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REVIEW

Flavaglines: Discovery From Plants Used in Traditional Chinese Medicine, Synthesis and Drug Development against Cancer and Immune Disorders

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Abstract: Flavaglines, a family of compounds coming from plants used in Traditional Chinese Medicine, exhibit a broad range of biological effects including anticancer, antiviral, cardioprotectant and anti-inflammatory activities. They exert their action by targeting the scaffold proteins called prohibitins-1 and -2, and the mRNA helicases eIF4A and DDX3. Flavaglines are densely functionalized cyclopenta[*b*]benzofurans that have attracted the attention of some of the most eminent organic chemists. This review provides an overview of the biosynthesis, total synthesis and pharmacological activities of flavaglines, which recently culminated with the entrance of a synthetic derivative, Zotatifin, into clinical trials against advanced solid tumors refractory or intolerant to standard treatments.

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1. INTRODUCTION

The plant genus *Aglaia* found in the tropical and subtropical rainforest of southern China, the Indo-Malayan region, some Pacific Islands and Northern Australia is characterized by benzo[*b*]oxepines, cyclopenta[*b*]benzofurans (also called flavaglines) and cyclopenta[*bc*]benzopyrans [1]. These trees have a long history in traditional medicine. In China, the branches and leaves of *Aglaia odorata* are often decocted or made into externally applied ointment to treat pain in rheumatic joints, injuries from falls, superficial infections and toxic swellings. Its flowers are recommended against distress of chest and diaphragm, common cold and cough [2]. The bark decoction of *Aglaia elliptica*, is used to treat tumors, whereas its flowers are applied to wounds [3].

In India, *Aglaia roxburghiana* is traditionally used in Ayurvedic medicine against inflammation, leprosy, throat infections, bilious and febrile complaint, and also to treat snake and scorpion bites [4, 5]. *Aglaia elaeagnoidea* and *Aglaia Lawii* are used to treat diarrhea, skin diseases, bacterial infection, headaches, liver diseases and tumours [6].

In Thailand, *Aglaia odorata* is used as a tonic, febrifuge and a remedy for menorrhagia during the menopause [7].

Rocaglamide (**1**, Figures 1 and 2) was isolated in 1982 from a plant used in Traditional Chinese Medicine (TCM), *Aglaia elliptifolia* by Taiwanese scientists, King and collaborators [8]. These authors identified the structure of rocaglamide and demonstrated its anticancer activity in a murine model of leukemia. Since then, more than 100 flavaglines have been isolated from *Aglaia* species, and recently from trees of the gender *Dysoxylum* [1, 9, 10-12].

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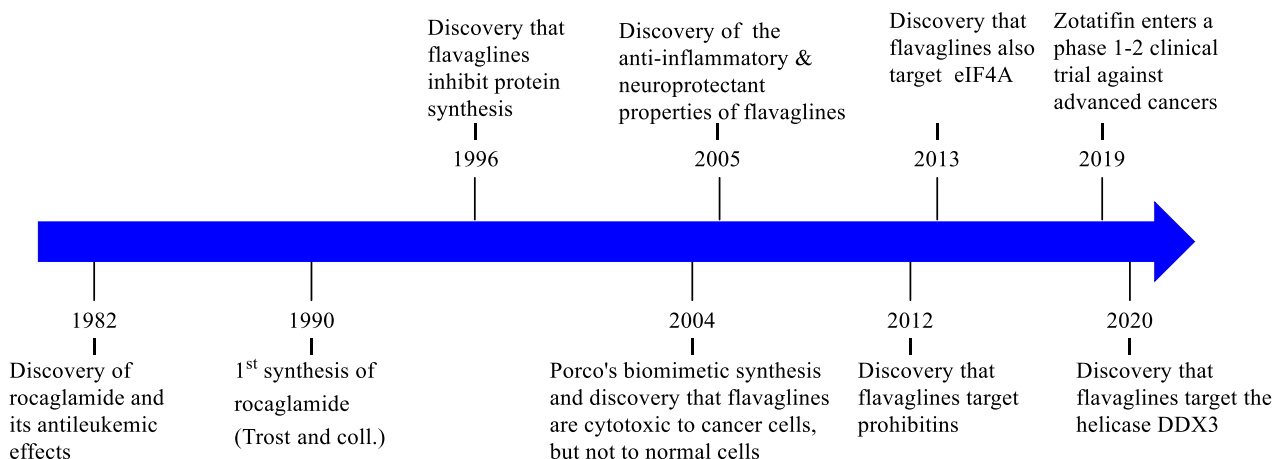


Figure 1. Major milestones achieved in the development of flavaglines as clinical candidates.

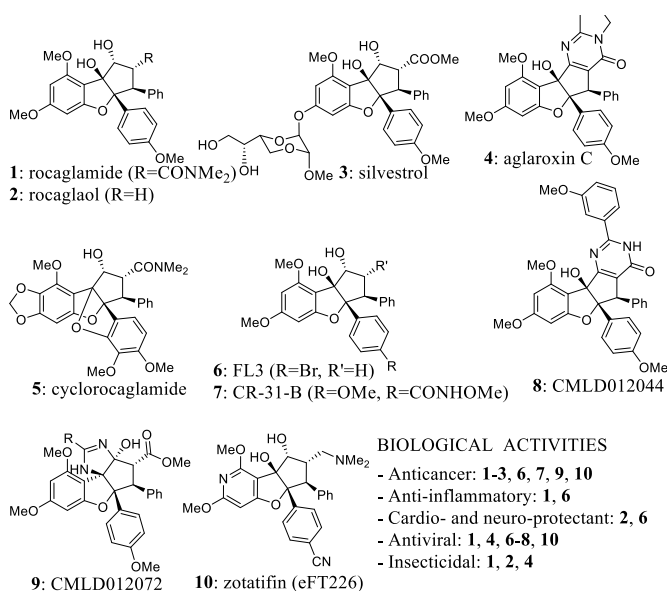


Figure 2. Representative examples of natural (1-5) and synthetic (6-10) flavaglines.

In the 1980's, this compound and some of its natural analogs were found to delay tumor growth in mice at the National Cancer Institute. But, as they did not eradicate these tumors, this investigation was interrupted.

In 2004, Marian and collaborators dubbed "flavaglines" this family of flavonol-cinnamate-derived cyclopenta[*b*] benzofurans as they stem for the metabolism of flavonoids in plants of the genus *Aglaiia*. Importantly, this team discovered that flavaglines induce the death of cancer cells without affecting normal cells [13].

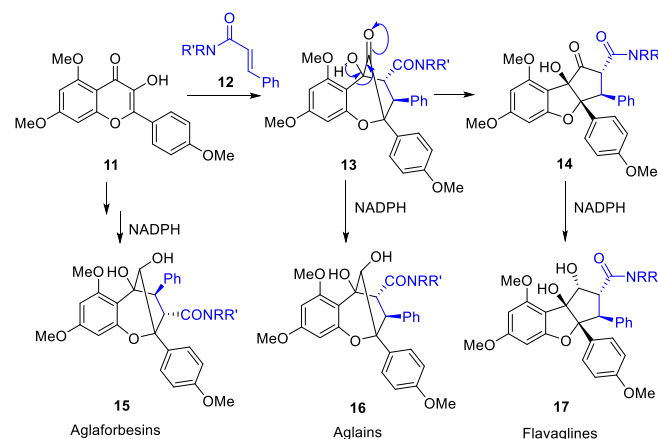
Thereafter, flavaglines were found to display anti-inflammatory, neuro- and cardioprotectant activities, suggesting that they not only display anticancer properties but also protect the organism against the adverse effect of chemotherapies.

The discovery in 2008 and 2012 that these drugs target the initiation factor of protein synthesis eIF4A [14-17] and prohibitins (PHBs) [18] greatly stimulated this field of research, leading to the advancement in 2019 of a synthetic

flavagline, zotatifin (also called eFT226) into of phase 1/2 clinical trial against advanced solid tumors refractory or intolerant to standard treatments [19]. Next year flavaglines were found to also target the mRNA helicase DDX3 [20].

2. BIOSYNTHESIS

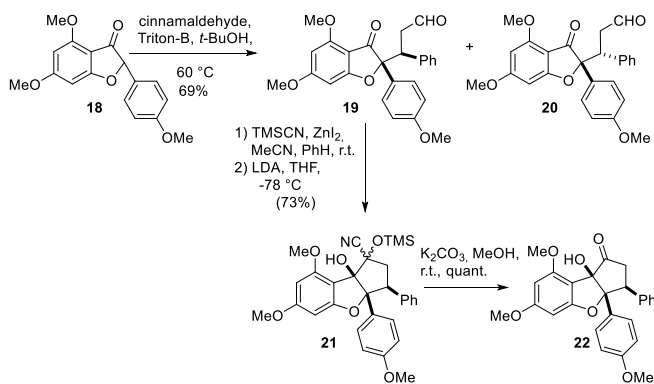
The coexistence of cinnamic amides **12**, aglaforbesins **15**, aglains **16** and flavaglines in the plants of the genus *Aglaiia*, led Proksch and coll. to propose the biosynthetic pathway presented in Scheme 1 [21]. A [3 + 2] condensation between a hydroxyflavone **11** and a cinnamic amide **12** generates benzo[*b*]oxepines **13**, which can be reduced to diols **16** or undergo acyloin rearrangement to afford flavaglines **17**. The presence of flavaglines in these plants probably stems from their potent insecticide activity [21-24].



Scheme 1. Biosynthesis of flavaglines proposed by Proksch and coll. [21].

3. TOTAL SYNTHESSES

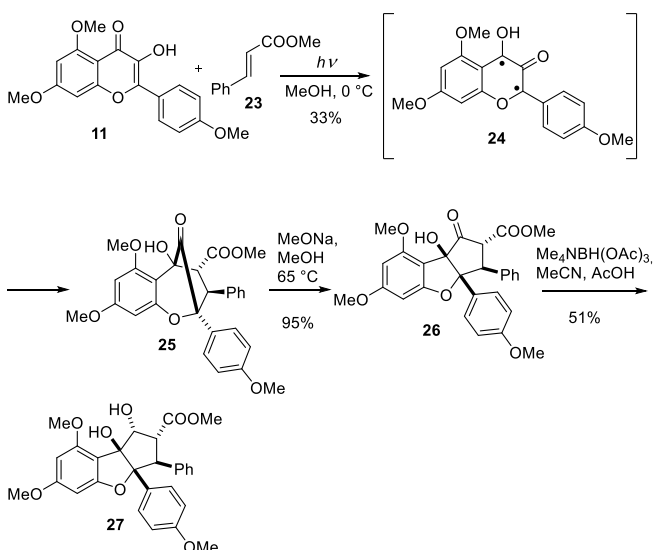
The densely functionalized tricyclic core of flavaglines represents a considerable challenge that was first taken up by Barry Trost [25]. Since then, other approaches have been described and recently reviewed [26]. However, only two strategies have been extensively used in medicinal chemistry



Scheme 2. Dobler's racemic synthesis of flavaglines [27].

programs. The first of these particularly practical approaches was originally developed by Richard Taylor and improved by Markus Dobler (Scheme 2) [27-29]. It is based on a Michael reaction between a benzofuranone **18** and cinnamaldehyde, followed by the formation of a cyanohydrin **21** that can be deprotonated to react with the ketone and provide the flavagline backbone.

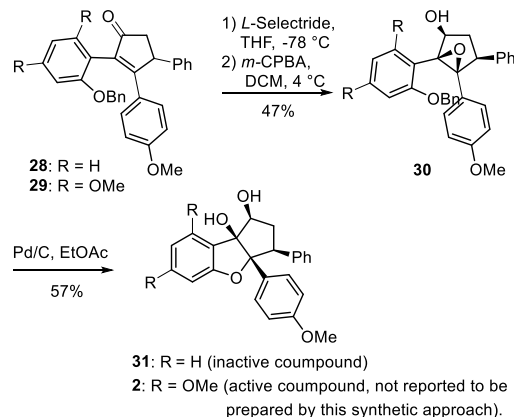
The second approach, inspired by the biosynthesis of flavaglines in plants, was developed by John Porco (Scheme 3) [30-33]. UV irradiation of a 3-hydroxyflavone **11** in the presence of a cinnamic ester or amide generates a photoexcited triplet biradical **24** capable of performing a [3 + 2] cycloaddition, to afford the aglain backbone (**25**). In the presence of a base, this adduct undergoes an α -acyloin rearrangement to generate the flavagline **26**.



Scheme 3. Porco's biomimetic synthesis of flavaglines [31].

Ragot and coll. at Bayer developed also a short synthesis of bis-demethoxyrocaglaol **31** that uses the intramolecular ring closure of epoxide **30** as a key step (Scheme 4) [34].

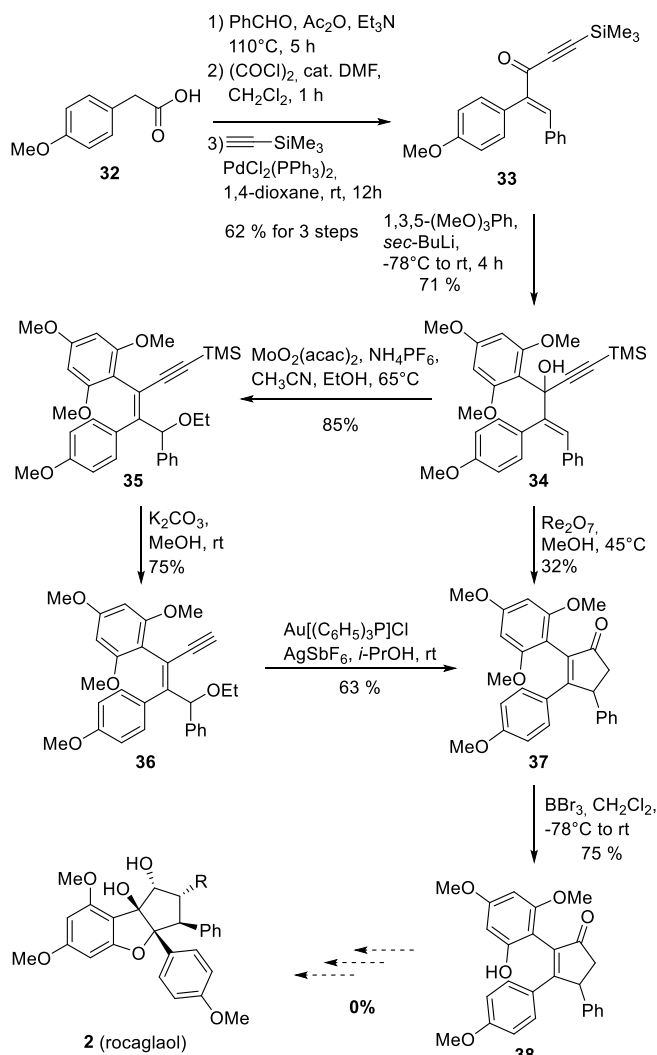
Unfortunately, this compound is not pharmacologically active, and the synthesis of rocaglaol (**2**) from cyclopentanone **29** was not reported.



Scheme 4. Bayer synthesis of bis-demethoxyrocaglaol **31**, a pharmacologically inactive analogue of rocaglaol (**2**) [34].

As part of our medicinal program to develop flavaglines with improved pharmacological properties, we considered using this strategy to prepare new derivatives. For this purpose, we developed two efficient syntheses of the cyclopentenone **37** substituted by the different aryl moieties necessary for the pharmacological activity (Scheme 5). The first approach lied on a gold(I)-catalyzed cyclopentanone formation that was originally described with tertiary silyl ethers [35]. This synthesis began with a Perkin condensation of acid **32** and benzaldehyde followed by the conversion to an acyl chloride and a Sonogashira coupling that afforded ketone **33** as a sole *E* isomer [36]. Condensation with lithiated trimethoxybenzene, molybdenum (VI)-catalyzed transposition and etherification of allylic alcohol **34** conveniently furnished the allylic ether **35**. Gratifyingly, gold(I)-catalyzed annulation of alkyne **36** afforded the cyclopentenone **37** in 63% yield.

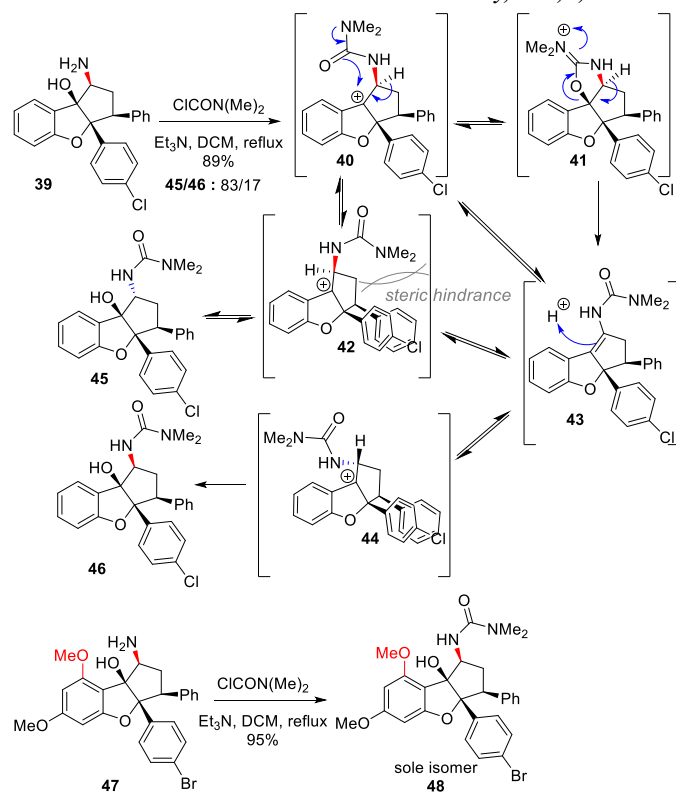
During the development of this synthesis, we serendipitously found that Re_2O_7 efficiently catalyzes the formation of cyclopentenone **37** directly from styryl-propargyl alcohol **34** [36]. This type of reaction has not been described before. It represents an interesting alternative to the Rautenstrauch rearrangement. Selective monodemethylation using BBr_3 efficiently afforded phenol **38** in a 75% yield (Scheme 5). Unfortunately, all our attempts to construct the flavagline scaffold from this compound, including variation around the strategy developed by Ragot and coll. were unsuccessful. This explains also why these authors didn't use this method to synthesize compounds substituted with the methoxy groups necessary for a pharmacological activity.



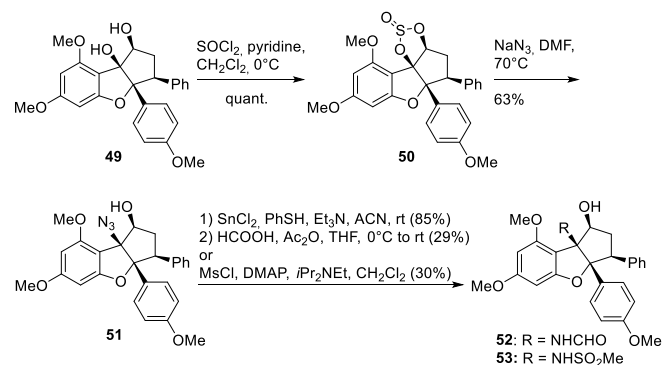
Scheme 5. Gold and rhenium-catalyzed formation of cyclopentanone **38** and failed attempt to prepare rocaglaol (**2**) [36].

These two methoxys were also found to modulate the chemical reactivity of flavaglines. Thus, we found that acylation of amine **39** with dimethylcarbamoyl chloride at reflux in dichloromethane afforded a mixture of carbamates **45** and **46** in a 83/17 ratio (Scheme 6) [37]. This unusual inversion of configuration of an aminoalcohol was not observed with flavagline **47**. The mechanism of this reaction probably involves the benzylic carbocation **40**, which may either afford the styrylurea **43** or undergo a ring closure to form the oxazolidinone dimethyliminium salt **41**. The latter may also undergo a rearrangement into **43**. Upon protonation and hydration **43** may generate the hydroxyureas **45** and **46** via the carbocations **42** and **44**, with a strong preference for the thermodynamically more stable isomer **45**.

This possibility to generate a stabilized carbocation was exploited to introduce an azide in position 1a from the cyclic sulfite **50** (Scheme 7) [38]. Reduction and acylation thereof provided the formamide **52** and the sulfonamide **53**, which, unfortunately, were found to be pharmacologically inactive.



Scheme 6. Carbamylation of flavaglines **39** and **47** [38].



Scheme 7. Synthesis of 1-azaisosteres **52** and **53** [38].

4. MECHANISM OF ACTION AND PHARMACOLOGICAL ACTIVITIES

Flavaglines mediate their biological activities by inhibiting the mRNA helicases eIF4A and DDX3 and also by modulating the activity of the scaffold proteins prohibitins-1 and [2 (PHB1/2) (Figure 3). eIF4A is a helicase that unwinds strongly structured mRNA. Only a small number of mRNAs, which mainly code for proteins involved in cancer, need this helicase for their translation. Flavaglines stabilize eIF4A complexed to mRNAs, which prevents the liberation and recycling of eIF4A, leading to an inhibition of its activity [39]. Importantly, this inhibition seems to affect every cancer cell type, including persister cells that usually tolerate anticancer drugs and are at the origin of acquired resistance

and cancer relapse. The inhibition of eIF4A also relieves the resistance to BRAF and MEK inhibitors in a murine model of metastatic melanoma, prevents the immune escape of tumor cells by blocking inhibitory checkpoints, abrogate taxane resistance in prostate cancer and synergizes with MEK inhibitors to kill NRAS-mutant cancer cell lines.

Recently, using the *O*-nitrobenzoxadiazole-conjugated derivative of rocaglamide **54**, Iwasaki and coll. found that flavaglines also target the helicase DDX3 [20]. Indeed this probe was found to perform a proximity-specific fluorescence labeling of both eIF4A and DDX3 (Figure 4).

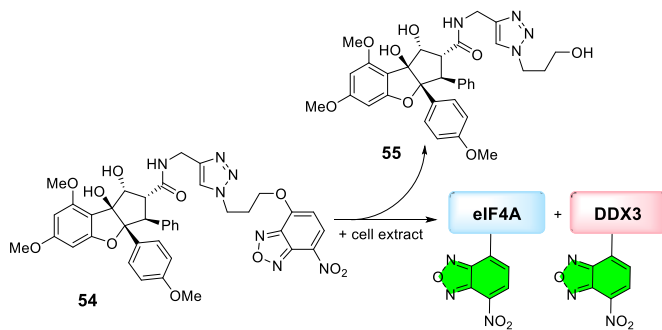


Figure 4. Proximity-specific fluorescence labeling of the mRNA helicases eIF4A and DDX3 [20].

Like eIF4A, DDX3 belongs to the DEAD-box helicase family, which is quite conservative, explaining why flavaglines inhibit both of these proteins that are attractive targets against cancers.

In addition to these helicases, flavaglines also target prohibitins-1 and -2 (PHB1/2). These scaffold proteins exist as two isoforms in the animal kingdom where they regulate the activity of a myriad of signaling proteins [40-43].

PHBs are characterized by a stomatin/prohibitin/flotillin/HflK/HflC (SPFH) domain that is present in an evolutionarily conserved family of proteins in archaea, bacteria and eukaryotes [44]. Thus, through their actions on PHBs, flavaglines inhibit the activation of KRAS and C-RAF, to block the C-RAF/MEK/ERK pathway critical to the survival of many cancer cell types [45, 46]. In bladder cancer, flavaglines inhibit PHB1 phosphorylation by Akt, leading to removal of PHB1 in mitochondria and also upregulate GADD45 α to arrest cell cycle progression at the G2/M phase [47]. They also promote the expression of Axin 1 to inhibit Wnt/ β -catenin signaling and combat intestinal tumorigenesis [48]. Moreover, flavaglines block mitophagy and energy productions by inhibiting the effects of PHB2 on the mitochondrial inner protease PARL and LC3-II and by disrupting the complex PHB/SH2D4/STAT3 in mitochondria [49]. Indeed, they prevent the interleukine-6-induced phosphorylation of STAT3 leading to a reduction STAT3 transcriptional activity and HIF1 α stabilization in hepatocellular carcinoma.

Flavaglines can also induce apoptosis of cancer cells by activating AIF, and caspase-8 through yet uncharacterized mechanisms.

In addition to their antitumor effects, flavaglines protect the heart of mice against the adverse effects of doxorubicin, a widely used anticancer medicine that induces a severe cardiotoxicity in patients. This cardioprotective effect is also mediated by prohibitins: flavaglines induce a cardioprotection by inducing a translocation of PHB1 and STAT3 to mitochondria, a phosphorylation of HSP27 and an overexpression of PHB1 in cardiomyocytes [50, 51]. Altogether, these data suggest that flavaglines could improve the efficacy of chemotherapies and alleviate in the same time their adverse effects.

In line with the use of *Aglaia* extracts in traditional Chinese medicine to treat inflammatory diseases, flavaglines protect mice in a model of Crohn's disease in which inflammation is driven by epithelial ulceration of the colon [52]. Indeed, FL3 (**6**) decreased the inflammation of the colon and in the same time promoted the survival of the intestinal epithelial cells against the inflammatory stress.

Through their effects on eIF4A and/or PHBs, flavaglines have been shown to display potent antiviral activities against several types of viruses, including Chikungunya virus and coronaviruses [53-58].

5. DEVELOPMENT OF ZOTATIFIN (EFT226)

Founded in 2012 in California, eFFECTOR Therapeutics is a pharmaceutical company that developed the first flavagline to enter clinical trials [19]. When this project started, many patents had been filed by academic laboratories and several pharmaceutical companies (*Bayer* and its spin-off, *IMD Natural Solutions* (Germany), *Infinity Pharmaceuticals* (USA) and *Pierre Fabre* (France)) [59-62]. To generate some intellectual property, the chemists at eFFECTOR came up with the idea of replacing one of the carbons in the flavagline backbone with a nitrogen. In the course of their investigations, they noticed that compounds with a 40-degree aryl-aryl torsion as a preferred low-energy conformation tend to display higher potency (Figure 5).

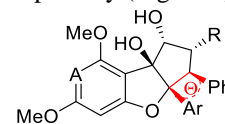


Figure 5. Conformational analysis. At the lowest energy conformation, $\Theta = 40^\circ$ is optimal for the inhibition of eIF4A [19].

This observation has been used prospectively to select the compounds to synthesize. The isostere **56** with a nitrogen in position 8 was found to be 25-fold less cytotoxic than rocaglamide in MDA-MB-231 breast cancer cells (Figure 6). In accordance with a previous report by another biotech company, *Infinity Pharmaceuticals* [61], the replacement of the methoxy in position 4' by a nitrile (**57**) enhanced the activity. Shifting the nitrogen and the methoxy (**57** \rightarrow **58**) improved further the cytotoxicity, but at the expense of CACO permeability and solubility. These two problems could be overcome by reducing the tertiary amide to a dimethylamine **59**. By shifting the nitrogen to position 7 and reinstalling the methoxy that had been removed, a compound

as cytotoxic as rocaglamide with improved solubility and permeability was identified. This compound, eFT226 (**10**), has successfully passed US regulatory preclinical requirements and entered phase 1/2 clinical trial against advanced solid tumors refractory or intolerant to standard treatments, under the name zotatifin [19]. To develop this clinical candidate, more than 20 000 flavagline derivatives were synthesized.

Thanks to the basic dimethylamino side chain, eFT226 is much more soluble than rocaglamide (>20 mg/mL), which greatly facilitates intravenous administration. eFT226 (1 mg/kg, intravenous administration) inhibited tumour growth in a MDA-MB-231 triple negative breast cancer orthotopic xenograft model treated once weekly for 2 weeks.

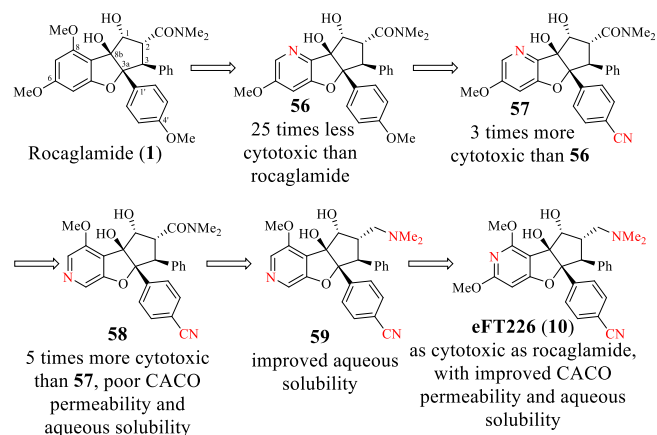


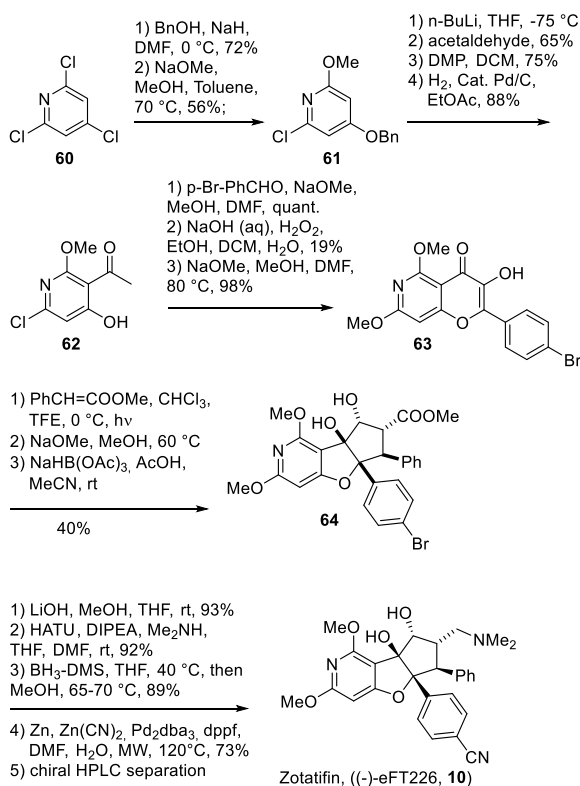
Figure 6. Summary of the development of eFT226 (Zotatifin) from rocaglamide by EFFECTOR scientists [19].

Biophysical studies demonstrated that eFT226 enhances the binding of polypurine RNA motifs to eIF4A independently of ATP similarly to eIF4A1. The mutation of phenylalanine 163 to leucine, which inhibits the binding of eIF4A to flavaglines, reduced the antiproliferative effects of eFT226 by a factor of 60, demonstrating that eIF4A is the main target to mediate its anticancer properties. Up to now, the effect of this compound on PHB signaling has not been reported. Zotatifin is not expected to be efficient against every type of tumors. EFFECTOR's scientist found that this drug is particularly effective in cancers where the kinase mTOR is driving mRNA translation, such as diffuse large B-cell lymphoma (DLBCL), and Burkitt lymphoma. In mouse models of these two types of lymphoma, eFT226 displayed impressive anticancer activities at low doses (1 mg/kg/week i.v.) [63].

The synthesis of zotatifin was achieved using Porco's biomimetic synthesis to construct the flavagline scaffold prepared by lithiation of pyridine derivative **61** using classical reactions.

6. Conclusion and perspective

Since their discovery in 1982, flavaglines have attracted the attention of many organic chemists due to the challenge posed by the complexity of their structure. So far only two



Scheme 8. Synthesis of zotatifin, ((-)-eFT226) [19].

methods are used in medicinal chemistry: that of Taylor and Dobler, and that of Porco.

Regarding the pharmacological studies of these compounds, these are dominated by their anticancer effects, with as a culmination the entry of Zotatifin in clinical trials against advanced solid tumors refractory or intolerant to standard treatments. In this area, the major obstacle is to identify how to combine flavaglines with other drugs to optimize their anticancer effects in patients. Although *in vivo* cytoprotective, antiviral, anti-inflammatory and immunosuppressive effects have been demonstrated, the exploration of these effects should increase in the coming years, even if it remains marginal for the moment compared to studies in oncology.

In addition to their potential, flavaglines have been shown to be useful as chemical tools to explore the function of prohibitins and eIF4A. To our knowledge, the involvement of these targets in the mechanism of action of traditional medicine preparations incorporating *Aglaia* extract has not yet been reported.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

- [1] Harneti, D.; Supratman, U., Phytochemistry and biological activities of *Aglaia* species. *Phytochemistry*, **2021**, *181*, 24.
- [2] Heyne, K.. *The Useful Indonesian Plants*, Research and Development Agency. Ministry of Forestry, Jakarta, Indonesia, pp. 1029–1045, **1987**.
- [3] Lemmens, R.H.M.J.; Soerianegara, I.; Wong, W.C. *Plant Resources of South-East Asia. No. 5(2): Timber trees: minor commercial timbers*. Backhuys Publishers: Leiden, **1995**.
- [4] Janaki, S.; Vijayasekaran, V.; Viswanathan, S.; Balakrishna, K., Anti-inflammatory activity of *Aglaia roxburghiana* var. *beddomei* extract and triterpenes roxburghiadiol A and B. *J.Ethnopharmacology*, **1999**, *67*, (1), 45-51.
- [5] Ayyanar, M.; Ignacimuthu, S., Traditional knowledge of Kani tribals in Kouthalai of Tirunelveli hills, Tamil Nadu, India. *J. Ethnopharmacology*, **2005**, *102*, (2), 246-255.
- [6] Khare, C.P. *Indian Herbal Remedies*. Springer-Verlag Berlin Heidelberg, **2004**.
- [7] Division., M.R. *Traditional medicine textbook (Thai drug)*. Office of the Permanent Secretary for Public Health, Ministry of Public Health, Bangkok, **1998**.
- [8] King, M.L.; Chiang, C.C.; Ling, H.C.; Fujita, E.; Ochiai, M.; McPhail, A.T., X-ray crystal structure of rocaglamide, a novel antileukemic 1H-cyclopenta[*b*]benzofuran from *Aglaia elliptifolia*. *J. Chem. Soc., Chem. Commun.*, **1982**, (20), 1150-1151.
- [9] Greger, H.; Comparative phytochemistry of flavaglines (= rocaglamides), a group of highly bioactive flavolignans from *Aglaia* species (Meliaceae). *Phytochem Rev.* **2021**, doi: 10.1007/s11101-021-09761-5.
- [10] Yang, H.J.; Li, Y.N.; Yan, C.; Yang, J.; Zeng, Y.R.; Yi, P.; Li, Y.M.; Hao, X.J.; Yuan, C.M. Discovery and synthesis of rocaglaol derivatives inducing apoptosis in HCT116 cells via suppression of MAPK signaling pathway. *Fitoterapia*. **2021**, *151*, 104876.
- [11] Schulz, G.; Victoria, C.; Kirschning, A.; Steinmann, E., Rocaglamide and silvestrol: a long story from anti-tumor to anti-coronavirus compounds. *Nat. Prod. Rep.*, **2021**, *38*, (1): 18-23.
- [12] Pan, L.; Woodard, J.L.; Lucas, D.M.; Fuchs, J.R.; Kinghorn A.D., Rocaglamide, silvestrol and structurally related bioactive compounds from *Aglaia* species. *Nat. Prod. Rep.*, **2014**, *31*, (7): 924-39.
- [13] Hausott, B.; Greger, H.; Marian, B., Flavaglines: a group of efficient growth inhibitors block cell cycle progression and induce apoptosis in colorectal cancer cells. *Int. J. Cancer*, **2004**, *109*, (6), 933-940.
- [14] Bordeleau, M.-E.; Robert, F.; Gerard, B.; Lindqvist, L.; Chen, S.M.H.; Wendel, H.-G.; Brem, B.; Greger, H.; Lowe, S.W.; Porco, J.A., Jr.; Pelletier, J., Therapeutic suppression of translation initiation modulates chemosensitivity in a mouse lymphoma model. *J. Clin. Invest.*, **2008**, *118*, (7), 2651-2660.
- [15] Cencic, R.; Carrier, M.; Galicia-Vázquez, G.; Bordeleau, M.E.; Sukarieh, R.; Bourdeau, A.; Brem, B.; Teodoro, J.G.; Greger, H.; Tremblay, M.L.; Porco, J.A. Jr.; Pelletier J. Antitumor activity and mechanism of action of the cyclopenta[*b*]benzofuran, silvestrol. *PLoS One* **2009**, *4*, (4), e5223.
- [16] Chambers, J.M.; Lindqvist, L.M.; Webb, A.; Huang, D.C.S.; Savage, G.P.; Rizzacasa, M.A., Synthesis of biotinylated Episilvestrol: highly selective targeting of the translation factors eIF4A/II. *Org. Lett.*, **2013**, *15*, **2013**, (6), 1406–1409.
- [17] Sadlish, H.; Galicia-Vazquez, G.; Paris, C.G.; Aust, T.; Bhullar, B.; Chang, L.; Helliwell, S.B.; Hoepfner, D.; Knapp, B.; Riedl, R.; Roggo, S.; Schuierer, S.; Studer, C.; Porco, J.A. Jr.; Pelletier, J.; Movva, N.R., Evidence for a functionally relevant rocaglamide binding site on the eIF4A-RNA complex. *ACS Chem. Biol.*, **2013**, *8*, (7), 1519–1527.
- [18] Polier, G.; Neumann, J.; Thuaud, F.; Ribeiro, N.; Gelhaus, C.; Schmidt, H.; Giaisi, M.; Koehler, R.; Mueller, W.W.; Proksch, P.; Leippe, M.; Janssen, O.; Désaubry, L.; Krammer, P.H.; Li-Weber, M., The Natural Anticancer Compounds Rocaglamides Inhibit the Raf-MEK-ERK Pathway by Targeting Prohibitin 1 and 2. *Chem. Biol.*, **2012**, *19*, (9), 1093-1104.
- [19] Ernst, J.T.; Thompson, P.A.; Nilewski, C.; Sprengeler, P.A.; Sperry, S.; Packard, G.; Michels, T.; Xiang, A.; Tran, C.; Wegerski, C.J.; Eam, B.; Young, N.P.; Fish, S.; Chen, J.; Howard, H.; Staunton, J.; Molter, J.; Clarine, J.; Nevarez, A.; Chiang, G.G.; Appleman, J.R.; Webster, K.R.; Reich, S.H., Design of Development Candidate eFT226, a First in Class Inhibitor of Eukaryotic Initiation Factor 4A RNA Helicase. *J. Med. Chem.*, **2020**, *63*, (11), 5879-5955.
- [20] Chen, M.; Asanuma, M.; Takahashi, M.; Shichino, Y.; Mito, M.; Fujiwara, K.; Saito, H.; Floor, S.N.; Ingolia, N.T.; Sodeoka, M.; Dodo, K.; Ito, T.; Iwasaki, S., Dual targeting of DDX3 and eIF4A by the translation inhibitor rocaglamide A. *Cell Chem. Biol.*, **2021**, *28*, (4), 475-486.
- [21] Nugroho, B.W.; Edrada, R.A.; Wray, V.; Witte, L.; Bringmann, G.; Gehling, M.; Proksch, P., An insecticidal rocaglamide derivatives and related compounds from *Aglaia adorata* (Meliaceae). *Phytochemistry*, **1999**, *51*, (3), 367-376.
- [22] Ishibashi, F.; Satasook, C.; Isman, M.B.; Towers, G.H.N., Insecticidal 1H-cyclopenta[*b*]benzofurans from *Aglaia odorata*. *Phytochemistry*, **1993**, *32*, (2), 307-310.
- [23] Nugroho, B.W.; Edrada, R.A.; Gussregen, B.; Wray, V.; Witte, L.; Proksch, P., Insecticidal rocaglamide derivatives from *Aglaia duppereana*. *Phytochemistry*, **1997**, *44*, (8), 1455-1461.
- [24] Greger, H.; Pacher, T.; Brem, B.; Bacher, M.; Hofer, O., Insecticidal flavaglines and other compounds from Fijian *Aglaia* species. *Phytochemistry*, **2001**, *57*, (1), 57-64.
- [25] Trost, B.M.; Greenspan, P.D.; Yang, B.V.; Saulnier, M.G., An unusual oxidative cyclization. A synthesis and absolute stereochemical assignment of (-)-rocaglamide. *J. Am. Chem. Soc.*, **1990**, *112*, (24), 9022–9024.

- [26] Zhao, Q.; Abou-Hamdan, H.; Désaubry, L., Recent Advances in the Synthesis of Flavaglines, a Family of Potent Bioactive Natural Compounds Originating from Traditional Chinese Medicine. *Eur. J. Org. Chem.*, **2016**, 2016, (36), 5908-5916.
- [27] Dobler, M.R.; Bruce, I.; Cederbaum, F.; Cooke, N.G.; Diorazio, L.J.; Hall, R.G.; Irving, E., Total synthesis of (+/-)-rocaglamide and some aryl analogues. *Tetrahedron Lett.*, **2001**, 42, (47), 8281-8284.
- [28] Davey, A.E.; Taylor, R.J.K., A novel 1,3-dithiane-based cyclopenta-annellation procedure: Synthesis of the rocaglamide skeleton. *Chem. Commun.*, **1987**, (1), 25-27.
- [29] Davey, A.E.; Schaeffer, M.J.; Taylor, R.J.K., Synthesis of the novel anti-leukaemic tetrahydrocyclopenta[*b*]benzofuran, rocaglamide and related synthetic studies. *Chem. Commun.*, **1991**, (16), 1137-1139.
- [30] Gerard, B.; Jones, G.; Porco, J.A., A biomimetic approach to the rocaglamides employing photogeneration of oxidopyryliums derived from 3-hydroxyflavones. *J. Am. Chem. Soc.*, **2004**, 126, (42), 13620-13621.
- [31] S. D. Stone, N. J. Lajkiewicz, L. Whitesell, A. Hilmy, J. A. Porco Jr., Biomimetic kinetic resolution: highly enantio- and diastereoselective transfer hydrogenation of aglain ketones to access flavagline natural products. *J. Am. Chem. Soc.* **2015**, 137, (1), 525-530.
- [32] Wang, W.; Cencic, R.; Whitesell, L.; Pelletier, J.; Porco, J.A., Synthesis of aza-rocaglates via ESIPT-Mediated [3+2] photocycloaddition. *Chem. Eur J.*, **2016**, 22, (34), 12006-12010.
- [33] Yueh, H.; Gao, Q.; Porco, J.A.; Beeler, AB. A photochemical flow reactor for large scale syntheses of aglain and rocaglate natural product analogues. *Bioorg. Med. Chem.*, **2017**, 25, (23), 6197-6202.
- [34] Thede, K.; Diedrichs, N.; Ragot, J.P., Stereoselective Synthesis of (±)-Rocaglaol Analogues. *Org. Lett.*, **2004**, 6, (24), 4595-4597.
- [35] An, S.E.; Jeong, J.; Baskar, B.; Lee, J.; Seo, J.; Rhee, Y.H., Gold(I)-Catalyzed Synthesis of Highly Substituted 2-Cyclopentenones from 5-Siloxypent-3-en-1-ynes. *Chem. Eur. J.*, **2009**, 15, (44), 11837-11841.
- [36] Basmadjian, C.; Zhao, Q.; Désaubry, L., Exploratory studies toward a synthesis of flavaglines. A novel access to a highly substituted cyclopentenone intermediate. *Tetrahedron Lett.*, **2015**, 56, (5), 727-730.
- [37] Abou-Hamdan, H.; Désaubry, L., Unexpected Inversion of Configuration During the Carbamoylation of 1-Azaflavaglines. *Synlett*, **2020**, 31, (20), 2023-2026.
- [38] Zhao, Q.; Tijeras-Raballand, A.; de Gramont, A.; Raymond, E.; Désaubry, L., Bioisosteric modification of flavaglines. *Tetrahedron Lett.*, **2016**, 57, (26), 2943-2944.
- [39] Chu, J.; Zhang, W.; Cencic, R.; O'Connor, P.B.F.; Robert, F.; Devine, W.G.; Selznick, A.; Henkel, T.; Merrick, W.C.; Brown, L.E.; Baranov, P.V.; Porco, J.A. Jr.; Pelletier, J. Rocaglates induce gain-of-function alterations to eIF4A and eIF4F. *Cell Rep.* **2020**; 30, (8): 2481-2488.e5.
- [40] Hernando-Rodríguez B, Artal-Sanz M., Mitochondrial quality control mechanisms and the PHB (Prohibitin) complex. *Cells.* **2018**, 7, (12), 238.
- [41] Ande, S.R.; Xu, Y.X.Z.; Mishra, S., Prohibitin: a potential therapeutic target in tyrosine kinase signaling. *Signal. Transduct. Target Ther.* **2017**, 2, 17059.
- [41] Zi Xu, Y.X.; Ande, S.R.; Mishra, S., Prohibitin: A new player in immunometabolism and in linking obesity and inflammation with cancer. *Cancer Lett.* **2018**, 415, 208-216.
- [43] Mishra, S.; Nyomba, B.G., Prohibitin - At the crossroads of obesity-linked diabetes and cancer. *Exp Biol Med (Maywood)*, **2017**, 242, (11), 1170-1177.
- [44] Wang, D.; Tabti, R.; Elderwish, S.; Djehal, A.; Chouha, N.; Pinot, F.; Yu, P.; Nebigil, C.G.; Désaubry, L., SFPH proteins as therapeutic targets for a myriad of diseases. *Bioorg. Med. Chem. Lett.*, **2020**, 30, (22), 127600.
- [45] Yurugi, H.; Marini, F.; Weber, C.; David, K.; Zhao, Q.; Binder, H.; Désaubry, L.; Rajalingam, K., Targeting prohibitins with chemical ligands inhibits KRAS-mediated lung tumours. *Oncogene*, **2017**, 36, (33), 4778-4789.
- [46] Yurugi, H.; Zhuang, Y.; Siddiqui, F.A.; Liang, H.; Rosigkeit, S.; Zeng, Y.; Abou-Hamdan, H.; Bockamp, E.; Zhou, Y.; Abankwa, D.; Zhao, W.; Désaubry, L.; Rajalingam, K., A subset of flavaglines inhibits KRAS nanoclustering and activation. *J. Cell Sci.*, **2020**, 133, (12).
- [47] Yuan, G.; Chen, X.; Liu, Z.; Wei, W.; Shu, Q.; Abou-Hamdan, H.; Jiang, L.; Li, X.; Chen, R.; Désaubry, L.; Zhou, F.; Xie, D., Flavagline analog FL3 induces cell cycle arrest in urothelial carcinoma cell of the bladder by inhibiting the Akt/PHB interaction to activate the GADD45 α pathway. *J. Exp. Clin. Cancer Res.*, **2018**, 37, (1), 21.
- [48] Jackson, D.N.; Alula, K.M.; Delgado-Deida, Y.; Tabti, R.; Turner, K.; Wang, X.; Venuprasad, K.; Souza, R.F.; Désaubry, L.; Theiss, A.L., The Synthetic Small Molecule FL3 Combats Intestinal Tumorigenesis via Axin1-Mediated Inhibition of Wnt/beta-Catenin Signaling. *Cancer Res.*, **2020**, 80, (17), 3519-3529.
- [49] Ploeger, C.; Huth, T.; Sugiyanto, R.N.; Pusch, S.; Goepfert, B.; Singer, S.; Tabti, R.; Hausser, I.; Schirmacher, P.; Désaubry, L.; Roessler, S., Prohibitin, STAT3 and SH2D4A physically and functionally interact in tumor cell mitochondria. *Cell Death Dis.*, **2020**, 11, (11), 1023.
- [50] Ribeiro, N.; Thuaud, F.; Bernard, Y.; Gaidon, C.; Cresteil, T.; Hild, A.; Hirsch, E.C.; Michel, P.P.; Nebigil, C.G.; Désaubry, L., Flavaglines as Potent Anticancer and Cytoprotective Agents. *J. Med. Chem.*, **2012**, 55, (22), 10064-10073.
- [51] Qureshi, R.; Yildirim, O.; Gasser, A.; Basmadjian, C.; Zhao, Q.; Wilmet, J.P.; Désaubry, L.; Nebigil, C.G., FL3, a Synthetic Flavagline and Ligand of Prohibitins, Protects Cardiomyocytes via STAT3

- from Doxorubicin Toxicity. *PLoS One*, **2015**, *10*, (11), e0141826.
- [52] Han, J.; Zhao, Q.; Basmadjian, C.; Désaubry, L.; Theiss, A.L., Flavaglines Ameliorate Experimental Colitis and Protect Against Intestinal Epithelial Cell Apoptosis and Mitochondrial Dysfunction. *Inflamm. Bowel Dis.*, **2016**, *22*, (1), 55-67.
- [53] Taroncher-Oldenburg, G.; Müller, C.; Obermann, W.; Ziebuhr, J.; Hartmann, R.K.; Grünweller, A. Targeting the DEAD-Box RNA helicase eIF4A with rocaglates- A pan-antiviral strategy for minimizing the impact of future RNA virus pandemics. *Microorganisms*. **2021**; *9*, (3), 540.
- [54] Müller, C.; Obermann, W.; Karl, N.; Wendel, H.G.; Taroncher-Oldenburg, G.; Pleschka, S.; Hartmann, R.K.; Grünweller, A.; Ziebuhr, J., The rocaglate CR-31-B (-) inhibits SARS-CoV-2 replication at non-cytotoxic, low nanomolar concentrations in vitro and ex vivo. *Antiviral res.*, **2021**, *186*, 105012.
- [55] Mueller, C.; Obermann, W.; Schulte, F. W.; Lange-Gruenweller, K.; Oestereich, L.; Elgner, F.; Glitscher, M.; Hildt, E.; Singh, K.; Wendel, H.-G.; Hartmann, R. K.; Ziebuhr, J.; Gruenweller, A. Comparison of broad-spectrum antiviral activities of the synthetic rocaglate CR-31-B (-) and the eIF4A-inhibitor Silvestrol. *Antiviral Res.* **2020**, *175*, 104706.
- [56] Liu, S.; Wang, W.; Brown, L. E.; Qiu, C.; Lajkiewicz, N.; Zhao, T.; Zhou, J.; Porco, J. A., Jr.; Wang, T. T. A Novel Class of Small Molecule Compounds that Inhibit Hepatitis C Virus Infection by Targeting the Prohibitin-CRaf Pathway. *EBioMedicine* **2015**, *2*, 1600-6.
- [57] Zhang, W.; Liu, S.; Maiga, R. I.; Pelletier, J.; Brown, L. E.; Wang, T. T.; Porco, J. A. Chemical Synthesis Enables Structural Reengineering of Aglaroxin C Leading to Inhibition Bias for Hepatitis C Viral Infection. *J. Am. Chem. Soc.* **2019**, *141*, 1312-1323.
- [58] Zhou, X.; Xu, L.; Wang, Y.; Wang, W.; Sprengers, D.; Metselaar, H. J.; Peppelenbosch, M. P.; Pan, Q. Requirement of the eukaryotic translation initiation factor 4F complex in hepatitis E virus replication. *Antiviral Res.* **2015**, *124*, 11-9.
- [59] Fahrig, T.; Gerlach, I.; Horvath, E. A synthetic derivative of the natural product rocaglaol is a potent inhibitor of cytokine-mediated signaling and shows neuroprotective activity *in vitro* and in animal models of Parkinson's disease and traumatic brain injury. *Mol. Pharmacol.* **2005**, *67*, (5), 1544-1555.
- [60] The Michael J. Fox Foundation for Parkinson's Research. IMD-026259: an innovative drug for diseasemodifying treatment of Parkinson's disease. <https://www.michaeljfox.org/grant/imd-026259-innovative-drug-disease-modifying-treatment-parkinsons-disease> (Accessed August 19, **2021**).
- [61] Liu, T.; Nair, S.J.; Lescarbeau, A.; Belani, J.; Peluso, S.; Conley, J.; Tillotson, B.; O'Hearn, P.; Smith, S.; Slocum, K.; West, K.; Helble, J.; Douglas, M.; Bahadoor, A.; Ali, J.; McGovern, K.; Fritz, C.; Palombella, V.J.; Wylie, A.; Castro, A.C.; Tremblay, M.R., Synthetic Silvestrol Analogues as Potent and Selective Protein Synthesis Inhibitors. *J. Med. Chem.*, **2012**, *55*, (20), 8859-8878.
- [62] Marion, F.; Kaloun, E.B.; Lieby-Muller, F.; Perez, M.; Annereau, J.P.; Créancier, L., Flavagline derivatives. EP3164393A1, September 19, **2018**.
- [63] Thompson, P.A.; Eam, B.; Young, N.P.; Fish, S.; Chen, J.; Barrera, M.; Howard, H.; Sung, E.; Parra, A.; Staunton, J.; Chiang, G.G.; Gerson-Gurwitz, A.; Wegerski, C.J.; Nevarez, A.; Clarine, J.; Sperry, S.; Xiang, A.; Nilewski, C.; Packard, G.K.; Michels, T.; Tran, C.; Sprengeler, P.A.; Ernst, J.T.; Reich, S.H.; Webster, K.R. Targeting Oncogene mRNA Translation in B-Cell Malignancies with eFT226, a Potent and Selective Inhibitor of eIF4A. *Mol. Cancer Ther.* **2021**; *20*: 26-36.