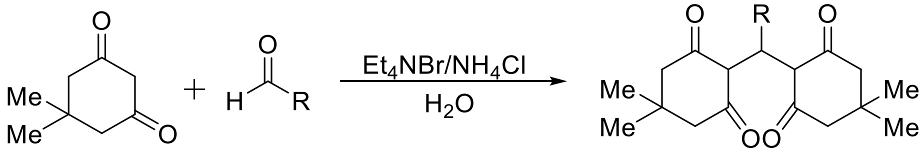


Fonte: RONG et al., 2006

O trabalho de Khan e colaboradores (2007) propõe um procedimento (esquema 2) alternativo para a produção de tetracetonas, compostos reconhecidos por suas capacidades de inibir a lipoxigenase e atuar como antioxidantes.

A abordagem sugerida emprega brometo de tetraetilamônio ($Et_4N^+Br^-$) como catalisador para a condensação da dimedona em diversos aldeídos, processo que ocorre em água e à temperatura natural. Este procedimento é notável pela sua simplicidade, altos rendimentos (90%-98%) e condições reacionais suaves, em contraste com métodos convencionais que muitas vezes exigem temperaturas elevadas ou condições mais severas (KHAN et al., 2007, p. De 272 a 274).

Esquema 2 - Síntese de tetracetonas utilizando dimedona, aldeídos aromáticos e brometo de tetraetilamônio como catalisador



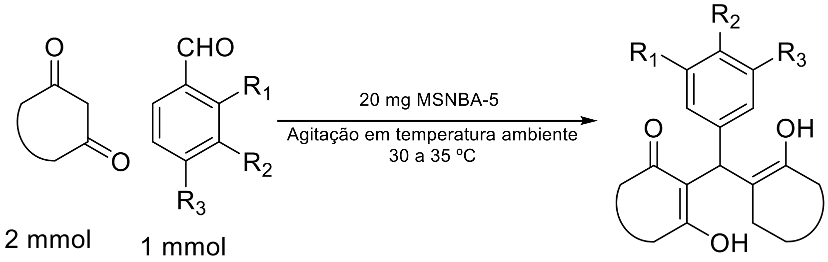
Fonte: KHAN et al., 2007

Ray et al. (2014, p. 174-173) propõem uma abordagem sustentável para a produção de tetracetonas e sua transformação em xantenos (esquema 3), empregando nanopartículas de sílica mesoporosa tratadas com ácido fluoróico (HBF_4). Este catalisador mescla ácidos de Brønsted e Lewis, distinguindo-se por métodos como a adsorção de N_2, HRTEM – High-

Resolution Transmission Electron Microscopy, EDX – *Energy-Dispersive X-ray Spectroscopy*, XPS – *X-ray Photoelectron Spectroscopy* e RMN de ^{29}Si. A proposta é notável por sua perspectiva ecológica e eficácia catalítica, consolidando os fundamentos da química verde.

A produção de tetracetonas acontece através de uma reação em cadeia de adição e eliminação entre cetoaldeídos e 1,3-ciclodionas, impulsionada por HBF_4 imobilizado. A utilização de etanol aquoso como solvente enfatiza a natureza ecológica do procedimento. Ademais, a transformação das tetracetonas em xantenos, heterocíclicos frequentemente empregados em materiais fluorescentes e aplicações biológicas, foi realizada com elevada eficiência e seletividade (RAY et al., 2014).

Esquema 3 – síntese de xantenos empregando nanopartículas de sílica mesoporosa tratadas com ácido tetrafluorobórico (HBF_4)

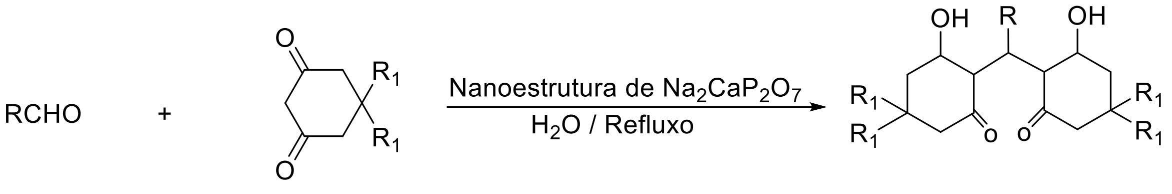


Fonte: Ray et al., 2014

A pesquisa mostrou que o $HSTBF_4$ fixado em nanopartículas de sílica mesoporosa mantém sua estabilidade estrutural e funcional mesmo após múltiplas reutilizações, demonstrando sua viabilidade econômica e ecológica. Estudos de lixiviação confirmaram a heterogeneidade do catalisador. A eficácia catalítica foi atribuída à combinação sinérgica das características ácidas e à estrutura porosa da sílica, que favorece o transporte molecular (RAY et al., 2014, p. 175-176).

Maleki et al. (2018) também relataram um método de síntese quimiosseletivo (esquema 4) para a produção de tetracetonas, usando água como meio reacional e o difosfato nanoestruturado de sódio e cálcio ($Na_2CaP_2O_7$) como catalisador heterogêneo. Este trabalho se enquadra no cenário da química verde, em busca de processos mais ecológicos, econômicos e benéficos para o meio ambiente. A abordagem sugerida proporciona elevada eficiência, seletividade, tempos de reação breves e altos rendimentos, além de possibilitar a reutilização do catalisador.

Esquema 4 – produção de tetracetonas usando água como meio reacional e o difosfato nanoestruturado de sódio e cálcio ($Na_2CaP_2O_7$) como catalisador heterogêneo



$R_1 = CH_3$, H

Fonte: Maleki et al., 2018

A produção de tetracetonas é realizada através da condensação de Knoevenagel e da adição de Michael entre aldeídos e dionas de 1,3-ciclo. A função do catalisador $Na_2CaP_2O_7$ revelou-se vital, proporcionando locais básicos e ácidos que favorecem a abstração de prótons e a polarização de ligações químicas. A pesquisa revelou que a utilização de água como solvente é mais eficaz em relação a outros métodos, estando em conformidade com os princípios de sustentabilidade. A técnica possibilitou produzir tetracetonas com variados substituintes aromáticos e alifáticos, alcançando rendimentos superiores a 90% e tempos de reação que oscilaram entre 5 e 20 minutos. Ademais, o catalisador demonstrou ser altamente reciclável, apresentando rendimentos constantes após diversas utilizações. Foi confirmada a reatividade seletiva, pois não se formaram subprodutos, como xantenos, mesmo após um aquecimento prolongado. Os autores ressaltam os benefícios do método sugerido, como sua simplicidade operacional, ausência de resíduos nocivos, separação simples do catalisador e sua possibilidade de reutilização. Conclui-se que o método é um progresso notável na síntese sustentável de compostos orgânicos, com potencial para uso em várias indústrias e indústrias farmacêuticas (MALEKI et al., 2018, p. Páginas 297-300).

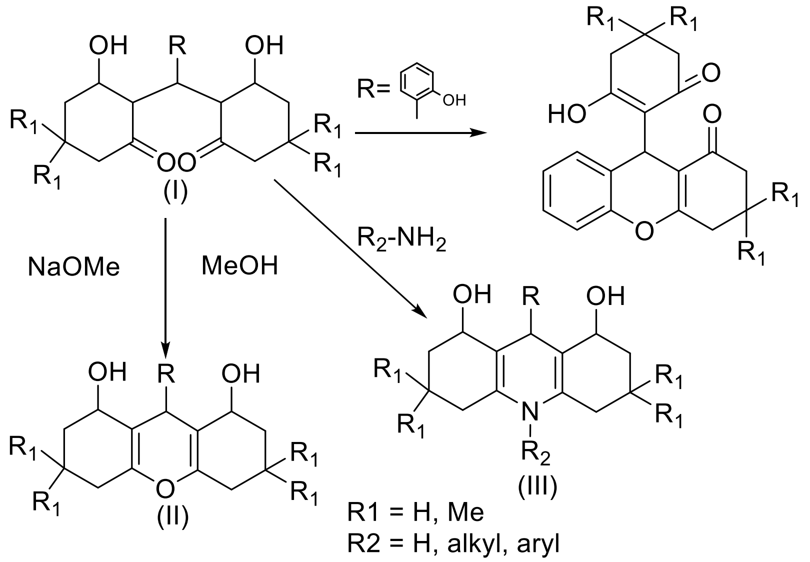
Anastas e Williamson (1998) apresentaram um método verde e eficaz para a síntese de tetracetonas, usando ácido bórico como catalisador. A tetracetona derivada, conhecida como 3a, foi caracterizada estruturalmente através da difração de raios X de um único cristal, complementada com uma análise adicional através da Teoria do Funcional da Densidade (DFT) e da análise da superfície de Hirshfeld. Esta abordagem tem como objetivo diminuir o efeito ambiental ligado às reações químicas convencionais.

A síntese foi feita sob condições suaves, usando uma combinação de etanol e água como solvente, demonstrando a viabilidade do processo. O ultrassom possibilitou reações rápidas e elevadas taxas de rendimento (até 95%), ultrapassando as restrições dos métodos tradicionais que exigem temperaturas elevadas, períodos de reação extensos e a utilização de catalisadores tóxicos ou dispendiosos. O composto é formado através de processos de condensação de Claisen e adição de Michael, como sugerido na pesquisa.

A técnica sugerida por Ren et al. (2002) para a produção de tetracetonas provou ser eficaz, alcançando rendimentos de 91 a 98% e condições reacionais suaves, usando água como solvente à temperatura ambiente. A utilização do brometo de tetraetilamônio como catalisador de mudança de fase melhorou a solubilidade dos reagentes, resultando em rendimentos superiores em relação a protocolos anteriores. A existência de grupos doadores de elétrons, tais como substituintes para-posicionados, foi crucial para a elevação da atividade inibidora dos compostos.

Yu et al. (2010) também sugeriram uma abordagem ecológica e eficaz para a produção de tetracetonas, usando apenas água como solvente, sem a necessidade de catalisador e à temperatura ambiente. O procedimento une uma condensação de Knoevenagel e uma adição de Michael numa reação em tandem, alcançando rendimentos que variam de 64% a 99% para vários substratos. Esta estratégia se distingue por não utilizar catalisadores, surfactantes ou líquidos iônicos, estando em conformidade com os princípios da química verde (esquema 5).

Esquema 5 – Síntese de tetracetonas usando apenas água como solvente sem uso de catalisador ocorrendo à temperatura ambiente



Fonte: Yu et al.,2010

PATIL et al., (2017) descreveu uma abordagem rápida, simples e direta para a síntese de xantenos abertos, sob condições livres de solventes usando poliborato sulfatado como catalisador altamente eficiente. O procedimento ofereceu várias vantagens, incluindo perfil de reação mais limpo, condição de reação suave, catalisador econômico, reciclável e ambientalmente benigno e altos rendimentos.

Um sistema híbrido de óxidos de cobre e zinco imobilizado em carragenina como matriz polimérica foi preparado como catalisador heterogêneo na síntese de tetracetonas funcionalizadas, foi desenvolvido por ESMAEILI et al., (2021). A superfície de carragenina foi magnetizada através da composição com nanopartículas de óxido de ferro. Sítios metálicos de cobre e zinco são empregados como os principais sítios catalíticos para catalisar a síntese de derivados de xantenodiona a partir de aldeído e dimedona. Devido ao comportamento magnético do catalisador, o processo de purificação foi realizado de forma simples.

Diante disso, o objetivo deste estudo foi realizar a síntese de tetracetonas (xantenodiona) catalisada $Al(OH)_3$ e avaliar seus efeitos bacteriológicos frente a cepas de *Staphylococcus aureus* (ATCC-6538P) e *Pseudomonas aeruginosa* (ATCC-9027).

2.1 OBJETIVO GERAL

Otimizar a síntese de tetracetonas funcionalizadas catalisadas por $Al(OH)_3$ e avaliar seus efeitos bacteriológicos.

2.2 OBJETIVOS ESPECÍFICOS

- Avaliar a influência do $Al(OH)_3$, como catalisador, no produto formado da reação;
- Estudar a influência dos parâmetros (temperatura, solvente, tempo de reação e grupos substituinte no anel aromático) na formação das tetracetonas;
- Propor um mecanismo sintético plausível envolvendo a formação de tetracetonas a partir do $Al(OH)_3$, como catalisador;
- Avaliar o potencial de reuso do catalisador na reação estudada;
- Estudar o efeito bactericida em *Staphylococcus aureus* (ATCC-6538P) e *Pseudomonas aeruginosa* (ATCC-9027) das tetracetonas obtidas.

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"Green" Synthesis of Substituted Tetraketones with Prominent Bactericide Effect

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Keywords: Tetraketone, eco-friendly synthesis, aluminum hydroxide, bactericide effect, tetraketones, aprotic solvents.

Abstract

Effective and “green” synthesis of tetraketone derivatives was elaborated. The last compounds developed prominent bactericide activity against both (ATCC-6538P) bacteria. The novelty of this approach is concluded in the application of $Al(OH)3$ catalyst for the Knoevenagel-Michael cascade reaction of aromatic aldehydes and 1,3-cyclic diketones in water. The process is chemoselective and affords high yield of tetraketones under benign conditions. The catalyst maintained 80% of initial activity within four cycles. The proposed method can be regarded as an alternative to the existing syntheses of biologically active tetraketones that utilize homogeneous and expensive heterogeneous catalysts.

1. Introduction

2,2’-Arylmethylene-bis(3-hydroxy-5,5-dimethyl-2-cyclo hex- ene-1-ones) or tetraketones are considered as important precursors for the synthesis of heterocyclic compounds such as xanthenes and acridinediones. The last ones demonstrated notable bactericide activity [1]. Noteworthy is that such structurally complex molecules can be synthesized by a simple condensation of aldehyde (1 equiv.) either with dimedone (2 equiv.) or cyclohexane-1,3-dione. Using $HClO_4$-SiO_2 or PPA-SiO_2 as a catalyst in aqueous media at 100°C. Kantevari et al. [2] were able to assemble the desired product with respectively 44-91% and 41-78% yield within 30-60 min. Kamali et al. [3] described the synthesis of tetraketones from a mixture of dimedone (2 mmol), aldehyde (1 mmol) and melamine (0.16 mmol) at 100ºC afforded 90-98% yield within 5-10 h. Li et al. [4] reported the ultrasonic enhancement of tetraketones yield up to 80-98% using aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione at 50°C in aqueous media. Recently, the same group reported the formation of dihydropyrano[3,2-b]chromenediones in three-components condensation reaction of kojic acid, aromatic aldehydes, and dimedone using a reusable alum [$KAl(SO_4)_2 \cdot 12H_2O$] as catalyst [5]. In another investigation, the water-soluble Pd (II) trigonal prism pre- pared through the coordination-driven self-assembly protocol was used as a template for the selective generation of both cyclized xanthenes and noncyclized tetraketones at different temperatures [6]. Rosati et al. [7] also observed that the reaction among ethyl cyanoacetate, benzaldehyde and 5,5-dimethylcyclohexane-1,3- dione, catalyzed by $Zr(KPO_4)_2$ at 60ºC led to a mixture of noncyclized tetraketone and tetrahydrochromene with 53% yield.

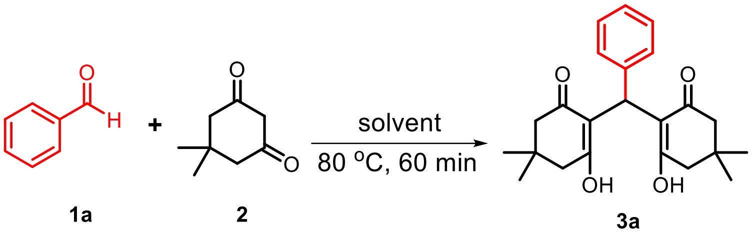
$CaCl_2$ (20 mol%), when dispersed in DMSO, at 90ºC and within 14h increased the yield of cyclized product up to 86%. Whereas in $CHCl_3$ the same salt enhanced chiefly the formation of noncyclized tetraketone with 91% yield of the latter [8]. On the other hand, improving the synthesis of such important compounds, particularly in eco-friendly conditions still remains a challenge for the researchers. Inspired by this, we reported the elaboration of a rapid and efficient method of tetrakeone synthesis upon “green” conditions focusing on its practical application in medicine [9-10].

2. RESULTS AND DISCUSSION

For optimization of the process conditions, we used the reaction between benzaldehyde (**1a**) and 5,5-dimethyl-1,3-cyclohexanedione (**2a**). For this purpose, several solvents with different polarities, such as ethanol, THF, hexane, CH_3CN, water, acetone, and EtOAc, were tested. $Al(OH)_3$ as a catalyst emerged in the desired product 3a formation, although with different yield (35-94%) depending on the reaction medium (Table 1). Its presence was confirmed by the emergence of two singlet peaks at 11.87

ppm and 5.57 ppm corre- sponding to -OH and methyne proton, respectively. Moderate yield (38-50 %) was observed in the aprotic solvents e.g. hexane (entry 1), CH_3CN (entry 2) and THF (entry 3). Almost the same perfor- mance regarding the yield was exhibited with EtOAc (entry 4) and acetone (entry 5) (35 and 55%, respectively). Similarly, carrying out the reaction at free-solvent conditions (entry 6) resulted in a moderate (47%) yield of **3a**. Whereas in polar solvents such as water (entry 7), EtOH (entry 8) and MeOH (entry 9), the attained values of yield were 94, 80 and 85%, respectively. It is well known that water, EtOH and MeOH are also efficient solvents for perform- ing the aldol reaction [11-12]. Then we decided to use water instead of organic solvents due to the high-polarity nature, affording more environmentally friendly synthesis and easier work up. As catalyst commercial $Al(OH)_3$ was decided to explore considering its cheapness, ecological nature, attainability, readiness of preparation and recycling. After selecting the reaction medium, an optimization of the process protocol by testing different temperatures and catalyst loads was accomplished (Table 2). As appeared, in the absence of a catalyst, the generation of **3a** was not detected either at 50ºC or 80ºC (entry 1-2). To improve the productivity, the reaction was tested with different amounts of $Al(OH)_3$. It resulted in figuring out the optimal yield, and catalyst load (entry 4-6, 9-10). On the other hand, pursuing the temperatures all through the tested interval re- vealed the most favorable, with respect to reaction performance. The endeavors undertaken were advantageous both for the reaction rate and the yields (entry 7-8) and clearly demonstrated that $Al(OH)_3$ is an effective catalyst in terms the reaction time and the yield of the aimed product. The best performance of this reaction developed at 80°C produced within 60 minutes **3a** with 94% yield (entry 7).

Table 1. Effect of solvents in the yield of **3a**.



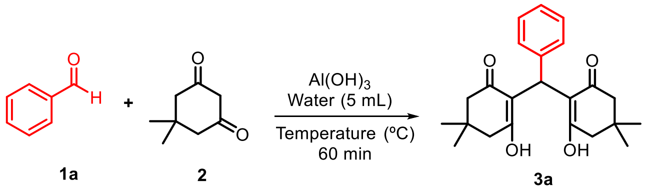
Entry	Solvent	Yield (%)
1	Hexane	29
2	CH_3CN	50
3	THF	38
4	EtOAc	35
5	Acetone	55
6	-	47
7	**Water**	**94**
8	EtOH	80
9	MeOH	85

Reaction conditions: catalyst $Al(OH)_3$ (1 mmol), reaction volume 5.0 mL, 80 ºC reaction time 60 min

It is known that tetraketones (**3a-k**) are inclined to cyclize by the elimination of water, affording the corresponding xanthenes. Then such feature may be used as a driving force for the dehydra- tion step of the reaction mechanism. In other words, lasting the intermediate 3a in the reaction mixture might afford the origination of cyclized product only [13]. However, in this work, we observed the formation solely of a noncyclized product **3a-k**.

After the determination of the optimal conditions, the performance of $Al(OH)_3$ as a catalyst for the synthesis of xanthene derivatives was evaluated from the reaction of dimedone with other aromatic aldehydes. In all cases, the yield of products was from good to excellent (Table 3). Based on the acquired results, a putative mechanism of catalysis in the presence of Al(OH)3 was elaborated (Scheme 1). At the first stage, Al(OH)3 triggers the formation of Knoevenagel type adduct (Scheme 1). At the first stage, Al(OH)3 triggers the formation of Knoevenagel type adduct. So far, aluminum hydroxide is amphoteric; at slightly acidic conditions, it works as Brønsted-Lowry base by coordinating the organic molecules (e.g. aldehyde) by their partially positively charged parts and triggering the ongoing of the forthcoming steps. Furthermore, it can undergo the Michael addition with another molecule of dimedone to form tetraketones.

Table 2. Optimization the synthesis of **3a** synthesis.



Entry	t (ºC)	τ (min)	Catalyst (mmol)	Yield (%)
1	50	60	---	traces
2	80	60	---	traces
3	Rt	60	0.1	22
4	Rt	60	0.5	37
5	Rt	60	1.0	48
6	50	60	1.0	62
7	**80**	**60**	**1.0**	**94**
8	80	60	1.0^{a}	84^{a}
9	80	60	0.5	74

Reaction was carried out by using benzaldehyde **1a** (1.0 mmol, 102 µL), dimedone **2** (2.5 mmol, 350.4 mg) in water (5.0 mL). ^{a}Reaction was performed by using dimedone **2** (2.0 mmol, 280.3 mg).

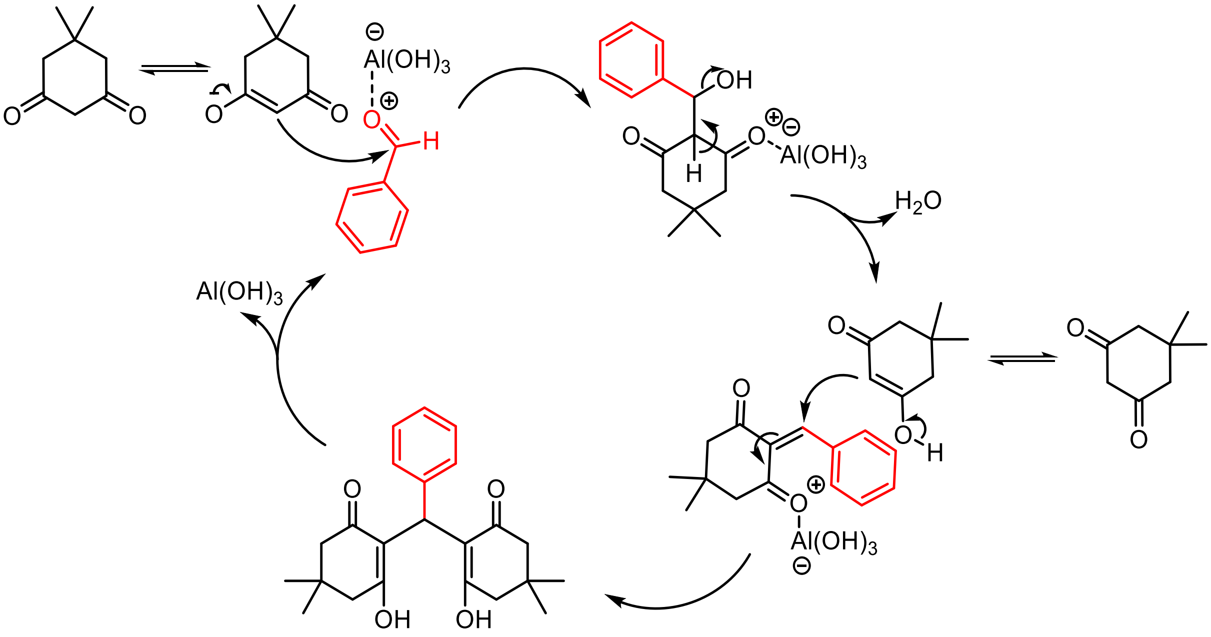
The performance of such a reaction was examined upon the dis- covered optimal conditions (Table 2, entry 7) for the series of aldehydes (Table 3). As revealed, using dimedone and halogenates substituents of benzaldehyde, such as 4-bromobenzaldeyde and 4- fluorbenzaldehyde was beneficial for the corresponding tetraketones **3b** and **3c** formation (yield 96.8 and 91.4%), respectively (entries 2 and 3). However, product **3d**, formed in the case of 4-chloro-3-nitrobenzaldehyde was obtained with a rather modest (73.4%) yield (entry 4). Performing the reaction between dimedone and aldehydes bore the powerful electron withdrawing groups (3-NO_2 and 4-CN) promoted the generation of the aimed products with excellent (88.4% and 96% for **3e** and **3f**, respectively) yields (entries 5 and 6). The last feature points out that this method is sensi- tive to the steric effect of the reactants exerted by the substituent bonded to the aromatic ring.

It is interesting that when the reaction was carried out using dimedone and aldehyde bore an electron-donating group, it resulted in the origination of the corresponding tetraketones **3g-3i** with an acceptable (>83%) level of yield (entries 8-10). These experiments show that the success of the reaction is not solely dependent on the electronic effects of the substituents attached to the aromatic ring of aldehyde. In view of that, using furfuraldehyde was beneficial for the formation of tetraketone **3k** (88.1% yield, entry 11).

One of the advantages of heterogeneous catalysts in relation to homogeneous catalysts is their ability to recycle after use. Such property contributes to reducing the operation costs [14]. In this study, the potential for reusing of $Al(OH)_3$ as a catalyst in the tetraketone synthesis was investigated as well. Fig. (1) shows the results from four consecutive reaction cycles under experimentally optimized conditions using aldehyde

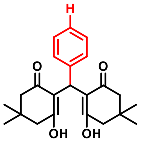
(**1a**), $Al(OH)_3$ as catalyst in water (80°C, 60 min). In the second and third cycles, the conditions were favorable for the formation of tetraketone 3a with about 83 and 80% yield, respectively.

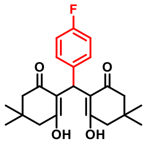
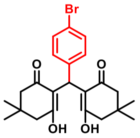
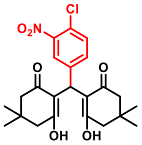
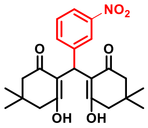
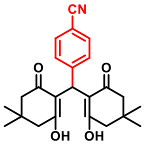
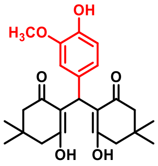
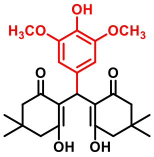
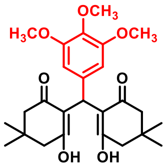
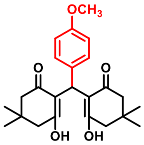
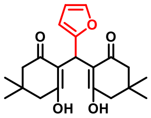
Furthermore, the performance of $Al(OH)_3$ as a catalyst was still acceptable in the fourth cycle in respect of 3a formation (71.5%, Fig. 1). However, starting from the fifth cycle onwards, there was a significant drop in product yield (to 57%). The loss of the catalyst efficiency may relate to a combination of several factors, such as blocking its active centers with organic molecules, losing the mass during the washing steps, etc. All these factors can lead to the deactivation of the catalyst [15-16]. Ultimately (Table 3), all synthesized compounds (**3a-k**) were tested in vitro for the antimicrobial activity against pathogenic bacteria *Staphylococcus aureus* (ATCC-6538P) and *Pseudomonas aeruginosa* (ATCC-9027). Compounds **3c, 3d, 3e, 3g, 3i, 3k** showed moderate effectiveness against both Gram-negative (ATCC-9027) and Gram-positive bacteria (ATCC-6538P), with MIC and MBC values of 250 $\mu g.mL^{-1}$ and 250 $\mu g.mL^{-1}$, respectively. Whereas compound **3b** (contains F atom), **3f** (contains CN group) and **3j** (contains $-OCH_3$ group) exhibited good MIC and MBC activity against *S. aureus* (ATCC-6538P) but no activity to wards *P. aeruginosa* (ATCC-9027) (Table 3). To obtain a comparative view of the application of the catalysts for the synthesis of tetraketone derivatives, Table 4 presents some literature examples. Given this data, one can conclude that $Al(OH)_3$ presents an interesting performance as a catalyst of **3a** synthesis in comparison with the other ones. Some of the enlisted catalysts showed excellent performances regarding the yield of product and short reaction time. However, $Al(OH)_3$ possesses notable ad vantages when compared to others, such as low cost, dispensability for previous treatment, ease of handling, commercial availability and storage stability.



Scheme 1. Putative mechanism of $Al(OH)_3$-catalyzed synthesis of **3a.**

Table 3. Synthesis of substituted tetraketone **3a-k** and effect bacterium [^{1}*Staphylococcus aureus* (ATCC-6538P) and ^{2} *Pseudomonas aeruginosa* (ATCC-9027)].

Product	Structure	Yield (%)	Mp. exp. (ºC) [Mp. (ºC) from lit.]	MIC^1 (µg.mL^{-1})	MBC^1 (µg.mL^{-1})	MIC^2 (µg.mL^{-1})	MBC^2 (µg.mL^{-1})
3a		52.3	189-191	125.0	125.0	62.5	62.5

3b		96.8	182-184	62.5	62.5	-	-
3c		91.4	170 – 174	187.5	250.0	250.0	250.0
3d		73.4	132-135	250.0	250.0	250.0	250.0
3e		88.4	187-190	250.0	250.0	250.0	250.0
3f		96	183-188	31.25	31.25	125.0	-
3g		82.3	201-205	250.0	250.0	250.0	250.0
3h		94	203-205	187.5	250.0	125.0	125.0
3i		85.13	205-209	250.0	250.0	250.0	250.0
3j		89.2	218-220	31.25	31.25	-	-
3k		88.1	172-175	250.0	250.0	250.0	250.0

3. EXPERIMENTAL ANALYTICAL DATA

All compounds were characterized using FTIR, ^{1}H and ^{13}C NMR spectra with full resonances assignments.

3.1. 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex 2-en-1-one) 3a

$C_{23}H_{28}O_4$, 368.2 g.mol^{-1}; (52.32% yield); White solid, m.p. = 189-191 ºC; FTIR νmax(cm^{-1}) = 2957.27, 2870.72, 1593.01, 1448.76, 1372.51, 1302.44, 1238.55, 1149.94, 1055.14, 1042.77, 776.93, 709.91.; 1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.91 (s, 1H), 7.30-7.26 (m, 2H), 7.20-7.15 (m, 1H), 7.12-7.09 (m, 2H), 5.55 (s, 1H), 2.55-2.23 (m, 7H), 1.26-1.23 (m, 8H), 1.11 (s, 6H). 13C (126 MHz, CDCl3) δ (ppm) = 203.6 carbonil-C, 190.5 olefinic-C, 189.4 olefinic-C, 138.1 *ipso*-C, 128.2 *m*-C, 126.7 *o*-C, 125.8 *p*-C, 115.6 *olefinic*-C, 57.3 CH_2-C, 54.1 CH_2-C, 47.1 quarternary-C, 46.5 quarternary-C, 32.7 quarternary-C, 31.5 quarternary-C, 29.6 CH_3-C, 28.4 CH_3-C, 28.2 CH_3-C, 27.4 CH_3-C.

3.2. 2,2'-((2-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimeth ylcyclohex-2-en-1-one) 3b

$C_{23}H_{27}FO_4$, 386.19 g.mol^{-1}; (96.8% yield); White solid, m.p. = 182-184 ºC; FTIR νmax(cm-1) = 2957.27, 2870.72, 1724.91, 1588.89, 1487.91, 1452.88, 1370.44, 1302.44, 1226.19, 1166.42, 1152, 1114.9, 1044.83, 752.2, 733.65, 702.74.; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.90 (s, 1H), 7.21-7.11 (m, 2H), 7.05 (t, J = 7.0 Hz, 1H), 6.94 (dd, J = 11.9, 8.1 Hz, 1H), 5.61 (s, 1H), 2.51-2.24 (m, 8H), 1.23-0.98 (m, 12H). ^{13}C NMR (101 MHz, CDCl3) δ (ppm) = 189.5 carbonil-C, 162.1 ipso-C, 159.7 ipso-C, 129.2 aromatic-C, 128.0 aromatic-C, 123.6 aromatic-C, 115.7 olefinic-C, 115.5 ole finic-C, 31.3 quarternary-C, 28.9 CH_3-C.

3.3. 2,2'-((4-bromophenyl)methylene)bis(3-hydroxy-5,5-dimeth ylcyclohex-2-en-1-one) 3c

$C_{23}H_{27}BrO_4$, 446.11 g.mol^{-1}; (91.4% yield); White solid, m.p. = 170-174 °C; FTIR vmax(cm-1) = 2957.27, 2870.72, 1712.54, 1584.77, 1485.85, 1366.32, 1300.38, 1250.92, 1120, 1166.42, 1154.06, 1067.5, 1009.8, 826.39.; 1H NMR (400 MHz, CDCl3) δ (ppm) = 11.86 (s, 1H), 7.39-7.35 (m, 2H), 6.98-6.94 (m, 2H), 5.44 (s, 1H), 2.38 (dq, J = 26.7, 17.9 Hz, 7H), 1.21 (s, 6H), 1.10 (s, 6H). 13C NMR (101 MHz, CDCl3) δ (ppm) = 190.6 carbonil-C, 189.4 carbonil-C, 137.3 ipso-C, 131.3 aromatic-C, 128.6 aromatic-C, 119.6 olefinic-C, 115.3 olefinic-C, 47.0 quarternary-C, 46.4 quar ternary-C, 32.5 quarternary-C, 31.4 CH2-C, 31.4 CH2-C, 29.6 CH3 C, 27.4 CH3-C.

3.4. 2,2'-((4-chloro-3-nitrophenyl)methylene)bis(3-hydroxy-5,5 dimethylcyclohex-2-en-1-one) 3d

$C_{23}H_{26}ClNO_6$, 447.14 g.mol^{-1}; (73.4% yield); Yellow pale solid, m.p. = 132-135 °C; FTIR vmax (cm^{-1}) = 2953.15, 2868.66, 1691.93, 1584.77, 1506.46, 1459.06, 1413.72, 1370.44, 1325.11, 1234.43, 1127.27, 1007.74, 886.15, 824.33.; 1H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.86 (s, 1H), 8.04 (ddt, J = 7.8, 2.6, 1.2 Hz, 1H), 7.46-7.39 (m, 2H), 5.55-5.53 (m, 1H), 2.53-2.31 (m, 8H), 1.28 (s, 6H), 1.12 (s, 6H). 13C NMR (126 MHz, CDCl3) δ (ppm) = 191.1 carbonil-C, 189.6 carbonil-C, 148.4 ipso-C, 140.7 aromatic-C, 132.9 aromatic-C, 129.1 aromatic-C, 121.0 olefinic-C, 114.8 ole finic-C, 47.0 quarternary-C, 46.4 quarternary-C, 32.9 CH2-C, 31.4 CH2-C, 29.7 CH3-C, 27.3 CH3-C.

3.5. 2,2'-((3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethyl cyclohex-2-en-1-one) 3e

$C_{23}H_{27}NO_6$, 413.18 g.mol-1; (88.4% yield); Orange pale solid, m.p. = 187-190 ºC; FTIR νmax(cm^{-1}) = 2959.34, 2870.72, 1586,83, 1527.07, 1469.36, 1448.76, 1370.44, 1345.71, 1304.5, 1250.92, 1166.42, 1154.06, 1067.5, 1044.83, 838.75, 803.72, 729.53, 702.74.; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.85 (s, 1H), 8.04 (ddt, J = 7.6, 2.4, 1.2 Hz, 1H), 8.00 (q, J = 2.1 Hz, 1H), 7.47-7.39 (m, 2H), 5.54 (s, 1H), 2.42 (dq, J = 28.5, 17.7 Hz, 7H), 1.27 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 191.1 carbonil-C, 189.6 olefinic-C, 148.41 ipso-C, 140.7 aromatic C, 132.9 aromatic-C, 129.1 aromatic-C, 122.2 aromatic-C, 121.0 aromatic-C, 114.8 olefinic-C, 47.0 quarternary-C, 46.4 quarter nary-C, 32.9 CH_2-C, 31.4 CH_2-C, 29.6 CH_3-C, 27.3 CH_3-C.

3.6. 4-(bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)met hyl)benzonitrile 3f

$C_{24}H_{27}NO_4$, 393.19 g.mol^{-1}; (96% yield); White solid, m.p. = 183-188 ºC; FTIR νmax(cm-1) = 3056.19, 2920.18, 2850.11, 1696.05, 1601.26, 1539.43, 1358.08, 1265.34, 1236.49, 1088.11, 1046.9, 894.4, 830.51, 729.53, 702.74.; 1H NMR (500 MHz, CDCl3) δ (ppm) = 11.79 (s, 1H), 7.58-7.54 (m, 2H), 7.22-7.17 (m, 2H), 5.52 (s, 1H), 2.51-2.29 (m, 8H), 1.23 (s, 6H), 1.11 (s, 6H). ^{13}C NMR (126 MHz, CDCl3) δ (ppm) = 190.9 carbonil-C, 189.5 olefin ic-C, 144.3 ipso-C, 132.1 aromatic-C, 127.6 aromatic-C, 118.9 olefinic-C, 114.8 olefinic-C, 109.7 CN-C, 47.0 quarternary-C, 46.4 quarternary-C, 33.2 CH_2-C, 31.5 CH_2-C, 29.5 CH_3-C, 27.5 CH_3-C.

3.7. 2,2'-((4-hydroxy-3-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) 3g

$C_{24}H_{30}O_6$, 414.20 g.mol^{-1}; (82.3% yield); White solid, m.p. = 201-205 ºC; FTIR νmax(cm-1) = 3462.18, 2955.21, 2868.66, 1710.48, 1580.65, 1514.7, 1448.76, 1362.2, 1306.56, 1238.55, 1209.7, 1152, 1106.66, 1053.08, 1038.65, 824.33, 807.84, 762.5.; ^{1}H NMR (500 MHz, CDCl3) δ (ppm) = 11.97 (s, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 2.2, 1.1 Hz, 1H), 6.59 (ddd, J = 8.3, 2.2, 1.3 Hz, 1H), 5.50 (s, 1H), 3.77 (s, 3H), 2.48 - 2.30 (m, 8H), 1.24 (s, 6H), 1.11 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) = 190.4 carbonil-C, 189.3 olefinic-C, 146.3 ipso-C, 143.6 ipso-C, 129.7 aromatic-C, 119.5 aromatic-C, 115.8 aromatic-C, 114.1 aromatic C, 109.9 aromatic-C, 55.6 OCH$_3$-C, 47.1 quarternary-C, 46.4 quarternary-C, 32.3 CH$_2$-C, 31.3 CH$_2$-C, 29.9 CH$_3$-C, 27.1 CH$_3$-C.

3.8. 2,2'-((4-hydroxy-3,5-dimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) 3h

$C_{25}H_{32}O_7$, 444.21 g.mol^{-1}; (94% yield); White solid, m.p. = 203-205 ºC; FTIR νmax(cm-1) = 3429.2, 2957.27, 2870.72, 1584.77, 1512.64, 1448.76, 1419.9, 1368.38, 1308.62, 1267.4, 1236.49, 1152, 1125.21, 1032.47, 807.84, 733.65.; 1H NMR (500 MHz, CDCl3) δ (ppm) = 12.02 (s, 1H), 6.35 (s, 2H), 5.50 (s, 1H), 3.77 (s, 6H), 2.47-2.34 (m, 8H), 1.24 (s, 6H), 1.12 (s, 6H). 13C NMR (126 MHz, CDCl3) δ (ppm) = 190.4 carbonil-C, 189.3 olefinic-C, 146.8 ipso-C, 132.7 ipso-C, 129.1 aromatic-C, 115.7 aromatic-C, 103.9 aromatic-C, 56.1 OCH3-C, 47.1 quarternary-C, 46.3 quarternary-C, 32.5 CH2-C, 31.1 CH2-C, 30.0 CH3-C, 26.8 CH3-C. 3.9. 2,2'-((3,4,5-trimethoxyphenyl)methylene)bis(3-hydroxy-5,5 dimethylcyclohex-2-en-1-one) 3i C26H34O7, 458.23 g.mol-1; (85.13% yield); Yellow solid, m.p. = 205-209 oC; FTIR νmax(cm-1) (pure) = 2916.06, 2848.05, 1617.74, 1580.65, 1467.3, 1380.75, 1306.56, 1224.13, 1193.21, 1032.47, 871.73, 818.14.; 1H NMR (500 MHz, CDCl3) δ (ppm) = 12.02 (s, 1H), 6.35 (d, J = 1.2 Hz, 2H), 5.50 (t, J = 1.3 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 6H), 2.48-2.34 (m, 8H), 1.25 (s, 6H), 1.12 (s, 6H). 13C NMR (126 MHz, CDCl3) δ (ppm) = 190.4 carbonil-C, 189.3 olefinic-C, 152.8 ipso-C, 135.9 ipso-C, 133.7 ipso-C, 115.6 aromatic-C, 106.7 aromatic-C, 104.2 aromatic-C, 60.9 OCH_3-C, 56.3 OCH_3-C, 55.9 OCH_3-C, 47.1 quarternary-C, 46.3 quarternary-C, 32.8 CH_2-C, 31.1 CH_2-C, 30.0 CH_3-C, 26.8 CH_3-C.

3.10. 2,2'-((4-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dim ethylcyclohex-2-en-1-one) 3j

$C_{24}H_{30}O_5$, 398.21 g.mol^{-1}; (89.2% yield); Yellow solid, m.p. = 218-220 ºC; FTIR νmax(cm^{-1}) = 3431.26, 2957.27, 2868.66, 1528.71, 1510.58, 1457, 1419.9, 1368.38, 1308.62, 1267.4, 1236.49, 1152, 1125.21, 1044.83, 1030.41, 805.78, 733.65.; ^{1}H NMR (400 MHz, CDCl3) δ (ppm) = 11.90 (s, 1H), 7.02-6.97 (m, 2H), 6.83-6.78 (m, 2H), 5.48 (s, 1H), 3.77 (s, 3H), 2.49-2.26 (m, 6H), 1.22 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ (ppm) = 190.4 carbonil-C, 189.3 olefinic-C, 157.6 ipso-C, 129.8 aromatic-C, 127.8 aromatic-C, 115.8 aromatic-C, 113.6 aromatic C, 55.2 OCH_3-C, 47.1 quarternary-C, 46.4 quarternary-C, 32.0 CH_2-C, 31.4 CH_2-C, 29.6 CH_3-C, 27.4 CH_3-C.

3.11. 2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyc lohex-2-en-1-one) 3k

$C_{21}H_{26}O_5$, 358.18 g.mol^{-1}; (88.1% yield); Brown solid, m.p. = 172-175 ºC; FTIR νmax(cm^{-1}) = 3410.65, 3058.25, 3004,67, 2961.4, 2872.78, 1710.48, 1601.26, 1419.9, 1360.14, 1220, 1092.23, 1013.92, 898.52, 834.63, 733.65.; 1H NMR (400 MHz, CDCl3) δ (ppm) = 12.14 (s, 1H), 7.25 (dt, J = 2.1, 0.9 Hz, 1H), 6.28 (dd, J = 3.3, 1.9 Hz, 1H), 5.93 (dt, J = 2.9, 1.3 Hz, 1H), 5.38 (t, J = 1.3 Hz, 1H), 2.36 (d, J = 6.3 Hz, 9H), 1.20-1.04 (m, 21H). 13C NMR (101 MHz, CDCl3) δ (ppm) = 189.5 olefinic-C, 151.7 ipso-C, 141.0 aromatic-C, 114.1 aromatic-C, 110.1 aromatic-C, 106.2 aromatic-C, 46.9 quarternary-C, 46.2 quarternary-C, 31.4 CH_2-C, 29.7 CH_2-C, 29.2 CH_3-C, 26.5 CH_3-C (supplementary material).

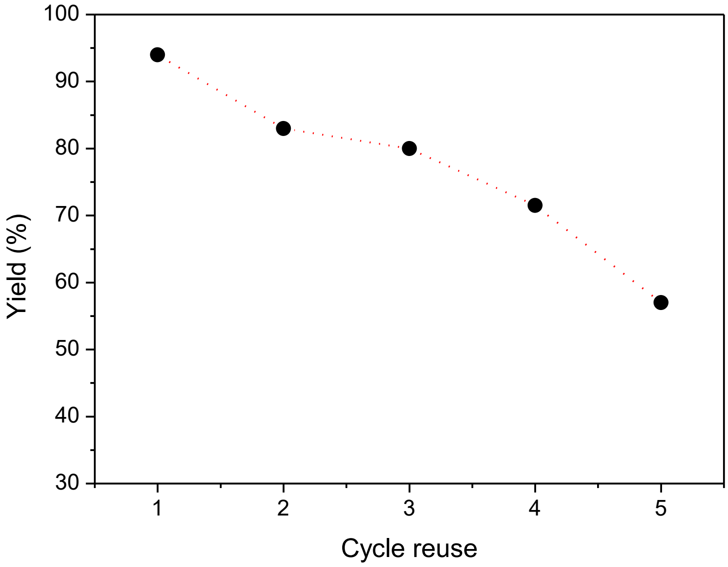


Figure 1. Reusability analysis on $Al(OH)_3$, used in tetraketone synthesis [the reaction was carried out using benzaldehyde 1a (1.0 mmol, 102 µL), dimedone 2 (2.5 mmol, 350.4 mg) in water (5.0 mL).

Table 4. Synthesis of tetra ketone **3a**, using different catalysts.

Catalyst	Temperature/°C	Solvent/ Time(min)	Yield (%)	Recycling	Ref.
Nano-ZnS	room temperature	Water/30	97	In 5 runs maintain 95% yield	17
NP	room temperature	Water/120	98	In 4 runs it maintains 93% yield, after the catalyst is calcined at 900 °C for 0.5 h	18
PVP-Ni	room temperature	without solvent/10	93	Up to the sixth cycle the yield was 74%.	19

Nano Fe/NaY	80	Ethanol/105	98	Yield loss (90%) over four cycles, due to pore blockage in the zeolite structure.	20
ZnO NPs PE	room temperature	H_2O (20% NaPTS)/20	95	It 13% activity loss after the fifth cycle of the reaction (82% yield).	21
GO/ZnO	100	Water/10	99	Maintained 95% yield until the 5th run.	22
$Al(OH)_3$	80	Water/60	97	Yield dropped to 57% in the 5th run, due to catalyst deactivation by solubilization or adsorption on active sites.	In the present work

4. MATERIALS AND METHODS

4.1. Reagents and Solvents

We used benzaldehyde (99%), 4-bromobenzaldehyde (99%), 3 nitro-4-chlorobenzaldehyde (97%), 4-fluorobenzaldehyde (98%), 3 nitro-fluorobenzaldehyde (97%), 2-fluorobenzaldehyde (97%), 4 methylbenzaldehyde (99%), 4-ciano-nitrobenzaldehyde (99%), 4 hydroxy-3-metoxy-benzaldehyde (98%), 3,4,5-trimethoxybenzaldehyde (98%), furfural (99%), ethyl acetoacetate (99%) and deuterated $CDCl_3$, purchased from Sigma Aldrich and used without further purification. Ethyl acetate, hexane, and ethanol were obtained from Synth. We performed the thin layer chromatography (TLC) on DC-Fertigfolien ALUGRAM® XTra SIL G/UV254 (lay er: 0.20 mm silica gel 60 with fluorescent indicator UV254).

4.2. Equipment

The samples were analyzed by Gas Chromatography-Mass Spectrometry (GC-MS) analyses coupled to a mass selective detector (Shimadzu GC2010plus) (Shimadzu MS2010plus) in electron ionization (EI, 70 eV) mode. Analyses were performed with a DB5 column (30 m × 0.25 mm × 0.25 µm, J & W Scientific). The initial oven temperature was 90 °C for 4 min, increased to 280 °C at 10 °C min^{-1} and held for 5 min, and finally, increased to 300 °C at 10 °C min^{-1} and held for 10 min. The total analysis time was 40 min. The temperatures of the injector and interface were maintained at 250 °C and 270 °C, respectively. Helium was used as carrier gas with an initial flow of 0.75 mL min^{-1}, and the injection volume was 1 µL (split ratio of 1:20). The fragment ions were detected in the range of 40-550 Da (Institute of Chemistry of São Carlos - IQSC/USP). The Fourier Transform Infrared (FT-IR) spectra were recorded on a Shimadzu IRAffinity spectrometer. The samples were prepared on KBr disks. The transmittance was reported in cm-1 of the band between 4000-400 cm^{-1} (IQSC/USP). The Nuclear Magnetic Resonance (NMR) spectra were recorded on an Agilent Technologies 500/54 Premium Shielded or Agilent Technologies 400/54 Premi um Shielded spectrometer, with CDCl3 (99.9%) as solvents and TMS as the internal standard. The chemical shifts given in ppm and coupling constants (J) values were reported in Hz. The chemical shifts of deuterated solvents used were CDCl3 (δH 7.26, δC 77.1) (IQSC/USP) [23].

4.3. General Procedure for the Preparation of 3a-k

A mixture of aldehyde (1 mmol), dimedone (2.5 mmol), $Al(OH)_3$ (0.1 mmol) was heated at 80ºC for 60 min. After completion of the reaction, the mixture was washed with water (15 mL). The crude product was purified by recrystallization from EtOH resulting in the white crystals of pure **3a-k.** ^{1}H NMR and ^{13}C NMR spectra were recorded on an

Agilent Technologies 500/54 Premium Shielded spectrometer, with $CDCl_3$ as the solvent and TMS as the internal standard unless otherwise noted. The chemical shifts are given in ppm and coupling constants (J) in Hz. 4.4. General Procedure of Reuse of $Al(OH)_3$ The $Al(OH)_3$ as a catalyst for tetraketone synthesis was investigated and observed a reuse cycle until 4 times in moderates yield up to 70 %. The experimental conditions for each cycle were: benzaldehyde **1a** (1 mmol, 102 µL), dimedone **2** (2.5 mmol, 350.4 mg), $Al(OH)_3$ (0.1 mmol,) in water (5 mL, 80 °C at 60 min). After com pletion of the reaction, the mixture was diluted in 20 mL of ethanol until solubility of tetrakone derivative. After the solution was filtrated, it was washed with 10 mL of ethanol and recover the $Al(OH)_3$. It was dried at room temperature.

4.5. Minimal Inhibitory and Bactericide Concentrations

The American Type Culture Collection (ATCC): *Staphylococcus aureus* (ATCC 6538P) and *Pseudomonas aeruginosa* (ATCC 9027) were maintained and cultured according to the specific conditions of National Committee for Clinical Laboratory Standards. The inoculum for the tests was prepared by culturing the bacterial strains in sterile BHI broth at 37 °C for 24 h. After culturing, the concentration was adjusted to 1.5 × 108 colony forming units $CFU.mL^{-1}$ (equivalent to 0.5 in the McFarland scale), which was further diluted to 1.5 × 106 $CFU.mL^{-1}$. The microdilution method was used to obtain the minimum inhibitory concentration (MIC) and minimal bactericidal concentration (MBC). Serial dilutions from the tested substances (250 $\mu g.mL^{-1}$ to 31.25 $\mu g.mL^{-1}$) in sterile BHI broth were transferred to a 96-well sterile microplate. MIC was defined as the lowest concentration that inhibited the inoculum growth. MBC was obtained by seeding aliquots obtained from the MIC and the two wells immediately above the MIC over MH agar plates and incubating for 24 h at 37 °C. It was defined as the mini mum concentration eliminating most (≥99.9%) viable bacteria, identified by the lack of colonies on the agar surface. All assays were performed in triplicate under strictly aseptic conditions.

CONCLUSION

The eco-friendly protocol of tetraketones synthesis involving $Al(OH)_3$ as a catalyst and water as a solvent has been elaborated. Notable features of this method include mild conditions, short reaction times, high yields, and catalyst reuse. The advantages of the worked-out method consist of high chemoselectivity accompanied by the yields of products from good to excellent. In addition, compounds **3b, 3f** and **3j** developed noteworthy effectiveness against Gram-negative bacteria (*S. aureus* (ATCC-6538P) [24].

AUTHOR'S CONTRIBUTION

RM and MJM were responsible for the conceptualization, methodology, formal analysis, data curation, writing - original draft, writing - review & editing of the manuscript. ANO was responsible for the conceptualization, methodology, formal analysis, data curation, writing - original draft, writing - review & editing of the manuscript. ALMP, AP, FFO, DEQJ and IMF were responsible for the con capitalization, project administration and funding acquisition of the manuscript.

LIST OF ABBREVIATIONS

$CHCl_3$ = Chloroform DMSO = Dimethylsulfoxide THF = Tetrahydrofurane EtOAc = Ethyl acetate EtOH = Ethanol MeOH = Methanol.

CONSENT FOR PUBLICATION Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available with in the article. FUNDING

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

REFERENCES

[1] Khan, K.M.; Maharvi, G.M.; Khan, M.T.H.; Jabbar, S.A.; Perveen, S.; Begum, S.; Choudhary, M.I. Tetraketones: A New Class of Tyrosinase Inhibitors. *Bioorg. Med. Chem.*, **2006**, *14*, 344–351.

[2] Kantevari, S.; Bantu, R.; Nagarapu, L. $HClO_4$-SiO_2 and PPA-SiO_2 Catalyzed Efficient One-Pot Knoevenagel Condensation, Michael Addition and Cyclodehydration of Dimedone and Aldehydes in Acetonitrile, Aqueous and Solvent-Free Conditions: Scope and Limitations. *J. Mol. Catal. A. Chem*., **2007**, *269*, 53–57.

[3] Kamali, F.; Shirini, F. Melamine: An Efficient Promoter for Some of the Multi-component Reactions. *Polycycl. Aromat. Compd*., **2021**, *41*, 73–94.

[4] Li, J.T.; Li, Y.W.; Song. Y.L.; Chen, G.F. Improved Synthesis of 2,20-Arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) Derivatives Catalyzed by Urea Under Ultrasound. *Ultrason. Sonochem*., **2012**, *19*, 1–4.

[5] Lin, L.W.; Qiang, W.L.; Lin, Y.F. Alum-Catalyzed One-Pot Synthesis of Dihydropyrano[3,2-b]chromenediones, *J. Braz. Chem. Soc*., **2011**, *22*, 2202-2205.

[6] Das, P.; Kumar, A.; Howlader, P.; Mukherjee, P.S. A Self-Assembled Trigonal Prismatic Molecular Vessel for Catalytic Dehydration Reactions in Water. *Chem. - Eur. J*., **2017**, *23*, 12565–12574.

[7] Rosati, O.; Pelosi, A.; Temperini, A.; Pace, V.; Curini, M. Potassium-Exchanged Zirconium Hydrogen Phosphate [α-Zr$(KPO_4)_2$]-Catalyzed Synthesis of 2-Amino-4*H*-Pyran Derivatives Under Solvent-Free Conditions. *Synthesis*., **2016**, *48*, 1533–1540.

[8] Ilangovan, A.; Muralidharan, S.; Sakthivel, P.; Malayappasamy. S.; Karuppusamy, S.; Kaushik, M.P. Simple and Cost-Effective Acid Catalysts for Efficient Synthesis of 9-Aryl-1,8-Dioxooctahydroxanthene. *Tetrahedron Lett*., **2013**, *54*, 491–494.

[9] Ferreira, I.M.; Casagrande, G.A.; Pizzuti, L.; Raminelli, C. Ultrasound-Promoted Rapid and Efficient Iodination of Aromatic and Heteroaromatic Compounds in the Presence of Iodine and Hydrogen Peroxide in Water. *Synth Commun*., **2014**, *44*, 2094–2102.

[10] Gallo, R.D.C.; Ferreira, I.M.; Casagrande, G.A.; Pizzuti, L.; Oliveira-Silva, D.; Raminelli, C. Efficient and Eco-Friendly Synthesis of Iodinated Aromatic Building Blocks Promoted by Iodine and Hydrogen Peroxide in Water: A Mechanistic Investigation by Mass Spectrometry. *Tetrahedron Lett*., **2012**, *53*, 5372–5375.

[11] Neves, F.B.; Zanin, L.L.; Pereira, R.R.; Júnior, J.O.C.S.; Costa, R.M.R.; Porto, A.L.M.; Yoshioka, S.A.; Oliveira, A.N.; Jimenez, D.E.Q.; Ferreira, I.M. Chitin and Silk Fibroin Biopolymers Modified by Oxone: Efficient Heterogeneous Catalysts for Knoevenagel Reaction. *Catalysts*., **2022**, *12*, 904-918.

[12] Jimenez, D.E.Q.; Ferreira, I.M.; Birolli, W.G.; Fonseca, L.P.; Porto, A.L.M. Synthesis and Biocatalytic Ene-Reduction of Knoevenagel Condensation Compounds by the Marine-Derived Fungus *Penicillium Citrinum* CBMAI 1186. *Tetrahedron*., **2016**, *72*, 7317–7322.

[13] Lasemi, Z.; Tajbakhsh, M.; Alinezhad, H.; Mehrparvar, F. 1,8-Diazabicyclo [5.4.0] undec-7-ene Functionalized Cellulose Nanofibers as an Efficient and Reusable Nanocatalyst for the Synthesis of Tetraketones in Aqueous Medium. *Res. Chem. Intermed*., **2020**, *46*, 3667–3682.

[14] Lopes, S.Q.; Holanda, F.H.; Jimenez, D.E.Q.; Oliveira, A.N.; Ferreira, I.M. Use of Oxone® as a Potential Catalyst in Biodiesel Production from Palm Fatty Acid Distillate (PFAD). *Catal. Lett*., **2021**, *152*, 1009–1019.

[15] De Oliveira, A.N.; Oliveira, D.T.; Angélica, R.S.; Andrade, E.L.A.; Silva, J.K.R.; Rocha-Filho, G.N.; Luque, R.; Nascimento, L.A.S. Efficient Esterification of Eugenol Using a Microwave-Activated Waste Kaolin. *React. Kinet. Mech. Catal*., **2020**, *130*, 633–653.

[16] De Oliveira, A.N.; Ferreira, IM.; Jimenez, D.E.Q.; Silva, L.S.; Costa, A.A.F.; Lima, E.T.L.; Costa, F.F.; Rocha-Filho, G.N.; Luque. R.; Nascimento, L.A.S. Mining Waste

Valorisation to Catalytically Active Mesoporous Materials for the Esterification of Fatty Acid Palm Oil Waste. *Mol. Catal*., **2022**, 528, 112504.

[17] Safaei-Ghomi, J.; Asadian, S.; Nazemzadeh, S.H.; Shahbazi-Alavi, H. Synthesis of Tetraketones Using ZnS Nanoparticles as an Efficient Catalyst. *J. Chin. Chem. Soc*., **2018**, *65*, 430-434.

[18] Fallah, A.; Tajbakhsh, M.; Vahedi, H.; Bekhradnia, A. Natural Phosphate as an Efficient and Green Catalyst for Synthesis of Tetraketone and Xanthene Derivatives. *Res. Chem. Intermed*., **2017**, *43*, 29-43.

[19] Khurana, J.M.; Vij, K. Nickel Nanoparticles: A Highly Efficient Catalyst for One Pot Synthesis of Tetraketones and Biscoumarins. *J. Chem. Sci*., **2012**, *124*, 907-912.

[20] Tajbakhsh, M.; Heidary, M.; Hosseinzadeh, R. Nano Fe/NaY Zeolite: An Efficient and Reusable Solid-Supported Catalyst for Synthesis of 1-Oxo-Hexahydroxanthene and Tetraketone Derivatives. *Res. Chem. Intermed*., **2016**, *42*, 1425-1439.

[21] Attar, S.R.; Shinde, B.; Kamble, S.B. Enhanced Catalytic Activity of Bio-Fabricated ZnO NPs Prepared by Ultrasound-Assisted Route for the Synthesis of Tetraketone and Benzylidenemalonitrile in Hydrotropic Aqueous Medium. *Res. Chem. Intermed*., **2020**, *46*, 4723-4748.

[22] Banakar, S.H.; Dekamin, M.G.; Yaghoubi, A. Selective and Highly Efficient Synthesis of Xanthenedione or Tetraketone Derivatives Catalyzed by ZnO Nanorod-Decorated Graphene Oxide. *New. J. Chem*., **2018**, *42*, 14246-14262.

[23] Jimenez, D. E. Q.; Zanin, L. L.; Ferreira, I. M.; Deflon, V. M.; Diniz, L. F.; Ellena, J.; Haiduke, R. L. A.; Porto, A. L. M. Sustainable Synthesis of Benzylidenemalononitrile Compounds Under Microwave- Irradiation. *Curr Org Chem* **2022**, *26*, 1552–1564. https://doi.org/10.2174/1385272827666221125091631.

[24] Araujo, J. T. C. de; Martin-Pastor, M.; Pérez, L.; Pinazo, A.; Sousa, F. F. O. de. Development of Anacardic Acid-Loaded Zein Nanoparticles: Physical Chemical Characterization, Stability and Antimicrobial Improvement. *J Mol Liq* **2021**, *332*, 115808. https://doi.org/10.1016/J.MOLLIQ.2021.115808.

5 CONSIDERAÇÕES FINAIS

Este trabalho analisou a produção “verde” de tetracetonas funcionalizadas, usando hidróxido de alumínio ($Al(OH)_3$) como catalisador e água como solvente, com o objetivo de produzir compostos de alto valor agregado e com potencial atividade biológica. A abordagem proposta se sobressaiu pela sua simplicidade, sustentabilidade e eficiência elevada, auxiliando no progresso de práticas mais sustentáveis no campo da química sintética. O $Al(OH)_3$ foi considerado favorável na reação, não só pela sua disponibilidade e custo acessível, mas também pelo seu desempenho catalítico na reação de condensação e adição Michael-Knoevenagel, garantindo rendimentos altos sob condições amenas e benéficas para o meio ambiente, como em temperatura ambiente.

Outro ponto favorável do comportamento do $Al(OH)_3$ nesta reação foi o reaproveitamento do catalisador em quatro ciclos consecutivos, sendo possível uma preservação de até 80% da atividade catalítica inicial. Esta informação é significativa, pois evidencia a capacidade de reciclagem do $Al(OH)_3$, auxiliando na diminuição de resíduos e despesas operacionais em processos industriais. No entanto, observou-se uma queda gradual no rendimento a partir do quinto ciclo, provavelmente por causa da desativação parcial do catalisador por solubilização ou bloqueio dos locais ativos. Esta observação indica um campo de pesquisa com grande potencial no futuro, onde a ênfase poderia ser a criação de métodos de regeneração do catalisador para estender sua vida útil e aprimorar ainda mais a eficácia do procedimento.

O estudo, além de trazer inovações em relação à sustentabilidade, também apresentou resultados encorajadores em relação à atividade biológica das tetracetonas produzidas. As análises *in vitro* contra *Staphylococcus aureus* e *Pseudomonas aeruginosa* indicaram que as tetracetonas obtidas exibiram potente atividade bactericida, particularmente aqueles que continham grupos funcionais específicos, como o flúor e o cianeto. Esses compostos apresentaram valores competitivos de MIC (concentração inibitória mínima) e MBC (concentração bactericida mínima), indicando que podem ser candidatos promissores para a criação de novos antimicrobianos.

Como perspectiva, recomenda-se investigar outros tipos de catalizadores derivados de alumínio, além de ampliar o alcance das reações com variados aldeídos e cetonas para ampliar os limites de reação. Adicionalmente, um estudo minucioso dos processos de desativação do catalisador e possíveis táticas para sua reativação pode melhorar ainda mais a eficácia do procedimento. Finalmente, sugere-se também expandir as pesquisas sobre a atividade biológica das tetracetonas, incluindo a análise contra uma variedade mais extensa de microrganismos patogênicos, o que poderia reforçar a utilização desses compostos como potenciais agentes terapêuticos, tornando-se uma possível alternativa no controle microbiano patogênicos.

ANASTAS, P. T.; WILLIAMSON, T. Green Chemistry Frontiers in Benign Chemical Synthesis and Process. **Oxford University Press**, 1998.

BIGDELI, M. A.; HERAVI, M. M.; HOSSEIN MAHDAVINIA, G. Wet cyanuric chloride catalyzed simple and efficient synthesis of 14-aryl or alkyl-14-H-dibenzo[a,j]xanthenes. **Catalysis Communications**, v. 8, n. 11, p. 1595–1598, nov. 2007.

CHUNG, T. W. et al. Multicomponent Synthesis of Functionalized Tetrahydroacridinones: Insights into a Mechanistic Route. **Organic Letters**, v. 17, n. 21, p. 5368–5371, 6 nov. 2015.

ESMAEILI, M. S. et al. Preparation and study of the catalytic application in the synthesis of xanthenedione pharmaceuticals of a hybrid nano-system based on copper, zinc and iron nanoparticles. **Research on Chemical Intermediates**, v. 47, n. 3, p. 973–996, 1 mar. 2021.

KHAN, Khalid Mohammed et al. An alternative method for the synthesis of tetraketones and their lipoxygenase inhibiting and antioxidant properties. **Letters in Drug Design & Discovery**, v. 4, n. 4, p. 272-278, 2007.

MALEKI, Behrooz et al. Chemoselective synthesis of tetraketones in water catalyzed by nanostructured diphosphate $Na_2CaP_2O_7$. **Organic Preparations and Procedures International**, v. 50, n. 3, p. 288-300, 2018.

PATIL, M. S. et al. Rapid, efficient and solvent-free synthesis of (un)symmetrical xanthenes catalyzed by recyclable sulfated polyborate. **Tetrahedron Letters**, v. 58, n. 29, p. 2859–2864, 2017.

RAY, Suman et al. Binary conjugate Brønsted–Lewis acid supported on mesoporous silica nanoparticles for the domino addition/elimination/addition and addition/elimination/addition/cyclization cascade. **Catalysis Communications**, v. 43, p. 173-178, 2014.

REN, Z.; CAO, W.; TONG, W.; JING, X. Knoevengel Condensation of Aldehydes with cyclic active methylene compounds in water. **Syn Commun**, v. 32, p. 1947–52, 2002.

RONG, L. et al. Reaction of imines with 5,5-dimethyl-1,3-cyclohexandione. **Synthetic Communications**, v. 36, n. 16, p. 2345–2353, 1 ago. 2006.

YU, Jian-Jun; WANG, Li-Min; LIU, Jin-Qian; GUO, Feng-Lou; LIU, Ying; JIAO, Ning. Synthesis of tetraketones in water and under catalyst-free conditions. **Green Chemistry**, v. 12, n. 2, p. 216–219, 2010. Disponível em: https://doi.org/10.1039/b913816a.

Supplementary Material

“Green” synthesis of tetraketones with prominent bactericide effect

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2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3a***

$C_{23}H_{28}O_4$, 368.20 g.mol^{-1}; (52.32% yield); White solid, m.p. = 189-191 °C; FTIR ν_{max}(cm^{-1}) (pure) = 2957.27, 2870.72, 1593.01, 1448.76, 1372.51, 1302.44, 1238.55, 1149.94, 1055.14, 1042.77, 776.93, 709.91.; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.91 (s, 1H), 7.30-7.26 (m, 2H), 7.20-7.15 (m, 1H), 7.12-7.09 (m, 2H), 5.55 (s, 1H), 2.55-2.23 (m, 7H), 1.26-1.23 (m, 8H), 1.11 (s, 6H). ^{13}C (126 MHz, $CDCl_3$) δ (ppm) = 203.6, 190.5, 189.4, 138.1, 128.2, 126.7, 125.8, 115.6, 57.3, 54.1, 47.1, 46.5, 32.7, 31.5, 31.4, 31.4, 31.4, 31.4, 31.4, 30.9, 29.6, 28.4, 28.2, 27.4.

2,2'-((2-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3b***

$C_{23}H_{27}FO_4$, 386.19 g.mol^{-1}; (96.8% yield); White solid, m.p. = 182-184 °C; FTIR ν_{max}(cm^{-1}) (pure) = 2957.27, 2870.72, 1724.91, 1588.89, 1487.91, 1452.88, 1370.44, 1302.44, 1226.19, 1166.42, 1152, 1114.9, 1044.83, 752.2, 733.65, 702.74.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.90 (s, 1H), 7.21-7.11 (m, 2H), 7.05 (t, *J* = 7.0 Hz, 1H), 6.94 (dd, *J* = 11.9, 8.1 Hz, 1H), 5.61 (s, 1H), 2.51-2.24 (m, 8H), 1.23-0.98 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 189.5, 162.1, 159.7, 129.2, 129.2, 128.0, 127.9, 123.6, 123.6, 115.7, 115.5, 115.5, 31.3, 28.9.

2,2'-((4-bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3c***

$C_{23}H_{27}BrO_4$, 446.11 g.mol^{-1}; (91.4% yield); White solid, m.p. = 170-174 °C; FTIR ν_{max}(cm^{-1}) (pure) = 2957.27, 2870.72, 1712.54, 1584.77, 1485.85, 1366.32, 1300.38, 1250.92, 1120, 1166.42, 1154.06, 1067.5, 1009.8, 826.39.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.86 (s, 1H), 7.39-7.35 (m, 2H), 6.98-6.94 (m, 2H), 5.44 (s, 1H), 2.38 (dq, *J* = 26.7, 17.9 Hz, 7H), 1.21 (s, 6H), 1.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 190.6, 189.4, 137.3, 131.3, 128.6, 119.6, 115.3, 115.2, 47.0, 46.4, 32.5, 31.4, 31.4, 31.4, 29.6, 27.4.

2,2'-((4-chloro-3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3d***

$C_{23}H_{26}ClNO_6$, 447.14 g.mol^{-1}; (73.4% yield); Yellow pale solid, m.p. = 132-135 °C; FTIR ν_{max}(cm^{-1}) (pure) = 2953.15, 2868.66, 1691.93, 1584.77, 1506.46, 1459.06, 1413.72, 1370.44, 1325.11, 1234.43, 1127.27, 1007.74, 886.15, 824.33.; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.86 (s, 1H), 8.04 (ddt, *J* = 7.8, 2.6, 1.2 Hz, 1H), 7.46-7.39 (m, 2H), 5.55-5.53 (m, 1H), 2.53-2.31 (m, 8H), 1.28 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 191.1, 189.6, 148.4, 140.7, 132.9, 129.1, 122.2, 121.0, 114.8, 47.0, 46.4, 32.9, 31.4, 29.7, 27.3.

2,2'-((3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3e***

$C_{23}H_{27}NO_6$, 413.18 g.mol^{-1}; (88.4% yield); Orange pale solid, m.p. = 187-190 ºC; FTIR ν_{max}(cm^{-1}) (pure) = 2959.34, 2870.72, 1586,83, 1527.07, 1469.36, 1448.76, 1370.44, 1345.71, 1304.5, 1250.92, 1166.42, 1154.06, 1067.5, 1044.83, 838.75, 803.72, 729.53, 702.74.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.85 (s, 1H), 8.04 (ddt, *J* = 7.6, 2.4, 1.2 Hz, 1H), 8.00 (q, *J* = 2.1 Hz, 1H), 7.47-7.39 (m, 2H), 5.54 (s, 1H), 2.42 (dq, *J* = 28.5, 17.7 Hz, 7H), 1.27 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 191.1, 189.6, 148.41, 140.7, 132.9, 129.1, 122.2, 121.0, 114.8, 47.0, 46.4, 32.9, 31.4, 29.6, 27.3.

4-(bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)benzonitrile ***3f***

$C_{24}H_{27}NO_4$, 393.19 g.mol^{-1}; (96% yield); White solid, m.p. = 183-188 ºC; FTIR ν_{max}(cm^{-1}) (pure) = 3056.19, 2920.18, 2850.11, 1696.05, 1601.26, 1539.43, 1358.08, 1265.34, 1236.49, 1088.11, 1046.9, 894.4, 830.51, 729.53, 702.74.; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.79 (s, 1H), 7.58-7.54 (m, 2H), 7.22-7.17 (m, 2H), 5.52 (s, 1H), 2.51-2.29 (m, 8H), 1.23 (s, 6H), 1.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 190.9, 189.5, 144.3, 132.1, 127.6, 118.9, 114.8, 109.7, 47.0, 46.4, 33.2, 31.5, 29.5, 27.5.

2,2'-((4-hydroxy-3-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3g***

$C_{24}H_{30}O_6$, 414.20 g.mol^{-1}; (82.3% yield); White solid, m.p. = 201-205 ºC; FTIR ν_{max}(cm^{-1}) (pure) = 3462.18, 2955.21, 2868.66, 1710.48, 1580.65, 1514.7, 1448.76, 1362.2, 1306.56, 1238.55, 1209.7, 1152, 1106.66, 1053.08, 1038.65, 824.33, 807.84, 762.5.; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 11.97 (s, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.62 (dd, *J* = 2.2, 1.1 Hz, 1H), 6.59 (ddd, *J* = 8.3, 2.2, 1.3 Hz, 1H), 5.50 (s, 1H), 3.77 (s, 3H), 2.48 - 2.30 (m, 8H), 1.24 (s, 6H), 1.11 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 190.4, 189.3, 146.3, 143.6, 129.7, 119.5, 115.8, 114.1, 109.9, 55.6, 47.1, 46.4, 32.3, 31.3, 31.3, 29.9, 27.1.

2,2'-((4-hydroxy-3,5-dimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3h***

$C_{25}H_{32}O_7$, 444.21 g.mol^{-1}; (94% yield); White solid, m.p. = 203-205 °C; FTIR ν_{max}(cm^{-1}) (pure) = 3429.2, 2957.27, 2870.72, 1584.77, 1512.64, 1448.76, 1419.9, 1368.38, 1308.62, 1267.4, 1236.49, 1152, 1125.21, 1032.47, 807.84, 733.65.; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 12.02 (s, 1H), 6.35 (s, 2H), 5.50 (s, 1H), 3.77 (s, 6H), 2.47-2.34 (m, 8H), 1.24 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 190.4, 189.3, 146.8, 132.7, 129.1, 115.7, 103.9, 56.1, 47.1, 46.3, 32.5, 31.1, 30.0, 26.8.

2,2'-((3,4,5-trimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3i***

$C_{26}H_{34}O_7$, 458.23 g.mol^{-1}; (85.13% yield); Yellow solid, m.p. = 205-209 °C; FTIR ν_{max}(cm^{-1}) (pure) = 2916.06, 2848.05, 1617.74, 1580.65, 1467.3, 1380.75, 1306.56, 1224.13, 1193.21, 1032.47, 871.73, 818.14.; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 12.02 (s, 1H), 6.35 (d, *J* = 1.2 Hz, 2H), 5.50 (t, *J* = 1.3 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 6H), 2.48-2.34 (m, 8H), 1.25 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 191.1, 190.4, 189.3, 152.8, 135.9, 133.7, 115.6, 106.7, 104.2, 60.9, 56.3, 55.9, 47.1, 46.3, 32.8, 31.1, 30.0, 26.8.

2,2'-((4-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3j***

$C_{24}H_{30}O_5$, 398.21 g.mol^{-1}; (89.2% yield); Yellow solid, m.p. = 218-220 °C; FTIR ν_{max}(cm^{-1}) (pure) = 3431.26, 2957.27, 2868.66, 1528.71, 1510.58, 1457, 1419.9, 1368.38, 1308.62, 1267.4, 1236.49, 1152, 1125.21, 1044.83, 1030.41, 805.78, 733.65.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.90 (s, 1H), 7.02-6.97 (m, 2H), 6.83-6.78 (m, 2H), 5.48 (s, 1H), 3.77 (s, 3H), 2.49-2.26 (m, 6H), 1.22 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 190.4, 189.3, 157.6, 129.8, 127.8, 115.8, 115.8, 113.6, 55.2, 47.1, 46.4, 32.0, 31.4, 31.4, 31.4, 29.6, 27.4.

2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) ***3k***

$C_{21}H_{26}O_5$, 358.18 g.mol^{-1}; (88.1% yield); Brown solid, m.p. = 172-175 °C; FTIR ν_{max}(cm^{-1}) (pure) = 3410.65, 3058.25, 3004,67, 2961.4, 2872.78, 1710.48, 1601.26, 1419.9, 1360.14, 1220, 1092.23, 1013.92, 898.52, 834.63, 733.65.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 12.14 (s, 1H), 7.25 (dt, J = 2.1, 0.9 Hz, 1H), 6.28 (dd, J = 3.3, 1.9 Hz, 1H), 5.93 (dt, J = 2.9, 1.3 Hz, 1H), 5.38 (t, J = 1.3 Hz, 1H), 2.36 (d, J = 6.3 Hz, 9H), 1.20-1.04 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 189.5, 151.7, 141.0, 114.1, 110.1, 106.2, 46.9, 46.2, 31.4, 31.4, 29.7, 29.2, 26.5.

Figure S1. FT-IR of 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3a**.

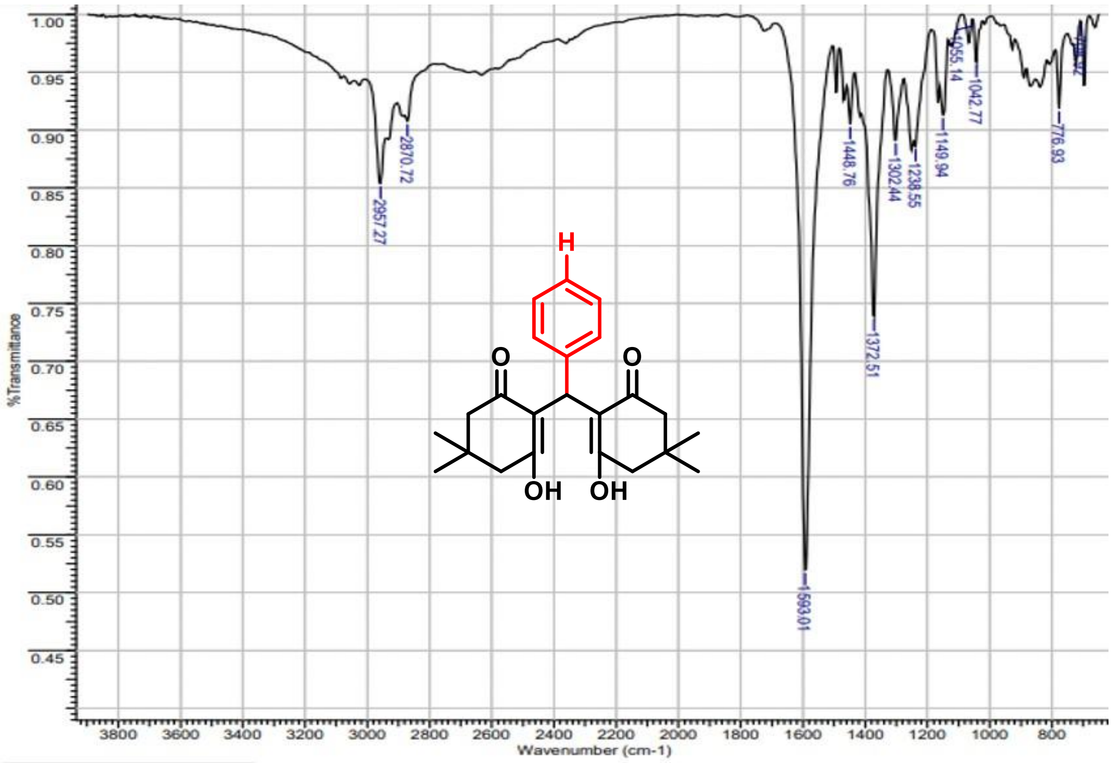

Figure S2. ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3a**.

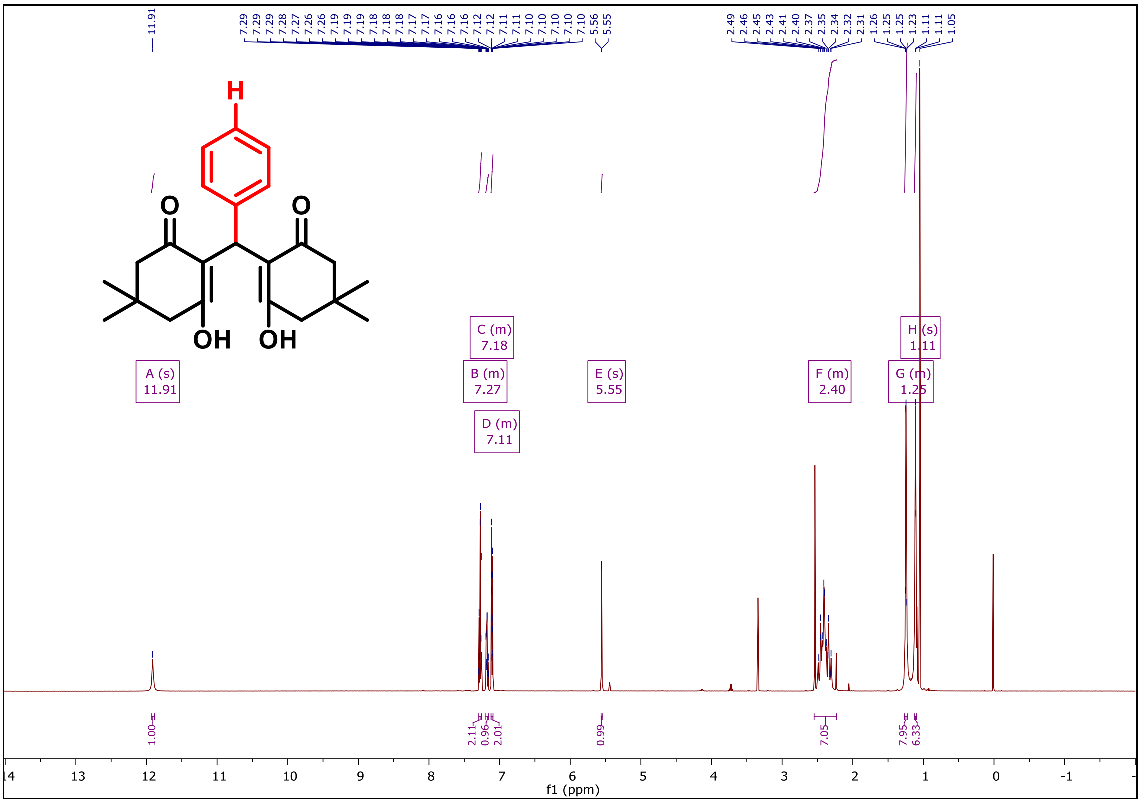

Figure S3. ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3a**.

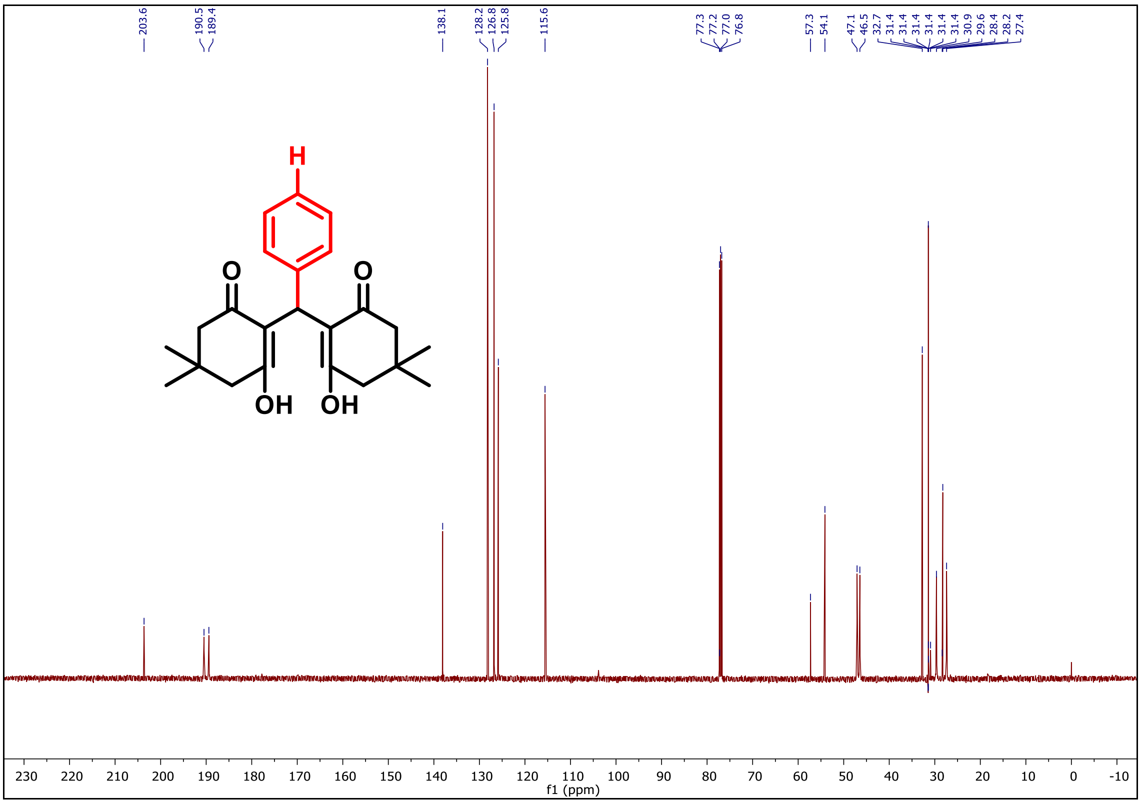

Figure S4. FT-IR of 2,2'-((2-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3b**.

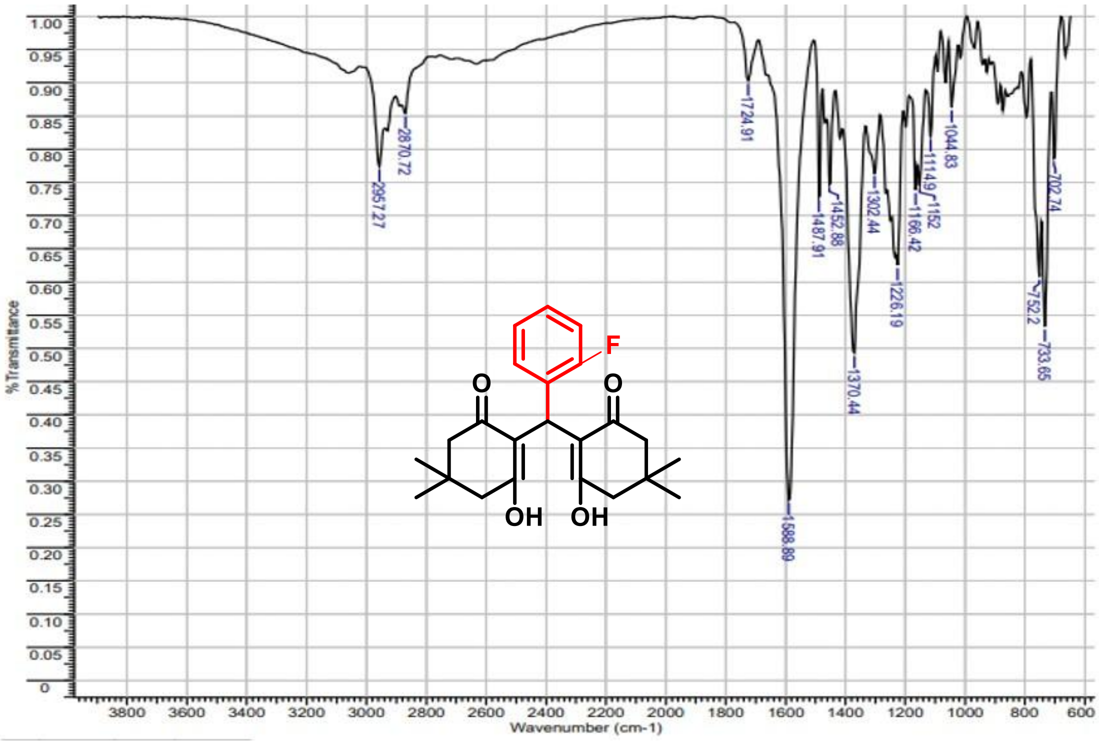

Figure S5. ^{1}H NMR (400 MHz, CDCl$_3$) of 2,2'-((2-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3b**.

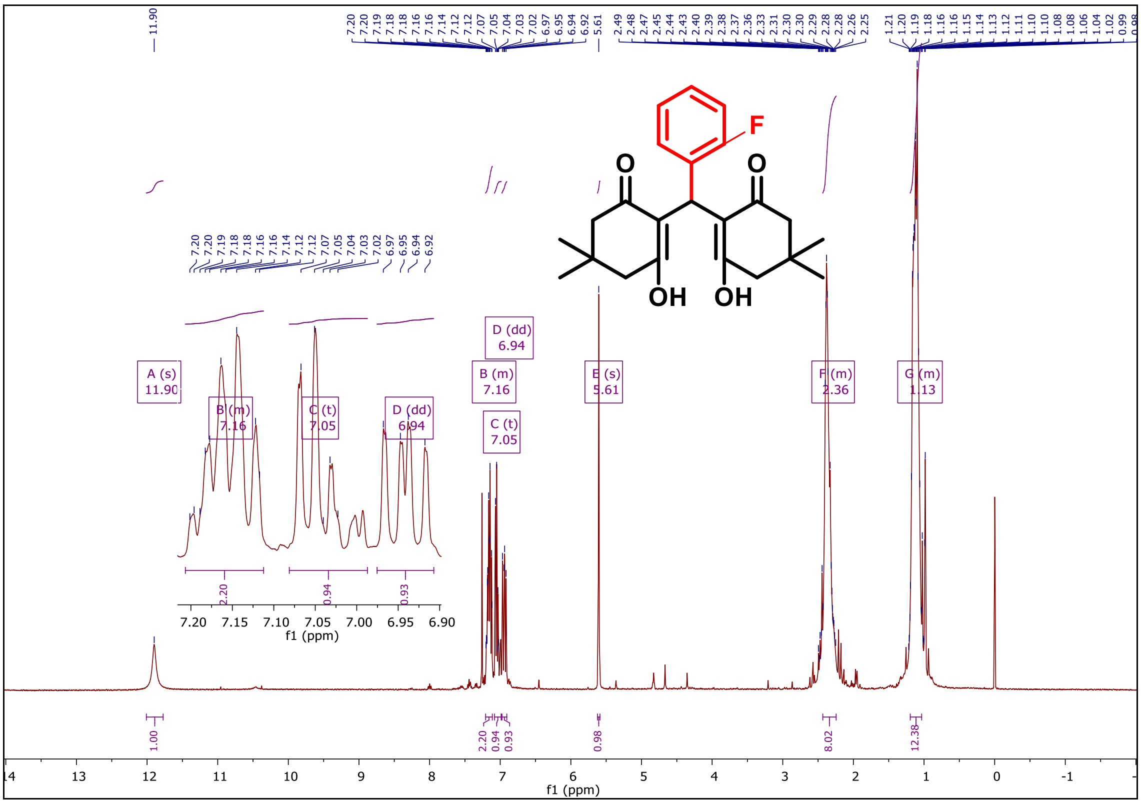

Figure S6. ^{13}C NMR (101 MHz, CDCl$_3$) of 2,2'-((2-fluorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3b**.

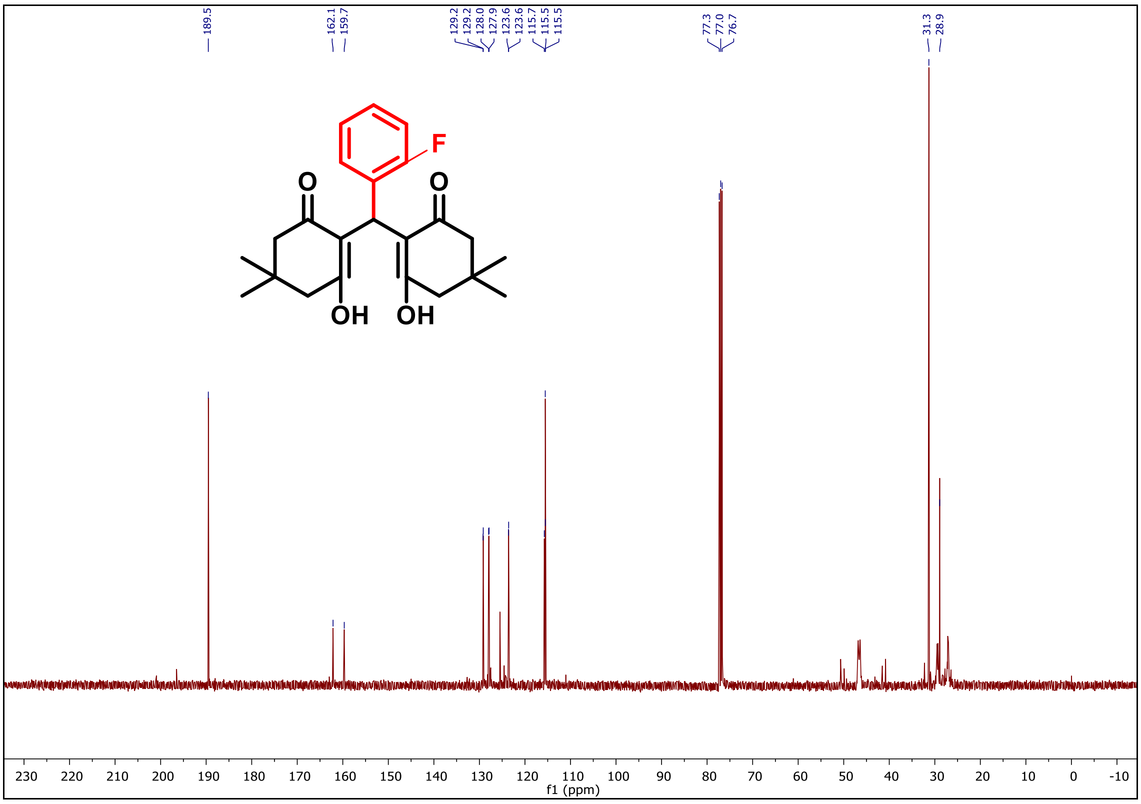

Figure S7. FT-IR of 2,2'-((4-bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3c**.

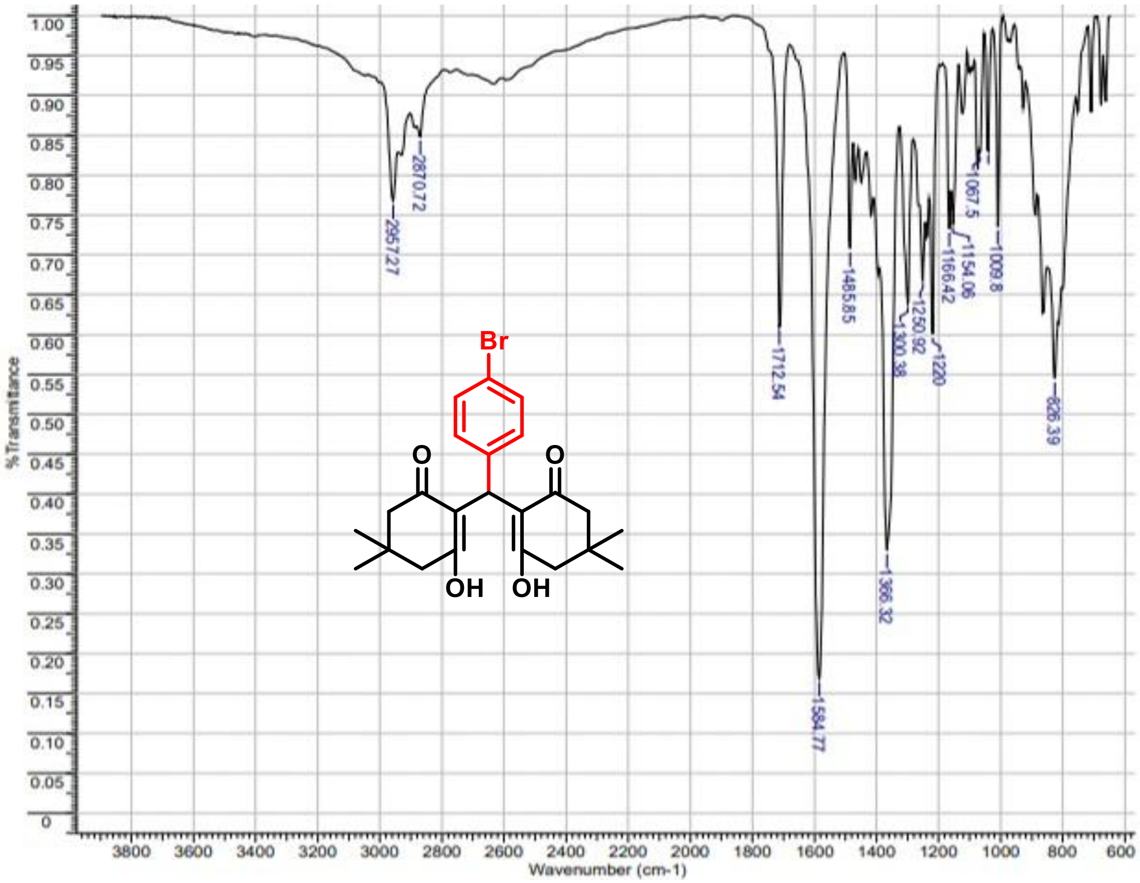

Figure S8. ^{1}H NMR (400 MHz, $CDCl_3$) of 2,2'-((4-bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3c**.

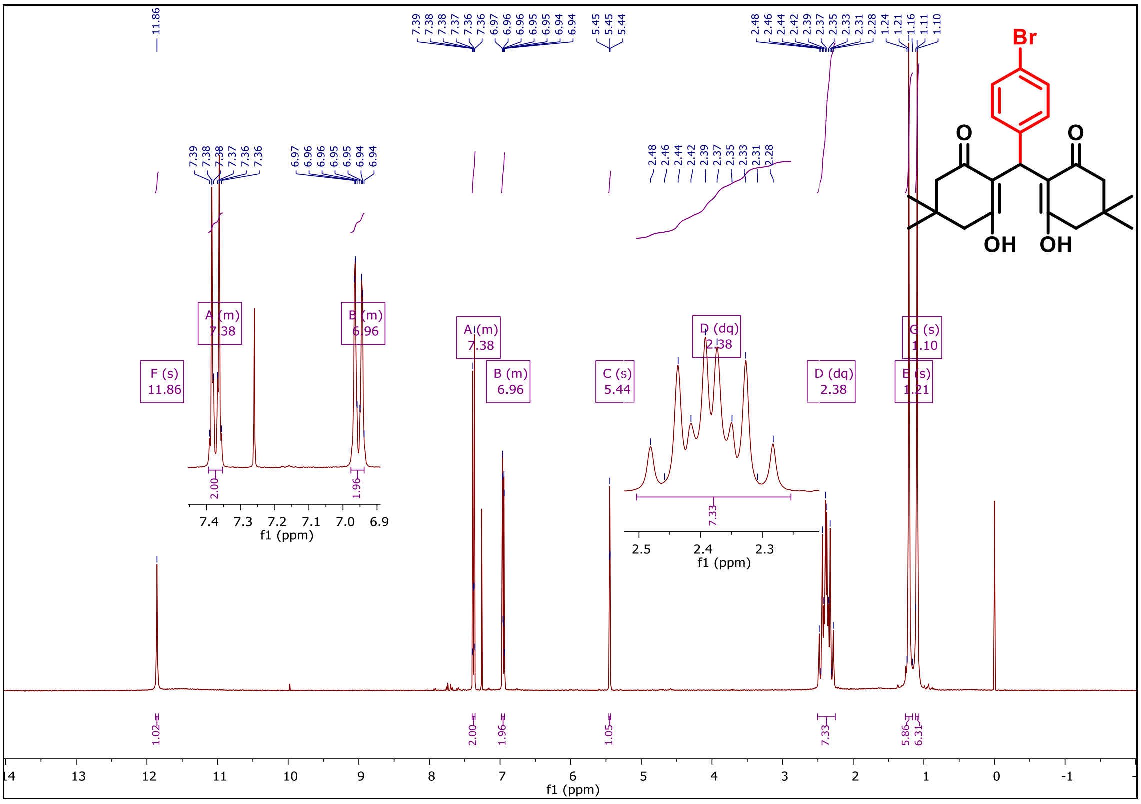

Figure S9. ^{13}C NMR (101 MHz, $CDCl_3$) of 2,2'-((4-bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3c**.

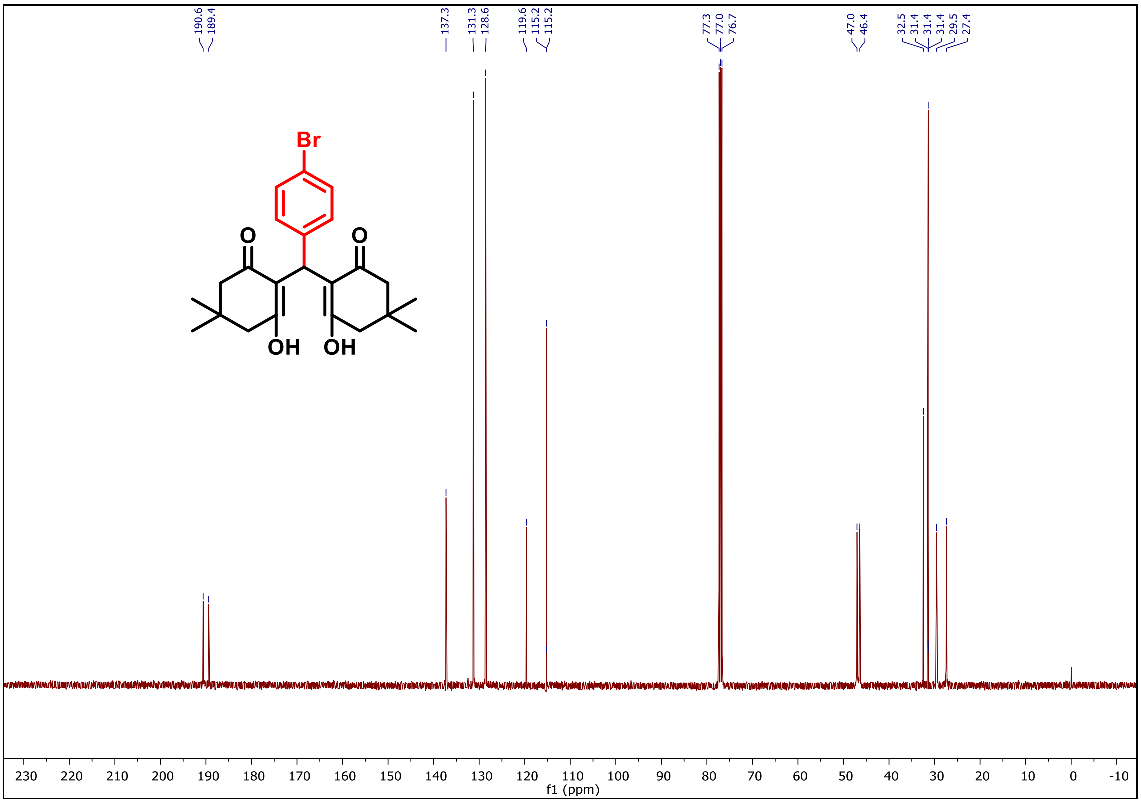

Figure S10. FT-IR of 2,2'-((4-chloro-3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3d**.

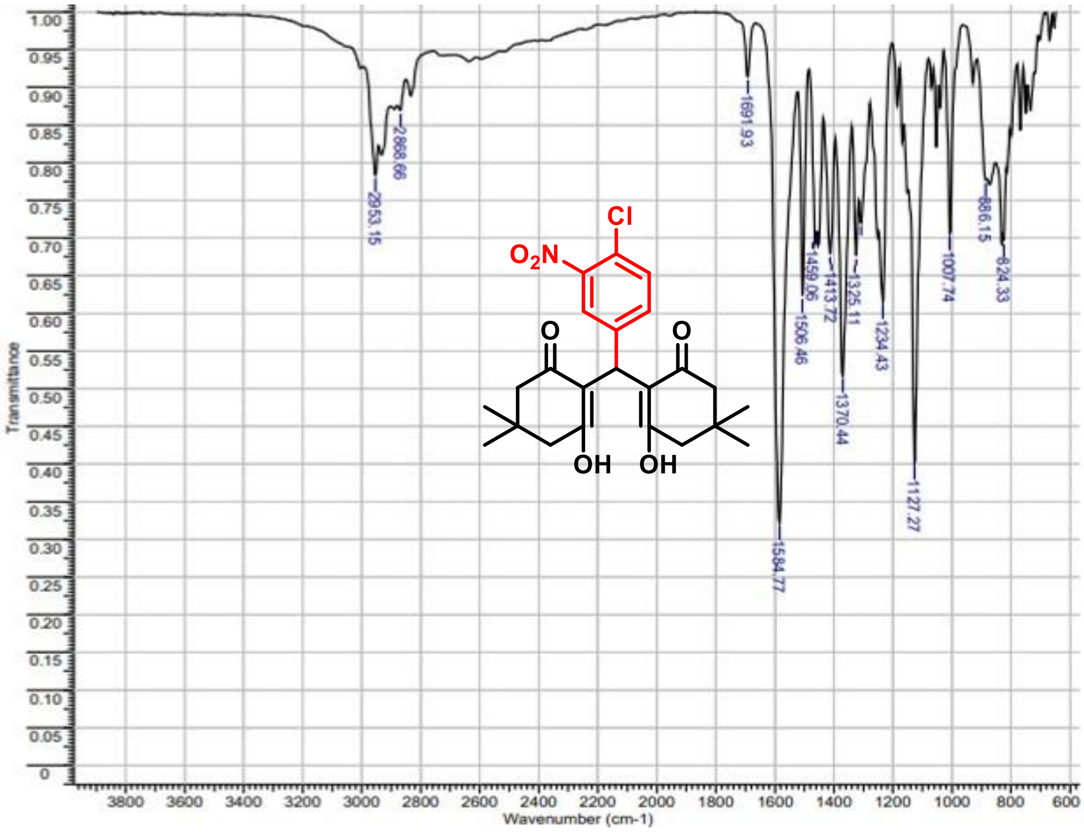

Figure S11. ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2'-((4-chloro-3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3d**.

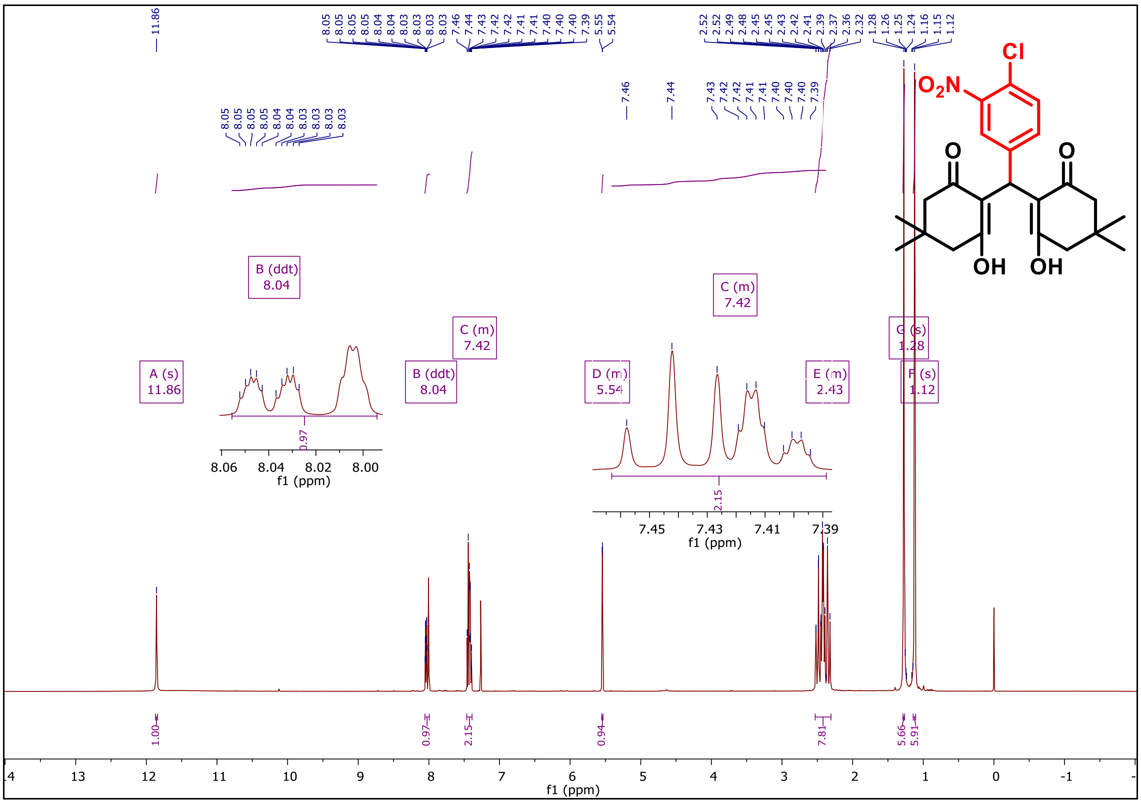

Figure S12. ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2'-((4-chloro-3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3d**.

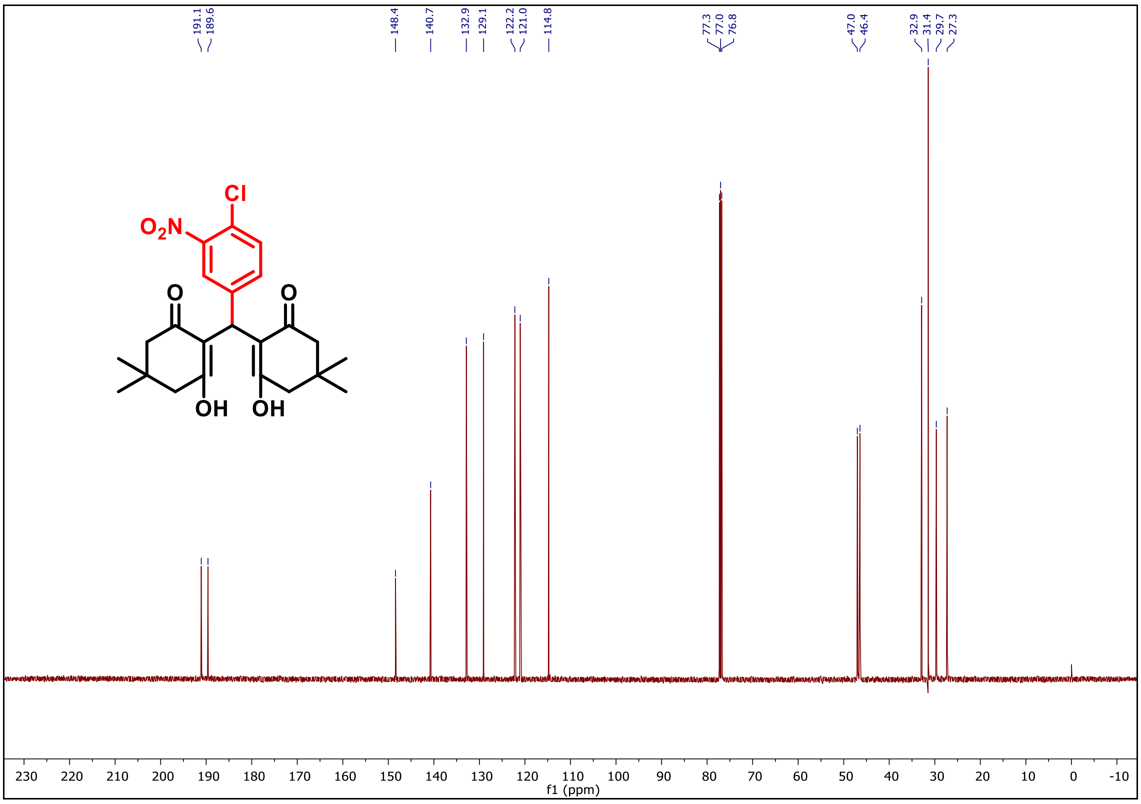

Figure S13. FT-IR of 2,2'-((3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3e**.

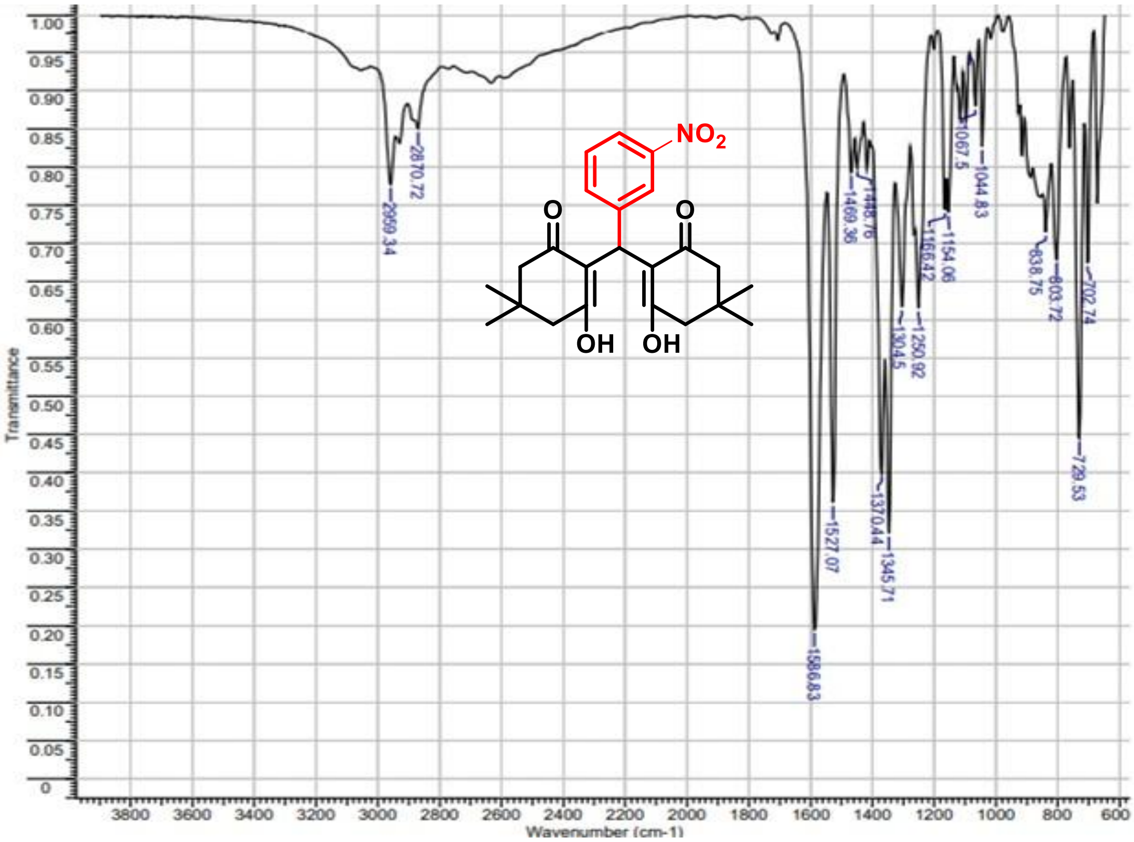

Figure S14. ^{1}H NMR (400 MHz, CDCl$_3$) of 2,2'-((3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3e**.

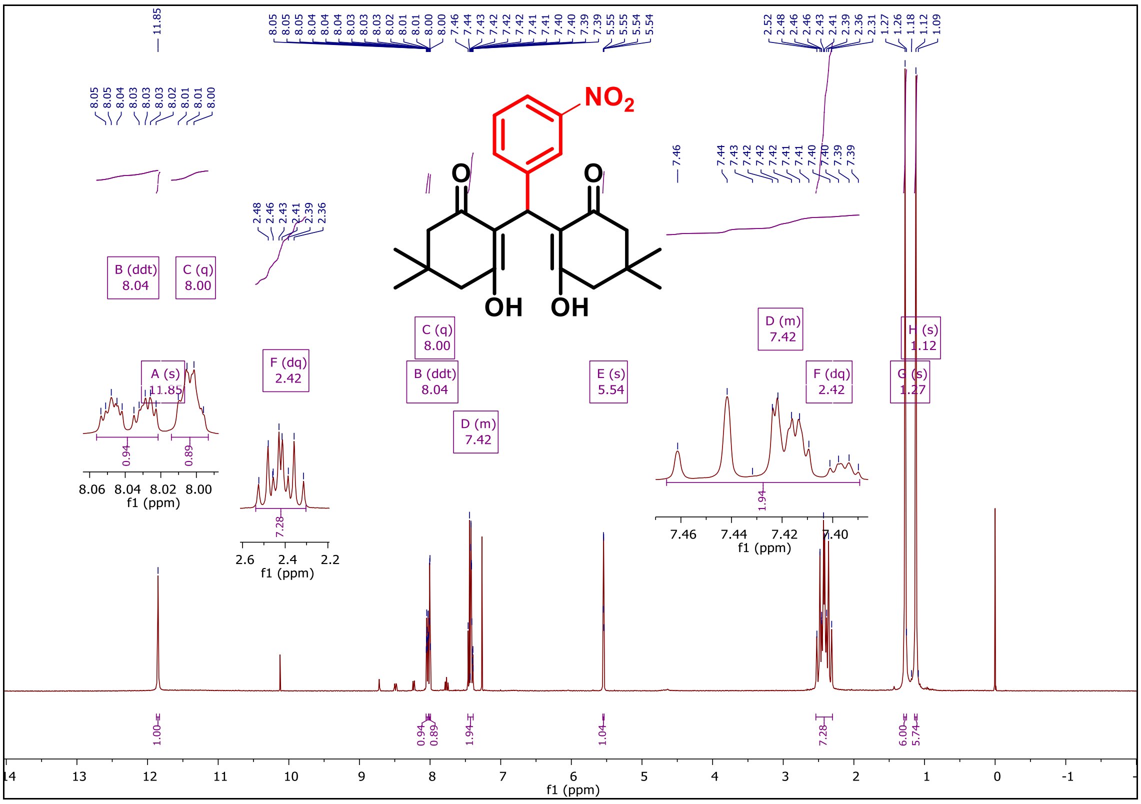

Figure S15. ^{13}C NMR (101 MHz, CDCl$_3$) of 2,2'-((3-nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) 3e

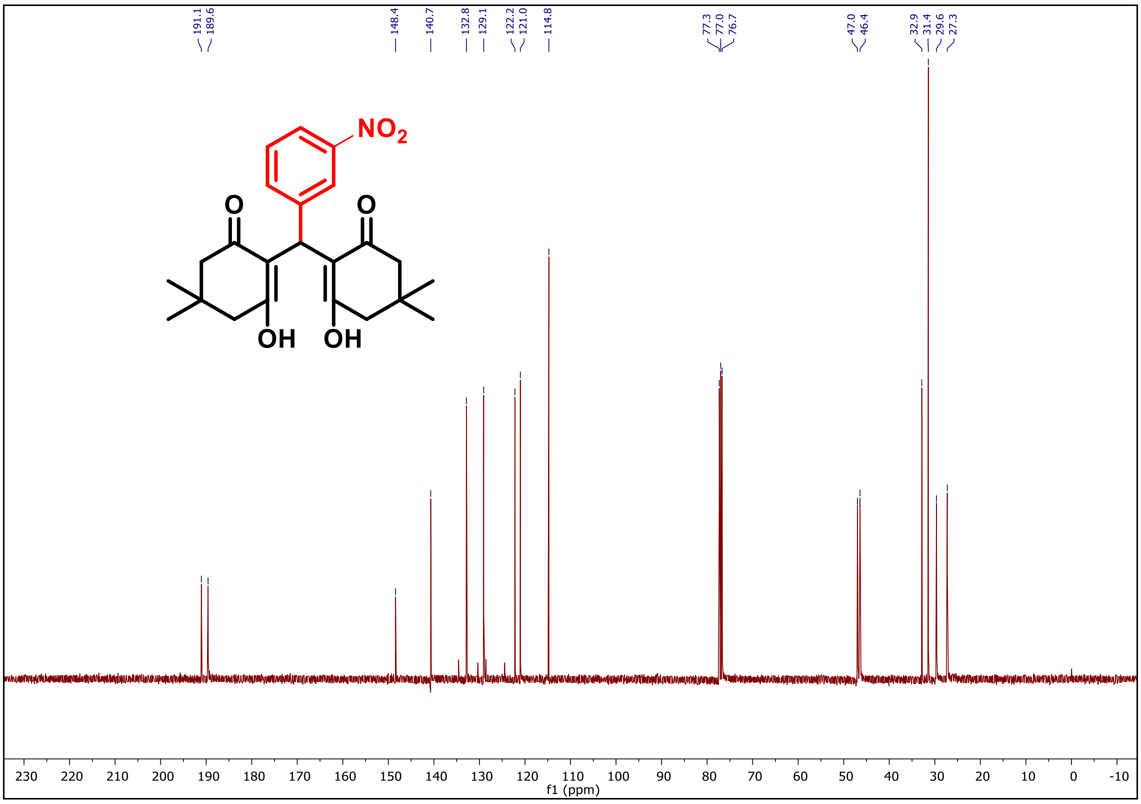

Figure S16. FT-IR of 4-(bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)benzonitrile **3f**.

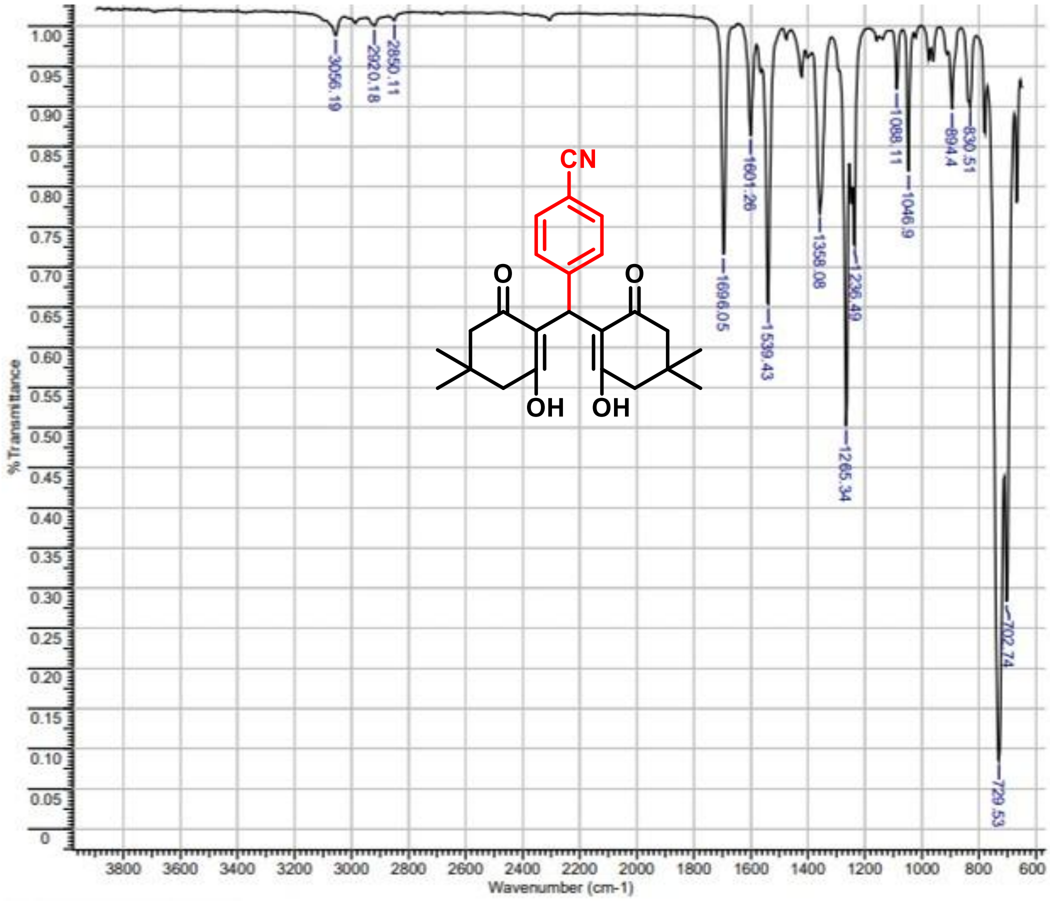

Figure S17. ^{1}H NMR (500 MHz, $CDCl_3$) of 4-(bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)benzonitrile **3f**.

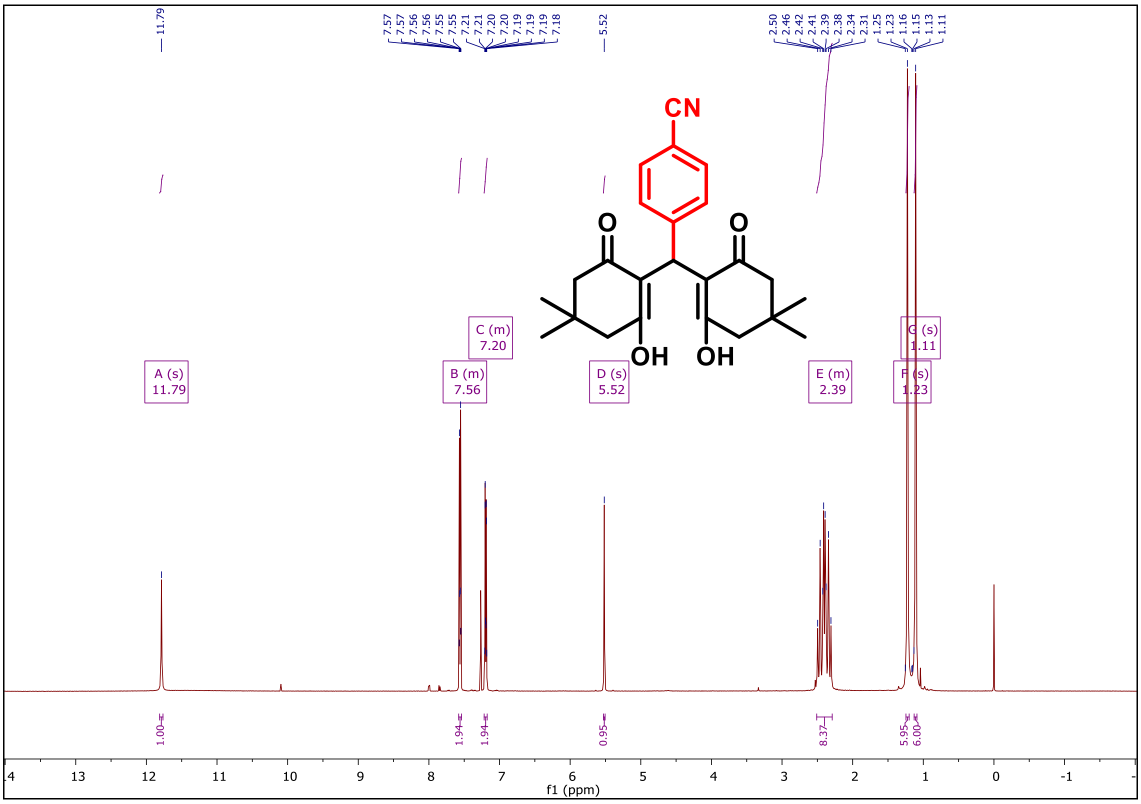

Figure S18. ^{13}C NMR (126 MHz, $CDCl_3$) of 4-(bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)benzonitrile **3f**.

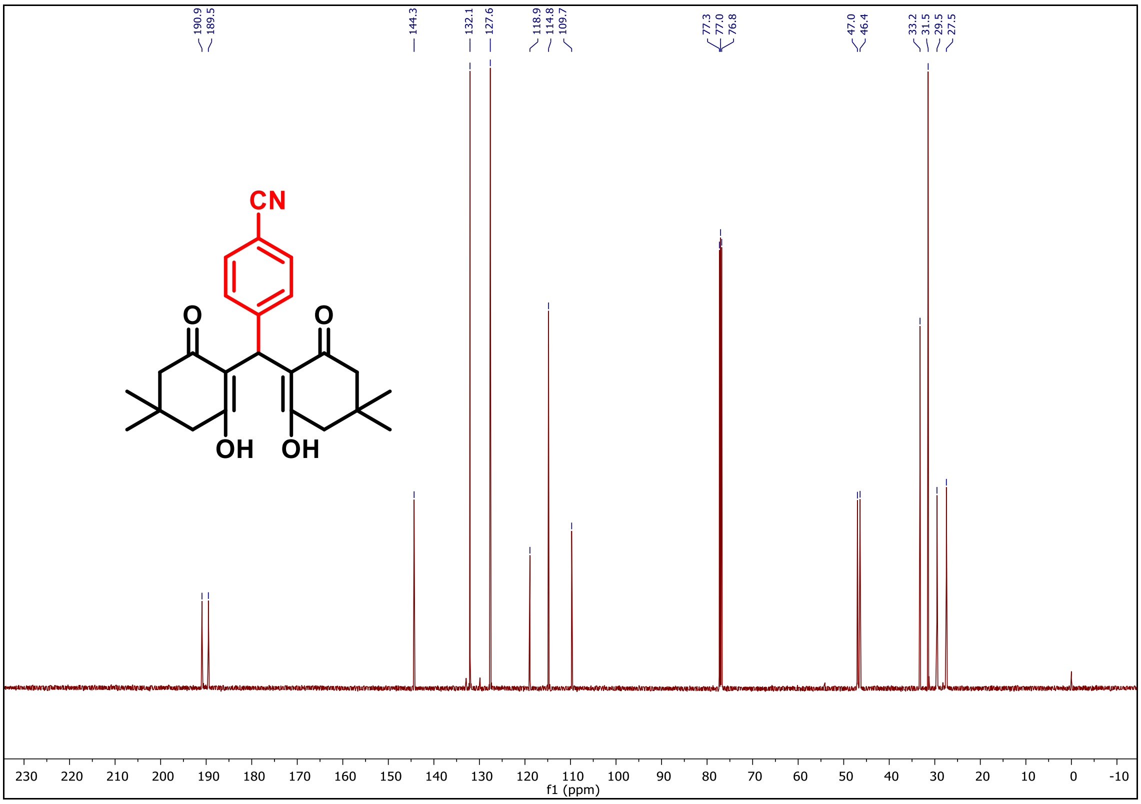

Figure S19. FT-IR of 2,2'-((4-hydroxy-3-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3g**.

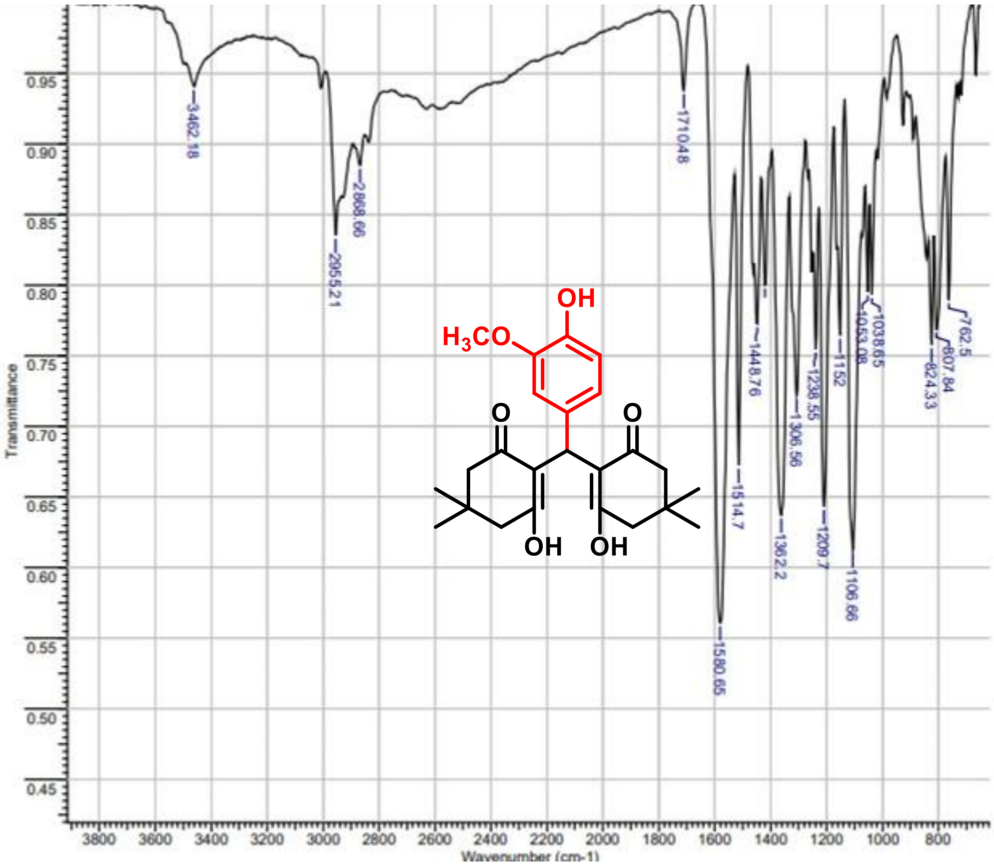

Figure S20. ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2'-((4-hydroxy-3-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3g**.

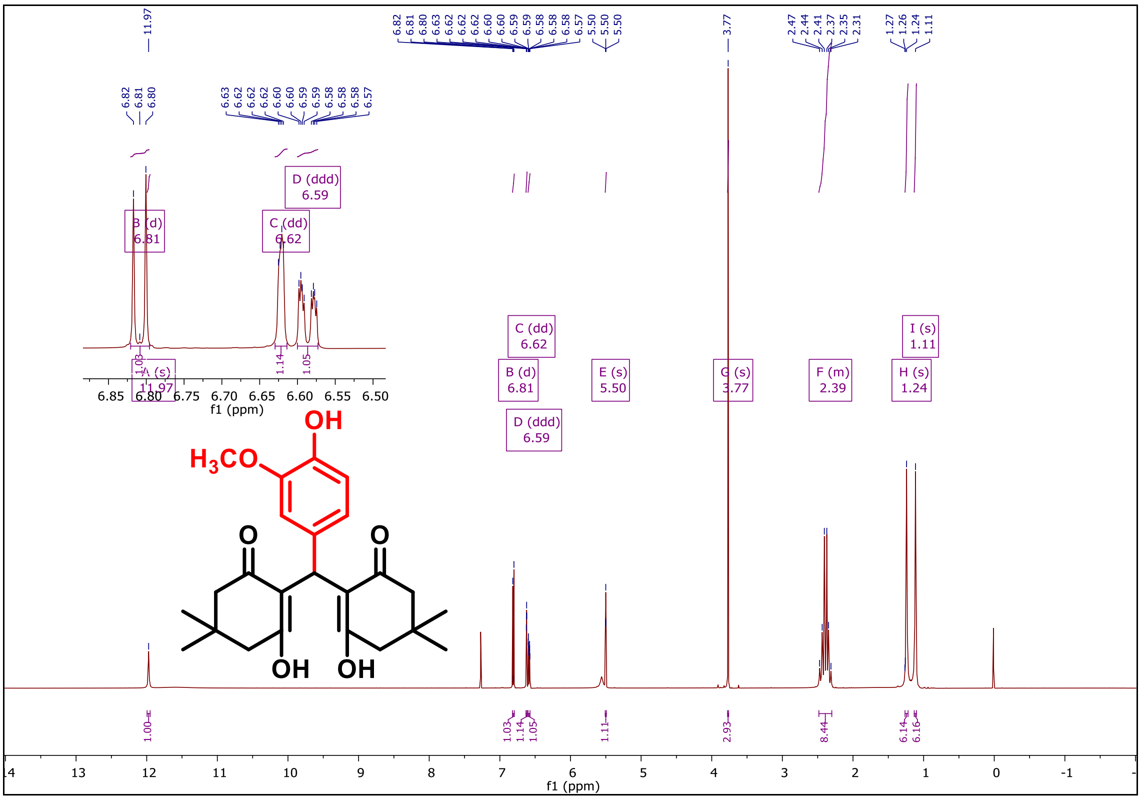

Figure S21. ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2'-((4-hydroxy-3-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3g**.

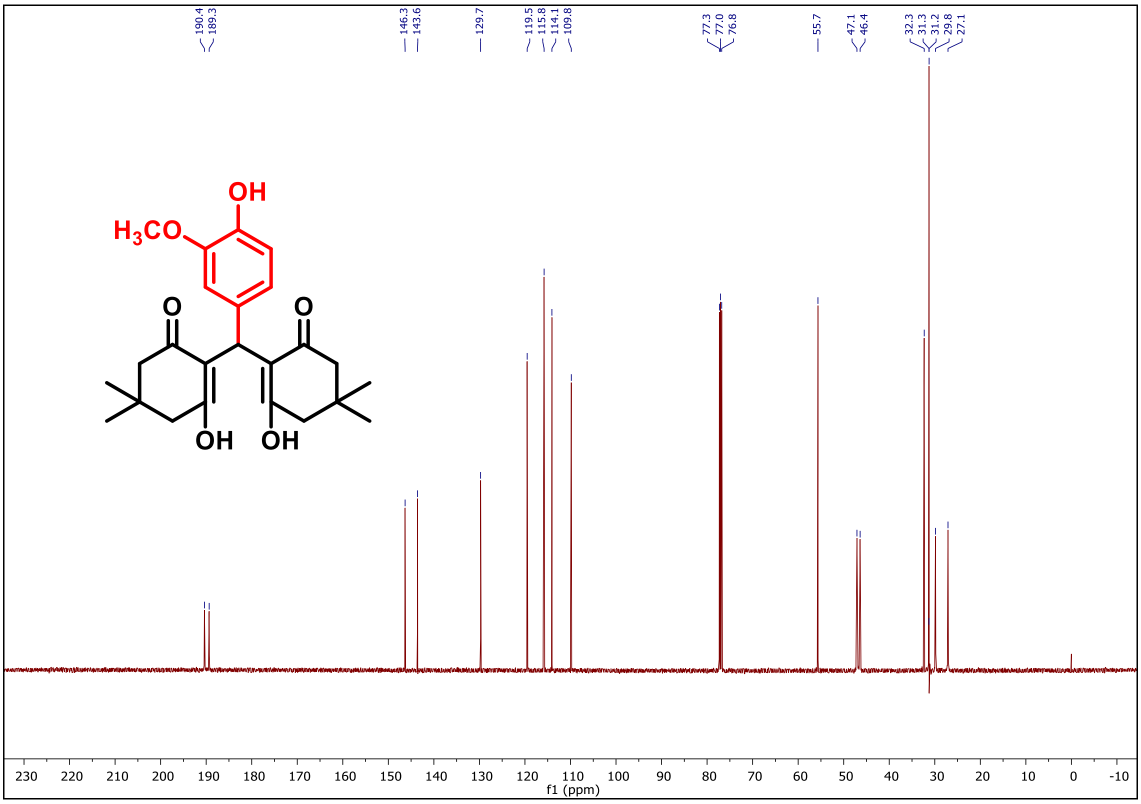

Figure S22. FT-IR of 2,2'-((4-hydroxy-3,5-dimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3h**.

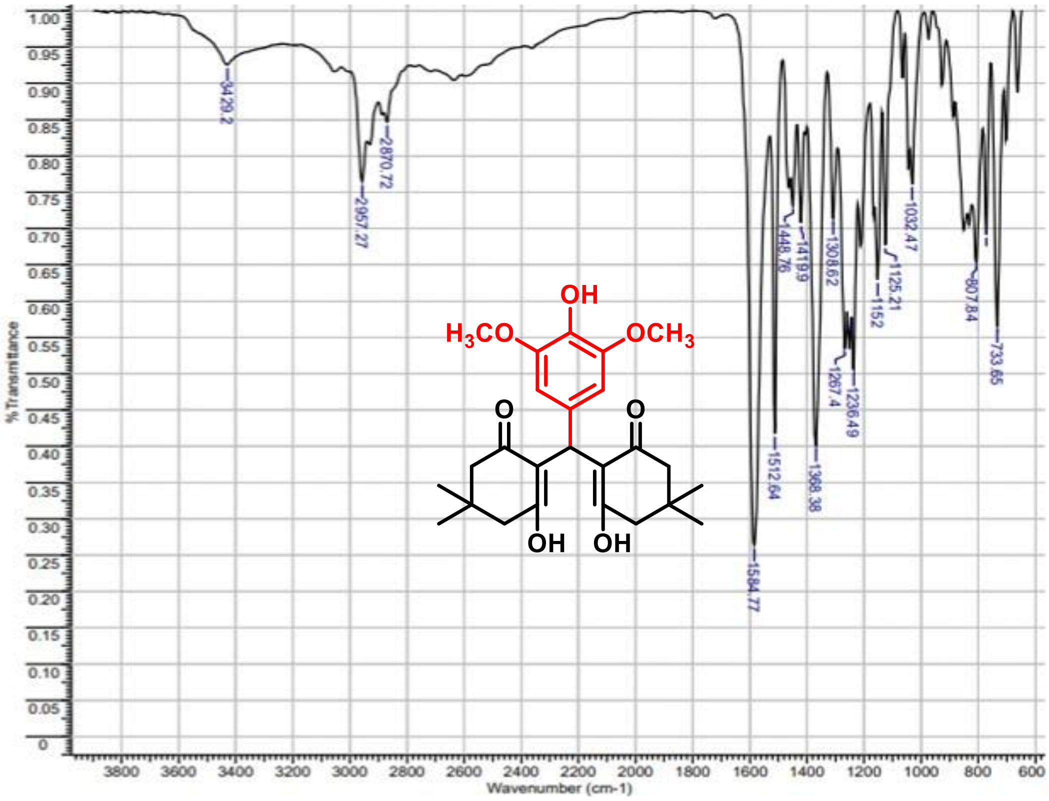

Figure S23. ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2'-((4-hydroxy-3,5-dimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3h**.

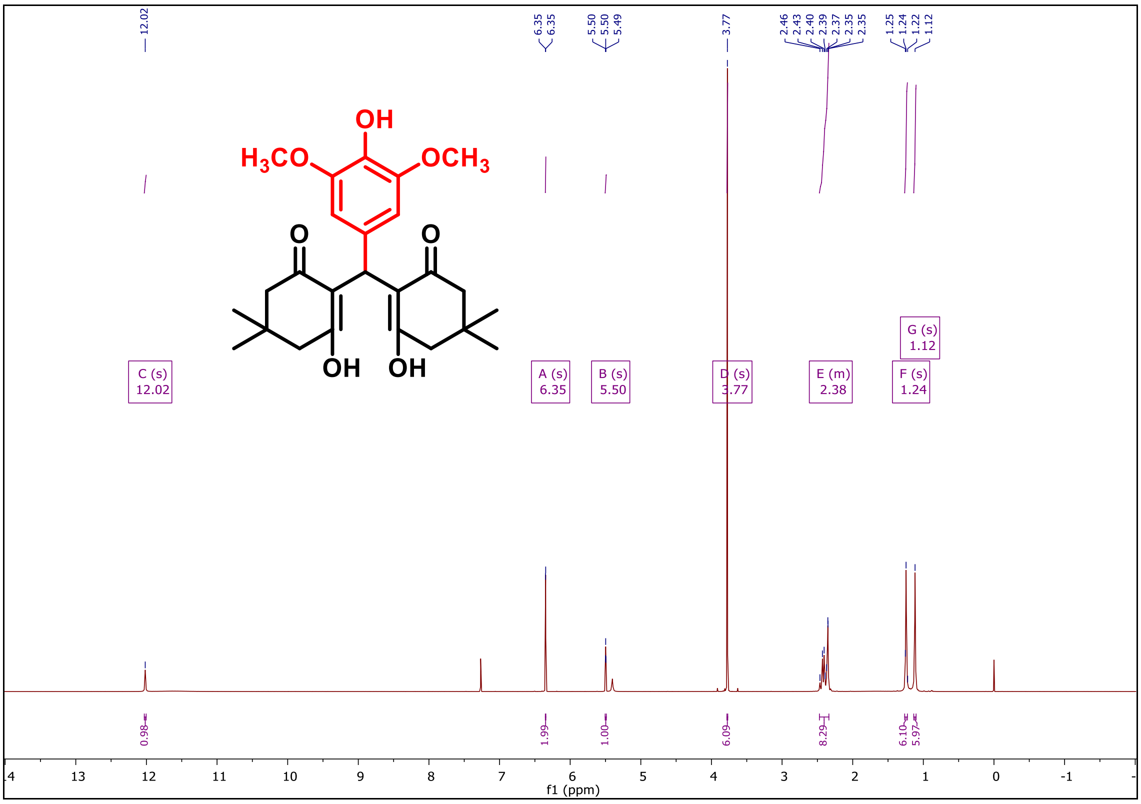

Figure S24. ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2'-((4-hydroxy-3,5-dimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3h**.

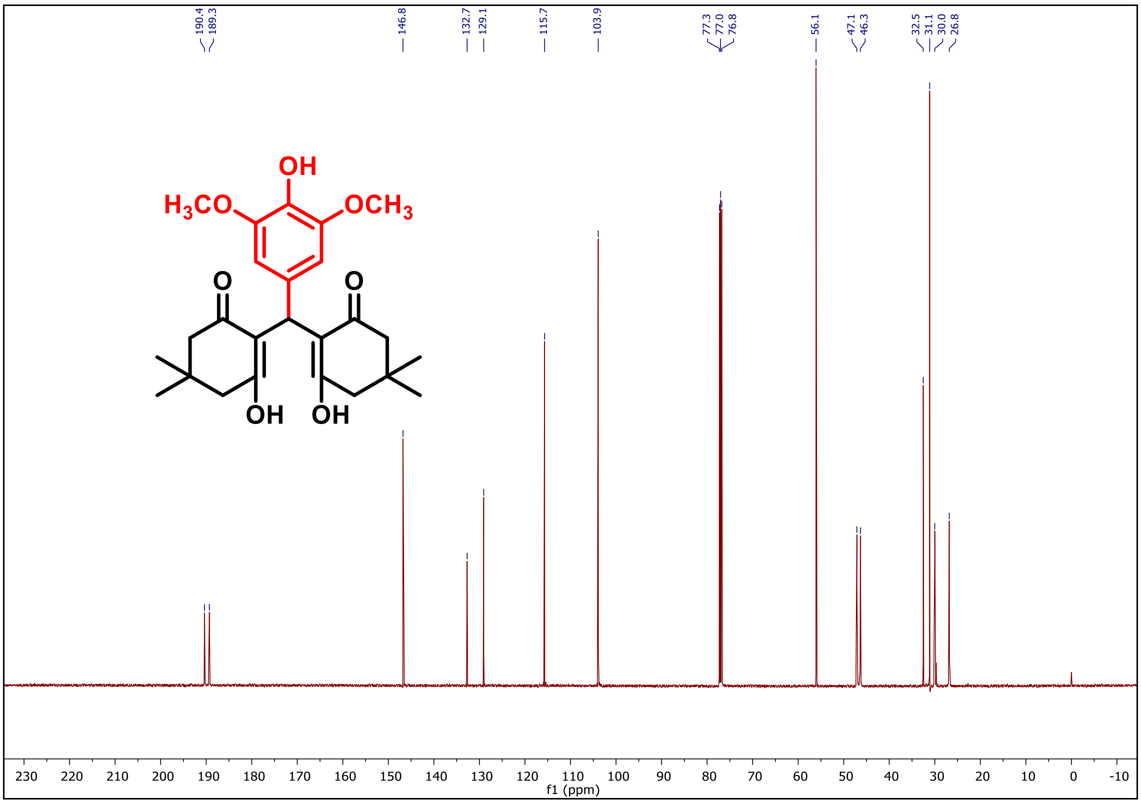

Figure S25. FT-IR of 2,2'-((3,4,5-trimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3i**.

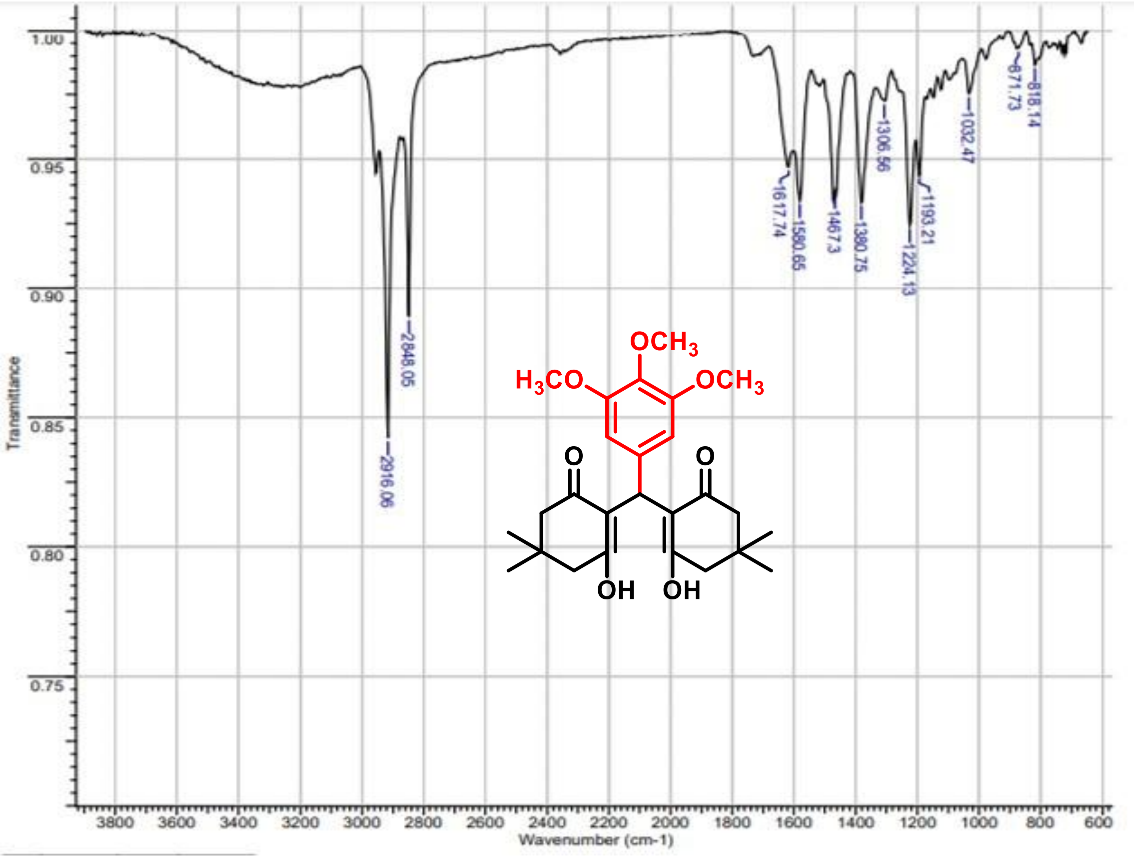

Figure S26. ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2'-((3,4,5-trimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3i**.

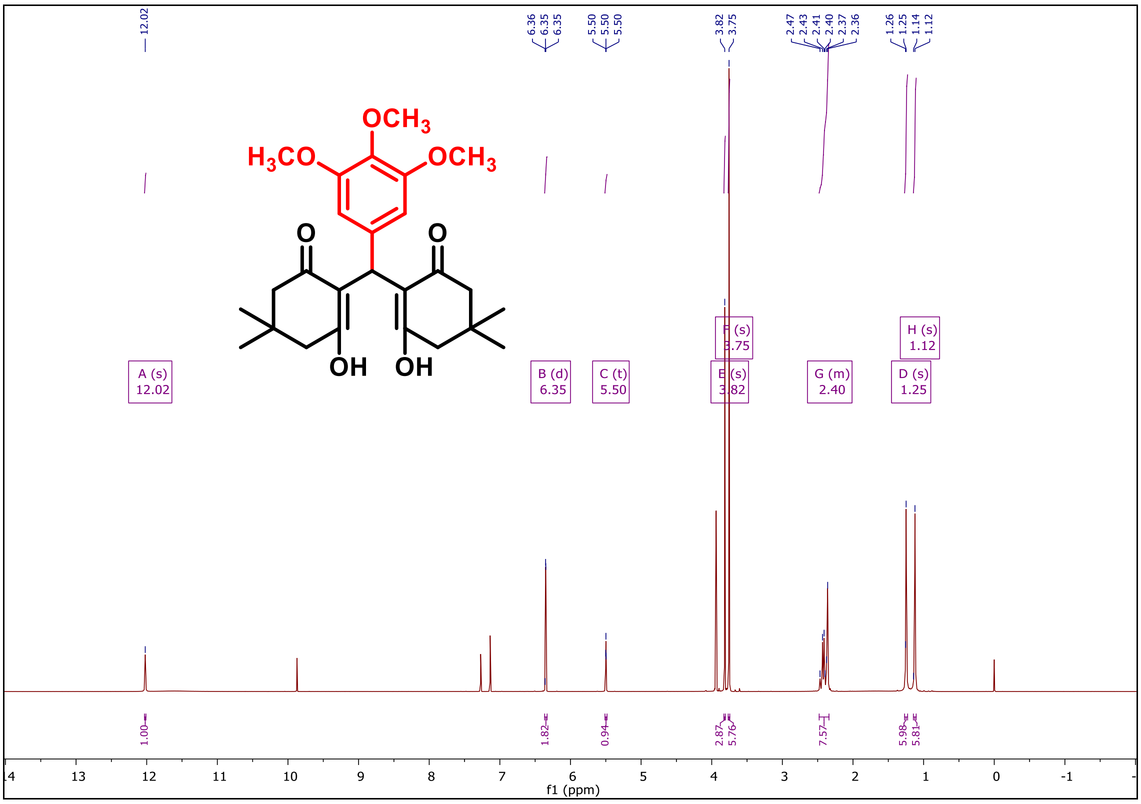

Figure S27. ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2'-((3,4,5-trimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3i**.

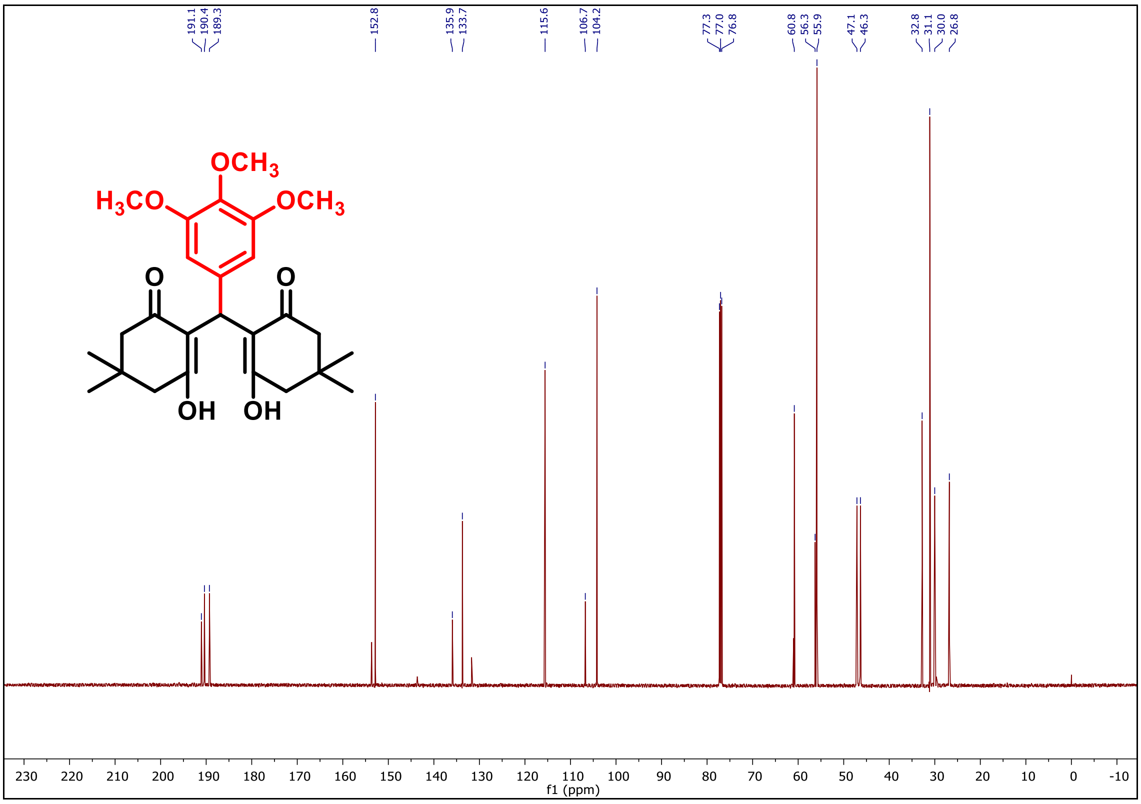

Figure S28. FT-IR of 2,2'-((4-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3j**.

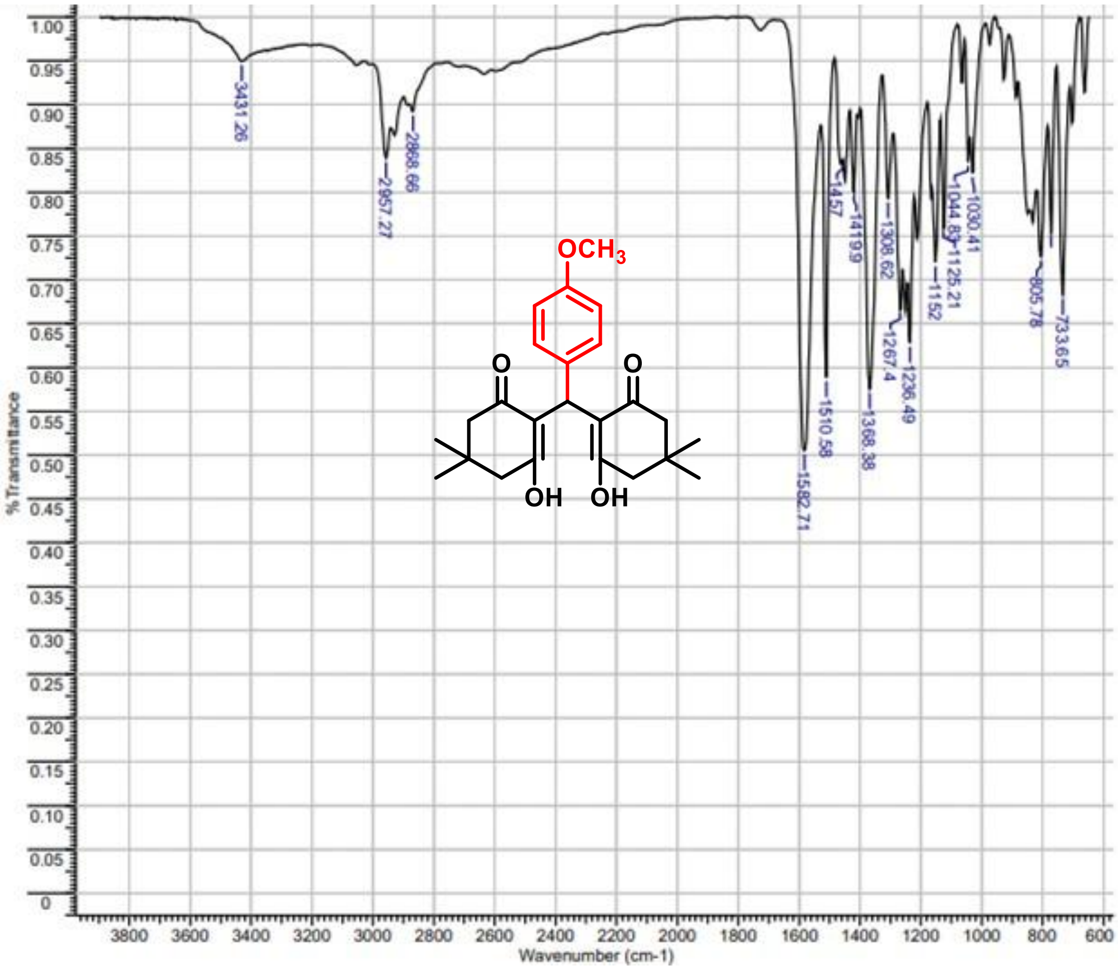

Figure S29. ^{1}H NMR (400 MHz, CDCl$_3$) of 2,2'-((4-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3j**.

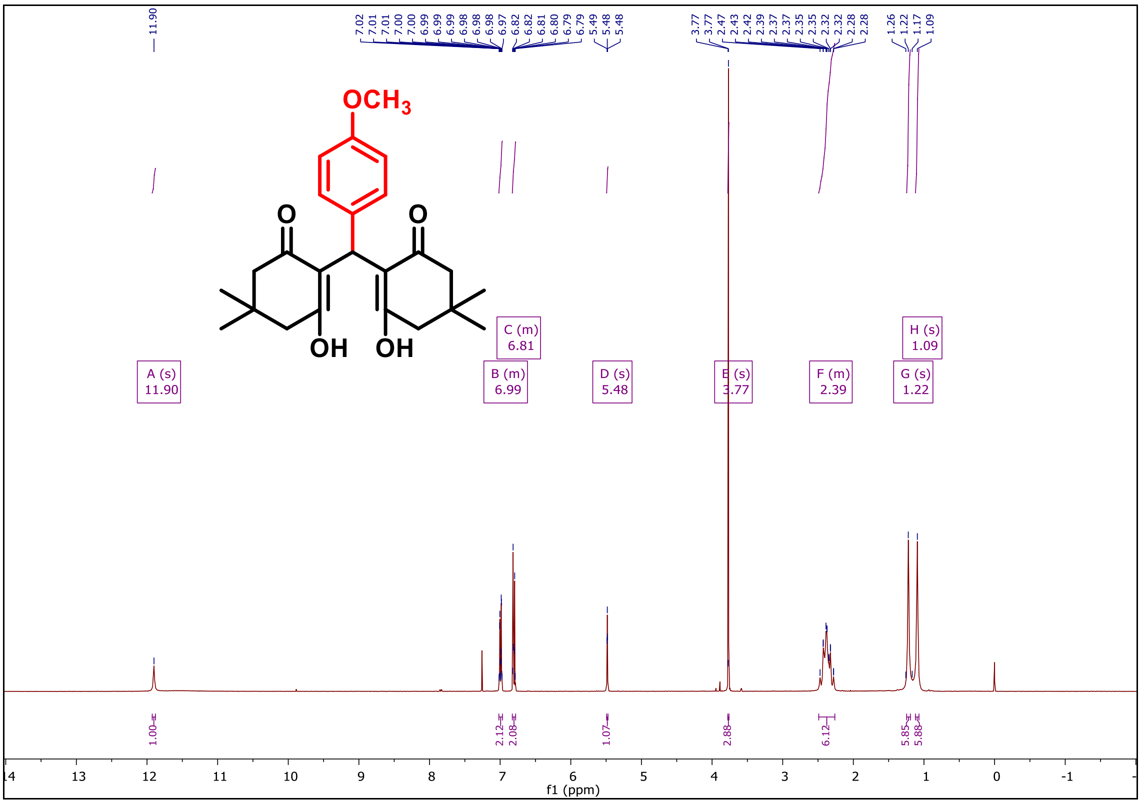

Figure S30. ^{13}C NMR (101 MHz, CDCl$_3$) of 2,2'-((4-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3j.**

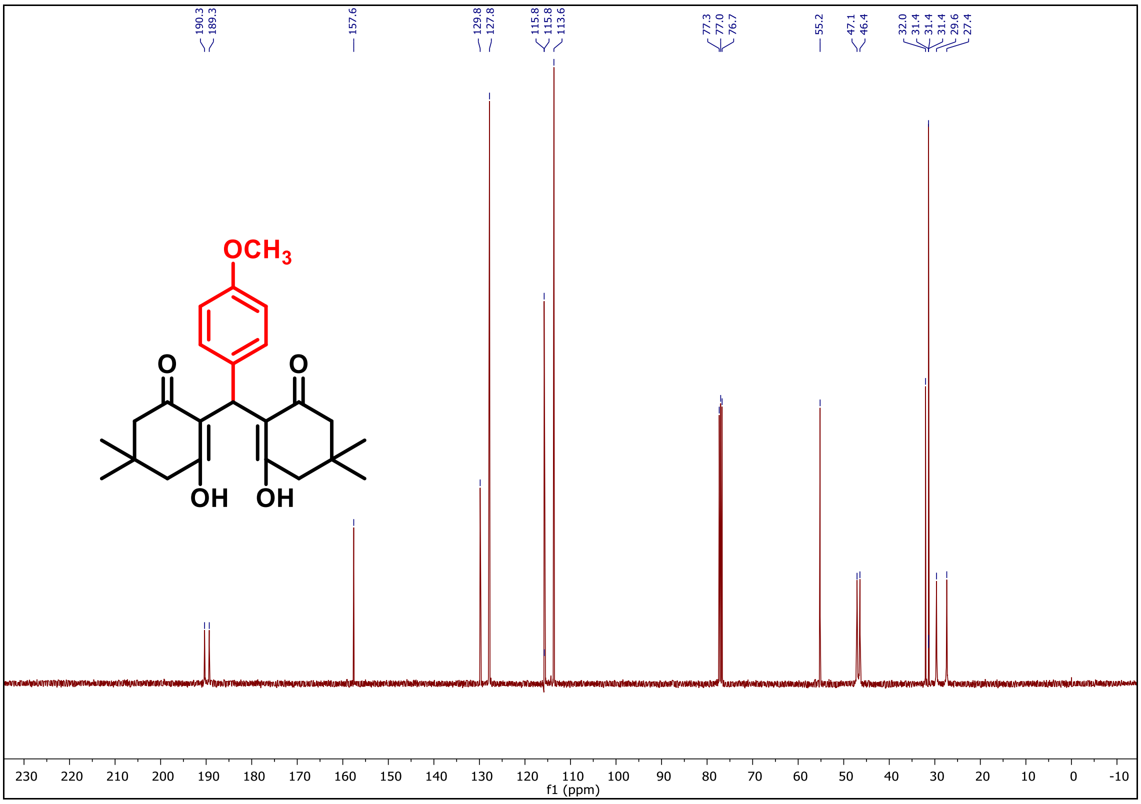

Figure S31. FT-IR of 2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3k**.

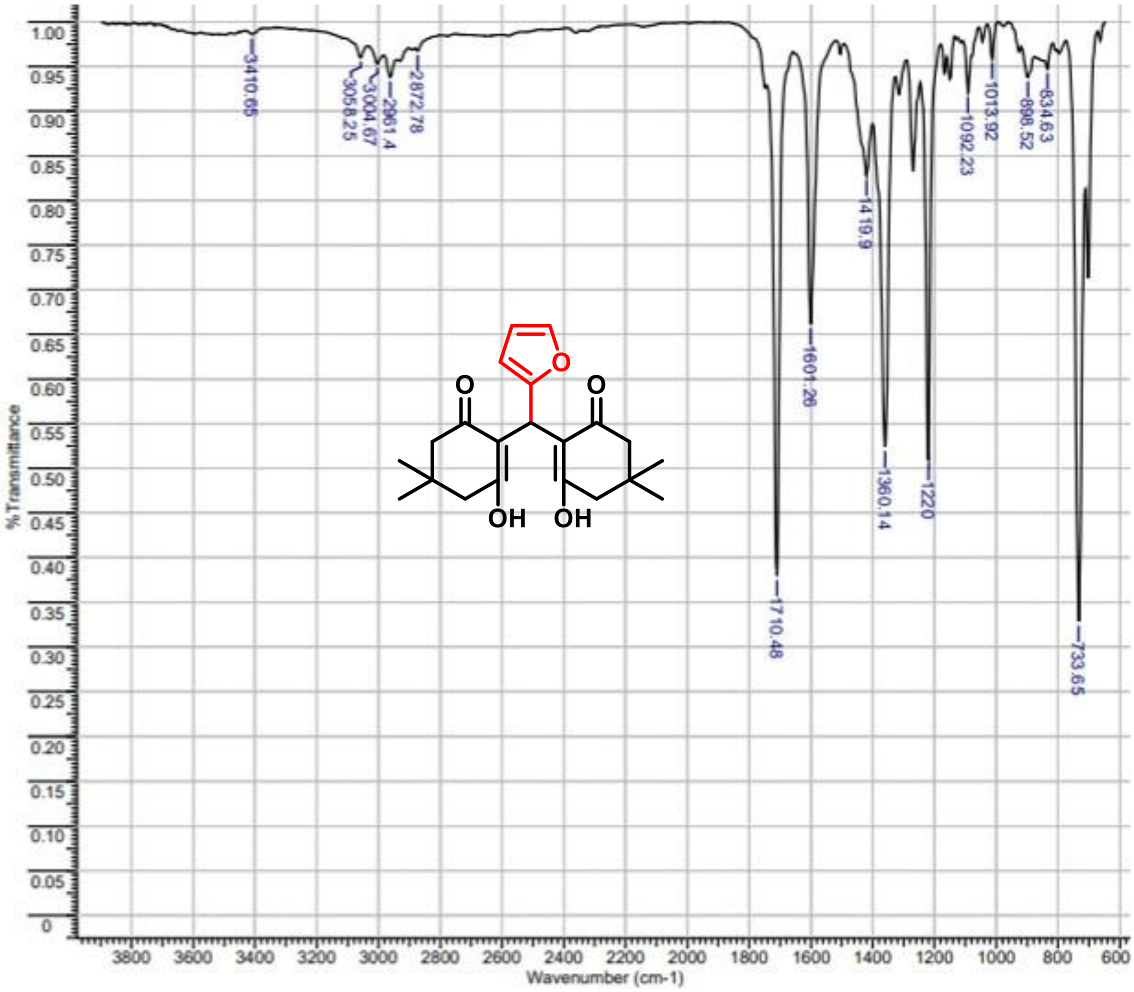

Figure S32. ^{1}H NMR (400 MHz, $CDCl_3$) of 2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3k**.

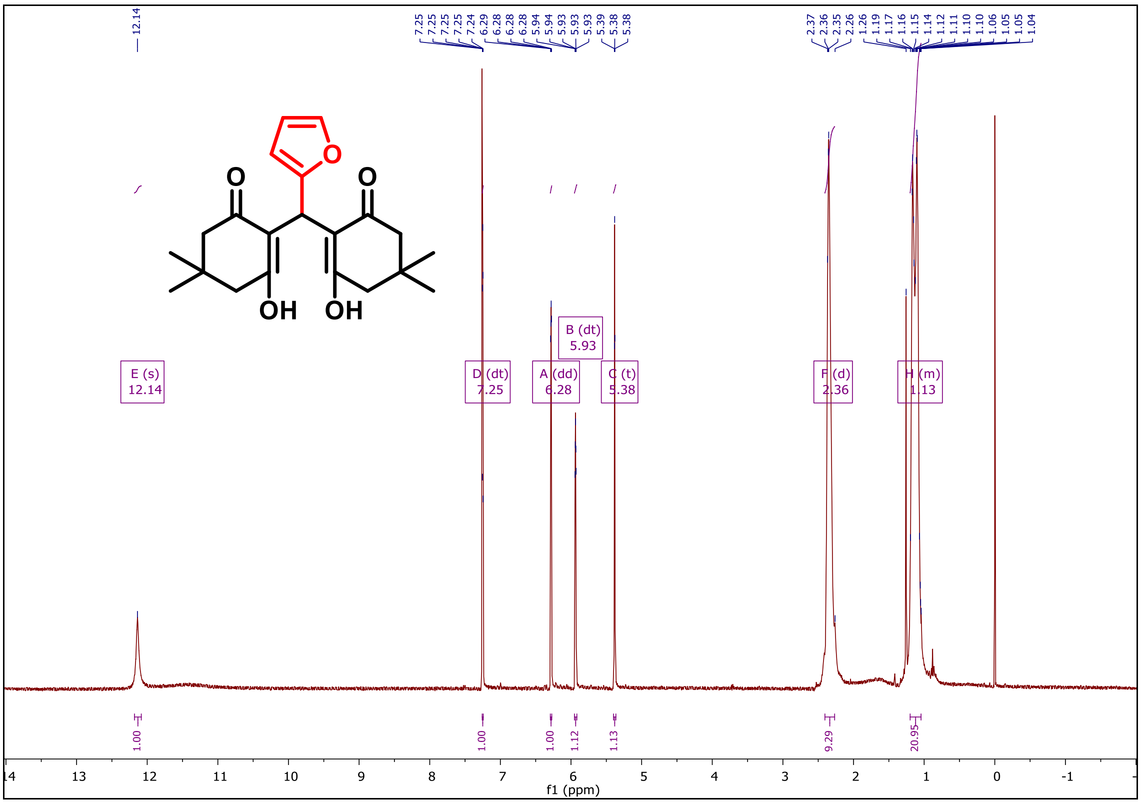

Figure S33. ^{13}C NMR (101 MHz, $CDCl_3$) of 2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **3k**.