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Synthesis and X-ray crystal structure of the calcium channel antagonist: dimethyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4H-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate

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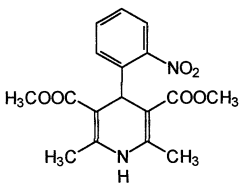
Abstract

The synthesis of the title compound via the Hantzsch method from 4′-flavone carboxaldehyde is described, and its molecular structure was determined by X-ray crystallography. The 1,4-dihydropyridine (1,4-DHP) ring adopts a boat conformation. The phenyl ring of the flavone is not exactly perpendicular to the DHP ring. Calcium antagonistic activity of this compound was evaluated in vitro by using $BaCl_2$-stimulated rat ileum.

Keywords: Flavonyldihydropyridine; Calcium antagonistic activity; X-ray structure analysis

1. Introduction

Calcium channel blocking agents are widely used in the management of angina pectoris and hypertension [1]. Within this class of cardiovascular agents, dihydropyridine (DHP) calcium antagonists have found widespread use in the clinic and have served as important tools for the study of calcium channel structure and function [2–5]. Nifedipine (Formula 1) has been approved for clinical use as an antianginal agent and represents the prototype 1,4-DHP structure found useful in both antianginal and antihypertensive therapy [6]. In the search for new and better nifedipine analogues, the replacement of the 4-substituent, i.e. the phenyl ring of nifedipine has been examined further. The chemical literature reports a great variety of these substituents and among them the chromone ones [7].



Formula 1

Flavonoids, either natural or synthetic, are known to exhibit various biological activities [8]. During the last years, flavonoids have been extensively studied for their medicinal applications. Their various biological properties, spasmolytic [9], capillary resistance activity [10] and coronary dilatory effect [11] have aroused considerable attention.

For reaching our target we followed the approach of replacing substituents on the phenyl ring of the 4-phenyl-1,4-DHP with a flavone moiety. This paper describes the synthesis and preliminary biological evaluation of dimethyl 1,4-dihydro-2,6-dimethyl-4-[4′-(4H-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (**I**).

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The biological activity of the 1,4-DHPs seems to depend on certain key structural and conformational features [12–14]. In the conformational arena, there have been some interesting findings. The aromatic ring at the C4 position must approximately bisect the plane of the DHP ring. Structural studies on nifedipine analogues have shown that the most active compounds possess the smallest deviation from planarity in the DHP ring [15]. These findings encouraged us to study the structural properties of **I**.

2. Chemistry

4′-Methyl flavone (**5**) was prepared using the general method which is known as Baker–Venkataraman. 2-(4-Methyl)-benzoyl-oxy-acetophenone (**3**) was prepared by heating 2′-hydroxy-acetophenone (**1**) and 4-methyl-benzoylchloride (**2**) in pyridine. Compound **3** was converted to dibenzoylmethane derivative **4** and then cyclized to 4′-methyl flavone (**5**). The methyl group of the flavone was changed to bromomethyl (**6**) and then oxidized to carboxaldehyde (**7**) by using hexamethylenetetramine (HMTA). **I** was prepared using the classical Hantzsch reaction [16] (Scheme 1).

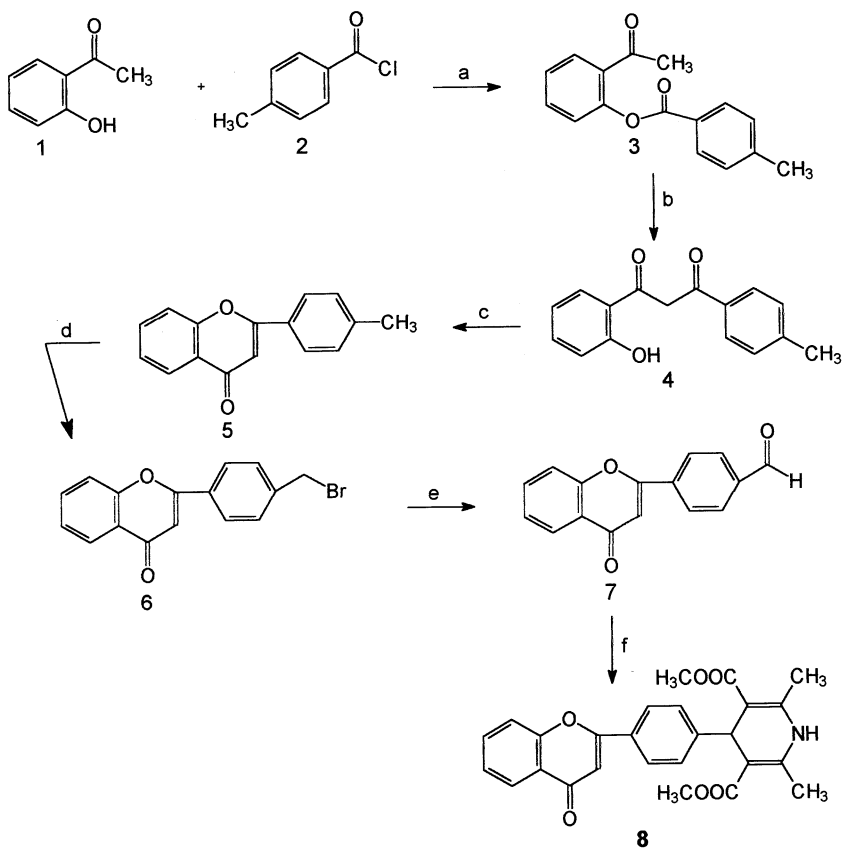
The structure of the prepared compound was elucidated by IR, ^{1}H NMR, mass spectra and elemental analyses. Some physical and spectral characteristics of the synthesized compound are presented in Section 3.

Electron impact mass spectroscopy (EI-MS) spectra of **I** showed molecular ion peak as expected. The fragmentation patterns (Scheme 2) confirmed the structure.

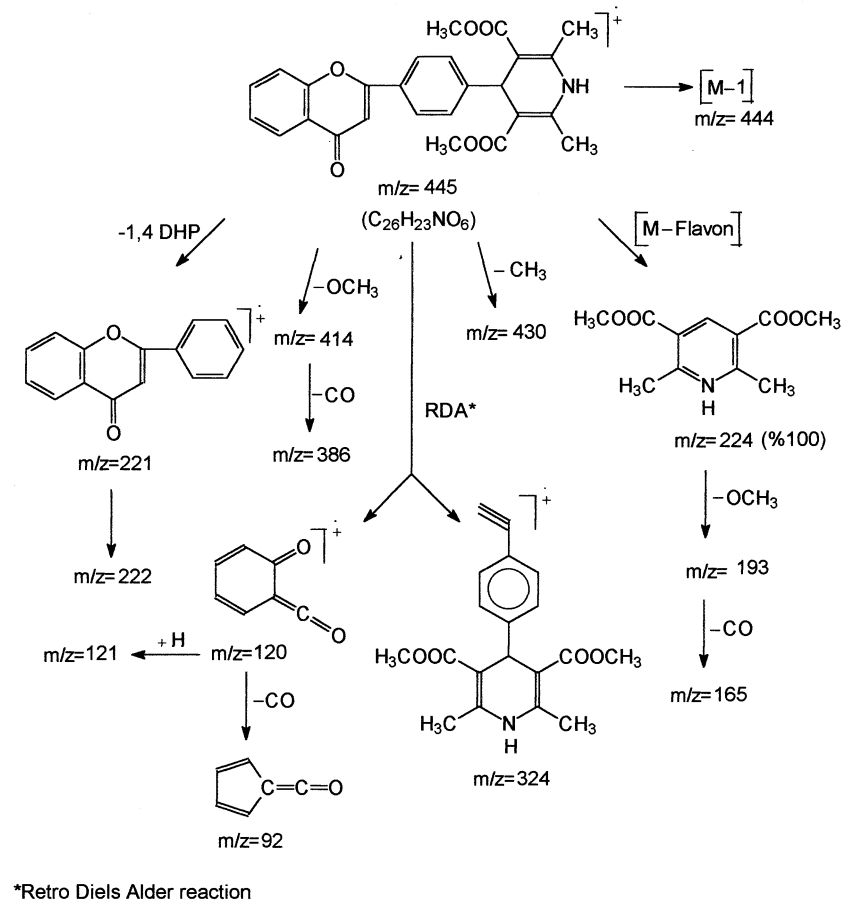
3. Experimental

3.1. Chemistry

Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP-1025 spectrophotometer as KBr pellets. The ^{1}H NMR spectra were determined with a Bruker AM 300 (300 MHz) spectrometer using $CDCl_3$ as solvent and TMS as an internal standard (chemical shift in ppm). Mass spectra were determined on a VG Analytical 70-250S spectrometer by using the electron impact (EI) technique: ionisation energy 70 eV. Microanalyses were performed on a Perkin–Elmer 240 analyzer and satisfactory results



Scheme 1. Preparation of **I**. Reagents: (a) pyridine; (b) KOH/pyridine; (c) H_2SO_4; (d) NBS, benzoyl peroxide; (e) HMTA; (f) methylacetoacetate, NH_3.



Scheme 2. Mass fragmentation of **I**.

were within $\pm 0.4\%$ of calculated values (C, H, N) obtained for the new compound. Chromatography was carried out using the flash method and Merck Silica Gel 60 (230–400 mesh ASTM). 4′-Methyl flavone (**5**) [17], 4′-bromomethylflavone (**6**) [18], 4′-flavone carboxaldehyde (m.p. 175°C, recrystallization from AcOH/H_2O) (**7**) [18] were prepared according to the literature.

3.1.1. Synthesis of dimethyl-1,4-dihydro-2,6-dimethyl-4-[4′-(4H-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate (I)

4′-Flavone carboxaldehyde (**7**) (0.8 mmol, 0.2 g), methylacetoacetate (1.6 mmol, 0.118 g) and 0.4 ml NH_3 (25% w/v) were refluxed in 4 ml isopropyl alcohol for 41 h. The solvent was removed and the residue was purified by column chromatography using 1:0.5 hexane:ethyl acetate as eluent, to give 0.166 g (46.63%) of **I**. Light yellow crystals. M.p. 234°C. IR (KBr) cm^{-1}: 3350(NH), 1685(C=O, ester), 1650(C=O, γ-pyrone). ^1H NMR ($CDCl_3$): δ 2.35 (s, 6H, 2,6-CH_3), 3.65 (s, 6H, $COOCH_3$), 5.10 (s, 1H, DHP 4-H), 6.30 (s, 1H, NH), 6.75 (s, 1H, 3-H), 7.40 (ddd, 1H, 6-H), 7.45 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2H, 3′,5′-H), 7.55 (dd, 1H, 8-H), 7.70 (ddd, 1H, 7-H), 7.80 (d, $J_{2',3'} = J_{5',6'} = 9$ Hz, 2H, 2′,6′-H), 8.25 (dd, $J_{5,6} = 8$ Hz, $J_{5,7} = 2$ Hz, 1H, 5-H). MS (70 eV): m/z (%) 445(3.7)$[M]^{\bullet +}$, 444(1.4), 430(1.9), 414(1.7), 386(4.9), 324(0.2), 224(100.0), 222(7.1), 221(2.6), 193(3.6), 165(2.6), 121(1.8), 120(1.2), 92(6.2).

3.2. X-ray structure determination of I

Crystal data: $C_{26}H_{23}NO_6$, $M_r = 445.48$, monoclinic, space group $P2_1/c$, $a = 14.437(2)$, $b = 10.452(1)$, $c = 14.651(2)$ Å, $\beta = 100.37(1)$ °, $V = 2174.6(4)$ $Å^3$, $Z = 4$, $D_{calc} = 1.361$ g cm^{-3}, $F(000) = 936$, λ(Mo Kα) = 0.71073, $\mu = 0.09$ mm^{-1}, $T = 296$ K.

Intensity data were measured on an Enraf–Nonius CAD-4 diffractometer using graphite monochromated Mo Kα radiation and the ω–2θ scan technique up to $\theta_{max} = 25.6°$. Reflections measured 4481, unique 4060, observed 2009 [$I > 2\alpha(I)$]. The structure was solved by direct methods using SIR in MolEN [19] and refined on F by full-matrix least-squares with MolEN. All H atoms were geometrically located 0.95 Å from their parent atoms and included using a riding model; displacement parameters were fixed at $1.3U_{eq}$ of the parent atom. The refinement converged at $R = 0.052$ and $wR = [\Sigma\, w(\Delta F)^2/wF_o^2]^{1/2} = 0.050$ for 2009 reflections and 298 parameters. Excursions in difference Fourier map between -0.099 and 0.497 e $Å^{-3}$.

3.3. Pharmacology

Albino rats of either sex, weighing 200–220 g were used in the present study (experiments were approved by Osmangazi University, School of Medicine, Animal Use and Care Committee). Animals entered the test fasted over-night. After the animals were sacrificed by cervical dislocation, the ileum (10–15 cm terminal portion) was immediately removed. Segments 1.5–2 cm long were mounted vertically in a 10 ml organ bath containing Tyrode solution of the following composition (mM): NaCl, 136.87; KCl, 2.68; $CaCl_2$, 1.80; $MgSO_4$, 0.81; NaH_2PO_4, 4.16; $NaHCO_3$, 11.9; glucose, 11.1. The bath contents were maintained at 37°C and aerated by 95% O_2 and 5% CO_2. A tension of 2 g was applied and isometric recording was carried out using an isometric transducer (FDT10-A) MAYTDA95 transducer data acquisition system (produced in Turkey). The preparations were allowed to equilibrate for 60 min, with regular washes every 15 min.

Table 1
Fractional atomic coordinates and equivalent displacement parameters of non-hydrogen atoms for **3b**[a]

	x	*y*	*z*	*B* (Å^2)
O1	0.8895(2)	0.5964(2)	0.8942(2)	3.71(6)
O2	1.1405(2)	0.5045(3)	0.8209(2)	4.94(7)
O32	0.4990(2)	0.2232(3)	0.7986(2)	4.14(6)
O33	0.4119(2)	0.3527(3)	0.8701(2)	4.84(7)
O52	0.7143(2)	−0.0900(3)	0.9651(2)	4.42(6)
O53	0.7368(2)	−0.1074(2)	1.1189(2)	4.39(6)
N1	0.5552(2)	0.2051(3)	1.1239(2)	3.19(7)
C2	0.5037(2)	0.2566(3)	1.0440(2)	2.71(8)
C2′	0.9152(2)	0.4722(3)	0.8873(2)	3.10(8)
C3	0.5253(2)	0.2206(3)	0.9617(2)	2.65(8)
C3′	0.9979(2)	0.4402(4)	0.8645(2)	3.58(9)
C4	0.6115(2)	0.1377(3)	0.9586(2)	2.85(8)
C4′	1.0667(3)	0.5319(4)	0.8465(3)	3.64(9)
C5	0.6418(2)	0.0627(3)	1.0477(2)	2.68(8)
C5′	1.1004(3)	0.7683(4)	0.8556(3)	4.1(1)
C6	0.6162(2)	0.1035(3)	1.1272(2)	2.94(8)
C6′	1.0727(3)	0.8904(4)	0.8697(3)	5.0(1)
C7′	0.9832(3)	0.9138(4)	0.8888(3)	5.0(1)
C8′	0.9219(3)	0.8150(4)	0.8961(3)	4.2(1)
C9′	0.9525(2)	0.6913(4)	0.8837(3)	3.29(9)
C10	0.8408(2)	0.3851(4)	0.9063(2)	3.02(8)
C10′	1.0402(2)	0.6645(4)	0.8619(3)	3.21(8)
C20	0.7759(2)	0.4274(4)	0.9590(2)	3.15(8)
C21	0.4302(2)	0.3486(4)	1.0625(3)	3.92(9)
C30	0.7051(2)	0.3473(3)	0.9766(2)	3.10(8)
C31	0.4782(2)	0.2639(4)	0.8704(2)	3.09(8)
C34	0.3659(3)	0.3986(5)	0.7803(3)	6.9(1)
C40	0.6949(2)	0.2249(3)	0.9412(2)	2.55(7)
C50	0.7607(2)	0.1819(4)	0.8889(3)	3.38(8)
C51	0.6994(2)	−0.0495(3)	1.0388(3)	3.22(8)
C54	0.7977(3)	−0.2139(4)	1.1141(3)	5.4(1)
C60	0.8325(2)	0.2600(4)	0.8730(3)	3.40(8)
C61	0.6439(3)	0.0504(4)	1.2237(2)	4.1(1)

[a] $B_{eq} = (8\pi^2/3)\Sigma_i \Sigma_j U_{ij}^* a_i^* a_i a_j$.

In order to check for antagonistic effect, contractions were induced with barium chloride (4×10^{-3} mol/l, bath concentration). After washing throughout, this process was repeated until the amplitude of the contraction became constant. Investigations of the substance to be tested were performed using the single-dose technique in which the barium chloride contractions were induced after addition of the test substance dissolved in dimethylsulfoxide at different concentrations (10^{-6}, 10^{-5}, 10^{-4} mol l^{-1}) for an exposure time of 5 min. The responses to $BaCl_2$ were recorded after the incubation with 0.1 ml DMSO. The response was expressed as percentage inhibition of $BaCl_2$ contractions.

4. Results and discussion

4.1. Crystallography

Single-crystal X-ray diffraction studies were performed on compound **I**. Selected bond distances, bond angles, torsion angles and atomic coordinates are contained in Tables 1 and 2. An ORTEP [20] drawing of the title compound showing the molecular conformation and atom-labeling scheme is depicted in Fig. 1.

As in other dihydropyridines, the 1,4-DHP ring adopts a boat conformation. The four double-bonded carbons (C2, C3, C5, C6) constitute the plane of the ring with N1 and C4 being 0.115(3) and 0.280(3) Å above the plane, respectively. For ethyl allyl 1,4-dihydro-2,6-dimethyl-4-[4-(4H-4-oxo-1-benzopyran-2-yl)-phenyl]-3,5-pyridine dicarboxylate [21] these distances are 0.130 and 0.276 Å, respectively. The torsion angles about the C4 ring bonds are greater than those for the N bonds, indicating that the puckering is greater at C4. For C2–C3–C4–C5 and C2–N1–C6–C5 the torsion angles are 22.6(5) and 12.1(5)° compared to −22.0 and −11.3° in nifedipine [22].

The flavone molecule deviates from planarity. The dihedral angle between the γ-pyrone and phenyl rings is 22.2(2)°. The phenyl ring is not exactly perpendicular to the DHP ring. The dihedral angle between the phenyl ring of the flavone and 1,4-DHP ring is 79.5(1)°. The torsion angles C3–C4–C40–C30 and C5–C4–C40–C30 are 33.7(4) and −89.4(4)° respectively, which should both be close to 60° if the aromatic ring bisects the DHP ring.

4.2. Pharmacology

Bioassay preparations such as isolated right (chronotropy) and left (inotropy) atria of Guinea pig, rabbit portal vein, aortic strips of rabbit, isolated papillary muscle of Guinea pig [23], Guinea pig taenia coli in K^+-depolarizing Tyrode solution [24], isolated Guinea pig ileum (Ba^{2+} stimulation) [23], radioligand binding

Table 2
Selected bond lengths (Å), bond angles and torsion angles (°) of compound **I**

O1–C2′	1.359(4)	C2′–C3′	1.339(5)
O1–C9′	1.373(4)	C2′–C10	1.473(5)
O2–C4′	1.226(5)	C3–C4	1.524(5)
O32–C31	1.220(5)	C3–C31	1.459(5)
O33–C31	1.333(4)	C3′–C4′	1.437(5)
O33–C34	1.445(5)	C4–C5	1.518(5)
O52–C51	1.214(5)	C4–C40	1.567(5)
O53–C51	1.344(4)	C4′–C10′	1.466(6)
O53–C54	1.428(5)	C5–C6	1.352(5)
N1–C2	1.378(4)	C5–C51	1.457(5)
N1–C6	1.375(4)	C5′–C10′	1.404(6)
C2–C3	1.352(5)	C6–C61	1.505(5)
C2–C21	1.493(5)		
C2′–O1–C9′	119.1(3)	C6–C5–C51	125.4(3)
C31–O33–C34	116.5(3)	C6′–C5′–C10′	120.6(4)
C51–O53–C54	117.5(3)	N1–C6–C5	119.1(3)
C2–N1–C6	125.1(3)	N1–C6–C61	112.2(3)
N1–C2–C3	118.3(3)	C5–C6–C61	128.7(3)
N1–C2–C21	112.9(3)	C2′–C10–C20	119.8(3)
C2–C3–C4	120.3(3)	C2′–C10–C60	122.2(3)
C2–C3–C31	126.0(3)	O32–C31–O33	121.8(3)
C3–C4–C5	112.2(3)	O32–C31–C3	122.4(3)
C3–C4–C40	109.2(3)	O33–C31–C3	115.7(3)
O2–C4′–C3′	124.6(4)	O52–C51–O53	120.8(3)
C4–C5–C6	119.8(3)	O52–C51–C5	123.7(3)
C4–C5–C51	114.8(3)	O53–C51–C5	115.4(3)
C2–N1–C6–C5	12.1(5)	C3–C4–C5–C6	−22.2(4)
O1–C2′–C10–C60	156.5(3)	C3–C4–C40–C30	33.7(4)
C2–C3–C4–C5	22.6(5)	C5–C4–C40–C30	−89.4(4)
C2–C3–C31–O33	4.2(5)	C6–C5–C51–O53	−7.1(5)
C8′–C9′–C10′–C4′	−177.9(4)		

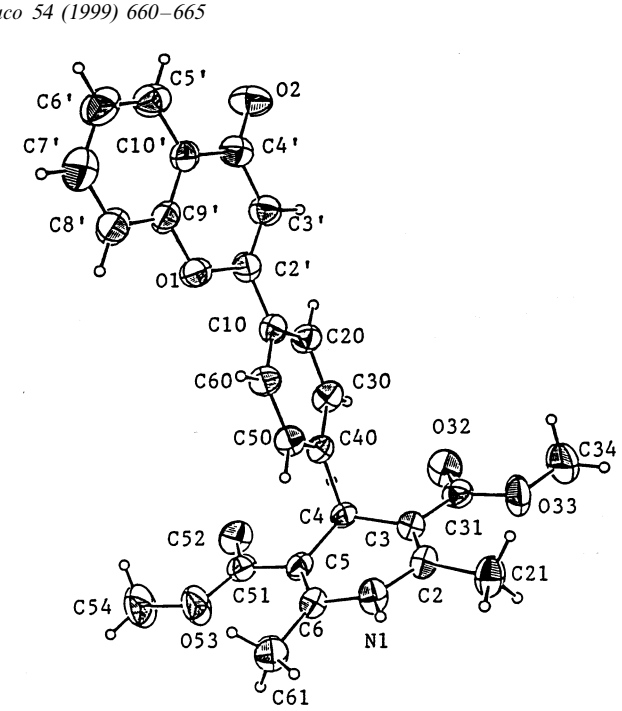


Fig. 1. Numbering scheme with thermal ellipsoids drawn at the 50% probability level. H atoms are shown as small circles with arbitrary radii.

method [25] and hypotensive activity [26] are appropriate for pharmacological screening tests of calcium antagonistic activity. In the present study $BaCl_2$-stimulated rat ileum was used. The DHPs exhibited organ specific activities at DHP receptors [27]. For example BAYK5552 and nifedipine showed their calcium antagonistic activities at low concentration on portal vein and aortic strips whereas their activities on ileum, right and left atrium and papillary muscle were observed at high concentration [23].

Additionally it is known that the DHP receptors exhibit stereospecifity: the optical antipodes of asymmetrical dihydropyridines often possess not only differing receptors affinities, but sometimes also generate opposing effects [28]. These are the first screening tests for the calcium antagonistic activities of this compound. Compound **I** exhibited $15.75 \pm 1.75\%$ ($n = 4$) inhibition on rat ileum at 10^{-4} M concentration and nifedipine showed 100% ($n = 5$) inhibition at the same concentration. No activity was observed at lower concentrations such as 10^{-5}, 10^{-6} M.

Further investigation such as the tests on isolated artery and vein preparations and radioligand binding assays are necessary to clarify these previous observations. Additionally the stability of the tested compound in solution towards the action of light is worthy of note.

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