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# Tetraketones: A new class of tyrosinase inhibitors

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**Abstract**—Twenty-eight tetraketones (**1**–**28**) with variable substituents at C-7 were synthesized and evaluated as tyrosinase inhibitors. Remarkably compounds **25** ($IC_{50}$ = 2.06 μM), **11** ($IC_{50}$ = 2.09 μM), **15** ($IC_{50}$ = 2.61 μM), and **27** ($IC_{50}$ = 3.19 μM) were found to be the most active compounds of the series, even better than both standards kojic acid ($IC_{50}$ = 16.67 μM) and L-mimosine ($IC_{50}$ = 3.68 μM). This study may lead to the discovery of therapeutically potent agents against clinically very important dermatological disorders including hyperpigmentation as well as skin melanoma.
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## 1. Introduction

In higher plants and fungi, the enzyme tyrosinase (Syn. Polyphenol Oxidase, PPO, EC 1.14.18.1) is an important member of '*Oxidase*' super-family, occurring in various isoforms such as immature, mature latent, and active forms; however, the biochemical description regarding the kinetic characterization and relationship between these isoforms has yet to be established. The biosynthetic pathway for melanin formation, operating in insects, animals, and plants has largely been elucidated.[1] The first two steps in the pathway are the hydroxylation of monophenol to *o*-diphenol (monophenolase or cresolase activity) and the oxidation of diphenol to *o*-quinones (diphenolase or catecholase activity), both using molecular oxygen followed by a series of non-enzymatic steps resulting in the formation of melanin which plays a crucial protective role against skin photocarcinogenesis. The production of abnormal melanin pigmentation (melasma, freckles, ephelide, and senile lentigines, etc.) is a serious esthetic problem in human beings. In fungi, the role of melanin is correlated with the differentiation of reproductive organs and spore formation, virulence of pathogenic fungi, and tissue protection after injury. In addition, tyrosinase is responsible for the undesired enzymatic browning of fruits and vegetables that takes place during senescence or damage at the time of post-harvest handling which makes the identification of novel tyrosinase inhibitors extremely important.[1] Losses of tyrosinase activity due to mutation cause occulocutaneous albinism, demonstrating the importance of the enzyme in pigmentation. Production of melanin causes many kinds of skin diseases, such as spots on the face, freckles or hyperpigmentation. Therefore, tyrosinase inhibitors should be clinically useful for the treatment of some dermatological disorders associated with melanin hyperpigmentation and also important in cosmetics for whitening and depigmentation after sunburn. In insects, several functions of this enzyme have been reported in the generation of *o*-diphenols and quinones for pigmentation, wound healing, parasite encapsulation, and sclerotization and in the molting process of insect. Therefore, tyrosinase is an alternative target site for the control of insect pests. In addition, tyrosinase is known to be involved in adhesion of marine organisms.[2,3]

Tetraketones (**I**), synthesized through the reaction of an aldehyde with cyclohexane-1,3-dione or dimedone (5,5-dimethyl-cyclohexane-1,3-dione), give rise to an important class of compounds which was for the first time described by Merling[4] in 1894 during his pioneering work synthesizing the cyclohexane-1,3-dione from resorcinol.

*Keywords*: Tetraketones; Tyrosinase; Hyperpigmentation.
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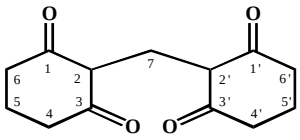


(I)

Several reports have appeared in the literature to attempt efficient synthesis of tetraketones.[5] Many of these methods involve the harsh reaction conditions, tedious reaction workup, and involvement of heat to afford the products.[6] Tetraketones are extensively used as important precursors for the synthesis of various acridinediones as laser dyes[7] or some heterocylic compounds.[8]

## 2. Results and discussion

### 2.1. Chemistry

Since last few years, we introduced a variety of compounds for their potential use in medicinal chemistry.[9] We herein report an improved synthesis of tetraketones at room temperature by stirring the starting materials in the presence of catalytic amount of piperidine affording a variety of compounds (**1**–**28**; Schemes 1 and 2), which were screened for tyrosinase inhibition. It is worth mentioning that the tetraketones produced from cyclohexane-1,3-dione and dimedone were so far not screened for any biological activity. In the light of previously known polyphenolic inhibitors of tyrosinase (Fig. 1), we designed and synthesized polyphenolics, polyoxygenated, and other tetraketones.

Polyoxygenated compounds have previously been reported as tyrosinase inhibitors.[2] Our hypothesis was the tetraketones having four-carbonyl functionalities along with their tautomeric, that is, keto–enol-forms, which might have some tyrosinase inhibitory properties and we found very exciting results from our experiments.

Twenty-eight tetraketones **1**–**28** were synthesized by condensing different alkyl and aryl aldehydes with cyclohexane-1,3-dione (series I) or 5,5-dimethyl cyclohexane-1,3-dione (series II) in the presence of catalytic amount of piperidine stirring at room temperature in high yields. The structures of the synthesized compounds were determined by different spectroscopic techniques, like $^1$H NMR, EIMS, IR, and UV, and purities were confirmed by CHN analysis. The tetraketones **1**–**28** were tested for their tyrosinase inhibitory activity, and their structure–activity relationship is discussed.

### 2.2. Biology

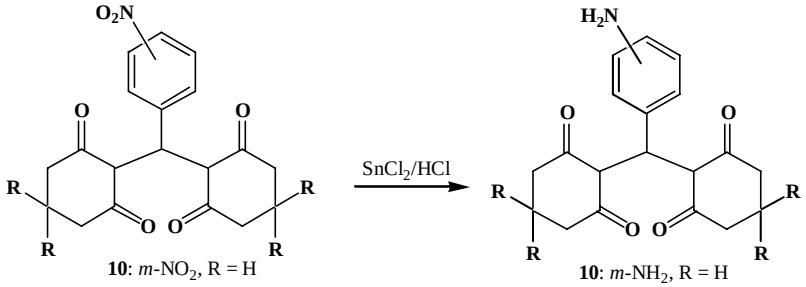
All the synthesized compounds were subjected for tyrosinase inhibition assay, according to the developed method formerly illustrated by Hearing, in 1987.[10] Tetraketones **15**–**28** (series II) bearing C-5/C-5′ methyl substituents demonstrated higher degrees of inhibitory activities than compounds **1**–**14** (series I) may be due to the enhanced lipophilicity of the former (Scheme 2). In addition, the inhibitory effects of variably substituted phenyl moieties at C-7 position of tetraketones **1**–**28** were also studied and discussed.

Parent compounds **1** and **15** were synthesized and both compounds with variably substituted phenyl on C-7 make series I and II, respectively. The enhanced inhibitory effects of compound **15** ($IC_{50}$ = 2.61 μM) than of compound **1** ($IC_{50}$ = 6.55 μM) may be due to the presence of four methyl substituents at C-5/C-5′ positions as distinctive feature. This rational supports our hypothesis of enhanced lipophilicity.

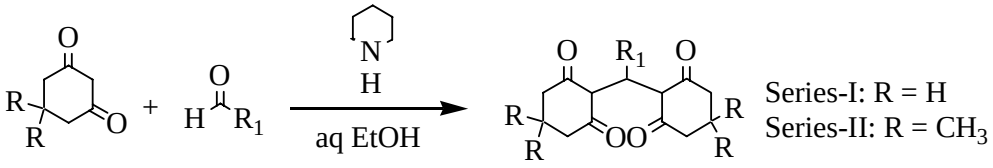
In compound **2** where a 4″-hydroxyl was present instead of hydrogen, a loss of activity was observed ($IC_{50}$ = 26.66 μM) than parent compound **1**. Addition of another OH at position-3″ in compound **2** gave rise to compound **3** with enhanced inhibition ($IC_{50}$ = 12.31 μM) compared to the mono-substituted compound **2**, what could be expected according to the known tyrosinase inhibitors with an *o*-diphenol structure.[2]

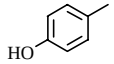
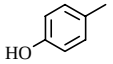
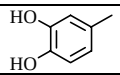
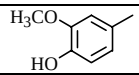
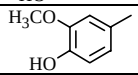
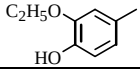
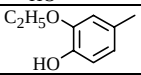
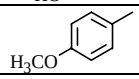
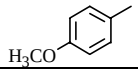
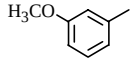
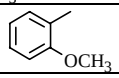
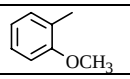
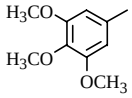
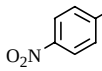
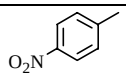
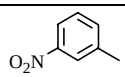
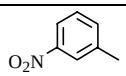
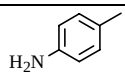
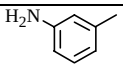
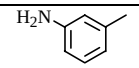
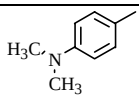
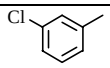
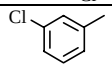
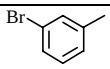
The comparison of activities of compound **1** ($IC_{50}$ = 6.55 μM) having phenyl at C-7 and compound **3** ($IC_{50}$ = 12.31 μM) having *o*-diphenol at C-7 suggests that tetraketone skeleton itself has greater inhibition due to the presence of four ketonic moieties, which may effectively coordinate with the copper atom present in the enzyme.

When the hydroxyl of compound **3** present at position-3″ was replaced with methoxy (–$OCH_3$) group as in compound **4**, a slight decline in activity ($IC_{50}$ = 16.99 μM) was observed which may be due to




**Scheme 1.**




| Comp. | $R_1$ | R | $IC_{50}$ (μM) | Comp. | $R_1$ | R | $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| **1** |  | **-H** | 6.55 | **15** |  | **-$CH_3$** | 2.61 |
| **2** |  | **-H** | 26.63 | **16** |  | **-$CH_3$** | 4.13 |
| **3** |  | **-H** | 12.31 | **17** |  | **-$CH_3$** | 14.58 |
| **4** |  | **-H** | 16.99 | **18** |  | **-$CH_3$** | 9.06 |
| **5** |  | **-H** | 11.77 | **19** |  | **-$CH_3$** | 3.70 |
| **6** |  | **-H** | 4.83 | **20** |  | **-$CH_3$** | 12.82 |
| **7** |  | **-H** | 19.73 | **21** |  | **-$CH_3$** | 15.36 |
| **8** |  | **-H** | 00 | **22** |  | **-$CH_3$** | 6.59 |
| **9** |  | **-H** | 4.80 | **23** |  | **-$CH_3$** | 71.47 |
| **10** |  | **-H** | 6.77 | **24** |  | **-$CH_3$** | 4.01 |
| **11** |  | **-H** | 2.09 | **25** |  | **-$CH_3$** | 2.06 |
| **12** |  | **-H** | 00 | **26** |  | **-$CH_3$** | 13.40 |
| **13** |  | **-H** | 00 | **27** |  | **-$CH_3$** | 3.19 |
| **14** |  | **-H** | 00 | **28** |  | **-$CH_3$** | 12.68 |

**Standards:** kojic acid ($IC_{50}$ = 16.67 μM), L-mimosine ($IC_{50}$ = 3.68 μM)

**Scheme 2.**

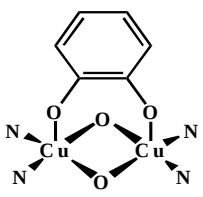


**Figure 1.** Binding model to the binuclear copper active center in the *oxy*-form of tyrosinase.

loss of complex formation ability with the copper of tyrosinase enzyme. While replacement of methoxy (–$OCH_3$) group of compound **4** with ethoxy (–$OC_2H_5$) group as in molecule **5** increased inhibition ($IC_{50}$ = 11.7 μM). This might be due to flexibility of the ethoxy substitution to allow this molecule to interact well with the enzyme. Methoxylation at the *para*-position as in compound **6** enhances the activity ($IC_{50}$ = 4.83 μM) as compared to those corresponding parent compound **2**. While, 2″-methoxylation as in com-

pound **7** ($IC_{50}$ = 19.73 μM) caused a decline in activity may be due to the steric crowding with the remaining part of the molecule to disturb its orientation by producing a steric strain, which might have caused decline in activity. This effect was more pronounced in 3″,4″,5″-trimethoxy-substituted derivative **8** and was found to be completely inactive.

Nitration at *para*-position enhances the activity as in compound **9** ($IC_{50}$ = 4.8 μM), whereas *meta*-nitration decreases the activity as in compound **10** ($IC_{50}$ = 6.77 μM). In the latter case, the orientation of nitro group at *meta*-position displayed steric crowding, which might have caused a decline in activity. In order to prove the above phenomenon of steric crowding, we subjected compound **10** to tin chloride-mediated reduction to obtain *meta*-substituted amino product **11** ($IC_{50}$ = 2.09 μM) which showed enhanced activity (Scheme 1). This visible gain of activity is due to the loss of bulky nitro to a relatively smaller amino substituent which provides an easy interaction with enzyme and proves our hypothesis that steric crowding causes a decline in activity.

Five halogenated derivatives **12**, **13**, **14**, **27**, and **28** were synthesized for their tyrosinase effect. Nevertheless, only two compounds **27** ($IC_{50}$ = 3.19 μM) and **28** ($IC_{50}$ = 12.68 μM) showed promising activity which may be due to inherent activity of compound **15** and the rest were completely inactive.

Conclusively, the compounds **15**–**28** belong to series II, which more or less followed the same inhibitory pattern as series I. Series II showed dominated inhibition maybe due to the presence of four extra methyl groups at the C-5/C-5′ position, for which it is proposed that methyl substituents at C-5/C-5′ might play a pivotal role in the orientation and geometry of the molecules to interact with enzyme besides increasing lipophilicity to behave like proteins.

So, a comprehensive study is required to synthesize variably substituted alkyl derivatives at C-5/C-5′ and C-7 for better inhibitory activities against tyrosinase.

## 3. General experimental

Melting points (mp) were determined with a Büchi 434 melting point apparatus and are uncorrected. NMR spectroscopy was performed on a Bruker AVANCE 400 MHz. Infrared spectra (IR) were recorded on a JASCO IR-A-302 Spectrophotometer. EIMS were recorded on a FINNIGAN MAT-311A (Germany). Thin-layer chromatography (TLC) was performed on pre-coated TLC (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by iodine vapors, ultraviolet light (UV) at 254 and 365 nm, ceric sulfate solution followed by heating or by Dragendroff's reagent.

### 3.1. Tyrosinase inhibition assay

Tyrosinase inhibition assays were performed in 96-well micro-plate format using SpectraMax® 340 (Molecular Devices, CA, USA) micro-plate reader according to the developed method described earlier by Hearing.[10] Briefly, all the compounds were dissolved in DMSO to a concentration of 2.5%. Thirty units of mushroom tyrosinase (28 nM) was first pre-incubated with the compounds, in 50 nM Na-phosphate buffer (pH 6.8), for 10 min at 25 °C. Then the D-DOPA (0.5 mM) was added to the reaction mixture and the enzyme reaction was monitored by measuring the change in absorbance at 475 nm (at 37 °C) of the formation of the DOPAchrome for 10 min. The percent inhibition of the enzyme and $IC_{50}$ values of the active compounds were calculated using a program developed with Java and Macro Excel® 2000 (Microsoft Corp., USA) for this purpose. The following equation has been used:

$$\text{percent inhibition } (\%) = [B - S/B] \times 100.$$

Here, the $B$ and $S$ are the absorbances for the blank and samples, respectively. All the studies have been carried out at least in triplicate and the results here represent means ± SEM (standard error of the mean). All the reagents, enzyme, substrate, and reference compounds were purchased from Sigma Chem. Co., MO, USA.

### 3.2. General procedure for the preparation of compounds 1–28

Cyclohexane-1,3-dione or 5,5-dimethylcyclohexnane-1,3-dione (2 mM) dissolved in 50% ethanol (10 mL) was added dropwise to a mixture of aldehyde (1 mM) dissolved in 50% ethanol (10 mL), piperidine (1–2 drops), and the reaction mixture was stirred at room temperature for 20 min (TLC monitored). Then, cold water (15 mL) was added to the reaction mixture and resultant precipitates were filtered and recrystallized from aqueous ethanol.

**3.2.1. Phenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 1.** Yield: 98%; mp: 217–218 °C; $R_f$: 0.57 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 255 (log ε = 4.11) nm; IR (KBr): $\nu_{max}$ 2951, 1660, 1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.05–7.25 (m, 5H, Ar-*H*), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m*/*z* 312 (14), 238 (4), 199 (100), 171 (21), 129 (20), 102 (52), 55 (86%); Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.10; H, 6.44.

**3.2.2. 4-Hydroxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 2.** Yield: 96%; mp: 196–197 °C; $R_f$: 0.51 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 276 (log ε = 4.18) nm; IR (KBr): $\nu_{max}$ 2945, 1645, 1500, 1453, 1333, 843; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.70 (d, *J* = 8.4 Hz, 2H, H-2/H-6), 7.54 (d, *J* = 8.4 Hz, 2H, H-3/H-5), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m*/*z* 328 (6), 310 (9), 254 (4), 215 (70), 160(26), 118 (42), 84 (57), 55 (100); Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.48; H, 6.14.

**3.2.3. 3,4-Dihydroxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 3.** Yield: 94%; mp: 251–253 °C; $R_f$: 0.39 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 291.4

(log ε = 4.28) nm; IR (KBr): $\nu_{max}$ 2951, 1655, 1510, 1450, 1339, 839; $^1$H NMR (400 MHz, $CD_3OD$): δ 6.67 (d, $J$ = 1.7 Hz, 1H, H-2), 6.57 (d, $J$ = 8.1 Hz, 1H, H-5), 6.53 (dd, $J$ = 1.7 Hz, $J$ = 8.1 Hz, 1H, H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 328 (6), 310 (9), 254 (4), 215 (70), 160(26), 118 (42), 84 (57), 55 (100); Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.25; H, 5.86.

**3.2.4. 3-Methoxy-4-hydroxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 4.** Yield: 90%; mp: 169–170 °C; $R_f$: 0.49 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 255 (log ε = 3.99) nm; IR (KBr): $\nu_{max}$ 2949, 1643, 1525, 1451, 1340, 844; $^1$H NMR (400 MHz, $CD_3OD$): δ 6.91 (d, $J$ = 1.5 Hz, 1H, H-2), 6.59–6.64 (m, 2H, H-5/H-6), 4.17 (m, 1H, H-7), 3.81 (s, 3H, $OCH_3$), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 358 (8), 340 (6), 273 (4), 246 (57), 229 (26), 215 (14), 190 (27), 160 (26), 118 (42), 84 (57), 55 (100); Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.25; H, 5.86.

**3.2.5. 3-Ethoxy-4-hydroxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 5.** Yield: 91%; mp: 211.5–213 °C; $R_f$: 0.50 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261.3 (log ε = 4.11) nm; IR (KBr): $\nu_{max}$ 2957, 1645, 1505, 1455, 1333, 845; $^1$H NMR (400 MHz, $CD_3OD$): δ 6.88 (d, $J$ = 2.0 Hz, 1H, H-2), 6.58–6.61 (m, 2H, H-5/H-6), 4.17 (m, 1H, H-7), 4.01 (dd, $J$ = 13.1 Hz, $J$ = 6.4 Hz, 1H, $OCH_2CH_3$), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′) 1.38 (t, $J$ = 6.4 Hz, 1H, $OCH_2CH_3$); EIMS: *m/z* 372 (4), 354 (3), 260 (27), 215 (15), 203 (4), 176 (7), 134 (11), 112 (13), 84 (27), 55 (100); Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.75; H, 6.51.

**3.2.6. 4-Methoxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 6.** Yield: 95%; mp: 199–201 °C; $R_f$: 0.52 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 272.5 (log ε = 4.21) nm; IR (KBr): $\nu_{max}$ 2951, 1630, 1505, 1443, 1335, 845; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.04 (d, $J$ = 8.3 Hz, 2H, H-2/H-6), 6.63 (d, $J$ = 8.3 Hz, 2H, H-3/H-5), 4.17 (m, 1H, H-7), 3.79 (s, 3H, $OCH_3$) 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 342 (6), 324 (100), 307 (38), 293 (70), 268 (32), 217 (80), 199 (18), 145 (12), 89 (23), 55 (44); Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.18; H, 6.47.

**3.2.7. 2-Methoxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 7.** Yield: 92%; mp: 190–191 °C; $R_f$: 0.51 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 283.7 (log ε = 4.05) nm; IR (KBr): $\nu_{max}$ 2958, 1660, 1519, 1460, 1339, 838; $^1$H NMR (400 MHz, $CD_3OD$): δ 6.75–7.17 (m, 4H, Ar-*H*), 3.69 (s, 3H, $OCH_3$), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 342 (6), 258 (70), 243 (32), 217 199 (100), 171 (23), 131 (12), 84 (23), 55 (44); Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.13; H, 6.48.

**3.2.8. 3,4,5-Trimethoxyphenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 8.** Yield: 88%; mp: 231.5–132.6 °C; $R_f$: 0.56 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 269.7 (log ε = 4.04) nm; IR (KBr): $\nu_{max}$ 2943, 1619, 1514, 1450, 1343, 847; $^1$H NMR (400 MHz, $CD_3OD$): δ 6.31 (s, 2H, H-2/H-5), 4.17 (m, 1H, H-7), 3.79 (s, 3H, $OCH_3$), 3.75 (s, 6H, $OCH_3$), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 402 (6), 290 (77), 259 (100), 219 (9), 149 (8), 112 (17), 84 (32), 55 (100); Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.63; H, 6.50.

**3.2.9. 4-Nitrophenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 9.** Yield: 91%; mp: 219–221 °C; $R_f$: 0.47 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 289 (log ε = 3.88) nm; IR (KBr): $\nu_{max}$ 3145, 2951, 1719, 1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CD_3OD$): δ 8.02 (d, $J$ = 8.4 Hz, 2H, H-3/H-5), 7.51 (d, $J$ = 8.4 Hz, 2H, H-2/H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 357 (13), 311 (16), 235 (7), 215 (67), 160 (28), 118 (39), 84 (57), 55 (100); Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.84; H, 5.37; N, 3.92.

**3.2.10. 3-Nitrophenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 10.** Yield: 93%; mp: 209–211 °C; $R_f$: 0.43 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261.3 (log ε = 4.11) nm; IR (KBr): $\nu_{max}$ 3145, 2951, 1719, 1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CD_3OD$): δ 8.13 (d, $J$ = 8.3 Hz, 1H, H-4), 7.97 (d, $J$ = 1.8 Hz, 1H, H-2), 7.68 (td, $J$ = 8.3 Hz, $J$ = 1.8 Hz, 1H, H-5), 7.39 (dd, $J$ = 8.3 Hz, $J$ = 1.8 Hz, 2H, H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 357 (19), 322 (37), 292 (15), 256 (9), 217 (48), 198 (10), 128 (11), 115 (14), 84 (36), 55 (100); Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.87; H, 5.35; N, 3.91.

**3.2.11. 3-Aminophenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 11.** Yield: 4.87 g, 99.65%; mp: 199–200 °C; $R_f$: 0.62 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261.3 (log ε = 4.11) nm; IR (KBr): $\nu_{max}$ 3145, 2951, 1719, 1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CD_3OD$): δ 6.91 (td, $J$ = 7.6 Hz, $J$ = 1.3 Hz, 1H, H-5), 6.64 (d, $J$ = 1.3 Hz, 1H, H-2), 6.57 (d, $J$ = 7.6 Hz, 1H, H-4), 6.48 (dd, $J$ = 7.6 Hz, $J$ = 1.3 Hz, 2H, H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 327 (11), 309 (28), 291 (13), 275 (8), 291 (22), 253 (13), 217 (48), 198 (10), 128 (11), 115 (14), 84 (36), 55 (100); Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.69; H, 6.48; N, 4.28.

**3.2.12. 2-Bromophenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 12.** Yield: 4.87 g, 99.65%; mp: 199–200 °C; $R_f$: 0.62 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261.3 (log ε = 4.11) nm; IR (KBr): $\nu_{max}$ 3145, 2951, 1719,

1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.55 (d, $J$ = 7.8 Hz, 1H, H-4), 7.33 (td, $J$ = 7.8 Hz, $J$ = 1.7 Hz, 1H, H-5), 7.21 (td, $J$ = 7.8 Hz, $J$ = 1.7 Hz, 1H, H-4), 6.98 (d, $J$ = 7.8 Hz, 1H, H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 393 (11), 391 (12), 310 (5), 227 (4), 199 (100), 129 (6), 101 (14), 84 (17), 55 (35); Anal. Calcd for $C_{19}H_{19}BrO_4$: C, 58.33; H, 4.89. Found: C, 58.30; H, 4.86.

**3.2.13. 2-Chlorophenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 13.** Yield: 4.87 g, 99.65%; mp: 199–200 °C; $R_f$: 0.62 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261.3 ($\log\varepsilon$ = 4.11) nm; IR (KBr): $\nu_{max}$ 3145, 2951, 1719, 1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.26 (d, $J$ = 7.4 Hz, 1H, H-4), 7.18 (td, $J$ = 7.4 Hz, $J$ = 1.2 Hz, 1H, H-5), 7.12 (td, $J$ = 7.4 Hz, $J$ = 1.2 Hz, 1H, H-4), 6.98 (d, $J$ = 7.8 Hz, 1H, H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 348 (5), 346 (6), 311 (3), 246 (4), 227 (3), 199 (100), 136 (10), 112 (9), 84 (16), 55 (26); Anal. Calcd for $C_{19}H_{19}ClO_4$: C, 58.33; H, 4.89. Found: C, 58.30; H, 4.88.

**3.2.14. 3-Chlorophenyl-2,2′-methylenebis-(cyclohexane-1,3-dione) 14.** Yield: 4.87 g, 99.65%; mp: 199–200 °C; $R_f$: 0.62 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261.3 ($\log\varepsilon$ = 4.11) nm; IR (KBr): $\nu_{max}$ 3145, 2951, 1719, 1515, 1343, 1453, 843; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.26 (d, $J$ = 7.4 Hz, 1H, H-4), 7.18 (td, $J$ = 7.4 Hz, $J$ = 1.2 Hz, 1H, H-5), 7.12 (td, $J$ = 7.4 Hz, $J$ = 1.2 Hz, 1H, H-4), 6.98 (d, $J$ = 7.8 Hz, 1H, H-6), 4.17 (m, 1H, H-7), 2.33–2.60 (m, 2H, H-2/H-2′), 2.09–2.32 (m, 8H, H-6/H-4/H-6′/H-4′), 1.97–2.0 (m, 4H, H-5/H-5′); EIMS: *m/z* 348 (5), 346 (6), 311 (3), 246 (4), 227 (3), 199 (100), 136 (10), 112 (9), 84 (16), 55 (26); Anal. Calcd for $C_{19}H_{19}ClO_4$: C, 58.33; H, 4.89. Found: C, 58.35; H, 4.89.

**3.2.15. Phenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 15.** Yield: 98%; mp: 194–195 °C; $R_f$: 0.61 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261 ($\log\varepsilon$ = 3.37) nm; IR (KBr): $\nu_{max}$ 3123, 2958, 1610, 1601, 1512, 1461, 1334, 849 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.06–7.26 (m, 5H, Ar-*H*), 5.52–5.54 (m, 1H, H-7), 3.69–3.80 (m, 2H, H-2/H-2′), 2.23–2.46 (m, 8H, H-4/H-6/H-4′/H-6′), 1.21 (s, 6H, 2× $CH_3$), 1.08 (s, 6H, 2× $CH_3$); EIMS: *m/z* 368 (31), 253 (4), 227 (100), 171 (28), 140 (23), 102 (27), 82 (3), 55 (62%); Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.95; H, 7.65.

**3.2.16. 4-Hydroxyphenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 16.** Yield: 93%; mp: 190–192 °C; $R_f$: 0.52 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 289 ($\log\varepsilon$ = 3.95) nm; IR (KBr): $\nu_{max}$ 3100, 1606, 1600, 1512, 1465, 1344, 848 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.32 (d, $J$ = 8.4 Hz, 2H, H-2″/H-6″), 6.72 (d, $J$ = 8.4 Hz, 2H, H-3″/H-5″), 5.06–5.10 (m, 1H, H-7), 3.68–3.80 (m, 2H, H-2/H-2′), 2.15–2.27 (m, 8H, H-4/H-6/H-4′/H-6′), 1.04 (s, 6H, 2× $CH_3$), 0.99 (s, 6H, 2× $CH_3$); EIMS: *m/z* 384 (22), 367 (12), 292 (4), 253 (11), 227 (45), 171 (7), 140 (19), 102 (17), 82 (3), 55 (100%); Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.81; H, 7.33.

**3.2.17. 3-Methoxy-4-hydroxyphenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 17.** Yield: 89%; mp: 176–178 °C; $R_f$: 0.51 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 278 ($\log\varepsilon$ = 3.48) nm; IR (KBr): $\nu_{max}$ 3123, 1611, 1603, 1511, 1465, 1338, 846 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.85 (d, $J$ = 1.8 Hz, 1H, H-2″), 6.61 (d, $J$ = 8.1 Hz, 1H, H-5″), 6.57 (dd, $J$ = 8.1 Hz, $J$ = 1.8 Hz, 1H, H-6″), 4.95–5.05 (m, 1H, H-7), 3.85 (s, 3H, OC*H*$_3$), 3.74–3.80 (m, 2H, H-2/H-2′), 2.13–2.59 (m, 8H, H-4/H-6/H-4′/H-6′), 1.09 (s, 6H, 2× $CH_3$), 0.99 (s, 6H, 2× $CH_3$); EIMS: *m/z* 414 (14), 396 (41), 349 (4), 257 (6), 217 (37), 160 (39), 133 (20), 83 (42), 55 (38%); Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.55; H, 7.29.

**3.2.18. 3-Ethoxy-4-hydroxyphenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 18.** Yield: 90%; mp: 182–184 °C; $R_f$: 0.52 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 266 ($\log\varepsilon$ = 3.39) nm; IR (KBr): $\nu_{max}$ 3123, 1615, 1601, 1520, 1470, 1341, 841 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.66 (d, $J$ = 2.0 Hz, 1H, H-2″), 6.60 (d, $J$ = 8.3 Hz, 1H, H-5″), 6.48 (dd, $J$ = 8.3 Hz, $J$ = 2.0 Hz, 1H, H-6″), 4.98–5.09 (m, 1H, H-7), 3.95 (dd, $J$ = 13.4 Hz, $J$ = 6.4 Hz, 2H, OC*H*$_2$CH$_3$), 3.74–3.80 (m, 2H, H-2/H-2′), 2.05–2.50 (m, 8H, H-4/H-6/H-4′/H-6′), 1.34 (t, $J$ = 6.4 Hz, 3H, OCH$_2$C*H*$_3$), 1.14 (s, 6H, 2× $CH_3$), 1.04 (s, 6H, 2× $CH_3$); EIMS: *m/z* 428 (11), 414 (3) 384 (6), 364 (7), 292 (12), 257 (16), 217 (33), 160 (39), 133 (20), 83 (42), 55 (38%); Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.01; H, 7.53.

**3.2.19. 4-Methoxyphenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 19.** Yield: 96%; mp: 185–186 °C; $R_f$: 0.56 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 301 ($\log\varepsilon$ = 3.45) nm; IR (KBr): $\nu_{max}$ 3123, 1614, 1605, 1512, 1470, 1343, 839 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.97 (d, $J$ = 8.4 Hz, 2H, H-2″/H-6″), 6.79 (d, $J$ = 8.4 Hz, 2H, H-3″/H-5″), 5.22–5.40 (m, 1H, H-7), 3.77 (s, 3H, $OCH_3$), 3.70–3.75 (m, 2H, H-2/H-2′), 2.26–2.45 (m, 8H, H-4/H-6/H-4′/H-6′), 1.20 (s, 6H, 2× $CH_3$), 1.07 (s, 6H, 2× $CH_3$); EIMS: *m/z* 398 (13), 349 (4), 273 (7), 257 (78), 227 (66), 146 (24), 117 (19), 83 (100), 55 (92%); Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.31; H, 7.60.

**3.2.20. 3-Methoxyphenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 20.** Yield: 94%; mp: 199–201 °C; $R_f$: 0.53 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 277 ($\log\varepsilon$ = 3.66) nm; IR (KBr): $\nu_{max}$ 3123, 1612, 1601, 1509, 1465, 1347, 844 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.15 (td, $J$ = 8.0 Hz, $J$ = 2.0 Hz, 1H, H-5″), 6.63–6.70 (m, 3H, H-2″/H-4″/H-6″), 5.31–5.49 (m, 1H, H-7), 3.70 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.68–3.75 (m, 2H, H-2/H-2′), 2.28–2.45 (m, 8H, H-4/H-6/H-4′/H-6′), 1.21 (s, 6H, 2× $CH_3$), 1.07 (s, 6H, 2× $CH_3$); EIMS: *m/z* 398 (38), 349 (11), 271 (100), 259 (83), 227 (90), 203 (39), 171 (29), 141 (22), 83 (30), 55 (8%); Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.35; H, 7.60.

**3.2.21. 2-Methoxyphenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 21.** Yield: 96%; mp: 181–183 °C; $R_f$: 0.55 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 274 ($\log\varepsilon = 3.90$) nm; IR (KBr): $\nu_{max}$ 3123, 1613, 1601, 1517, 1461, 1339, 841 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.15–7.24 (m, 2H, H-5″/H-4″), 6.87 (td, $J = 7.9$ Hz, $J = 1.8$ Hz, 1H, H-4″), 6.77 (d, $J = 7.9$ Hz, 1H, H-6″), 5.33–5.50 (m, 1H, H-7), 3.70 (s, 3H, $OCH_3$), 3.72–3.80 (m, 2H, H-2/H-2′), 2.13–2.45 (m, 8H, H-4/H-6/H-4′/H-6′), 1.14 (s, 6H, 2× $CH_3$), 1.08 (s, 6H, 2× $CH_3$); EIMS: *m/z* 398 (77), 366 (9), 282 (70), 271 (83), 227 (100), 199 (31), 171 (36), 131 (52), 83 (8), 55 (83%); Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.38; H, 7.59.

**3.2.22. 4-Nitrophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 22.** Yield: 93%; mp: 188–190 °C; $R_f$: 0.43 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 310 ($\log\varepsilon = 3.91$) nm; IR (KBr): $\nu_{max}$ 3123, 1675, 1626, 1512, 1366, 1344, 1465, 848 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 8.09 (d, $J = 8.7$ Hz, 2H, H-3″/H-5″), 7.26 (d, $J = 8.7$ Hz, 2H, H-2″/H-6″), 5.10–5.19 (m, 1H, H-7), 3.71–3.78 (m, 2H, H-2/H-2′), 2.05–2.40 (m, 8H, H-4/H-6/H-4′/H-6′), 1.10 (s, 6H, 2× $CH_3$), 1.00 (s, 6H, 2× $CH_3$); EIMS: *m/z* 413 (33), 396 (13), 286 (11), 255 (36), 225(30), 161 (23), 84 (59), 55 (100%); Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.85; H, 6.57; N, 3.39.

**3.2.23. 3-Nitrophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 23.** Yield: 91%; mp: 196–198 °C; $R_f$: 0.65 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 307 ($\log\varepsilon = 4.07$) nm; IR (KBr): $\nu_{max}$ 3123, 1655, 1616, 1595, 1366, 841 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 8.12 (d, $J = 8.4$ Hz, 1H, H-4″), 7.27 (d, $J = 1.8$ Hz, 1H, H-2″), 7.22 (td, $J = 1.8$ Hz, $J = 8.4$ Hz, 1H, H-5″), 6.87 (dd, $J = 1.8$ Hz, $J = 8.4$ Hz, 1H, H-4″), 4.91–5.01 (m, 1H, H-7), 3.71–3.78 (m, 2H, H-2/H-2′), 2.05–2.40 (m, 8H, H-4/H-6/H-4′/H-6′), 1.10 (s, 6H, 2× $CH_3$), 1.00 (s, 6H, 2× $CH_3$); EIMS: *m/z* 413 (33), 396 (13), 286 (11), 255 (36), 225 (30), 161 (23), 84 (59), 55 (100%); Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.79; H, 6.58; N, 3.38.

**3.2.24. 4-Aminophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 24.** Yield: 88%; mp: 181–183 °C; $R_f$: 0.43 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 288 ($\log\varepsilon = 3.45$) nm; IR (KBr): $\nu_{max}$ 3400, 3133, 1635, 1609, 1501, 1314, 848 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 8.09 (d, $J = 8.7$ Hz, 2H, H-3″/H-5″), 7.50 (d, $J = 8.7$ Hz, 2H, H-2″/H-6″), 4.80–4.93 (m, 1H, H-7), 3.64-3.75 (m, 2H, H-2/H-2′), 2.10–2.58 (m, 8H, H-4/H-6/H-4′/H-6′), 1.09 (s, 6H, 2× $CH_3$), 0.97 (s, 6H, 2× $CH_3$); EIMS: *m/z* 383 (13), 348 (19), 310 (3), 273 (100), 217 (28), 169 (4), 161 (23), 115 (5), 84 (17), 55 (41%); Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.00; H, 7.63; N, 3.65.

**3.2.25. 3-Aminophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 25.** Yield: 93%; mp: 166–167 °C; $R_f$: 0.41 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 276 ($\log\varepsilon = 3.73$) nm; IR (KBr): $\nu_{max}$ 3405, 3131, 1641, 1612, 1508, 1319, 842 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 6.92 (td, $J = 1.2$ Hz, $J = 7.6$ Hz, 1H, H-5″), 6.67 (d, $J = 1.2$ Hz, 1H, H-2″), 6.54 (d, $J = 7.6$ Hz, 1H, H-4″), 6.46 (dd, $J = 1.2$ Hz, $J = 7.6$ Hz, 1H, H-6″), 4.79–4.86 (m, 1H, H-7), 3.59–3.67 (m, 2H, H-2/H-2′), 2.11–2.43 (m, 8H, H-4/H-6/H-4′/H-6′), 1.13 (s, 6H, 2× $CH_3$), 0.99 (s, 6H, 2× $CH_3$); EIMS: *m/z* 383 (19), 348 (11), 310 (5), 273 (100), 217 (22), 169 (7), 161 (18), 115 (4), 84 (21), 55 (50%); Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.08; H, 7.62; N, 3.64.

**3.2.26. 4-*N*,*N*-Dimethylaminophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 26.** Yield: 93%; mp: 194–195 °C; $R_f$: 0.54 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 261 ($\log\varepsilon = 3.372$) nm; IR (KBr): $\nu_{max}$ 3129, 1628, 1611, 1506, 1311, 850 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 6.93 (d, $J = 8.4$ Hz, 2H, H-3″/H-5″), 6.70 (d, $J = 8.4$ Hz, 2H, H-2″/H-6″), 4.99–5.24 (m, 1H, H-7), 3.59–3.67 (m, 2H, H-2/H-2′), 2.89 (s, 6H, $N(CH_3)_2$), 2.17–2.39 (m, 8H, H-4/H-6/H-4′/H-6′), 1.11 (s, 6H, 2× $CH_3$), 1.01 (s, 6H, 2× $CH_3$); EIMS: *m/z* 411 (56), 327 (3), 284 (12), 272 (100), 214 (11), 174 (24), 169 (3), 144 (47), 121 (73), 83 (69), 55 (66%); Anal. Calcd for $C_{23}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.90; H, 8.09; N, 3.41.

**3.2.27. 3-Chlorophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 27.** Yield: 92%; mp: 222–224 °C; $R_f$: 0.56 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 301 ($\log\varepsilon = 4.00$) nm; IR (KBr): $\nu_{max}$ 3122, 1621, 1619, 1520, 1318, 846, 612 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 7.27 (dd, $J = 1.5$ Hz, $J = 7.7$ Hz, 1H, H-4″), 7.24 (d, $J = 1.5$ Hz, 1H, H-2″), 7.16 (td, $J = 1.5$ Hz, $J = 7.7$ Hz, 1H, H-5″), 7.12 (dd, $J = 1.5$ Hz, $J = 7.7$ Hz, 1H, H-6″), 5.03–5.14 (m, 1H, H-7), 3.59–3.67 (m, 2H, H-2/H-2′), 2.17–2.39 (m, 8H, H-4/H-6/H-4′/H-6′), 1.11 (s, 6H, 2× $CH_3$), 1.01 (s, 6H, 2× $CH_3$); EIMS: *m/z* 404 (5), 402 (12), 367 (18), 275 (20), 255 (26), 227 (100), 199 (14), 171 (22), 115 (22), 83 (22), 55 (27%); Anal. Calcd for $C_{23}H_{27}ClO_4$: C, 68.56; H, 6.75. Found: C, 68.52; H, 6.74.

**3.2.28. 3-Bromophenyl-2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione) 28.** Yield: 89%; mp: 229–231 °C; $R_f$: 0.56 ($CH_2Cl_2$/EtOAc, 8:2); UV ($CHCl_3$): $\lambda_{max}$ 2.93 ($\log\varepsilon = 3.88$) nm; IR (KBr): $\nu_{max}$ 3129, 1628, 1611, 1506, 1311, 850, 608 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 7.47 (dd, $J = 1.7$ Hz, $J = 7.9$ Hz, 1H, H-4″), 7.42 (d, $J = 1.7$ Hz, 1H, H-2″), 7.23 (td, $J = 1.7$ Hz, $J = 7.9$ Hz, 1H, H-5″), 7.17 (dd, $J = 1.7$ Hz, $J = 7.9$ Hz, 1H, H-6″), 5.12–5.24 (m, 1H, H-7), 3.58–3.69 (m, 2H, H-2/H-2′), 2.17–2.39 (m, 8H, H-4/H-6/H-4′/H-6′), 1.16 (s, 6H, 2× $CH_3$), 0.98 (s, 6H, 2× $CH_3$); EIMS: *m/z* 449 (4), 447 (5), 349 (12), 320 (4), 255 (5), 227 (100), 171 (23), 115 (8), 83 (21), 55 (35%); Anal. Calcd for $C_{23}H_{27}BrO_4$: C, 61.75; H, 6.08. Found: C, 661.74; H, 6.08.

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