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REVIEW

Rocaglamide, Silvestrol and Structurally Related Bioactive Compounds from *Aglaia* Species

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Investigations on the chemistry and biology of rocaglamide, silvestrol and structurally related bioactive compounds from *Aglaia* species during the period 2006-2013 are reviewed. Included are new phytochemical studies of naturally occurring rocaglamide derivatives, an update on synthetic methods for cyclopenta[*b*]benzofurans, and a description of the recent biological evaluation and mechanism-of-action studies on compounds of this type.

1 Introduction

Aglaia Lour. is the largest genus of the angiosperm plant family Meliaceae, which contains more than 120 species and is distributed mainly in the tropical and sub-tropical rainforest areas of southeast Asia and the Pacific region.[1,2] Besides the well-known insecticidal properties ascribed to *Aglaia* plants, members of this genus provide useful timber for building purposes and edible fruits as local food sources, as well as scented flowers for ornamental purposes and fragrance components. In addition, certain *Aglaia* species have been used as traditional medicines for the treatment of fever, cough, diarrhea, inflammation, and contused wounds.[1-4] *Aglaia* species have attracted considerable interest in the area of natural products-based drug discovery in past two decades, since they are a rich source of the cyclopenta[*b*]benzofuran or "flavagline" class of bioactive agents, which are found exclusively in *Aglaia* species, and their presence is considered to be a major chemotaxonomic characteristic.[5-8] Since the 1982 discovery by King et al. of rocaglamide (**1**), the first member of the cyclopenta[*b*]benzofuran class from *A. elliptifolia*,[9] more than 100 naturally occurring derivatives of rocaglamide have been isolated and their structures characterized from over 30 *Aglaia* species.[5-8] Among these taxa, ten species comprising *Aglaia argentea*, *A. cordata*, *A. duperreana*, *A. edulis*, *A. elliptica*, *A. elliptifolia*, *A. foveolata*, *A. odorata, A. oligophylla* and *A. silvestris* are the most extensively investigated for their phytochemistry.[5-8] Seven species, *Aglaia crassinervia*,[10] *A. edulis*,[11] *A. elliptica*,[12,13] *A. foveolata*,[14-16] *A. perviridis*,[17] *A. ponapensis*,[18] and *A. rubiginosa*,[19] mainly collected from Indonesia, have been investigated previously as promising candidate plants in our laboratories in a search for new potential anticancer analogues.

The skeletal structures of the rocaglamide derivatives include a flavonoid unit and a cinnamic acid amide moiety. For their postulated biogenetic origin, it has been suggested that the cycloaddition of a flavonoid nucleus and a cinnamic acid amide moiety leads to the formation of a cyclopenta[*bc*]benzopyran ring system, which is considered to be the key intermediate in the biosynthesis process.[20-24] Thus, through rearrangements, including the opening of C-5a and C-5 bond and connection of C-5a with C-10, the cyclopenta[*bc*]benzopyran ring can convert to a cyclopenta[*b*]benzofuran ring.[22,23] In addition, benzo[*b*]oxepine derivatives can be formed from cyclopenta[*bc*]benzopyrans by oxidative cleavage of the methylene bridge between C-5 and C-10.[22,23] Accordingly, the rocaglamide derivatives have been grouped previously into three subclasses based on their core structures: (i)

cyclopenta[*b*]benzofurans (also known as "flavagline" or "rocaglate" derivatives); (ii) cyclopenta[*bc*]benzopyrans (also known as "thapsakins"; and (iii) benzo[*b*]oxepines (also known as "thapoxepines").[22,23] Rocaglamide derivatives have attracted growing attention because of their interesting biological activities.[e.g., 25-29] In particular, the cyclopenta[*b*]benzofurans have potential anticancer activity, and two compounds of this type have been studied the most in this regard. Rocaglamide (**1**) and silvestrol (**2**) were found to show antiproliferative activity against various human cancer cell lines at nanomolar concentrations, and both have been reported to exhibit efficacy *in vivo* in tumor-bearing experimental animal models.[5-9,14] Due to the unique chemical structures and their fascinating biological activities, cyclopenta[*b*]benzofurans have continued to attract great interest in terms of their phytochemical occurrence, methods of synthesis, *in vitro* and *in vivo* biological evaluation, structure-activity-relationships, and determination of their mechanism of action. The present review will focus on the most recent advances in these areas.

2 Newly isolated rocaglamide derivatives since 2006

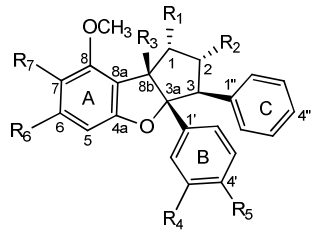
In an earlier review published by our group, all natural occurring rocaglamide derivatives isolated from the genus *Aglaia* up to 2006 were described.[6] This update summarizes new phytochemical reports of naturally derived compounds of this type made during the period 2006-2013, and mentions the *in vitro* biological activity for each compound, if reported.

2.1 Cyclopenta[*b*]benzofurans

All known naturally occurring cyclopenta[*bc*]benzopyran derivatives elucidated structurally thus far show variations in the cyclopentane moiety at C-1, C-2, and C-8b, as well as in the phenyl rings A and B. The substituent groups on C-1 are usually found to be hydroxy and acetoxy groups, with aldehyde, oxo, and oxime groups being less common. The substituent located on C-2 is typically a methyl ester, carboxyl group, or a simple amide or diamide residue. Rocaglamide derivatives with C-1 and C-2 fused by a pyrimidinone unit were also isolated from several different *Aglaia* species. Hydroxy, methoxy and ethoxy groups are the known substituent groups found at the ring junction carbon C-8b. Thus far, no natural occurring epimers have been found at the chiral carbons, C-2, C-3 and C-8b. For the phenyl rings A and B, hydroxy, methoxy and dioxymethylene groups have been found to be the most common substituents.[6,7] 3′-Glucosyl-rocaglaol and 3′-(2-acetoxy-3-methoxyrhamnosyl)-rocaglaol, with a monosaccharide unit located on the *meta* position of ring B, are the only two naturally occurring rocaglaol glycosides reported so far.[24,30] Silvestrol (**2**), with an unprecedented dioxanyloxy unit attached to the phenyl ring A, represents a significant structural variation in this compound class.[14]

From the first isolation of rocaglamide in 1982, to 2006, over 60 naturally derived cyclopenta[*b*]benzofurans were reported.[6,7] During the last seven years, ten new rocaglamide analogues of this sub-type were obtained and identified from four *Aglaia* species, with their structures shown in Figures 1 and 2.

In 2006, Chumkaew and colleagues documented two new compounds, 1-*O*-formylrocagloic acid (**3**) and 3′-hydroxyrocagloic acid (**4**), along with five known rocaglaol derivatives, from the hexane and dichloromethane extracts of the fruits of *Aglaia cucullata* collected in Thailand.[31] When compared with the ^{1}H NMR spectrum of rocagloic acid, besides a singlet ascribed to the formyl group that appeared at δ_H 7.95, a downfield shift of approximately 1.3 ppm for H-1 was observed due to the hydroxy group at C-1 of rocagloic acid being substituted by an aldehyde group in compound **3**. The CD curve of **3** was found to be quite comparable with that of rocaglamide, with a characteristic absorption at 274 nm. Thus, the absolute configuration of **3** was determined as 1*R*, 2*R*, 3*S*, 3a*R*, 8b*S*, the same as other known rocaglate derivatives. In compound **4**, with a hydroxy group located at C-3′, the AA′BB′ spin system of the phenyl ring B in rocagloic acid was replaced by an ABX spin system, which was deduced by studying the ^{1}H NMR spectroscopic coupling pattern of the aromatic proton signals belonging to the phenyl ring. Compounds **3** and **4** showed cytotoxic activities against the HeLa (human cervical carcinoma) and BC (human breast cancer) cell lines, against which rocagloic acid was found to be inactive. The



1	R_1 = OH	R_2 = $CON(CH_3)_2$	R_3 = OH	R_4 = H	R_5 = OCH_3	R_6 = OCH_3	R_7 = H
3	R_1 = OCHO	R_2 = COOH	R_3 = OH	R_4 = H	R_5 = OCH_3	R_6 = OCH_3	R_7 = H
4	R_1 = OH	R_2 = COOH	R_3 = OH	R_4 = OH	R_5 = OCH_3	R_6 = OCH_3	R_7 = H
5	R_1 = OH	R_2 = $CONHCH_3$	R_3 = OCH_3	R_4 = H	R_5 = OCH_3	R_6 = OCH_3	R_7 = H
6	R_1 = OH	R_2 = $CON(CH_3)_2$	R_3 = OCH_3	R_4 = OH	R_5 = OCH_3	R_6 = OCH_3	R_7 = H
7	R_1 = OH	R_2 = H	R_3 = OCH_3	R_4,R_5 = OCH_2O		R_6 = OCH_3	R_7 = H
8	R_1 = OH	R_2 = $COOCH_3$	R_3 = OCH_3	R_4,R_5 = OCH_2O		R_6 = OCH_3	R_7 = H
9	R_1 = OAc	R_2 = $CON(CH_3)_2$	R_3 = OH	R_4 = H	R_5 = OCH_3	R_6,R_7 = OCH_2O	
10	R_1 = OAc	R_2 = $CON(CH_3)_2$	R_3 = OH	R_4 = OCH_3	R_5 = OCH_3	R_6,R_7 = OCH_2O	

Figure 1. Structures of rocaglamide (**1**) and new natural occurring cyclopenta[*b*]benzofuran derivatives (**3**-**10**) isolated during the period 2006-2013 from species in the plant genus *Aglaia*.

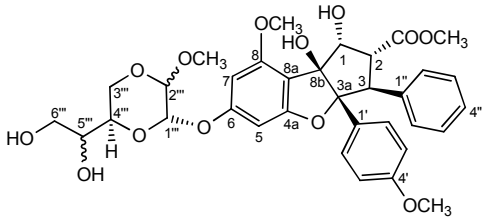
substitution by a formyl group at C-1 in compound **3** resulted in a dramatic (more than 500-fold) decrease of activity for the NCI-H187 (human small cell lung cancer) cell line, while an OH group substitution on C-3′ in compound **4** resulted in a greater than ten-fold increase in activity, when compared with rocagloic acid using this same bioassay.

Aglaia odorata var. *microphyllina*, a species cultivated in the south of mainland China, was found recently to be a new plant source of rocaglamides.[32] Two new rocaglamide derivatives, 8b-methoxy-desmethylrocaglamide (**5**) and 3′-hydroxy-8b-methoxyrocaglamide (**6**), were isolated by Liu et al. from the twigs of this plant.[32] The substitution of a hydroxy group with a methoxy group on C-8b led to a downfield shift of around 7 ppm for the ^{13}C NMR signal of C-8b. The corresponding proton signal of the methoxy group was recognized at around δ_H 2.4 ppm as a singlet. Neither **5** nor **6** was found to be active (IC_{50} < 10 μg/mL) against the K562 human myeloid leukemia cell line utilized in this investigation.[32]

Two other 8b-methoxy-substituted rocaglaol derivatives, 8b-*O*-methyl-4′-demethoxy-3′,4′-methylenedioxyrocaglaol (**7**) and 8b-*O*-methyl-4′-demethoxy-3′,4′-methylenedioxy methyl rocaglate (**8**), were isolated from various plant parts of *Aglaia perviridis* collected in Vietnam.[17] The new compounds **7** and **8**, were found to be much less potently cytotoxic against HT-29 human colon cancer cells when compared with other rocaglaol analogues with a free hydroxy group on C-8b, consistent with earlier observations.[17,33]

Aglaroxin A 1-*O*-acetate (**9**) and 3′-methoxyaglaroxin A 1-*O*-acetate (**10**) were isolated by Kim et al. from the bark of *Aglaia edulis* collected in Indonesia through a bioassay-guided purification procedure.[11] When comparing the structure of **9** with rocaglamide, the free hydroxy group at C-1 was found to be substituted by an acetate group, and instead of having a methoxy group at C-6, a methylenedioxy group is located at C-6 and C-7 of the phenyl ring A. In comparison with compound **9**, compound **10** possesses an extra hydroxy group at C-3′ on the phenyl ring B. Compounds **9** and **10**, together with the known rocaglamide, aglaroxin A, were shown to be cytotoxic against a small panel of human cancer cell lines. Compound **9** showed more potent growth inhibitory effects against several of these cell lines when compared with aglaroxin A, while compound **10** was less active when evaluated against the same cell lines. Aglaroxin A 1-*O*-acetate (**9**) was further evaluated in an *in vivo* P388 lymphocytic leukemia model, using intraperitoneal administration, but was found to be inactive at the doses used.

When silvestrol (**2**) and 5‴-*epi*-silvestrol (**11**) were reported in 2004, it was established that the presence of the 1,4-dioxanyloxy ring greatly enhances the resultant cytotoxicity when compared with rocaglate analogues lacking this moiety. In 2010, a large-scale recollection of the stem bark of *Aglaia foveolata* from Indonesia was reported, which was carried out in order for the scale-up isolation of silvestrol (**2**) to be conducted at the gram level, so that more extensive biological testing could be performed on this compound. This re-isolation work led also to the purification of two new minor analogues of silvestrol, 2‴-*epi*-silvestrol (**12**) and 2‴,5‴-*diepi*-silvestrol (**13**) (Figure 2).[16] In **12** and **13**, the methoxy group at C-2‴ on the 1,4-dioxanyloxy ring adopts an α-equatorial orientation, rather than a β-axial orientation as in silvestrol (**2**) and 5‴-*epi*-silvestrol (**11**).[14] By comparison of the ^{1}H NMR data of the new analogues **12** and **13** versus their parent compounds, the major differences were focused on the 1,4-dioxanyloxy ring. An obvious downfield shift of the proton signal of the methoxy group at C-2‴ from δ_H 3.48 to δ_H 3.63 was observed. Moreover, subtle differences were also detected for these protons proximate to C-2‴. In the ^{13}C NMR spectrum, due to the absence of a cis-γ substitution effect of the methoxy group on C-2‴ to H-3‴, a corresponding downfield shift of approximately 7.5 ppm of the carbon signal of C-3‴ was observed. In the initial biological testing conducted on compounds **12** and **13**, their cytotoxicity against HT-29 cells decreased dramatically when compared with both silvestrol (**2**) and 5‴-*epi*-silvestrol (**11**).[16] In 2012, Rizzacasa et al. confirmed the structure of 2‴,5‴-di*epi*-silvestrol (**13**) by conducting a total synthesis of this compound using a biogenesis-based approach.[34] In an *in vitro* protein synthesis inhibitory assay conducted in a rabbit reticulocyte lysate system, the synthesized **13** was also found to be much less active than 5‴-episilvestrol (**11**).[16] These observations demonstrate that the configuration of C-2‴ in the 1,4-dioxanyloxy unit of silvestrol analogues plays an important role in mediating biological activity among these compounds. Silvestrol appears to be a very rare compound in the genus *Aglaia*, but, in addition to its initial isolation from *A. foveolata*,[14-16] this compound has been reported as a constituent of the Malaysian plant, *Aglaia leptantha*[35] (later reidentified as *A. stellatopilosa*).[36]



2 (2‴*S*, 5‴*R*)
11 (2‴*S*, 5‴*S*)
12 (2‴*R*, 5‴*R*)
13 (2‴*R*, 5‴*S*)

Figure 2. Structures of silvestrol and three naturally occurring analogues (**2**, **11-13**).

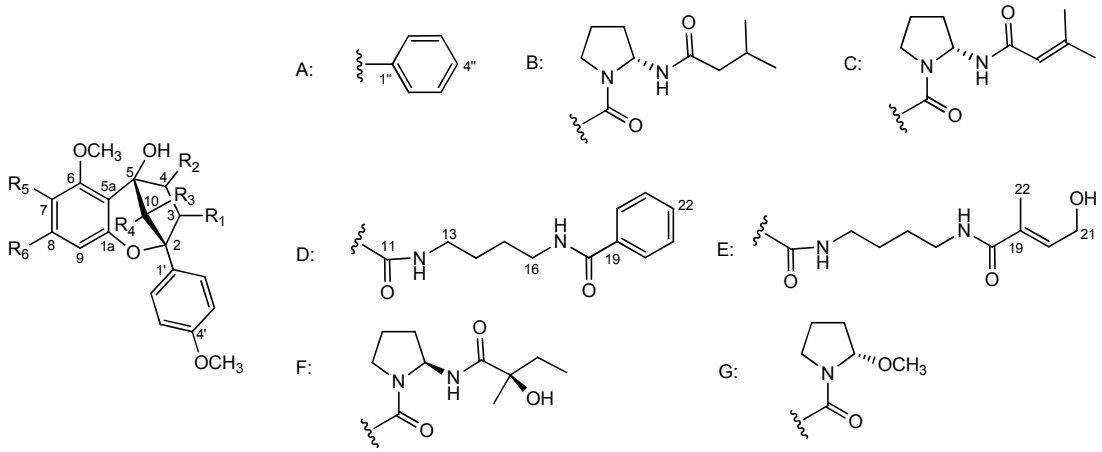
2.2 Cyclopenta[*bc*]benzopyrans and benzo[*b*]oxepines

As mentioned previously, cyclopenta[*bc*]benzopyrans are considered to be biosynthetic precursors of the structurally related cyclopenta[*b*]benzofurans and cyclopenta[*b*]oxepines. During the cycloaddition reaction between a cinnamoyl moiety and a flavonoid nucleus, important building blocks of cyclic or open-chained cinnamoyl bisamides isolated from *Aglaia* species, such as aglairubine, aglamide C, odorine, odorinol, piriferine, or pyramidatine, as well as the cinnamoyl amide-alcohol derived moieties such as aglamide D, are incorporated into a benzopyran unit. This maintains the cyclopenta[*bc*]benzopyran overall skeleton and permits the introduction of a varied substitution pattern at C-3 and C-4.[20-24,37] Besides similar substitution patterns on the phenyl rings A and B as those occurring in cyclopenta[*b*]benzofurans, the phenyl ring C and the bisamide chain in cyclopenta[*bc*]benzopyrans can be located either at C-3 or C-4, with both configurations possible. On the bridge carbon, C-10, in addition to the commonly non-stereoselective substitutions of a free hydroxy group or acetoxy group, two derivatives with a glucosyl group were also reported.[38] Overall, cyclopenta[*bc*]benzopyrans exhibit a greater degree of structural variation potential than cyclopenta[*b*]benzofurans. From 2006 to the end of 2013, a total of 16 new cyclopenta[*bc*]benzopyrans have been reported from five different *Aglaia* species (Figure 3).

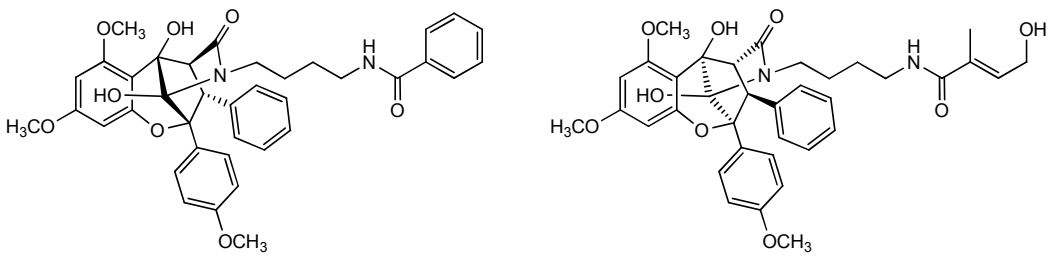
Besides the two new cyclopenta[*bc*]benzopyrans, **9** and **10**, five new cyclopenta[*bc*]benzopyrans, edulirin A (**14**), edulirin A 10-*O*-acetate (**15**), 19,20-dehydroedulirin A (**16**), isoedulirin A (**17**), and edulirin B (**18**), were also isolated from the bark of *Aglaia edulis* by Kim et al.[11] Compounds **14-16** possess an aglamide C- or dehydroaglamide C-derived pyrrolidine-type bisamide group at C-4. The relative configurations of C-3, C-4 and C-10 of compounds **14-16** were deduced based on the analysis of NOESY NMR spectra. In

addition, the observed vicinal coupling constant of around 9.5 Hz between H-3 and H-4 was also consistent with the H-3α and H-4β configurations ascribed to this type of compound. Isoedulirin A (**17**) and edulirin B (**18**) were also found to have the aglamide C-derived bisamide group. However, HMBC correlation analysis indicated that the substituents at C-3 and C-4 were mutually exchanged in these two compounds. The observed coupling constant between H-3 and H-4 for compound **17** was 7.0 Hz, which implied a H-3β and H-4α configuration, different from compounds **14**-**16**. Compound **18** is a 3,4-di-epimer of **17**, and its structure was deduced by NOESY experiments. This was confirmed by the large coupling constant of 10.5 Hz between H-3 and H-4, as well as the high-field shift of nearly 1.0 ppm observed for the proton signals of the methoxy group on C-6 due to the shielding effect from an α-oriented phenyl group on C-4. None of compounds **14**-**18** was found to be active against a small panel of human cancer cell lines, consistent with the generally lesser bioactive potency of the cyclopenta[*bc*]benzopyrans when compared with the cyclopenta[*bc*]benzopyrans.[6,11]

In 2007, Salim et al. isolated four cyclopenta[*bc*]benzopyrans, including foveoglin A (**19**), foveoglin B (**20**), isofoveoglin (**21**) and cyclofoveoglin (**22**), from the leaves and bark of the silvestrol-rich plant, *Aglaia foveolata*.[15] Pyramidatine, which also was isolated in this study, might be a general biosynthetic building block for flavaglines **19**-**22**. Foveoglins A (**19**) and B (**20**) both have a benzoyl-1,4-butanediamide moiety at C-3 and a phenyl ring substituted at C-4, and adopt the H-3α and H-4β configurations. The only difference between these two structures is the configuration of C-10. In foveoglin A (**19**), the hydroxy group on C-10 has an *exo* relationship with H-4, while in foveoglin B (**20**), the hydroxy group is located at an *endo* position to H-4. Isofoveoglin (**21**) is a di-epimer



14	R_1 = β-A	R_2 = α-B	R_3 = OH	R_4 = H	R_5,R_6 = OCH_2O	
15	R_1 = β-A	R_2 = α-B	R_3 = OAc	R_4 = H	R_5,R_6 = OCH_2O	
16	R_1 = β-A	R_2 = α-C	R_3 = OH	R_4 = H	R_5,R_6 = OCH_2O	
17	R_1 = α-B	R_2 = β-A	R_3 = OH	R_4 = H	R_5,R_6 = OCH_2O	
18	R_1 = β-B	R_2 = α-A	R_3 = OH	R_4 = H	R_5,R_6 = OCH_2O	
19	R_1 = β-D	R_2 = α-A	R_3 = H	R_4 = OH	R_5 = H	R_6 = OCH_3
20	R_1 = β-D	R_2 = α-A	R_3 = OH	R_4 = H	R_5 = H	R_6 = OCH_3
21	R_1 = α-A	R_2 = β-D	R_3 = OH	R_4 = H	R_5 = H	R_6 = OCH_3
23	R_1 = β-A	R_2 = α-D	R_3 = OH	R_4 = H	R_5 = H	R_6 = OCH_3
24	R_1 = β-A	R_2 = α-D	R_3 = H	R_4 = OH	R_5 = H	R_6 = OCH_3
25	R_1 = α-E	R_2 = β-A	R_3 = H	R_4 = OH	R_5 = H	R_6 = OCH_3
26	R_1 = α-E	R_2 = β-A	R_3 = OH	R_4 = H	R_5 = H	R_6 = OCH_3
28	R_1 = β-A	R_2 = α-F	R_3, R_4 = O	R_4 = H	R_5 = H	R_6 = OCH_3
29	R_1 = β-A	R_2 = α-G	R_3 = OH	R_4 = H	R_5 = H	R_6 = OCH_3



22 **27**

Figure 3. Structures of new natural occurring cyclopenta[*bc*]benzopyrans (**14**-**29**) isolated during the period 2006-2013 from species in the plant genus *Aglaia*.

of foveoglin B (**20**) at C-3 and C-4. The H-3β and H-4α configurations were suggested based on the vicinal coupling constant of 5.4 Hz, and the deduction was confirmed by NOE effects between H-3/H-2′,H-6′, and H-4/H-2″,H-6″. Cyclofoveoglin (**22**) is derived from isofoveoglin (**21**) by formation of a new bond between C-10 and N-12, the nitrogen atom in the bisamide chain substituted on C-4, to build a five-membered cyclic amide, which is an unprecedented structural feature among the cyclopenta[*bc*]benzopyran derivatives. This new connection results in a conformational change of the molecule. For example, the H-3 and H-4 both appeared as a singlet in the ^{1}H NMR spectrum. This implied that the dihedral angle between H-3 and H-4 is close to 90°, which was confirmed by a 3D modeling analysis. Among these compounds, only foveoglin A (**19**) exhibited cytotoxicity against Lu1, LNCaP and MCF-7 cancer cells, with ED_{50} values ranging from 1.4 to 1.8 μM.

Flavaglines possessing the same benzoyl-1,4-butanediamide substituent were also isolated from the leaves of *Aglaia forbesii* by Joycharat et al. in 2008.[39] In comparison to foveoglin A (**19**), the substituents at C-3 and C-4 were mutually exchanged in desacetylpyramidaglains A (**23**) and B (**24**), but still having the same H-3α and H-4β configurations. Compound **24** is an epimer of **23** at C-10. Although desacetylpyramidaglain C was also reported as a new compound in this study, the structure reported was identical to that of isofoveoglin (**21**) isolated by Salim et al. from *A. foveolata*.[15] Desacetylpyramidaglain C (isofoveoglin, **21**) exhibited antituberculosis activity against *Mycobacterium tuberculosis* H37Ra with a minimum inhibitory concentration (MIC) value of 25 μg/mL, and was compared to the two positive controls, isoniazid (MIC, 0.25 μg/mL) and kanamycin (MIC, 1.25 μg/mL). This compound also showed moderate anti-*Herpes simplex* virus type 1 (HSV-1) activity in this study.

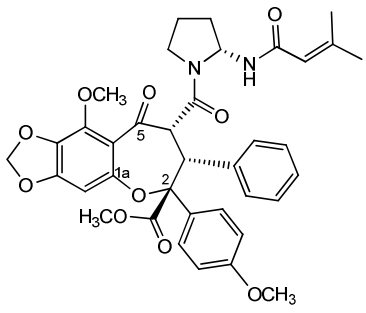
Perviridisin A (**25**) and its 10-epimer, perviridisin B (**26**) are two new flavaglines isolated from *Aglaia perviridis* collected in Vietnam.[17] Compounds **25** and **26** both have an α-oriented amidic putrescinyl 4-hydroxytiglate moiety at C-3 and a β-oriented phenyl ring at C-4, which are derived from aglairubine. The H-3β and H-4α configurations as well as the *endo* relationship between H-10 and H-3 were established based on the NOESY analysis. In the NOESY spectrum of perviridisin B (**26**), NOE cross peaks of OH-10/H-3, H-2'(6') and H-2"(6") were recognized, which, in combination with a downfield shift of 0.78 ppm observed for H-3 caused by the deshielding effect from OH-10, demonstrated that OH-10 and H-3 are spatially close to one another. Perviridisin B (**26**) showed potent cytotoxicity (ED_{50} 0.46 μM) against HT-29 cells and moderate NF-κB inhibitory activity (ED_{50} 2.4 μM) when evaluated in an ELISA assay.

Compound **27**, possessing the same substituent groups as perviridisins A and B (**25** and **26**), with their location mutually exchanged at C-3 and C-4, was isolated by Ahmed et al. from the leaves of *Aglaia cucullata* (syn. *Amoora cucullata*), collected in Bangladesh.[40] A similar five-membered amide ring to that present in cyclofoveoglin (**22**) was formed by the coupling of C-10 and the nitrogen atom of the α-oriented amide putrescinyl 4-hydroxytiglate side chain at C-4. Although compound **27** showed strong tumor necrosis factor (TNF)-related ligand (TRAIL) resistance-overcoming activity in human gastric adenocarcinoma (AGS) cells, it was less potent in this regard than the known cyclopenta[*bc*]benzopyran, 1-*O*-formylrocagloic acid.

10-Oxo-aglaxiflorin D (**28**) was purified from the leaves of *Aglaia odorata* collected in southwest mainland China by Wang et al.[41] In compound **28**, the free hydroxy group at C-10 possessed by cyclopenta[*bc*]benzopyran derivatives is substituted by an oxo group, with the corresponding carbonyl signal of C-10 appearing at δ_C 207.5 ppm in the ^{13}C NMR spectrum. The chiral carbons C-3 and C-4 were found to adopt the H-3α and H-4β configurations, respectively, based on the large coupling constant of 12.9 Hz between H-3 and H-4. The substitutions on C-3 and C-4 could be derived from ordorinol, which contains a cinnamoyl moiety, a pyrrolidine bisamide residue and a 2-hydroxy-2-methylbutanoyl group. No obvious cytotoxic activity was found for 10-oxo-aglaxiflorin D (**28**) toward human liver cancer (SMMC-7721) cells at the concentration tested.

(-)-Ponapensin (**29**), a new cyclopenta[*bc*]benzopyran, was isolated from the $CHCl_3$-soluble extract of the leaves and twigs of *Aglaia ponapensis*.[18] A monocyclic amide moiety, a 2-methoxypyrrolidine-1-carbonyl group, is located at the α position of C-4. The configuration of the methoxy group on the pyrrolidine ring was solved by NOE NMR spectroscopic analysis based on an optimized 3D model of **29**. Ponapensin (**29**) exhibited significant NF-κB inhibitory activity by ELISA (IC_{50} value of 0.06 μM), and was more potent than the positive control rocaglamide (**1**). Other cyclopenta[*bc*]benzopyrans isolated in this study, including 4-epiaglain A, aglain B, 10-*O*-acetylaglain B, and aglain C, were inactive in the same assay. This indicates that a change in the pyrrolidine side chain of the cyclopenta[*bc*]benzopyran-type compounds from a methylbutanoylamino group to a methoxy group dramatically increases the resultant NF-κB inhibitory activity. The structure of (-)-ponapensin (**29**) was confirmed by chemical synthesis of the (+)-enantiomeric form of this substance by the Porco group.[42]

Only two new natural cyclopenta[*b*]oxepines have been isolated from *Aglaia* species since 2006 (Figure 4). Phytochemical studies on the bark of *Aglaia edulis* led to the purification of a cyclopenta[*b*]oxepine derivative, 19,20-dehydroedulisone A (**30**),[11] which shares the same substitution pattern at C-3 and C-4 as that of



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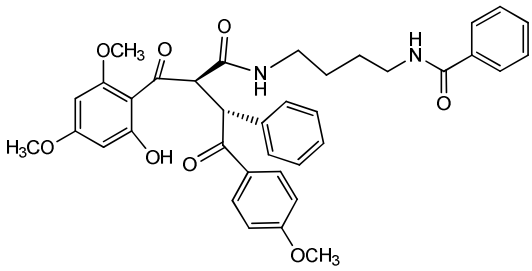

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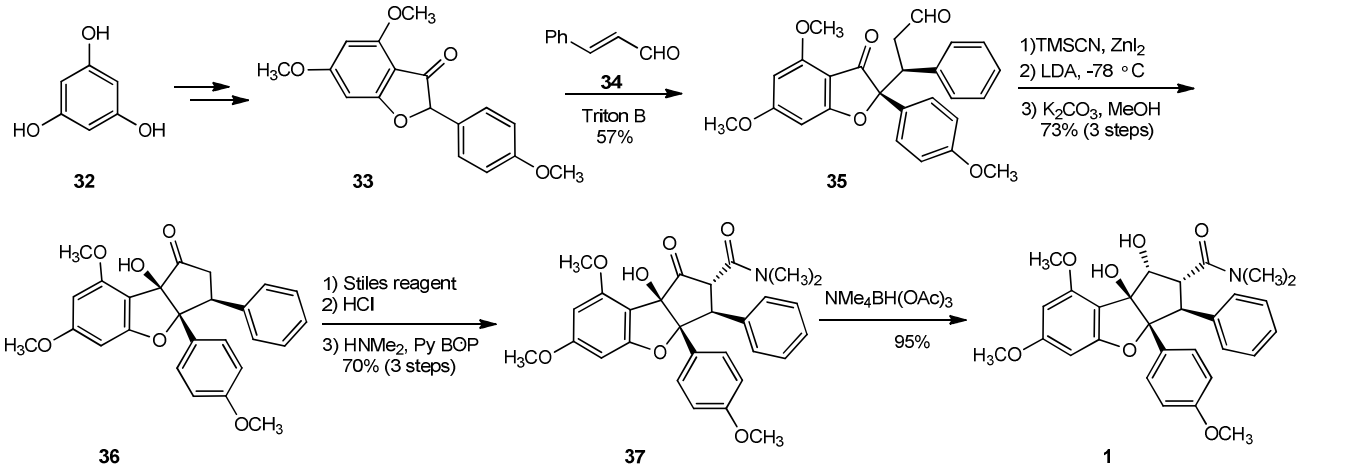
Figure 4. Structures of new natural occurring benzo[*b*]oxepines (**30** and **31**) isolated during the period 2006-2013 from species in the plant genus *Aglaia*.

19,20-dehydroedulirin A (**16**). Secofoveoglin (**31**), the first naturally occurring *seco*-benzo[*b*]oxepine derivative, formed by a carbon-oxygen bond cleavage of the oxepine ring, was isolated from *Aglaia foveolata* leaves in 2007 by Salim et al.[15] This compound possesses the same substituent groups on C-3 and C-4 as isofoveoglin (**20**). With the oxepine ring being opened, a hydroxy group and an oxo group occur at the C-1a and C-2 positions, respectively. Neither of these two additional benzo[*b*]oxepine derivatives showed cytotoxicity against the small panel of cancer cell lines employed for their biological evaluation.[11,15]

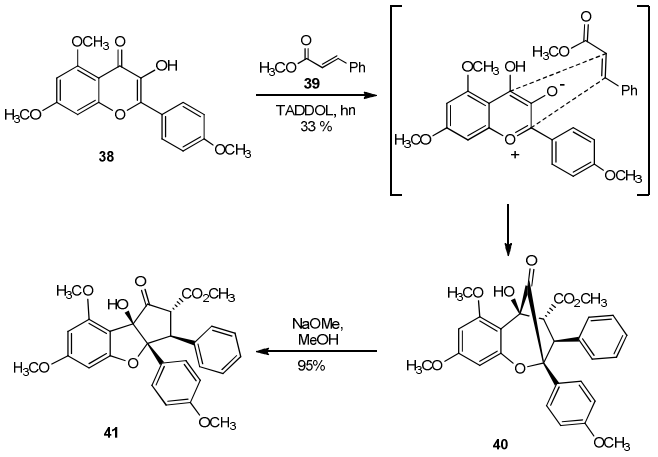
3 Update on synthetic methods for cyclopenta[*b*]benzofurans

Since the initial isolation and structure characterization of rocaglamide by King and coworkers in 1982,[9] the synthetic challenges associated with this class of natural products, including the construction of the densely functionalized cyclopenta[*b*]benzofuran core and its five contiguous stereogenic centers, have drawn the attention of the synthetic community. While numerous elegant approaches towards the core of rocaglamide and structurally related compounds have been reported, the strategies developed by Taylor, Dobler, and Porco represent the most convenient and thus the most widely utilized routes both for the synthesis of rocaglamide and the development of derivatives.[8] In 1991, Taylor and coworkers reported the synthesis of racemic rocaglamide in eight steps from the benzofuran intermediate **33**.[43] The key steps utilized in this synthesis were an intermolecular Michael addition of the benzofuran intermediate with *trans*-cinnamaldehyde and the subsequent SmI_2-catalyzed intramolecular reductive cyclization for the construction of the tricyclic core of rocaglamide. More recently, Dobler and coworkers reported a total synthesis of racemic rocaglamide that improved upon Taylor's pioneering work.[44] While Dobler utilized the same intermolecular Michael addition into *trans*-cinnamaldehyde **34** to generate the aldehyde adduct **35**, the subsequent construction and functionalization of the core proved to be somewhat more efficient than the methodology developed by Taylor. Instead of using the SmI_2-catalyzed intramolecular coupling of aldehyde **35** reported by Taylor, Dobler employed TMSCN and ZnI_2 to convert the aldehyde to a cyanohydrin intermediate in quantative yield. Addition of LDA to the cyanohydrin intermediate facilitated a cyclization with the benzofurone ring system. Finally, K_2CO_3-mediated cleavage of the cyanide unmasked the ketone, completing the transformation to the tricyclic core **36**. Compound **36** was subjected sequentially to Stiles reagent and acid to form the β-keto carboxylic acid, which was directly converted to the β-keto amide **37** via coupling with dimethylamine. Selective reduction of the ketone to the secondary alcohol completed the total synthesis of rocaglamide (**1**) in eight steps (overall yield of 28%) from the benzofuran intermediate **33** (Scheme 1).

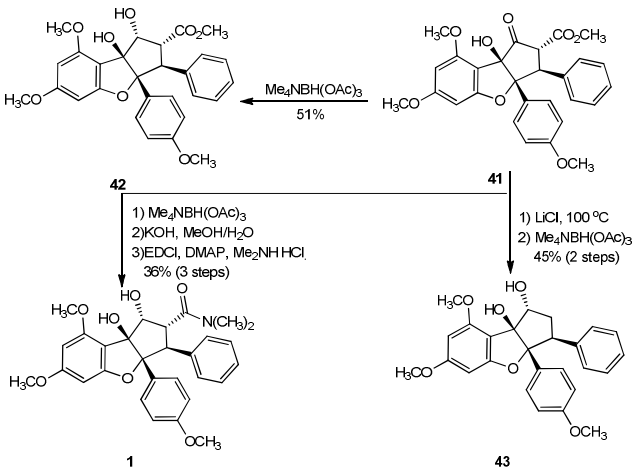
In 2004, Porco and coworkers introduced an elegant biosynthetically inspired [3+2] photocycloaddition for the construction of the racemic rocaglamide core and structurally related natural products. This synthetic approach relies on photoirradiation of 3-hydroxyflavone **38**, giving rise to an oxidopyrylium species derived from an excited-state intramolecular proton transfer (ESIPT) that can be trapped with an appropriate dipolarophile, in this case *trans*-methyl cinnamate **39**.[45] The [3+2] photocycloaddition affords the bridged bicyclic aglain intermediate **40**. Oxidation of this intermediate provided access to the forbaglin class of natural products, while the cyclopenta[*b*]benzofuran core **41** was generated through a base-mediated α-ketol shift (Scheme 2). This methodology



Scheme 1. Dobler's synthesis of (±) rocaglamide (**1**).



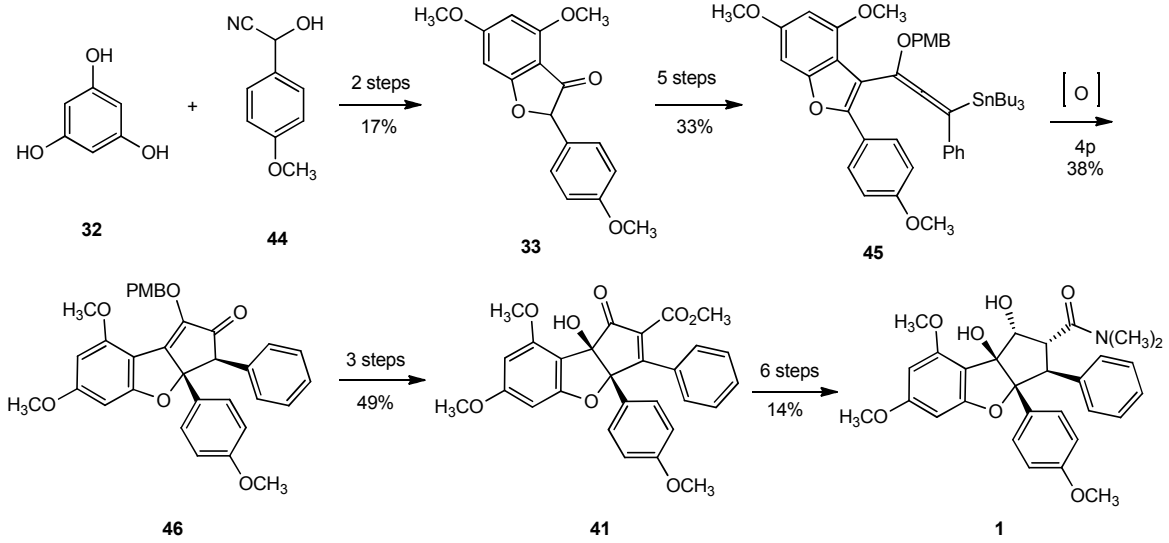
Scheme 2. Porco's [3+2] photocycloaddition for the construction of the rocaglamide skeleton.



Scheme 3. Porco's synthesis of (-)-rocaglamide (**1**), (-)-methyl rocaglate (**42**), and (-)- rocaglaol (**43**).

was improved upon in 2006 when the Porco group reported the synthesis of (-)-methyl rocaglate (**42**), (−)-rocaglaol (**43**), and (-)-hydroxyflavone for generation of the cyclopenta[*b*]benzofuran core, which possessed a free phenol at the C-6 position. A Mitsunobu reaction was then employed by both groups to append a dioxyanyloxy fragment onto the free phenol to complete the first total syntheses of silvestrol (**2**).[47,48] Porco's group more recently applied this methodology towards the first synthesss of (+)-ponapensin and (+)-elliptifoline (*vide supra*), members of the cyclopenta[*bc*]benzopyran-containing aglain family of natural products.[42]

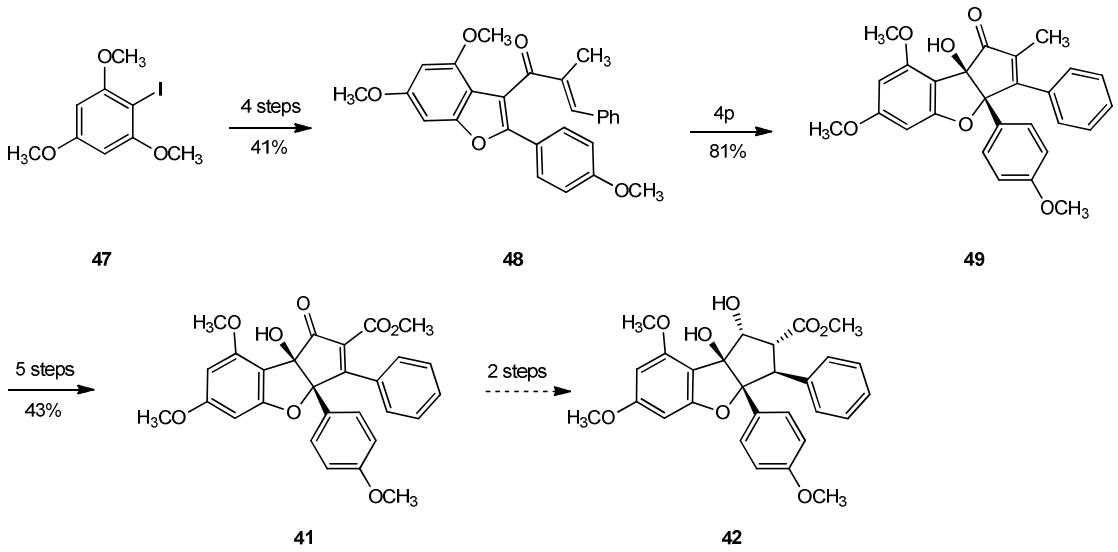
Since the publication of the recent reviews detailing the syntheses of rocaglamides in 2011 and 2012,[7,8] there have been only two newly reported syntheses of members of this class of natural products. In 2012, Frontier and coworkers[49] disclosed the total synthesis of (±)-rocaglamide (**1**) while the Magnus group[50] reported a formal synthesis of (±)-methyl rocaglate (**42**). Both approaches utilized a Nazarov cyclization as the key step for the preparation of the tricyclic rocaglamide core. Starting from phloroglucinol (**32**) and benzeneacetonitrile (**44**), Frontier's group successfully synthesized (±)-rocaglamide (**1**) in 17 steps (Scheme 4). This effort also facilitated generation of (±)-methyl rocaglate and (±)-rocagloic acid in 15 and 16 steps, respectively. The key step in the approach employed an oxidation-initiated Nazarov cyclization of the highly functionalized alkoxyallene **45** in order to generate the cyclopentenone ring found in the tricyclic core **46** and simultaneously establish the configuration of the C-3-phenyl and C-



Scheme 4. Frontier's synthesis of (±)-rocaglamide (**1**).

rocaglamide (**1**) utilizing an enantioselective [3+2] photocycloaddition in the presence of a functionalized TADDOL derivative to generate the chiral cyclopenta[*b*]benzofuran core **41**.[46] The chiral cyclopenta[*b*]benzofuran core **41** was constructed via an enantioselective [3+2] photocycloaddition in the presence of a functionalized TADDOL derivative followed by an α-ketol shift in two steps (31% yield) from the 3-hydroxyflavone intermediate **38**. Intermediate **41** was converted to (-)-methyl rocaglate (**42**) through a stereoselective reduction of the ketone to the secondary alcohol. (-)-Rocaglaol (**43**) was synthesized from intermediate (**41**) through a decarboxylation followed by a diastereoselective reduction, while (-)-rocaglamide (**1**) was generated from **41** via a reduction/saponification/amide coupling sequence (Scheme 3). Another major advancement with this methodology was seen in 2007 when the Porco and Rizzacasa groups both utilized the [3+2] photocycloaddition with a differentially functionalized 3-3a-anisole substituents. The synthesis was then completed through the introduction of the remaining cyclopentane ring functionality in nine steps to furnish (+)-rocaglamide (**1**). The formal synthesis of (+)-methyl rocaglate (**42**) was accomplished by Magnus starting from 2-iodo-1,3,5-trimethoxybenzene (**47**). The iodide was initially converted to the cross-conjugated pentadienone intermediate **48**, which underwent subsequently an unprecedented acetyl bromide mediated Nazarov to furnish the core ring system of methyl rocaglate **49**. Compound **49** was then further functionalized to the previously reported intermediate **41**, which had been previously converted to (+)-methyl rocaglate (**42**) by both Trost and Frontier.[51,52]

Both the Michael addition utilized by Dobler for the synthesis of rocaglamide and Porco's biosynthetically inspired [3+2] photocycloaddtion have since been utilized by multiple groups for the synthesis of rocaglamide analogs, with these derivatives having



Scheme 5. Magnus's formal synthesis of (±)-methyl rocaglate (**42**).

been used for the generation of a preliminary structure-activity-relationships (SAR) for this class of natural products.[53-58] Replacement of the rocaglamide C-4′ (R^4) methoxy with an electron-withdrawing group increases the resultant cytotoxicity of the analogues, while replacement with either a methyl or hydrogen substituent decreases the cytotoxicity, suggesting the preference for hydrophobic/electron withdrawing substituents in this *para*-position. However, changing the functionality of the C-3″(R_6) or C-4″(R_5) to substituents other than a hydrogen have been shown to have an growth inhibitory activity exhibited by rocaglaol derivatives. The substituents of methoxy at C-8b resulted in an obvious loss of cytotoxic potencies against cancer cells when compared with other rocaglaol analogues. Finally, compounds possessing an 8-desmethoxy substituent are significantly less active than their parent rocaglamide compounds, indicating the necessity of the C-8 methoxy substituent for the cytotoxic activity displayed by rocaglamide and structurally related derivatives. In Figure 5, a structure-activity relationship is shown for the rocaglate derivatives

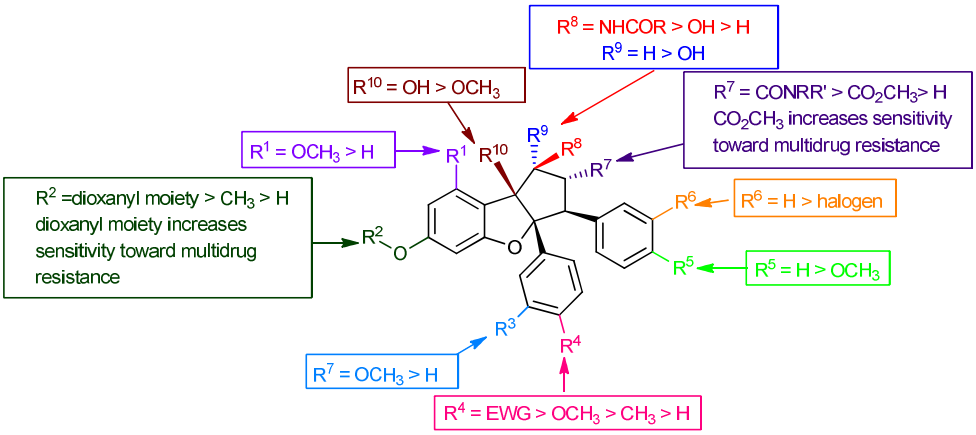


Figure 5. Structure-activity-relationship for cytotoxicity against cancer cell lines of cyclopenta[b]benzofuran derivatives.

adverse effect on the cytotoxicity of the rocaglamides. Substitution at the C-2 position (R_7) of the cyclopentane ring with an amide, ester or carboxylic acid improves the cytotoxicity as compared to a hydrogen; however, these substituents cause the compound to be more susceptible to transport by P-glycoprotein, which is responsible for multi-drug resistance. As indicated earlier in this review, introduction of the C-6 dioxanyloxy side chain, possessed only by silvestrol (**2**), dramatically increases the cytotoxicity for cancer as compared to other rocaglamide derivatives; however, this functionality also significantly increases silvestrol's sensitivity toward multi-drug resistance. As mentioned above, a free hydroxy group at the ring junction carbon C-8b is essential for tumor cell for cytotoxicity against human cancer cell lines.

4 Recent biological evaluation and mechanism-of-action studies on cyclopenta[*b*]benzofurans

Since their first isolation and purification from *A. elliptifolia* in the early 1980's, rocaglamide derivatives have been shown to exhibit a remarkably diverse range of biological effects. Although their potential anticancer activity has been the most widely described,[6-8] other reported activities include insecticidal,[59] anti-fungal,[25] anti-inflammatory,[27] cardioprotective[29] and neuroprotective effects.[26]

Subsequent to our most recent review that included the biological effects of cyclopenta[*b*]benzofurans,[60] a considerable amount of additional experimental work has been performed on the compound silvestrol (**2**) at The Ohio State University, with some of the results obtained having been published, as will be summarized briefly in the following paragraphs. A sensitive liquid chromatography tandem mass spectrometric method was developed and validated for the quantification of silvestrol in C57BL/6 mice, which were dosed with **2** via varied routes of administration and formulated in hydroxypropyl-β-cyclodextrin. Although only about 1% of this compound was bioavailable on oral dosing, it was found that the intraperitoneal systemic availability of the compound under the conditions used was 100%, and that in mouse and human plasma gradual degradation of silvestrol occurred, leading to about 60% of the parent drug remaining after 6 h. It was considered that an overall favorable pharmacokinetic profile was observed for silvestrol (**2**) in mice.[61]

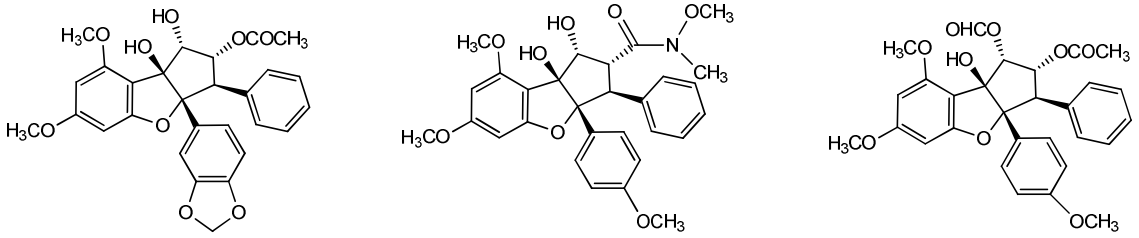


Figure 6. Structures of additional cyclopenta[*b*]benzofuran derivatives used in mechanism-of-action investigations.

Additional *in vitro* and *in vivo* investigations on the effects of silvestrol (**2**) on various B-cell malignancies have been published. To explore potential mechanisms of silvestrol resistance and the possible role of efflux transporters in the disposition of this compound, a silvestrol-resistant acute lymphoblastic leukemia cell line (ALL) was generated using the 697 ALL cell line. It was found that resistance to **2** using this cell line is mediated by *ABCB1*/P-glycoprotein overexpression, which may explain its poor oral bioavailability noted above.[61,62] However, this effect may be inhibited by the P-glycoprotein inhibitors, verapamil and cyclosporine A.[62] In a later study in acute myeloid leukemia (AML), silvestrol was active *in vitro* in both *FTL3*-wt overexpressing and *FLT3*-ITD (MV4-11)-expressing AML cell lines, with IC_{50} values of 3.8 and 2.7 nM, respectively. It was found that silvestrol inhibited *FLT3* translation and reduced FLT3 protein expression by 80-90%. In an MV4-11 mouse xenograft model, silvestrol showed a median survival time of 63 days compared with 39 days for the control after engraftment, under the conditions used.[63] Since it has been found that silvestrol reduces cyclin D1 expression in breast cancer and lymphoma cell lines, the efficacy of this compound was investigated in a mantle cell lymphoma (MCL), a malignancy characterized by elevated cyclin D1 levels. Silvestrol showed low nanomolar inhibitory potencies for both MCL cell lines and primary MCL tumor cells, and it was demonstrated that it showed depletion of D-cyclins at a low dose after 16 hours. At the dosing schedule used, silvestrol significantly prolonged survival in a MCL xenograft model without discernible toxicity.[64] Currently, silvestrol (**2**) is undergoing preclinical toxicological investigation as a potential agent for the treatment of B-cell malignancies at the U.S. National Cancer Institute, under the auspices of the NExT program.

Hepatocellular carcinoma (HCC) is a serious health problem in areas of the world where hepatitis is endemic, including parts of Africa and Asia, and has an extremely poor prognosis. Since there is a dire need for new agents that target HCC, the efficacy of silvestrol (**2**) in this regard was investigated using various *in vitro* and *in vivo* methods. Initially, this compound was found to inhibit the cellular growth of four different HCC cell lines, with an IC_{50} range of 12.5-86 nM, and showed increased apoptosis and enhanced activity of caspases 3 and 7, with a loss of mitochondrial membrane potential and decreased expression of Mcl-1 and Bcl-2. In addition, synergistic effects were found *in vitro* when silvestrol was combined with sorafenib or rapamycin.[65] An anti-tumor effect was found for silvestrol (**2**) *in vivo* when given as a single agent at 0.4 mg/kg in an orthotopic human HCC xenograft system in nude mice.[65] These results were achieved in the absence of obvious toxicity, thus leaving open the potential of combining silvestrol with other agents that may have efficacy in this disease. As suggested by others as well,[66,67] the inclusion of silvestrol in combination therapeutic strategies may significantly sensitize highly refractory tumors to established agents.

Early studies into the antineoplastic activity possessed by rocaglamide and structurally related derivatives, suggested that these compounds were cytostatic in nature rather than cytotoxic. Utilizing a human lung carcinoma (Lu1) cell line, Pezzuto and coworkers demonstrated that 4′-demethoxy-3′,4′-methylenedioxy-methyl rocaglate (**50**, Figure 6) induced accumulation in the G_1/G_0 phase of the cell with negligible cell death.[12] Based upon ^{3}H-leucine incorporation, it was demonstrated that this rocaglamide derivative was able to inhibit protein biosynthesis (IC_{50} 25 ng/mL) while not affecting nucleic acid biosynthesis at concentrations as high as 1 μg/mL. Additionally, this novel 1*H*-cyclopenta[b]benzofuran inhibited the growth of a human breast cancer cell line (BC1) both *in vitro* and *in vivo*.[12] Other studies have demonstrated the ability of various rocaglamide derivatives to inhibit cell proliferation in a variety of malignant human cell lines by blocking the G_2/M phase of the cell cycle, while simultaneously resulting in minimal cell death. These results suggest that the cyclopenta[*b*]benzofuran anti-tumor activity is derived from their ability to inhibit translation.

To date, the identified molecular targets of cyclopenta[*b*]benzofurans are limited to prohibitins (PHBs), a small but ubiquitous family of membrane-localized proteins with multiple purported functions,[68,69] and the RNA helicase eIF4A, a component of the eukaryotic translation initiation complex.[70] Inhibition of either of these targets could potentially explain most or perhaps all of the reported biological effects of cyclopenta[*b*]benzofurans, and agents that interfere with the function of either PHBs or eIF4A would be of substantial biomedical interest. Direct interaction of rocaglamide (**1**) to PHBs was recently demonstrated by Polier et al. using affinity chromatography,[71] supporting PHBs as a relevant *in vivo* molecular target. The group led by Pelletier first demonstrated that the translation initiation factor eIF4A is the likely target of silvestrol (**2**).[66,72] More recently, two different groups used genetic or affinity chromatography approaches to confirm eIF4A as the molecular target of rocaglamides[73] or episilvestrol (**11**),[11,34] respectively.

4.1 Prohibitins

PHBs 1 and 2 are typically described as scaffolding proteins localized to the cytoplasmic or mitochondrial membrane, but they are found as well in the nucleus and endoplasmic reticulum. PHB1 and PHB2 co-associate to regulate myriad signaling pathways, although it is unclear how they function in this regard. The broad subcellular distribution is consistent with the observation that PHBs have a wide range of activities that may in fact vary by cell type or organism. A further confounding factor in understanding the functional role of PHBs is that they are post-translationally modified,[69] altering their interactions with binding partners in ways that have not yet been characterized. In the mitochondria, the interaction of PHBs with other factors promotes chaperone activity, mitochondrial DNA organization, and production of mitochondrial proteins.[68] PHBs associate with a variety of nuclear proteins that regulate apoptosis (e.g., p53),[74] chromatin remodeling (e.g., HDACs)[75] and transcription (e.g., E2Fs).[76] In the cytoplasm, the picture is similarly complex, as interactions of PHBs are reported with proteins involved in the PI3K/AKT, MEK/ERK, and NF-κB pathways, providing explanations for earlier biological observations with cyclopenta[*b*]benzofurans.[27,77] Thus, the biological impact of inhibiting PHBs with these agents is difficult to predict, and may produce both pro-apoptosis and pro-survival effects in different cell types or even within one cell type. Owing to the numerous PHB interactions with other proteins in multiple subcellular compartments, many if not all the biological effects of the cyclopenta[*b*]benzofurans may be explained by PHB inhibition. For example, binding of rocaglamide (**1**) to PHBs 1 and 2 was shown to block their interaction with C-Raf, thus inhibiting C-Raf mediated MEK/ERK signaling.[71] This activity could not only impede several different pro-survival signaling pathways, but potentially could be responsible for the negative impact of cyclopenta[*b*]benzofurans on translation via the loss of MNK-mediated eIF4E phosphorylation.[78] Certainly interfering with mitochondrial function via PHB inhibition may contribute to the rapid cytotoxicity induced by the cyclopenta[*b*]benzofurans, and this mitochondrial pathway of cell death could be further amplified by the effects of these compounds on the Bcl-2 family of proteins via the MEK/ERK pathway[77] or the inhibition of translation, especially of the short half-life mitochondrial-stabilizing protein Mcl-1, as has been reported by several groups.[72,79] Thus, it seems likely that cyclopenta[*b*]benzofurans, even if they target only PHBs, could induce cell death via multiple mechanisms simultaneously. Interestingly, PHB1 was recently shown to be vital to the viability of Colorado potato beetle larvae, suggesting an explanation for the insecticidal properties of the cyclopenta[*b*]benzofurans.[80]

4.2 eIF4A

In eukaryotes, translation of mRNA is the rate limiting step of initiation, a key process in protein synthesis. This step is regulated by a family of proteins known as the eukaryotic initiation factors (eIF). Most mRNAs are translated in a cap-dependent manner with translation being facilitated by the eukaryotic initiation factor 4F (eIF4F) cap-binding (initiation) complex. This complex is composed of three key proteins: eIF4A (an ATP-dependent RNA helicase), the cap-binding protein eIF4E, and the scaffold protein eIF4G. Translation is initiated the through the binding of eIF4E to the 5′-mRNA, which allows recruitment of the other eIF4 proteins to form eIF4F complex. The complex then interacts with the 5′ terminus of mRNA, which ultimately results in stimulation of ribosomal recruitment and translation.[7,8,81]

The eukaryotic translation initiation factor eIF4A (DDX2) is an RNA helicase of the DEAD box family. This factor is now known to consist of eIF4A I (DDX2A), II (DDX2B), and III (DDX48). Although eIF4A I and II are highly similar and in some situations interchangeable, new information indicates they possess different functions.[82,83] However, due to their high sequence similarity and the fact that both eIF4A I and II were identified in an affinity purification study using episilvestrol (**11**),[34] they are both likely to be cyclopenta[*b*]benzofuran targets. eIF4A is believed to be responsible for unwinding the 5′ untranslated region (UTR) of mRNA, thus providing a "landing pad" for the 43S pre-initiation complex. The importance of this activity in the efficiency of translation varies between different mRNAs; mRNA species with more structured/GC-rich 5′ UTRs are more sensitive to loss of eIF4A activity than mRNA with simple, less-structured 5′ UTRs.[84] This is a key point for the potential clinical application of cyclopenta[*b*]benzofurans, as mRNAs with structured 5′ UTRs are more likely to encode proteins required for tumor survival, growth and metastasis rather than housekeeping functions. Such proteins include those that promote cell cycle entry (cyclin D1), apoptosis resistance (Bcl-2, Mcl-1, Bcl-XL), angiogenesis (VEGF, MMP-9), transcription (myc, fos) and metabolism (ornithine decarboxylase). This difference in protein synthesis inhibition across different mRNAs is one possible explanation for the observed therapeutic index of cyclopenta[*b*]benzofurans [e.g., silvestrol (**2**) and the rocaglamide derivative, rohinitib (**51**, Figure 6)] in mouse models.[56,63,72,79,85] Pelletier's group first demonstrated that the translation initiation factor eIF4A was the likely target of the cyclopenta[*b*]benzofurans, using biochemical assays to show that 1-*O*-formylaglafoline (**52**, Figure 6) and silvestrol (**2**) stimulated an abnormal interaction of eIF4A with mRNA and prevented successful assembly of the mRNA:eIF4A dimer with the eIF4F translation initiation complex.[66,72] As noted previously, this finding was separately confirmed by two groups using genetic and biochemical approaches.[34,72] These and later publications[86] support direct inhibition of translation (particularly of mRNA with a structured 5′ UTR) as the major biological effect of silvestrol (**2**), especially in tumors highly sensitive to loss of a particular protein, as is seen with Mcl-1 in primary chronic lymphocytic leukemia cells.[87] Importantly, a recent report by Meijer et al.[83] demonstrates that eIF4AII is a key component of the complex that allows microRNAs to inhibit translation; thus, interaction of eIF4AII with cyclopenta[*b*]benzofurans could add an additional layer of complexity to the translational inhibition mechanism. Nevertheless, a reliable catalog of cytotoxicity-related proteins whose translation is affected by cyclopenta[*b*]benzofurans in a particular cell type is lacking, and inhibition of only one or a few of these proteins identified to date is unlikely to explain all of the biological effects of these agents.[88]

4.3 Alternative mechanisms of action

In this review thus far, it has been considered that all bioactive cyclopenta[*b*]benzofurans (despite differences in potency) share the same basic mechanism of action, and indeed there is evidence to support this view. However, other mechanisms of cyclopenta[*b*]benzofurans-induced cytotoxicity or cytostasis have been advanced as well that may not be necessarily related to inhibition of either PHBs or eIF4A. Recently, Neumann et al. showed that rocaglamide (**1**) induces rapid phosphorylation and loss of Cdc25A, leading to cell cycle arrest at the G1-S transition. Interestingly, this effect appears to be due to DNA replication stress-mediated activation of the ATM/ATR pathway and not inhibition of translation.[89] Additionally, the

levels of certain microRNA species were found to be affected by silvestrol (**2**) in acute myeloid leukemia cells via an unknown mechanism.[62] As microRNAs have been shown to be involved in the regulation of key cell functions as well as the development of malignancy, this finding introduces an entirely new area of investigation into the reasons for the diverse biological effects of cyclopenta[*b*]benzofurans.[83] The structural diversity within the cyclopenta[*b*]benzofuran class as well as the variety of biological effects assigned to them suggest that we have not yet identified all interacting partners with these compounds. In conducting SAR studies and optimizing leads for clinical development, it will be important to delineate additional biological activities that can perhaps be eliminated or amplified via structural modifications.

4.4 Therapeutic potential

The differential effect of cyclopenta[*b*]benzofurans toward cancer vs. normal cells has been reported by multiple groups. The reasons behind this are not well understood, although several possibilities have been presented. As previously mentioned, tumor cells may be more reliant on the continued production of certain proteins (e.g., Mcl-1, c-Myc) and more sensitive to even temporary depletion of these. Thus, the application of cyclopenta[*b*]benzofurans as translation inhibitors in cancer is a compelling idea, regardless of whether this activity is through eIF4A binding or dephosphorylation of eIF4E via inhibition of the MEK/ERK pathway. Components of the translational machinery are potentially powerful therapeutic targets in cancer.[90-92] Indeed, translation is an especially well-established target in the context of inhibitors of the mTOR pathway, which have clear efficacy in certain malignancies, and the translation inhibitor omacetaxine mepesuccinate was recently approved for kinase inhibitor-resistant chronic myelogenous leukemia. Secondly, Neumann et al. showed a differential activity of rocaglamide (**1**) in leukemic but not normal T-cells that could potentially be due to an enhanced DNA replication stress response in the leukemic cells.[88] This pathway is commonly activated in tumor cells, and could represent a tumor liability.[93] Furthermore, Santagata et al. reported that rocaglamide-mediated inhibition of translation led to specific changes in gene expression driven by inactivation of the transcription factor HSF1.[85] HSF1 is an important mediator of the malignant state through its control of genes involved in stress responses, and thus constitutes a potentially useful therapeutic target in cancer.[94] Downstream effects of rocaglamide-mediated HSF1 inactivation included increased expression of thioredoxin-interacting protein (TXNIP), with a concomitant decrease in glucose uptake. This effect should promote stronger anti-proliferative effects in tumor cells, which exhibit (and rely on) increased glucose uptake and metabolism.

Obviously, multiple challenges remain before cyclopenta[*b*]benzofurans could be clinically tested, including but not limited to structural improvement toward more "drug-like" properties, large-scale production (due to their complex structures that complicate synthesis), determination of optimal dose and schedule, and completion of detailed pharmacological and toxicological investigations. Several groups are already taking on some of these challenges, and have reported novel structures with biological activity.[54-57] Interestingly, at least in mice silvestrol (**2**) has been shown to exert single-agent activity without substantial toxicity,[62,72,79] even at the higher doses tested (1.5 mg/kg every 48 hr).[63] Assuming that cyclopenta[*b*]benzofuran-based compounds could be validated to show efficacy at tolerable levels in additional animal models of cancer, they would represent an entirely new class of anti-cancer agents with a unique mechanism. Such agents would be a truly valuable addition to the cancer armamentarium, either alone or in combination.

5 Conclusions

Unlike the small-molecular-weight natural product constituents of terrestrial microbes and marine organisms, it is rare for an entirely new structurally distinct class of secondary metabolites to have been discovered from a higher plant as recently as 1982, as a result of the report of the isolation of rocaglamide (**1**) from the roots and stems of *A. elliptifolia* collected in Taiwan.[9] While X-ray crystallography was used to help establish the relative configuration of this compound,[9] the absolute configuration assignment was not determined until 1990, as a result of the total synthesis of (-)-rocaglamide by the Trost group.[51] Although King et al. showed that rocaglamide showed promising *in vivo* antineoplastic activity when this compound was first reported, using the P-388 murine lymphocytic leukemia model (T/C *ca*. 156% at 1.0 mg/kg),[9] the initial biological focus of the phytochemical investigators working on the elucidation of new cyclopenta[*b*]benzofuran derivatives in the 1990s was on their potential application as insecticides.[6,59] A renewed emphasis on the potential anticancer activities of members of this compound class was stimulated through the purification, structural characterization, and initial biological evaluation of silvestrol (**2**) as having *in vivo* inhibitory activity in tumor-bearing mouse models.[14,35] Isolation chemistry work on the rocaglamide derivatives has been complicated by the taxonomic complexity of the arboreal genus *Aglaia*,[1,2] which in the case of silvestrol (**2**) required both of its source plants found to date to be re-identified.[14,36] The continued reports in the last decade of efficacy of silvestrol and other rocaglate derivatives at the nanomolar level against human cancer cell lines, and the positive results obtained when evaluated in human tumor mouse xenograft models,[e.g.,6,60] have resulted in widespread scientific interest in these substances, including from the organic and medicinal chemistry communities.[5-8,42-58] This level of interest may be expected to continue in the future, and has greatly intensified as a result of reports of the cyclopenta[*b*]benzofurans acting mechanistically as direct inhibitors of translation initiation,[34,66,71,72] which is a rare target among anticancer agents of natural origin.[60]

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Graphical abstract

Rocaglamide, Silvestrol and Structurally Related Bioactive Compounds from *Aglaia* Species

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This review summarizes recent investigations on the chemistry and biology of rocaglamide, silvestrol and structurally related bioactive compounds from *Aglaia* species published during the period 2006-2013.