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SYNTHESIS OF SYMMETRICAL MONOCARBONYL ANALOGS OF CURCUMIN (MACS) CONTAINING 2-BROMOBENZYLIDENE MOIETY AND SPECTROPHOTOMETRIC ASSESSMENT OF THEIR REACTIVITY WITH 2-(DIMETHYLAMINO)ETHANTHIOL

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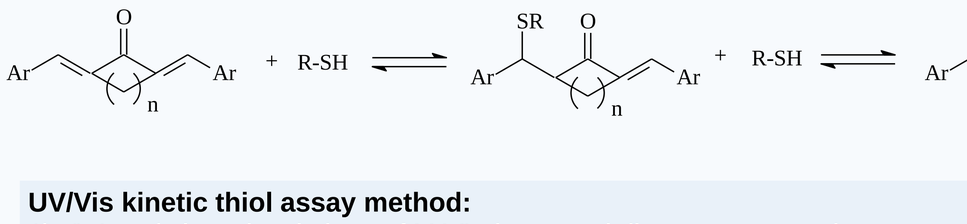
INTRODUCTION

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 electron-withdrawing group at the ortho position of the benzene ring. Their biological activity most likely stems from selective Michael reaction with thiols. It has been reported in the literature that in vitro certain MACs (in particular, **EF24**) react as electrophiles with glutathione and form bis adducts. Five MACs were prepared ((2*E*,5*E*)-2,5-bis(2-bromobenzylidene)cyclopentanone, (**2BrCP**), (2*E*,6*E*)-2,6-bis(2-bromobenzylidene)cyclohexanone (**2BrCX**, **B2BrBC**), 4-*tert*-butyl-(2*E*,6*E*)-2,6-bis(2-bromobenzylidene)cyclohexanone (**4tB2BrCX**), (3*E*,5*E*)-3,5-bis(2-bromobenzylidene)-4-piperidone, (**2Br4PIP**), and (3*E*,5*E*)-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 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 was **EF24** > **2Br4PIP** > **2BrCX** > **2BrCP**> **4tB2BrCX**.

MATERIALS AND METHODS

The synthetic route for the analogs followed coupling 1 eq. of the appropriate ketone with 2 eq. of substituted benzaldehyde via a base catalyzed Claisen–Schmidt condensation reaction [1].



ketone — 2-bromobenzaldehyde

2BrCX: n = 3, X = CH_2; **4tB2BrCX**: n = 3, X = HCtBu;
2BrCP: n = 2, X = CH_2; **2Br4PIP**: n = 3, X = N-H

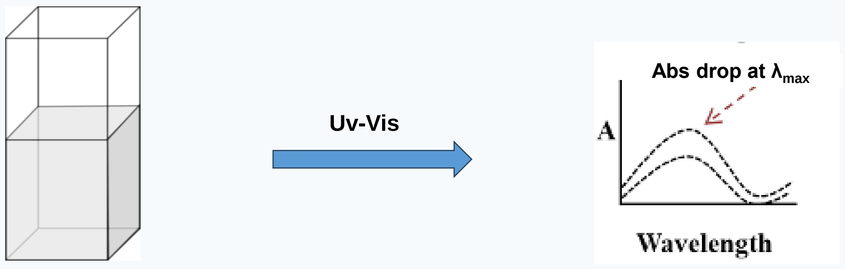
X=N-H,CH_2 or HC-tBu;

MACs

***Scheme 1*: Generalized synthetic route for the obtained MACs**
(solvent: methanol/96% ethanol; catalyst: 10/20% aq. NaOH)

UV/Vis kinetic thiol assay

Based on kinetic measurement for the reaction between MACs with 2-(dimethylamino)ethanethiol hydrochloride (2DMAESH) [2]. Absorption spectra were recorded from 200 to 600 nm using an UV−Vis spectrophotometer for a span of 120 min at different 2, 5, 15 and 30 min intervals (12 data points were collected in the 2 hour 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.



MACs+2DMAESH→mono-adduct and/or bis-adduct

***Figure 1*: UV/Vis kinetic thiol assay with 2DMAESH**

UV/Vis kinetic thiol assay method:

1) 0.4 mg/ml stock solutions of MACs in acetonitrile were prepared;
2) Just prior to measurements 2.5 mg/ml 2DMAESH solution was prepared in the 80:20 v/v acetonitrile/water mixture;
3) 3 ml of the 2DMAESH solution were added in the cuvette
4) 100-200 µL of MACs stock solutions were combined with the thiol and the reaction mixture was thoroughly mixed;
5) Absorption spectra were recorded from 200 to 600 nm for a span of 120 min at different time points;
6) The absorbance drop at maximum absorption wavelength was calculated.

RESULTS

Spectrophotometric study

All analogs show an intense long-wavelength absorption band (LAB) that can be assigned to n−π* type transitions (λ_{max} from 282 nm for 2BrCH to 341 nm for the cyclopentanone derivative, 2BrCP) and one more band at shorter wavelengths that corresponds to π −π* type transition (λ_{max} from 235 nm to 242 nm).

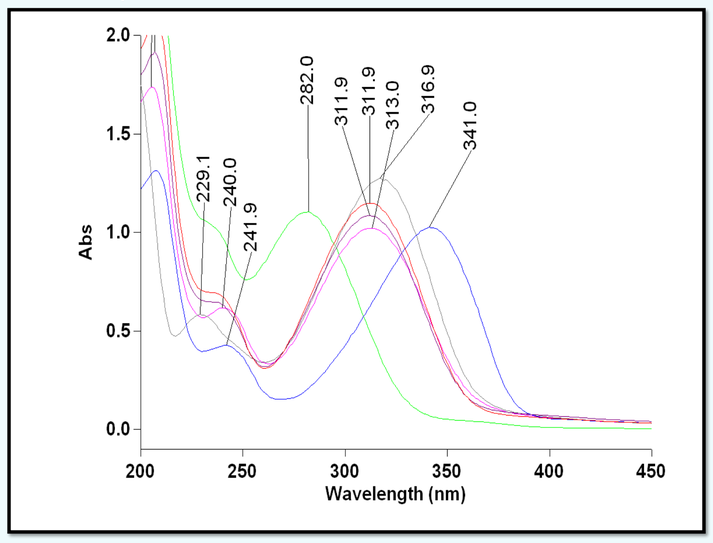


***Figure 2.* UV-Vis spectra in acetonitrile of symmetrical 2-bromobenzylidene MACs.**
2BrCP (blue trace) **2-BrCX** (violet), **4tB2BrCX** (red), **2BrCH(ep)** (green trace), **2-Br4PIP**(-pink), **2-F4PIP** (**EF24**, gray).

Order of relative reactivity of the analogs toward 2-(dimethylamino)ethanethiol (2DMAESH):
EF24 > **2Br4PIP** > **2BrCX** > **2BrCP** > **4tB2BrCX** in 80/20 (*v/v*) CH_3CN/H_2O

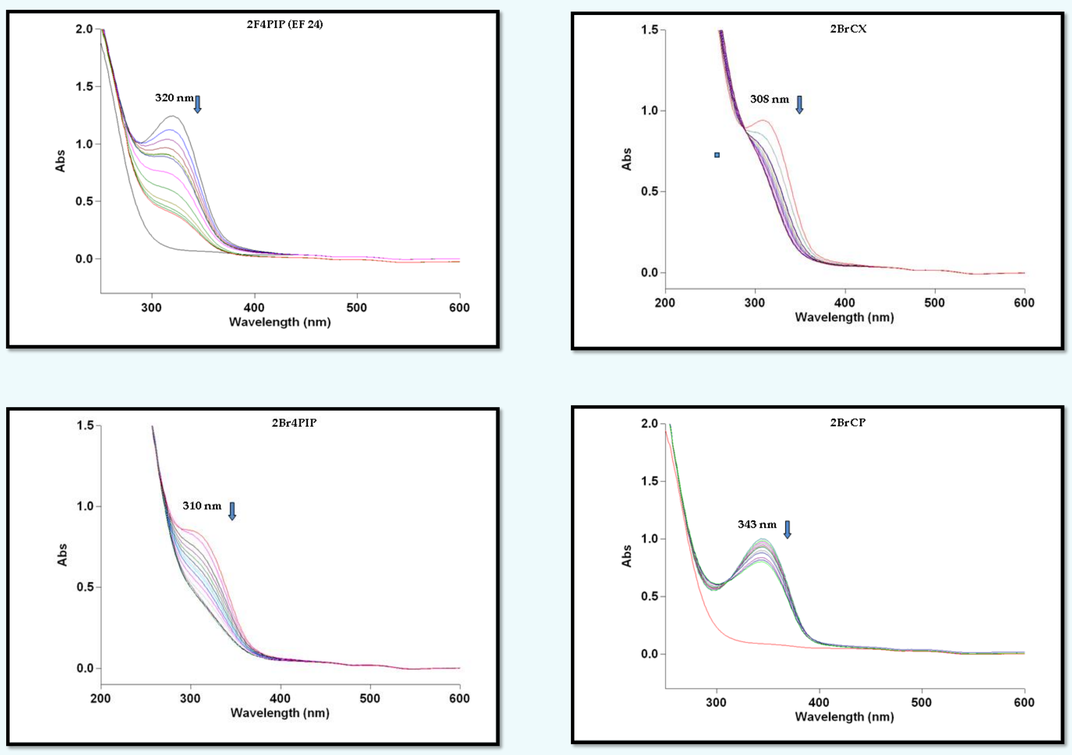


***Figure 3.* UV-VIS spectra of MACs added to 2-(dimethylamino)ethanethiol (2.5 mg/mL) in 80:20 acetonitrile/H2O (0 to 150 minutes)**: red trace in (d) is just from a solution of 2-(dimethylamino) ethanethiol (2.5 mg/mL)).The top trace from corresponds to 0 min. The rest correspond consecu-tively to reaction times of 5min, 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 be-tween 2BrCX and 2DMAESH; (c) Monitoring reaction between 2BrPIP and 2DMAESH; (d) Monitoring reaction between 2BrCP and 2DMAESH.

CONCLUSIONS

This A series of MACs containing 2-bromobenzylidene moiety and (3*E*,5*E*)-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 cysteamine was further simplified and utilized to establish relative reactivity of the MACs. From the tested compounds, the fastest drop of the long-wavelength absorption band (LAB) were observed in the reaction of **2DMAESH** with **EF 24**, followed by **2Br4PIP** and **2BrCX**. The least reactive is the herein presented compound, **4tB2BrCX**, which after 3 hours has only minor changes in the UV spectrum. Acetonitrile and water are suitable solvents, and they can also be 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.

LITERATURE

[1] Todorovska, I.; Dragarska, K.; Bogdanov, J. A Combined 2D- and 3D-QSAR Study, Design and Synthesis of Some Monocarbonyl Curcumin Analogs as Potential Inhibitors of MDA-MB-231 Breast Cancer Cells. Chem. Proc. 2022, 12, 5, doi:10.3390/ecsoc-26-13572.
[2] Lozanovski, Z.; Petreska-Stanoeva, J.; Bogdanov, J. Development of a Spectrophotometric Method for Assessment of the Relative Reactivity of Monocarbonyl Analogs of Curcumin with 2-(Dimethylamino)Ethanethiol. Maced. J. Chem. Chem. Eng. 2023, 42, 13–24, doi:10.20450/mjcce.2023.2638.