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Article

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Novel Hypoxia-Inducible Factor 1α (HIF-1α) Inhibitors for Angiogenesis-Related Ocular Diseases: Discovery of a Novel Scaffold via Ring-Truncation Strategy

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ABSTRACT

Ocular diseases featuring pathologic neovascularization are the leading cause of blindness, and anti-VEGF agents have been conventionally used to treat these diseases. Recently, regulating factors upstream of VEGF, such as HIF-1α, has emerged as a desirable therapeutic approach because the use of anti-VEGF agents is currently being reconsidered due to the VEGF action as a trophic factor. Here, we report a novel scaffold discovered through the complete structure-activity relationship of ring-truncated deguelin analogs in HIF-1α inhibition. Interestingly, analog **6i** possessing a 2-fluorobenzene moiety instead of a dimethoxybenzene moiety exhibited excellent HIF-1α inhibitory activity, with an IC_{50} value of 100 nM. In particular, the further ring-truncated analog **34f**, which showed enhanced HIF-1α inhibitory activity compared to analog **2** previously reported by us, inhibited in vitro angiogenesis and effectively suppressed hypoxia-mediated retinal neovascularization. Importantly, the heteroatom-substituted benzene ring as a key structural feature of analog **34f**, was identified as a novel scaffold for HIF-1α inhibitors that can be used in lieu of a chromene ring.

INTRODUCTION

Ocular diseases featuring pathologic neovascularization are the leading cause of vision loss worldwide. These ocular diseases include diabetic retinopathy (DR), wet age-related macular degeneration (wet AMD), and retinopathy of prematurity (ROP).[1] Vascular endothelial growth factor (VEGF) is known to play key roles in the pathogenesis of these diseases;[2] thus, the administration of anti-VEGF biologics, including bevacizumab and ranibizumab, has been one of the standard therapies for angiogenesis-related ocular diseases. Despite the convincing therapeutic effects of anti-VEGF agents, this treatment is being reevaluated in view of the function of VEGF in maintaining neurons as well as its action as a trophic factor.[3, 4] Recently, *VEGFA* knockout in adult mice was reported to lead to vision loss and downregulation of multiple angiogenic genes, highlighting the necessity of a long-term safety study of VEGF antagonism in the eye.[5] Accordingly, regulating factors upstream of VEGF has received attention as a desirable therapeutic approach to eliminate off-target effects.

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor consisting of an oxygen-regulated α-subunit and a constitutively expressed β-subunit.[6] Under normal oxygen concentrations, HIF-1α is hydroxylated by prolyl hydroxylases (PHDs), using molecular oxygen and 2-oxoglutarate as co-substrates. Subsequently, hydroxylated HIF-1α is recognized by the tumor suppressing protein von Hippel-Lindau (VHL) and then polyubiquitinated for degradation by proteasomes. Under hypoxic conditions, however, the function of PHD is limited, and the stabilized HIF-1α dimerizes with HIF-1β for translocation into the nucleus to activate the transcription of target genes, including VEGF.[7] The molecular biology of HIF-1 has been well studied in solid tumors due to their hypoxic conditions, which are caused by high proliferation. Additionally, the roles of the HIF-VEGF axis in the eye

have been studied over the last ten years, and it has become clear that HIF plays an important role in the pathogenesis of many ocular diseases.[8-10]

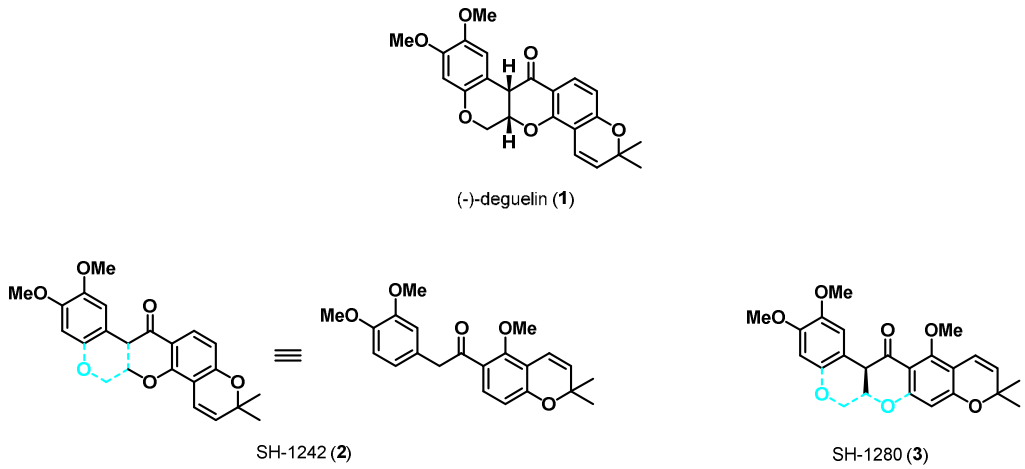


Figure 1. Structures of (−)-deguelin (**1**), SH-1242 (**2**), and SH-1280 (**3**). The turquoise color indicates a part eliminated from the parent compound.

We recently reported that (−)-deguelin (**1**) interferes with ATP binding to heat shock protein 90 (HSP90), a molecular chaperone associated with the translocation and stabilization of HIF-1α.[11] We also identified a series of ring-truncated deguelin analogs using a synthetic strategy for the synthesis of (−)-deguelin.[12] The two representative analogs, SH-1242 (**2**) and SH-1280 (**3**) exhibited potent cell growth inhibition and inhibitory activities of HIF-1α, a client protein of HSP90, and concentration-dependent antiangiogenic activities in zebrafish embryos.[13] In particular, analogs **2** and **3** showed the ability to suppress hypoxia-mediated retinal neovascularization and vascular leakage in the diabetic retina by destabilizing HIF-1α, implying that these compounds can be used as alternatives to direct VEGF inhibition for the treatment of angiogenesis-related ocular diseases.[14] Additional studies on the mode of action of **2** also revealed its therapeutic potential as a potent antitumor agent with minimal toxicity.[15]

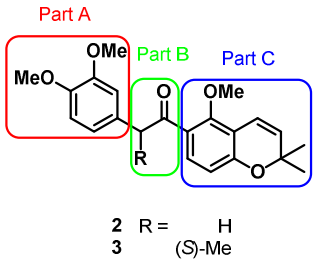


Figure 2. Strategy for structure-activity relationship studies of **2** and **3**.

Despite the therapeutic potential of ring-truncated deguelin analogs, structure-activity relationship (SAR) studies of **2** and **3** have been limited in terms of structural diversity.[13, 16, 17] In addition, we have been interested in structural features of analogs related to their physicochemical properties, especially aqueous solubility and their biological activities, since intravitreal injection is the most commonly used administrative method for the ocular diseases. In this article, we fully describe the design, synthesis, and biological evaluation of ring-truncated deguelin analogs to establish a complete SAR and identify novel and advanced HIF-1α inhibitors having therapeutic potential for angiogenesis-related ocular diseases. We first investigated the role of the three pharmacophoric parts of **2** and **3** shown in Figure 2. For part A, the substituent effects of the dimethoxy benzene ring were examined. Part B was investigated through replacement with various functional moiety that may play an important role for HIF-1α inhibition. Particularly, the role of substituents on the benzylic position was intensively studied and built on our earlier work.[13] The C part-modified analogs were designed on the basis of a chromene-truncation strategy to discover a novel scaffold for potent HIF-1α inhibitors. Truncation of the chromene unit could be more interesting as hydrophobic chromene ring was replaced by diverse hydrophilic moieties to increase water solubilities of the analogs. The synthesized analogs were evaluated for HIF-1α inhibitory activity by performing luciferase-reporter assays with HRE-A549 cells. The selected analogs based on the primary in vitro assay were further evaluated by in vitro angiogenesis assays,

including proliferation, migration, and tube formation assays, and solubility for intravitreal injection. Finally, the suppressing effect of hypoxia-mediated retinal neovascularization was assessed using a mouse oxygen-induced retinopathy (OIR) model.[18]

RESULTS AND DISCUSSION

Chemistry Two synthetic methods for coupling the A and C parts, which concomitantly produce the B part, are outlined in Figure 3. We previously reported the addition of aryl anions to aldehydes to afford secondary alcohols that were transformed into the corresponding ketones by oxidation (method A).[12, 13] However, the chromene-containing aryl bromide **5** was prepared via a relatively long six-step sequence from resorcinol. To overcome this drawback of method A, we adapted reverse anionic coupling between the phenyl sulfonyl intermediates **7** and the chromene-containing aldehyde **8** (method B).[16, 19] The chromene unit was efficiently prepared from 2,4-dihydroxybenzaldehyde in two steps.

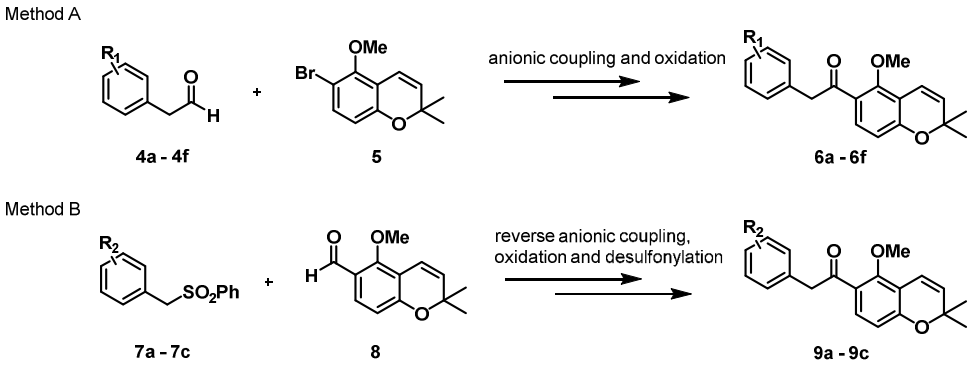
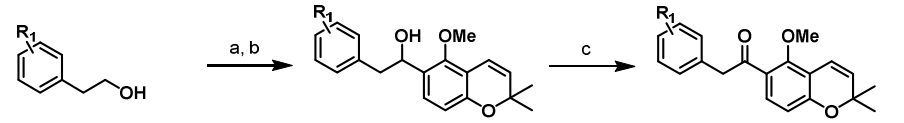


Figure 3. Synthetic methods for coupling parts A and C.

Syntheses of the analogs modified at part A by method A are summarized in Scheme 1. Phenethyl alcohol **10** was oxidized to afford the corresponding aldehyde **4**, which was directly subjected to addition of an aryl anion generated by treatment of aryl bromide **5**[13] with

n-butyllithium to produce secondary alcohol **11**. Dess-Martin periodinane oxidation of **11** afforded the ketone analog **6**.

Scheme 1. Synthesis of the part A-modified analogs.[a]



10a R_1 = (none)
10b R_1 = 3,4-methylenedioxy
10c R_1 = 3,4-ethylenedioxy
10d R_1 = 3,4-di-F
10e R_1 = 3,4-di-Cl
10f R_1 = 2-OMe
10g R_1 = 3-OMe
10h R_1 = 4-OMe
10i R_1 = 2-F
10j R_1 = 3-F
10k R_1 = 4-F

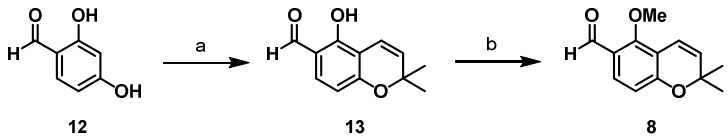
11a R_1 = (none)
11b R_1 = 3,4-methylenedioxy
11c R_1 = 3,4-ethylenedioxy
11d R_1 = 3,4-di-F
11e R_1 = 3,4-di-Cl
11f R_1 = 2-OMe
11g R_1 = 3-OMe
11h R_1 = 4-OMe
11i R_1 = 2-F
11j R_1 = 3-F
11k R_1 = 4-F

6a R_1 = (none)
6b R_1 = 3,4-methylenedioxy
6c R_1 = 3,4-ethylenedioxy
6d R_1 = 3,4-di-F
6e R_1 = 3,4-di-Cl
6f R_1 = 2-OMe
6g R_1 = 3-OMe
6h R_1 = 4-OMe
6i R_1 = 2-F
6j R_1 = 3-F
6k R_1 = 4-F

[a]Reagents and conditions: (a) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt; (b) **5**, *n*-BuLi, THF, −78 °C to rt, 17−60% (over 2 steps); (c) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 20−83%.

The chromene-containing moiety **8** was prepared from 2,4-dihydroxybenzaldehyde **12**, which possesses an electron-withdrawing group intrinsically required for regioselective electrocyclization.[20-22] The previously reported procedure[13] using aryl bromide **5** to synthesize the chromene-containing analogs was inefficient in terms of chemical yields and the number of steps. Thus, resorcinol **12** was condensed with 3-methyl-2-butenal to give the cyclized products, which were *O*-methylated to afford aldehyde **8**.

Scheme 2. Preparation of a chromene unit.[a]

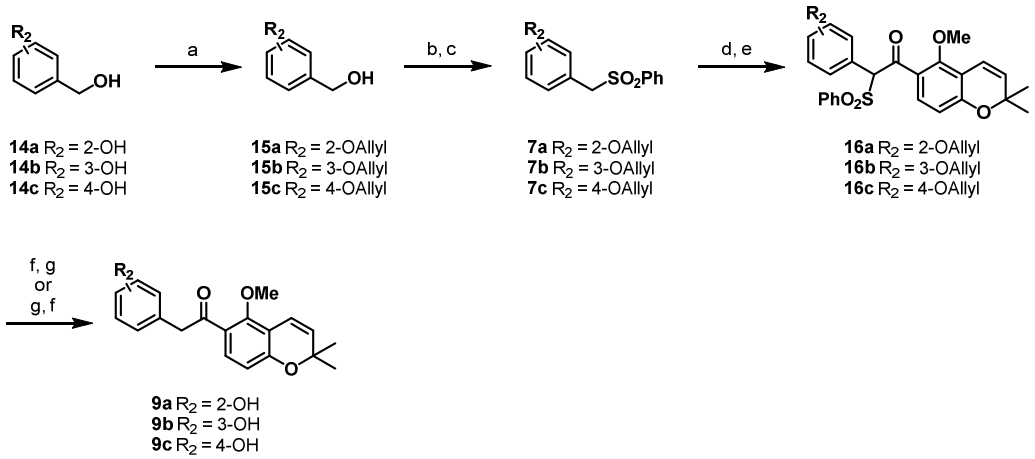


12 **13** **8**

[a]Reagents and conditions: (a) 3-methyl-2-butenal, $CaCl_2 \cdot 2H_2O$, Et_3N, EtOH, reflux, 65%; (b) MeI, K_2CO_3, acetone, reflux, 83%.

The syntheses of the analogs with modifications to part A via a phenyl sulfonyl intermediate (method B) are shown in Scheme 3. Hydroxyphenyl methanol **14** was treated with allyl bromide to afford allyloxyphenyl methanol **15**. Bromination of **15** with phosphorus tribromide followed by substitution using sodium *p*-toluenesulfinate gave phenyl sulfonyl intermediates **7**. The anion of **7**, which was generated by treatment with *n*-butyllithium, was coupled with aldehyde **8** to yield the corresponding secondary alcohol, which was converted to ketone intermediate **16** by Dess-Martin oxidation. Finally, Pd-catalyzed allyl deprotection of **16**, followed by desulfonylation, produced ketone **9**.

Scheme 3. Synthesis of the part A-modified analogs.[a]



14a R_2 = 2-OH
14b R_2 = 3-OH
14c R_2 = 4-OH

15a R_2 = 2-OAllyl
15b R_2 = 3-OAllyl
15c R_2 = 4-OAllyl

7a R_2 = 2-OAllyl
7b R_2 = 3-OAllyl
7c R_2 = 4-OAllyl

16a R_2 = 2-OAllyl
16b R_2 = 3-OAllyl
16c R_2 = 4-OAllyl

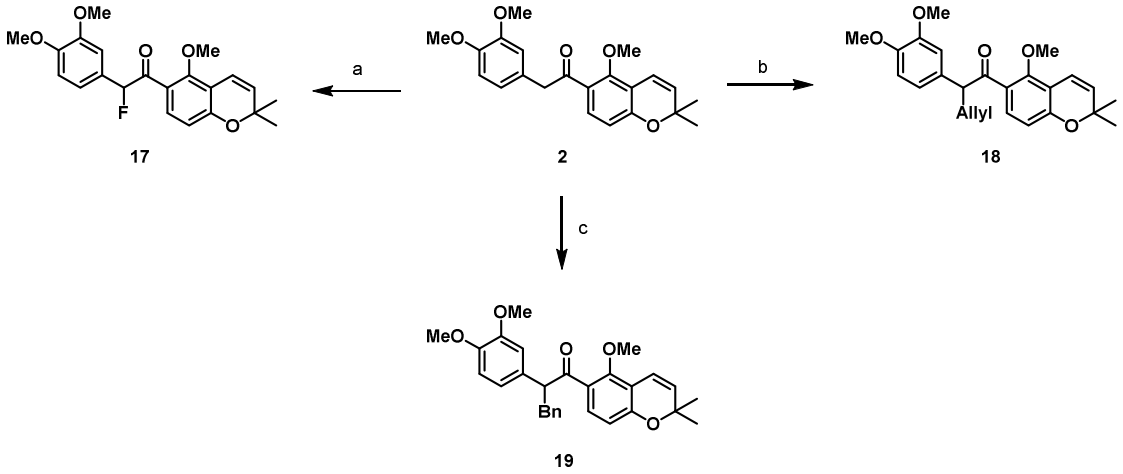
9a R_2 = 2-OH
9b R_2 = 3-OH
9c R_2 = 4-OH

[a]Reagents and conditions: (a) allyl bromide, K_2CO_3, acetone, reflux, 89–97%; (b) PBr_3, CH_2Cl_2, 0 °C to rt; (c) $PhSO_2Na$, DMF, rt to 80 °C, 88–92% over 2 steps; (d) **8**, *n*-BuLi, THF, −78 °C; (e) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 76–86% over 2 steps; (f) $Pd(PPh_3)_4$, MeNHPh, THF; (g) Zn, NH_4Cl, THF, reflux, 91–100% over 2 steps.

The analogs modified at the benzylic position in part B were synthesized from ketone **2**. The treatment of ketone **2** with trimethylsilyl trifluoromethanesulfonate afforded the corresponding silyl enol, which was subjected to electrophilic fluorination to afford

fluorination product **17**.[23] Allylated analog **18** and benzylated analog **19** were prepared by alkylation of ketone **2** with allyl bromide or benzyl bromide, respectively (Scheme 4).

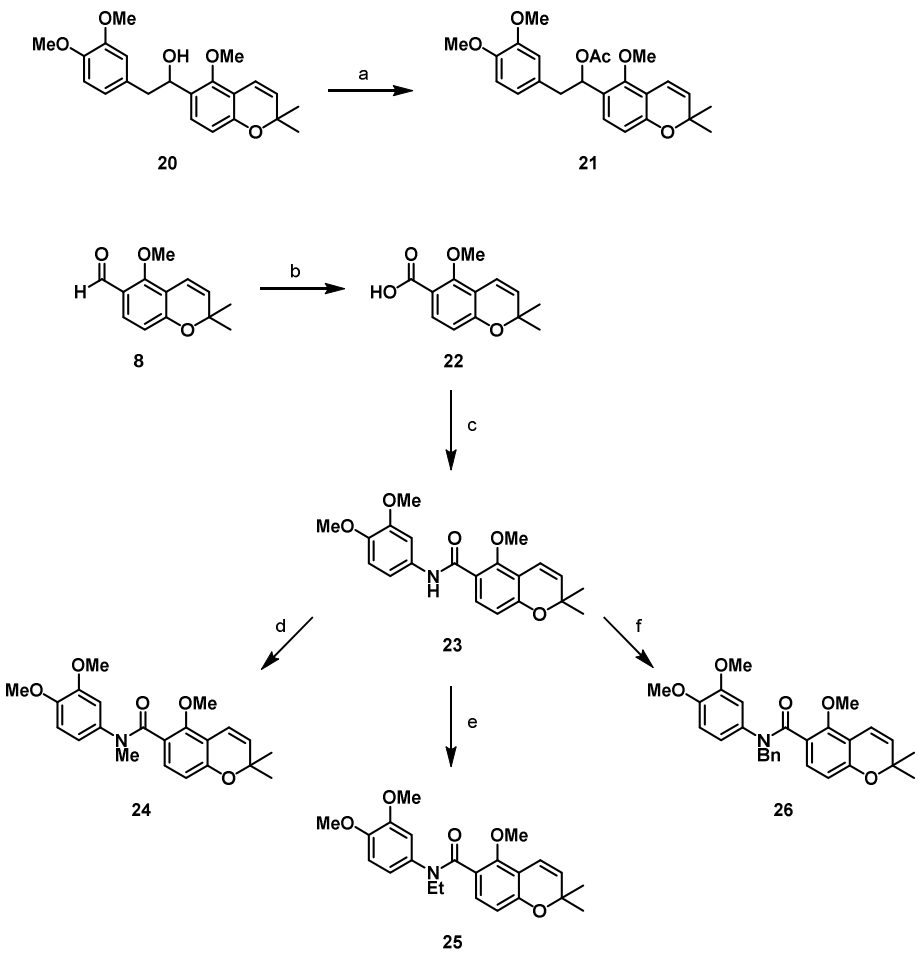
Scheme 4. Synthesis of part B-modified analogs having benzylic substituents.[a]



[a]Reagents and conditions: (a) TMSOTf, Et_3N, CH_2Cl_2; *N*-Chloromethyl-*N*'-fluorotriethylenediammonium bis(tetrafluoroborate), TBAF, DMF, 67% over 2 steps; (b) allyl bromide, NaH, THF, 0 °C to RT, 61%; (c) benzyl bromide, NaH, THF, 0 °C to RT, 70%.

To synthesize the B part-modified analogs as outlined in Scheme 5, known alcohol **20**[13] was acetylated using acetic anhydride in the presence of DMAP and trimethylamine to yield acetate **21**. Amide **23** was prepared by oxidation of aldehyde **8** using silver nitrate and coupling the resulting acid **22** with 3,4-dimethoxyaniline in the presence of PyBOP and diisopropylethylamine. Tertiary amide analogs **24**–**26** were prepared by alkylation using the corresponding electrophiles and sodium hydride as a base.

Scheme 5. Synthesis of the part B-modified analogs containing alcohol, ester, and amide moieties.[a]

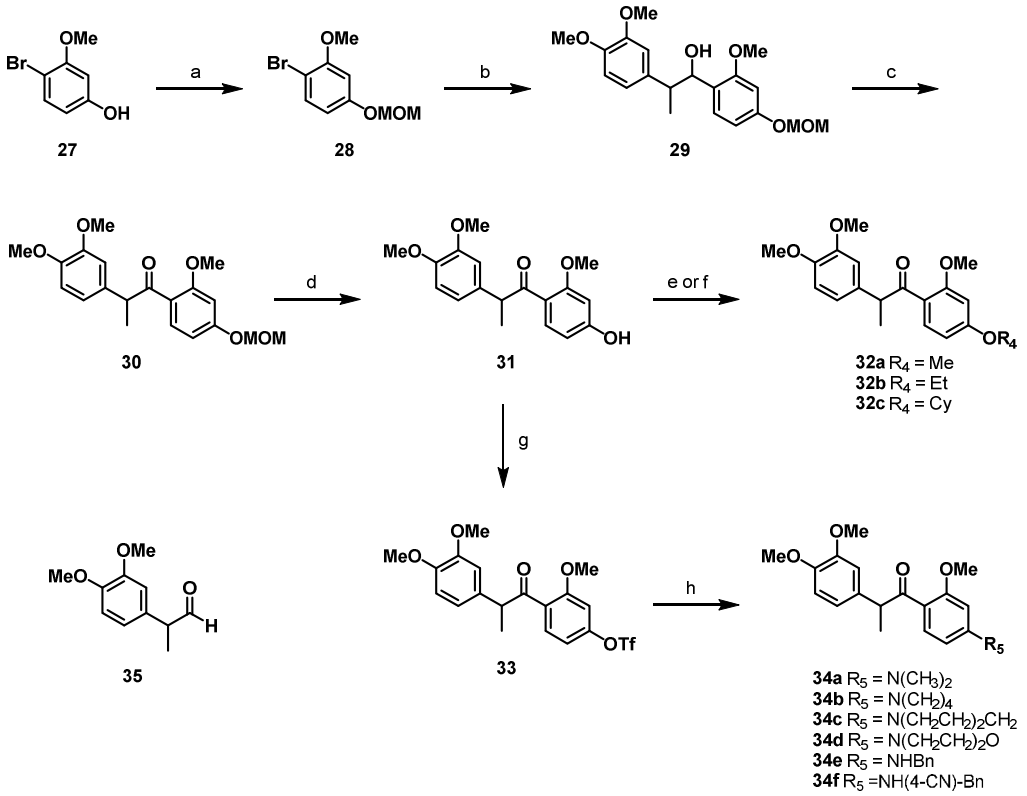


[a]Reagents and conditions: (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 63%; (b) $AgNO_3$, NaOH, EtOH, H_2O, reflux, 35%; (c) 3,4-dimethoxyaniline, PyBOP, *i*Pr_2NEt, CH_2Cl_2, 75%; (d) MeI, NaH, THF, 0 °C to rt, 85%; (e) EtI, NaH, THF, 0 °C to rt, 97%; (f) BnBr, NaH, THF, 0 °C to rt, 87%.

The syntheses of the chromene-truncated analogs are shown in Scheme 6. MOM protection of the hydroxyl group of 4-bromo-3-methoxyphenol (**27**) followed by treatment with *n*-butyllithium gave the bromobenzene anion, which was coupled with the known aldehyde **35**[13] to provide corresponding alcohol **29**. Oxidation of the alcohol using Dess-Martin periodinane produced ketone **30**. MOM deprotection with hydrochloric acid afforded phenol intermediate **31**, which could be transformed into both oxygen-substituted chromene-truncated analogs **32a** to **32c** and a precursor for nitrogen-substituted chromene-truncated analogs **34a** to **34d**.

Ether analogs **32a** and **32b** were synthesized by alkylation of **31** using iodomethane and iodoethane, respectively. Cyclohexyl ether **32c** was prepared via a Mitsunobu reaction with cyclohexanol. To prepare the nitrogen-containing chromene-truncated analogs, phenol **31** was treated with phenyl triflimide to yield triflate **33**. Finally, amine analogs **34a** to **34f** were synthesized by palladium-catalyzed Buchwald-Hartwig reactions of triflate **33** with the corresponding amines in the presence of palladium acetate.

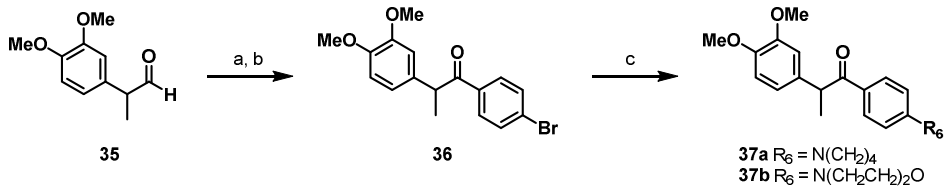
Scheme 6. Synthesis of chromene-truncated analogs modified at part C.[a]



[a]Reagents and conditions: (a) MOMCl, NaH, DMF, 0 °C to rt, 96%; (b) **35**, *n*-BuLi, THF, –78 °C, 72%; (c) DMP, CH_2Cl_2, 0 °C to rt, 82%; (d) 2*N*-HCl, MeOH, 60 °C, 94%; (e) alkyl iodide, Cs_2CO_3, CH_3CN, 0 °C to rt. **32a**: MeI, 71%. **32b**: EtI, 91%; (f) **32c**: cyclohexanol, DEAD, PPh_3, THF, 42%; (g) $PhNTf_2$, K_2CO_3, DMF, quant.; (h) amines, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C. **34a**: dimethylamine, 41%. **34b**: pyrrolidine, 90%. **34c**: piperidine, 45%. **34d**: morpholine, 53%. **34e**: benzylamine, 88%. **34f**: 4-cyanobenzylamine, 91%.

Syntheses of the chromene-truncated analogs without a methoxy group on the original chromene moiety are described in Scheme 7. Treatment of 1,4-dibromobenzene with *n*-butyllithium gave the 4-bromobenzene anion, which was then coupled with the known aldehyde **35**[13] to provide the corresponding alcohol. The alcohol was then oxidized with Dess-Martin periodinane to afford ketone **36**. Palladium-catalyzed amination of **36** produced the desired chromene-truncated analogs **37a** and **37b**.

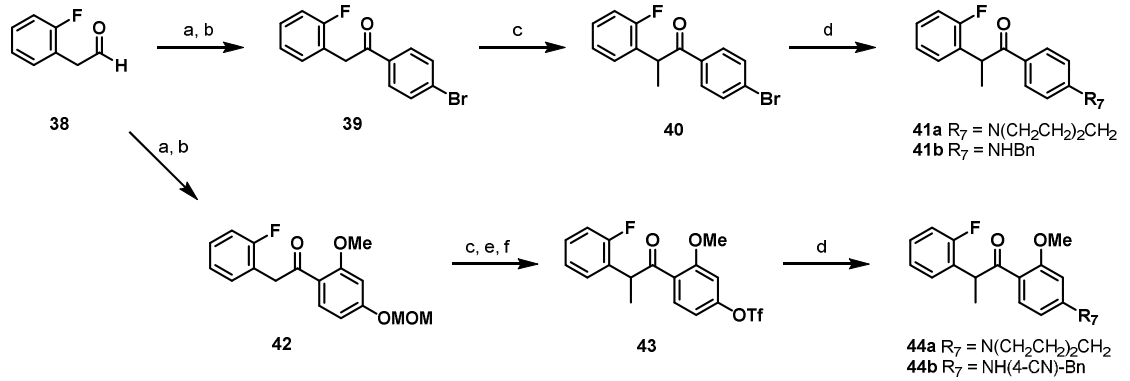
Scheme 7. Synthesis of the chromene-truncated analogs without a methoxy group on the original chromene moiety.[a]



[a]Reagents and conditions: (a) 1,4-dibromobenzene, *n*-BuLi, THF, −78 °C; (b) DMP, CH_2Cl_2, 0 °C to rt, 71% over 2 steps. (c) amines, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C. **37a**: pyrrolidine, 57%. **37b**: morpholine, 53%.

We also synthesized the analogs possessing the key structural features of parts A, B, and C responsible for high HIF-1α inhibition as shown in Scheme 8. Starting from 2-fluoro benzeneacetaldehyde **38**, we prepared intermediates **40** and **43** for Pd-catalyzed reaction which gave analogs **41a-b** and **44a-b**.

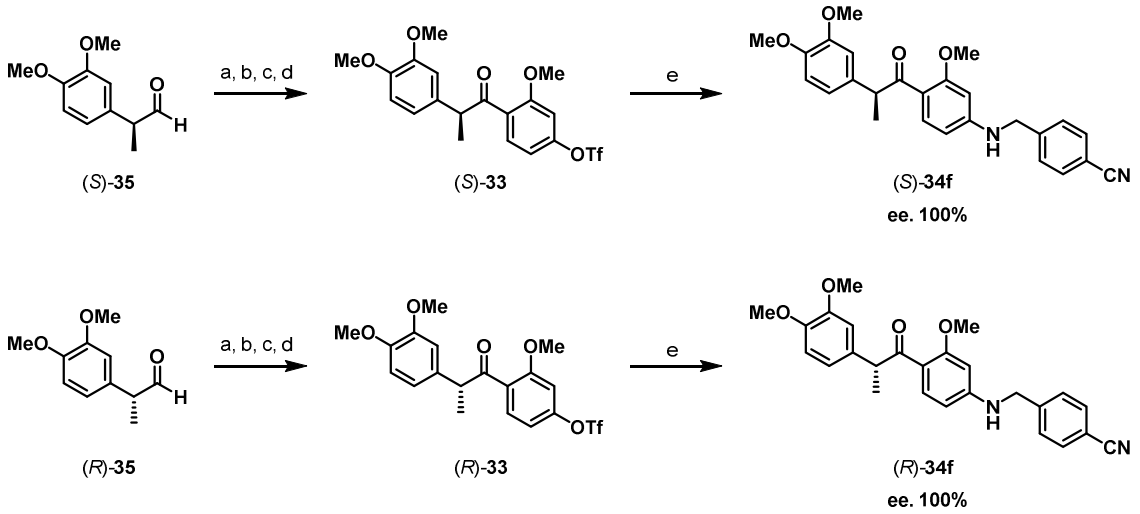
Scheme 8. Synthesis of the chromene-truncated analogs combined with the pharmacophoric structural features of part A and B.[a]



[a]Reagents and conditions: (a) 1,4-dibromobenzene (for **39**) or **28** (for **42**), *n*-BuLi, THF, −78 °C; (b) DMP, CH_2Cl_2, 0 °C to rt, **39**: 55%. **42**: 38% over 2 steps; (c) MeI, NaH, THF, 0 °C to rt, **40**: 93%. **43**: 64%; (d) amines, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C. **41a**: 68%. **41b**: 71%. **44a**: 67%. **44b**: 58%; (e) 2*N*-HCl, MeOH, 60 °C, 97%; (f) $PhNTf_2$, K_2CO_3, DMF, quant.

Finally, we prepared (*S*)- and (*R*)-enantiomers of racemate **34f** as outlined in Scheme 9. Syntheses commenced with active aldehydes **(*S*)-35** and **(*R*)-35**[13] and followed the same procedure for the racemic analog except for the last step to avoid racemization at high temperature and long reaction time. (Supporting Information Figure 1)

Scheme 9. Synthesis of optically active analogs (*S*)-34f and (*R*)-34f



[a]Reagents and conditions: (a) **28**, *n*-BuLi, THF, −78 °C; (b) DMP, CH_2Cl_2, 0 °C to rt; (c) 2*N*-HCl, MeOH, 60 °C; (d) $PhNTf_2$, K_2CO_3, DMF, **(*S*)-33**: 34%, **(*R*)-33**: 42% over 4 steps; (e) 4-

cyanobenzylamine, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 60 ℃ to 100 ℃, **(*S*)-34f**: 83%, **(*R*)-34f**: 92%.

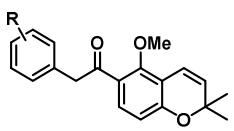
Structure-activity relationship (SAR) study based on an HRE-luciferase reporter assay

Our previous studies[13-15] to elucidate the structural features of deguelin mainly focused on the B- and C-ring truncation of deguelin although analog **2** not only showed antiangiogenic effects and antitumor effect with minimal toxicity,[15] but also suppressed hypoxia-mediated retinal neovascularization.[14] Specifically, investigation of a distinctive moiety, such as the dimethoxy benzene ring in part A and the terminal chromene moiety in part C, were quite limited. Thus, we have initially established the complete SAR focusing on analog **2**. The HRE-luciferase assay in the A549 cell line was used for the primary evaluation of the newly synthesized analogs. We also examined calculated molecular descriptors such as log P and log S to predict aqueous solubilities of the analogs.

We first investigated substituent effects in part A of **2** on HIF-1α inhibitory activities. The two methoxy groups in part A were originally considered essential for HIF-1α inhibition because we observed a loss of antiproliferative activity upon demethylation of one or both methoxy groups of deguelin.[13] Van Meir and coworkers reported a similar observation about the dimethoxybezene moiety, which played a crucial role in HIF-1α inhibitory activities in their sulfonamide analogs.[24, 25] Thus, we prepared analogs devoid of one or both methoxy groups or analogs possessing alkoxy-replacing substituents at the 3- and 4-positions. Interestingly, analog **6a**, with no substituent on the benzene ring in A-part, exhibited considerably increased inhibition, with an IC_{50} value of 880 nM, which implied the necessity of investigation into the substituent effects on HIF-1α inhibition. Analog **6b**, which has a dioxolane ring instead of two methoxy substituents, showed a lower inhibitory activity than

analog **2**, while analog **6c**, which has a dioxane ring, exhibited slightly enhanced activity. The 3,4-difluoro analog **6d** exhibited enhanced activity compared to analog **2**, whereas the dichloro analog **6e** showed lower activity. All the monofluoro analogs showed improved inhibitory activities compared to analog **2** and the most potent 2-fluoro analog **6i** exhibited 20-fold higher activity than analog **2**, with an IC_{50} value of 100 nM. The monomethoxy analogs **6f** and **6h** exhibited lower activity than analog **2** and the 3-methoxy analog **6g** showed the improved activity. Curiously, 2-hydroxy analog **9a** and 4-hydroxy analog **9c** showed significantly increased activity compared to the corresponding methoxy analogs, which contradicted the previous SAR study of deguelin using antiproliferative assays.[13] (Table 1). Overall, the function of the methoxy groups of part A in analog **2** for HIF-1α inhibitory activities was not clearly revealed. However, a small substituent or no substituent at the 2-, 3-, or 4-position seems beneficial for improved inhibitory activity regardless of electronic effect. The excellent HIF-1α inhibition of 2-fluoro analog **6i** is currently not explained although the small 2-fluoro substituent seems specifically optimized for an interaction with the corresponding binding site and not associated with electronic interaction or hydrogen bonding. Calculated hydrophilicity descriptor (log S) and lipophilicity descriptor (log P) were not dramatically changed with substituent variation except two chlorines at *para* and *meta* positions (**6e**) and hydroxy substituent at *ortho* (**9a**), *meta* (**9b**), and *para* (**9c**) position. Lipophilicity parameter π of substituents[26] seems significant as hydrophilic substituent could be beneficial for intravitreal drugs to have better aqueous solubility.

Table 1. HIF-1α inhibitory activities of the part A-modified analogs.



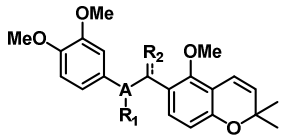
Compound	R	IC_{50}[a] (μM)	S.E.[b]	log S[c]	log P[c]

2	3,4-dimethoxy	2.15	0.52	- 5.36	4.68
6a	none	0.88	0.32	- 5.27	4.53
6b	3,4-methylenedioxy	3.41	0.71	- 5.15	4.30
6c	3,4-ethylenedioxy	1.33	0.34	- 5.23	4.61
6d	3,4-di-F	1.27	0.40	- 5.38	4.31
6e	3,4-di-Cl	2.88	0.54	- 6.49	5.43
6f	2-OMe	3.21	0.74	- 5.34	4.50
6g	3-OMe	0.82	0.20	- 5.38	4.52
6h	4-OMe	6.21	2.39	- 5.38	4.53
6i	2-F	0.10	0.01	- 5.36	4.21
6j	3-F	0.36	0.15	- 5.39	4.34
6k	4-F	1.02	0.29	- 5.39	4.47
9a	2-OH	0.94	0.41	- 4.69	4.45
9b	3-OH	1.44	0.88	- 4.82	4.45
9c	4-OH	0.79	0.49	- 4.85	4.47

[a]Data are the mean values of three independent experiments. [b]Standard error. [c]The log S and log P values of the analogs were calculated with the software ALOGPS 2.1 (VCCLAB Virtual Computational Chemistry Laboratory)[27]

We next examined the effects of variations to part B on HIF-1α inhibitory activity. We first examined substitution effects at the benzylic position by incorporating diverse substituents. In accordance with a previous study,[13] bulky substituents generally decreased HIF-1α inhibitory activities apart from methyl-substituted **rac-3**, which seemed to have beneficial conformation induced by a structural constraint. We also examined alcohol analog **20** since deguelol, a naturally occurring reduced form of deguelin, exhibited 10-fold higher antiproliferative activity than deguelin. Both alcohol **20** and acetate **21** exhibited lower inhibitory activity compared to **2**. The amide analogs **23**-**25** showed increased log S value although their inhibitory potencies were not satisfactory. The inhibitory activity of the *N*-alkylated amides **24**–**26** decreased as the size of the alkyl group increased (Table 2). The size effect of the *N*-alkyl group was quite similar to the trend shown in the corresponding ketone series.

Table 2. HIF-1α inhibitory activities of analogs with part B modified.



Compound	A	R_1	R_2	IC_{50}[a] (μM)	S.E.[b]	log S[c]	log P[c]
2	C	H	O	2.15	0.52	- 5.36	4.68
rac-3	C	Me	O	1.36	0.50	- 5.55	4.87
17	C	F	O	6.35	6.49	- 5.38	3.86
18	C	Allyl	O	8.45	5.58	- 5.99	5.34
19	C	Bn	O	12.03	6.91	- 6.61	5.87
20	C	H	OH	8.88	2.75	- 5.01	4.18
21	C	H	OAc	3.04	0.96	- 5.83	4.79
23	N	H	O	2.04	0.78	- 4.89	3.73
24	N	Me	O	3.15	2.75	- 4.91	3.49
25	N	Et	O	5.25	2.53	- 4.94	3.72
26	N	Bn	O	10.78	2.35	- 5.80	4.67

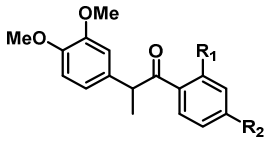
[a]Data are the mean values of three independent experiments. [b]Standard error. [c]The log S and log P values of the analogs were calculated with the software ALOGPS 2.1 (VCCLAB Virtual Computational Chemistry Laboratory)[27]

The modification of part C of **2** included truncation of the terminal chromene unit, one of the key parts of deguelin. The chromene unit was traditionally known as a 'privileged structure' with versatile binding properties,[28] and many natural products containing chromene units were reported along with their various biological activities.[29] For this reason, various attempts to incorporate chromene units into therapeutic agents have been made. Nicolaou et al. constructed natural product-like chemical libraries via the solid-phase synthesis of chromene units.[30-32] Van Meir et al. recently developed a group of HIF-1α inhibitors possessing chromene units based on a hit compound from Nicolaou's library.[24, 25, 33, 34]

Our early work on deguelin,[13] a parent natural product of **2**, revealed that the terminal chromene unit is crucial for cell growth inhibition via its interaction with HSP90. However, studies on the truncation of the chromene unit were not included. To establish a complete SAR study of ring-truncated analog **2**, a series of analogs with part C-modification was evaluated on the basis of a chromene truncation strategy. Specifically, chromene ring truncation was anticipated to provide improved physicochemical properties, which would be beneficial for intravitreal injection. We introduced a methyl substituent at the benzylic position for the chromene-truncated analogs because our early work[13] confirmed that the B, C-ring-truncated analog **3** with a methyl substituent at the benzylic position exhibited better activity than analog **2** without a methyl substituent. Additionally, the methyl substituent might limit the flexibility of the chromene-truncated analogs via conformational rigidity. We examined the HIF-1α inhibitory activities of the chromene-truncated analogs in racemic form because we focused on the effect of the chromene-truncation at this stage, although our previous work[13] revealed that the β-methyl substituted chromene analog was twice as potent as the α-methyl chromene analog for cell growth inhibition. However, we investigated stereochemical effects on the in vitro and in vivo activities via chiral switching for the finally selected analog. HIF-1α inhibitory activities of the chromene-truncated analogs are summarized in Table 3. Generally, the methoxy substituent at the 2-position corresponding to the methoxy group of the chromene unit was kept intact. The alkoxy (**31**, **32a**–**32c**) and amine (**34a**–**34f**) substituents at the 4-position correspond to the alkoxy moiety of the chromene ring. HIF-1α inhibitory activities of the alkoxy-substituted analogs increased as the size of the alkyl group increased. The same pattern was observed in all alkyl/cyclic amine analogs (**34a**–**34d**), except for the morpholine analog which showed possible advantage with regard to aqueous solubility. The introduction of benzylamine (**34e**) at the 4-position exhibited enhanced inhibitory activities compared to the alkyl/cyclic amine substituted

analogs although its log S value decreased. Interestingly, analog **34f**, which possesses a 4-cyanobenzylamine substituent, showed higher activity than analog **2**, with an IC_{50} value of 600 nM. The calculated molecular descriptors predicted better aqueous solubility for analog **34f** compared to **34e**, which is likely due to a negative lipophilicity parameter π of the cyano-substituent.[26] Those results also suggested that a heteroatom-substituted benzene ring could be used as a scaffold for HIF-1α inhibitors instead of a chromene unit. Next, we investigated the role of the methoxy substituent at the 2-position by comparing analogs **34b** and **37a** as well as analogs **34d** and **37b**. Unlike the chromene ring case, the 2-methoxy group of the chromene-truncated analogs did not exert any significant role in HIF-1α inhibitory activity.

Table 3. HIF-1α inhibitory activities of analogs modified in part C



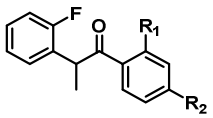
Compound	R_1	R_2	IC_{50}[a] (μM)	S.E.[b]	log S[c]	log P[c]
31	OMe	OH	N.A.[d]	-	- 4.11	3.23
32a	OMe	OMe	N.A.	-	- 4.44	3.41
32b	OMe	OEt	11.68	9.45	- 4.69	3.89
32c	OMe	OCy	2.59	2.45	- 5.87	5.29
34a	OMe	$N(CH_3)_2$	N.A.	-	- 3.94	3.93
34b	OMe	$N(CH_2)_4$	2.82	1.66	- 4.13	4.66
34c	OMe	$N(CH_2CH_2)_2CH_2$	1.85	0.57	- 4.50	5.15
34d	OMe	$N(CH_2CH_2)_2O$	8.74	8.00	- 4.08	3.73
34e	OMe	NHBn	1.43	0.76	- 5.95	5.12
34f	OMe	NH(4-CN)-Bn	0.60	0.23	- 5.21	4.38
37a	H	$N(CH_2)_4$	2.61	1.27	- 4.20	4.49
37b	H	$N(CH_2CH_2)_2O$	6.85	2.74	- 3.80	3.73

[a]Data are the mean values of three independent experiments. [b]Standard error. [c]The log S and log P values of the analogs were calculated with the software ALOGPS 2.1 (VCCLAB Virtual Computational Chemistry Laboratory)[27] [d]No activity (N.A.) indicates that the

analog exhibits activity with an IC_{50} higher than 15 μM.

We explored additive effects by combining structural features of each part, which were considered important for high HIF-1α inhibitory activity. Unfortunately, analogs **41a**/**44a**, **41b**, and **44b**, which consist of a 2-fluoro benzene ring in part A, did not exhibited improved activities compared to the corresponding analogs (**34c**, **34e**, and **34f**) possessing a dimethoxybenzene unit possibly due to a conformational change by chromene-ring truncation (Table 4).

Table 4. HIF-1α inhibitory activities of analogs modified in parts A–C



Compound	R_1	R_2	IC_{50}[a] (μM)	S.E.[b]	log S[c]	log P[c]
41a	H	$N(CH_2CH_2)_2CH_2$	2.06	0.72	- 4.76	4.98
41b	H	NHBn	7.35	4.15	- 5.92	5.13
44a	OMe	$N(CH_2CH_2)_2CH_2$	6.52	2.00	- 4.63	4.86
44b	OMe	NH(4-CN)-Bn	5.28	2.13	- 5.35	4.90

[a]Data are the mean values of three independent experiments. [b]Standard error. [c]The log S and log P values of the analogs were calculated with the software ALOGPS 2.1 (VCCLAB Virtual Computational Chemistry Laboratory)[27]

We finally examined stereochemical effects on the HIF-1α inhibitory activity for racemate **34f**. As shown in Figure 4, (*R*)-**34f** exhibited more potent HIF-1α inhibitory activity than its antipode (*S*)-**34f**. It is interesting that absolute configuration of the stereogenic center of (*R*)-**34f** is opposite to that of analog **3**[13], which was previously reported as a B, C-ring truncation analog. This change is likely due to a conformational change induced by the chromene-truncation.

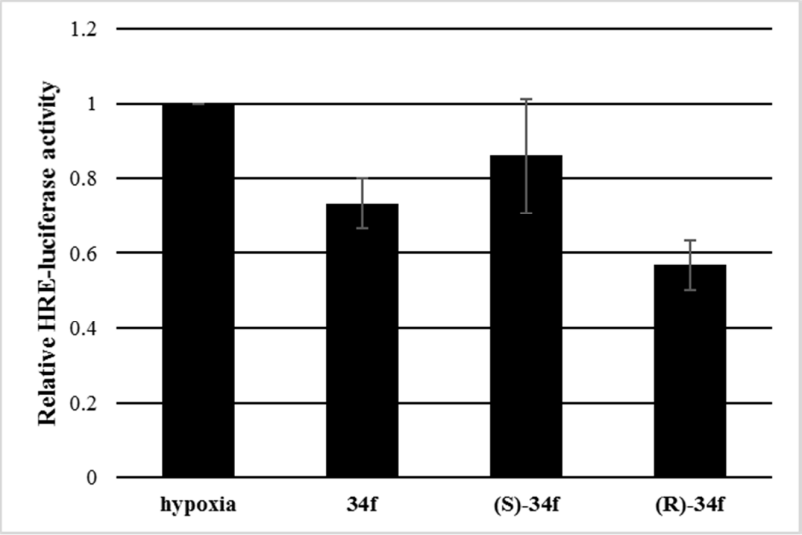


Figure 4. Relative HRE-luciferase activities of analog **34f** and its enantiomers at 1 μM.

Aqueous solubility of the representative analogs Through this intensive SAR study of ring-truncated deguelin analogs, we successfully identified potent HIF-1α inhibitors with IC_{50} of submicromolar level. With several novel and potent HIF-1α inhibitors in hand, we examined their physicochemical properties to select a suitable candidate for additional biological evaluation and determined their therapeutic potential for the treatment of ocular diseases via intravitreal injection. We compared the water solubility of analog **2** (IC_{50} = 2.15 μM) with those of analogs **6i** (IC_{50} = 0.10 μM), **34c** (IC_{50} = 1.85 μM), and **34f** (IC_{50} = 0.60 μM), which were selected based on their HIF-1α inhibitory activities and structural novelties (Figure 5). The water solubilities of analogs **34c** and **34f** were 93-fold and 17-fold higher, respectively, than that of parent compound **2**. The improved solubility is likely due to a result of the increase in polarity induced by the amine moiety and the increase in flexibility induced by the truncation of the fused ring system (i.e., the chromene ring). Unfortunately, the most potent analog, **6i**, was much less water soluble than parent compound **2**. For these reasons, analogs **34c** and **34f** were chosen for further biological evaluation associated with angiogenesis-related ocular diseases. Both analogs also have a structural advantage over

analog **2** in terms of structural novelty since analog **2**, which was developed from widely used natural products, consists of a popular chromene moiety.

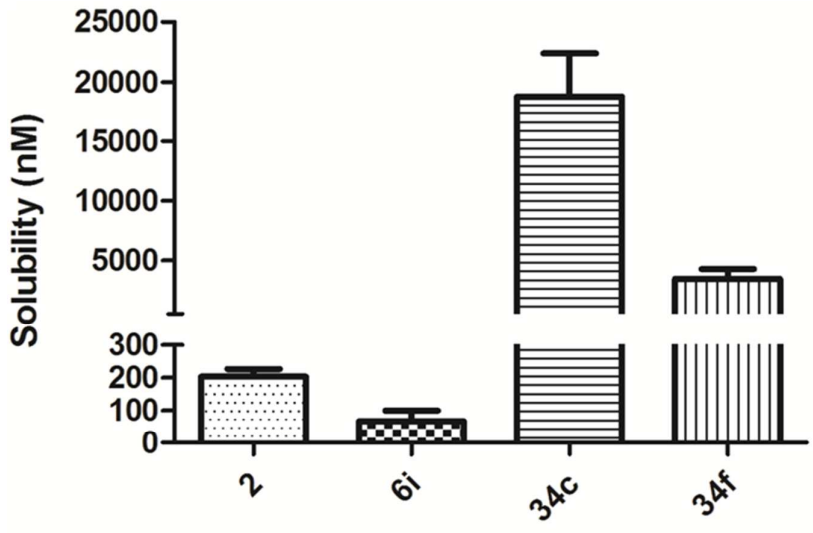


Figure 5. Water solubility of the representative analogs.

In vitro validation of analogs 34c and 34f We initially examined the inhibitory effects of analog **34c** and **34f** on hypoxia-mediated angiogenic processes because angiogenesis is an important process involving extensive interaction between cells, soluble factors and extracellular matrix components.[35] Construction of a vascular network involves consecutive steps, including cell proliferation, migration, and tube formation.[36] Thus, we used conditioned media (CM) extracted from human colon cancer HCT116 cells or HeLa cells treated with or without analogs **2**, **34c**, and **34f** under hypoxia. The antiangiogenic effects of the analogs were evaluated by observing changes in angiogenic processes following the treatment of human umbilical vein endothelial cells (HUVECs) with CM. Analog **34c** effectively suppressed the hypoxia-induced proliferation, migration, and tube formation of HUVECs and was nearly equipotent to analog **2**[14] (Supporting Information Figure 2). More interestingly, analog **34f** exhibited better anti-angiogenic effects than analog **2**. Analog **34f** suppressed the

angiogenic processes of human retinal microvascular endothelial cells (HRMECs) by treatment of CM extracted from retinal pigment epithelial (RPE) cells (Figure 6).

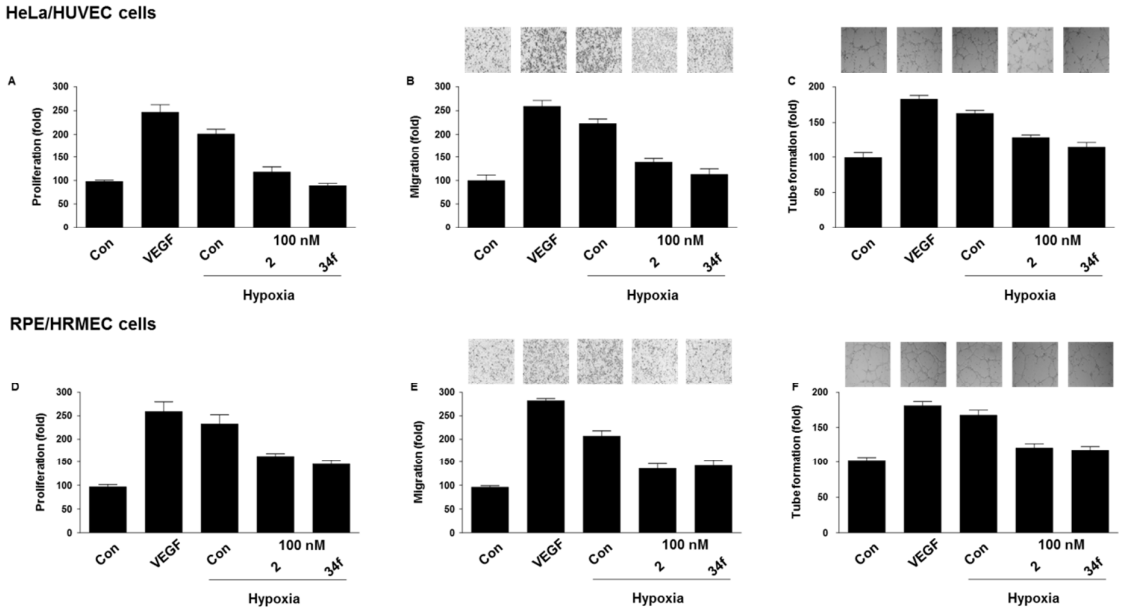


Figure 6. In vitro antiangiogenic effect of analog **34f** in HUVECs (A–C) and HRMECs (D–F) at 100 nM. Effect of analog **34f** on cell proliferation determined by [^{3}H]-thymidine incorporation assay (A, D). Analog **34f** inhibited cell migration (B, E) and suppressed tube formation (C, F). Error bars indicate the mean ± SEM. Control (Con).

We also compared HIF-1α regulations by analog **2** and **34f** using Western blot analysis. Analog **34f** effectively induced the destabilization of HIF-1α on the HCT116 cell line at 100 nM (Figure 7a). With the destabilization of HIF-1α, analog **34f** effectively reduced the production of VEGF (Figure 7b) and inhibited the expression of *VEGFA*, an angiogenesis-related target gene of HIF-1α (Figure 7c).

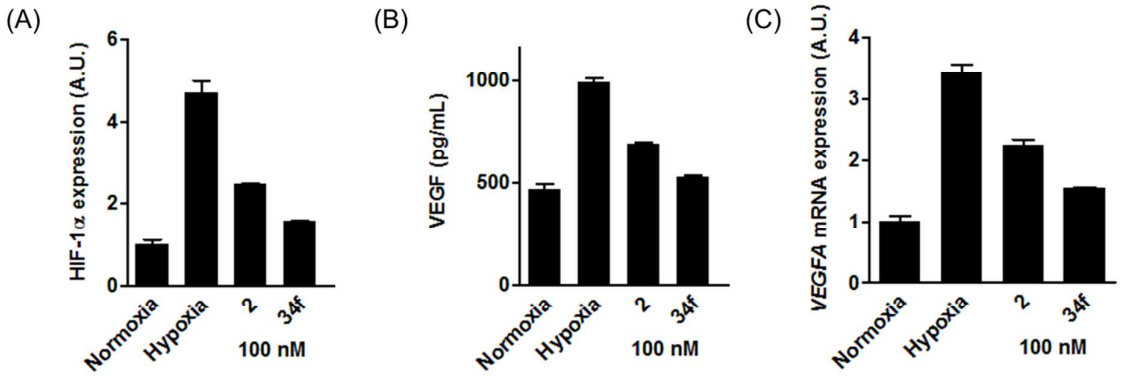


Figure 7. Destabilization of HIF-1α by analogs **2** and **34f** suppresses hypoxia-induced expression of VEGF in HCT116 cells at 100 nM. (A) Destabilization of HIF-1α (upregulated by hypoxia) by analogs **2** and **34f**. (B) Inhibition of VEGF secretion by analogs **2** and **34f** in enzyme-linked immunosorbent assay. (C) Inhibition of *VEGFA* expression, a target gene of HIF-1α, by analogs **2** and **34f**.

Finally, we confirmed an association of HSP90 in the HIF-1α inhibition by analog **34f** via immunoprecipitation and immunoblotting assays using A549 cell lysates. As anticipated, analog **34f** interrupted the interaction between HIF-1α and HSP90 in vitro as shown in the previous ring-truncation analogs (Supporting Information Figure 3).

Suppression of hypoxia-mediated retinal neovascularization Following examination of the in vitro antiangiogenic activities of **34c** and **34f**, we confirmed their in vivo efficacy using a mouse OIR model.[18, 37, 38] Analogs **2**, **34c**, and **34f** were injected intravitreally at a concentration of 100 nM or 1 μM. Staining of whole-mounted retinal tissues and their quantitative analysis revealed that analog **34c** suppressed retinal neovascularization comparable to analog **2** (Supporting Information Figure 4). In particular, **34f** at a concentration of 100 nM effectively reduced retinal neovascular tufts at an enhanced level compared to analog **2** (Figure 8). We also confirmed that analogs (*S*)-**34f** and (*R*)-**34f**, the

stereoisomers of analog **34f**, did not show significant difference in vivo antiangiogenic activities at a concentration of 100 nM (Supporting Information Figure 5).

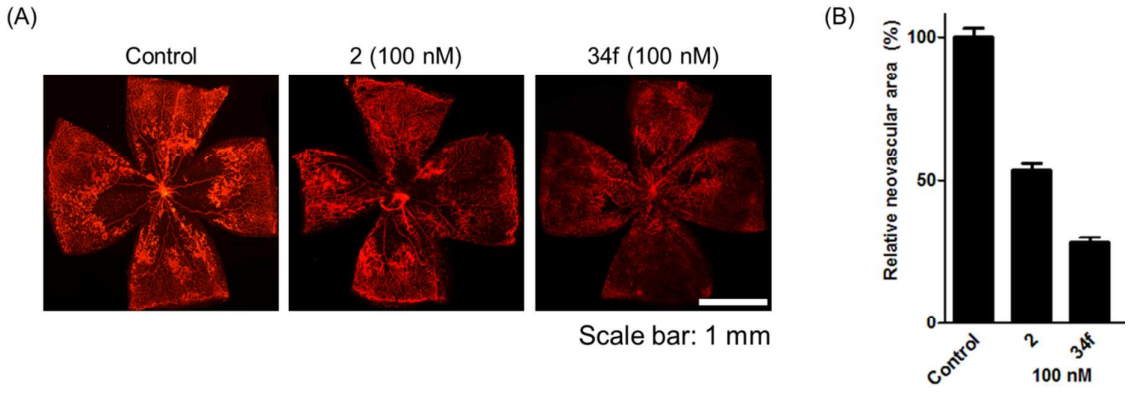


Figure 8. Suppression of retinal neovascularization by analog **34f** at 100 nM. (A) Reduction of retinal neovascular tufts by analogs **2** and **34f**. Scale bar = 1 mm (B) Quantitative analysis was performed using the ImageJ image processing program by measuring the neovascular area per retina (n = 6). Error bars indicate the mean ± SEM.

CONCLUSION

In summary, we fully elucidated structural features by establishing the SAR of the ring-truncated deguelin analog **2** for potent HIF-1α inhibitory activity using an HRE-luciferase reporter assay. Analog **6i**, in which part A contains a 2-fluorobenzene system, was identified as a highly potent HIF-1α inhibitor, with an IC_{50} of 100 nM. Analog **6i** is currently under investigation for its anticancer activities, as well as the distinctive physicochemical properties required for intravitreal drugs. The modification of part B, including the benzylic position and the ketone moiety, confirmed the benefits of structural constraints to induce proper conformation of the ring-truncated deguelin analogs. Noticeably, the C-part modified analog **34f**, which possesses a 4-cyanobenzylamine-substituted benzene moiety in place of the original chromene unit, exhibited enhanced HIF-1α inhibitory activity and in vitro

antiangiogenic activity compared to analog **2**. Particularly, analog **34f** exhibited highly improved solubility and suppression of retinal neovascularization in the OIR model compared to parent analog **2**. These results support the therapeutic potential of the ring-truncation analogs with the heteroatom-substituted benzene ring as a novel scaffold replacing the chromene moiety, which is known as a privileged structure for natural product-based HIF-1α inhibitors targeting angiogenesis, for the development of novel HIF-1α inhibitors targeting pathological angiogenesis in ocular diseases.

EXPERIMENTAL SECTION

Chemistry. General Methods. Unless otherwise described, all commercial reagents and solvents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl and dichloromethane, acetonitrile, triethylamine and pyridine were freshly distilled with calcium hydride. Flash column chromatography was carried out using silica-gel 60 (230-400 mesh, Merck) and preparative thin layer chromatography was used with glass-backed silica gel plates (1mm, Merck). Thin layer chromatography was performed to monitor reactions. All reactions were performed under dry argon atmosphere in flame-dried glassware. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 300 (300MHz), JEOL JNM-GCX (400MHz), BRUKERAMX-500 (500MHz), JEOL (600MHz) or Bruker Avance III HD (800MHz, with a 5-mm CPTCI CryoProbe) spectrometers. Chemical shifts are provided in parts per million (ppm,δ) downfield from tetramethylsilane (internal standard) with coupling constant in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), quintet (quin) multiplet (m) and broad (br). Mass spectra and HRMS were recorded on VG Trio-2 GC-MS instrument and JEOL JMS-AX, respectively. All the final compounds were purified up to more than 95% purity. The purity

of the compounds was determined by normal phase high performance liquid chromatography (HPLC), (Waters, CHIRALPAK® AD-H (4.6 × 250 mm)). The detailed analytical conditions are available in Supporting Information

General procedure A for Dess-Martin oxidation of alcohols 10a-h and 11a-h.

To a solution of alcohol (1 equiv.) in CH_2Cl_2 were added $NaHCO_3$ (3 equiv) and Dess-Martin periodinane (1.5 equiv) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, quenched with 10% sodium thiosulfate solution, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the corresponding carbonyl products.

General procedure B for anionic coupling of parts A and C.

To a solution of aryl bromide or phenylsulfone (1.8 equiv) in THF was added dropwise *n*-BuLi solution (1.6 M solution in *n*-hexane, 1.7 equiv) at -78 °C. The resulting solution was stirred for 30 min at -78 °C, and aldehyde (1.0 equiv) in THF was added. The reaction mixture was stirred for 1 h at -78 °C, washed with saturated NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the corresponding coupled product.

General procedure C for *O*-alkylation of phenols 14a-c.

To a solution of phenol (1.0 equiv) in acetone were added K_2CO_3 (3.0 equiv) and alkyl halide (3.0 equiv) at room temperature. The resulting mixture was refluxed for 12 h and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous

$MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding aryl ethers.

General procedure D for conversion of alcohols 15a-c to bromides.

To a solution of alcohol (1.0 equiv) in dried CH_2Cl_2 was added dropwise PBr_3 (1.4 equiv) at 0 ^oC. The reaction mixture was stirred for 3 h at room temperature, quenched with absolute EtOH, and stirred for additional 30 min. After Na_2CO_3 powder was added, the mixture was stirred for 30 min. and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the corresponding bromides.

General procedure E for conversion of bromides to sulfones 7a-c.

To a solution of bromide (1.0 equiv) in DMF were added benzenesulfinic acid sodium salt (1.1 equiv) at room temperature. The resulting solution was heated to 80 ^oC and stirred for 1 h at the same temperature. The reaction mixture was cooled to room temperature and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the corresponding sulfone.

General procedure F for deallylation of allyl ethers 16a-c.

To a solution of allyl ether (1.0 equiv) in THF were added $Pd(PPh_3)_4$ (0.1 equiv) and MeNHPh (0.2 equiv) at room temperature. The reaction mixture was stirred for 4h, quenched with water and 2*N*-HCl solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the corresponding phenol.

General procedure G for desulfonylation of ketones 16a-c.

To a solution of β-ketosulfone (1 equiv) in THF was added activated zinc (10 equiv) in saturated aqueous ammonium chloride solution. The mixture was refluxed for 8h, cooled to room temperature, and extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the corresponding desulfonylated product.

General procedure H for conversion (Buchwald-Hartwig reaction) of 33/36/40 to 34a-f/37a-b/41a-b.

To a mixture of palladium acetate (0.1 equiv), BINAP (0.2 equiv), and cesium carbonate (1.4 equiv) were added aryl triflate or aryl bromide (1.0 equiv) and amine (1.2 equiv) in toluene. The mixture was stirred for 30 min at room temperature, heated to 100 °C, and stirred overnight at the same temperature. The reaction mixture was cooled to room temperature and filtered through Celite pad. The residue was purified by flash column chromatography on silica gel to afford the corresponding coupling product.

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-phenylethan-1-one (6a). Oxidation of secondary alcohol **11a** (65 mg, 0.2 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 13 mg (20%) of **6a** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.49 (d, J = 8.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.26 - 7.16 (m, 3H), 6.58 (d, J = 10.1 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 10.0 Hz, 1H), 5.98 (d, J = 2.0 Hz, 1H), 4.24 (s, 2H), 3.74 (s, 3H), 1.42 (s, 6H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ

198.3, 157.7, 156.4, 135.1, 131.2, 130.5, 129.6 (two carbons), 128.4 (two carbons), 126.6, 124.8, 116.5, 114.8, 112.6, 63.2, 48.6 (two carbons), 28.0 (two carbons); HR-MS (ESI) calcd for $C_{20}H_{21}O_3$ ($M + H^+$) 309.1485, found 309.1492.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6b). Oxidation of secondary alcohol **11b** (55 mg, 0.2 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 30 mg (55%) of **6b** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.48 (d, J = 8.6 Hz, 1H), 6.75 - 6.65 (m, 3H), 6.59 (d, J = 4.8 Hz, 1H), 6.56 (d, J = 3.3 Hz, 1H), 5.90 (s, 2H), 5.66 (d, J = 10.1 Hz, 1H), 4.15 (s, 2H), 3.76 (s, 3H), 1.43 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 198.4, 157.8, 156.4, 147.6, 146.3, 131.1, 130.5, 128.7, 124.7, 122.6, 116.5, 114.8, 112.7, 110.1, 108.2, 100.8, 63.2, 48.2, 29.6, 28.0 (two carbons); HR-MS (FAB) Calcd for $C_{21}H_{21}O_5$ ($M + H^+$) 353.1389, Found 353.1386.

2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6c). Oxidation of secondary alcohol **11c** (30 mg, 0.1 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 21.3 mg (71%) of **6c** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, J = 8.7 Hz, 1H), 6.80 - 6.71 (m, 3H), 6.09 (dd, J = 8.7, 2.1 Hz, 1H), 5.85 (d, J = 1.9 Hz, 1H), 4.75 (q, J = 6.9 Hz, 1H), 3.82 (s, 2H), 3.82(s, 2H), 3.79 (s, 3H), 3.32 - 3.27 (m, 2H), 1.43 (d, J = 7.2 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 200.0, 160.9, 152.0, 148.6, 147.3, 135.8, 133.4 (two carbons), 120.1 (two carbons), 115.3, 111.1, 110.9, 104.4, 93.6, 55.8, 55.0, 49.9, 47.6, 25.4, 19.8 (two carbons); HR-MS (ESI) Calcd for $C_{22}H_{23}O_5$ ($M + H^+$) 367.1540, Found 367.1554

2-(3,4-Difluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6d). Oxidation of secondary alcohol **11d** (33 mg, 0.1 mmol) via general procedure A was

followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 8 mg (25%) of **6d** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, J = 4.3 Hz, 1H), 7.10 - 6.92 (m, 3H), 6.50 - 6.52 (m, 2H), 5.68 (d, J = 4.9 Hz, 2H), 4.20 (s, 2H), 3.76 (s, 3H), 1.44(s, 6H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 197.3, 158.1, 156.5, 131.9 (q, $J_{C\text{-}F}$ = 3.4 Hz), 131.1, 130.6, 125.6 (q, $J_{C\text{-}F}$ = 3.2 Hz), 124.3, 118.6, 118.5, 117.1, 117.0, 116.9, 114.8, 112.9, 63.3, 47.5 (two carbons), 28.0 (two carbons); HR-MS (FAB) Calcd for $C_{20}H_{19}F_2O_3$ ($M + H^+$) 345.1302, Found 345.1299.

2-(3,4-Dichlorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6e). Oxidation of secondary alcohol **11e** (18 mg, 0.1 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 8 mg (45%) of **6e** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 6.9 Hz, 1H), 7.33 (s, 1H), 7.07 (dd, J = 8.4, 2.4 Hz, 1H), 6.60 - 6.56 (m, 2H), 5.68 (d, J = 9.9 Hz, 1H), 4.19 (s, 2H), 3.76 (s, 3H), 1.43 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 196.9, 158.2, 156.6, 135.3, 132.3, 131.6, 131.2, 130.8, 130.6, 130.2, 129.1, 124.4, 116.4, 114.8, 112.9, 77.1, 63.3, 47.5, 28.0, 28.0; HR-MS (FAB) calcd for $C_{20}H_{19}Cl_2O_3$ ($M+H^+$) 377.0711, found 377.0709.

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(2-methoxyphenyl)ethan-1-one (6f). Oxidation of secondary alcohol **11f** (18 mg, 0.1 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 8 mg (45%) of **6f** as pale yellow solid: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.54 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 8.2, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.90 (dd, J = 8.7, 7.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 10.1 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 4.23 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 1.43 (s, 6H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 198.3, 157.5, 157.4, 156.3, 131.3, 131.0, 130.4, 128.2, 125.3, 124.4, 120.5, 116.7, 114.8, 112.4,

110.4, 76.8, 63.1, 55.3, 43.6, 28.0 (two carbons); HR-MS (ESI) calcd for $C_{21}H_{23}O_4$ ($M+H^+$) 339.1591, found 339.1580.

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(3-methoxyphenyl)ethan-1-one (6g). Oxidation of secondary alcohol **11g** (60 mg, 0.3 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:9) to afford 48 mg (80%) of **6g** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.48 (d, J = 8.7 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.79 (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 10.5 Hz, 1H), 6.57 (d, J = 8.2 Hz, 1H), 5.66 (d, J = 9.6 Hz, 1H), 4.21 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 1.42 (s, 6H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 198.1, 159.5, 157.7, 156.4, 136.5, 131.1, 130.4, 129.3, 124.7, 121.9, 116.5, 115.1, 114.7, 112.6, 112.2, 76.8, 63.1, 55.0, 48.6, 27.9, 27.9; HR-MS (FAB) calcd for $C_{21}H_{23}O_4$ ($M+H^+$) 339.1596, found 339.1602.

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(4-methoxyphenyl)ethan-1-one (6h). Oxidation of secondary alcohol **11h** (61mg, 0.2 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:10) to afford 40 mg (66%) of **6h** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, 1H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.3 Hz), 6.82 (d, 2H, J = 8.3 Hz), 6.57 (t, 2H, J = 10.6 Hz), 5.66 (d, 1H, J = 9.9 Hz), 4.1 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 1.42 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 198.7, 158.3, 157.6, 156.3, 131.1, 130.5, 130.5, 130.5, 127.1, 124.8, 116.5, 114.8, 113.9, 113.9, 112.6, 76.8, 63.2, 55.1, 47.7, 28.0, 28.0; HR-MS (FAB) calcd for $C_{21}H_{23}O_4$ ($M+H^+$) 339.1596, found 339.1605.

2-(2-Fluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6i). Oxidation of secondary alcohol **11i** (59 mg, 0.2 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:15) to afford 39 mg

(66%) of **6i** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.56 (d, J = 8.7 Hz, 1H), 7.24 - 7.19 (m, 2H), 7.09 - 7.02 (m, 2H), 6.60 (d, J = 2.2 Hz, 1H), 6.59 (d, J = 4.1 Hz, 1H), 5.67 (d, J = 10.0 Hz, 1H), 4.30 (s, 2H), 3.81 (s, 3H), 1.43 (s, 6H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 196.5, 161.0 (d, $J_{C\text{-}F}$ = 244 Hz), 157.9, 156.6, 131.8 (d, $J_{C\text{-}F}$ = 4.3 Hz), 131.1, 130.5, 128.6 (d, $J_{C\text{-}F}$ = 7.8 Hz), 124.5, 123.9 (d, $J_{C\text{-}F}$ = 21.5 Hz), 122.6 (d, $J_{C\text{-}F}$ = 15.8 Hz), 116.5, 115.16 (d, $J_{C\text{-}F}$ = 21.5 Hz), 114.8, 112.7, 63.1, 42.1 (two carbons), 27.9 (two carbons); HR-MS (FAB) calcd for $C_{20}H_{20}FO_3$ ($M+H^+$) 327.1396, found 327.1401.

2-(3-Fuorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6j). Oxidation of secondary alcohol **11j** (43 mg, 0.1 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:30) to afford 27 mg (62%) of **6j** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, J = 8.4 Hz, 1H), 7.24 - 7.20 (m, 1H), 7.04 - 6.83 (m, 3H), 6.60 (s, 1H), 6.56 (s, 1H), 5.67 (d, J = 10.2 Hz, 1H), 4.23 (s, 2H), 3.75 (s, 3H), 1.43 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 197.5, 163.7 (d, $J_{C\text{-}F}$ = 244.0 Hz), 158.0, 156.5, 137.5 (d, $J_{C\text{-}F}$ = 7.7 Hz), 131.1, 130.5, 129.7 (d, $J_{C\text{-}F}$ = 8.2 Hz), 125.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 124.5, 116.6 (d, $J_{C\text{-}F}$ = 21.3 Hz), 116.4, 114.8, 113.5 (d, $J_{C\text{-}F}$ = 20.8 Hz), 112.7, 63.2, 48.2, 48.2, 28.0 (two carbons); HR-MS (FAB) calcd for $C_{20}H_{20}FO_3$ ($M+H^+$) 327.1396, found 327.1399.

2-(4-Fluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (6k). Oxidation of secondary alcohol **11k** (37 mg, 0.1 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:15) to afford 25 mg (69%) of **6k** as yellow solid: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.48 (d, 1H, J = 8.2 Hz), 7.21 - 7.17 (m, 2H), 6.97 (t, 2H, J = 8.7 Hz), 6.59 (d, 1H, J = 2.7 Hz), 6.57 (d, 1H, J = 1.3 Hz), 5.67 (d, 1H, J = 9.6 Hz), 4.21 (s, 2H), 3.75 (s, 3H), 1.43(s, 6H); ^{13}C-NMR ($CDCl_3$, 150

MHz) δ 198.0, 161.7 (d, $J_{C\text{-}F}$ = 242.7 Hz), 157.9, 156.5, 131.1, 131.0, 130.8, 130.7, 130.5, 124.6, 116.4, 115.2, 115.1, 114.8, 112.7, 63.2, 47.7 (two carbons), 28.0 (two carbons); HR-MS (FAB) calcd for $C_{20}H_{20}FO_3$ ($M+H^+$) 327.1396, found 327.1404.

1-(Allyloxy)-2-((phenylsulfonyl)methyl)benzene (7a). Bromination of alcohol **15a** (220 mg, 1.3 mmol) via general procedure D and sulfonylation of the resulting bromide via general procedure E were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 348 mg (90%, 2 steps) of **7a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.58 - 7.49 (m, 3H), 7.38 - 7.31 (m, 3H), 7.26 - 7.20 (m, 3H), 6.92 (td, J = 7.5, 1.1 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 5.74 - 5.70 (m, 1H), 5.20 (dq, J = 8.4, 1.6 Hz, 1H), 5.15 (t, J = 1.6 Hz, 1H), 4.47 (s, 2H), 4.04 (dt, J = 5.1, 1.6 Hz, 2H)

1-(Allyloxy)-3-((phenylsulfonyl)methyl)benzene (7b). Bromination of **15b** (209 mg, 1.3 mmol) via general procedure D and sulfonylation of the resulting bromide via general procedure E were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3) to afford 337mg (92%, 2 steps) of **7b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.64 - 7.56 (m, 3H), 7.46 - 7.41 (m, 2H), 7.12 (t, J = 1H), 6.85 - 6.82 (m, 1H), 6.62 - 6.59 (m, 2H), 5.99 - 5.95 (m, 1H), 5.35 (dq, J = 17.1, 1.6 Hz, 1H), 5.25 (dq, J = 10.4, 1.4 Hz, 1H), 4.41 (dt, J = 5.1, 1.4 Hz, 2H), 4.25 (s, 2H).

1-(Allyloxy)-4-((phenylsulfonyl)methyl)benzene (7c). Bromination of **15c** (206 mg, 1.3 mmol) via general procedure D and sulfonylation of the resulting bromide via general procedure E were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3) to afford 320 mg (88%, 2 steps) of **7c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.62 - 7.55 (m, 3H), 7.45 - 7.40 (m, 2H), 6.95 (dt, J = 8.7, 2.1 Hz, 2H), 6.77 (dt, J = 8.7, 2.9 Hz, 2H), 6.03 - 5.99 (m, 1H), 5.37 (dq, J = 17.2, 1.6 Hz, 1H), 5.27 (dq, J = 10.4, 1.4 Hz, 1H), 4.49 (dt, J = 5.3, 1.4 Hz, 2H), 4.22 (s, 2H).

5-Methoxy-2,2-dimethyl-2H-chromene-6-carbaldehyde (8). To a solution of phenol **13** (20.0g, 97.9 mmol) in acetone were added potassium carbonate (13.53 g, 293.8 mmol) and iodomethane (18.3 mL, 293.8 mmol) at room temperature. The mixture was refluxed for 12 h, and extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:20) to afford 17.73 g (83%) of **8**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 10.15 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.57 (d, J = 10.0 Hz, 1H), 5.67 (d, J = 10.0 Hz, 1H), 3.88 (s, 3H), 1.44 (s, 6H).

2-(2-Hydroxyphenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (9a). Deallyation of **16a** (42 mg, 0.1 mmol) via general procedure F and desulfonylation of the resulting phenol via general procedure G were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane =1:6) to afford 25 mg (91%, 2 steps) of **9a** as colorless oil: ^{1}H-NMR (MeOD, 500 MHz) δ 7.57 (d, J = 8.6 Hz, 1H), 7.07 - 7.03 (m, 2H), 6.76 - 6.73 (m, 2H), 6.63 (d, J = 10.0 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 5.77 (d, J = 10.0 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 3H) 1.42 (s, 6H); ^{13}C-NMR (MeOD, 125 MHz) δ 202.1, 159.9, 158.6, 157.4, 133.1, 133.0, 132.6, 129.8, 126.9, 124.4, 121.2, 118.2, 117.0, 116.6, 114.1, 78.8, 64.4, 45.2, 29.0, 29.0; HR-MS (FAB) calcd for $C_{20}H_{21}O_4$ ($M+H^+$) 325.1440, found 325.1446.

2-(3-Hydroxyphenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (9b). Deallyation of **16b** (129 mg, 0.2 mmol) via general procedure F and desulfonylation of the resulting phenol via general procedure G were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane =1:4) to afford 79 mg (95%, 2 steps) of **9b** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.50 (d, J = 8.6 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H), 6.75 - 6.73 (m, 2H), 6.68 (d, J = 7.8 Hz, 1H), 6.64 (s, 1H), 6.58 (d, J = 3.5 Hz, 1H), 6.56 (s, 1H), 5.65 (d, J = 10.0 Hz, 1H), 4.18 (s, 2H) 3.72 (s, 3H), 1.42 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 199.1,

158.0, 156.6, 156.1, 136.2, 131.3, 130.5, 129.5, 124.4, 121.4, 116.5, 116.4, 114.8, 113.9, 112.6, 76.9, 63.1, 48.3, 27.9, 27.9; HR-MS (FAB) calcd for $C_{20}H_{21}O_4$ ($M+H^+$) 325.1440, found 325.1445.

2-(4-Hydroxyphenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (9c). Deallyation of **16c** (49 mg, 0.1 mmol) via general procedure F and desulfonylation of the resulting phenol via general procedure G were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane =1:6) to afford 32 mg (100%, 2 steps) of **9c** as pale yellow oil: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.49 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 8.2 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 5.79 (s, 1H), 5.66 (d, J = 10.0 Hz, 1H), 4.16 (s, 2H) 3.74 (s, 3H), 1.42 (s, 6H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 199.3, 157.8, 156.4, 154.6, 131.2, 130.6, 130.6, 130.5, 126.7, 124.7, 116.4, 115.4, 115.4, 114.8, 112.6, 76.9, 63.2, 47.7, 28.0, 28.0; HR-MS (FAB) calcd for $C_{20}H_{21}O_4$ ($M+H^+$) 325.1440, found 325.1443..

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-phenylethan-1-ol (11a). Condensation of phenylacetaldehyde (77 mg, 0.6 mmol) via general procedure B was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 72 mg (36%) of **11a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.31 - 7.18 (m, 6H), 6.61 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 9.9 Hz, 1H), 5.63 (d, J = 10.1 Hz, 1H), 5.13 - 5.07 (m, 1H), 3.68 (s, 3H), 3.08 - 2.92 (m, 2H), 1.41 (d, J = 6.2 Hz, 6H).

2-(Benzo[d][1,3]dioxol-5-yl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11b). Oxidation of phenethyl alcohol **10b** (53 mg, 0.3 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 61 mg (54%, 2 steps) of **11b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, J = 8.4 Hz, 1H), 6.73-6.67 (m, 3H), 6.60-6.55

(m, 2H), 5.91 (d, *J* = 0.8 Hz, 2H), 5.63 (d, *J* = 9.9 Hz, 1H), 5.06-5.00 (m, 1H), 3.72 (d, *J* = 0.6 Hz, 3H), 2.92 - 2.87 (m, 2H), 1.41 (d, *J* = 6.8 Hz, 6H).

2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11c). Oxidation of phenethyl alcohol **10c** (33mg, 0.2 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 41 mg (60%, 2 steps) of **11c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, *J* = 10.6 Hz, 1H), 6.79 - 6.68 (m, 3H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 9.9 Hz, 1H), 5.63 (d, *J* = 9.9 Hz, 1H), 5.07 - 5.02 (m, 1H), 4.22 (s, 4H), 3.72 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 6H).

2-(3,4-difluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11d). Oxidation of phenethyl alcohol **10d** (54 mg, 0.3 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 47mg (39%, 2 steps) of **11d**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, *J* = 8.4 Hz, 1H), 7.06 - 7.02 (m, 2H), 6.95 - 6.87 (m, 1H), 6.60 - 6.52 (m, 2H), 5.64 (d, *J* = 9.9 Hz, 1H), 5.07 - 5.03 (m, 1H), 3.71 (s, 3H), 2.95 - 2.89 (m, 2H), 2.01 (d, *J* = 3.8 Hz, 1H), 1.41 (d, *J* = 5.9 Hz, 6H).

2-(3,4-Dichlorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11e). Oxidation of phenethyl alcohol **10e** (44 mg, 0.2 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B followed were by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 18 mg (21%, 2 steps) of **11e** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.28 - 7.22 (m, 2H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.47 (d, *J* = 9.9 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H), 5.00 (dt, *J* = 7.6, 5.3 Hz, 1H), 3.66 (s, 3H), 2.92 - 2.88 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H).

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(2-methoxyphenyl)ethan-1-ol (11f). Oxidation of phenethyl alcohol **10f** (44 mg, 0.2 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 18 mg (21%, 2 steps) of **11f**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, J = 8.2, 2H), 7.12 (d, J = 7.3, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 5.62 (d, J = 9.8 Hz, 1H), 5.20 - 5.00 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.13 - 2.95 (m, 2H), 2.58 (s, 1H), 1.40 (d, J = 7.1 Hz, 6H)

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(3-methoxyphenyl)ethan-1-ol (11g). Oxidation of phenethyl alcohol **10g** (102 mg, 0.7 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:8) to afford 73 mg (33%, 2 steps) of **11g**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, J = 6.9 Hz, 2H), 6.83 (d, J = 7.5 Hz, 1H), 7.78 - 7.74 (m, 2H), 6.60 (d, J = 8.6 Hz, 1H), 6.53 (d, J = 9.8 Hz, 1H), 5.63 (d, J = 9.9 Hz, 1H), 5.09 (dt, J = 8.0, 3.6 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.02 (dd, J = 13.5, 4.3 Hz, 1H), 2.91 (dd, J = 13.5, 8.6 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H).

1-(5-Methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(4-methoxyphenyl)ethan-1-ol (11h). Oxidation of phenethyl alcohol **10h** (101 mg, 0.7 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 71 mg (32%, 2 steps) of **11h**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 9.8 Hz, 1H), 5.63 (d, J = 9.9 Hz, 1H), 5.05 (dt, J = 8.0, 3.6 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 2.98 (dd, J = 13.7, 4.5 Hz, 1H), 2.88 (dd, J = 13.7, 8.6 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H).

2-(2-Fluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11i). Oxidation of phenethyl alcohol **10i** (113 mg, 0.8 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:10) to afford 61mg (25%, 2 steps) of **11i**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.22 - 7.15 (m, 3H), 7.07 - 6.98 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 9.9 Hz, 1H), 5.63 (d, J = 9.9 Hz, 1H), 5.14 (dt, J = 8.6, 4.2 Hz, 1H), 3.73 (s, 3H), 3.11 (dd, J = 13.9, 3.8 Hz, 1H), 3.00 (dd, J = 13.5, 8.7 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H).

2-(3-Fluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11j). Oxidation of phenethyl alcohol **10j** (113 mg, 0.8 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:10) to afford 46mg (17%, 2 steps) of **11j**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24 - 7.22 (m, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.00 - 6.86 (m, 3H), 6.59 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 9.8 Hz, 1H), 5.64 (d, J = 13.9 Hz, 1H), 5.08 (dd, J = 8.2, 4.9 Hz, 1H), 3.69 (s, 3H), 3.02 (dd, J = 13.7, 4.9 Hz, 1H), 2.95 (dd, J = 13.5, 8.2 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H)

2-(4-Fluorophenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-ol (11k). Oxidation of phenethyl alcohol **10k** (101 mg, 0.7 mmol) via general procedure A and condensation of the resulting aldehyde via general procedure B were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:8) to afford 63 mg (27%, 2 steps) of **11k**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.26 - 7.22 (m, 3H), 7.09 - 7.01 (m, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 10.0 Hz, 1H), 5.74 (d, J = 10.0 Hz, 1H), 5.15 (dd, J = 7.8, 5.1 Hz, 1H), 3.76 (s, 3H), 3.10 (dd, J = 13.7, 5.1 Hz, 1H), 3.03 (dd, J = 13.7, 8.0 Hz, 1H), 1.52 (s, 3H), 1.50 (s, 3H).

5-Hydroxy-2,2-dimethyl-2H-chromene-6-carbaldehyde (13). To a solution of phenol **12** (7.15 g, 51.8 mmol) in EtOH (172 mL) were added 3-metyl-2-butenal (10.3 mL, 103.6 mmol), $CaCl_2 \cdot 2H_2O$ (6.32g, 43.0 mmol), and triethylamine (24.0 mL, 172.1 mmol) at room temperature. The mixture was refluxed for 1 h, acidified with 2*N*-HCl, and extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:30) to afford 6.88 g (65%) of **13**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 11.62 (s, 1H), 9.63 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 10.0 Hz, 1H), 6.41 (d, J = 8.6 Hz, 1H), 5.59 (d, J = 10.0 Hz, 1H), 1.44 (s, 6H).

(2-(Allyloxy)phenyl)methanol (15a). Allylation of hydroxyphenyl methanol **14a** (426 mg, 3.4 mmol) with allyl bromide (0.58 mL, 6.8 mmol) via general procedure C was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:6) to afford 539 mg (97%) of **15a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.28 - 7.20 (m, 2H), 6.93 (td, J = 7.3, 0.9 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.07 - 6.03 (m, 1H), 5.40 (dq, J = 17.1, 1.4 Hz, 1H), 5.28 (dq, J = 10.4, 1.2 Hz, 1H), 4.70 (s, 2H), 4.58 (dt, J = 5.1, 1.6 Hz, 2H), 2.31 (s, 1H).

(3-(allyloxy)phenyl)methanol (15b). Allylation of hydroxyphenyl methanol **14b** (408 mg, 3.3 mmol) with allyl bromide (0.55 mL, 6.5 mmol) via general procedure C was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:6) to afford 473 mg (89%) of **15b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.27 - 7.22 (m, 1H), 6.93 - 6.91 (m, 2H), 6.85 - 6.81 (m, 1H), 6.06 - 6.02 (m, 1H), 5.39 (dq, J = 17.4, 1.6 Hz, 1H), 5.27 (dq, J = 10.4, 1.2 Hz, 1H), 4.65 (s, 2H), 4.53 (dt, J = 5.3, 1.4 Hz, 2H), 1.65 (s, 1H).

(4-(Allyloxy)phenyl)methanol (15c). Allylation of hydroxyphenyl methanol **14c** (405 mg, 3.2 mmol) with allyl bromide (0.55 mL, 6.5 mmol) via general procedure C was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:3) to afford 483 mg (91%)

of **15c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.27 (dt, J = 8.6, 2.0 Hz, 2H), 6.89 (dt, J = 9.3, 2.7 Hz, 2H), 6.06 - 6.02 (m, 1H), 5.39 (dq, J = 17.2, 1.6 Hz, 1H), 5.27 (dq, J = 10.4, 1.2 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 4.52 (dt, J = 5.3, 1.4 Hz, 2H), 4.22 (s, 2H).

2-(2-(allyloxy)phenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(phenylsulfonyl) ethan-1-one (16a). Condensation of sulfone **7a** (208.8 mg, 0.551 mmol) with aldehyde **8** via general procedure B and oxidation of the resulting alcohol via general procedure A were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3) to afford 278 mg (76%, 2 steps) of **16a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.68 (dd, J = 7.8, 1.6 Hz, 1H), 7.59 (d, J = 7.3 Hz, 2H), 7.50 (t, J = 6.9 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.23 (dd, J = 15.9, 1.4 Hz, 1H), 7.11 (s, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 6.7 Hz, 1H), 6.48 (d, J = 5.6 Hz, 1H), 5.86 - 5.82 (m, 1H), 5.62 (d, J = 10.0 Hz, 1H), 5.31 (dd, J = 17.4, 1.6 Hz, 1H), 5.22 (dd, J = 10.4, 0.9 Hz, 1H), 4.33 (dd, J = 13.0, 5.1 Hz, 1H), 4.14 - 4.06 (m, 1H), 3.69 (s, 3H), 1.39 (s, 3H), 1.39 (s, 3H).

2-(3-(Allyloxy)phenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(phenylsulfonyl) ethan-1-one (16b). Condensation of sulfone **7b** (213 mg, 0.7 mmol) with aldehyde **8** via general procedure B and oxidation of the resulting alcohol via general procedure A were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 321 mg (86%, 2 steps) of **16b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.60 - 7.52 (m, 3H), 7.44 - 7.35 (m, 3H), 7.14 (t, J = 7.8 Hz, 1H), 6.90 - 6.85 (m, 3H), 6.54 (d, J = 8.9 Hz, 1H), 6.49 (d, J = 9.8 Hz, 1H), 6.43 (s, 1H), 5.96 - 5.92 (m, 1H), 5.65 (d, J = 10.0 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.24 (d, J = 10.6 Hz, 1H), 4.37 (s, 2H) 3.55 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H).

2-(4-(Allyloxy)phenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)-2-(phenylsulfonyl) ethan-1-one (16c). Condensation of sulfone **7c** (222 mg, 0.8 mmol) with aldehyde **8** via

general procedure B and oxidation of the resulting alcohol via general procedure A were followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 330 mg (85%, 2 steps) of **16c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.58 - 7.51 (m, 3H), 7.43 - 7.34 (m, 3H), 7.24 (s, 1H), 7.22 (s, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.53 (d, J = 8.5 Hz, 1H), 6.48 (d, J = 9.9 Hz, 1H), 6.39 (s, 1H), 6.02 - 5.98 (m, 1H), 5.65 (d, J = 10.0 Hz, 1H), 5.65 (d, J = 10.0 Hz, 1H), 5.37 (dd, J = 17.2, 1.4 Hz, 1H), 5.27 (dd, J = 10.4, 1.2 Hz, 1H), 4.48 (d, J = 5.3 Hz, 2H), 3.54 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H).

2-(3,4-Dimethoxyphenyl)-2-fluoro-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethan-1-one (17). To a solution of **2** (7 mg, 0.02 mmol) in CH_2Cl_2 were added trimethylsilyl trifluoromethanesulfonate (7 μL, 0.04 mmol) and triethylamine (8 μL, 0.06 mmol) at room temperature. The mixture was stirred for 3h, quenched with $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in DMF and Selectfluor® (7.1 mg, 0.02 mmol) was added. The mixture was stirred for 15 min and TBAF (1.0 M in THF, 0.02 mL, 0.02 mmol) and water were added. The reaction mixture was stirred for 2 h, filtered through Celite pad, and extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 5 mg (67%) of **17** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 8.7 Hz, 1H), 6.97 - 6.93 (m, 1H), 6.92 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.61 - 6.55 (m, 2H), 6.51 (s, 1H), 5.65 (d, J = 10.1 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 1.41 (s, 6H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 194.8 (d, $J_{C\text{-}F}$ = 21.3 Hz), 158.4, 156.3, 149.8 (d, $J_{C\text{-}F}$ = 2.5 Hz), 149.1, 131.3, 130.6, 126.8 (d, $J_{C\text{-}F}$ = 20.6 Hz), 122.1, 120.9 (d, $J_{C\text{-}F}$ = 5.5 Hz) 116.2,

114.5, 113.0, 110.9, 110.3 (d, $J_{C\text{-}F}$ = 4.5 Hz), 94.1 (d, $J_{C\text{-}F}$ = 181.4 Hz), 77.0, 63.4, 55.9, 55.8, 28.1, 28.0; HR-MS (ESI) Calcd for $C_{22}H_{23}FNaO_5$ ($M + Na^+$) 409.1422, Found 409.1426

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)pent-4-en-1-one (18). To a suspension of sodium hydride (60% in dispersion, 2 mg, 0.05 mmol) in THF (1 mL) was added a solution of ketone **2** (19 mg, 0.05 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 30 min and allyl bromide (0.01 mL, 0.06 mmol) was added at 0 °C. The reaction mixture was stirred overnight at room temperature, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 13 mg (61%) of **18** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, J = 8.6 Hz, 1H), 6.80 - 6.71 (m, 3H), 6.54 (m, 1H), 6.48 (m, 1H), 5.74 (m, 1H), 5.62 (d, J = 10.0 Hz, 1H), 5.04 (m, 1H), 4.94 (m, 1H), 4.55 (t, J = 7.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.59 (s, 3H), 2.88 (m, 1H), 2.49 (m, 1H), 1.39 (s, 3H), 1.39 (s, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 201.1, 157.2, 155.9, 148.9, 147.9, 136.3, 131.6, 130.9, 130.5, 125.5, 120.7, 116.5, 116.4, 114.8, 112.4, 111.2, 111.0, 63.4, 55.9, 55.8, 55.7 (two carbons), 38.1, 28.0 (two carbons); HR-MS (FAB) calcd for $C_{25}H_{29}O_5$ ($M+H^+$) 409.2015; found 409.2003.

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)-3-phenylpropan-1-one (19). To a suspension of sodium hydride (60% in dispersion, 3 mg, 0.06 mmol) in THF (1 mL) was added a solution of ketone **2** (25 mg, 0.07 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 30 min and benzyl bromide (0.01 mL, 0.07 mmol) was added at 0 °C and stirred overnight at room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column

chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 13 mg (61%) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$, 800 MHz) δ 7.18 (t, J = 8.6 Hz, 3H), 7.13 (d, J = 7.0 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 6.74 (m, 2H), 6.70 (d, J = 10.3 Hz, 1H), 6.49 (d, J = 10.2 Hz, 1H), 6.43 (d, J = 8.7 Hz, 1H), 5.60 (d, J = 10.8 Hz, 1H), 4.78 (dd, J = 8.0, 6.6 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.52 (dd, J = 13.5, 8.2 Hz, 1H), 3.34 (s, 3H), 2.96 (dd, J = 13.5, 6.6 Hz, 1H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 201.2, 157.2, 155.8, 148.8, 140.3, 131.7, 130.9, 130.5, 129.4, 128.2, 126.0, 125.6, 120.7, 116.4, 114.7, 112.4, 111.3, 111.0, 68.0, 63.2, 58.4, 55.8, 55.7, 29.7, 28.0; HR-MS (ESI) Calcd for $C_{29}H_{31}O_5$ ($M + H^+$) 459.2166, Found 459.2174.

2-(3,4-Dimethoxyphenyl)-1-(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)ethyl acetate (21). To a solution of alcohol **20** (25 mg, 0.07 mmol), triethylamine (96 µL, 0.7 mmol), and 4-(dimethylamino)pyridine (1 mg, 0.01 mmol) in CH_2Cl_2 was added acetic anhydride (0.02 mL, 0.2 mmol). The mixture was stirred for 2 h, quenched with water, and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 18 mg (63%) of **21** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (d, J = 8.7 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.57 (dd, J = 8.1, 1.8 Hz, 1H), 6.43 (m, 3H), 6.05 (t, J = 6.9 Hz, 1H), 5.51 (d, J = 9.9 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.55 (s, 3H), 2.90 (m, 2H), 1.89 (s, 3H), 1.30 (d, J = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 153.6, 153.5, 148.3, 147.4, 130.2, 129.8, 127.1, 125.1, 121.5, 117.0, 114.4, 112.7, 112.4, 110.8, 75.8, 71.4, 62.3, 55.7, 55.6, 41.8, 27.8, 27.6, 21.2; HR-MS (ESI) Calcd for $C_{24}H_{28}NaO_6$ ($M + Na^+$) 435.1778, Found 435.1791.

5-Methoxy-2,2-dimethyl-2H-chromene-6-carboxylic acid (22). To a solution of sodium hydroxide (635 mg, 15.4 mmol) in water (7.0 mL) was added silver nitrate (865 mg, 5.1

mmol). The mixture was stirred for 20 min and aldehyde **8** (505 mg, 2.3 mmol) was added. The resulting mixture was refluxed overnight and filtered through Celite pad. The aqueous phase was acidified with 2*N*-HCl and extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford 190 mg (35%) of crude **22**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 10.1 Hz, 1H), 5.71 (d, J = 9.9 Hz, 1H), 3.91 (s, 3H), 1.45 (s, 6H).

***N*-(3,4-Dimethoxyphenyl)-5-methoxy-2,2-dimethyl-2H-chromene-6-carboxamide (23).** To a solution of carboxylic acid **22** (79 mg, 0.4 mmol) in CH_2Cl_2 (3.5 mL) were added 3,4-dimethoxyaniline (63 mg, 0.4 mmol), PyBOP (179 mg, 0.4 mmol), and *N*,*N*-diisopropylethylamine (130.0 μL, 0.7 mmol). The mixture was stirred overnight and concentrated under reduced pressure. The reaction mixture was treated with 2*N*-HCl solution and extracted with EtOAc. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford 93 mg (75%) of **23** as a white solid: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.60 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 2.4, 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 9.0 Hz, 1H), 6.58 (d, J = 10.1 Hz, 1H), 5.71 (d, J = 10.1 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 1.44 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 157.2, 154.4, 149.1, 145.7, 132.3, 132.0, 131.1, 118.6, 116.2, 114.3, 113.7, 111.6, 111.4, 105.0, 76.8, 63.1, 56.1, 56.0, 28.0, 28.0; HR-MS (FAB) Calcd for $C_{21}H_{24}NO_5$ ($M+H^+$): 370.1654, Found: 370.1651.

***N*-(3,4-Dimethoxyphenyl)-5-methoxy-*N*,2,2-trimethyl-2H-chromene-6-carboxamide (24).** *N*-Methylation of amide **23** (20 mg, 0.1 mmol) with iodomethane by the procedure described for the preparation of **18** and purification of the crude product via flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 17 mg (85%) of **24** as a

colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.60 - 6.47 (m, 6H), 5.57 (d, J = 9.7 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 3.42 (s, 3H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.4, 154.4, 152.9, 148.6, 147.5, 137.3, 130.5, 128.0, 128.0, 124.0, 118.2, 116.6, 114.6, 111.9, 110.7, 76.0, 63.1, 55.8, 55.8, 37.5, 27.6 (two carbons); HR-MS (ESI) Calcd for $C_{22}H_{26}NO_5$ ($M + H^+$) 384.1805, Found 384.1807

***N*-(3,4-Dimethoxyphenyl)-*N*-ethyl-5-methoxy-2,2-dimethyl-2H-chromene-6 carboxamide (25).** *N*-Ethylation of amide **23** (15 mg, 0.04 mmol) with iodoethane by the procedure described for the preparation of **18** and purification of the crude product via flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 16 mg (97%) of **25** as a colorless oil: ^{1}H NMR ($CDCl_3$, 800 MHz) δ 6.71 (d, J = 12.9 Hz, 1H), 6.61 (s, 2H), 6.56 (s, 1H), 6.42 (d, J = 15.6, 1H), 6.29 (d, J = 12.9, 1H), 5.55 (d, J = 15.6, 1H), 3.89 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 1.32 (s, 6H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 168.8, 154.1, 152.7, 148.5, 147.6, 135.5, 130.5, 127.8, 124.4, 119.3, 116.6 (two carbons), 114.5, 111.8, 110.6, 75.9, 63.1, 55.8, 55.8, 44.2, 27.6 (two carbons), 13.1; HR-MS (ESI) Calcd for $C_{23}H_{28}NO_5$ ($M + H^+$) 398.1962, Found 398.1958.

***N*-benzyl-*N*-(3,4-dimethoxyphenyl)-5-methoxy-2,2-dimethyl-2H-chromene-6-carboxamide (26).** *N*-Benzylation of amide **23** (17 mg, 0.1 mmol) with benzyl bromide by the procedure described for preparation of **18** and purification of the crude product via flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 18 mg (87%) of **26** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 800 MHz) δ 7.30 (m, 5H), 6.74 (d, J = 8.2 Hz, 1H), 6.52 (d, J = 8.5, 1H), 6.49 (d, J = 7.9, 1H), 6.42 (d, J = 9.8, 1H), 6.37 (s, 1H), 6.30 (d, J = 8.2 Hz, 1H), 5.56 (d, J = 9.9 Hz, 1H), 5.04 (s, 2H), 3.87 (s, 3H), 3.72 (s, 3H), 3.53 (s, 3H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 169.3, 154.2, 152.7, 148.2, 147.5, 137.7, 135.5, 130.5, 128.6 (two carbons), 128.4 (two carbons), 127.7, 127.2, 124.1, 119.4, 116.5, 114.6,

111.8, 111.7, 110.3, 75.9, 63.2, 55.6 (two carbons), 52.9, 27.5 (two carbons); HR-MS (ESI) Calcd for $C_{28}H_{30}NO_5$ ($M + H^+$) 460.2118, Found 460.2125.

1-Bromo-2-methoxy-4-(methoxymethoxy)benzene (28). To a suspension of sodium hydride (60% in dispersion, 912.8 mg, 22.82 mmol) in DMF (20 mL) was added a solution of 4-bromo-3-methoxyphenol (**27**) (2632.4 mg, 12.97 mmol) in DMF (6 mL) at 0 °C. The mixture was stirred for 30 min and chloromethyl methyl ether (1.76 mL, 21.78 mmol) was added at 0 °C. The reaction mixture warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with water, and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6 to 1:4) to afford 3079.9 mg (96%) of **28** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, 1H, *J* = 8.6 Hz), 6.60 (d, 1H, *J* = 2.7 Hz), 6.53 (dd, 1H, *J* = 8.6, 2.5 Hz), 5.13 (s, 2H), 3.85 (s, 3H), 3.45 (s, 3H).

2-(3,4-dimethoxyphenyl)-1-(2-methoxy-4-(methoxymethoxy)phenyl)propan-1-ol (29). Condensation of aryl bromide **28** (2.16 g, 8.74 mmol) with aldehyde **35** (0.87 g, 4.48 mmol) via general procedure B was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4 to 1:2) to afford 1169 mg (72%) of the corresponding secondary alcohol **29**: ^{1}H-NMR (Acetone-d_6, 300 MHz) δ 7.27 (d, 1H, *J* = 8.2 Hz), 6.78 – 6.75 (m, 3H), 6.58 – 6.51 (m, 2H), 5.14 (s, 2H), 4.99 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.64 (m, 1H), 3.40 (s, 3H), 3.01 (m, 1H), 1.21 (d, 3H, *J* = 6.9 Hz) as a major isomer.

2-(3,4-Dimethoxyphenyl)-1-(2-methoxy-4-(methoxymethoxy)phenyl)ethan-1-one (30). Oxidation of secondary alcohol **29** (985.3 mg, 2.72 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6 to 1:3) to afford 803.7 mg (82%) of **30** as a yellow solid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, 1H, *J*

= 8.6 Hz), 6.74 – 6.71 (m, 3H), 6.56 (dd, 1H, *J* = 8.6, 2.0 Hz), 6.49 (d, 1H, *J* = 1.9 Hz), 5.14 (s, 2H), 4.67 (q, 1H, *J* = 6.9 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.43 (s, 3H), 1.44 (d, 3H, *J* = 6.9 Hz).

2-(3,4-Dimethoxyphenyl)-1-(4-hydroxy-2-methoxyphenyl)ethan-1-one (31). To a solution of MOM ether **30** (877 mg, 2.4 mmol) in methanol was added 2*N*-HCl solution (10.0 mL). The mixture was stirred for 4 h at 60 °C and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:1) to afford 723 mg (94%) of phenol **31**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, *J* = 8.7 Hz, 1H), 6.79 - 6.71 (m, 3H), 6.40 - 6.37 (m, 2H), 5.52 (s, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 3.82 (s, 6H), 3.82 (s, 3H).

1-(2,4-Dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)propan-1-one (32a). To a solution of phenol **31** (34 mg, 0.1 mmol) in acetonitrile (1.0 mL) were added cesium carbonate (52 mg, 0.2 mmol) and iodomethane (12.0 μL, 0.2 mmol) at 0 °C. The mixture was stirred for 20 min at 0 °C and stirred for 1 h at room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:2) to afford 25 mg (71%) of methyl ether **32a** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, *J* = 8.7 Hz, 1H), 6.72 (m, 3H), 6.42 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 4.68 (q, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 201.8, 163.9, 159.8, 148.7, 147.6, 134.6, 132.8, 121.5, 120.2, 111.2, 111.0, 104.9, 98.3, 55.8, 55.7, 55.4, 55.3, 50.6, 19.1; HR-MS (ESI) calcd for $C_{19}H_{23}O_5$ ($M + H^+$) 331.1540, found 331.1537.

2-(3,4-Dimethoxyphenyl)-1-(4-ethoxy-2-methoxyphenyl)propan-1-one (32b). Etherification of phenol **31** (10 mg, 0.03 mmol) with iodoethane (5.0 μL, 0.1 mmol) via the procedure described for the preparation of **32a** was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 10 mg (91%) of ethyl ether **32b** as a pale yellow oil: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.60 (d, J = 8.7 Hz, 1H), 6.73 (m, 3H), 6.41 (dd, J = 8.7, 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 1H), 4.68 (q, J = 6.9 Hz, 1H), 4.01 (q, J = 7.0 Hz, 1H), 3.81 (s, 6H), 3.80 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 201.8, 163.3, 159.8, 148.7, 147.5, 134.6, 132.8, 121.2, 120.2, 111.1, 110.9, 105.4, 98.8, 63.6, 55.7, 55.7, 55.3, 50.5, 19.1, 14.6; HR-MS (ESI) calcd for $C_{20}H_{25}O_5$ ($M + H^+$) 345.1697, found 345.1695.

1-(4-(Cyclohexyloxy)-2-methoxyphenyl)-2-(3,4-dimethoxyphenyl)propan-1-one (32c). To a solution of phenol **31** (26 mg, 0.1 mmol), cyclohexanol (9 μL, 0.1 mmol), and triphenylphosphine (22 mg, 0.1 mmol) in THF (1.0 mL) was added diethyl azodicarboxylate (0.02 mL?, 0.1 mmol) in THF (1.0 mL). The mixture was stirred overnight and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/n-Hexane = 1:6) to afford 42 mg (43%) of cyclohexyl ether **32c** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.59 (d, J = 8.7 Hz, 1H), 6.73 (m, 3H), 6.41 (dd, J = 8.7, 2.1 Hz, 1H), 6.34 (d, J = 2.1 Hz, 1H), 4.69 (q, J = 6.9 Hz, 1H), 4.26 - 4.22 (m, 1H), 3.80 (s, 6H), 3.79 (s, 3H), 1.96 - 1.90 (m, 2H), 1.79 - 1.73 (m, 2H), 1.54 - 1.46 (m, 2H), 1.33 - 1.27 (m, 4H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 201.7, 162.4, 160.0, 148.8, 147.6, 134.7, 132.8, 121.0, 120.2, 111.2, 111.0, 106.3, 100.0, 75.4, 55.8 (two carbons), 55.3, 50.5, 31.7, 31.6, 25.4, 23.6 (two carbons), 19.2; HR-MS (ESI) calcd for $C_{24}H_{31}O_5$ ($M + H^+$) 399.2166, found 399.2164.

4-(2-(3,4-Dimethoxyphenyl)propanoyl)-3-methoxyphenyl trifluoromethanesulfonate (33). To a solution of phenol **31** (242 mg, 0.8 mmol) in DMF (4 mL) were added potassium

carbonate (122 mg, 0.9 mmol) and $PhNTf_2$ (331 mg, 0.9 mmol). The mixture was stirred for 4 h and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:4) to afford 343 mg (100%) of triflate **33**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, J = 8.5 Hz, 1H), 6.80 (dd, J = 8.6, 2.1 Hz, 1H), 6.74 (d, J = 2.1 Hz, 1H), 6.71 - 6.67 (m, 2H), 4.52 (q, J = 6.9 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H).

2-(3,4-Dimethoxyphenyl)-1-(4-(dimethylamino)-2-methoxyphenyl)propan-1-one (34a). Amination of triflate **33** (20 mg, 0.04 mmol) with diethylamine (2.0M THF solution, 0.23 mL, 0.5 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3 to 1:1) to afford 6 mg (41%) of amine **34a** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.71 (d, J = 8.9 Hz, 1H), 6.79 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.22 (dd, J = 8.9, 2.2 Hz, 1H), 5.98 (d, J = 2.0 Hz, 1H), 4.74 (q, J = 7.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 2.99 (s, 6H), 1.42 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 200.3, 160.7, 154.4, 148.6, 147.3, 135.6, 133.2, 120.1, 115.9, 111.1, 110.9, 104.3, 93.8, 55.7 (two carbons), 54.9, 50.0, 40.0 (two carbons), 19.6; HR-MS (ESI) calcd for $C_{20}H_{26}NO_4$ ($M + H^+$) 344.1856, found 344.1860

2-(3,4-Dimethoxyphenyl)-1-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)propan-1-one (34b). Amination of triflate **33** (26 mg, 0.1 mmol) with pyrrolidine (7 μL, 0.1 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2 to 1:1) to afford 19 mg (90%) of amine **34b** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (dd, J = 8.7, 1.2 Hz, 1H), 6.75 - 6.65 (m, 3H), 6.04 (dd, J = 8.7, 2.0 Hz, 1H), 5.79 (s, 1H), 4.69 (q, J = 6.9 Hz, 1H), 3.77 - 3.72 (m, 9H), 3.24 -3.22 (m, 4H), 1.97 - 1.90 (m, 4H), 1.37 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 200.1, 160.9, 152.0, 148.6,

147.3, 135.7, 133.4, 120.1, 115.3, 111.1, 110.9, 104.4, 93.6, 55.7 (two carbons), 54.9, 49.9, 47.5 (two carbons), 25.3 (two carbons), 19.7; HR-MS (FAB) calcd for $C_{22}H_{28}NO_4$ ($M+H^+$) 370.2018, found 370.2032.

2-(3,4-Dimethoxyphenyl)-1-(2-methoxy-4-(piperidin-1-yl)phenyl)propan-1-one (34c). Amination of triflate **33** (26 mg, 0.1 mmol) with piperidine (8 µL, 0.1 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 10 mg (45%) of amine **34c** as a pale yellow oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, J = 8.7 Hz, 1H), 6.73 - 6.65 (m, 3H), 6.35 (dd, J = 8.7, 2.1 Hz, 1H), 6.16 (d, J = 1.8 Hz, 1H), 4.67 (q, J = 6.9 Hz, 1H), 3.76 (s, 6H), 3.75 (s, 3H), 3.21 - 3.20 (m, 4H), 1.65 - 1.60 (m, 6H), 1.37 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 200.5, 160.4, 155.5, 148.6, 147.3, 135.3, 133.0, 120.1, 117.4, 111.1, 110.9, 106.8, 96.8, 55.7 (two carbons), 55.0, 50.1, 48.8 (two carbons), 25.4 (two carbons), 24.3, 19.5; HR-MS (FAB) calcd for $C_{23}H_{30}NO_4$ ($M+H^+$) 384.2175, found 384.2170.

2-(3,4-Dimethoxyphenyl)-1-(2-methoxy-4-morpholinophenyl)propan-1-one (34d). Amination of triflate **33** (16 mg, 0.03 mmol) with morpholine (4 mg, 0.04 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2 to 2:1) to afford 7 mg (53%) of amine **34d** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.65 (d, J = 8.8 Hz, 1H), 6.75 (m, 2H), 6.72 (d, , J = 8.0 Hz, 1H), 6.40 (dd, J = 8.9, 2.2 Hz, 1H), 6.23 (d, J = 2.2 Hz, 1H), 4.70 (q, J = 6.9 Hz, 1H), 3.82 (s, 3H), 3.90 - 3.70 (m, 10H), 3.22 (dd, J = 5.9, 3.9 Hz, 4H), 1.43 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 200.9, 160.1, 155.2, 148.7, 147.4, 135.0, 132.9, 120.2, 119.0, 111.1, 110.9, 106.6, 96.9, 66.5 (two carbons), 55.7, 55.7, 55.1, 50.3, 47.7 (two carbons), 19.4; HR-MS (ESI) calcd for $C_{22}H_{28}NO_5$ ($M + H^+$) 386.1962, found 386.1963.

1-(4-(benzylamino)-2-methoxyphenyl)-2-(3,4-dimethoxyphenyl)propan-1-one (34e). Amination of triflate **33** (25 mg, 0.06 mmol) with benzylamine (0.01 mL, 0.08 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 20 mg (88%) of amine **34e** as a yellow oil: ^{1}H-NMR (Acetone-d_6, 300 MHz) δ 7.55 (d, J = 8.6 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.22 (m, 1H), 6.86 (d, J = 1.8 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.26 – 6.18 (m, 3H), 4.78 (q, J = 6.9 Hz, 1H), 4.40 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 200.4, 160.8, 152.9, 148.7, 147.4, 138.3, 135.4, 133.5, 128.8 (two carbons), 127.5, 127.4 (two carbons), 120.1, 117.4, 111.2, 110.9, 105.1, 94.7, 55.8 (two carbons), 55, 50, 47.7, 19.6; HRMS (FAB) calcd for $C_{25}H_{28}NO_4$ ($M+H^+$): 406.2018, Found: 406.2024.

4-(((4-(2-(3,4-Dimethoxyphenyl)propanoyl)-3-ethoxyphenyl)amino)methyl)benzonitrile (34f). Amination of triflate **33** (18 mg, 0.04 mmol) with 4-cyanobenzylamine (11 mg, 0.08 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 16 mg (91%) of amine **34f** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.61 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.76 (s, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.10 (dd, J = 8.6, 2.2 Hz, 1H), 5.94 (d, J = 2.1 Hz, 1H), 4.68 (q, J = 7.0 Hz, 1H), 4.58 (t, J = 5.8 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 200.6, 160.6, 152.2, 148.7, 147.4, 144.1, 135.2, 133.6, 132.6 (two carbons), 127.6 (two carbons), 120.2, 118.6, 118.1, 111.4, 111.2, 110.9, 105.0, 95.1, 55.8 (two carbons), 55.0, 50.2, 47.2, 19.6; HRMS (ESI) calcd for $C_{26}H_{26}N_2O_4$ (M^+): 430.1893, Found: 430.1887.

(*S*)-4-(((4-(2-(3,4-Dimethoxyphenyl)propanoyl)-3-methoxyphenyl)amino)methyl) benzonitrile ((*S*)-34f). To a mixture of palladium acetate (2 mg, 0.01 mmol), BINAP (10 mg, 0.02 mmol), and cesium carbonate (36 mg, 0.1 mmol) were triflate **(*S*)-33** (35 mg, 0.08 mmol) and 4-cyanobenzylamine (21 mg, 0.2 mmol) in toluene. The mixture was stirred for 30 min at room temperature, heated to 60 °C, and stirred for 1 h, then heated to 100 °C, and stirred for 2.5 h. The reaction mixture was cooled to room temperature and filtered through Celite pad. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 28 mg (83%) of amine **(*S*)-34f** as a yellow oil: $[\alpha]_D^{25}$ -52 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.61 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.76 (s, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.10 (dd, J = 8.6, 2.2 Hz, 1H), 5.94 (d, J = 2.1 Hz, 1H), 4.68 (q, J = 7.0 Hz, 1H), 4.58 (t, J = 5.8 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 200.6, 160.6, 152.2, 148.7, 147.4, 144.1, 135.2, 133.6, 132.6 (two carbons), 127.6 (two carbons), 120.2, 118.6, 118.1, 111.4, 111.2, 110.9, 105.0, 95.1, 55.8 (two carbons), 55.0, 50.2, 47.2, 19.6; HRMS (ESI) calcd for $C_{26}H_{26}N_2O_4$ (M^+): 430.1893, Found: 430.1887.

(*R*)-4-(((4-(2-(3,4-Dimethoxyphenyl)propanoyl)-3-methoxyphenyl)amino)methyl) benzonitrile ((*R*)-34f). To a mixture of palladium acetate (1 mg, 0.004 mmol), BINAP (6 mg, 0.01 mmol), and cesium carbonate (21 mg, 0.1 mmol) were added triflate **(*R*)-33** (20 mg, 0.05 mmol) and 4-cyanobenzylamine (12 mg, 0.1 mmol) in toluene. The mixture was stirred for 30 min at room temperature, heated to 60 °C, and stirred for 1 h. The resulting reaction mixture was heated to 100 °C and stirred for 2.5 h. The reaction mixture was cooled to room temperature and filtered through Celite pad. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2) to afford 18 mg (92%) of amine **(*R*)-**

34f as a yellow oil: $[\alpha]_D^{25}$ 46 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.61 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.76 (s, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.10 (dd, J = 8.6, 2.2 Hz, 1H), 5.94 (d, J = 2.1 Hz, 1H), 4.68 (q, J = 7.0 Hz, 1H), 4.58 (t, J = 5.8 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 200.6, 160.6, 152.2, 148.7, 147.4, 144.1, 135.2, 133.6, 132.6 (two carbons), 127.6 (two carbons), 120.2, 118.6, 118.1, 111.4, 111.2, 110.9, 105.0, 95.1, 55.8 (two carbons), 55.0, 50.2, 47.2, 19.6; HRMS (ESI) calcd for $C_{26}H_{26}N_2O_4$ (M^+): 430.1893, Found: 430.1887.

1-(4-Bromophenyl)-2-(3,4-dimethoxyphenyl)propan-1-one (36). Condensation of 1,4-dibromobenzene (216 mg, 0.9 mmol) with aldehyde **35** (87 mg, 0.5 mmol) via general procedure B was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:4) to afford 136 mg (86%) of the corresponding secondary alcohol: ^{1}H-NMR (Acetone-d_6, 300 MHz) δ 7.37 - 7.33 (m, 2H), 7.17 - 7.14 (m, 2H), 6.72 - 6.62 (m, 3H), 4.70 (dd, J = 6.7, 4.4 Hz, 1H), 4.36 (d, J = 4.4 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 2.95 (q, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H)

Oxidation of above alcohol (121 mg, 0.3 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 100 mg (83%) of ketone **36**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 6.77 (s, 2H), 6.71 (s, 1H), 4.52 (q, J = 6.7 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 1.49 (d, J = 6.7 Hz, 3H).

2-(3,4-Dimethoxyphenyl)-1-(4-(pyrrolidin-1-yl)phenyl)propan-1-one (37a). Amination of aryl bromide **36** (23 mg, 0.1 mmol) with pyrrolidine (15 µL, 0.2 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to

afford 11 mg (57%) of amine **37a** as a pale yellow oil: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, J = 8.9 Hz, 2H), 6.83 (dd, J = 8.1, 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 8.9 Hz, 2H), 4.55 (q, J = 6.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.29 (t, J = 6.6 Hz, 4H), 2.00 - 1.96 (m, 4H), 1.46 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 198.4, 150.7, 149.0, 147.6, 135.3, 131.0, 131.0, 123.8, 119.8, 111.3, 110.6, 110.6, 110.5, 55.8, 55.8, 47.4, 47.4, 46.2, 25.3, 25.3, 19.6.; HR-MS (FAB) calcd for $C_{21}H_{26}NO_3$ ($M+H^+$) 340.1913, found 340.1904.

2-(3,4-Dimethoxyphenyl)-1-(4-morpholinophenyl)propan-1-one (37b). Amination of aryl bromide **36** (16mg, 0.04 mmol) with morpholine (5 mg, 0.1 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:2 to 1:1) to afford 12 mg (80%) of amine **37b** as a yellow oil: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.88 (d, J = 9.1 Hz, 2H), 6.81 (dd, J = 8.2, 2.1 Hz, 1H), 6.76 (m, 4H), 4.54 (q, J = 6.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 3.23 (t, J = 5.0 Hz, 4H), 1.45 (d, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 198.7, 153.9, 149.1, 147.7, 134.7, 130.7 (two carbons), 127.1, 119.9, 113.2 (two carbons), 111.3, 110.5, 66.5 (two carbons), 55.8, 55.8, 47.4 (two carbons), 46.7, 19.5; HR-MS (ESI) calcd for $C_{21}H_{26}NO_4$ ($M + H^+$) 356.1856, found 356.1851.

1-(4-Bromophenyl)-2-(2-fluorophenyl)ethan-1-one (39). Condensation of 1,4-dibromobenzene (845 mg, 3.5 mmol) with aldehyde **38** (270 mg, 2.0 mmol) via general procedure B was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:5) to afford 402 mg (70%) of the corresponding secondary alcohol: ^{1}H-NMR (Acetone-d6, 300 MHz) δ 7.39 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.17 - 7.12 (m, 1H), 7.08 - 7.03 (m, 1H), 7.01 - 6.94 (m, 2H), 4.86 - 4.84 (m, 1H), 3.04 - 2.88 (m, 2H).

Oxidation of above alcohol (402 mg, 1.4 mmol) via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 316 mg (79%)

of ketone **39**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.24 - 7.14 (m, 2H), 7.07 - 6.98 (m, 2H), 4.22 (s, 2H).

1-(4-Bromophenyl)-2-(2-fluorophenyl)propan-1-one (40). To a suspension of sodium hydride (60% in dispersion, 31 mg, 0.8 mmol) in THF (4.0 mL) was added a solution of ketone **39** (230 mg, 0.8 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 30 min and iodomethane (0.06 mL, 0.9 mmol) was added at 0 °C and stirred overnight at room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:10) to afford 224 mg (93%) of **40** as a pale yellow oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.19 - 7.06 (m, 2H), 7.01 - 6.96 (m, 2H), 4.88 (q, J = 7.0 Hz, 1H), 1.44 (d, J = 7.0 Hz, 3H).

2-(2-Fluorophenyl)-1-(4-(piperidin-1-yl)phenyl)propan-1-one (41a). Amination of aryl bromide **40** (31 mg, 0.1 mmol) with piperidine (15 µL, 0.2 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1: 5) to afford 24 mg (68%) of amine **41a** as a yellow solid: ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 7.85 (d, 2H, J = 9.0 Hz), 7.24 – 7.22 (m, 1H), 7.15 – 7.12 (m, 1H), 7.02 (d, 1H, J = 8.3 Hz), 7.01 (d, 1H, J = 8.2 Hz), 6.76 (d, 2H, J = 9.0 Hz), 4.96 (q, 1H, J = 6.9 Hz), 3.30 (s, 4H), 1.61 (s, 6H), 1.47 (d, 3H, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 197.8, 159.6 (d, $J_{C\text{-}F}$ = 243 Hz), 154.2, 130.7, 129.3, 129.2, 128.9 (d, $J_{C\text{-}F}$ = 3.9 Hz), 128.2, 128.1, 125.2, 124.5 (d, $J_{C\text{-}F}$ = 3.3 Hz), 115.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 113.2, 48.4, 38.4, 38.4, 25.3 (two carbons), 24.3, 18.2; HRMS (ESI) calcd for $C_{20}H_{23}FNO$ ($M+H^+$): 312.1764, Found: 312.1758.

1-(4-(Benzylamino)phenyl)-2-(2-fluorophenyl)propan-1-one 2 (41b). Amination of aryl bromide **40** (24 mg, 0.1 mmol) with morpholine (13 µL, 0.1 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:5) to afford 18 mg (71%) of amine **41b** as white solid: ^{1}H-NMR (CDCl3, 600 MHz) δ 7.83 – 7.82 (m, 2H), 7.33 – 7.25 (m, 5H), 7.22 – 7.21 (m, 2H), 7.15 – 7.12 (m, 2H), 7.02 – 6.99 (m, 2H), 6.52 – 6.51 (m, 2H), 4.94 (q, 1H, J = 8.6 Hz), 4.53 (broad, 1H), 4.33 (s, 2H), 1.46 (d, 3H, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 197.7, 159.6 (d, $J_{C\text{-}F}$ = 243 Hz), 151.8, 138.1, 131.0, 131.0, 129.2 (d, $J_{C\text{-}F}$ = 15.0 Hz), 128.8 (d, $J_{C\text{-}F}$ = 4.3 Hz), 128.7, 128.7, 128.1 (d, $J_{C\text{-}F}$ = 7.8 Hz), 127.5, 127.3, 127.3, 125.6, 124.5, (d, $J_{C\text{-}F}$ = 3.5 Hz), 115.3 (d, $J_{C\text{-}F}$ = 22.2 Hz), 111.6, 111.6, 47.5, 38.3 (d, $J_{C\text{-}F}$ = 2.1 Hz), 18.2; HRMS (ESI) calcd for $C_{22}H_{21}FNO$ ($M+H^+$): 334.1607, Found: 334.1611.

2-(2-Fluorophenyl)-1-(2-methoxy-4-(methoxymethoxy)phenyl)ethan-1-one (42). Condensation of aryl bromide **28** (201 mg, 1 mmol) with aldehyde **38** (90 mg, 0.7 mmol) via general procedure B was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3) to afford a diastereomeric mixture of the corresponding alcohols. Oxidation of above alcohol via general procedure A was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:6) to afford 75 mg (38% over 2 steps) of **42** as a colorless liquid: ^{1}H- NMR (800 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.16 (td, J = 7.5, 1.5 Hz, 1H), 7.05 (td, J = 7.5, 1.1 Hz, 1H), 7.04 – 7.01 (m, 1H), 5.20 (s, 2H), 4.28 (s, 2H), 3.88 (s, 3H), 3.47 (s, 3H), 1.55 (s, 2H).

4-(2-(2-Fluorophenyl)propanoyl)-3-methoxyphenyl trifluoromethanesulfonate (43). To a suspension of sodium hydride (60% in dispersion, 10 mg, 0.3 mmol) in THF (2.0 mL) was added a solution of ketone **42** (75 mg, 0.3 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 30 min and iodomethane (0.02 mL, 0.3 mmol) was added at 0 °C. The resulting

mixture was stirred overnight at room temperature and quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:5) to afford an α-methylated ketone intermediate as a pale yellow oil: ^{1}H-NMR (800 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.00 – 6.94 (m, 2H), 6.59 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 5.14 (s, 1H), 5.01 (q, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H).

To a solution of above ketone in methanol was added 2*N*-HCl solution (3.0 mL). The mixture was stirred for 4 h at 60 °C and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:1) to afford the corresponding phenol intermediate as pale yellow solid: ^{1}H-NMR (800 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 1H), 7.13 – 7.07 (m, 2H), 6.96 (t, *J* = 8.2 Hz, 2H), 6.39 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.31 (d, *J* = 2.2 Hz, 1H), 5.03 (q, *J* = 7.0 Hz, 1H), 3.64 (s, 2H), 1.43 (d, *J* = 7.0 Hz, 2H).

To a solution of above phenol in DMF (2 mL) were added potassium carbonate (38 mg, 0.3 mmol) and $PhNTf_2$ (103 mg, 0.3 mmol). The mixture was stirred for 4 h and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-Hexane=1:5) to afford 63 mg (62% for 3 steps) of triflate intermediate **43**: ^{1}H-NMR (800 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.6 Hz, 1H), 7.14 (dddd, *J* = 8.0, 7.2, 5.3, 1.8 Hz, 1H), 7.09 (td, *J* = 7.6, 1.7 Hz, 1H), 7.00 (td, *J* = 7.5, 1.1 Hz, 1H), 6.98 – 6.93 (m, 1H), 6.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 4.89 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H).

2-(2-Fluorophenyl)-1-(2-methoxy-4-(piperidin-1-yl)phenyl)propan-1-one (44a). Amination of triflate **43** (24 mg, 0.1 mmol) with piperidine (10 µL, 0.1 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3) to afford 14 mg (67%) of amine **44a** as a pale yellow oil: ^{1}H-NMR (800 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.97 (dtd, *J* = 16.1, 7.8, 1.1 Hz, 2H), 6.42 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 5.04 (q, *J* = 6.9 Hz, 1H), 3.72 (s, 3H), 3.29 – 3.24 (m, 4H), 1.65 – 1.59 (m, 6H), 1.40 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (201 MHz, $CDCl_3$) 198.8, 160.7, 160.4 (d, $J_{C\text{-}F}$ = 244.8 Hz), 155.7, 133.1, 130.2 (d, $J_{C\text{-}F}$ = 15.7 Hz), 128.8 (d, $J_{C\text{-}F}$ = 4.4 Hz), 127.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 123.9 (d, $J_{C\text{-}F}$ = 3.3 Hz), 116.6, 114.9 (d, $J_{C\text{-}F}$ = 22.7 Hz), 106.7, 96.4, 54.7, 48.7 (two carbons), 43.5, 25.4 (two carbons), 24.3, 18.2; HR-MS (FAB) calcd for $C_{21}H_{25}FNO_2$ ($M+H^+$) 342.1864, found 342.1874.

4-(((4-(2-(3,4-Dimethoxyphenyl)propanoyl)phenyl)amino)methyl)benzonitrile (44b). Amination of triflate **43** (27 mg, 0.1 mmol) with 4-cyanobenzylamine (18 mg, 0.1 mmol) via general procedure H was followed by flash column chromatography on silica gel (EtOAc/*n*-Hexane = 1:3) to afford 15 mg (58%) of amine **44b** as pale yellow solid: ^{1}H-NMR (800 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.07 (m, 2H), 6.99 – 6.93 (m, 2H), 6.12 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 5.00 (q, *J* = 6.9 Hz, 1H), 4.64 (s, 1H), 4.41 (d, *J* = 5.7 Hz, 2H), 3.63 (s, 3H), 1.39 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (201 MHz, $CDCl_3$) 198.9, 160.9, 160.3 (d, $J_{C\text{-}F}$ = 244.8 Hz), 152.4, 144.1, 133.6, 132.5 (two carbons), 129.9 (d, $J_{C\text{-}F}$ = 15.7 Hz), 128.8 (d, $J_{C\text{-}F}$ = 4.2 Hz), 127.6 (two carbons), 123.9 (d, $J_{C\text{-}F}$ = 3.3 Hz), 118.6, 117.3, 114.9 (d, $J_{C\text{-}F}$ = 22.6 Hz), 111.3, 105.0, 94.8, 54.8, 47.1, 43.5, 43.5, 18.2; HR-MS (FAB) calcd for $C_{24}H_{22}FN_2O_2$ ($M+H^+$) 389.1660, found 389.1664.

Biological Assay. Hypoxia Response Element Reporter Gene Assay. Hypoxia response element (HRE)-A549 cell line was established by transfection of HRE-luciferase reporter plasmid[39] into the human lung carcinoma cell line, A549, using FuGENE reagent (Roche) and subsequently selected by treatment with G418 (600 μg/mL; GIBCO). HRE-A549 cells were incubated in growth medium containing DMEM, 10% fetal bovine serum, and 1% penicillin-streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. For all experiments, cells were grown to 80% to 90% confluence and were deprived of serum for overnight before treatment. Following overnight serum deprivation, the cells were exposed to hypoxia for 24 h with or without pretreatment of HIF-1α inhibitor compounds for 1 h. Luciferase activity was measured by adding luciferase assay reagent (Promega) with a Centro LB960 luminometer (Berthold Technologies). To create hypoxic conditions, cells were transferred to a hypoxic chamber (Forma Scientific), where they were maintained at 37 °C in an atmosphere containing 5% CO_2, 1% O_2, and 94% N_2. One-way analysis of variance tests or Student t tests were used to assess significant differences among treatment groups.

Immunoblot. Proteins were extracted from cell lysates at 4 hours from the treatment with/without hypoxia or each compound and separated by 7.5% SDS-PAGE. Then, the membrane was treated with primary antibodies against HIF-1α (BD) overnight and species-specific peroxidase-conjugated secondary antibody for 1 hour. The blots were visualized with EZ-Western Lumi Pico™ Western Blot Detection Kit (Biomax).

Quantitative real-time polymerase chain reaction (qRT-PCR). Total RNA was extracted from cell lysates at 24 hours from the treatment with/without hypoxia or each compound using TRIzol® reagent (Life Technologies). The cDNAs were prepared with high capacity RNA-to-cDNA kit (Life Technologies). Real-time PCR was performed using a Taqman assay for *VEGFA* (assay ID, Hs00900055_m1; Life Technologies) according to the manufacturer's

instructions. The signal intensity was normalized using the estimated values with a Taqman assay for *GAPDH* (assay ID, Hs99999905_m1; Life Technologies). All the measurement was performed using the StepOne™ Real-Time PCR System (Life Technologies) in accordance with the MIQE guidelines.

Preparation of conditioned media (CM). HCT116, HeLa or RPE cells were cultured with M199 containing 1% FBS and treated with hypoxia or each compound. The media were collected and centrifuged through a centrifugal filter device (3 kDa cut-off; Millipore). The centrifugation was regarded as effective to remove any trace of compounds from CM

Enzyme-linked immunosorbent assay (ELISA). CM were prepared at 48 hours after the treatment with/without hypoxia or each compound. The VEGF levels were measured with VEGF Human ELISA kit (KHG0111, Invitrogen) according to the manufacturer's instructions.

Migration assay. Migration assay was performed as previously described[40] using Transwell plates (8.0 μm pores). The lower wells were filled with fresh M199 (1% FBS) with VEGF or both compounds for the evaluation of VEGF-induced migration and CM based on M199 (1% FBS) for the evaluation of hypoxia-mediated migration. HUVECs or HRMECs (1×10^5 cells) were loaded on the upper well. After the incubation for 4 hours, the cells were fixed and stained with H&E. Migration was quantified by counting the migratory cells using inverted phasecontrast microscope (Leica, Wetzlar, Germany).

Proliferation assay. HUVECs or HRMECs (5×10^3 cells) were seeded in gelatin-coated 96-well plates. After the incubation for 24 hours, the media were changed with CM based on M199 (1% FBS) and the cells were cultured for additional 24 hours. Cell proliferation was determined by [^{3}H]-thymidine incorporation assays as previously described. Labeled DNA

was solubilized in 0.2 N NaOH/0.1% SDS and quantitatively analyzed by a liquid scintillation counter (Beckman Coulter, Brea, CA).

Tube formation assay. Tube formation was evaluated as previously described.[40] HUVECs or HRMECs (2 x 10^5 cells) were plated on Matrigel (BD, San Jose, CA)-coated 24-well plates in CM based on M199 (1% FBS) and incubated for 20 hours. Tube formation was quantitatively analyzed by measuring the length of tubes in 5 randomly selected fields (x100 magnification) from each well using the Image-Pro Plus (v 4.5; Media Cybernetics, San Diego, CA).

Immunoprecipitation and Immunoblotting Assay. In vitro assay was performed using the lysates of A549 cells that had been treated with 100 μM $CoCl_2$ for 5 h. The cell lysates were incubated with 1.25 μM of analog **34f** in the presence or absence of 20 mM ATP for 30 min at 37 °C. The resulting samples were incubated with anti-HIF-1α antibody overnight at 4 °C. The antigen-antibody complex was then precipitated following incubation for 2 h at 4 °C with protein G-agarose. The immune complex was solubilized in 2×Laemmli buffer and boiled for 5 min. The samples were resolved and analyzed using 6% SDS-PAGE and then transferred to nitrocellulose membrane. They were then immunoblotted with the antibody directed against HSP90.

Oxygen Induced Retinopathy in mice. All animal experiments were performed in accordance with the Association for Research in Vision and Ophthalmology statement for the use of animals in ophthalmic and vision research and all the procedures regarding animal experiments were approved by the Institutional Animal Care and Use Committee of Seoul National University. OIR was induced in newborn mice using a closed chamber in hyperoxia (75% ± 0.5% O_2) for 5 days from postnatal day (P) 7 to P12.[18, 37] At P14, PBS or each

compound was injected into the vitreous cavity of mice (n = 6). At P17, the eyes were prepared for immunostaining of whole-mounted retinas with isolectin B4-594 (1:100; cat. no. I21413, Invitrogen). The neovascular area was quantitatively analyzed by outlining neovascular tufts in Adobe Photoshop and measuring the area using ImageJ program (NIH).[41] The relative area in each treatment group were normalized to that in the control group.

Solubility test. Solubility of analogs **2**, **34c**, **34f** and **6i** was determined in DPBS (Welgene Inc., Daegu, Korea). For the determination of equilibrium solubility, the excess amount of each compound was dissolved in DPBS, and the mixture agitated for 24 hours in room temperature. The mixture was centrifuged at 13,200 rpm for 10 minutes (Eppendorf 5415R, Hamburg, Germany), and filtered with a filter (0.2 μm pore size syringe filter, Minisart RC15, Sartorius Stedim Biotech, Goettingen, Germany). The supernatant of the sample was diluted with methanol (1:10 dilution for **2** and **6i**; 1:100 dilution for **34c;** 1:1000 dilution for **34f**) and the mixture analyzed by LC/MS/MS system (Applied Biosystems 3200 Qtrap MS/MS system with Alliance Waters e2695 LC system) for their concentration in the media.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications webstie at DOI:

Purity table and molecular formula strings of all analogs. Supportive data of in vitro / in vivo angiogenesis experiments and inhibition of HSP90 and HIF-1α binding by the representative analogs. HPLC analysis for enantiomers (*S*)-**34f** and (*R*)-**34f** (PDF)

Molecular formula strings (CSV)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

HIF, hypoxia-inducible factor; DR, diabetic retinopathy; AMD, age-related macular degeneration; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor; PHD, prolyl hydroxylase; VHL, von Hippel-Lindau; ATP, adenosine triphosphate; HSP, heat shock protein; SAR, structure-activity relationship; HRE, hypoxia response element; OIR, oxygen-induced retinopathy; DMP, Dess-Martin periodinane; BuLi, butyllithium; PCC, pyridinium chlorochromate; NaHMDS, sodium bis(trimethylsilyl)amide; TBAF, tetrabutylammonium fluoride; DMF, dimethylformamide; DMAP, 4-dimethylaminopyridine;

PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate; MOM, methoxymethyl; DEAD, diethyl azodicarboxylate; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; IC_{50}, half maximal inhibitory concentration; S.E., standard error; CM, conditioned media; HUVEC, human umbilical vein endothelial cell; SEM, standard error of the mean;

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Table of Contents Graphic