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Flavone–Nitrogen Heterocycle Conjugate Formation by 1,3-Dipolar Cycloadditions

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Azomethine ylides generated in situ from the reaction of *N*-[2-, 3- and 4-(chromon-2-yl)phenyl]glycine and paraformaldehyde can be trapped with dipolarophiles in 1,3-dipolar cycloaddition reactions to yield flavone–nitrogen heterocycle dyads. These azomethine ylides proved to be reactive with electron-poor dipolarophiles, affording the expected adducts. The use of microwave irradiation as an alternative source of heating has significant advantages and allows a reduction of both reaction time and temperature. The use of benzaldehydes as dipolarophiles afforded flavone–oxazolidine dyads, and the results indicate that electron-withdrawing groups in the *para* position of the benzaldehyde increases the dipolarophile reactivity. This work was also extended to the use of *meso*-tetrakis(pentafluorophenyl)porphyrin as a dipolarophile, allowing new flavone–dihydroporphyrin conjugates to be prepared.

Introduction

Flavonoids are phenolic secondary plant metabolites that are ubiquitous in the plant kingdom. At present, they comprise more than 6000 chemically distinct natural compounds,[1] and are assigned to different groups according to their structure.[2] Owing to their ubiquity in plants, they are important constituents of the human diet and this constant exposure to a wide variety of flavonoids seems to have health benefits.[3] A wealth of beneficial properties have been reported,[4] with the main proposed health optimizing activities being due to the following actions: (i) antioxidant properties through the ability to scavenge reactive species or through their influence on the redox status;[5] (ii) modulation of several enzymes or cell receptors;[6] (iii) protecting neurons against stress-induced injury;[7] (iv) inhibition of enzymes that can be associated with several diseases, in particular, those that can inactivate carcinogens.[8] These findings suggest that flavonoids can be used in active medicinal formulations.[9] Among the flavonoid classes, flavones are the most important, not only because they display interesting biological activities,[10] but also because several of the naturally occurring flavones and their synthetic analogues display anticancer,[11] anti-inflammatory,[12] and antioxidant[13] activities, to mention just a few examples.

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Taking into consideration the important properties of flavone derivatives, and the fact that drug resistance influences the successful outcomes of the treatment of several diseases, a major research effort to find alternative compounds has been undertaken. In this context, the synthesis of molecules with dual functions may be a good strategy for the discovery of new drugs or improvements to already known biological properties. For instance, flavone–amino acid conjugates improve the bioavailability of flavones,[14] and flavone-17β-estradiol conjugates improve the binding affinity towards estrogen receptors.[15] In fact, the most important targets are flavone–nitrogen heterocycle conjugates. To give a few examples, we can highlight the monoamides based on benzimidazole–flavones, such as compound **1**, which exhibit significant antibacterial activity,[16] or the imidazole–flavone derivative **2**, which significantly inhibits aromatase,[17] and flavopiridol **3**, which is a cyclin-dependent kinase inhibitor that is now in Phase II clinical trials for a number of different malignancies (Figure 1).[18]

1,3-Dipolar cycloaddition reactions are one of the most used methodologies in the synthesis of heterocycles, including natural compounds and new promising drugs.[19] The application of this type of reaction was also reported for the synthesis of tetrazoles linked to flavones.[20] In our research group, we also obtained new flavone–fullerene derivatives[21] by 1,3-dipolar cycloaddition reactions of azomethine ylides to C_{60}. Taking into account all the described applications and potential biological activities, we have designed a synthetic route to flavone–nitrogen heterocycle conjugates that involves the 1,3-dipolar cycloaddition of azomethine ylides, generated in situ from the reaction of *N*-

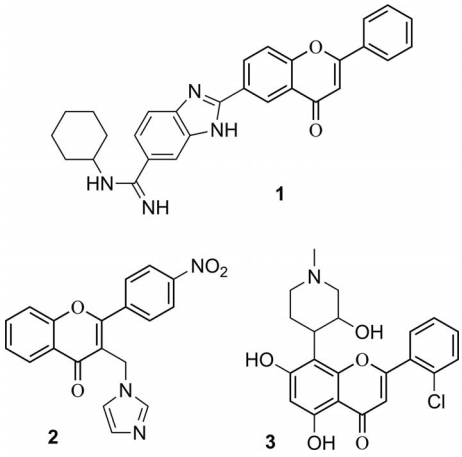


Figure 1. Chemical structures of flavone–nitrogen heterocycle dyads presenting important biological properties: *N*-cyclohexyl-2-(4-oxo-2-phenyl-4*H*-chromen-6-yl)-1*H*-benzo[*d*]imidazole-6-carboximidamide (**1**), 3-[(1*H*-imidazol-1-yl)methyl]-2-(4-nitrophenyl)-4*H*-chromen-4-one (**2**), and flavopiridol [2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-chromen-4-one] (**3**).

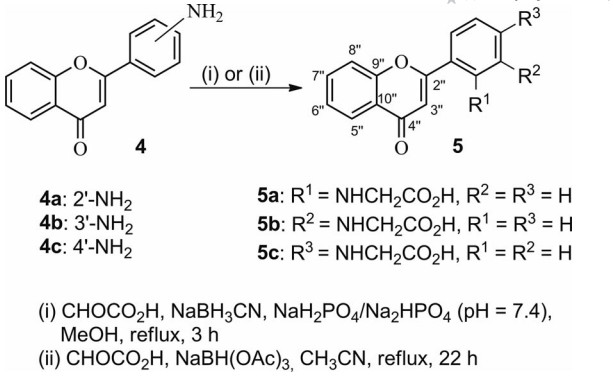
[2-, 3- and 4-(chromon-2-yl)phenyl]glycine and paraformaldehyde, with several dipolarophiles [*N*-methylmaleimide, dimethyl fumarate, dimethyl maleate, dimethyl acetylenedicarboxylate (DEAD), 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD)].

Furthermore, following our interest in the synthesis of flavonoid–porphyrin conjugates,[22] and in the functionalization of porphyrins through cycloaddition reactions,[23] namely using 1,3-dipolar cycloaddition approaches,[24] the studies were extended to the use of *meso*-tetrakis(pentafluorophenyl)porphyrin as a dipolarophile.

In fact, the efficiency of porphyrinic derivatives as photosensitizers in the photodynamic therapy (PDT) of cancer diseases, age-related macular degeneration,[25] and in the photodynamic inactivation of several pathogenic microorganisms,[26–28] is strongly dependent of their structural features. In this context, the synthesis of new flavone–chlorin conjugates can be a good approach to obtain new active molecules.

Results and Discussion

Our study started with the synthesis of 2-{[2-, 3- and 4-(4-oxo-4*H*-chromen-2-yl)phenyl]amino}acetic acids **5a**–**c**, here designated as *N*-flavonylglycine derivatives. Taking into consideration that we had developed an efficient methodology for the synthesis of nitroflavone derivatives[29] and from those also the corresponding amino-derivatives,[30] we set up a strategy to obtain the *N*-flavonylglycine derivatives **5a**–**c** by using the aminoflavones and glyoxylic acid as starting materials (Scheme 1).



Scheme 1. Synthesis of *N*-flavonylglycine derivatives **5a**–**c**.

Our first choice was to test a recent methodology in which the reductive amination of aldehydes and ketones is effected by sodium triacetoxyborohydride.[31] We tested this approach with aminoflavone **4c**, but the desired product **5c** was obtained in only modest yield (46%). Therefore, we tested another reducing agent, sodium cyanoborohydride,[32] in the reductive amination of aminoflavone **4c** and glyoxylic acid. The procedure was efficient and simple, and the desired compound **5c** was obtained with very good yield (78%). The other *N*-flavonylglycine derivatives **5a**–**b** were also obtained in very good yields (75–80%), by using the same methodology. The characterization of these new *N*-flavonylglycine derivatives was accomplished by NMR spectroscopic analysis, and the most important features in the ^{1}H and ^{13}C NMR spectra are the resonances of 3′′-H (δ = 6.80–6.94 ppm) and 5′′-H (δ = 8.02–8.19 ppm), and of C-3′′ (δ = 103.3–106.9 ppm) and C-4′′ (δ = 176.6–177.2 ppm), which confirm the chromone skeleton. The glycine moiety presents the characteristic resonances due to 2-H (δ = 3.56–3.94 ppm), C-2 (δ = 44.1–46.0 ppm), and C-1 (δ = 171.9–172.6 ppm). The flavone B ring presents a different substitution pattern and, consequently, the numbering system of this ring is different from one derivative to another (Figure 2), and the ^{1}H and ^{13}C NMR spectra also present some differences. The ^{1}H NMR spectrum of *N*-flavonylglycine **5c** is the simplest, with two doublets at δ = 6.72 and 7.88 ppm (J = 8.8 Hz), corresponding to the *para*-substi-

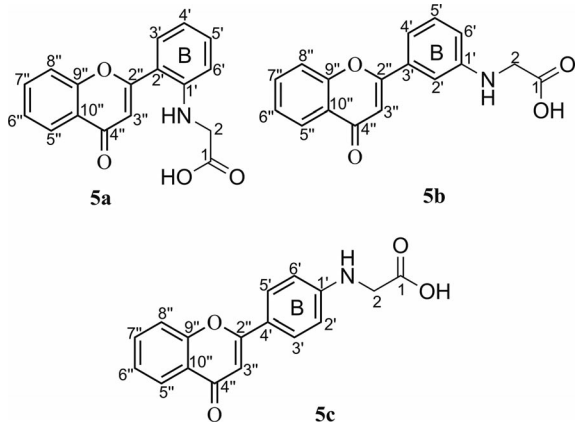
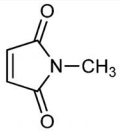
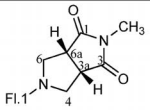
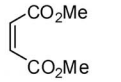
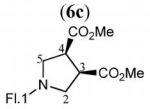
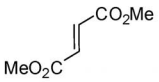
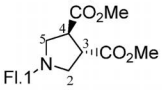
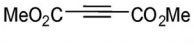
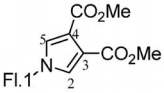
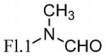
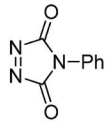
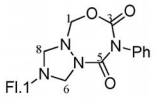
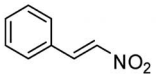
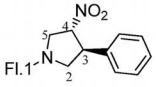
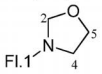
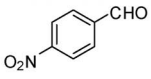
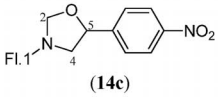
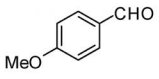
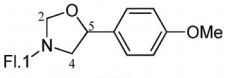


Figure 2. Numbering system of *N*-flavonylglycine derivatives **5a**–**c**.

tuted aromatic ring. For the other *N*-flavonylglycine derivatives, the ^{1}H NMR spectra present more signals, however, their multiplicity and coupling constants still allowed their unequivocal assignment. For instance, the broad singlet due to 2′-H resonance (δ = 7.25 ppm) in the ^{1}H NMR spectrum of **5b** is characteristic of a *meta*-substitution pattern.

Subsequently, we studied the reactivity of azomethine ylides, which were obtained from *N*-flavonylglycine derivatives and paraformaldehyde, in 1,3-dipolar cycloaddition reactions with electron-poor and electron-rich dipolarophiles. To start this study, we chose the least sterically hindered *N*-flavonylglycine **5c**, and the dipolarophiles shown in Table 1. Initially, the reaction of *N*-flavonylglycine **5c**, paraformaldehyde, and *N*-methylmaleimide was studied in a range of solvents, such as *N*,*N*-dimethylformamide (DMF), toluene, 1,2-dichlorobenzene, and 1,2,4-trichlorobenzene. Our results indicate that, at lower temperature (less than 200 °C), only traces of the expected product were obtained, but by conducting the reaction in 1,2,4-trichlorobenzene at reflux temperature there was almost full conversion of the *N*-flavonylglycine **5c** into the expected adduct **6c** (Table 1, entry 1). Confirmation of the structure was accomplished mainly by analysis of the ^{1}H and ^{13}C NMR spectra, with the ^{13}C NMR spectral assignments facilitated by 2D NMR

Table 1. 1,3-Dipolar cycloaddition reactions of azomethine ylides, generated in situ from the reaction of *N*-flavonylglycine **5c** and paraformaldehyde, with several dipolarophiles.

Entry	Dipolarophile	Product[a]	Classical heating		MW heating	
			Reaction time (min)	η (%)	Reaction time (min)	η (%)
1		 (**6c**)	75	92	10	95
2		 (**7c**)	90	93	20	79
3		 (**8c**)	100	87	20	78
4		 (**9c**)	30	61	5	66
5	$EtO_2C-N=N-CO_2Et$	 (**10c**)	210	67	–	–
6		 (**11c**)	20	16	–	–
7		 (**12c**)	30	24	–	–
8		 (**13c**)	60	54	–	–
9	Without dipolarophile	 (**13c**)	60	87	–	–
10		 (**14c**)	60	73	–	–
11		 (**15c**)	60	14	–	–

[a] Fl.1 = flavone type c.

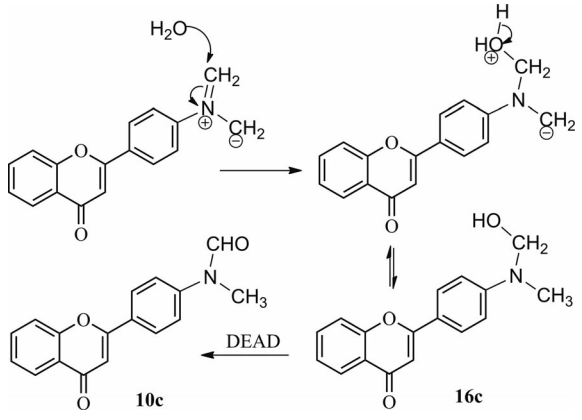
experiments. The ^{1}H NMR spectrum of compound **6c** shows, in addition to the flavone protons, a singlet at δ = 3.07 ppm due to the resonance of the methyl protons NCH_3 and two doublets at δ = 3.55 and 4.07 ppm corresponding to 3a,6a-H and 4_{trans},6_{trans}-H, respectively. The *trans* configuration is, in this example, related to the protons 3a,6a-H, which only shows a vicinal coupling constant (J = 10.7 Hz) with 4_{cis},6_{cis}-H. The less shielded protons 4_{cis},6_{cis}-H (δ = 3.35–3.45 ppm), due to the close proximity to the carbonyl groups, appear as a multiplet. The carbon resonance assignment of the carbonyl groups C-1 and C-3 was made on the basis of the HMBC spectrum. The correlations between protons NCH_3, 4,6-H and 3a,6a-H, and the signal at δ = 178.3 ppm indicate that the carbon resonance of C-1 and C-3 appears at the same chemical shift as carbon C-4′′. Methylenic carbon atoms C-4,6, as well as the methynic carbon atoms C-3a,6a, were assigned by analysis of the HSQC correlations, and all present the expected chemical shifts. This satisfactory result prompted us to extend our studies to other electron-poor dipolarophiles, such as dimethyl maleate, dimethyl fumarate (Table 1, entries 2 and 3), and dimethyl acetylenedicarboxylate (Table 1, entry 4), which afforded the expected dyads in good to excellent yields (61–93%).

We then explored the possibility of using microwave irradiation as an alternative heating source to obtain the desired adducts. It was seen that lower temperatures and shorter reaction times [from 75 to 10 min in the case of **6c** (Table 1, entry 1)] can be used. In all the other cases, microwave irradiation led to reductions in reaction times of around 20%.

Verification of the structures of the obtained adducts was, again, made possible by conducting NMR experiments. In the ^{1}H and ^{13}C NMR spectra of adducts **7c**, **8c**, and **9c** some similarities were found, such as the singlet at δ = 3.75–3.89 ppm due to methyl protons, and the signals at δ = 51.8–52.6 and 163.5–172.2 ppm corresponding to the carbon resonances of the methoxycarbonyl group. In the case of compound **9c**, the resonance of the carbonyl is less deshielded due to the fact that it is linked to an aromatic carbon atom. The ^{1}H NMR spectrum of compound **9c** is also in agreement with the oxidized form, showing, in addition to the flavone protons, only a singlet in the aromatic region (δ = 7.71 ppm), corresponding to 2,5-H resonances. Analysis of the 2D HSQC spectrum allowed the assignment of C-2,5 resonances at δ = 125.9 ppm. In the case of compounds **7c** and **8c**, the ^{1}H NMR spectra clearly points to the presence of a pyrrolidine system. The configuration could not be confirmed due to the fact that the protons appeared as multiplets, and coupling constant calculations and other NMR experiments were not possible. Therefore, due to the fact that in compound **7c**, 2,5-H protons resonate at δ = 3.71–3.86 ppm and those of 3,4-H resonate at δ = 3.50–3.55 ppm (assignments that were confirmed by the 2D HSQC spectrum correlations), the dipolarophile stereochemistry is preserved. In addition, in the case of compound **8c**, 2,5-H resonances occur at different chemical shifts: two protons at δ = 3.64–3.68 ppm and a second two at δ = 3.72–3.89 ppm, suggesting that the *trans* configuration of the methoxycarbonyl groups can cause this effect.

When β-nitrostyrene was used (Table 1, entry 7) the desired dyad **12c** was obtained in low yield, and attempts to improve it were unsuccessful. The structure was corroborated by detailed analysis of ^{1}H, ^{13}C, HSQC, and HMBC NMR spectra. The ^{1}H NMR spectrum of compound **12c** shows, in addition to the flavone protons, two multiplets in the aromatic region due to the resonance of the phenyl protons, and in the aliphatic region the pyrrolidine protons. Analysis of the COSY and NOESY NMR spectra of this compound allowed the assignment of these proton resonances and to establish the configuration of the pyrrolidine ring as depicted in Table 1, entry 7. These data indicate that 3-H (δ = 4.25 ppm) and 4-H (δ = 5.17 ppm) have *trans* configuration, which means that the dipolarophile configuration was preserved.

Use of DEAD or PTAD (Table 1, entries 5 and 6) did not afforded the desired dyads and, again, all attempts to obtained the dyads failed. When the former reagent was used, we always obtained a compound in very good yield that was identified as *N*-methyl-*N*-[4-(4-oxo-4*H*-chromen-2-yl)phenyl]formamide (**10c**) (Scheme 2). The structure was proposed on the basis of the mass spectrum (m/z = 280 $[M + H]^+$) and on the fact that the ^{1}H NMR spectrum of compound **10c** shows, in addition to the flavone protons, two singlets at δ = 3.40 and 8.67 ppm; the first signal being characteristic of an *N*-methyl group and the second being characteristic of an aldehyde proton. The correlation found in the 2D HSQC spectrum confirms that the carbon resonances are also characteristic of these types of carbon atoms (δ = 31.6 ppm for *N*-CH_3 and δ = 161.8 ppm for *N*-CHO). Because all the data point to a structure containing the formamide group bearing a flavonyl moiety attached to the nitrogen atom, we presume that the formed azomethine ylide reacts with water to form the alcohol **16c**, which is oxidized in situ to product **10c** by DEAD (Scheme 2). It is known that water is produced during the in situ formation of the azomethine ylide and can be more reactive than DEAD. On the other hand, there is evidence that DEAD can act as an oxidant[33] (Scheme 2).



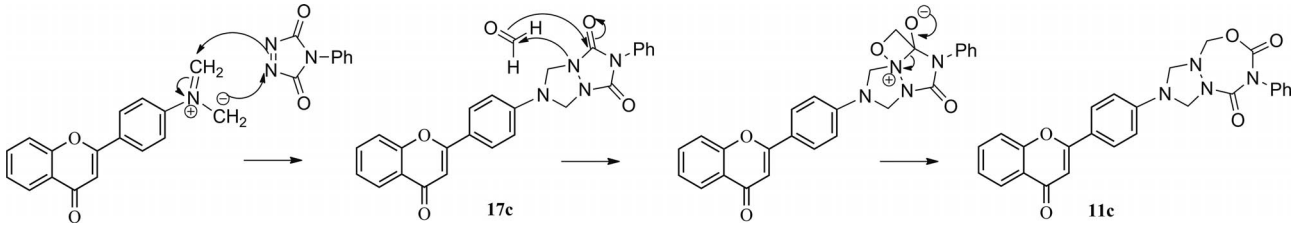
Scheme 2. Proposed mechanism for the synthesis of *N*-methyl-*N*-[4-(4-oxo-4*H*-chromen-2-yl)phenyl]formamide (**10c**).

In the reaction with PTAD, we also obtained the unexpected product **11c** in low yield (Table 1, entry 6; 16%). Nevertheless, we were able to validate the proposed structure and suggest a mechanism (Scheme 3). Again, the structure was confirmed by the obtained mass spectrum (*m*/*z* = 469 $[M + H]^+$) and from the results of NMR spectroscopic experiments. In the aromatic region of the ^{1}H NMR spectrum, in addition to the flavone protons, two multiplets were observed due to the proton resonances of the *N*-phenyl group. The ^{1}H NMR spectrum of **11c** shows three singlets between δ = 5 and 6 ppm, each one corresponding to one methylene group. In the proposed structure we have placed two methylene groups in the 1,2,4-triazolidine moiety and one in the 1,3,4,6-oxatriazepane-5,7-dione moiety. Based on their correlation in 2D HMBC it was possible to assign the resonance of 1-H at δ = 5.40 ppm and of C-3 at δ = 148.4 ppm, whereas 6-H and 8-H were unequivocally assigned to the signals at δ = 5.61 and 5.14 ppm, respectively. It was also possible to assign the resonance of carbon C-5 at δ = 152.0 ppm. These data indicated the structure depicted in Table 1, entry 6, so we think that the 1,3-dipolar cycloaddition occurs first to give intermediate **17c**, which, by reaction with paraformaldehyde and intramolecular rearrangements, afforded product **11c** (Scheme 3).

Because the latter three electron-poor dipolarophiles were not as successful as hoped, we decided to test the reactivity of the azomethine ylide with 2,3-dihydrofuran, which is an electron-rich dipolarophile. However, the reaction product was not the expected adduct, but a new compound, which was obtained in moderate yield (Table 1, entry 8). The proposed structure could be confirmed by its mass spectrum (*m*/*z* = 294 $[M + H]^+$) and by NMR analysis as 2-[4-(oxazolidin-3-yl)phenyl]-4*H*-chromen-4-one (**13c**). The ^{1}H NMR spectrum of compound **13c** shows just the flavone resonances in the aromatic region and the oxazolidine resonances in the aliphatic region. The 4-H and 5-H resonances appear at δ = 3.51 and 4.23 ppm, respectively, as triplets due to their coupling to each other (J = 6.4 Hz). The other signal is a singlet at δ = 4.95 ppm due to 2-H. This result led us to conclude that the azomethine ylide did not react with the electron-rich dipolarophile 2,3-dihydrofuran but with another formaldehyde molecule. With some experience of reactions between ylides and aldehydes,[34] we performed the reaction without dipolarophile (Table 1, entry 9) and obtained the oxazolidine derivative **13c** in very good yield. To establish the scope and/or limitations of this method towards the synthesis of oxazolidine derivatives, we tested the reactivity of one of our azomethine ylides with 4-nitro- and 4-methoxybenzaldehyde (Table 1, entries 10 and 11). The obtained results showed that there is an enhancement in the reactivity of our azomethine ylide with benzaldehyde bearing an electron-withdrawing group, confirming their good reactivity relative to electron-poor dipolarophiles. The ^{1}H NMR spectra of compounds **14c** and **15c** shows extra signals in the aromatic region due to the 5-aryl group of the oxazolidine ring; two doublets characteristic of a *para*-substituted aromatic ring. We can highlight the doublets at δ = 8.29 and 6.94 ppm corresponding to the resonance of the protons *ortho* to the nitro and methoxy groups, respectively. The chemical shifts observed are in agreement with the literature data for the deshielding effect of the nitro group and shielding effect of the methoxyl group. The aliphatic region of the ^{1}H NMR spectra of these compounds is more complicated than in the case of oxazolidine **13c**, due to the presence of a stereocenter at carbon C-5. Consequently, protons 4-H are inequivalent in these cases and the most relevant resonance in the aliphatic region is the resonance corresponding to 5-H at δ = 5.23 and 5.41 ppm for **15c** and **14c**, respectively. In each case, the signal appears as a broad double doublet consistent with a *cis* ($J \approx 6$ Hz) and *trans* ($J \approx 8$ Hz) coupling constant with two 4-H, and a long distance coupling with 2-H ($J \approx 3$ Hz).

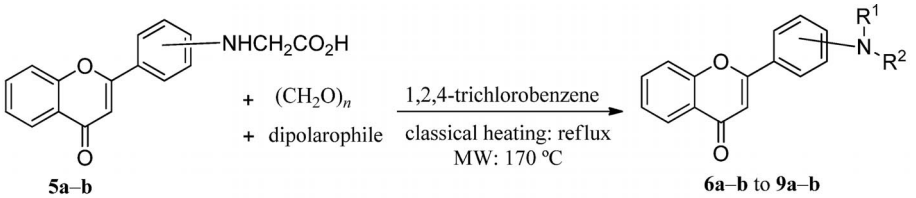
The results obtained in 1,3-dipolar cycloaddition reactions of the azomethine ylide generated in situ from the reaction of *N*-flavonylglycine **5c** and paraformaldehyde with electron-poor dipolarophiles, encouraged us to study the scope of the reaction by using *N*-flavonylglycines **5a** and 5**b**, but using only the electron-poor dipolarophiles that gave good results with **5c** (Table 2). The yields were, in almost all cases, very good and the use of microwave irradiation was also found to be a good approach because it allowed the reaction time to be reduced and, in some cases, improved the yields, except in the reaction of *N*-flavonylglycine **5a** with dimethyl acetylenedicarboxylate (Table 2, entry 4). All the expected adducts were obtained and the structures were established by NMR spectroscopic analysis and by comparing their data with those of the previous discussed compounds. It is clear that, in all cases, the best results were obtained when *N*-methylmaleimide and dimethyl fumarate were used as dipolarophiles.

When the reactions were performed in the presence of *meso*-tetrakis(pentafluorophenyl)porphyrin (**18**), the conditions had to be adapted to this dipolarophile. It was observed that the best yields for the expected chlorin adducts

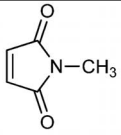
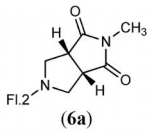
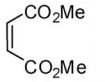
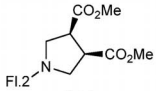
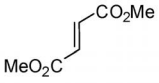
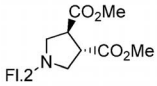
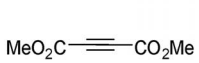
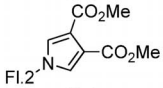
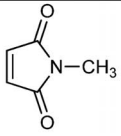
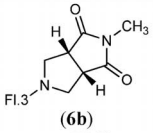
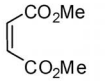
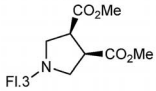
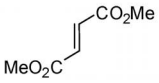
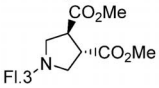
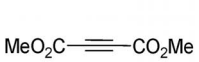
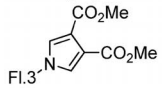


Scheme 3. Proposed mechanism for the synthesis of 8-[4-(4-oxo-4*H*-chromen-2-yl)phenyl]-4-phenyldihydro-1*H*-[1,2,4]triazolo[1,2-*c*][1,3,4,6]oxatriazepine-3,5(4*H*,7*H*)-dione (**11c**).

Table 2. 1,3-Dipolar cycloaddition reactions to azomethine ylides generated in situ from the reaction of *N*-flavonylglycine **5a** or *N*-flavonylglycine **5b** and paraformaldehyde.[a]



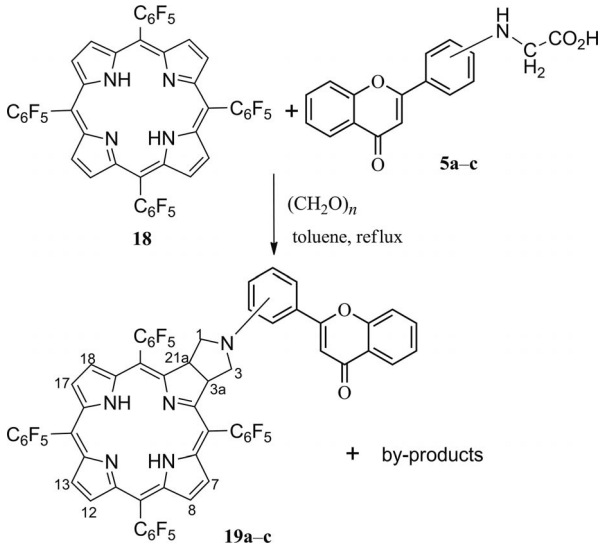
5a–b **6a–b** to **9a–b**

Entry	Flavone (Fl)	Dipolarophile	Product[a]	Classical heating Reaction time (min)	Classical heating η (%)	MW heating Reaction time (min)	MW heating η (%)
1	**5a**		 **(6a)**	50	77	10	80
2	**5a**		 **(7a)**	50	44	10	77
3	**5a**		 **(8a)**	50	86	10	86
4	**5a**		 **(9a)**	30	68	5	47
5	**5b**		 **(6b)**	70	81	10	78
6	**5b**		 **(7b)**	70	80	10	83
7	**5b**		 **(8b)**	70	85	10	82
8	**5b**		 **(9b)**	30	32	5	43

[a] Fl.2 = flavone type a; Fl.3 = flavone type b.

19a–**c** were obtained in toluene heated to reflux, and using successive additions of paraformaldehyde and *N*-[(chromon-2-yl)phenyl]glycines **5a**–**c** (Scheme 4). Good yields were obtained for **19b** (53%) and **19c** (57%) when the less hindered glycines **5b** and **5c** were used, whereas for the more hindered glycine **5a**, the expected chlorin adduct **19a** was obtained in lower yield (22%). For the more reactive ylides, minor amounts of other compounds were also detected. Their mass spectra (*m*/*z* = 1502 [M + H]$^+$) and UV/Vis spectra suggested that bis-addition occurred, affording bacteriochlorins and isobacteriochlorins, which is consistent with previous observations noted the literature.[35a,35b]

The obtained results show that this methodology can be applied successfully to obtain several flavone–chlorin conjugates. The visible spectrum of the main conjugates confirms the chlorin-type structure (λ_{max} = 651 nm) and the ^{1}H NMR spectra shows two multiplets (δ = 3.66–3.71 and 3.89–4.00 ppm) in the aliphatic region, corresponding to the methylene protons of the tetrahydropyrrole ring and one multiplet (δ = 5.51–5.56 ppm) that can be assigned to the H-β pyrrolic proton, which is typical of chlorin-type compounds. The aromatic region of the ^{1}H NMR spectra shows, in addition to the flavone resonances, a singlet at δ = 8.49 ppm due to the resonance of β-pyrrolic protons



Scheme 4. Synthesis of flavone–porphyrin conjugates **19a**–**c**.

12,13-H and two doublets at δ = 8.43–8.45 and 8.74–8.75 ppm with a characteristic coupling constant (J = 4.9 Hz) of β-pyrrolic protons 7,18-H and 8,19-H. Finally, it is worth mentioning that a resonance at $\delta \approx -1.8$ ppm can also be seen, which is due to internal NH protons and is a characteristic singlet in the ^{1}H NMR spectra of chlorin-type compounds.

Conclusions

Reactions of paraformaldehyde with *N*-[2-, 3- and 4-(chromon-2-yl)phenyl]glycine can successfully generate azomethine ylides, which can be subsequently trapped with electron-poor dipolarophiles. These 1,3-dipolar cycloaddition reactions have been studied and a new synthesis of flavones–nitrogen heterocyclic conjugates has been established. Under microwave irradiation conditions, these pyrrole and/or pyrrolidine derivatives were obtained in shorter reaction times and, in some cases, in better yields. The use of benzaldehydes and *meso*-tetrakis(pentafluorophenyl)porphyrin as dipolarophiles was also studied and afforded the corresponding flavone–oxazolidine or flavone–chlorin dyads. In this study, an unexpected dyad was obtained, flavone[1,2,4]triazolo[1,2-*c*][1,3,4,6]oxatriazepine. The yield in this case was not good, but the important features in the obtained dyad indicate that further studies would be beneficial.

In summary, almost all these described reactions allowed new and efficient synthetic methods to be established that can be used to generate novel flavone–pyrrole, –pyrrolidine, –chlorin and –oxazolidine conjugates. Considering the important biological properties established for the flavone skeleton, the synthesis of these dyads deserves to be further explored because we envisage that this procedure can be used to generate important new heterocycles.

Experimental Section

General Methods: Melting points were determined with a Büchi melting point apparatus and are uncorrected. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded with a Bruker 300 spectrometer [300.13 MHz (^{1}H), 75.47 MHz (^{13}C), 282.38 MHz (^{19}F)]. TMS (δ = 0 ppm) was used as internal reference for ^{1}H and ^{13}C NMR spectra, and C_6F_6 (δ –163 ppm) for ^{19}F NMR spectra. Data for ^{1}H NMR spectra are presented as follows: chemical shift (δ, ppm), multiplicity [s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet)], coupling constant [J, Hz] and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm). Unequivocal ^{1}H assignments were made with the aid of 2D COSY (^{1}H/^{1}H) and NOESY (800 ms mixing time) spectra; ^{13}C assignments were made on the basis of 2D HSQC (^{1}H/^{13}C) and HMBC (delays for one-bond and long-range J_{C-H} couplings were optimized for 145 and 7 Hz, respectively) experiments. High-resolution mass spectral analyses (HRMS-ESI$^+$) were performed with a microTOF (focus) mass spectrometer. Ions were generated with an ApolloII (ESI) source. Ionization was achieved by electrospray, with the use of a voltage of 4500 V applied to the needle, and a counter voltage between 100 and 150 V applied to the capillary. High-resolution mass spectra (HRMS-EI, 70 eV) were measured with a VG Autospec M spectrometer. Elemental analyses were obtained with a Carlo–Erba 1108 CHNS analyzer. Reactions under microwave irradiation were performed with an Ethos SYNTH microwave labstation (Milestone Inc.) using glassware setup for atmospheric-pressure reactions (temperature measurement with a fiber-optic probe). Silica gel (60 F254, Merck) was used for TLC, and the spots were detected with UV light (254 nm). Flash column chromatography was carried out with silica gel 60 (Merck).

General Procedure for the Preparation of the *N*-Flavonylglycine Derivatives 5a–c

Method A: Glyoxylic acid (61.3 mg, 0.67 mmol) was added to a suspension of the appropriate aminoflavone **4a**–**c** (66.3 mg, 0.28 mmol) in methanol (2 mL) and phosphate buffer solution (1 M, 0.4 mL, pH 7.4). Sodium cyanoborohydride (56.9 mg, 0.91 mmol) was then slowly added. The mixture was heated at reflux under nitrogen for 5 h (**5a**), 2 h (**5b**), 3 h (**5c**). The reaction mixture was then poured onto ice (5 g) and water (10 mL) and acidified to pH 3 with 20% hydrochloric acid. The obtained solid was removed by filtration and recrystallized from methanol to afford the title compounds in moderate to good yields: **5a** (62.0 mg, 75%), **5b** (66.1 mg, 80%), **5c** (64.4 mg, 78%).

Method B: Glyoxylic acid (59.8 mg, 0.65 mmol) was added to a suspension of 4′-aminoflavone **4c** (51.4 mg, 0.22 mmol) in acetonitrile (3 mL). Sodium triacetoxyborohydride (276 mg, 1.30 mmol) was then added in one portion. The mixture was heated to reflux under nitrogen for 22 h. The reaction mixture was then poured onto ice (10 g) and water (20 mL) and acidified to pH 3 with 20% hydrochloric acid. The obtained solid was removed by filtration, washed with water, and purified by silica gel column chromatography with gradient elution (CH_2Cl_2 to CH_2Cl_2/MeOH, 1:1) to afford the title compound **5c** in moderate yield (29.3 mg, 46%).

2-{[2-(4-Oxo-4*H*-chromen-2-yl)phenyl]amino}acetic Acid (5a): Yellow solid; m.p. 226.9–227.4 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.56 (br. s, 2 H, 2-H), 6.89 (s, 1 H, 3′′-H), 6.90 (t, J = 8.0 Hz, 1 H, 4′-H), 7.20 (d, J = 8.0 Hz, 1 H, 6′-H), 7.23–7.25 (m, 2 H, 5′,3′-H), 7.40 (dt, J = 1.0, 7.7 Hz, 1 H, 6′′-H), 7.50 (dd, J = 1.0, 7.7 Hz, 1 H, 8′′-H), 7.68 (dt, J = 1.4, 7.7 Hz, 1 H, 7′′-H), 8.19 (dd, J = 1.4, 7.7 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR

(75.47 MHz, $CDCl_3$, 20 °C): δ = 46.0 (C-2), 106.9 (C-3′′), 112.1 (C-6′), 118.1 (C-4′), 118.4 (C-3′), 118.6 (C-8′′), 123.2 (C-10′′), 124.9 (C-5′′), 125.4 (C-6′′), 131.8 (C-2′), 132.6 (C-5′), 134.0 (C-7′′), 148.6 (C-1′), 156.0 (C-9′′), 163.9 (C-2′′), 171.9 (C-1), 176.7 (C-4′′) ppm. MS (FAB^+): *m*/*z* (%) = 296 (100) $[M + H]^+$. $C_{17}H_{13}NO_4$: calcd. C 69.15, H 4.41, N 4.75; found C 69.43, H 4.34, N 4.55.

2-{[3-(4-Oxo-4*H*-chromen-2-yl)phenyl]amino}acetic Acid (5b): Yellow solid; m.p. 233.9–234.6 °C (ethanol). ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.94 (br. s, 2 H, 2- H), 6.80–8.84 (m, 1 H, 4′-H), 6.94 (s, 1 H, 3′′-H), 7.25 (br. s, 1 H, 2′-H), 7.28–7.30 (m, 2 H, 5′,6′-H), 7.51 (t, *J* = 7.5 Hz, 1 H, 6′′-H), 7.76 (d, *J* = 8.0 Hz, 1 H, 8′′-H), 7.85 (ddd, *J* = 1.5, 7.5, 8.0 Hz, 1 H, 7′′-H), 8.06 (dd, *J* = 1.5, 7.5 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 44.5 (C-2), 106.7 (C-3′′), 109.3 (C-2′), 114.3 (C-5′ or C-6′), 115.9 (C-4′), 118.5 (C-8′′), 123.4 (C-10′′), 124.8 (C-5′′), 125.5 (C-6′′), 129.7 (C-5′ or C-6′), 131.8 (C-3′), 134.4 (C-7′′), 148.9 (C-1′), 155.7 (C-9′′), 163.5 (C-2′′), 172.6 (C-1), 177.2 (C-4′′) ppm. MS (FAB^+): *m*/*z* (%) = 296 (100) $[M + H]^+$. $C_{17}H_{13}NO_4$: calcd. C 69.15, H 4.41, N 4.75; found C 69.39, H 4.44, N 4.55.

2-{[4-(4-Oxo-4*H*-chromen-2-yl)phenyl]amino}acetic Acid (5c): Yellow solid; m.p. 231.6–232.9 °C (ethanol). ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.94 (br. s, 2 H, 2-H), 6.72 (d, *J* = 8.8 Hz, 2 H, 2′,6′-H), 6.80 (s, 1 H, 3′′-H), 7.46 (dt, *J* = 1.2, 7.8 Hz, 1 H, 6′′-H), 7.79 (d, *J* = 7.8 Hz, 1 H, 8′′-H), 7.79 (dt, *J* = 1.5, 7.8 Hz, 1 H, 7′′-H), 7.88 (d, *J* = 8.8 Hz, 2 H, 3′,5′-H), 8.02 (dd, *J* = 1.2, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 44.1 (C-2), 103.3 (C-3′′), 112.1 (C-2′,6′), 117.7 (C-4′), 118.2 (C-8′′), 123.4 (C-10′′), 124.7 (C-5′′), 125.1 (C-6′′), 127.8 (C-3′,5′), 133.8 (C-7′′), 151.6 (C-1′), 155.5 (C-9′′), 163.7 (C-2′′), 172.0 (C-1), 176.6 (C-4′′) ppm. MS (FAB^+): *m*/*z* (%) = 296 (100) $[M + H]^+$. $C_{17}H_{13}NO_4$: calcd. C 69.15, H 4.41, N 4.75; found C 69.25, H 4.34, N 4.80.

General Procedure for the Synthesis of Flavone–Nitrogen Heterocycle Dyads 6a–c, 7a–c, 8a–c, 9a–c, and 10c–12c under Classical Heating Conditions: Paraformaldehyde (15.2 mg, 0.51 mmol) and the appropriate dipolarophile (5 equiv.) were added to a solution of flavonylglycine **5a**–**c** (30.0 mg, 0.10 mmol) in 1,2,4-trichlorobenzene (3 mL). The mixture was heated to reflux under nitrogen from 20 to 210 min (Table 1 and Table 2). The solution was cooled to room temperature, and the solvent was removed by silica gel column chromatography eluting with hexane. Changing the eluting system to a (9:1) mixture of CH_2Cl_2/acetone afforded the title compounds in moderate to good yields: **6a** (29.3 mg, 77%), **6b** (30.8 mg, 81%), **6c** (34.9 mg, 92%), **7a** (18.2 mg, 44%), **7b** (33.1 mg, 80%), **7c** (38.5 mg, 93%), **8a** (35.6 mg, 86%), **8b** (35.2 mg, 85%), **8c** (36.0 mg, 87%), **9a** (27.9 mg, 68%), **9b** (13.1 mg, 32%), **9c** (24.9 mg, 61%), **10c** (18.8 mg, 67%), **11c** (11.2 mg, 16%), **12c** (10.0 mg, 24%).

(3a*R,6a*S**)-2-Methyl-5-[2-(4-oxo-4*H*-chromen-2-yl)phenyl]tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6a):** Yellow solid; m.p. 168–169 °C (ethanol). ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.07 (s, 3 H, N-CH_3), 3.03–3.13 (m, 2 H, 4_{cis},6_{cis}-H), 3.28 (dd, *J* = 1.9, 5.3 Hz, 2 H, 3a,6a-H), 3.74 (d, *J* = 10.1 Hz, 2 H, 4_{trans},6_{trans}-H), 6.58 (s, 1 H, 3′′-H), 7.06 (d, *J* = 8.1 Hz, 1 H, 6′-H), 7.17 (ddd, *J* = 1.0, 7.6, 7.7 Hz, 1 H, 4′-H), 7.41–7.43 (m, 2 H, 5′,6′′-H), 7.43 (d, *J* = 8.0 Hz, 1 H, 8′′-H), 7.58 (dd, *J* = 1.6, 7.7 Hz, 1 H, 3′-H), 7.68 (ddd, *J* = 1.7, 7.8, 8.0 Hz, 1 H, 7′′-H), 8.26 (dd, *J* = 1.7, 8.2 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 25.5 (N-*C*H_3), 44.1 (C-3a,6a), 54.1 (C-4,6), 110.9 (C-3′′), 118.1 (C-8′′), 118.5 (C-6′), 123.2 (C-4′), 123.9 (C-10′′), 125.3 (C-6′′), 125.9 (C-5′′,2′), 130.5 (C-3′), 131.8 (C-5′), 133.5 (C-7′′), 145.9 (C-1′), 156.6 (C-9′′), 163.7 (C-2′′), 177.9 (C-4′′), 178.3 (C-1,3) ppm. MS (ESI^+): *m*/*z* (%) = 375 (64) $[M + H]^+$, 397 (100) $[M + Na]^+$, 413 (6) $[M + K]^+$. $C_{22}H_{18}N_2O_4$: calcd. C 70.58, H 4.85, N 7.48; found C 70.36, H 4.87, N 7.05.

(3a*R,6a*S**)-2-Methyl-5-[3-(4-oxo-4*H*-chromen-2-yl)phenyl]tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6b):** Yellow solid; m.p. 268–269 °C (ethanol). ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.05 (s, 3 H, N-CH_3), 3.29–3.37 (m, 2 H, 4_{cis},6_{cis}-H), 3.53 (d, *J* = 7.8 Hz, 2 H, 3a,6a-H), 4.11 (d, *J* = 10.4 Hz, 2 H, 4_{trans},6_{trans}-H), 6.81 (s, 1 H, 3′′-H), 6.88–6.92 (m, 1 H, 6′-H), 7.26 (s, 1 H, 2′-H), 7.36–7.47 (m, 2 H, 4′,5′-H), 7.44 (ddd, *J* = 1.0, 7.7, 7.7 Hz, 1 H, 6′′-H), 7.60 (d, *J* = 8.0 Hz, 1 H, 8′′-H), 7.73 (ddd, *J* = 1.7, 7.7, 8.0 Hz, 1 H, 7′′-H), 8.24 (dd, *J* = 1.7, 7.7 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 25.5 (N-*C*H_3), 44.2 (C-3a,6a), 51.3 (C-4,6), 107.9 (C-3′′), 112.1 (C-2′), 117.3 (C-4′), 117.8 (C-6′), 118.1 (C-8′′), 124.0 (C-10′′), 125.3 (C-6′′), 125.7 (C-5′′), 130.0 (C-5′), 132.9 (C-3′), 133.8 (C-7′′), 148.0 (C-1′), 156.3 (C-9′′), 163.6 (C-2′′), 178.5 (C-1,3,4′′) ppm. MS (ESI^+): *m*/*z* (%) = 375 (100) $[M + H]^+$, 397 (46) $[M + Na]^+$, 413 (13) $[M + K]^+$. HRMS: calcd. for $[C_{22}H_{19}N_2O_4]^+$ 375.13393; found 375.13368.

(3a*R,6a*S**)-2-Methyl-5-[4-(4-oxo-4*H*-chromen-2-yl)phenyl]tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6c):** Yellow solid; m.p. 263–265 °C (ethanol). ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.04 (s, 3 H, N-CH_3), 3.35–3.45 (m, 2 H, 4_{cis},6_{cis}-H), 3.55 (d, *J* = 8.0 Hz, 2 H, 3a,6a-H), 4.07 (d, *J* = 10.7 Hz, 2 H, 4_{trans},6_{trans}-H), 6.71 (s, 1 H, 3′′-H), 6.79 (d, *J* = 8.9 Hz, 2 H, 2′,6′-H), 7.40 (ddd, *J* = 0.7, 7.7, 7.8 Hz, 1 H, 6′′-H), 7.54 (d, *J* = 8.1 Hz, 1 H, 8′′-H), 7.68 (ddd, *J* = 1.7, 7.7, 8.1 Hz, 1 H, 7′′-H), 7.84 (d, *J* = 8.9 Hz, 2 H, 3′,5′-H), 8.21 (dd, *J* = 1.7, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 25.5 (N-*C*H_3), 44.1 (C-3a,6a), 50.6 (C-4,6), 105.3 (C-3′′), 114.3 (C-2′,6′), 117.9 (C-8′′), 121.5 (C-4′), 123.9 (C-10′′), 125.0 (C-6′′), 125.6 (C-5′′), 127.7 (C-3′,5′), 133.4 (C-7′′), 149.8 (C-1′), 156.1 (C-9′′), 163.5 (C-2′′), 178.3 (C-1,3,4′′) ppm. MS (ESI^+): *m*/*z* (%) = 375 (100) $[M + H]^+$, 397 (6) $[M + Na]^+$, 749 (3) $[2M+H]^+$. $C_{22}H_{18}N_2O_4$: calcd. C 70.58, H 4.85, N 7.48; found C 70.36, H 4.87, N 7.05.

(3*R,4*S**)-Dimethyl 1-[2-(4-Oxo-4*H*-chromen-2-yl)phenyl]pyrrolidine-3,4-dicarboxylate (7a):** Yellow oil. ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.32–3.35 (m, 2 H, 3,4-H), 3.55–3.60 (m, 4 H, 2,5-H), 3.66 (s, 6 H, CO_2CH_3), 6.52 (s, 1 H, 3′′-H), 6.94 (ddd, 1 H, 4′-H, *J* = 2.0, 8.2, 8.2 Hz), 6.96 (dd, 1 H, 6′-H, *J* = 2.0, 8.0 Hz), 7.37–7.51 (m, 3 H, 6′′,5′,3′-H), 7.50–7.52 (m, 1 H, 8′′-H), 7.70 (ddd, 1 H, 7′′-H, *J* = 1.6, 7.8, 7.8 Hz), 8.26 (dd, 1 H, 5′′-H, *J* = 1.6, 8.0 Hz) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 45.0 (C-3,4), 51.9 (C-2,5), 52.2 (CO_2CH_3), 111.6 (C-3′′), 115.2 (C-6′), 118.1 (C-8′′), 118.7 (C-4′), 119.9 (C-2′), 123.8 (C-10′′), 125.2 (C-6′′), 125.7 (C-5′′), 131.5 (C-3′), 131.7 (C-5′), 133.7 (C-7′′), 146.7 (C-1′), 156.3 (C-9′′), 166.2 (C-2′′), 171.7 (CO_2CH_3), 178.4 (C-4′′) ppm. MS (ESI^+): *m*/*z* (%) = 408 (100) $[M + H]^+$, 430 (85) $[M + Na]^+$. HRMS: calcd. for $[C_{23}H_{21}NO_6]^+$ 407.1369; found 407.1361.

Dimethyl (3*R,4*S**)-1-[3-(4-Oxo-4*H*-chromen-2-yl)phenyl]pyrrolidine-3,4-dicarboxylate (7b):** Yellow solid; m.p. 152–153 °C (ethanol). ^1H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.49–3.53 (m, 2 H, 3,4-H), 3.75 (s, 6 H, CO_2CH_3), 3.70–3.84 (m, 4 H, 2,5-H), 6.74 (dd, *J* = 2.1, 8.0 Hz, 1 H, 6′-H), 6.83 (s, 1 H, 3′′-H), 7.06 (t, *J* = 2.1 Hz, 1 H, 2′-H), 7.28 (d, *J* = 8.0 Hz, 1 H, 4′-H), 7.38 (t, *J* = 8.0 Hz, 1 H, 5′-H), 7.43 (ddd, *J* = 1.0, 7.8, 7.9 Hz, 1 H, 6′′-H), 7.60 (d, *J* = 8.0 Hz, 1 H, 8′′-H), 7.71 (ddd, *J* = 1.7, 7.8, 8.0 Hz, 1 H, 7′′-H), 8.24 (dd, *J* = 1.7, 7.9 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 45.0 (4, C-3), 49.6 (C-2,5), 52.3 (CO_2CH_3), 107.7 (C-3′′), 109.1 (C-2′), 114.7 (C-4′), 114.9 (C-6′), 118.2 (C-8′′), 124.0 (C-10′′), 125.2 (C-6′′), 125.7 (C-5′′), 129.9 (C-5′), 132.7 (C-

3′), 133.7 (C-7′′), 147.2 (C-1′), 156.3 (C-9′′), 164.2 (C-2′′), 171.9 (*C*O$_2$CH$_3$), 178.6 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 408 (100) [M + H]$^+$, 430 (20) [M + Na]$^+$. $C_{23}H_{21}NO_6$: calcd. C 67.80, H 5.20, N 3.44; found C 67.78, H 5.20, N 3.45.

Dimethyl (3*R,4*S**)-1-[4-(4-Oxo-4*H*-chromen-2-yl)phenyl]pyrrolidine-3,4-dicarboxylate (7c):** Yellow solid; m.p. 197–198 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.50–3.55 (m, 2 H, 3,4-H), 3.75 (s, 6 H, CO$_2$C*H*$_3$), 3.71–3.86 (m, 4 H, 2,5-H), 6.65 (d, *J* = 9.0 Hz, 2 H, 2′,6′-H), 6.74 (s, 1 H, 3′′-H), 7.40 (ddd, *J* = 1.0, 7.7, 7.8 Hz, 1 H, 6′′-H), 7.55 (d, *J* = 8.1 Hz, 1 H, 8′′-H), 7.62 (ddd, *J* = 1.6, 7.7, 8.1 Hz, 1 H, 7′′-H), 7.85 (d, *J* = 9.0 Hz, 2 H, 3′,5′-H), 8.22 (dd, *J* = 1.6, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 44.9 (C-3,4), 49.4 (C-2,5), 52.4 (CO$_2$*C*H$_3$), 104.6 (C-3′′), 111.8 (C-2′,6′), 117.8 (C-8′′), 119.0 (C-4′), 124.0 (C-10′′), 124.8 (C-6′′), 125.2 (C-5′′), 127.8 (C-3′,5′), 133.3 (C-7′′), 149.2 (C-1′), 156.1 (C-9′′), 164.2 (C-2′′), 171.7 (*C*O$_2$CH$_3$), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 408 (100) [M + H]$^+$, 430 (13) [M + Na]$^+$, 446 (4) [M + K]$^+$. $C_{23}H_{21}NO_6$: calcd. C 67.80, H 5.20, N 3.44; found C 68.00, H 5.24, N 3.55.

Dimethyl (3*R,4*R**)-1-[2-(4-Oxo-4*H*-chromen-2-yl)phenyl]pyrrolidine-3,4-dicarboxylate (8a):** Yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.45–3.52 (m, 6 H, 2,3,4,5-H), 3.64 (s, 6 H, CO$_2$C*H*$_3$), 6.60 (s, 1 H, 3′′-H), 6.94 (d, *J* = 5.0 Hz, 1 H, 6′-H), 6.99 (ddd, *J* = 0.4, 4.5, 4.5 Hz, 1 H, 4′-H), 7.39–7.45 (m, 2 H, 6′′, 5′-H), 7.48–7.50 (m, 2 H, 8′′,3′-H), 7.70 (ddd, *J* = 1.0, 4.7, 4.7 Hz, 1 H, 7′′-H), 8.25 (dd, *J* = 1.0, 4.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 45.3 (C-3,4), 52.4 (C-2,5), 52.6 (CO$_2$*C*H$_3$), 111.3 (C-3′′), 116.0 (C-6′), 118.2 (C-8′′), 119.8 (C-4′), 121.5 (C-2′), 123.8 (C-10′′), 125.2 (C-6′′), 125.7 (C-5′′), 131.5 (C-3′), 131.7 (C-5′), 133.7 (C-7′′), 146.5 (C-1′), 156.3 (C-9′′), 166.1 (C-2′′), 172.4 (*C*O$_2$CH$_3$), 178.5 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 408 (100) [M + H]$^+$, 430 (74) [M + Na]$^+$. HRMS: calcd. for $[C_{23}H_{21}NO_6]^+$ 407.1369; found 407.1369.

Dimethyl (3*R,4*R**)-1-[3-(4-Oxo-4*H*-chromen-2-yl)phenyl]pyrrolidine-3,4-dicarboxylate (8b):** Yellow solid; m.p. 124–126 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.63–3.67 (m, 4 H, 3,4-H and 2,5-H), 3.79 (s, 6 H, CO$_2$C*H*$_3$), 6.74 (dd, *J* = 1.6, 7.8 Hz, 1 H, 6′-H), 6.82 (s, 1 H, 3′′-H), 7.06 (t, *J* = 1.6 Hz, 1 H, 2′-H), 7.30 (dd, *J* = 1.6, 7.8 Hz, 1 H, 4′-H), 7.38 (t, *J* = 7.8 Hz, 1 H, 5′-H), 7.43 (ddd, *J* = 1.1, 7.6, 7.7 Hz, 1 H, 6′′-H), 7.60 (d, *J* = 8.0 Hz, 1 H, 8′′-H), 7.71 (ddd, *J* = 1.7, 7.7, 8.0 Hz, 1 H, 7′′-H), 8.24 (dd, *J* = 1.7, 7.6 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 45.4 (C-3,4), 50.2 (C-2,5), 52.6 (CO$_2$*C*H$_3$), 107.7 (C-3′′), 109.5 (C-2′), 115.0 (C-4′), 115.3 (C-6′), 118.2 (C-8′′), 124.0 (C-10′′), 125.2 (C-6′′), 125.7 (C-5′′), 130.0 (C-5′), 132.7 (C-3′), 133.7 (C-7′′), 147.2 (C-1′), 156.3 (C-9′′), 164.1 (C-2′′), 172.5 (*C*O$_2$CH$_3$), 178.6 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 408 (100) [M + H]$^+$, 430 (12) [M + Na]$^+$. $C_{23}H_{21}NO_6$: calcd. C 67.80, H 5.20, N 3.44; found C 67.69, H 5.46, N 3.76.

Dimethyl (3R*,4*R)-1-[4-(4-Oxo-4*H*-chromen-2-yl)phenyl]pyrrolidine-3,4-dicarboxylate (8c):** Yellow solid; m.p. 217–219 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.64–3.68 (m, 4 H, 3,4-H and 2,5-H), 3.78 (s, 6 H, CO$_2$C*H*$_3$), 3.72–3.89 (m, 2 H, 2,5-H), 6.64 (d, *J* = 8.9 Hz, 2 H, 2′,6′-H), 6.72 (s, 1 H, 3′′-H), 7.39 (ddd, *J* = 1.1, 7.6, 7.8 Hz, 1 H, 6′′-H), 7.54 (d, *J* = 7.9 Hz, 1 H, 8′′-H), 7.67 (ddd, *J* = 1.6, 7.6, 7.9 Hz, 1 H, 7′′-H), 7.84 (d, *J* = 8.9 Hz, 2 H, 3′,5′-H), 8.22 (dd, *J* = 1.6, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 45.4 (C-3,4), 48.2 (C-2,5), 52.6 (CO$_2$*C*H$_3$), 104.7 (C-3′′), 112.0 (C-2′,6′), 117.8 (C-8′′), 119.2 (C-4′), 124.9 (C-10′′), 125.2 (C-6′′), 125.6 (C-5′′), 127.8 (C-3′,5′), 133.3 (C-7′′), 149.1 (C-1′), 156.1 (C-9′′), 164.1 (C-2′′), 172.2 (*C*O$_2$CH$_3$), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 408 (100) [M + H]$^+$, 430 (6) [M + Na]$^+$. $C_{23}H_{21}NO_6$: calcd. C 67.80, H 5.20, N 3.44; found C 67.62, H 5.58, N 3.76.

Dimethyl 1-[2-(4-Oxo-4*H*-chromen-2-yl)phenyl]-1*H*-pyrrole-3,4-dicarboxylate (9a): Yellow solid; m.p. 185–186 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.78 (s, 6 H, CO$_2$C*H*$_3$), 6.50 (s, 1 H, 3′′-H), 7.12 (dd, *J* = 0.9, 8.4 Hz, 1 H, 8′′-H), 7.39 (ddd, *J* = 0.9, 7.6, 7.8 Hz, 1 H, 6′′-H), 7.39 (s, 2 H, 2,5-H), 7.49 (dd, *J* = 1.6, 7.5 Hz, 1 H, 6′-H), 7.59–7.71 (m, 3 H, 7′′,4′′,5′′-H), 7.77 (dd, *J* = 1.8, 7.5 Hz, 1 H, 3′-H), 8.17 (dd, *J* = 1.6, 78 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 51.6 (CO$_2$*C*H$_3$), 112.0 (C-3′′), 117.0 (C-3,4), 118.0 (C-8′′), 123.5 (C-10′′), 125.5 (C-5′′,6′′), 127.5 (C-6′), 128.8 (C-2,5), 129.1 (C-2′), 129.5 (C-4′), 130.6 (C-3′), 132.2 (C-5′), 134.2 (C-7′′), 137.4 (C-1′), 156.0 (C-9′′), 162.0 (C-2′′), 163.4 (*C*O$_2$CH$_3$), 177.9 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 404 (13) [M + H]$^+$, 426 (100) [M + Na]$^+$. HRMS: calcd. for $[C_{23}H_{17}NO_6]^+$ 403.1056; found 403.1057.

Dimethyl 1-[3-(4-Oxo-4*H*-chromen-2-yl)phenyl]-1*H*-pyrrole-3,4-dicarboxylate (9b): Yellow solid; m.p. 208–209 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.90 (s, 6 H, CO$_2$C*H*$_3$), 6.89 (s, 1 H, 3′′-H), 7.47 (ddd, *J* = 1.1, 7.7, 7.8 Hz, 1 H, 6′′-H), 7.58–7.70 (m, 2 H, 6′,5′-H), 7.65 (d, *J* = 8.1 Hz, 1 H, 8′′-H), 7.71 (s, 2 H, 2,5-H), 7.76 (ddd, *J* = 1.7, 7.7, 8.1 Hz, 1 H, 7′′-H), 7.92 (dt, *J* = 1.7, 7.7 Hz, 1 H, 4′-H), 8.00 (t, *J* = 1.7 Hz, 1 H, 2′-H), 8.25 (dd, *J* = 1.7, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 51.8 (CO$_2$*C*H$_3$), 108.5 (C-3′′), 118.0 (C-3,4), 118.2 (C-8′′), 118.8 (C-2′), 123.89 (C-6′), 123.93 (C-10′′), 125.4 (C-4′), 125.6 (C-6′′), 125.8 (C-5′′), 126.3 (C-2,5), 130.8 (C-5′), 134.0 (C-3′), 134.2 (C-7′′), 140.0 (C-1′), 156.2 (C-9′′), 161.5 (C-2′′), 163.6 (*C*O$_2$CH$_3$), 178.1 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 404 (23) [M + H]$^+$, 426 (100) [M + Na]$^+$. HRMS: calcd. for $[C_{23}H_{17}NO_6]^+$ 403.1056; found 403.1054.

Dimethyl 1-[4-(4-Oxo-4*H*-chromen-2-yl)phenyl]-1*H*-pyrrole-3,4-dicarboxylate (9c): Yellow solid; m.p. 231–232 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.89 (s, 6 H, CO$_2$C*H*$_3$), 6.86 (s, 1 H, 3′′-H), 7.46 (ddd, *J* = 0.9, 7.5, 7.7 Hz, 1 H, 6′′-H), 7.58–7.62 (m, 3 H, 2′,6′-H and 8′′-H), 7.71 (s, 2 H, 2,5-H), 7.71–7.75 (m, 1 H, 7′′-H), 8.07 (d, *J* = 8.8 Hz, 2 H, 3′,5′-H), 8.25 (dd, *J* = 1.5, 7.7 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 51.8 (CO$_2$*C*H$_3$), 108.0 (C-3′′), 118.1 (C-3,4), 118.2 (C-8′′), 121.2 (C-2′,6′), 123.9 (C-10′′), 125.5 (C-6′′), 125.8 (C-5′′), 125.9 (C-2,5), 128.1 (C-3′,5′), 131.0 (C-4′), 134.0 (C-7′′), 141.0 (C-1′), 156.2 (C-9′′), 161.7 (C-2′′), 163.5 (*C*O$_2$CH$_3$), 178.2 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 404 (12) [M + H]$^+$, 426 (100) [M + Na]$^+$, 442 (8) [M + K]$^+$. HRMS: calcd. for $[C_{23}H_{17}NO_6]^+$ 403.1056; found 403.1054.

***N*-Methyl-*N*-[4-(4-oxo-4*H*-chromen-2-yl)phenyl]formamide (10c):** Yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 3.40 (s, 3 H, N-C*H*$_3$), 6.83 (s, 1 H, 3′′-H), 7.34 (d, *J* = 8.8 Hz, 2 H, 3′,5′-H), 7.45 (ddd, *J* = 1.0, 7.6, 7.8 Hz, 1 H, 6′′-H), 7.59 (br. d, *J* = 8.1 Hz, 1 H, 8′′-H), 7.73 (ddd, *J* = 1.7, 7.6, 8.1 Hz, 1 H, 7′′-H), 8.00 (d, *J* = 8.8 Hz, 2 H, 2′,6′-H), 8.24 (dd, *J* = 1.7, 7.8 Hz, 1 H, 5′′-H), 8.67 (s, 1 H, *N*-C*H*O) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 31.6 (N-*C*H$_3$), 107.5 (C-3′′), 118.0 (C-8′′), 121.4 (C-2′,6′), 123.9 (C-10′′), 125.4 (C-6′′), 125.8 (C-5′′), 127.7 (C-3′,5′), 129.2 (C-4′), 133.9 (C-7′′), 144.8 (C-1′), 156.2 (C-9′′), 161.8 (N-*C*HO), 162.2 (C-2′′), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 280 (63) [M + H]$^+$, 430 (15) [M + Na]$^+$. HRMS: calcd. for $[C_{22}H_{19}N_2O_4]^+$ 375.13393; found 375.13366.

8-[4-(4-Oxo-4*H*-chromen-2-yl)phenyl]-4-phenyldihydro-1*H*-[1,2,4]triazolo[1,2-*c*][1,3,4,6]oxatriazepine-3,5(4*H*,7*H*)-dione (11c): Yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 5.14 (s, 2 H, 8-H), 5.40 (s, 2 H, 1-H), 5.61 (s, 2 H, 6-H), 6.75 (s, 1 H, 3′′-H), 7.14 (d, *J* = 8.2 Hz, 2 H, 2′′′,6′′′-H), 7.31 (d, *J* = 7.8 Hz, 2 H, 2′,6′-H),

7.30–7.38 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.42 (br. dd, *J* = 7.5, 7.8 Hz, 1 H, 6′′-H), 7.55 (dd, *J* = 0.9, 8.1 Hz, 1 H, 8′′-H), 7.70 (ddd, *J* = 1.6, 7.5, 8.1 Hz, 1 H, 7′′-H), 7.89 (d, *J* = 7.8 Hz, 2 H, 3′,5′-H), 8.23 (dd, *J* = 1.6, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): *δ* = 63.3 (C-6), 72.0 (C-1), 83.4 (C-8), 106.6 (C-3′′), 117.5 (C-2′,6′), 118.0 (C-8′′), 123.9 (C-10′′), 125.2 (C-6′′), 125.6 (C-2′′′,6′′′), 125.7 (C-5′′), 127.9 (C-3′,5′), 128.5 (C-4′′′), 129.2 (C-3′′′,5′′′), 130.8 (C-4′), 133.7 (C-7′′), 142.6 (C-1′′′), 145.7 (C-1′), 148.4 (C-3), 152.0 (C-5), 156.2 (C-9′′), 168.8 (C-2′′), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 469 (100) [M + H]$^+$, 491 (34) [M + Na]$^+$, 507 (6) [M + K]$^+$. HRMS: calcd. for $[C_{25}H_{21}N_2O_4]^+$ 413.14958; found 413.14932.

2-{4-[(3*S,4*S**)-3-Nitro-4-phenylpyrrolidin-1-yl]phenyl}-4*H*-chromen-4-one (12c):** Yellow solid; m.p. 226–227 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): *δ* = 3.77 (dd, *J* = 4.8, 10.0 Hz, 1 H, 2-H), 4.01–4.16 (m, 3 H, 2,5-H), 4.25 (dt, *J* = 4.8, 7.1 Hz, 1 H, 3-H), 5.17 (dt, *J* = 4.3, 7.1 Hz, 1 H, 4-H), 6.73 (d, *J* = 8.9 Hz, 2 H, 2′,6′-H), 6.76 (s, 1 H, 3′′-H), 7.27 (dd, *J* = 1.7, 7.9 Hz, 2 H, 2′′′,6′′′-H), 7.34–7.44 (m, 4 H, 6′′,3′′′,4′′′,5′′′-H), 7.56 (d, *J* = 7.9 Hz, 1 H, 8′′-H), 7.68 (ddd, *J* = 1.7, 7.8, 7.9 Hz, 1 H, 7′′-H), 7.90 (d, *J* = 8.9 Hz, 2 H, 3′,5′-H), 8.23 (dd, *J* = 1.7, 8.0 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): *δ* = 48.5 (C-3), 50.8 (C-5), 52.4 (C-2), 89.4 (C-4), 105.0 (C-3′′), 112.3 (C-2′,6′), 117.9 (C-8′′), 120.1 (C-4′), 124.0 (C-10′′), 125.0 (C-6′′), 125.6 (C-5′′), 127.0 (C-2′′′,6′′′), 128.0 (C-3′,5′), 128.3 (C-4′′′), 129.4 (C-3′′′,5′′′), 133.4 (C-7′′), 137.9 (C-1′′′), 148.5 (C-1′), 156.2 (C-9′′), 163.9 (C-2′′), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 413 (100) [M + H]$^+$, 435 (5) [M + Na]$^+$, 451 (3) [M + K]$^+$. HRMS: calcd. for $[C_{22}H_{19}N_2O_4]^+$ 375.13393; found 375.13385.

General Procedure for the Synthesis of Flavone–Nitrogen Heterocycle Dyads 13c: Paraformaldehyde (15.7 mg, 0.52 mmol) was added to a solution of *N*-flavonylglycine **5c** (30.8 mg, 0.10 mmol) in 1,2,4-trichlorobenzene (3 mL). The mixture was heated to reflux under nitrogen for 60 min. The solution was cooled to room temperature, and the solvent was removed by silica gel column chromatography eluting with hexane. Changing the eluting system to a (1:2) mixture of hexane/ethyl acetate afforded the title compound **13c** in good yield (26.7 mg, 87%).

2-[4-(Oxazolidin-3-yl)phenyl]-4*H*-chromen-4-one (13c): Yellow solid; m.p. 180–182 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): *δ* = 3.51 (t, *J* = 6.4 Hz, 2 H, 4-H), 4.23 (t, *J* = 6.4 Hz, 2 H, 5-H), 4.95 (s, 2 H, 2-H), 6.57 (d, *J* = 9.0 Hz, 2 H, 2′,6′-H), 6.71 (s, 1 H, 3′′-H), 7.40 (ddd, *J* = 1.0, 7.7, 7.8 Hz, 1 H, 6′′-H), 7.54 (dd, *J* = 1.0, 8.0 Hz, 1 H, 8′′-H), 7.67 (ddd, *J* = 1.7, 7.7, 8.1 Hz, 1 H, 7′′-H), 7.84 (d, *J* = 9.0 Hz, 2 H, 3′,5′-H), 8.22 (dd, *J* = 1.7, 7.8 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): *δ* = 45.6 (C-4), 67.4 (C-5), 80.3 (C-2), 104.8 (C-3′′), 112.0 (C-2′,6′), 117.8 (C-8′′), 119.6 (C-4′), 124.0 (C-10′′), 124.9 (C-6′′), 125.6 (C-5′′), 128.0 (C-3′,5′), 133.3 (C-7′′), 147.4 (C-1′), 156.1 (C-9′′), 164.0 (C-2′′), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 294 (100) [M + H]$^+$, 316 (15) [M + Na]$^+$, 332 (6) [M + K]$^+$. HRMS: calcd. for $[C_{18}H_{15}NO_3]^+$ 293.1052; found 293.1053.

General Procedure for the Synthesis of Flavone–Nitrogen Heterocycle Dyads 14c–15c: Paraformaldehyde (15.8 mg, 0.53 mmol) and the appropriate benzaldehyde [*para*-nitrobenzaldehyde (16.0 mg, 0.11 mmol) or *para*-methoxybenzaldehyde (30.6 mg, 0.22 mmol)] were added to a solution of *N*-flavonylglycine **5c** (31.1 mg, 0.11 mmol) in 1,2,4-trichlorobenzene (3 mL). The mixture was heated to reflux under nitrogen for 60 min. The solution was cooled to room temperature, and the solvent was removed by silica gel column chromatography eluting with hexane. Changing the eluting system to a (1:2) mixture of hexane/ethyl acetate afforded the title compounds in poor (**15c**; 5.7 mg, 14%) and good yields (**14c**; 30.0 mg, 73%).

2-{4-[5-(4-Nitrophenyl)oxazolidin-3-yl]phenyl}-4*H*-chromen-4-one (14c): Yellow solid; m.p. 229–230 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): *δ* = 3.39 (t, *J* = 8.5 Hz, 1 H, 4_{trans}-H), 3.99 (dd, *J* = 6.5, 8.5 Hz, 1 H, 4_{cis}-H), 5.15 (d, *J* = 2.6 Hz, 1 H, 2-H), 5.30 (d, *J* = 2.6 Hz, 1 H, 2-H), 5.41 (dd, *J* = 6.5, 8.5 Hz, 1 H, 5-H), 6.61 (d, *J* = 9.0 Hz, 2 H, 2′,6′-H), 6.73 (s, 1 H, 3′′-H), 7.64 (d, *J* = 8.7 Hz, 2 H, 2′′′,6′′′-H), 7.41 (ddd, *J* = 1.1, 7.5, 7.7 Hz, 1 H, 6′′-H), 7.55 (dd, *J* = 1.1, 8.4 Hz, 1 H, 8′′-H), 7.66–7.71 (m, 1 H, 7′′-H), 7.87 (d, *J* = 9.0 Hz, 2 H, 3′,5′-H), 8.22 (dd, *J* = 1.6, 7.7 Hz, 1 H, 5′′-H), 8.29 (d, *J* = 8.7 Hz, 2 H, 3′′′,5′′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): *δ* = 52.8 (C-4), 79.0 (C-5), 81.2 (C-2), 105.1 (C-3′′), 112.3 (C-2′,6′), 117.9 (C-8′′), 120.6 (C-4′), 124.0 (C-3′′′,5′′′ and C-10′′), 125.0 (C-6′′), 126.8 (C-2′′′,6′′′), 128.0 (C-3′,5′), 125.6 (C-5′′), 133.4 (C-7′′), 145.8 (C-1′′′), 147.0 (C-1′), 148.0 (C-4′′′), 156.2 (C-9′′), 163.7 (C-2′′), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 415 (100) [M + H]$^+$, 437 (35) [M + Na]$^+$, 453 (6) [M + K]$^+$. HRMS: calcd. for $[C_{24}H_{18}N_2O_5 + H]^+$ 415.1288; found 415.1283.

2-[4–85-(4-Methoxyphenyl)oxazolidin-3-yl]phenyl-4*H*-chromen-4-one (15c): Yellow solid; m.p. 163–164 °C (ethanol). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): *δ* = 3.42 (t, *J* = 8.4 Hz, 1 H, 4_{trans}-H), 3.83 (s, 3 H, OCH_3), 3.85 (dd, *J* = 6.3, 8.4 Hz, 1 H, 4_{cis}-H), 5.08 (d, *J* = 2.7 Hz, 1 H, 2-H), 5.23 (dd, *J* = 6.3, 8.4 Hz, 1 H, 5-H), 5.24 (d, *J* = 2.7 Hz, 1 H, 2-H), 6.59 (d, *J* = 8.9 Hz, 2 H, 2′,6′-H), 6.73 (s, 1 H, 3′′-H), 6.94 (d, *J* = 8.8 Hz, 2 H, 3′′′,5′′′-H), 7.38 (d, *J* = 8.8 Hz, 2 H, 2′′′,6′′′-H), 7.36–7.43 (m, 1 H, 6′′-H), 7.54 (d, *J* = 8.0 Hz, 1 H, 8′′-H), 7.67 (ddd, *J* = 1.6, 7.7, 8.0 Hz, 1 H, 7′′-H), 7.86 (d, *J* = 8.9 Hz, 2 H, 3′,5′-H), 8.22 (dd, *J* = 1.6, 8.0 Hz, 1 H, 5′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): *δ* = 52.7 (C-4), 55.3 (OCH_3), 80.0 (C-5), 80.7 (C-2), 104.9 (C-3′′), 112.0 (C-2′,6′), 114.1 (C-3′′′,5′′′), 117.9 (C-8′′), 119.8 (C-4′), 124.0 (C-10′′), 124.9 (C-6′′), 127.8 (C-2′′′,6′′′), 128.0 (C-3′,5′), 129.3 (C-1′′′), 130.0 (C-5′′), 133.3 (C-7′′), 147.4 (C-1′), 156.2 (C-9′′), 159.9 (C-4′′′), 164.0 (C-2′′), 178.3 (C-4′′) ppm. MS (ESI$^+$): *m*/*z* (%) = 400 (100) [M + H]$^+$, 422 (6) [M + Na]$^+$. HRMS: calcd. for $[C_{25}H_{21}NO_4]^+$ 399.1471; found 399.1462.

General Procedure for the Synthesis of Flavone–Nitrogen Heterocycle Dyads 6a–c, 7a–c, 8a–c, and 9a–c under Microwave Irradiation: A mixture of paraformaldehyde (15.2 mg, 0.51 mmol), the appropriate dipolarophile (5 equiv.), and *N*-flavonylglycine **5a–c** (30.0 mg, 0.10 mmol) in 1,2,4-trichlorobenzene (3 mL), in a two-necked glassware apparatus, provided with a magnetic stirring bar, fiber-optic temperature control and reflux condenser, was irradiated [800 W maximum power, 170 °C maximum temperature and from 10 to 5 min. (see Tables 1 and 2)]. The solution was cooled to room temperature, and the solvent was removed by silica gel column chromatography eluting with hexane. Changing the eluting system to a (9:1) mixture of CH_2Cl_2/acetone afforded the title compounds in moderate to good yields: **6a** (30.4 mg, 80%), **6b** (29.7 mg, 78%), **6c** (36.1 mg, 95%), **7a** (31.9 mg, 77%), **7b** (34.4 mg, 83%), **7c** (32.7 mg, 79%), **8a** (35.6 mg, 86%), **8b** (33.9 mg, 82%), **8c** (32.3 mg, 78%), **9a** (19.3 mg, 47%), **9b** (17.6 mg, 43%), **9c** (27.0 mg, 66%).

General Procedure for the Synthesis of Flavone–Chlorin Dyads 19a–c: Paraformaldehyde (6.5 mg, 0.22 mmol) and *N*-flavonylglycine **5a–c** (10.2 mg, 0.035 mmol) were added to a solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (**18**; 20.8 mg, 0.021 mmol) in toluene (4 mL). The mixture was heated to reflux under nitrogen for 16 h. During this period, the reaction was monitored by TLC and, if necessary, two more portions of paraformaldehyde and *N*-

flavonylglycine **5a**–**c** were added. Water (20 mL) was then added and the resulting mixture was extracted with chloroform. The organic layer was collected and dried with anhydrous sodium sulfate, and the solution was concentrated to dryness. The residue was purified by silica gel column chromatography with gradient elution (light petroleum/CH_2Cl_2, 1:1 to 1:2) to afford the title compounds **19a** (5.7 mg, 22%), **19b** (13.8 mg, 53%), or **19c** (14.8 mg, 57%).

2-[2-(4-Oxo-4*H*-chromen-2-yl)phenyl]-5,10,15,20-tetrakis(pentafluorophenyl)-3,3a,21,21a-tetrahydropyrrolo[3,4-*b*]porphyrin (19a): Green solid. UV/Vis λ_{max} (CH_2Cl_2) [log(ε/10^3 mol^{-1} cm^{-1})] = 404 (5.33), 503 (4.03), 598 (3.24), 651 (4.68) nm. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = –1.79 (s, 2 H, N*H*), 3.66–3.71 (m, 2 H, 1-H or 3-H), 3.89–3.94 (m, 2 H, 1-H or 3-H), 5.51–5.53 (m, 2 H, 3a,21a-H), 6.50 (d, *J* = 8.6 Hz, 1 H, 6′-H), 6.63 (s, 1 H, 3′′-H), 7.07–7.33 (m, 3 H, 3′,4′,5′-H), 7.43 (t, *J* = 7.9 Hz, 1 H, 6′′-H), 7.56 (d, *J* = 7.9 Hz, 1 H, 8′′-H), 7.75 (t, *J* = 7.9 Hz, 1 H, 7′′-H), 8.20 (d, *J* = 7.9 Hz, 1 H, 5′′-H), 8.45 (d, *J* = 4.9 Hz, 2 H, 7,18-H or 8,17-H), 8.49 (s, 2 H, 12,13-H), 8.75 (d, *J* = 4.9 Hz, 2 H, 7,18-H or 8,17-H) ppm. ^{19}F NMR (282.38 MHz, $CDCl_3$, 20 °C): δ = –184.87 (dt, *J* = 8.2, 21.5 Hz, 2 F, Ar-F-*meta*), –183.67 (dt, *J* = 8.6, 22.9 Hz, 2 F, Ar-F-*meta*), –182.86 (dt, *J* = 6.7, 22.9 Hz, 2 F, Ar-F-*meta*), –175.01 (t, *J* = 21.5 Hz, 2 F, Ar-F-*para*), –173.92 (t, *J* = 22.9 Hz, 2 F, Ar-F-*para*), –160.47 (dd, *J* = 8.6, 22.9 Hz, 2 F, Ar-F-*ortho*), –160.36 to –160.28 (m, 4 F, Ar-F-*ortho*), –158.49 (dd, *J* = 6.7, 22.9 Hz, 2 F, Ar-F-*ortho*) ppm. MS (FAB$^+$): *m*/*z* (%) = 1238 (100) [M + H]$^+$, 975 (15) [M + H]$^+$-C_2H_4N-flavone. HRMS: calcd. for [$C_{61}H_{23}F_{20}N_5O_2$ + H]$^+$ 1238.1605; found 1238.1585.

2-[3-(4-Oxo-4*H*-chromen-2-yl)phenyl]-5,10,15,20-tetrakis(pentafluorophenyl)-3,3a,21,21a-tetrahydropyrrolo[3,4-*b*]porphyrin (19b): Green solid. UV/Vis λ_{max} (CH_2Cl_2) [log(ε/10^3 mol^{-1} cm^{-1})] = 405 (5.31), 503 (4.05), 598 (3.24), 651 (4.68) nm. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = –1.81 (s, 2 H, N*H*), 3.66–3.71 (m, 2 H, 1-H or 3-H), 3.91–3.97 (m, 2 H, 1-H or 3-H), 5.51–5.53 (m, 2 H, 3a,21a-H), 6.64 (dd, *J* = 1.8, 7.9 Hz, 1 H, 6′-H), 6.70 (s, 1 H, 3′′-H), 7.10–7.28 (m, 3 H, 2′,4′,5′-H), 7.42 (t, *J* = 7.5 Hz, 1 H, 6′′-H), 7.56 (d, *J* = 8.3 Hz, 1 H, 8′′-H), 7.75 (ddd, *J* = 1.6, 7.5, 8.3 Hz, 1 H, 7′′-H), 8.20 (dd, *J* = 1.6, 7.5 Hz, 1 H, 5′′-H), 8.45 (d, *J* = 4.9 Hz, 2 H, 7,18-H or 8,17-H), 8.49 (s, 2 H, 12,13-H), 8.75 (d, *J* = 4.9 Hz, 2 H, 7,18-H or 8,17-H), ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 51.6 (C-3a,21a), 55.2 (C-1,3), 96.7, 106.5, 107.6 (C-3′′), 111.4, 116.5, 116.9, 117.8 (C-8′′), 123.9 (C-12,13), 125.2 (C-6′′), 125.3 (C-5′′), 128.2 (C-7,18 or C-8,17), 129.0, 129.8, 132.5 (C-7,18 or C-8,17), 132.6 (C-7′′), 133.8, 135.3, 140.4, 147.6, 152.9, 156.2, 163.3 (C-1′), 168.6 (C-3′), 178. 4 (C-4′′) ppm. ^{19}F NMR (282.38 MHz, $CDCl_3$, 20 °C): δ = –184.87 (dt, *J* = 8.2, 21.5 Hz, 2 F, Ar-F-*meta*), –183.67 (dt, *J* = 8.6, 22.9 Hz, 2 F, Ar-F-*meta*), –182.86 (dt, *J* = 6.7, 22.9 Hz, 2 F, Ar-F-*meta*), –175.01 (t, *J* = 21.5 Hz, 2 F, Ar-F-*para*), –173.92 (t, *J* = 22.9 Hz, 2 F, Ar-F-*para*), –160.47 (dd, *J* = 8.6, 22.9 Hz, 2 F, Ar-F-*ortho*), –160.36 to –160.28 (m, 4 F, Ar-F-*ortho*), –158.49 (dd, *J* = 6.7, 22.9 Hz, 2 F, Ar-F-*ortho*) ppm. MS (FAB$^+$): *m*/*z* (%) = 1238 (100) [M + H]$^+$, 975 (17) [M + H]$^+$-C_2H_4N-flavone. HRMS: calcd. for [$C_{61}H_{23}F_{20}N_5O_2$ + H]$^+$ 1238.1605; found 1238.1582.

2-[4-(4-Oxo-4*H*-chromen-2-yl)phenyl]-5,10,15,20-tetrakis(pentafluorophenyl)-3,3a,21,21a-tetrahydropyrrolo[3,4-*b*]porphyrin (19c): Green solid. UV/Vis λ_{max} (CH_2Cl_2) [log(ε/10^3 mol^{-1} cm^{-1})] = 405 (5.33), 503 (4.05), 598 (3.25), 651 (4.69) nm. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = –1.80 (s, 2 H, N*H*), 3.66–3.70 (m, 2 H, 1-H or 3-H), 3.93–4.00 (m, 2 H, 1-H or 3-H), 5.53–5.56 (m, 2 H, 3a,21a-H), 8.43 (d, *J* = 4.9 Hz, 2 H, 7,18-H or 8,17-H), 8.49 (s, 2 H, 12,13-H), 8.74 (d, *J* = 4.9 Hz, 2 H, 7,18-H or 8,17-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 51.5 (C-3a,21a), 54.6 (C-1,3), 96.6, 105.1 (C-3′′), 106.6, 113.5 (C-2′,6′), 117.8 (C-8′′), 120.7, 123.9 (C-12,13), 124.0 (C-6′′), 124.9 (C-5′′), 125.6 (C-3′,5′), 127.7 (C-7,18 or C-8,17), 128.2 (C-7,18 or C-8,17), 132.6 (C-7′′), 133.3, 135.4, 140.3, 149.3, 153.0, 156.1, 163.6, 168.2, 178. 3 (C-4′′) ppm. ^{19}F NMR (282.38 MHz, $CDCl_3$, 20 °C): δ = –184.93 to –184.75 (m, 4 F, Ar-F-*meta*), –183.31 (dt, *J* = 8.4, 21.8 Hz, 2 F, Ar-F-*meta*), –182.87 (dt, *J* = 8.4, 21.8 Hz, 2 F, Ar-F-*meta*), –174.95 (t, *J* = 20.9 Hz, 2 F, Ar-F-*para*), –173.78 (t, *J* = 21.8 Hz, 2 F, Ar-F-*para*), –160.53 to –160.26 (m, 6 F, Ar-F-*ortho*), –158.43 (dd, *J* = 5.8, 21.8 Hz, 2 F, Ar-F-*ortho*) ppm. MS (FAB$^+$): *m*/*z* (%) = 1237 (100) [M]$^+$, 975 (17) [M + H]$^+$-C_2H_4N-flavonyl. HRMS: calcd. for [$C_{61}H_{23}F_{20}N_5O_2$ + H]$^+$ 1238.1605; found 1238.1588.

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[1] J. B. Harborne, C. A. Williams, *Phytochemistry* **2000**, *55*, 481–504.
[2] a) E. Wollenweber, *Flavones and flavonols*, in: *The Flavonoids: Advances in Research Since 1986* (Ed.: J. B. Harborne), Chapman and Hall, London, **1993**, p. 259–336; b) P. M. Dewick, *Isoflavonoids*, in: *The Flavonoids: Advances in Research Since 1986* (Ed.: J. B. Harborne), Chapman and Hall, London, **1993**, p. 117–237; c) D. Strack, V. Wray, *The anthocyanins*, in: *The Flavonoids: Advances in Research Since 1986* (Ed.: J. B. Harborne), Chapman and Hall, London, **1993**, p. 1–19; d) B. A. Bohm, *The minor flavonoids*, in: *The Flavonoids: Advances in Research Since 1986* (Ed.: J. B. Harborne), Chapman and Hall, London, **1993**, p. 387–433.
[3] a) D. F. Birt, S. Hendrich, W. Wang, *Pharmacol. Ther.* **2001**, *90*, 157–177; b) C. Manach, G. Williamson, C. Morand, A. Scalbert, C. Rémésy, *Am. J. Clin. Nutr.* **2005**, *81*, 230S–242S; c) M. Wang, *Toxicol. Sci.* **2007**, *96*, 203–205; d) J. M. Patel, *Lethbridge Underg. Res. J.* **2008**, *3* (ISSN 1718-8482).
[4] B. H. Havsteen, *Pharmacol. Ther.* **2002**, *96*, 67–202.
[5] a) C. A. Rice-Evans, N. J. Miller, G. Paganga, *Free Radical Biol. Med.* **1996**, *20*, 933–956; b) H. L. Madsen, C. M. Andersen, L. V. Jørgensen, L. H. Skibsted, *Eur. Food Res. Technol.* **2000**, *211*, 240–246; c) R. J. Williams, J. P. E. Spencer, C. Rice-Evans, *Free Radical Biol. Med.* **2004**, *36*, 838–849; d) S. E. Pollard, G. G. C. Kuhnle, D. Vauzour, K. Vafeiadou, X. Tzounis, M. Whiteman, C. Rice-Evans, J. P. E. Spencer, *Biochem. Biophys. Res. Commun.* **2006**, *350*, 960–968; e) M. Guo, C. Perez, Y. Wei, E. Rapoza, G. Su, F. Bou-Abdallah, N. D. Chasteen, *Dalton Trans.* **2007**, 4951–4961.
[6] a) P. Hodek, P. Trefil, M. Stiborová, *Chem.-Biol. Interact.* **2002**, *139*, 1–21; b) J. P. E. Spencer, C. Rice-Evans, R. J. Williams, *J. Biol. Chem.* **2003**, *278*, 34783–34793.
[7] a) H. Kim, B.-S. Park, K.-G. Lee, C. Y. Chol, S. S. Jang, Y.-H. Kim, S.-E. Lee, *J. Agric. Food Chem.* **2005**, *53*, 8537–8541; b) M. Jung, M. Park, *Molecules* **2007**, *12*, 2130–2139; c) J. P. E. Spencer, *Proc. Nutr. Soc.* **2008**, *67*, 238–252; d) Y.-P. Lin, T.-Y. Chen, H.-W. Tseng, M.-H. Lee, S.-T. Chen, *Phytochemistry* **2009**, *70*, 1173–1181; e) J. P. E. Spencer, *Chem. Soc. Rev.* **2009**, *38*, 1152–1161.
[8] a) R. W. Brueggemeier, J. A. Richards, S. Joomprabutra, A. S. Bhat, J. L. Whetstone, *J. Steroid Biochem. Mol. Biol.* **2001**, *79*, 75–84; b) D. E. C. Van Hoorn, R. J. Nijveldt, P. A. M. Van Leeuwen, Z. Hofman, L. M'Rabet, D. B. A. De Bont, K.

Van Norren, *Eur. J. Pharmacol.* **2002**, *451*, 111–118; c) Y. J. Moon, X. Wang, M. E. Morris, *Toxicol. in vitro* **2006**, *20*, 187–210; d) B. Siedle, A. Hrenn, I. Merfort, *Planta Med.* **2007**, *73*, 401–420; e) W. M. Loke, J. M. Proudfoot, S. Stewart, A. J. McKinley, P. W. Needs, P. A. Kroon, J. M. Hodgson, K. D. Croft, *Biochem. Pharmacol.* **2008**, *75*, 1045–1053.

[9] O. N. Voskresensky, A. P. Levitsky, *Curr. Med. Chem.* **2002**, *9*, 1367–1383.

[10] A. K. Verma, R. Pratap, *Nat. Prod. Rep.* **2010**, *27*, 1571–1593.

[11] a) J. Cummings, J. A. Double, M. C. Bibby, P. Farmer, S. Evans, D. J. Kerr, S. B. Kaye, J. F. Smyth, *Cancer Res.* **1989**, *49*, 3587–3593; b) M. Cárdenas, M. Marder, V. C. Blank, L. P. Roguin, *Bioorg. Med. Chem.* **2006**, *14*, 2966–2971; c) Y.-P. Lin, F.-L. Hsu, C.-S. Chen, J.-W. Chern, M.-H. Lee, *Phytochemistry* **2007**, *68*, 1189–1199; d) J. T. T. Zhu, R. C. Y. Choi, G. K. Y. Chu, A. W. H. Cheung, Q. T. Gao, J. Li, Z. Y. Jiang, T. T. X. Dong, K. W. K. Tsim, *J. Agric. Food Chem.* **2007**, *55*, 2438–2445.

[12] a) K. Y. Park, S.-H. Lee, B.-K. Min, K.-S. Lee, J.-S. Choi, S. R. Chung, K. R. Min, Y. Kim, *Planta Med.* **1999**, *65*, 457–459; b) T. Nagaoka, A. H. Banskota, Y. Tezuka, K. Midorikawa, K. Matsushige, S. Kadota, *Biol. Pharm. Bull.* **2003**, *26*, 487–491; c) V. Moscatelli, O. Hnatyszyn, C. Acevedo, J. Megias, M. J. Alcaraz, G. Ferrana, *Planta Med.* **2006**, *72*, 72–74.

[13] a) G. Beyer, M. F. Melzig, *Planta Med.* **2003**, *69*, 1125–1129; b) J. Vaya, S. Mahmood, A. Goldblum, M. Aviram, N. Volkova, A. Shaalan, R. Musa, S. Tamir, *Phytochemistry* **2003**, *62*, 89–99.

[14] a) M. V. Veselovskaya, M. M. Garazd, A. S. Ogorodniichuk, Ya. L. Garazd, V. P. Khilya, *Chem. Nat. Compd.* **2008**, *44*, 704–711; b) M. Ninomiya, K. Tanaka, Y. Tsuchida, Y. Muto, M. Koketsu, K. Watanabe, *J. Med. Chem.* **2011**, *54*, 1529–1536.

[15] N. Ahmed, C. Dubuc, J. Rousseau, F. Benard, J. E. Van Lier, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3212–3216.

[16] H. Göker, D. W. Boykin, S. Yıldız, *Bioorg. Med. Chem.* **2005**, *13*, 1707–1714.

[17] S. Gobbi, A. Cavalli, A. Rampa, F. Belluti, L. Piazzi, A. Paluszcak, R. W. Hartmann, M. Recanatini, A. Bisi, *J. Med. Chem.* **2006**, *49*, 4777–4780.

[18] a) K. K. Murthi, M. Dubay, C. McClure, L. Brizuela, M. D. Boisclair, P. J. Worland, M. M. Mansuri, K. Pal, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1037–1041; b) B. Kosmider, R. Osiecka, *Drug Dev. Res.* **2004**, *63*, 200–211; c) F. Teillet, A. Boumendjel, J. Boutonnat, X. Ronot, *Med. Res. Rev.* **2008**, *28*, 715–745; d) T. Ahmadi, T. Maniar, S. Schuster, E. Stadtmauer, *Curr. Treat. Opt. Oncol.* **2009**, *10*, 16–32; e) I. Diaz-Padilla, L. L. Siu, I. Duran, *Invest. New Drugs* **2009**, *27*, 586–594; f) M. Hallek, N. Pflug, *Blood Rev.* **2011**, *25*, 1–9.

[19] A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, New York, **2002**.

[20] T. Patonay, A. Lévai, *Arch. Pharm.* **1994**, *327*, 181–186.

[21] M. D. L. de la Torre, A. G. P. Rodrigues, A. C. Tomé, A. M. S. Silva, J. A. S. Cavaleiro, *Tetrahedron* **2004**, *60*, 3581–3592.

[22] a) M. G. P. M. S. Neves, A. M. S. Silva, M. G. Vicente, M. F. P. N. Condesso, J. A. S. Cavaleiro, *Proceedings of the International Bioflavonoid Symposium*, **1995**, p. 355–359; b) R. M. Domingues, M. G. O. Santana-Marques, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, A. J. Ferrer-Correia, *Proceedings of Advances in Mass Spectrometry*, Elsevier, Amsterdam, **1998**; c) V. Vaz Serra, F. Camões, S. I. Vieira, M. A. F. Faustino, J. P. C. Tomé, D. C. G. A. Pinto, M. G. P. M. S. Neves, A. C. Tomé, A. M. S. Silva, E. F. da Cruz e Silva, J. A. S. Cavaleiro, *Acta Chim. Slov.* **2009**, *56*, 603–611.

[23] J. A. S. Cavaleiro, A. C. Tomé, M. G. P. M. S. Neves, *meso-Tetraarylporphyrin derivatives: new synthetic methodologies*, in: *Handbook of Porphyrin Synthesis* (Eds.:K. M. Kadish, K. M. Smith, R. Guilard), World Scientific Publisher, Singapore **2010**, vol. 12, p. 193.

[24] A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, *J. Org. Chem.* **2002**, *67*, 726–732.

[25] K. Kadish, K. M. Smith, R. Guilard, *The Porphyrin Handbook*, Academic Press, New York, **2000**, vol. 6.

[26] a) M. J. Wainwright, *J. Antimicrob. Chemother.* **1998**, *42*, 13–28; b) L. Costa, E. Alves, C. M. B. Carvalho, J. P. C. Tomé, M. A. F. Faustino, M. G. P. M. S. Neves, A. C. Tomé, J. A. S. Cavaleiro, Â. Cunha, A. Almeida, *Photochem. Photobiol. Sci.* **2008**, *7*, 415–422.

[27] J. P. C. Tomé, E. M. P. Silva, A. M. V. M. Pereira, C. M. A. Alonso, M. A. F. Faustino, M. G. P. M. S. Neves, A. C. Tomé, J. A. S. Cavaleiro, S. A. P. Tavares, R. R. Duarte, M. F. Caeiro, M. L. Valdeira, *Bioorg. Med. Chem.* **2007**, *15*, 4705–4713.

[28] R. F. Donnelly, P. A. McCarron, M. M. Tunney, *Microbiol. Res.* **2008**, *163*, 1–12.

[29] A. I. R. N. A. Barros, A. M. S. Silva, *Monatsh. Chem.* **2006**, *137*, 1505–1528.

[30] A. I. R. N. A. Barros, A. M. S. Silva, *Magn. Reson. Chem.* **2006**, *44*, 1122–1127.

[31] A. F. Abdel-Magid, S. J. Mehrman, *Org. Process Res. Dev.* **2006**, *10*, 971–1031.

[32] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

[33] H. T. Cao, R. Grée, *Tetrahedron Lett.* **2009**, *50*, 1493–1494.

[34] O. Tsuge, S. Kanemasa, M. Ohe, S. Takenaka, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079–4089.

[35] a) A. C. Tomé, P. S. S. Lacerda, M. G. P. M. S. Neves, J. A. S. Cavaleiro, *Chem. Commun.* **1997**, 1199–1200; b) A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, *Chem. Commun.* **1999**, 1767–1768; c) A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, D. Perrone, A. Dondoni, *Tetrahedron Lett.* **2002**, *43*, 603–605.

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