chemistry proceedings

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Synthesis of Symmetrical Monocarbonyl Analogs of Curcumin Containing a 2-Bromobenzylidene Moiety and Spectrophotometric Assessment of Their Reactivity with 2-(Dimethylamino)ethanthiol †

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† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

Abstract: The cross-conjugated dienones containing the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore have diverse biological activities. These sometimes-called monocarbonyl analogs of curcumin (MACs) have especially pronounced biological activity when containing an electron-withdrawing group at the ortho-position of the benzene ring. Their biological activity most likely stems from a selective Michael reaction with thiols. It has been reported in the literature that certain MACs (in particular, **EF24**) react as electrophiles with glutathione and form bis adducts in vitro. Five MACs were prepared ((*2E*,*5E*)-2,5-bis(2-bromobenzylidene)cyclopentanone, (**2BrCP**), (*2E*,*6E*)-2,6-bis(2-bromobenzylidene)cyclohexanone (**2BrCX**, **B2BrBC**), (*2E*,*6E*)-2,6-bis(2-bromobenzylidene)- 4-*tert*-butyl-cyclohexanone (**4tB2BrCX**), (*3E*,*5E*)-3,5-bis(2-bromobenzylidene)-4-piperidone, (**2Br4PIP**) and (*3E*,*5E*)-3,5-bis(2-fluorobenzylidene)-4-piperidone, **EF24**), purified and characterized by spectroscopic means. The relative reactivity of these MACs towards 2-(dimethylamino)ethanethiol was assessed via a previously developed UV-Vis spectroscopic method and compared to **EF24**, which reacts readily in solution with thiols such as glutathione and cysteamine. All of the bis(2-bromobenzylidene) MACs react slower with 2-(dimethylamino)ethanethiol in 80:20 (v/v) acetonitrile/water compared to **EF24**. The relative reactivity of the analogs with 2-(dimethylamino)ethanethiol followed the order **EF24** > **2Br4PIP** > **2BrCX** > **2BrCP** > **4tB2BrCX**.

Keywords: monocarbonyl analogs of curcumin; symmetrical 2-bromobenzylidene MACs; synthesis; 2-(dimethylamino)ethanethiol; Michael reaction with thiols; UV-Vis spectroscopy

Citation: Lozanovski, Z.; Todorovska, I.; Dragarska, K.; Bogdanov, J. Synthesis of Symmetrical Monocarbonyl Analogs of Curcumin Containing a 2-Bromobenzylidene Moiety and Spectrophotometric Assessment of Their Reactivity with 2-(Dimethylamino)ethanthiol. *Chem. Proc.* **2023**, *14*, 7. https://doi.org/10.3390/ecsoc-27-16084

Academic Editor: Julio A. Seijas

Published: 15 November 2023

1. Introduction

It is well established that compounds containing the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore have pronounced biological activity(ies) [1–5]. These cross-conjugated dienones are cytotoxic/antiproliferative to tumor cells, and they also exhibit anti-inflammatory, antimicrobial and antiparasitic activity [3]. They target the ubiquitin–proteasome system (UPS), which is known to be crucial for the viability of tumor cells, and are involved in the inhibition of deubiquitinases (DUBs). The Ar-CH=CH-CO-CH=CH-Ar moiety usually contains molecular scaffolds such as cycloalkanes, tetrahydropyrans, tetrahydrothiopyrans, piperidines, *N*-alkylpiperidines and *N*-acylpiperidines (Figure 1). One of the common features of the biologically active dienones is the presence of an electron-withdrawing substituent in the benzene ring, especially in the ortho-position. In the literature, these

dienones are referred to as C5-curcuminoids [6] or monocarbonyl analogs of curcumin (MACs), and they have been extensively studied from different angles [7–13].

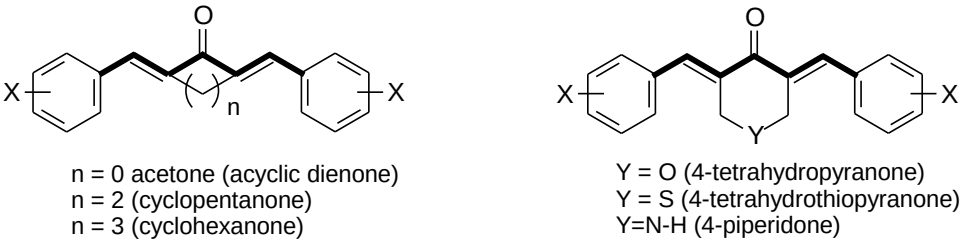

Figure 1. General structure of biologically active compounds containing the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore.

This biological activity according to Dimmock and co-workers [1,14] stems from the electrophilicity of their selectivity towards thiols. The reactivity of these Michael acceptors roughly depends on the electrophilicity, which in turn can be tuned by the substituents on the benzene ring. Indeed, it has been shown in vitro that certain compounds, e.g., **EF24**, **EF31**, **EF25** and **GO-Y030**, react with glutathione and form bis adducts. MACs have especially pronounced biological activity when containing an electron-withdrawing group at the ortho-position of the benzene ring. Several derivatives, namely **EF24** [15,16], **C66** ((2*E*,6*E*)-2,6-bis[2-(trifluoromethyl)benzylidene]cyclohexanone) [17–20], **Y20** ((2*E*,6*E*)-2-(2-bromobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone) [21] and **B2BrBC** ((2*E*,6*E*)-2,6-bis(2-bromobenzylidene)cyclohexanone) [22–25], have been extensively studied. Care needs to be taken when evaluating the properties and activities of these analogs because, similarly to curcumin [26], many of these cross-conjugated derivatives are pan-assay interference compounds (PAINS) [3,27].

In the past several years, our research efforts have been focused on the synthesis and experimental and theoretical studies of these *ortho*-substituted analogs [20,24,25,28,29]. We have established that symmetrical bis 2-fluorobenzylidene, 2-(trifluoromethyl)benzylidene and bis 2-bromobenzylidene derivatives are quite potent. Additionally, we were inspired by the study of Fioravanti et al., who discovered that cyclic bis-(2-bromobenzylidene) compounds behaved as dual p300/CARM1 inhibitors and induced apoptosis in cancer cells [23]. Recently, we developed a spectrophotometric assay for the comparison of the reactivity of MACs towards thiol, and instead of commonly used cysteamine, we employed 2-(dimethylamono)ethanethiol (2DMAESH) [25].

Herein, we present the preparation of symmetrical MACs containing a 2-bromobenzylidene moiety (Figure 2) and a spectrophotometric assessment of their reactivity towards 2DMAESH. Emphasis will be placed on the synthesis and characterization of (2*E*,6*E*)-2,6-bis(2-bromobenzylidene)-4-*tert*-butyl-cyclohexanone (**4tB2BrCX**), since the 4-*tert*-butylcyclohexanone analogs of curcumin are scarcely addressed in the literature.

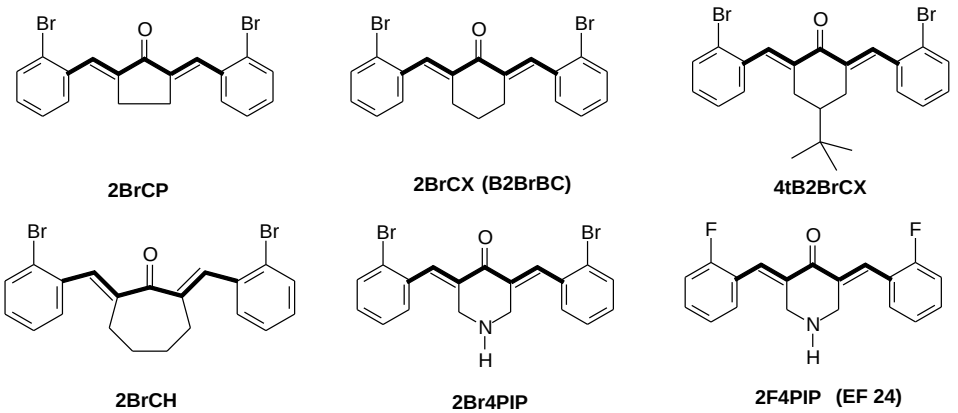

Figure 2. Structures of symmetrical MACs containing a 2-bromobenzylidene moiety and **EF24**.

2. Materials and Methods

2.1. General

All of the reagents and solvents were of analytical and HPLC grade and obtained from Sigma Aldrich (2-bromobenzaldehyde, cyclopentanone, cyclohexanone, 2-(dimethylamino)-ethanethiol hydrochloride), Merck (ethyl acetate, hexane, methanol, acetonitrile (HPLC-grade)), Alfa Aesar (4-piperidone hydrochloride monohydrate) and Alkaloid AD Skopje (96% ethanol, methylene chloride, sodium hydroxide). All the chemicals were used without further purification. The melting point measurements were performed with a Mel-Temp II capillary apparatus (Us Lab. devices) and were uncorrected. Infrared spectra were recorded with the ATR (attenuated total reflection) technique using a Cary 630 FTIR spectrometer with a diamond system. UV spectra were recorded in acetonitrile along with UV kinetic measurements taken with a Varian Cary 50 Scan UV–Vis spectrophotometer. The UV-Vis spectra of each analog in acetonitrile are given in the supplemental materials section (Figure S1). TLC analysis was carried out using silica plates with 10:1 dichloromethane/ethyl acetate (for the 4-piperidone analogues) and 8:1 hexane/ethyl acetate (for the rest of the MACs) as mobile phases, and subsequently, R_f values were calculated. The synthesis of the analogs **2BrCP**, **2BrCX**, **2Br4PIP**, and **EF24** has been previously reported in the literature [22,24,28]. A sample of (2*E*,7*E*)-2,7-bis(2-bromobenzylidene)cycloheptanone **2BrCH(ep)** was obtained from a collaborator's lab, and its purity was checked by TLC and GC-MS.

*2.2. Preparation of **4tB2BrCX***

The analog was prepared using a previously reported procedure [24,28] with minor modifications. A total of 7.5 mmol of 4-tert-butylcyclohexanone (7.5 mmol) was mixed with 2 equivalents of 2-bromobenzaldehyde (15 mmol) in a round-bottom flask. After adding 10 mL of methanol, the reaction mixture was stirred for 5 min at room temperature with an electromagnetic stirrer, followed by the dropwise addition of 20% (*w*/*v*) aqueous NaOH solution (2.5 mL) over a 10 min period. While adding the base, the mixture acquired a yellow color, and after a few minutes, a yellow precipitate was obtained. The reaction mixture was then vigorously stirred at ambient temperature for 5 h. Then, the reaction mixture was cooled in an ice bath for about 10 min, followed by vacuum filtration on a Büchner funnel. The yellow precipitates were washed with distilled H_2O and ice-cold methanol. After drying, the obtained solid was purified by recrystallization from 7:3 methanol/dichloromethane.

(2*E*,6*E*)-2,6-bis(2-bromobenzylidene)-4-*tert*-butyl-cyclohexanone (4tB2BrCX): rec. from 7:3 CH_3OH/CH_2Cl_2. Yield (2.708 g, 74%). Mp 159–161 °C. R_f (8:1 hexane/ethyl acetate) = 0.28. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 2.7 Hz, 2H), 7.65 (dd, *J* = 8.0, 0.9 Hz, 2H), 7.37–7.29 (m, 4H), 7.23–7.17 (m, 2H), 2.94 (dd, *J* = 14.9, 2.7 Hz, 2H), 2.38–2.19 (m, 2H), 1.52 (tt, *J* = 12.5, 3.2 Hz, 1H), 0.85 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.05 (C=O), 137.60 (C), 136.56 (CH), 136.49 (C), 133.22 (CH), 130.47 (CH), 129.87 (CH), 127.14 (CH), 125.26 (C), 44.59 (CH), 32.84 (C), 29.47 (CH_2), 27.33 (CH_3). **FT-IR** (KBr): 1661 cm^{-1} (C=O); **UV-Vis**: λ_{max} (CH_3CN) = 312 nm (ε = 23,577 $L{\cdot}mol^{-1}{\cdot}cm^{-1}$), 235 nm (ε = 14,274 $L{\cdot}mol^{-1}{\cdot}cm^{-1}$); **GC-MS**, t_R = 23.176 min; **EI-MS** (*m*/*z*, rel. intensity): M^+ + 4 (490, 0.23%), M^+ + 2 (488, 0.48%), M^+ (486, 0.23%), 410 (28%), 409 (100%), 408 (28%), M^+-Br (407, 100%), 271 (20%), 269(8.8%), 165 (7.8%), 128 (10.1%), 115(22.8%), 57 (10.7%).

2.3. UV/Vis Kinetic Thiol Assay

The thiol assay was performed with slight modifications from the original [25]. Quartz cuvettes were used with a path length of 1 cm and supplied with caps used to cover the reaction mixture during the measurements. As a solvent system, a 80:20 *v*/*v* acetonitrile/water mixture was used. All measurements were taken at ambient temperature (25 °C).

To perform the assay, 0.4 mg/mL stock solutions of MACs in acetonitrile were prepared. Just prior to measurements, 2.5 mg/mL thiol (2-(dimethylamino)ethanethiol hydrochloride—2DMAESH) solution was prepared in the 80:20 *v*/*v* acetonitrile/water

mixture. Then, 3 mL of the thiol solution was added in the cuvette, combined with 100–200 µL of the MAC stock solutions, and the reaction mixture was thoroughly mixed. The kinetic measurement was taken immediately afterwards. Absorption spectra were recorded from 200 to 600 nm using an UV−Vis spectrophotometer for a span of 120 min at different intervals, 2, 5, 15 and 30 min (12 data points were collected in the 2 h time interval), and the absorbance drop at maximum absorption wavelength was monitored for each of the MACs. The raw maximum absorbance data were corrected vs. blank (80:20 *v*/*v* acetonitrile/water mixture) to correct for the absorbance of the thiol alone. The UV-Vis spectra for monitoring of the reaction of 2DMAESH and **4tB2BrCX** and **2BrCH(ep)** are given in the supplemental materials section (Figure S2).

3. Results and Discussion

3.1. Chemistry

The MACs presented herein were prepared using literature-described procedures via the Claisen–Schmidt reaction (crossed-aldol reaction). We took special precautions with the purity of the compounds and developed a gas chromatographic–mass spectrometric (GC-MS) method for the assessment of their purity. Care was taken to protect the samples from light during storage and especially in the solution because these compounds are prone to *E*/*Z* isomerization. **4tB2BrCX** was prepared with a 74% yield, and its structure was established by spectroscopic means. In the IR spectrum, the peak below 1670 cm^{-1} indicates a conjugated carbonyl group, which is also supported by the UV-vis spectral data (λ_{max} = 312 nm). The presence of two bromine atoms can be deduced from the isotope pattern in the MS spectrum. The key data come from the ^{1}H NMR, where the *tert*-butyl group corresponds to the singlet at 0.85 ppm, and the ^{13}C NMR, where an intense peak at 27.33 ppm can be observed. The rest of the peaks in the NMR spectra are in agreement with the proposed structure. The relevant spectroscopic and chromatographic data for the 2-bromobenzylidene analogs and **EF24** are given in Table 1.

Table 1. Melting points and key spectroscopic/chromatographic data of the synthesized symmetrical monocarbonyl analogs of curcumin (MACs).

Comp.	mp (°C)	FT-IR (cm^{-1})	UV-VIS λ_{max1} (nm)	UV-VIS λ_{max2} (nm)	GC-MS t_R (min)	EI-MS (*m*/*z*)
2BrCP	165–166	1693 (C=O)	341	242 nm	22.702	M^+ + 4 (420), M^+ + 2 (418), M^+ (416)
2BrCX	131–133	1662 (C=O)	312 nm	237 nm	21.206	M^+ + 4 (434), M^+ + 2 (432), M^+ (430)
4tB2BrCX	159–161	1670 (C=O)	312 nm	236 nm	23.176	M^+ + 4 (490), M^+ + 2 (488), M^+ (486)
2BrCH	109–112	1664 (C=O)	282 nm	235 nm	21.437	M^+ + 4 (448), M^+ + 2 (446), M^+ (444)
2Br4PIP	162–163	1669 (C=O)	313 nm	240 nm	24.775	M^+ + 4 (435), M^+ + 2 (433), M^+ (431)+
EF 24	134–136	1660 (C=O)	317 nm	229 nm	24.316	M^+ (311)

3.2. Spectrophotometric Study

All analogs showed an intense long-wavelength absorption band (LAB) (λ_{max} from 282 nm for **2BrCH** to 341 nm for the cyclopentanone derivative, **2BrCP**) and one more band at shorter wavelengths (Figure 3 and Figure S1). The LABs can be assigned to n − π*-type transitions, while the shorter-wavelength bands correspond to π − π*-type transitions (λ_{max} from 235 nm to 242 nm). The key data are provided in Table 1, and the UV-Vis spectra of all pertinent analogs are depicted in Figure 3.

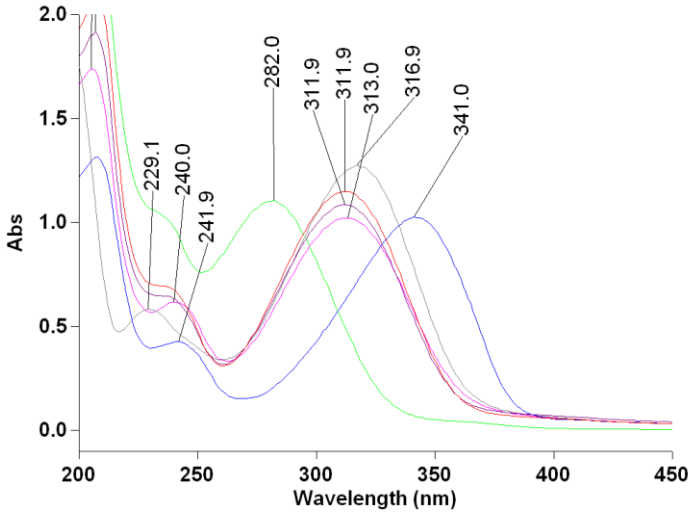

Figure 3. UV-Vis spectra in acetonitrile of symmetrical 2-bromobenzylidene MACs. **2BrCP** (blue line) **2-BrCX** (violet line), **4tB2BrCX** (red), **2BrCH(ep)** (green line), **2-Br4PIP** (pink line), and **2F4PIP** (**EF24**, gray line).

Based on our experience, cysteamine is usually not ideal for assays investigating the electrophilicity of MACs because it has a reactive nucleophilic primary amine that can react in a 1,2-fashion with the ketone to give 1,4-thiazepines [25]. Since MACs have two electrophilic sites, this intermediate can affect the addition of the second equivalent of thiol. We decided to eliminate the addition of the EDTA (for the prevention of the oxidation of thiol) and focus on short assays of 3 h with a freshly prepared solution of 2DMAESH. This turned out not to affect the results, and one can use relatively concentrated solutions (2.5 mg/mL, 0.0174 M), i.e., a 400-fold excess compared to the concentration of MACs, and have a spectral window ranging from 290 nm to 800 nm. Unfortunately, we were not able to carry out this thiol assay with (2*E*,7*E*)-2,7-bis(2-bromobenzylidene)cycloheptanone **2BrCH(ep)**, because its LAB was at 282 nm (Figure 3, Figure S2a and Figure S1b).

The "proven" analog **EF24** reacted the fastest of all the compounds. It is known that **EF24** reacts reversibly with glutathione in vitro [30], and it is reasonable to use it for comparison purposes (Figure 4a). Based on the time-dependent decrease at λ_{max}, the next most reactive compound was the other 4-piperidone derivative **2Br4PIP** (Figure 4c), followed by **2BrCX** and **2BrCP**; the least reactive was the *tert*-butyl cyclohexanone derivative **4tB2BrCX**, which within a 3 h window had a noticeable change (Figure S2b). These processes may have complex kinetics, which will be explored in detail by our group in the future. It could be concluded that the *ortho*-bromo substituents influenced the electrophilicity of the MACs, and in this case, the 4-piperidone derivative (**2-Br4PIP**) was the most reactive of the 2-bromobenzylidene analogs.

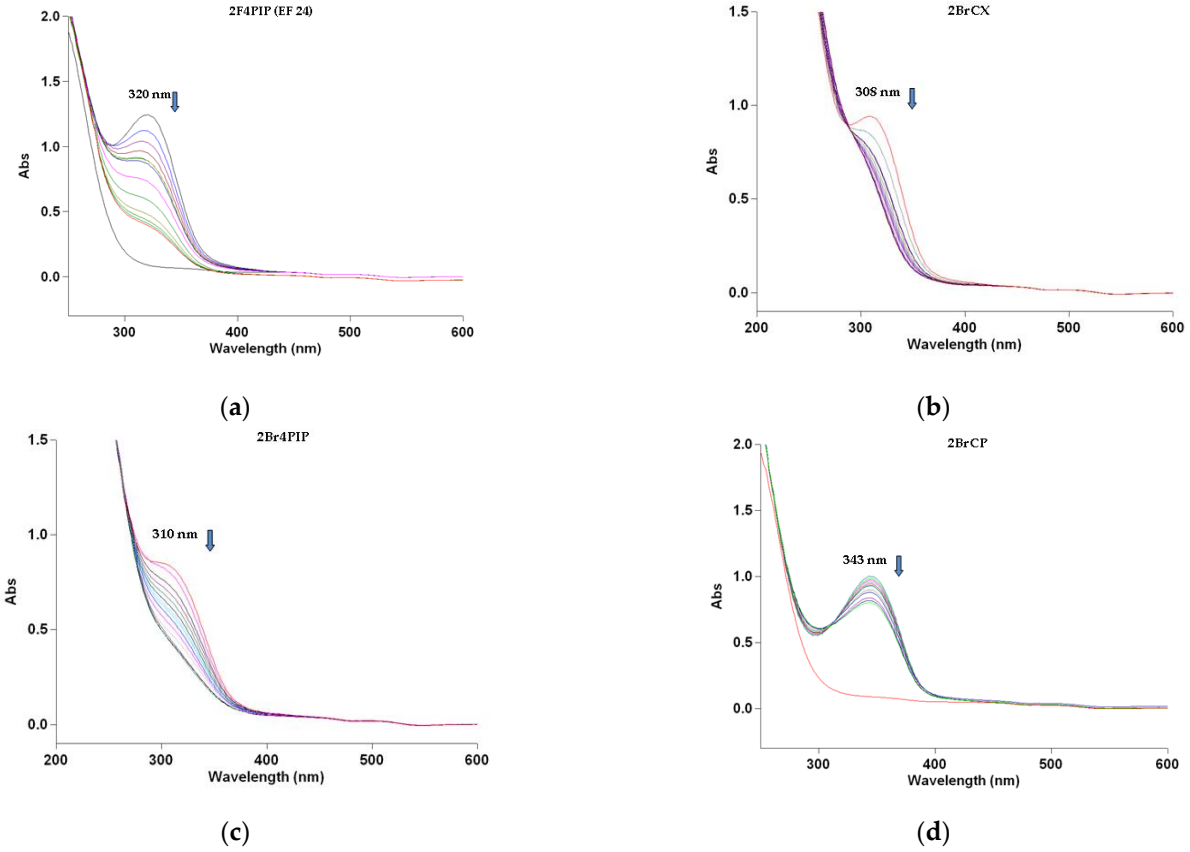

Figure 4. UV-VIS spectra of MACs added to 2-(dimethylamino)ethanethiol (2.5 mg/mL) in 80:20 acetonitrile/H_2O (0 to 150 min: red line in (**d**) is just from a solution of 2-(dimethylamino) ethanethiol (2.5 mg/mL)).The top line from corresponds to 0 min. The rest correspond consecutively to reaction times of 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, 60 min, 90 min and 120 min. (**a**) Monitoring reaction between **EF24** and 2DMAESH; (**b**) monitoring reaction between **2BrCX** and 2DMAESH; (**c**) monitoring reaction between **2BrPIP** and 2DMAESH; (**d**) monitoring reaction between **2BrCP** and 2DMAESH.

4. Conclusions

A series of MACs containing a 2-bromobenzylidene moiety and (*3E*,*5E*)-3,5-bis(2-fluorobenzylidene)-4-piperidone (**EF 24**) were prepared and carefully purified. A previously reported thiol assay method using 2-(dimethylamino)ethanethiol (2DMAESH) instead of cystamine was further simplified and utilized to establish the relative reactivity of the MACs. Among the tested compounds, the fastest LAB changes were observed in the reaction of 2DMAESH with **EF 24**, followed by **2Br4PIP**, **2BrCX** and **2BrCP**. The least reactive was the herein-presented compound **4tB2BrCX**, which after 3 h had only minor changes in the UV spectrum. Acetonitrile and water are appropriate solvents, and they are also suitable for the salts of the 4-piperidone derivatives. This method can be used for other MACs and related systems that have a relatively intense LAB above 300 nm.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ecsoc-27-16084/s1, Figure S1: UV-Vis spectra of symmetrical MACs containing a 2-bromobenzylidene moiety and **EF24** in acetonitrile; Figure S2: UV-VIS spectra of MACs added to 2-(dimethylamino)ethanethiol (2DMAESH) (2.5 mg/mL) in 80:20 acetonitrile/H_2O.

Author Contributions: Conceptualization, J.B.; methodology, J.B., Z.L., K.D. and I.T.; formal analysis, Z.L., I.T. and K.D.; investigation, Z.L., I.T. and K.D.; data curation, I.T. and K.D.; writing—J.B., I.T., K.D. and Z.L.; writing—review and editing, J.B., I.T. and K.D.; supervision, J.B.; project administration. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We would like to thank Zoran Zdravkovski for his help with GC-MS analyses.

Conflicts of Interest: The authors declare no conflict of interest.

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