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

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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*]benzofuran natural products possess potent anticancer properties due to 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] Due to 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 reported a biomimetic approach to 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 transfer (ESIPT) of 3-HF's. Photoirradiation of **4** affords the oxidopyrylium intermediate **6** which undergoes [3+2] photocycloaddition with methyl cinnamate **5a** to provide the corresponding aglain core **7a**, which was converted to methyl rocaglate **8a** in two steps (Scheme 1). Herein, we describe the scope of the photocycloaddition with various

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Dedicated to the memory of Pierre Potier and Christian Marazano for their outstanding contributions in biomimetic synthesis

dipolarophiles, mechanistic and photophysical studies, and evaluation of the rocaglates produced as inhibitors of eukaryotic protein 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 3-HF **4** and methyl cinnamate **5a** in order to study the role of proton transfer in the ESIPT process. We initiated an extensive screening of H-bond donors, Brønsted acids and additives to optimize the cycloaddition of 3-HF **4** and methyl cinnamate **5a** (0 °C, 12 h, $\lambda > 330$ nm to avoid photodimerization[8] of **5a**).[9] Results of additive screening indicated that trifluoroethanol (TFE) improved both the isolated yield of cycloadduct **7a** (55%) and *endo-exo* diastereoselectivity (5:1 dr).[9,10] 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] Indeed, excitation of 3-HF **4** in the presence of TFE resulted in a large ESIPT fluorescence emission band (λ (T*) = 530 nm) corresponding to oxidopyrylium phototautomers **6**/**6′**.[9] The presence of a shoulder emission band (λ (N*) = 440 nm) may be attributed to excited state intramolecular charge transfer (ESICT) of 3-HF **4** by superposition with the emission band of the corresponding 3-methoxyflavone **9** (Figure 2).[9] After excitation of 3-HF **4**, the normal excited form (N*) may undergo charge transfer to stabilize the accumulated dipole moment through ESICT resulting in phototautomers **6″**/**6‴** and a second λ(N*) emission.[11] Our photophysical data indicates that both excited state phototautomers **6**/**6′** and **6″**/**6‴** generated *via* 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 an evaluation of over 40 dipolarophiles **5** for their reactivity in the [3+2] photocycloaddition.[9] The set of dipolarophiles tested contained cinnamate derivatives modified at both termini (commercially available or readily prepared) and unactivated alkenes. We were pleased to find that a broad range of dipolarophiles were workable in photocycloadditions. Unfortunately, all β–alkylacrylate derivatives[9] proved to be unreactive under the reaction conditions (yield <10%), likely due to the lack of positive charge or radical stabilization at the β-position of the α,β-unsaturated ester (*vide infra*). As the use of TFE as cosolvent significantly increases the population of oxidopyrylium species **6**/**6′** (*cf.* 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). Use of electron withdrawing groups for LUMO 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** (40% and 0% yield, **7b**/**7c** respectively, which was in agreement with fluorescence quenching experiments[9]) 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*). On the other hand, 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 photocycloaddition diastereoselection. Unexpectedly, reaction of cinnamate **5r** bearing a free phenol gave an inverse *endo-exo* diastereoselectivity (1:2 dr) of rocaglate **8r**. In

comparison, cinnamate **5q** lacking a free phenol led to the formation of rocaglate **8q** (2:1 dr) 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 dr) affording cycloadduct **7h** (38%). Examination of the diastereoselectivity outcome of rocaglate adducts **8k–m** (from 2:1 to 5:1 to 10:1 dr) revealed an interesting trend for the dipolarophiles. These results suggest that electron poor aryl substituents at the *β*-position of the cinnamate (*cf.* Figure 3, **5m**) may be involved in donor-acceptor (**π**-stacking) interactions[13] with the electron rich aromatic ring of the oxidopyrylium **6** in the excited state, thereby reinforcing substrate interactions in the *endo* transition state. The corresponding acceptor-donor interactions may also be considered wherein the charged delocalized oxidopyrylium phototautomer **6′** may interact with electron rich cinnamates (*cf.* Figure 3, **5o**).[13] An equilibrium between phototautomers **6** and **6′** may explain the high diastereoselectivity observed for both electron-deficient (**5l–m**, 5–10:1 dr) and electron-rich cinnamates (**5i**, **5o–p**, 10:1 dr).

During our study, aglain derivative **7a** was isolated as a solid material, encouraging us to separate the major *endo*-diastereomer by crystallization. Interestingly, the aglain core was found to exist preferentially as a hydrated bridgehead ketone (also observed for other aglain derivatives[9]) which may result from double hydrogen bond stabilization of the hydrate with the benzopyran ether oxygen and α-hydroxyl moieties (Figure 4).[14] Such stabilization highlights the high degree of electrophilicity of the bridgehead ketone and may be of importance for the further manipulation 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 to the corresponding rearranged cyclopenta[*b,c*]benzofurans and further reduced to afford the desired rocaglates **8h–r** accordingly to Method A (Schemes 2 and 3). As shown in Scheme 3 (Method A, Eq.1), alkaline conditions[5] may be used to convert aglain **7a** to 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** (Schemes 2 and 3, Method A, Eq. 2). Apparently the electron poor thioester, amide, and imide moieties of aglains **7b–f** favored retro-cycloaddition rather than the expected ketol-shift 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 hydroxyl-directed reduction (43% yield, three steps, Scheme 2 and 3, Method B, Eq. 3). Lewis acid-mediated ketol shift may occur through a concerted mechanism thus 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** (Scheme 2, Method B). Notably, the Weinreb amide derivative **8d** could be prepared using both methods (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 to the desired rocaglate **8g** under alkaline conditions followed by reduction (Method A, 55% yield, 1:1 dr).

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 3-

HF **4**.[9] Use of styrene **5u** as dipolarophile afforded a complex mixture of regioisomeric and diastereoisomeric products. On the other hand, when *trans*-stilbene **5v** was employed in the [3+2] photocycloaddition, a clean reaction was observed and furnished the aglain cycloadduct **7v** in 40% yield (5:1 dr) (Scheme 4). The structure of **7v** was determined by single x-ray crystal structure analysis and indicated the presence of a bridgehead ketone moiety.[9] 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 3-HF **4** in the presence of the triplet quencher 9,10-dibromoanthracene did not lead to cycloadduct formation.[9,20] In another experiment, addition of benzophenone (triplet sensitizer, ET = 68.8 kcal/mol) to the reaction between *trans*-stilbene **5v** and 3-HF **4** significantly increased the yield (from 40 to 56%) of the cycloadduct **7v**[9] which supports involvement of the photoexcited triplet **14**.[21] Based on our current studies, a radical ion mechanism involving photoinduced electron transfer (PET) from triplet excited state **14** to the dipolaraphile cannot be excluded.[19] Treatment of aglain **7v** under alkaline conditions (Method A) did not effect ketol rearrangement. Under TMSOTf conditions (Method B), derivative **7v** smoothly rearranged to a mixture of cyclopenta[*b,c*]benzofuran isomers and silylated products (*vide infra*). Protodesylilation of this mixture afforded an oxidized enone product which was further reduced to rocaglate **8v** (56% yield, three steps).

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 >50% inhibition of protein translation at 10 μM, all *endo* cycloaddition diastereomers (for a complete list of derivatives tested and % inhibition see Supporting information).[9] Titration of the six compounds (Figure 5A)[9] revealed that **8e** and **8f** were the most potent inhibitors with IC_{50}'s of 300–400 nM. Silvestrol **2** showed an IC_{50} of approximately 100 nM in the same experiment (Figure 5A). We further tested the potency of these analogues *in vivo* for their ability to inhibit protein synthesis (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**.

In conclusion, we have expanded the biomimetic ESIPT photocycloaddition methodology to a broad range of dipolarophiles and further 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-HF **4**. A pinacol-type rearrangement provided an alternative to the base-mediated ketol shift protocol and enabled expedient access to hitherto inaccesible 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*. Further studies regarding ESIPT-mediated photocycloadditions and applications to complex molecule synthesis are currently in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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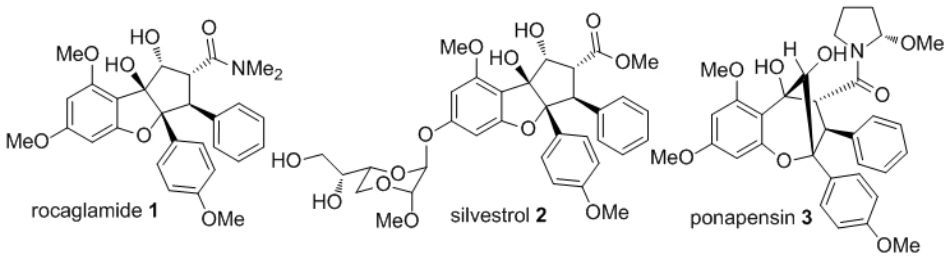


Figure 1.
Representative aglain and rocaglate metabolites from *Aglaia*

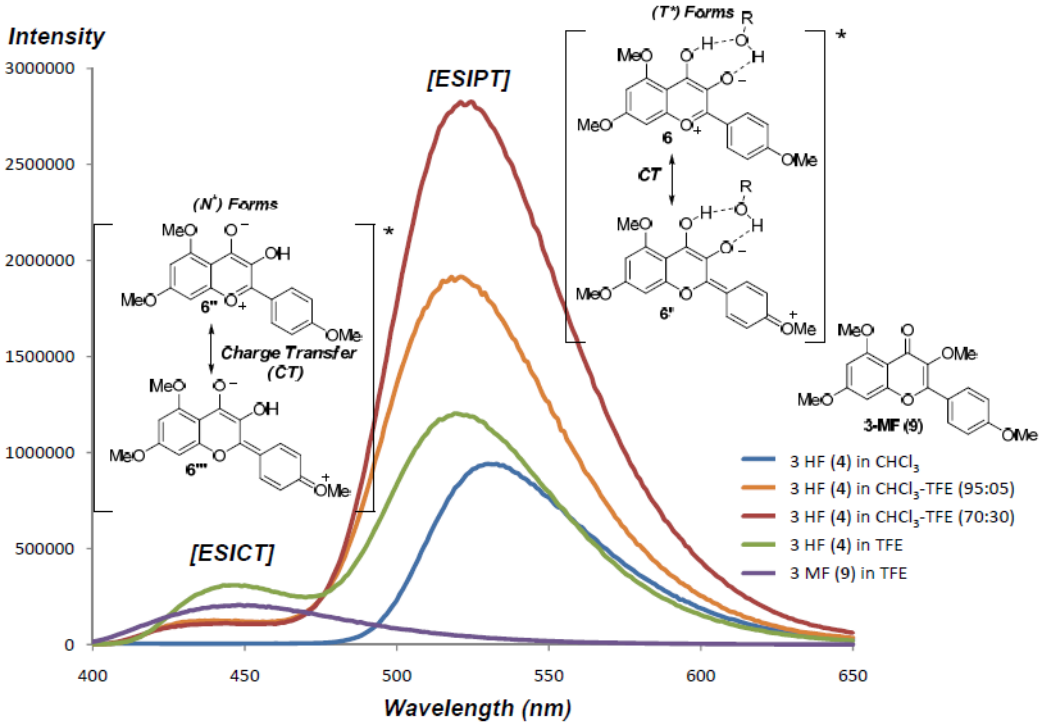


Figure 2.

Fluorescence mission of 3-HF **4** and 3-MF **9** indicating both ESICT and ESIPT processes with presumed charge transfer in both excited states from phototautomers **6/6′** and **6″/6‴.**

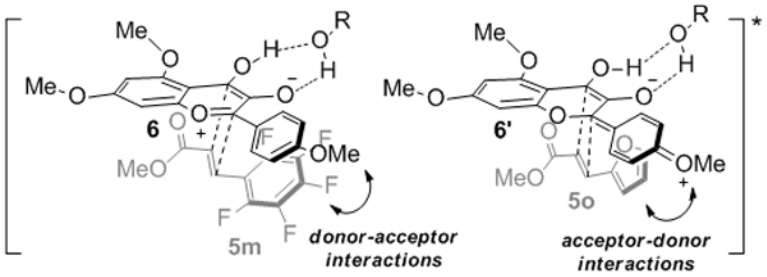


Figure 3.

Proposed *endo* transition state arrangements from phototautomers **6/6′** in the excited state with dipolarophilese **5m** and **5o**

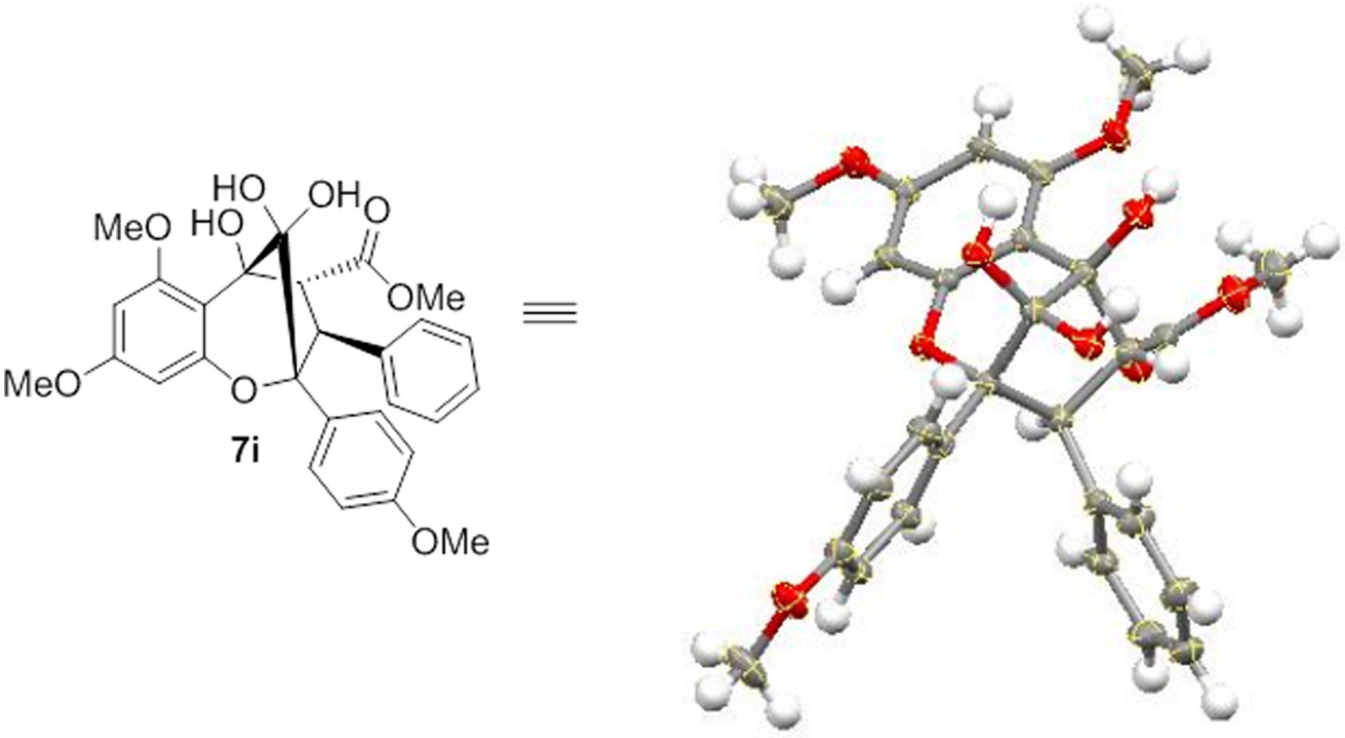


Figure 4.
X-ray structure showing the hydrated form of the aglain derivative **7a**

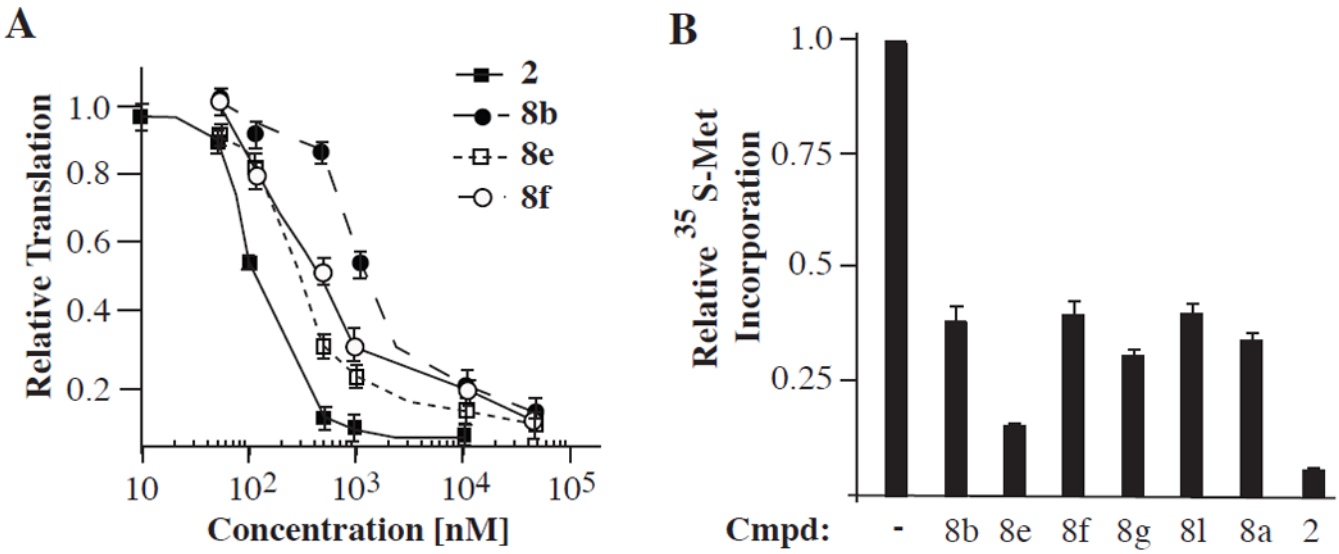
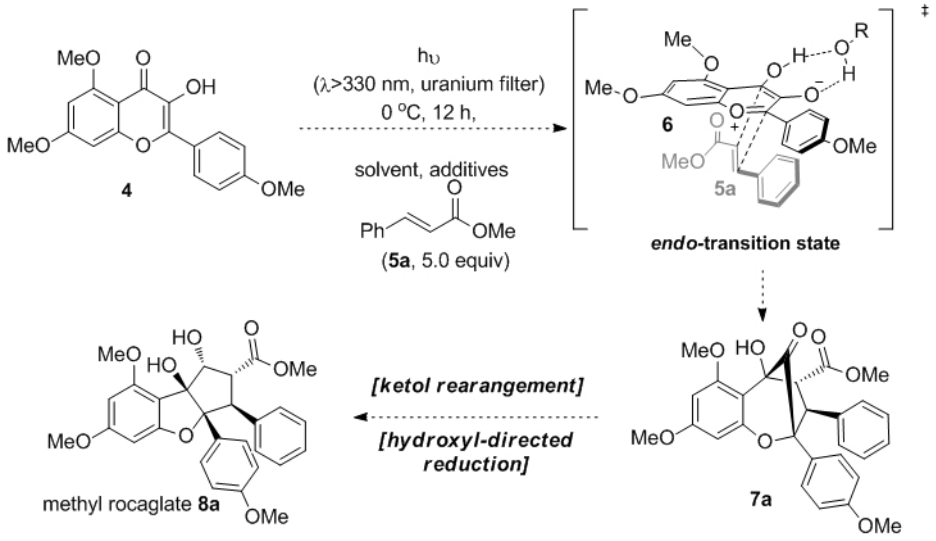
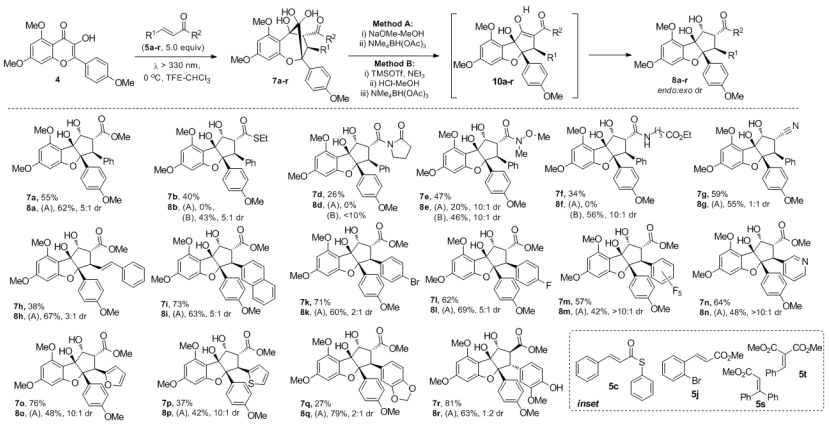


Figure 5.

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.[9]

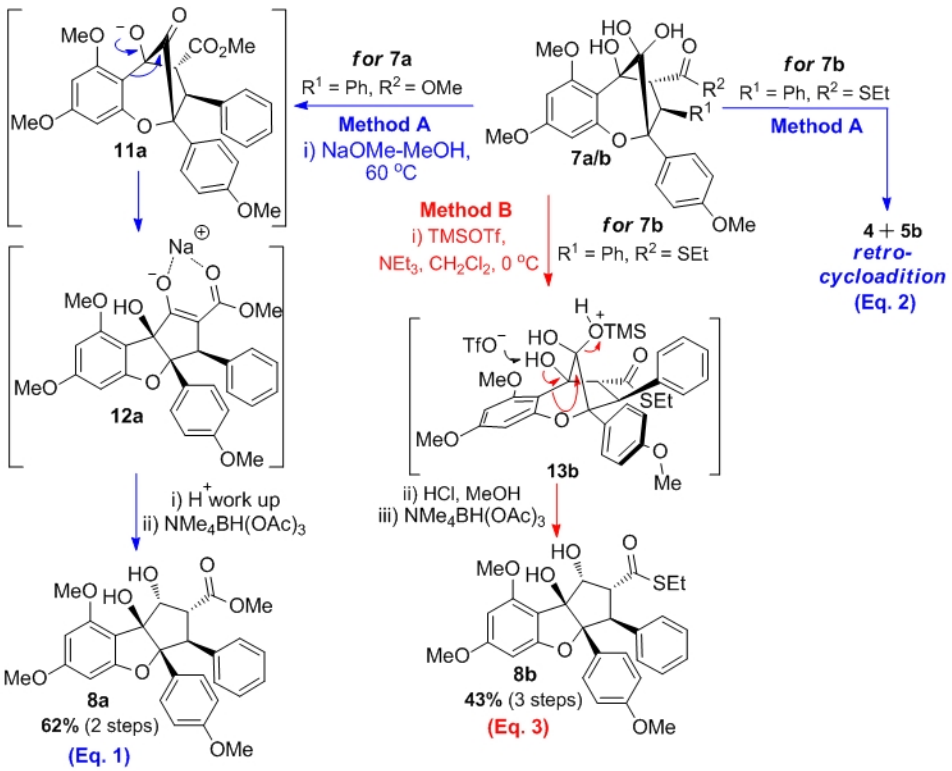


Scheme 1.
[3+2] Photocycloaddition approach to the cyclopenta[*b*]benzofurans

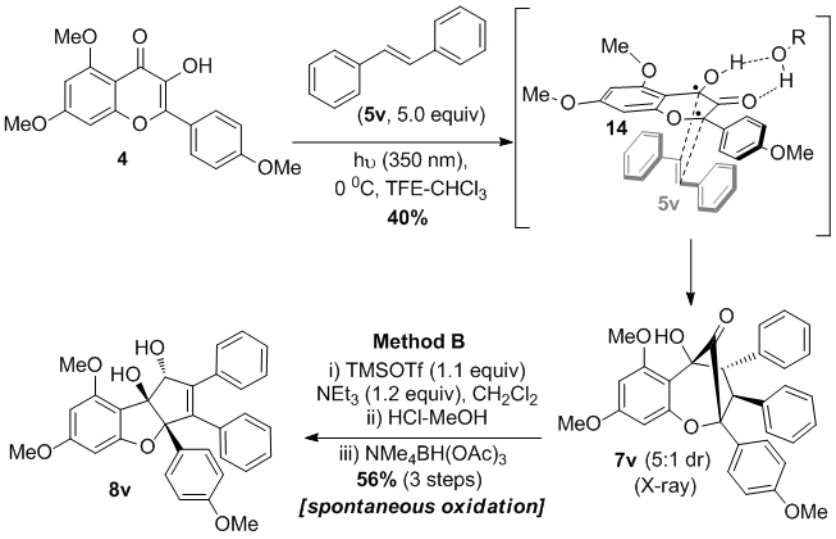


Scheme 2.

Scope of the [3+2] photocycloaddition to produce aglains **7a–r** and rocaglates **8a–r** (*major diastereomer shown, dr obtained by* ^{1}*H NMR integration*)



Scheme 3.
Basic *vs.* Lewis acid-mediated ketol rearrangements.



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