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Recent advances in the biology and chemistry of the flavaglines

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ABSTRACT

The flavaglines are a family of plant natural products that induce potent anticancer and neuroprotective activities. This review summarizes recent synthetic approaches to flavaglines and the current status of their pharmacological properties.

1. Introduction

The flavaglines are a family of plant natural products that are structurally characterized by a unique cyclopenta[*b*]benzofuran skeleton. The first of these compounds, rocaglamide (**1**), was isolated in 1982 by King and colleagues based on its antileukemic activity (Fig. 1).[1] Since then, about 50 other flavaglines, such as rocaglaol (**2**) or silvestrol (**3**) have been found in the plant of the genus *aglaia* (*Meliaceae*) mainly by the pharmacognosy laboratories of Kinghorn, Pezzuto and Proksch.[2,3] These compounds display a unique array of biological effects as insecticidal, antifungal, anti-inflammatory and neuroprotective agents. But, by far, their most studied biological property concern their unique profile of anticancer activity.

The flavaglines inhibit the proliferation of tumor cells in a low nanomolar range without displaying any significant toxicity on normal cells, such as human umbilical vein endothelial cells (HUVEC),[4] intestinal epithelial cells,[5] normal peripheral blood lymphocytes, bone marrow stem cells[6] and cardiomyocytes.[7] Moreover, these compounds do not display any sign of toxicity in mice.[8,9] Early reports demonstrated that rocaglamide and its analogs delay the growth of tumors implanted in mice. Because tumors were not eradicated, further studies were interrupted. It is currently considered that flavaglines are rather cytostatic than cytotoxic, and the development of targeted therapies in the 90's and years 2000 changed radically the way we now look at cytostatic compounds.[10] That is probably why there is currently a renewed interest for the anticancer properties of flavaglines these recent years. To date, 15 total syntheses of flavaglines have been reported, attesting to the fascination of these highly compact functionalized heterocycles from the synthetic community.

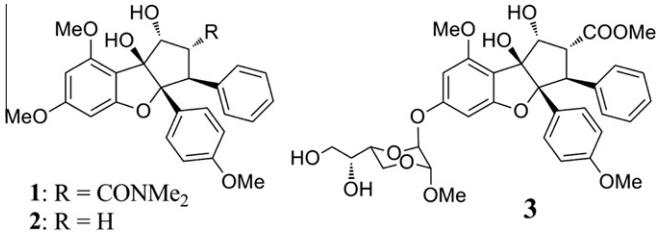

Figure 1. Representative examples of naturally occurring flavaglines: rocaglamide (**1**), rocaglaol (**2**) and silvestrol (**3**).

The chemistry, biology, and structure–activity relationships (SAR) of flavaglines have been comprehensively reviewed in 2001 and 2006.[2,3] Some aspects of their anticancer properties were also described in a review on traditional Chinese medicine.[11] The purpose of this article is to highlight the most recent advances on the total synthesis and the exploration of the biological properties of these exciting anticancer agents.

2. Anticancer properties

2.1. SAR studies

While the SAR displayed in precedent reviews were restricted to natural compounds, the development of convenient syntheses

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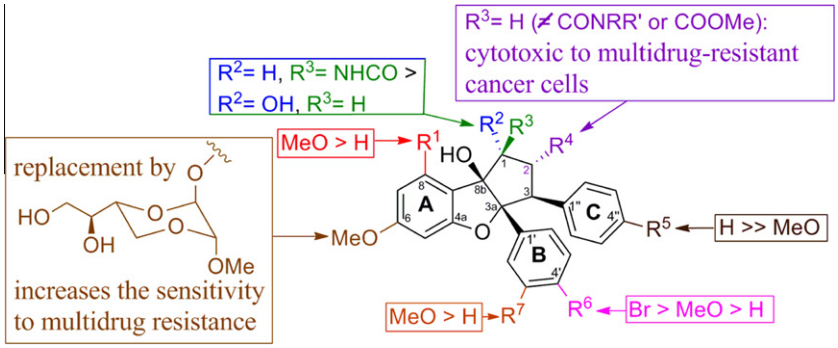


Figure 2. Summary of the structural requirements of flavaglines for their anticancer effects.

by Dobler and Porco's teams[12,13] opened the road to medicinal chemistry programs.[7,14] Replacement of the methoxy group in position 4′ of rocaglaol by a bromine atom (R^6 = Br) improved cytotoxicity, while its deletion (R^6 = H) decreased potency more than three orders of magnitude, suggesting a preference for a hydrophobic substituent in this *para* position. Introduction of a methoxy in position 4″ on the other phenyl moiety was detrimental for cytotoxicity (Fig. 2). Substitution in position 2 by an amide or an ester significantly decreased the cytotoxicity on cancer cells that developed resistance to chemotherapy by overexpressing the P-glycoprotein (P-gp), a plasma membrane protein encoded by the multidrug resistance (MDR1) gene.[14] Similarly, the introduction of a dioxanyl pseudo-sugar in position 6 as in silvestrol seems to enhance the in vitro cytotoxicity but makes the drug very sensitive to multidrug resistance.[15] 8-Demethoxy compounds were significantly less active (ED_{50} 4–20 times higher) than cognate compounds, indicating a preference but not an absolute requirement of a methoxy group in position 8 for cytotoxicity.[14]

2.2. Effect on signaling pathways

Flavaglines have been showed to inhibit protein synthesis in cancer cells for over a decade. In 2009, Pelletier and co-workers demonstrated that these compounds inhibit the activity of the eukaryotic translation initiation factor 4A (eIF4A).[16,8] Most of the mRNAs require an insignificant amount of eIF4A for their translation. Alternatively, many mRNAs coding for proteins involved in oncogenesis, angiogenesis and chemoresistance absolutely require eIF4A for ribosome loading. Silvestrol was shown to prevent the recycling of eIF4A by increasing its RNA binding properties. These authors examined the translation of the oncogenes cyclin D1 and c-myc and the anti-apoptotic proteins Bcl-2, survivin, and Mcl-1 and showed that silvestrol inhibited the translation of these transcripts. Recently, Li-Weber and coworkers demonstrated that this inhibition of eIF4 is due to a blockage of the MEK-ERK-Mnk1 pathway which mediates the Ras-dependant activation of eIF4E.[17] However, how flavaglines prevent the activation of MEK by Ras remains currently unexplained. These authors demonstrated also

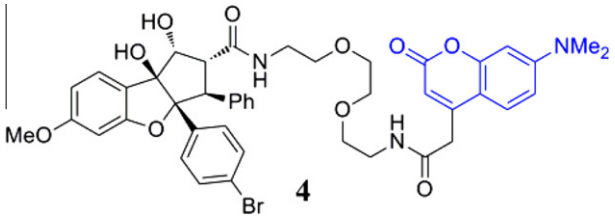


Figure 3. Fluorescent probe used to determine the localization of the molecular target of flavaglines in the endoplasmic reticulum.

that the inhibition of translation down-regulate only short-lived proteins, such as c-FLIP, which is responsible for the resistance to the extrinsic apoptotic pathway. Together with in vivo studies (vide infra Section 2.5.), all of these data strongly support the view that anticancer effects of flavaglines are linked to their ability to selectively suppress the translation of proteins involved in malignancy.

Albeit the Molecular Target of Flavaglines (MTF) remains unidentified, the use of a fluorescent probe designed according to a methodology developed by La Clair and co-workers.[18] gave some hints about the intracellular localization of this target. The flavagline probe **4**, which is coupled to a fluorescent coumarin (Fig. 3), was shown to accumulate specifically in the endoplasmic reticulum (ER) of HeLa cells,[7] suggesting that flavaglines bind to their target in the ER, where it triggers a cascade of events that leads to growth arrest and apoptosis (Fig. 4).

2.3. Mechanisms of cancer cell death

Anticancer drug may trigger the death of cancer cells through a myriad of mechanisms such as, apoptosis, autophagy, necroptosis, and mitotic catastrophe. So far, apoptosis has been the only mechanism involved in the death of cancer cells induced by flavaglines. Apoptosis is classically induced through the intrinsic (mitochondrial) pathway or the extrinsic (receptor-mediated) pathway. Both pathways may be induced by flavaglines. The intrinsic pathway involves the release of cytochrome C from mitochondria to activate pro-caspase-9 within the apoptosome (Fig. 4). Caspase-9 subsequently activates caspase-3, which cleaves and inactivates PARP (poly(ADP-ribose) polymerase) and ICAD (inhibitor of caspase-activated DNase), leading to apoptosis. The extrinsic apoptotic pathway is triggered by the activation of death receptors, such as TNF-α receptor, TRAIL receptors or FAS (also called CD95 or Apo-1).

Rocaglaol was shown to induce the intrinsic apoptosis pathway through caspase-7, in LNCap cells.[19] Similarly, Li-Weber and her co-workers have shown that flavaglines trigger the intrinsic apoptosis pathway through caspases-9, -8, -3 and -2 in several leukemia cell lines isolated from patients.[6] In addition, normal lymphocytes were not affected by flavaglines. The selectivity toward leukemic cells was proposed to be due to a prolonged inactivation of ERK and activation of the stress-response mitogen-activated protein kinases p38 and JNK in malignant but not normal lymphocytes.[6] This activation of p38 induces a cleavage of Bid, an inducer of the intrinsic apoptotic pathway. More recently, these authors have shown that flavaglines may also induce the extrinsic apoptotic pathway through a prolonged JNK activation in malignant T cells enhancing the activity of the transcriptional factor AP-1 and suppressing that of NF-AT, leading to an upregulation of CD95 ligand and downregulation of c-FLIP expression. c-FLIP regulates the extrinsic apoptotic pathway by inactivating caspase-8 at the level

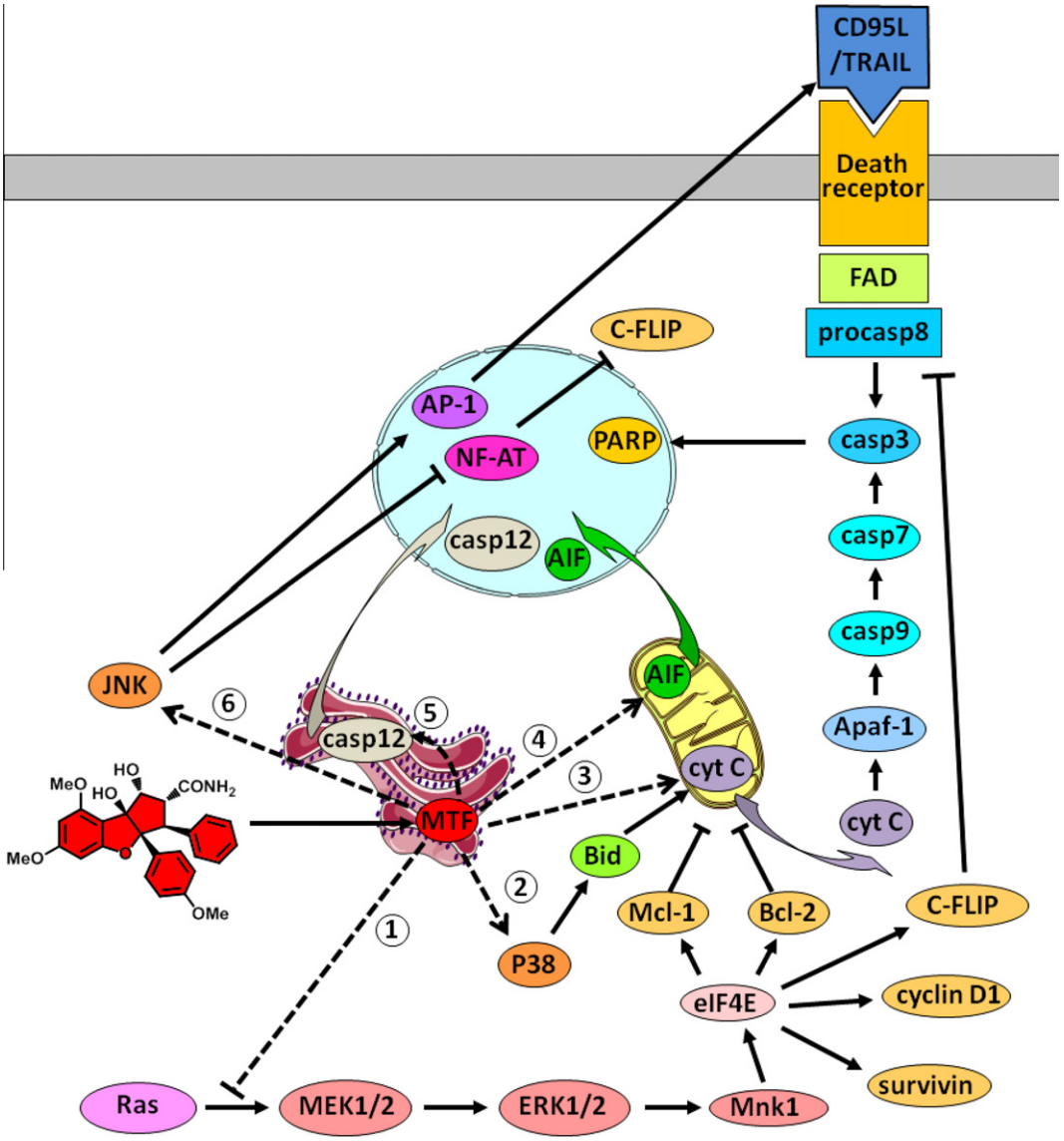


Figure 4. Schematic model accounting for the different death pathways of cancer cells triggered by the binding of flavaglines to their molecular target (MTF). (1) Inhibition of MEK blocks the ERK-Mnk1-eIF4E pathway suppressing the synthesis of proteins involved in cell survival and proliferation.[8,16,17] (**2**) p38 activation affects Bcl-2 family proteins leading to depolarization of the mitochondrial potential, release of cytochrome C and activation of the intrinsic apoptosis pathway.[6] (**3**) Induction of the release cytochrome C triggers the intrinsic apoptotic pathway through the successive activation of Apaf-1, caspases-9 and -3.[6,19] (**4** and **5**) Induction of the translocation of AIF and caspase-12 to the nucleus induces apoptosis independently of caspase-3.[7] (**6**) JNK activation regulates the activity of the transcriptional factors AP-1 and NF-AT, altering the expression of CD95 ligand and c-FLIP thereby inducing the extrinsic apoptotic pathway.[20]

of the death-inducing signaling complex (DISC).[20] Akin to these observations, Ishibashi and co-workers demonstrated that flavaglines sensitize TRAIL-resistant human gastric adenocarcinoma (AGS) cells through the upregulation of the death receptors DR4 and DR5 and the activation of caspase-3/7.[21]

Surprisingly, silvestrol and aglaiastatin have been shown to induce apoptosis without activating caspase-3 in SW480 and LNCap cells.[22,5] Similarly, both rocaglaol and the synthetic drug FL3 were shown to induce apoptosis of HeLa cells without inducing caspases-3, -7, -8 and -9.[7] Beyond the canonical induction of apoptosis through convergence toward caspase-3, other modes of induction of apoptosis exist, which involve proteins such as Apoptosis Inducing Factor (AIF) and caspase-12.[23] AIF and procaspase-12 reside in mitochondria and the ER respectively. Their cleavage and translocation to the nucleus induces apoptosis independently of caspases-3, -7, -8 and -9. Rocaglaol and FL3 were shown to induce apoptosis of HL60 and Hela cells through AIF and caspase-12, suggesting that these compounds would retain their activity in cells refractory to activation of caspases-7, -8 and -9 (Fig. 4).[7] Interestingly AIF and caspase-12 are known to be involved in a cross-talk in ER stress-induced apoptosis,[24,25] which suggests a link between the inhibition of cap-dependant protein synthesis and the mechanism of induction of apoptosis by flavaglines.

Swanson and co-workers noticed a difference between rocaglaol and silvestrol regarding caspase activation in LNCaP (prostate cancer) cells: rocaglaol induced the cleavage of caspases-7 and -9 leading to an activation of the intrinsic apoptosis pathway.[19] Surprisingly silvestrol activated caspases-2, -9 and -10 but not the executioners caspase-3 and -7 in the same cell line.[26] This difference suggests that silvestrol, which has the peculiarity to be substituted by a complex dioxanediol moiety, may act through mechanisms that partially differ from those of the other flavaglines. Using DNA microarray analysis, these authors showed that silvestrol modulates the transcription of 20 genes involved in

apoptosis and cell cycle progression at the G2/M checkpoint in LNCaP cells.[26] Interestingly, silvestrol decreased the protein level of p53, which is the central regulator of genes that control apoptosis, indicating that the cytostatic effects of silvestrol are not mediated by p53 in LNCaP cells.

Altogether, these studies clearly indicate that flavaglines may trigger apoptosis by different pathways according to the cancer cell types. Moreover, silvestrol and episilvestrol, may exhibit pharmacodynamic properties that differs from those of other flavaglines.

2.4. Potentiation of the effects of other anticancer drugs

In 2002, Proksch, Wirth, and co-workers showed that flavaglines sensitize in vitro therapy-resistant leukemic T cells to apoptosis induced by TNF-α, cisplatin, and γ-irradiation.[27] Complementary studies recently showed that flavaglines potentiate also doxorubicin, rapamycin, etoposide, cytarabin and ABT-737 (Bcl-XL/Bcl-2 inhibitor) cytotoxicity (Table 1). These observations are reminiscent of Stockwell's observation that inhibitors of protein synthesis (cycloheximide, emetine, and dihydrolycorine) potentiate doxorubicin's lethality.[28]

Surprisingly silvestrol potentiated the cytotoxicity of etoposide, Ara-C, and daunorubicin in acute myelogenous leukemia in a biphasic manner: a low concentration (2.5 nM) of silvestrol alleviates the cytotoxicity of etoposide, Ara-C, or daunorubicin, while higher concentrations (7.5–25 nM) potentiates this cytotoxicity in HL-60, OCI/AML-2 and OCI/AML-3 cells.[29] In the case of U937 cells, it is the opposite: at high concentration (100 nM) silvestrol decreases the cytotoxic effects of these agents, but potentiates them at 7.5 and 10 nM.

More importantly, Pelletier and co-workers demonstrated that silvestrol also enhances doxorubicin chemosensitivity in mouse lymphoma models in which phosphatase and tensin homolog (PTEN) is invalidated or eIF4E is overexpressed.[16,8] Independently, Li-Weber and collaborators showed that monodesmethyl rocaglamide increased the antileukemia effect of concanavalin A in vivo in a mouse T lymphoma xenograft model.[20]

2.5. In vivo studies in mouse models of cancers

The in vivo antileukemic activity of rocaglamide was demonstrated by King and co-workers following their immediate discovery of this compound.[1] Later, Pezzuto and co-workers showed that a rocaglate derivative delays for 23 days the growth of a human breast cancer cell line (BC1) in athymic mice.[9] New in vivo studies have been recently performed (Table 2). Probably, the most impressive one was performed by Pelletier and collaborators who found that silvestrol suppresses human tumor growth in MDA-MB-231 breast cancer xenografts.[8] In this experiment, an increased apoptosis and a decreased proliferation were coupled with an inhibition of angiogenesis. The potent activity of silvestrol in this model might be explained by the concept of oncogene addiction: cancer cells constitutively activate a signaling pathway, which is required for their survival and growth. In that case, the addiction of MDA-MB-231 for eIF4A signaling would be responsible for silvestrol efficacy.

Lucas and collaborators showed that silvestrol extends the life of mice in xenograft models of acute lymphoblastic leukemia.[32] Altogether, these in vivo studies prompted NCI to pursue the examination of silvestrol in preclinical models of cancers.[32] Importantly, in all of these in vivo studies, neither silvestrol, nor monodesmethyl rocaglamide displayed any overt sign of toxicity in mice.

3. Hypothesis on the mode of action

Previous studies by Bayer scientists demonstrated the in vivo neuroprotective effects of flavaglines in animal models of stroke and Parkinson's disease.[33] It may seem odd than an anticancer drug could also display some neuroprotective effects; however there are some precedents in the literature. Rapamycin derivatives, which are currently used to treat cancers, display a potent neuroprotection in animal models of neurodegeneration and traumatic brain injury.[34,35] Similarly, histone deacetylase inhibitors, which were originally developed to treat cancers, have emerged as promising drug candidates for the treatment of neurodegenerative disorders.[36,37]

A puzzling question is: Why do flavaglines promote the death of cancer cells and cell survival in neurons? We hypothesize that these compounds cause a stress of the endoplasmic reticulum that will induce a pre-conditioning response in non-cancer cells (i.e., the induction of a defense mechanism that will prepare the cells to overcome a major insult) and provocate apoptosis in cancer cells. This theory is supported by the following observations:

Table 1
In vitro potentiation of anticancer agents' cytotoxicity by flavaglines

Flavagline	Anticancer drug	Cancer cell line	Refs.
Silvestrol	Doxorubicin and rapamycin	MDA-MB-231 (breast cancer)	8
Rocaglaol and FL3	Doxorubicin	HepG2 (hepatocellular carcinoma)	7
Silvestrol	Etoposide, Ara-C, daunorubicin and ABT-737 (Bcl-XL/Bcl-2 inhibitor)	NB4 (acute myelogenous leukemia)	29
1-*O*-Formyl-rocaglaic acid	TRAIL	TRAIL-resistant human gastric adenocarcinoma cells	21
1-Oxo-11,12-methylenedioxy-rocaglaol*	TRAIL and CD95 ligand	HTLV-1 associated leukemia/lymphoma	17

* Healthy T cells were not sensitized toward CD95 ligand and TRAIL-induced apoptosis.

Table 2
In vivo activity of flavaglines in mouse models of cancers

Compounds	Murine models of cancer	Refs.
Silvestrol	P388 murine leukemia	30
Silvestrol	PC3 human prostate cancer	31
Silvestrol + doxorubicin*	*Pten*$^{+/-}$*Eμ-Myc* and *Eμ-Myc*/*eIF4E*	16
Monodesmethyl rocaglamide + concanavalin A*	RMA mouse T lymphoma	20
Silvestrol	*Eμ-Tcl-1* transgenic mice and 697 xenograft SCID mice	32
Silvestrol	MDA-MB-231 breast and PC-3 prostate cancer xenograft	8

* Neither silvestrol alone nor monodesmethyl rocaglamide alone displayed any significant effect in these models.

- flavaglines activate the stress-responsive MAP kinases JNK and p38,
- flavaglines induces the translocation of caspase-12 to the nucleus of cancer cells, which indicate a disturbance of endoplasmic reticulum homeostasis. Moreover, they may also induce the formation of stress granules in cancer cells,
- it was recently demonstrated that abnormal number of chromosomes in cancer cells (phenomenon called as aneuploidy) triggers a so-called proteotoxic stress to correct the protein overload caused by the chromosome discrepancy, which makes cancer cells particularly vulnerable to autophagy inhibitors, heat shock protein 90 (Hsp90) inhibitor and inducers of the AMP-activated protein kinase (AMPK).[38,39]

It is therefore tempting to assume that, similarly, flavagline-induced stress synergizes with this proteotoxic stress to induce apoptosis selectively in cancer cells.

4. Newly discovered flavaglines

Since the review of Kinghorn and collaborators in 2006, six new flavaglines have been identified: 1-*O*-formylrocagloic acid (**6**), 3′-hydroxy rocagloic acid (**7**),[40] aglaroxin A 1-*O*-acetate (**8**), 3′-methoxyaglaroxin A 1-*O*-acetate (**9**),[41] 2‴-episilvestrol (10) and 2‴,5‴-diepisilvestrol (**11**)[42] (Fig. 5). All of these compounds exhibited potent cytotoxicity on human cancer cell lines.

5. Total syntheses

Rocaglamide has been first synthesized, in an enantiospecific manner in 1990, and since then, flavaglines have continued to attract the attention of the synthetic chemists due to their challenging compact structure that embeds two contiguous quaternary chiral centers and *cis* aryl groups on two adjacent carbons of a sterically congested cyclopentane ring. Since 2006, four new syntheses of flavaglines have been devised by the groups of Qin, Frontier, Moser and Magnus.[43–46] Additionally Porco and Rizacaza reported the synthesis of silvestrol that includes an unprecedented complex dioxanyl ring.[47,48] At the present time the strategies that remained the most convenient are those developed by Taylor, Dobler and Porco. Taylor developed a convenient synthesis of rocaglamide[49] that was later improved by Dobler: the Michael addition of benzofuranones **12** to cinnamaldehydes **13** resulting in adducts **14**. Formation and ring closure of cyanohydrins **15**, followed by a deprotection and stereospecific reduction of the ketones with $Me_4NBH(OAc)_3$ provided flavaglines **16** (Scheme 1).[12]

While the precedent approach is better suited for rocaglaol derivatives, the biomimetic approach developed by John Porco is more convenient to prepare flavaglines substituted by an ester in position 2 (Scheme 2). Photocycloaddition [3+2] of hydroxyflavones **17** with methyl cinnamate **18**, afforded cycloadducts **20** that underwent an acyloin rearrangement to build the flavagline cytoskeleton (**21**). Porco and collaborators recently examined the scope of the [3+2] photocycloaddition of hydroxyflavone **17** with various dipolarophiles and discovered that this reaction may involve a photoexcited triplet biradicaloid **19**.[50]

5.1. Qin's synthesis

Qin and colleagues modified Dobbler's approach by introducing an extra methoxycarbonyl to the Michael acceptor, eliminating the need to introduce this moiety in a later stage of the synthesis using Stiles carboxylation (Scheme 3).[44] Condensation of benzofuranone

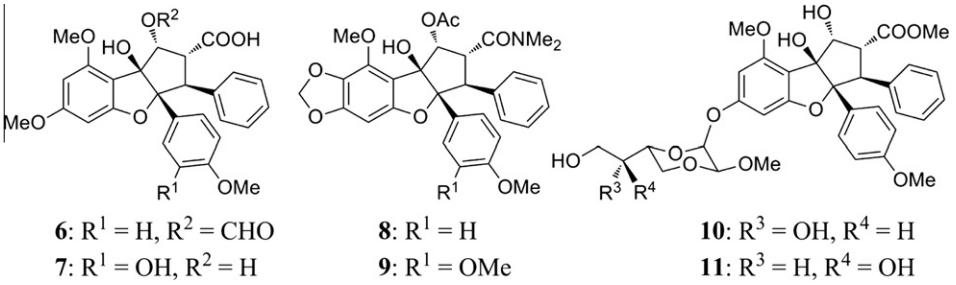
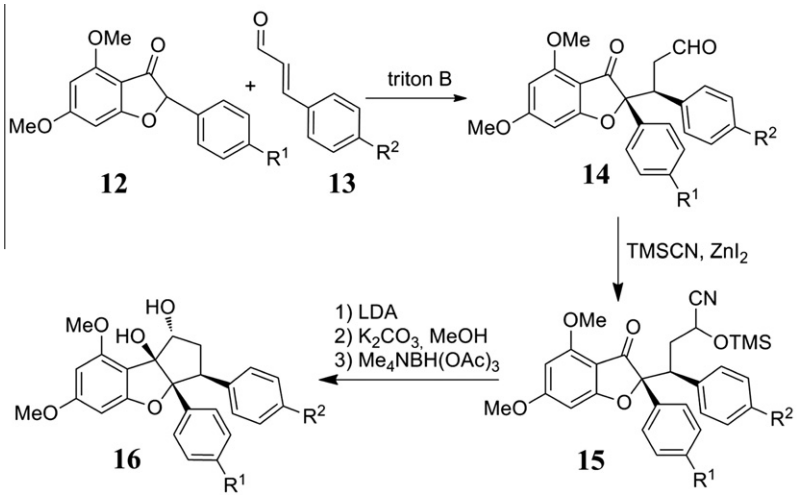
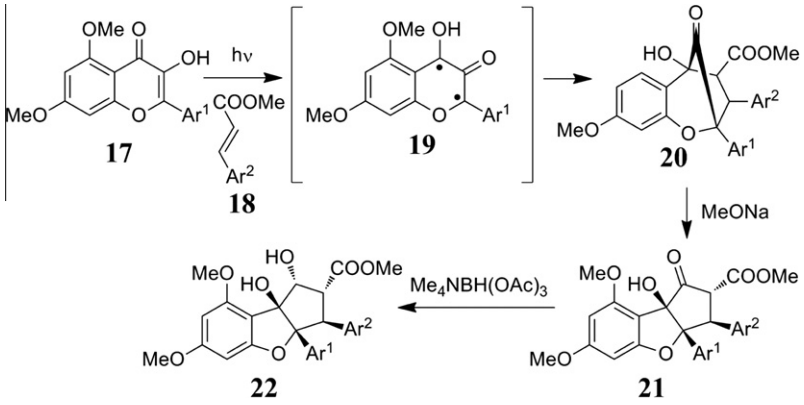


Figure 5. Recently discovered flavaglines.



Scheme 1.



Scheme 2.

12 with dimethyl benzylidenemalonate **23** afforded adduct **24** in 36% yield. Subsequent pinacol coupling promoted by SmI_2 afforded tricyclic adduct **25**, which was further transformed into rocaglamide **1** following Taylor's synthesis.

5.2. Frontier's synthesis

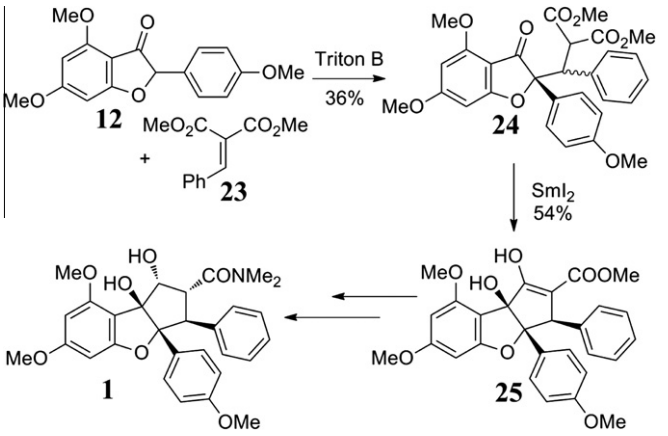
Frontier and co-workers developed an elegant Nazarov-type reaction to gain access to the skeleton of flavaglines (Scheme 4).[46] Similarly to Taylor, Dobler and Qin's approaches, their synthesis starts from benzofuranone **12** that was converted into aldehyde **26** by alkylation with vinyl magnesium bromide and cleavage of the resulting allylic alcohol. Introduction of the phenylacetylene moiety and protection of the propargylic alcohol afforded adduct **27** that was deprotonated with *tert*-BuLi and quenched with *n*-Bu_3SnCl to give the key intermediate **28**. The tricyclic core of flavaglines was then assembled through a Nazarov-type cyclization from highly reactive allenyl oxide **29** generated in situ with *m*-CPBA. The tributylstannyl group was cleaved off during this remarkable tandem oxidation-ring closure reaction. The resulting hydroxycyclopentenone **31** gave access to ester **32** using palladium-mediated carbonylation.

5.3. Moser's synthesis

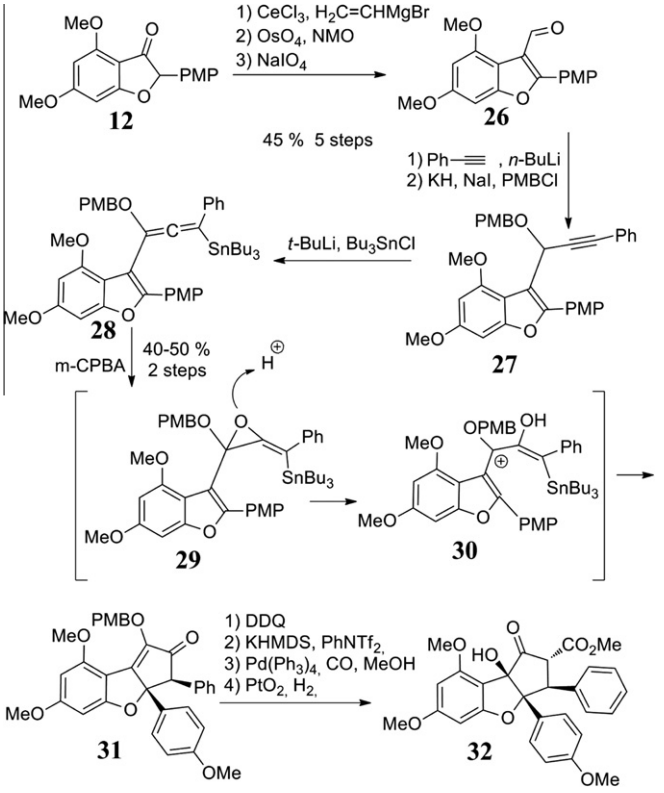
Giese and Moser prepared the tricyclic core of the flavaglines using a methodology developed in this laboratory.[43] Condensation of Fischer alkoxycarbene complex **33** with phenolate **34** afforded the adduct **35**, which was converted upon heating to a mixture of benzofuranes **36** and **37** (Scheme 5). [4+1] Annulation reaction with phenyldiazomethane and removal of the $Cr(CO)_3$ moiety led to **38**, which has the cyclopenta[*b*]tetrahydrobenzofuran core of the flavaglines but, unfortunately, not the substituents required for biological activities.

5.4. Magnus' synthesis

Magnus and co-workers prepared flavagline analog **44** through also a Nazarov type reaction in the key step. Intermediate **40** was prepared in 6 steps from **39** (Scheme 6).[45] Treatment with $SnCl_4$ induced its cyclization to **41**. Subsequent hydrosilylation, introduction of a carboxymethyl group and hydroxylation afforded 1,2-anhydro methyl rocaglate **44**.



Scheme 3.



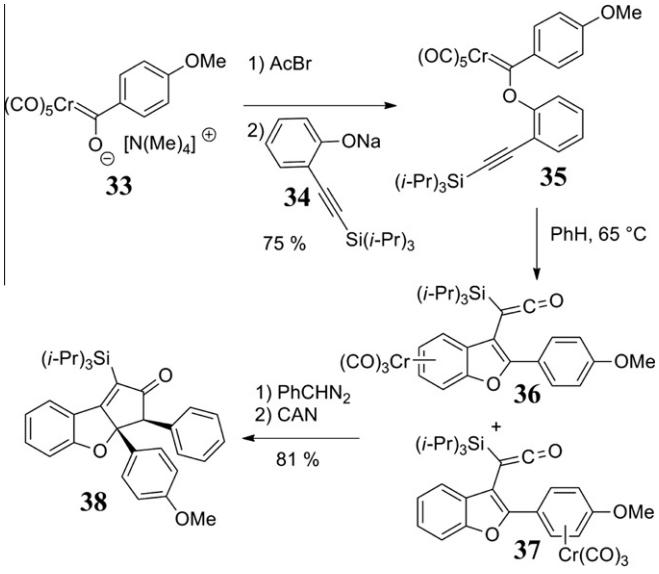
Scheme 4.

5.5. Porco and Rizzacasa syntheses of silvestrol

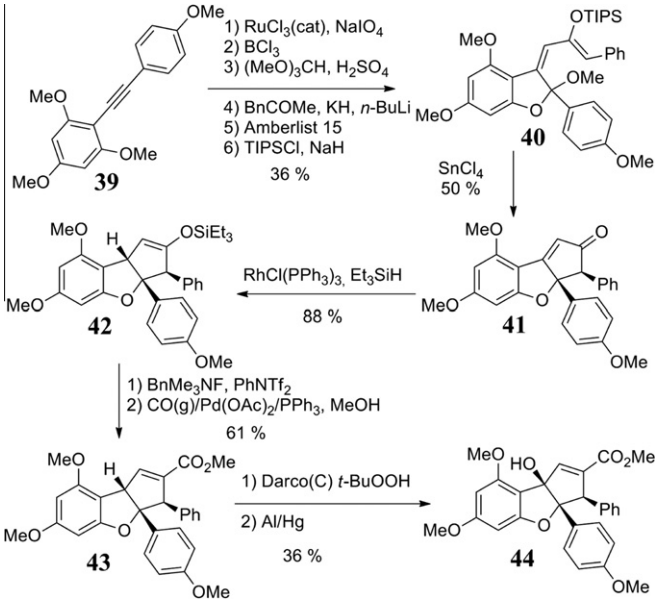
The total synthesis of silvestrol **3** has been independently reported by the teams of Porco and Rizzacasa in the same issue of *Angewandte Chemie*.[47,48] Both approaches relied on the synthesis of phenol **46** using Porco's biomimetic approach (Scheme 7). Mitsunobu coupling with dioxanyloxy fragment **47** and a final deprotection furnished silvestrol.

The main differences between Porco and Rizzacasa's approaches lied on:—the preparation of hydroxyflavone **45**, the manner to obtain enantiomerically pure the flavagline skeleton and the synthesis of the 1,4-dioxanyloxy intermediate **47**.

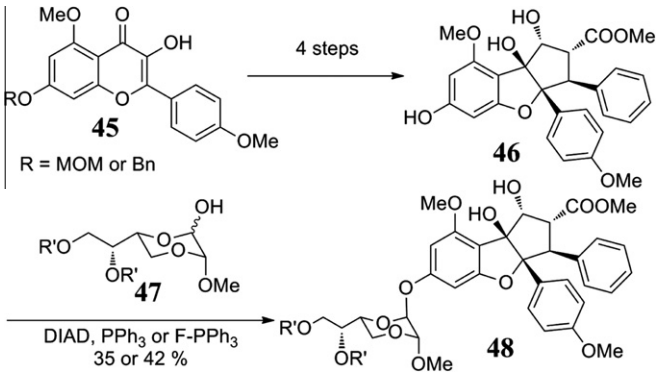
Porco and collaborators condensed diol **49** with 2-bromo-2-methoxy acetate to obtain lactone **50** that was reduced by DIBAL to afford **47a** (Scheme 8).[48]



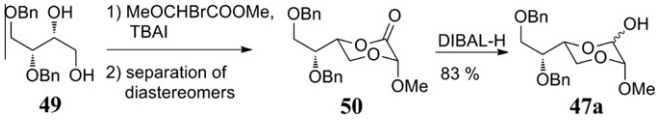
Scheme 5.



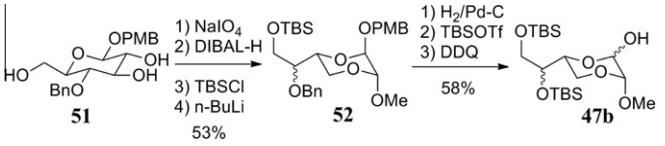
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

Rizzacasa's approach was based on the periodic cleavage of D-glucose derivative **51**, followed by a reduction with DIBALH, protection with TBSCl, and O-methylation to afford **52** (Scheme 9).[51,47] Replacement of the benzyl ether by a TBS ether followed by oxidative removal of the *p*-methoxybenzyl group yielded the expected lactol **47b**, which underwent a Mitsunobu coupling with the cyclopenta[*b*]benzofuran core of silvestrol.

6. Conclusion and future directions

Albeit their molecular target remains unknown, the mechanism of action of flavaglines begins to be unraveled. In particular, the inhibition of the MEK-ERK-Mnk1-eIF4A pathway may account for the specific cytostatic and cytotoxic effects toward cancer cells. Several teams demonstrated that flavaglines enhance the in vivo efficacy of anticancer treatments, and may limit the resistance of cancer cells to chemotherapies. These data suggest a great therapeutic potential for flavaglines as adjuvants of chemotherapies for the treatment of cancers.

In 2005, Bayer scientist reported that flavaglines display spectacular neuroprotective activity, both in vitro and in mouse models of brain trauma and Parkinson's disease.[33] Surprisingly, no other reports regarding this neuroprotection appeared since then. Considering the current societal impact of neurodegenerative diseases, it should be rewarding to pursue this line of investigation.

The continuous interest in the pharmacology of flavaglines is likely to grow and to lead to the identification of their molecular target. Understanding the molecular mode of action will allow a determination of which optimal clinical context these drugs may prove their usefulness. Hopefully, a unique pharmacological profile associated to a lack of toxicity will prompt further studies that will be translated in clinical trials.

Note Added in Proof

While this paper was under review, another review appeared on the same topic.[52]

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