Journal of Medicinal Chemistry

Brief Article

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Synthesis of Rocaglamide Hydroxamates and Related Compounds as Eukaryotic Translation Inhibitors: Synthetic and Biological Studies

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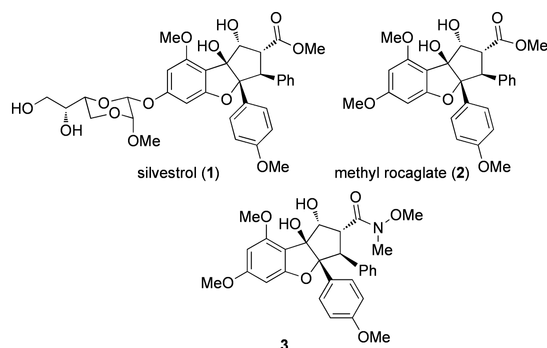
Supporting Information

ABSTRACT: The rocaglates/rocaglamides are a class of natural products known to display potent anticancer activity. One such derivative, silvestrol, has shown activity comparable to taxol in certain settings. Here, we report the synthesis of various rocaglamide analogues and identification of a hydroxamate derivative (−)-**9** having activity similar to silvestrol in vitro and ex vivo for inhibition of protein synthesis. We also show that (−)-**9** synergizes with doxorubicin in vivo to reduce Eμ-Myc driven lymphomas.

■ INTRODUCTION

A wealth of biologically active complex natural products have been isolated from the genus *Aglaia*, including the cyclopenta[*b*]benzofurans silvestrol (**1**) and methyl rocaglate (**2**), shown in Chart 1.[1] Silvestrol shows potent antiproliferative activity against lung, breast, and prostate cancer cell lines in vitro[1,2] comparable to the cancer chemotherapeutic agent taxol.[3] The compound reverses chemoresistance in an engineered murine lymphoma model by resensitizing tumor cells to standard-of-care agents such as doxorubicin,[4] dramatically suppresses tumor growth as a single agent in breast cancer and prostate cancer xenografts, and is well tolerated in animal models.[2,5] Previous characterization of silvestrol has shown that it inhibits the ribosome recruitment step of eukaryotic translation initiation through modulation of the RNA helicase, eukaryotic initiation factor (eIF) 4A.[4] Silvestrol has been the target of synthetic studies by both the Porco and Rizzacasa groups in which a convergent strategy was employed to join the cyclopenta[*b*]-benzofuran and dioxanyl fragments.[6] Given the synthetic challenge of preparing silvestrol, our group has endeavored to prepare cyclopenta[*b*]benzofuran analogues lacking the dioxanyl moiety present in silvestrol and to assess the resulting molecules as inhibitors of translation. A similar strategy has been adopted by Desaubry and co-workers, who reported synthetic cyclopenta[*b*]benzofurans that are active against various human cancer cell lines in vitro.[7]

Chart 1. Silvestrol (1), Methyl Rocaglate (2), and the Related Hydroxamate (3)



As part of a previous investigation of the substrate scope of the [3 + 2] photocycloaddition to construct the cyclopenta[*b*]benzofuran core, various analogues were prepared with substitutions of the C2 position, and (±)-rocaglamide hydroxamate **3**[8] was identified as having eukaryotic translation inhibition activity.[9] The features of the hydroxamate moiety present in **3** that relate to its properties as an inhibitor of translation may be due to its ability to act as a hydrogen bond acceptor or to chelate metals in the target binding site as depicted in **4** in Figure 1.[10] The carbonyl oxygen and atom "Y" in **5** and **6** may serve as a bidentate chelating moiety when Y is an atom with nonbonded electrons. This Lewis basic moiety may bind amino acid side chains or Lewis acidic metals represented as "A". Hydroxamate esters have been charac-

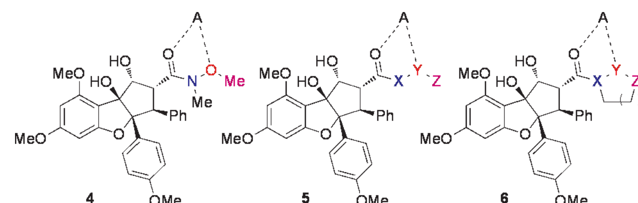


Figure 1. Possible coordination modes of **4**, **5**, and **6**.

Received: September 21, 2011
Published: November 30, 2011

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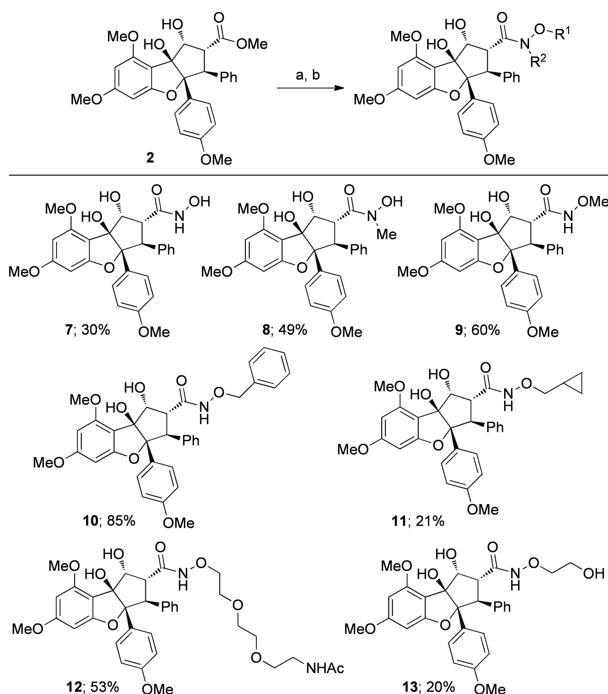
terized as MEK inhibitors in which case they appear to serve as hydrogen bond acceptors of lysine residues.[11]

■ RESULTS AND DISCUSSION

Using hydroxamate **3** as a lead structure, hydroxamates **7–9** were prepared with varying substitution of the *N*- and *O*-positions of the hydroxamate (Chart 2). *N*-Methoxy amide **9**

Chart 2. Hydroxamate Derivatives 7–13[a]



[a]Conditions: (a) LiOH, 1,4-dioxane, H_2O, 60 °C, 5 h; (b) EDCI, HOBt, $R^1ONR^2H{\cdot}HCl$, Et_3N, CH_2Cl_2.

was identified as the most potent derivative in translation assays, prompting the preparation of additional hydroxamate esters **10–13** from rocaglaic acid, prepared from the hydrolysis of methyl rocaglate (**2**).

Additional rocaglamides bearing the *N*-methoxyamide functionality were prepared in an effort to further establish SAR and optimize potency. Accordingly, methyl rocaglate (**2**) was investigated as a substrate for electrophilic aromatic substitution of the electron-rich phloroglucinol ring. It was anticipated that regioselectivity in the halogenation reactions could be observed based on a report suggesting the reaction of aromatics with NBS and $AuCl_3$ proceeded through an arylgold intermediate.[12] As shown in Table 1, quantitative conversion of methyl rocaglate was observed when reacted with NBS in THF for 50 min, yielding **14c** (60%) and an inseparable 1:2 mixture of **14a** and **14b**. Addition of $AuCl_3$ had no effect on the regioselectivity. Reaction of **2** with NCS, $AuCl_3$ (10 mol %) in THF at −78 °C proceeded to partial conversion, yielding a separable mixture of products **14d** (23%) and **14e** (29%), along with recovered **2** (47%), as proceeding to full conversion led to an inseparable mixture of **14e** and **14f**. Reaction of methyl rocaglate with Selectfluor in methanol formed product **14h** (40%) in addition to an inseparable mixture of **14g** and numerous undesired side products. Nitration of methyl rocaglate with $Cu(NO_3)_2$ in Ac_2O yielded **14i** in <5% yield and 26% of regioisomer **14j**. The halogenated and nitrated

Table 1. Conversion of Methyl Rocaglate to Halogenated and Nitrated *O*-Methylhydroxamates 15a–j[a]

(Scheme: 2 → (conditions) → 14a-j → (f, g) → 15a-j)

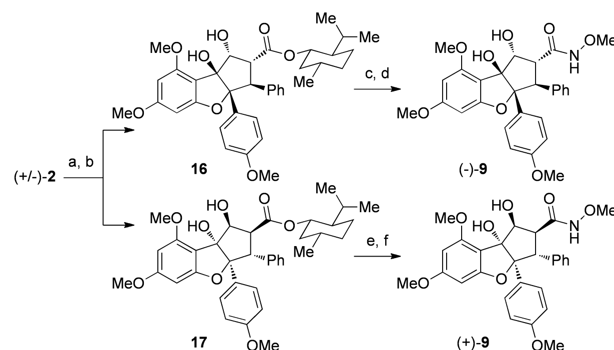
compound	R^1	R^2	conditions	compound	R^1	R^2	conditions
a	Br	Br	a	**f**	Cl	Cl	c
b	Br	H	a	**g**	H	F	d
c	H	Br	a	**h**	F	H	d
d	H	Cl	b	**i**	H	NO_2	e
e	Cl	H	b	**j**	NO_2	H	e

[a]Conditions: (a) NBS, THF, rt, 50 min; (b) NCS, $AuCl_3$ (10 mol %), THF, −78 °C, 5 h; (c) NCS, THF, rt, 6 h; (d) Selectfluor, methanol, rt; (e) $Cu(NO_3)_2$, Ac_2O, 6 h; (f) LiOH, 1,4-dioxane, H_2O, 60 °C, 5 h; (g) EDCI, HOBt, $MeONH_2{\cdot}HCl$, Et_3N, CH_2Cl_2.

methyl esters **14** were carried forward to the corresponding hydroxamates **15** by hydrolysis with lithium hydroxide in aqueous dioxane and subsequent *N*-methoxyamide formation with EDCI and HOBt.

For further biological studies, an enantiopure sample of the lead hydroxamate **9** was needed to compare to the enantiopure natural product, silvestrol (**1**). We have previously reported the asymmetric synthesis of methyl rocaglate (−)-**2**.[13] In the current study, we wished to prepare both natural and unnatural enantiomers of hydroxamate **9** for biological evaluation (Scheme 1). To achieve this goal, methyl rocaglate (±)-**2** was

Scheme 1. Preparation of Enantiomers of Hydroxamate 9[a]



[a]Conditions: (a) LiOH, 1,4-dioxane, H_2O, 60 °C, 5 h; (b) (−)-menthol, DCC, DMAP, CH_2Cl_2, 12 h, 60% combined for **16** and **17** (2 steps); (c) LiOH, 1,4-dioxane, H_2O, 60 °C, 5 h; (d) EDCI, HOBt, $MeONH_2{\cdot}HCl$, Et_3N, CH_2Cl_2, 65%; (e) LiOH, 1,4-dioxane, H_2O, 60 °C, 5 h; (f) EDCI, HOBt, $MeONH_2{\cdot}HCl$, Et_3N, CH_2Cl_2, 67%.

hydrolyzed and was esterified using (−)-menthol, DCC, and DMAP to yield menthyl esters **16** and **17**. The diastereomers were resolved by flash column chromatography and hydrolyzed to give both enantiomers of rocaglaic acid (>98% ee). Each enantiomer of rocaglaic acid was carried forward to *N*-methoxyamides (−)-**9** and (+)-**9** using methoxylamine hydrochloride, EDCI, HOBt, and Et_3N in CH_2Cl_2 in 65–67% yield.

To investigate the hypothesis that the hydroxamate moiety may serve as a chelating group to metals or as a hydrogen bond acceptor, a number of heterocyclic aromatic ketones and

amides with the appropriate heteroatoms were prepared.[14] Encouraged by a report that 2-lithiobenzothiazole undergoes single addition to esters due to the formation of a stable tetrahedral intermediate,[15] we anticipated that heterocyclic aromatic ketone analogues may be prepared directly from methyl rocaglate (Chart 3). Indeed, 2-lithiobenzothiazole (3.1 equiv) was prepared and reacted with methyl rocaglate at −78 °C for 1 h to yield the desired benzothiazole ketone **25** in 50% yield based on recovered starting material (BRSM). In a similar manner, 2-lithiopyridine was reacted with methyl rocaglate, and the desired pyridyl ketone **26** was formed in 40% yield (BRSM). Efforts to react other lithio heterocycles with methyl rocaglate were unsuccessful, and unreacted methyl rocaglate was recovered in most cases. Weinreb amide **3** was also investigated as a substrate for ketone formations and was found to react with a range of lithiated heterocycles including 2-lithiothiophene, 2-lithiofuran, and 2-lithiothiazole (Chart 4). Additional furan derivatives **27**−**28** were prepared by reaction of the lithiofurans with hydroxamate **3**.

Chart 3. Tetrahedral Intermediates From Reaction of Lithio-Heterocycles with Ester 2 and Hydroxamate 3

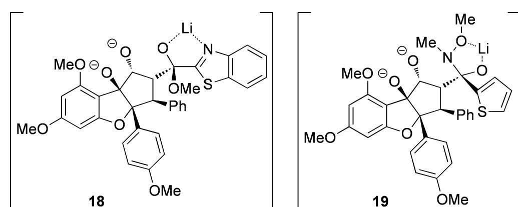
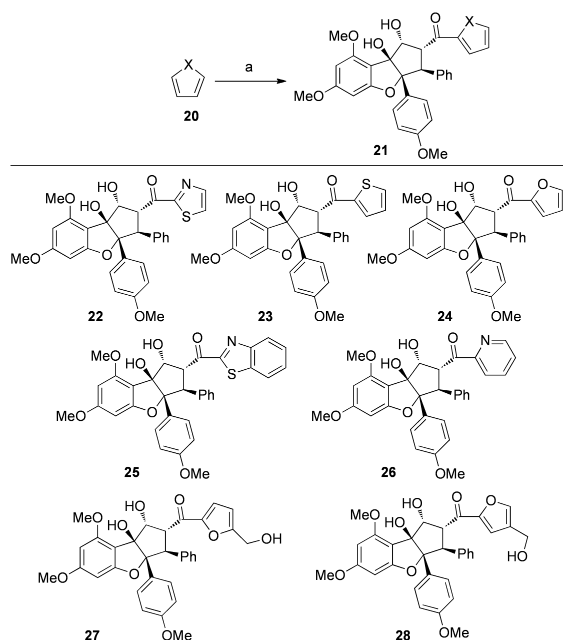


Chart 4. Synthesis of Ketones 22−28[a]



[a]Conditions: (a) (i) *n*-BuLi, THF, −78 or 0 °C, 30 min−1 h; (ii) **2** or **3**, THF, −78 °C to rt, 2 h.

Testing of all derivatives for translation inhibition activity revealed that only hydroxamate (−)-**9** inhibited eukaryotic protein synthesis to the same extent as silvestrol in vitro (Figure 2a,b). Hydroxamate (+)-**9** showed no activity, and the racemic mixture displayed partial activity (Figure 2a). Of the derivatives from series **10**−**13**, hydroxamates **11**−**13** also inhibited protein synthesis, with **11** showing similar activity to **9** (Figure 2a). Other derivatives such as furyl ketone **27** showed moderate activity, indicating that the furyl ketone can function as a hydroxamate replacement (cf. Figure 1). We therefore prepared (−)-**11** to compare its activity to (−)-**9**. Ex vivo testing of these active hydroxamates displayed a similar rank order for inhibition of translation (Figure 2c). Derivatives **12**−**13** appeared to be less potent in vitro and ex vivo (Figure 2a,c). The target of silvestrol has been previously identified by Pelletier and co-workers to be eIF4AI and eIF4AII, two RNA helicases required to load 40S ribosomes onto mRNA templates during the initiation phase of translation.[4] eIF4AI and eIF4AII (collectively referred to as eIF4AI/II) are 90% identical and functionally interchangeable. Silvestrol stimulates nonproductive binding of eIF4AI/II to RNA, sequestering it from the eIF4F complex, where it usually resides and from which it is delivered to mRNA templates to participate in ribosome recruitment.[4] In a filter binding assay designed to retain eIF4AI:^{32}P-RNA complexes, eIF4AI shows very little RNA binding activity (Figure 2d). eIF4AI RNA binding is increased in a dose-dependent manner by both silvestrol[6b] and

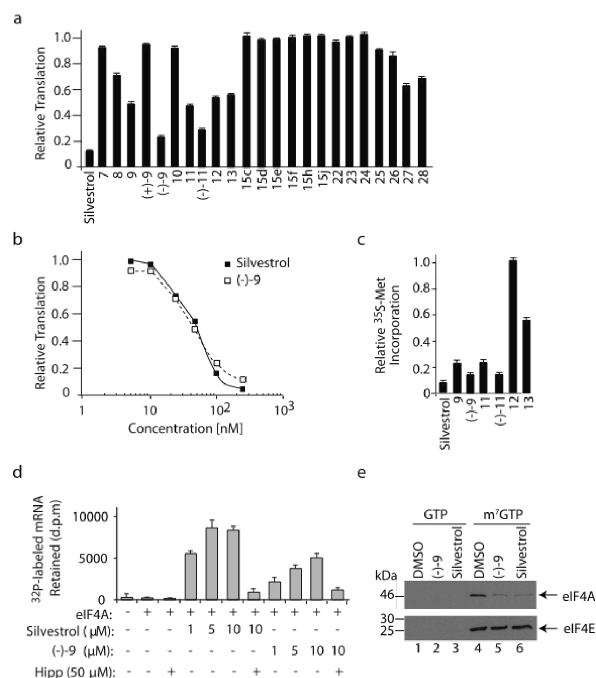


Figure 2. Hydroxamate (−)-**9** is equipotent to silvestrol in vitro. (a) Effect of hydroxamates and related compounds on cap-dependent in vitro translation. The activity relative to DMSO is presented. Results are the average of duplicates with the error of the mean shown. (b) Hydroxamate (−)-**9** inhibits cap-dependent in vitro translation in a dose-dependent manner. The activity relative to DMSO is presented. Values represent the average of duplicates with the error of the mean shown. (c) Inhibition of protein synthesis in HeLa cells by the most potent analogues tested in (a). Relative ^{35}S-Met incorporation is presented with values standardized against total protein content and plotted relative to vehicle (DMSO). Results are the average of duplicates with the error of the mean shown. (d) Hydroxamate (−)-**9** stimulates binding of eIF4AI to radiolabeled RNA. The average of three experiments with the standard error of the mean is presented. (e) Hydroxamate (−)-**9** depletes eIF4AI/II from the eIF4F complex. Eluents after m^{7}GTP affinity purification were resolved on a 10% SDS-PAGE gel followed by Western blot analysis for eIF4E and eIF4AI/II.

(−)-**9**. This property is inhibited by hippuristanol, a selective RNA binding inhibitor of eIF4AI/II.[16] The net effect of increased binding of eIF4A to RNA by silvestrol and (−)-**9** is depletion of eIF4AI/II from the eIF4F complex (Figure 2d).

Hydroxamate (−)-**9** and silvestrol displayed similar potencies toward inhibiting translation ex vivo in BJAB lymphoma cells that ranged from an $IC_{50} \sim 20$ nM when cells were exposed to compound for 1 h to an $IC_{50} \sim 0.5$ nM when cells were exposed to compound for 72 h (Figure 3a). The IC_{50} for inducing cell death in BJAB cells was found to be ∼1.5 nM following 72 h exposure, indicating that the observed effects on protein synthesis are not secondary consequences of cell death (Figure 3b). We have previously used engineered Pten$^{+/-}$Eμ-myc lymphoma cells to show that silvestrol and doxorubicin can synergize to extend tumor-free survival in this chemoresistant model.[4] We took advantage of this preclincial model and utilized Eμ-Myc(Myr)Akt tumors (with constitutive AKT activation) to show that (−)-**9** synergized with doxorubicin (DOX) to extend tumor-free survival to the same extent as silvestrol (Figure 3c). Hence, we have demonstrated that silvestrol is capable of synergizing with DOX against Eμ-Myc(Myr)Akt lymphomas and that (−)-**9** show activity that is indistinguishable from silvestrol.

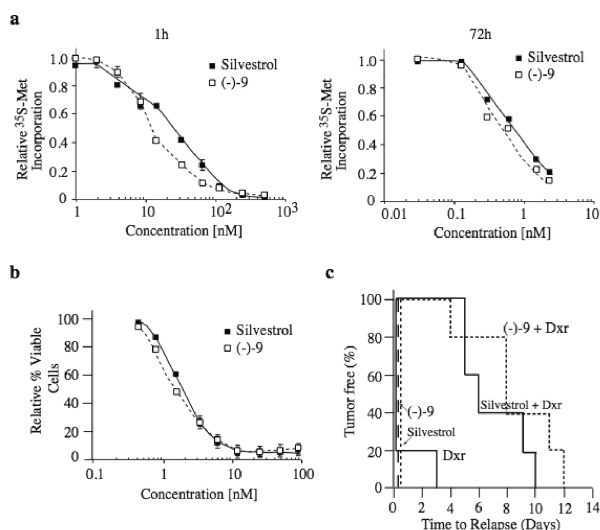


Figure 3. Hydroxamate (−)-**9** is equipotent to silvestrol ex vivo and in vivo. (a) Inhibition of protein synthesis by hydroxamate (−)-**9** in human Burkitts' lymphoma BJAB cells. Relative ^{35}S-Met incorporation is presented with values standardized to total protein content and plotted relative to vehicle (DMSO). Results are the average of duplicates with the error of the mean shown. (b) Effect on cell viability. BJAB cells treated for 72 h with the indicated concentrations of silvestrol or (−)-**9**, followed by propidium iodine staining and flow cytometry analysis. Results are the average of three experiments and plotted against vehicle controls. (c) Hydroxamate (−)-**9** synergizes with doxorubicin in vivo. Kaplan−Meier plot showing tumor free survival of mice bearing Eμ-myc/(myr)Akt tumors following treatment with doxorubicin (Dxr, n = 5), silvestrol (n = 5), (−)-**9** (n = 5), silvestrol and doxorubicin (Silvestrol+Dxr, n = 5), or (−)-**9** and doxorubicin ((−)-**9**+Dxr, n = 5). Treatment studies were performed on 6−8 week old C57Bl/6 mice that had received 10^6 Eμ-myc/(myr)Akt lymphoma cells intravenously. When tumors were palpable, mice were treated with silvestrol (0.2 mg/kg daily for 5 d), hydroxamate (−)-**9** (0.2 mg/kg daily for 5 d), or doxorubicin (once at 10 mg/kg), or combinations thereof. Compounds were administered in PEG 400/5.2% Tween 80 via intraperitoneal (ip) injection. For combination studies, mice were treated with silvestrol or hydroxamate (−)-**9** for five consecutive days, with doxorubicin being delivered once on the second day. $p < 0.001$ for combination vs single agent treatments.

In vitro pharmacokinetic properties of hydroxamate (−)-**9** were also evaluated (see Supporting Information (SI). The solubility of the compound was assessed to be high (>150 mg/mL) at three physiologically relevant pH levels (5.0, 6.2, and 7.4). The compound exhibited moderate to high permeability as measured by the parallel artificial membrane permeation assay (PAMPA) at pH 5.0, 6.2, and 7.4. The compound was significantly bound by human plasma proteins (82−84% bound after 4 h exposure), showed excellent stability (100% remaining after 3 h) in human plasma, and exhibited significant hepatic stability in the presence of human and murine liver microsomes (>95% compound remaining after 1 h exposure). These data suggest that hydroxamate (−)-**9** should exhibit significant metabolic stability in vivo. In vivo, hydroxymate (−)-**9** showed little toxicity toward the pre-B/B cell (B220+), myeloid (Ly6G+), and T cell (CD11b and CD4) populations from mice treated for 5 consecutive days (see SI, section III). These results indicate that at the doses used here, (−)-**9** does not lead to general depletion of normal cells of the hematopoietic system. The significant effects of eIF4A inhibition on BJAB viability (Figure 3b) as well as on global protein synthesis (Figure 2c) is more pronounced than has been described for suppression of eIF4E, another subunit of the eIF4F complex.[17] These results are consistent with global translation being more dependent on eIF4A activity than on eIF4E.[2]

CONCLUSION

In conclusion, various hydroxamates and heterocyclic ketone derivatives of cyclopenta[*b*]benzofurans (rocaglates) were prepared that could function as hydrogen bond acceptors or as metal chelators. Hydroxamate (−)-**9** was identified in this study as a potent eukaryotic translation inhibitor (Figures 2 and 3). Further characterization revealed that the compound is capable of synergizing with doxorubicin in extending tumor-free survival in a preclinical murine lymphoma model.

EXPERIMENTAL SECTION

General Methods. Proton NMR spectra were recorded at 500 MHz at ambient temperature in CD_3OD. High-resolution mass spectra were obtained using a Waters Q-TOF API-US mass spectrometer. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200−400 mesh silica gel (Scientific Absorbents, Inc.). Purities for all compounds were determined to be >95% by UPLC-MS. Methyl rocaglate (**2**) and hydroxamate (**3**) were prepared according to the methods of Porco and co-workers.[9] All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

***N*-Methoxy Rocaglamide (−)-9.** A round-bottom flask was charged with (−)-rocaglaic acid (27.0 mg, 0.06 mmol), CH_2Cl_2 (4 mL), EDCI (16 mg, 0.08 mmol), HOBt (11 mg, 0.07 mmol), methoxylamine hydrochloride (24 mg, 0.28 mmol), and triethylamine (39 μL, 0.28 mmol) and was stirred at room temperature for 12 h. The reaction was quenched with 1 M HCl, concentrated, and purified by flash chromatography (gradient elution 50−100% ethyl acetate in hexanes) to afford a (−)-**9** as white solid (14 mg, 49%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.15 (d, J = 9.0 Hz, 2H), 7.09−6.99 (m, 3H), 6.94 (d, J = 6.9 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 6.32 (d, J = 1.9 Hz, 1H), 6.21 (d, J = 1.9 Hz, 1H), 4.79 (d, J = 6.2 Hz, 1H), 4.32 (d, J = 14.2 Hz, 1H), 3.87 (s, 1H), 3.85 (s, 1H), 3.72 (dd, J = 14.2, 6.2 Hz, 1H), 3.69 (s, 1H), 3.60 (s, 1H). HRMS calcd for $[C_{28}H_{29}NO_8Na]^+$ requires m/z

530.1791; found 530.1772 (ES+). $[a]_D^{20}$ = −38.4 (*c* 0.5, CH_3OH, at >98% ee).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, pharmacologic data, biological methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

[∥]C.M.R. prepared compounds (+)-**9** and (−)-**9**, **11−17**, and **22−28**, and composed the manuscript. R.C. performed eukaryotic translation assays, RNA filter and affinity pull down assays, animal studies, and composed the manuscript. S.P.R. prepared compounds **7−10**. J.P. and J.A.P., Jr., conceived and directed the research and composed the manuscript.

■ ACKNOWLEDGMENTS

We thank Dr. Layton Smith (Sanford-Burnham Medical Research Institute) for pharmacokinetic studies of (−)-**9**. We also thank Dr. Paul Ralifo (Boston University) for NMR assistance. C.M.R. gratefully acknowledges a postdoctoral fellowship from the American Cancer Society (PF-11-077-01-CDD). R.C. gratefully acknowledges a postdoctoral fellowship from the Cole Foundation. Funding is gratefully acknowledged from the NIH (GM-073855 to J.A.P., Jr.) and the Canadian Cancer Society Research Institute (17099 to J.P.)

■ ABBREVIATIONS USED

DCC, *N*,*N*-dicyclohexylcarbodiimide; DMAP, 4-(dimethylamino)pyridine; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole hydrate; MEK, mitogen activated protein kinase kinase; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; THF, tetrahydrofuran; DMSO, dimethylsulfoxide; eIF4A, eukaryotic initiation factor 4A; eIF4E, eukaryotic initiation factor 4E; eIF4F, eukaryotic initiation factor 4F

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