Photochemical Synthesis

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Biomimetic Photocycloaddition of 3-Hydroxyflavones: Synthesis and Evaluation of Rocaglate Derivatives as Inhibitors of Eukaryotic Translation**

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In memory of Pierre Potier and Christian Marazano

The plant genus *Aglaia* produces a number of secondary metabolites including the cyclopenta[*b*]benzofurans[1] rocaglamide (**1**), silvestrol (**2**), and cyclopenta[*b,c*]benzopyrans[2] (aglains) including ponapensin (**3**; Figure 1). Cyclopenta[*b*]-

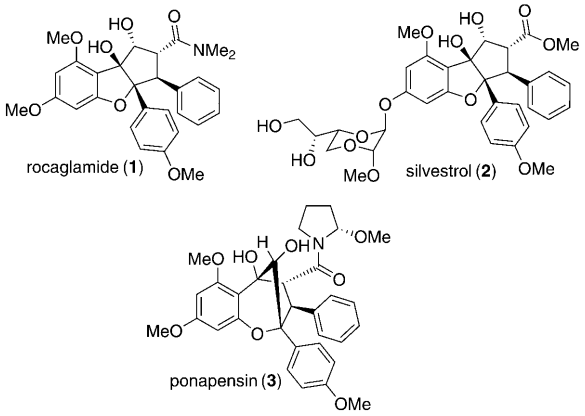
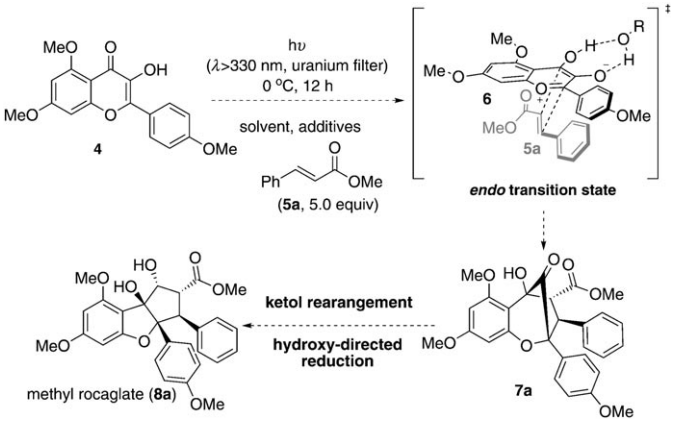


Figure 1. Representative aglain and rocaglate metabolites from *Aglaia*.

benzofuran natural products possess potent anticancer properties due to the modulation of the activity of the RNA helicase eukaryotic initiation factor 4A (eIF4A) which is involved in loading ribosomes onto mRNA templates during translation initiation, a step frequently deregulated in cancer.[3] As a result of its unusual structure and important biological activity, rocaglamide (**1**) has been targeted by many research groups and has inspired a number of elegant synthetic strategies.[4] We have previously reported a biomimetic approach to the cyclopenta[*b*]benzofuran natural products involving a photocycloaddition/ketol shift rearrangement/reduction sequence using 3-hydroxyflavone (3-HF) derivatives such as **4** and methyl cinnamate (**5a**). This strategy enabled total syntheses of both **1** and **2** (Figure 1 and Scheme 1)[5] utilizing excited-state intramolecular proton



Scheme 1. [3+2] Photocycloaddition approach to the cyclopenta[*b*]benzofurans.

transfer (ESIPT) of 3-HF's. Photoirradiation of **4** affords the oxidopyrylium intermediate **6** which undergoes [3+2] photocycloaddition with **5a** to provide the corresponding aglain core **7a** which was converted into methyl rocaglate (**8a**) in two steps (Scheme 1). Herein, we describe the scope of the photocycloaddition with various dipolarophiles, mechanistic and photophysical studies, and evaluation of the rocaglates produced as inhibitors of eukaryotic translation.

Although extensive photophysical studies concerning ESIPT of 3-HF derivatives have been conducted,[6] the reactivity of the resulting oxidopyrylium species (e.g., **6**) still remains largely unexplored.[7] We first examined achiral photocycloadditions between **4** and **5a** to study the role of proton transfer in the ESIPT process. We initiated an extensive screening of hydrogen-bond donors, Brønsted acids, and additives to optimize the cycloaddition of **4** and **5a** (0 °C, 12 h, $\lambda > 330$ nm to avoid photodimerization[8] of **5a**;

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see the Supporting Information). Results of additive screening indicated that trifluoroethanol (TFE) improved both the yield of the isolated cycloadduct **7a** (55%) and *endo/exo* diastereoselectivity (5:1 d.r.).[9] Protic polar solvents may facilitate proton tunneling of the 3-HF excited state (N*), thereby stabilizing and increasing the population of the oxidopyrylium phototautomers (T*) **6**/**6′** (Figure 2).[6b–e]

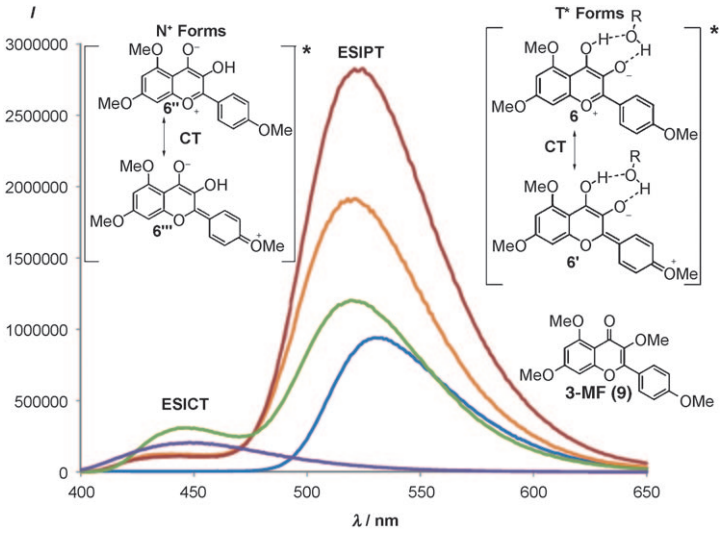


Figure 2. Fluorescence emission of 3-HF (**4**) and 3-MF (**9**) indicating both ESICT and ESIPT processes with presumed charge transfer (CT) in both excited states from phototautomers **6**/**6′** and **6″**/**6‴**. Light blue: **4** in $CHCl_3$, orange: **4** in $CHCl_3$/TFE (95:05), red: **4** in $CHCl_3$/TFE (70:30), green: **4** in TFE, purple: **9** in TFE.

Indeed, excitation of **4** in the presence of TFE resulted in a large ESIPT fluorescence emission band ($\lambda(T^*) = 530$ nm) corresponding to oxidopyrylium phototautomers **6**/**6′**. The presence of a shoulder emission band ($\lambda(N^*) = 440$ nm) may be attributed to excited-state intramolecular charge transfer (ESICT) of **4** by superposition with the emission band of the corresponding 3-methoxyflavone (3-MF; **9**; Figure 2). After excitation of **4**, the normal excited form (N*) may undergo charge transfer to stabilize the dipole moment developed through ESICT, resulting in phototautomers **6″**/**6‴** and a second λ(N*) emission.[10] Our photophysical data indicates that both excited-state phototautomers **6**/**6′** and **6″**/**6‴** generated by ESICT and ESIPT, respectively, are present upon irradiation and may be of relevance in the photocycloaddition.

Using the optimum reaction conditions ($CHCl_3$/TFE = 70:30), we next turned our attention to evaluation of over 40 dipolarophiles (**5**) for their reactivity in the [3+2] photocycloaddition. The set of dipolarophiles tested contained cinnamate derivatives modified at both termini (commercially available or readily prepared)[11] and unactivated alkenes. We were pleased to find that a broad range of dipolarophiles were workable in the photocycloadditions. Unfortunately, all β-alkylacrylate derivatives proved to be unreactive under the reaction conditions (yield < 10%), likely as a result of the lack of positive charge or radical stabilization at the β position of the α,β-unsaturated ester (see below). As the use of TFE as a cosolvent significantly increases the population of oxidopyrylium species **6**/**6′** (see Figure 2), less reactive dipolarophiles such as **5b–g** were found to participate in the photocycloaddition. Accordingly, we were able to obtain novel cycloadducts including thioester **7b**, imide **7d**, Weinreb amide **7e**, amide **7f**, and cyanide **7g** in moderate to good yields (Scheme 2). The use of electron-withdrawing groups for LUMO (lowest unoccupied molecular orbital) lowering of dipolarophiles **5b–g** appears to impact the yield of the reaction (e.g., 26% for **7d**; 59% for **7g**). Different reactivity was observed for ethyl and phenyl thioesters **5b** and **5c** (**7b** (40%) and **7c** (0%), respectively, which was in agreement with fluorescence quenching experiments; see the Supporting Information), thus indicating that steric factors may greatly influence photocycloadditions. Steric hindrance at the terminus of α,α-disubstituted dipolarophiles **5s–t** may also be responsible for their lack of reactivity in photocycloadditions (Scheme 2, see inset). In contrast, the substitution pattern of the aryl substituents (**5h–r**) appears to be very flexible. Interestingly, the *ortho* substituent present in **5j** did not lead to favorable cycloaddition, whereas the *para*-substituted dipolarophile **5k** afforded the desired aglain cycloadduct **7k** (71%). Other electronic effects for reaction partners (**5k–r**) did not affect the course of the reaction, leading to isolation of cycloadducts **8i–r**.

Comparison of dipolarophile reactivity also revealed new insights concerning the photocycloaddition diastereoselection. Unexpectedly, reaction of cinnamate **5r** bearing a free phenol gave an inverse *endo/exo* diastereoselectivity (1:2 d.r.) of rocaglate **8r**. In comparison, cinnamate **5q** lacking a free phenol led to the formation of rocaglate **8q** (2:1 d.r.) favoring the *endo* diastereomer. Interestingly, reaction of dienoate **5h** resulted in complete chemo- and regioselectivity in the [3+2] photocycloaddition for the α,β-unsaturated moiety with moderate *endo/exo* diastereoselectivity (3:1 d.r.) to afford cycloadduct **7h** (38%). Examination of the diastereoselectivity outcome of rocaglate adducts **8k–m** (from 2:1 to 5:1 to 10:1 d.r.) revealed an interesting trend for the dipolarophiles. These results suggest that electron-poor aryl substituents at the β position of the cinnamate (Figure 3, **5m**) may be involved in donor–acceptor (π-stacking) interactions[12] with the electron-rich aromatic ring of the oxidopyrylium **6** in the excited state, thereby reinforcing substrate interactions in the *endo* transi-

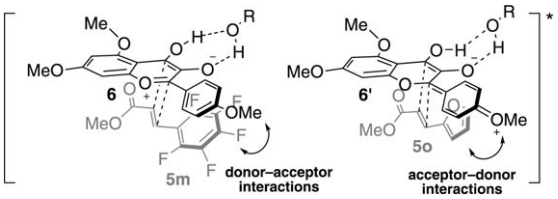
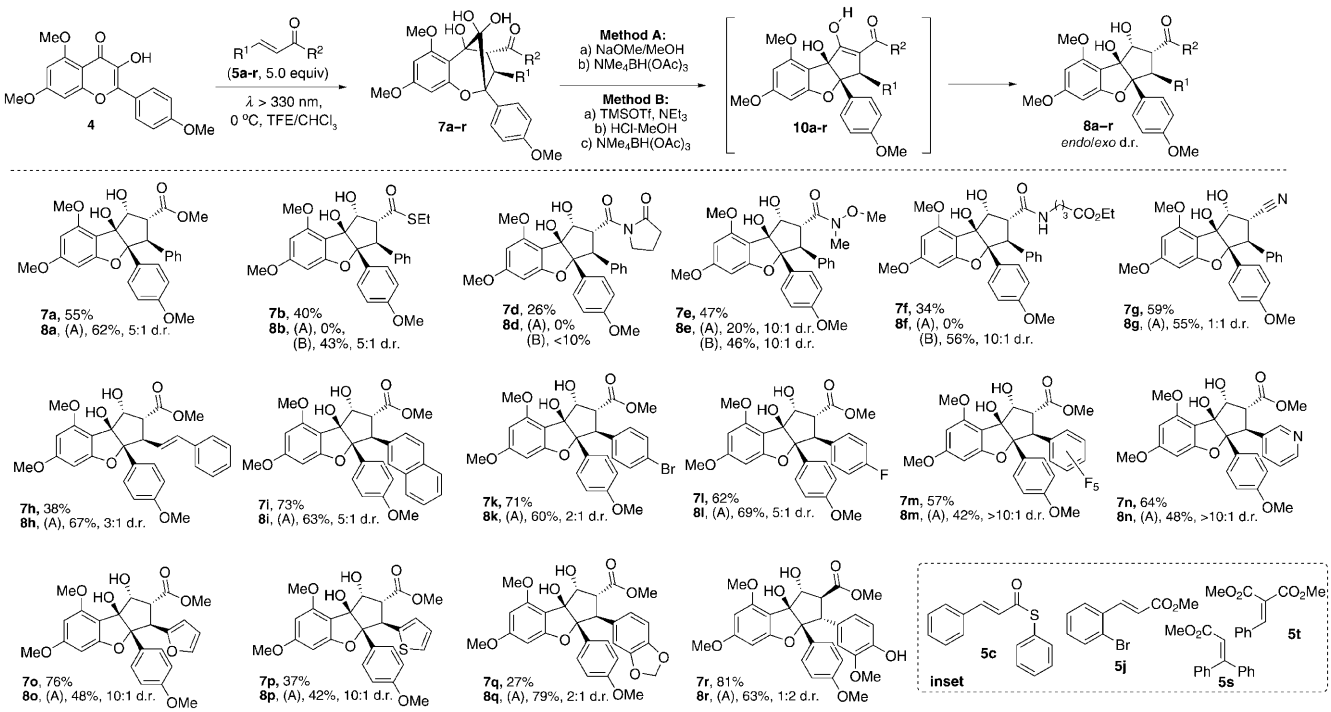


Figure 3. Proposed *endo* transition-state arrangements from phototautomers **6**/**6′** in the excited state with dipolarophiles **5m** and **5o**.



Scheme 2. Scope of the [3+2] photocycloaddition to produce aglains **7a–r** and rocaglates **8a–r** (major diastereomer shown, d.r. obtained by ^{1}H NMR). See the Supporting Information for details. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

tion state. The corresponding acceptor–donor interactions may also be considered wherein the charged delocalized oxidopyrylium phototautomer **6′** may interact with electron-rich cinnamates (Figure 3, **5o**).[12] An equilibrium between phototautomers **6** and **6′** may explain the high diastereoselectivity observed for both electron-deficient (**5l–m**, 5–10:1 d.r.) and electron-rich cinnamates (**5i**, **5o–p**, 10:1 d.r.).

During our study, aglain derivative **7a** was isolated as a solid material, encouraging us to separate the major *endo* diastereomer by crystallization.[13] Interestingly, the aglain core was found to exist preferentially as a hydrated bridgehead ketone (also observed for other aglain derivatives) which may result from double hydrogen-bond stabilization of the hydrate with the benzopyran ether oxygen atom and tertiary hydroxyl (Figure 4).[14] Such stabilization highlights the high degree of electrophilicity of the bridgehead ketone and may be of importance for additional manipulations such as stereocontrolled reduction to access aglain natural products including ponapensin **3**.[2]

All aglain cycloadducts bearing a methyl ester moiety **7h–r** were readily converted into the corresponding rearranged cyclopenta[*b,c*]benzofurans and additionally reduced to afford the desired rocaglates **8h–r** according to Method A

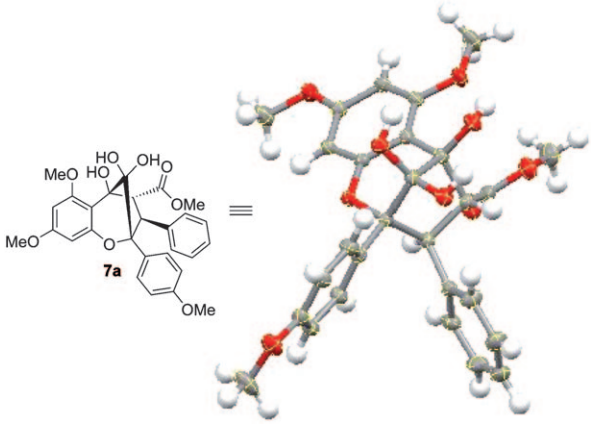
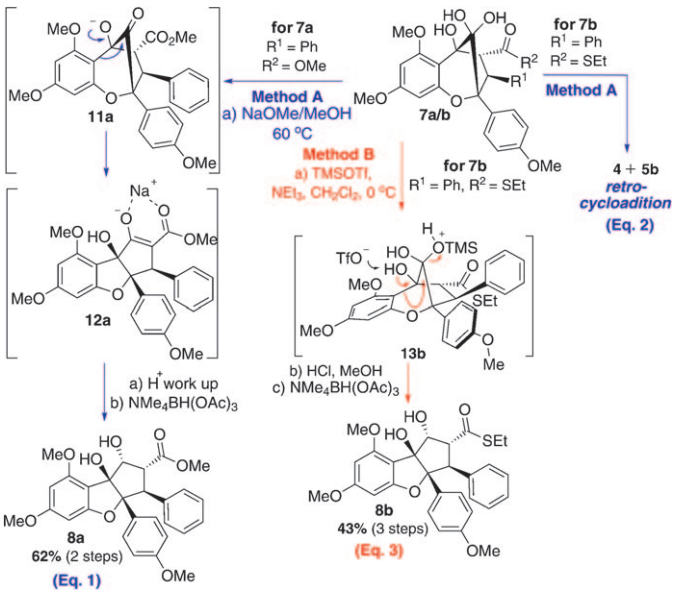


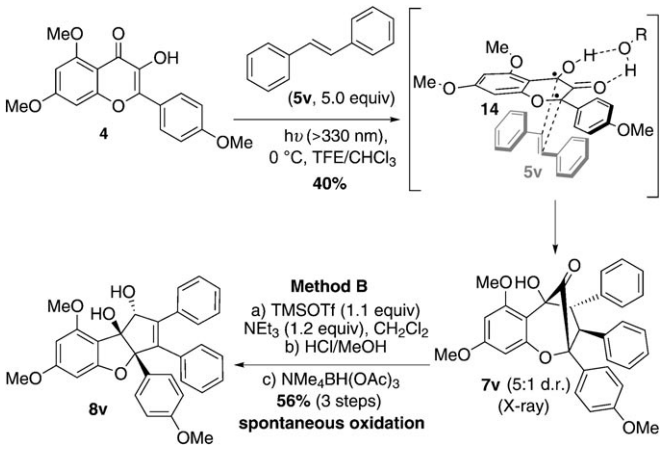
Figure 4. X-ray structure showing the hydrated form of aglain derivative **7a**.



Scheme 3. Base versus Lewis acid mediated ketol rearrangements.

(Schemes 2 and 3). As shown in Scheme 3 [Eq. (1)], alkaline conditions[5] may be used to convert aglain **7a** into alkoxide **11a** which may undergo α-ketol rearrangement to afford β-ketoester enolate **12a** prior to workup and reprotonation to afford cyclopenta[*b*]benzofuran **10a**. Further reduction produced the desired rocaglates **8a** in 62% yield (two steps). Unfortunately, upon similar treatment aglain thioester **7b**, imide **7d**, and amides **7e–f** were found to undergo retro-cycloaddition leading to regeneration of 3-HF **4** and the corresponding dipolarophiles **5b–f** [Scheme 2 and Scheme 3, Eq. (2)]. Apparently the electron-poor thioester, amide, and imide moieties of aglains **7b–f** favored retro-cycloaddition rather than the expected ketol rearrangement. Accordingly, we evaluated alternative conditions for ketol rearrangement and found that Lewis acids such as trimethylsilyltrifluoromethanesulfonate (TMSOTf) mediated the desired transformation and afforded the cyclopenta[*b*]benzofuran **8b** after protodesilylation and hydroxy-directed reduction [Scheme 2 and Scheme 3, Eq. (3)]. A Lewis acid mediated ketol shift may occur through a concerted mechanism, thereby avoiding retro-cycloaddition.[15] Hydrated ketone **7b** may be silylated by TMSOTf to afford hemiketal **13b**, which may undergo pinacol-type rearrangement[16] involving a [1,2]-aryl shift to deliver the corresponding β-ketothioester. Using the TMSOTf protocol, aglain thioester **7b**, Weinreb amide **7e**, and amide **7f** were successfully rearranged and transformed into rocaglates **8b**, **8e**, and **8f**, respectively (Scheme 2, Method B). Notably, the Weinreb amide derivative **8d** could be prepared using both methods (Scheme 2, Method A: 20% yield (two steps); Method B: 46% (three steps)). Despite our efforts, aglain imide **7d** could not be rearranged in a satisfactory manner. Finally, the aglain nitrile derivative **7g** was readily converted into the desired rocaglate **8g** by treatment under alkaline conditions and subsequent reduction (Scheme 2, Method A).

Given the effectiveness of dipolarophiles bearing β-aryl and related substituents, we next investigated *trans*-methylstyrene (**5u**) and *trans*-stilbene (**5v**) in the photocycloaddition with **4** (see the Supporting Information for details). Use of **5u** as dipolarophile afforded a complex mixture of regioisomeric and diastereoisomeric products. In contrast, when **5v** was employed in the [3+2] photocycloaddition, a clean reaction was observed providing the aglain cycloadduct **7v** in 40% yield (Scheme 4). The structure of **7v** was determined by single-crystal X-ray structure analysis and indicated the presence of a bridgehead ketone moiety.[13] The utility of stilbene as dipolarophile and our results from the overall dipolarophile screening suggest the involvement of the triplet biradicaloid[17] form of phototautomer **6** in the photocycloaddition.[18] Indeed, photocycloaddition of methyl cinnamate **5a** and **4** in the presence of the triplet quencher 9,10-dibromoanthracene did not lead to cycloadduct formation.[19] In another experiment, addition of benzophenone (triplet sensitizer, $ET = 68.8\ kcal\,mol^{-1}$) to the reaction between *trans*-stilbene (**5v**) and **4** significantly increased the yield (from 40 to 56%) of the cycloadduct **7v** (see the Supporting Information), thus supporting involvement of the photoexcited triplet biradical **14**.[20] Based on our current studies, a radical ion mechanism involving photoinduced electron transfer (PET) from the



Scheme 4. Use of stilbene **5v** as dipolarophile in the [3+2] photocycloaddition.

triplet excited state **14** to the dipolaraphile cannot be excluded.[21] Treatment of aglain **7v** under alkaline conditions (Method A) did not effect ketol rearrangement. Under TMSOTf conditions (Scheme 4, Method B), derivative **7v** smoothly rearranged to a mixture of cyclopenta-[*b,c*]benzofuran isomers and silylated products. Protodesilylation of this mixture afforded an oxidized enone product which was further reduced to rocaglate **8v**.

Having an efficient access to various rocaglate derivatives in racemic form, we evaluated their potencies as inhibitors of eukaryotic translation in comparison to enantiopure silvestrol **2**.[3b] When tested for potency in vitro, 6 out of 25 compounds showed greater than 50% inhibition of translation at 10 μM, all *endo* cycloaddition diastereomers (for a complete list of derivatives tested and % inhibition see the Supporting information). Titration of the six compounds (Figure 5a) revealed that **8e** and **8f** were the most potent inhibitors with IC_{50} values within the range of 300–400 nM. Silvestrol **2** showed an IC_{50} value of approximately 100 nM in the same experiment (Figure 5a). We further tested the potency of these analogues for their ability to inhibit protein synthesis in vivo (Figure 5b). In this case, hydroxymate **8e**[22] was the most potent analogue, inhibiting 85% of protein synthesis over the course of an hour, similar to silvestrol **2**.

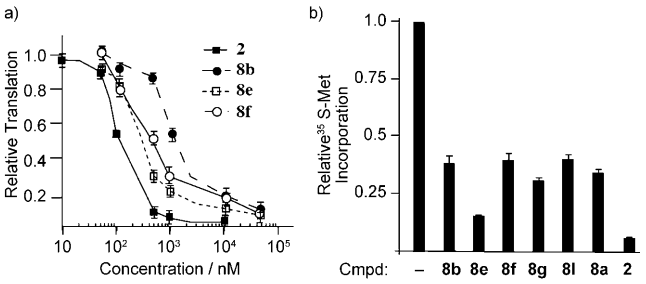


Figure 5. Evaluation of rocaglate derivatives as inhibitors of eukaryotic translation. a) Dose-dependent inhibition of in vitro translation. b) In vivo inhibition of protein synthesis in HeLa cells by rocaglate derivatives. See the Supporting Information for details.

In conclusion, we have expanded the biomimetic ESIPT photocycloaddition methodology to a broad range of dipolarophiles and additionally validated the [3+2] photocycloaddition pathway for concise access to a range of aglain and rocaglate structures. Evaluation of dipolarophiles revealed that donor–acceptor interactions of phototautomers **6**/**6′** may result in increased diastereocontrol. Our results also strongly support that photocycloadditions may proceed via a photoexcited triplet biradicaloid derived from 3-hydroxyflavone **4**. A pinacol-type rearrangement provided an alternative to the base-mediated ketol shift protocol and enabled expedient access to hitherto inaccessible rocaglate derivatives. Finally, evaluation of rocaglates as inhibitors of eukaryotic translation led to the identification of a modified rocaglate derivative with potency similar to silvestrol **2** in vitro and in vivo. Additional studies regarding ESIPT-mediated photocycloadditions and applications to complex molecule synthesis are currently in progress and will be reported in due course.

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[13] CCDC 775793 (**7a**) and 775792 (**7v**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for complete experimental details.

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