European Journal of Medicinal Chemistry 46 (2011) 2386–2396

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

HIF-1α inhibitors: Synthesis and biological evaluation of novel moracin O and P analogues

Yan Xia [a,1], Yinglan Jin [a,1], Navneet Kaur [a], Yongseok Choi [b], Kyeong Lee [a,*]

[a] College of Pharmacy, Dongguk University-Seoul, Seoul 100-715, South Korea
[b] Department of Life Science and Biotechnology, Korea University, Seoul 136-701, South Korea

ARTICLE INFO

Article history:
Received 27 January 2011
Received in revised form
9 March 2011
Accepted 12 March 2011
Available online 21 March 2011

Keywords:
Moracin
Arylbenzofuran
HIF-1α
Structure-activity relationships

ABSTRACT

The natural products moracins O and P exhibited potent in vitro inhibitory activity against hypoxia-inducible factor (HIF-1), which is a key mediator during adaptation of cancer cells to tumour hypoxia. Systematic variations of the structures of benzofuran type moracins were made and structure-activity relationship analysis showed the importance of the 2-arylbenzofuran ring and the (*R*)-configuration of the core scaffold. Further evaluation of the representative compound **5** showed its inhibitory effect on HIF-1α protein accumulation and target gene expression under hypoxia.

© 2011 Elsevier Masson SAS. All rights reserved.

1. Introduction

Tumour cells exhibit many adaptive responses to hypoxic conditions, such as transcriptional activation of angiogenic vascular endothelial growth factor (VEGF), erythropoietin (EPO), and other genes in order to enhance the delivery of oxygen to the cells [1,2]. This adaptation is mediated by hypoxia-inducible factor-1 (HIF-1), a heterodimer of bHLH-PAS proteins HIF-1α and HIF-1β. HIF-1α protein is degraded rapidly under normoxic conditions and stabilized under hypoxic conditions, while HIF-1β protein is constitutively expressed [3–6]. Under hypoxia, the transcription factor HIF-1 binds to the hypoxia response element (HRE) in the promoters of the target genes and activates transcription [7]. However, overexpression of the oxygen-regulated HIF-1α causes proliferation of tumour cells and resistance against chemotherapy and radiotherapy in cancer treatment [8]. Accordingly, inhibition of HIF-1α can play an important role in cancer therapy [9].

A number of small molecule inhibitors, including some natural products are known to be HIF-1 inhibitors [10,11]. All of these inhibitors share ability to decrease HIF-1α protein levels, inhibit the expression of HIF-1 target genes, such as *VEGF* and *EPO*, and impair tumour growth in animal models. In addition, a number of inhibitors targeting the HIF regulation pathways and signal-transduction pathways have been reported [12–17].

The arylbenzofuran type natural products moracins O and moracin P, isolated from *Morus* sp., possess potent inhibitory effects against HIF-1 (−)-moracin O (**1**) and (−)-moracin P (**2**) exhibited the strongest inhibitory activity (IC_{50} = 6.76 nM and 10.7 nM, respectively) in a cell-based HRE reporter assay in Hep3B cells (Fig. 1) [18]. These interesting biological properties persuaded us to do an in depth study of these compounds, looking for HIF inhibitory activity. In our studies on these molecules, we recently reported the first efficient synthesis of (±)-moracins O and P via O-prenylated phenolic intermediates as a common precursor. Meanwhile, asymmetric synthesis of (*R*)-and (*S*)-moracin O have been synthesized and the absolute configuration of bioactive natural moracin O has been demonstrated [19].

Herein, we describe a structure-activity relationship (SAR) study of various moracin analogues with the 2-arylbenzofuran moiety as HIF-1α inhibitors. The analogues were divided into three series and the design of these analogues was based upon the structures of moracins O and P. Moracins O and P differ by the fact that the A ring in the former is five-membered, while the latter bears a 6-membered ring. In both moracins O and P, the 2-arylbenzofuran is a common unit, consisting of B, C, and D rings (Fig. 1).

The design principal for analogues of the first series was based upon the design of moracin O derivatives (Fig. 2); we kept the same basic skeleton (A–C rings) but the appending unit (ring D) changed with various types of substituents in this series. These substitutions

* Corresponding author. Tel.: +82 2 22608906; fax: +82 2 22608769.
E-mail address: kaylee@dongguk.edu (K. Lee).
[1] These authors equally contributed to this work.

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.03.022

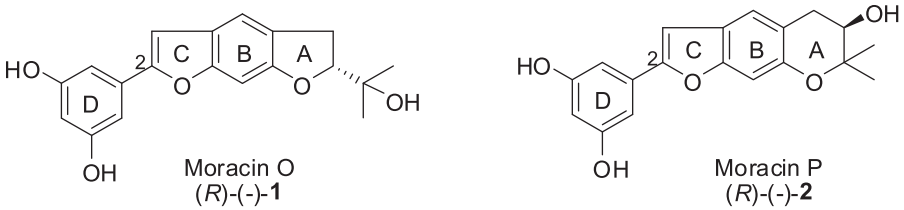


Fig. 1. Structures of moracins O and P.

included the removal of one –OH group (**4**), change in the position of an –OH group (**5**), removal of both –OH groups (**11**–**13**), etherification of both –OH groups (**3**), etherification of the –OH group at o, m, and p positions (**8**–**10**), and replacement with a heteroaromatic ring (**14**,**15**).

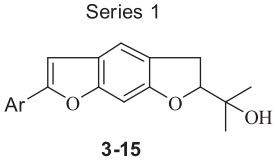
The benzofuran ring was the second common feature of both moracins O and P. Thus the second and third series were developed to investigate the effect of benzofurans in the design of these analogues. The second series describes the role of benzofurans in the design of moracin O and the third series describes the role of benzofurans in the design of moracin P derivatives. Variations in the design of moracin O were made after replacement with an ester group (**16**–**20**). Similarly, the third series was devised to investigate the effect on the activity of moracin P of replacement with an ester group (**21**–**32**). This replacement with an ester group was also studied with changes of the group on the appending unit as described in the first series.

2. Chemistry

Accordingly, all the compounds (**3**–**32**) shown in Fig. 2 were prepared as described in Schemes 1–4. The key intermediates for synthesis of novel moracin O or P derivatives were prepared as outlined in Scheme 1. Protection of 2,4-dihydroxybenzaldehyde with Boc_2O followed by reduction in the presence of $NaBH_4$ afforded an intermediate benzylic alcohol **34**, which was then subjected to prenylation to afford **35**. A prenylated derivative **35** was used as a common precursor for the synthesis of key intermediates **37** and **39**. As we reported earlier, under basic conditions (LiOH) **35** cleanly afforded benzohydropyran **37**, whilst, under acidic condition (pTSA) a racemic benzohydropyran core structure **38** was constructed, which on further deprotection provided a key intermediate **39** in good yield [19].

Further, the terminal acetynyl derivatives were either procured from commercial sources (**40e**–**l**) or prepared (**40a**–**d**). The synthesis of acetynyl compounds were based on the procedures previously developed for the protection of hydroxyl groups with methyl, *tert*-butyldimethylsilyl or benzyl groups and the Ramirez–Corey–Fuchs reaction and yielded terminal acetylene compounds **40a**–**d** in good yields for the three steps [20] (see Supporting Information). For the synthesis of moracin O analogues (Series 1), which covered a variety of substituents on the D-ring, the key intermediate **37** was selectively iodinated to afford the corresponding compound **41** (Scheme 2), whose yield was increased by modification of the synthetic route in the sequence of intermolecular cyclization and iodination, similar to the previous work reported by us. The Sonogashira coupling of terminal acetylenes **40a**–**l** with substituted o-iodophenol compound **41** in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ gave the moracin O analogues **42a,b** and **1**, **3**–**15**. Compounds **42a**,**b** was deprotected with HF/Pyridine to provide the corresponding phenol analogues **4** and **5** in good yields. Reaction of compound **5** with ethyl chloroacetate afforded the alkylated compound **6**.

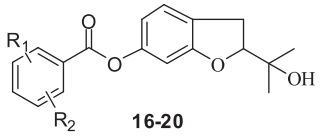
For synthesis of moracins O and P analogues (Series 2 and 3) with a simplified C-ring as shown in Scheme 3, the requisite benzoic acid derivatives **43a**–**d** with benzylated hydroxy groups were synthesized in two steps starting with benzylation and followed by hydrolysis (see Supporting Information). EDCI mediated coupling of acids **43a** with precursor **37** afforded the corresponding final product **17** which through deprotection under catalytic dehydrogenation (Pd/C, H_2) produced **16**. The reaction of commercially available 4-bromo-benzoyl chloride **44** with **37** yielded the analogue **18**. Further coupling of the 4′-bromo-benzoic acid derivative **18** with the appropriate aryl boronic acids via Suzuki reactions afforded cross-coupled products **19**,**20**. Similarly, for the synthesis of moracin P analogues **21**–**32**, the reaction of key intermediate **39** with various



Series 1

3-15

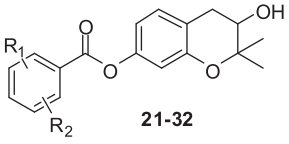
3	3′,5′-$(OMe)_2$Ph
4	3′-OHPh
5	4′-OHPh
6	(4′-OCH_2CO_2Et)Ph
7	(4′-OBn)Ph
8	2′-OMePh
9	3′-OMePh
10	4′-OMePh
11	Ph
12	4′-MePh
13	3′,5′-F_2Ph
14	4-Pyridyl
15	1-Melmidazolyl



Series 2

16-20

	R_1	R_2
16	3′-OH	5′-OH
17	3′-OBn	5′-OBn
18	4′-Br	H
19	4′-(*m*-OMePh)	H
20	4′-(*m*-NO_2Ph)	H

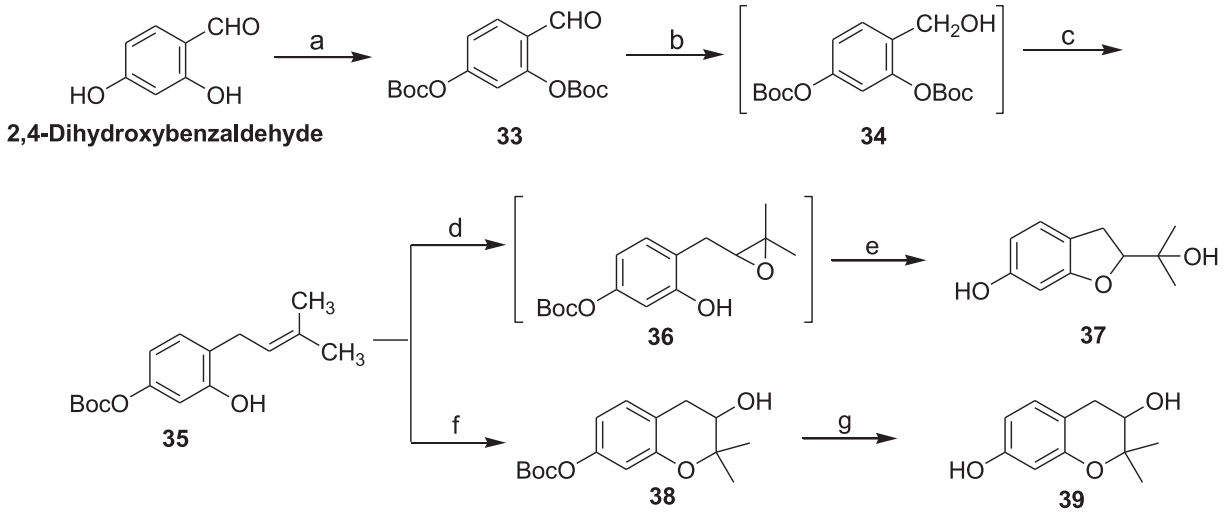


Series 3

21-32

	R_1	R_2
21	3′-OH	5′-OH
22	3′-OH	4′-OH
23	4′-OH	H
24	3′-OBn	5′-OBn
25	3′-OBn	4′-OBn
26	4′-OBn	H
27	3′-OBn	H
28	4′-Br	H
29	4′-(*m*-OMePh)	H
30	4′-(*m*-NO_2Ph)	H
31	4′-(*m*-CNPh)	H
32	4′-(*o*,*p*-F_2Ph)	H

Fig. 2. Structures of new moracin analogues.



Scheme 1. Reaction conditions: (a) $(Boc)_2O$, K_2CO_3, ether; (b) $NaBH_4$, THF, conc. HCl, AcOH; (c) 2-methyl-1-propenyl magnesium bromide, THF; (d) mCPBA, EtOAc; (e) LiOH, MeOH; (f) mCPBA, pTSA, CH_2Cl_2; (g) 1 M HCl in dioxane, MeOH.

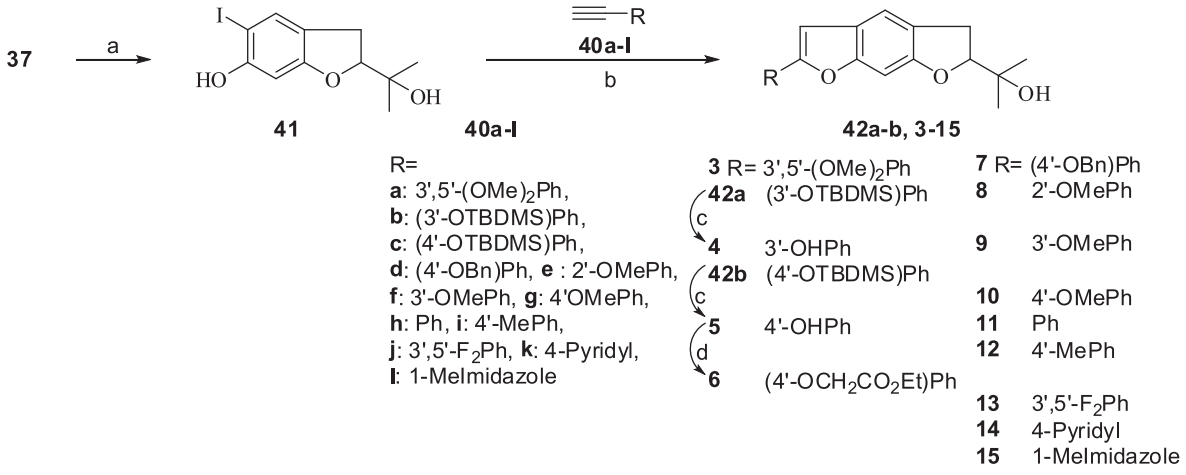
benzoic acid derivatives **43a**–**d** and 4-bromo-benzoyl chloride **44** yielded compounds **24**–**28** in excellent yields. Further reductive deprotection of **24**, **25** and **26** with Pd/C, H_2 gave the corresponding analogues **21**, **22** and **23**. Suzuki cross coupling of **26** with appropriate aryl boronic acids yielded compounds **29**–**32** in good yields.

Previously, we reported that the (*R*)-isomer of moracin O was more potent than the (*S*)-isomer of moracin O than (±)-moracin O (**1**), but the stereogenic centre of the above described analogues was created in a nonstereospecific manner. Therefore, the corresponding (*R*)-stereoisomer of the most potent of the above described analogues **5** was prepared for further investigation in Scheme 4. The key intermediate, an enantiomerically pure iodobenzofuran derivative (*R*)-(−)-**41** at the ortho-position was obtained from the prenylated derivative **35** through five steps, according to a reported procedure [19]. This key intermediate was reacted with the protected ethynyl benzene compound **40c** through a Sonogashira reaction to afford (*R*)-(−)-**42b** followed by deprotection with HF/pyridine to provide (*R*)-(−)-**5**.

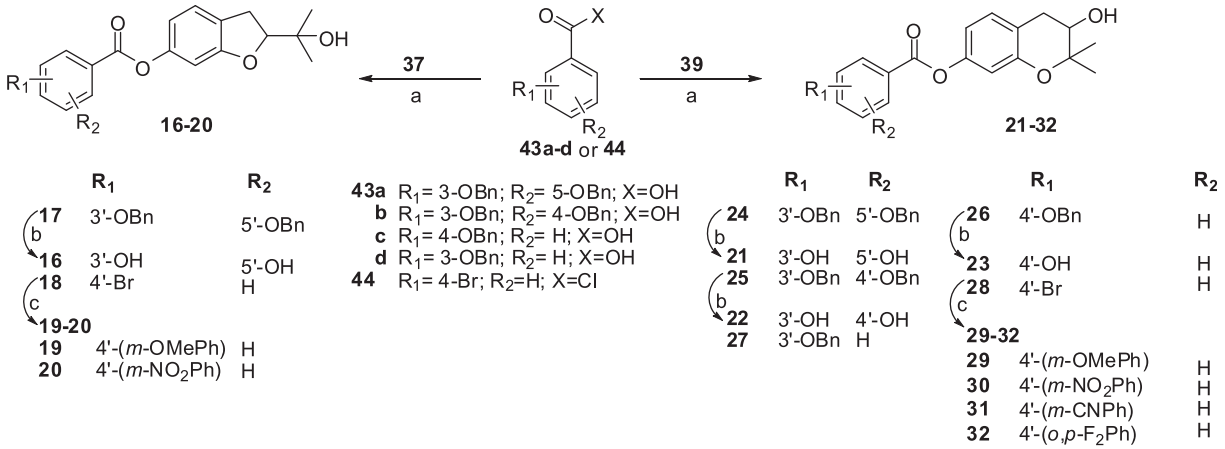
3. Biological evaluation

The newly synthesized compounds were evaluated for their ability to inhibit HIF-1 activation induced by hypoxia (1% O_2, 94% N_2, and 5% CO_2) using a cell-based HRE (hypoxia responsive element)-luciferase reporter assay in human hepatoblastoma Hep3B cell line (Tables 1 and 2). All the HRE-Luc assays were performed under standard assay conditions using hypoxic conditions and following a previously described assay protocol [21]. Cell viability, as measured by the MTT assay, showed that most of the compounds had no significant cytotoxicity at concentrations at which they effectively inhibited HIF-1 activation. Analyzing the data from Table 1 showed that the removal of one of the hydroxyl groups (**4**) from the parent compound (±)-moracin O led to a decline in activity, but having a hydroxyl group at the para position of the D-ring (**5**) improved the activity. This indicated that, although both products (**4** and **5**) were monohydroxylated, the position of the hydroxyl group mattered in improving the inhibitory activity (IC_{50} values 46 and 4.2 nM, respectively). Further, the functionalization of the para substituted product **5** generated compounds **6**, **7**, and **10**; this funtionalization reduced its inhibitory activity. On the other hand, O-methylated product (**3**) of natural product moracin O had a relatively negligible effect. The complete removal of hydroxyl groups from the parent compound (**11**) and replacement with either halogens (**13**) or with heterocyclic rings (**14** and **15**) drastically reduced inhibitory activity.

The replacement of the C-ring with an ester moiety to give a more conformationally flexible bicyclic ring led to significant loss in activity. None of the compounds had activity as potent as that of the parent compound (±)-moracin O (Table 2). This indicated the



Scheme 2. Reaction conditions: (a) ICl, AcOH (b) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, dioxane, 85 °C; (c) HF/Pyridine, THF/Pyridine, 0 °C to rt; (d) $ClCH_2COOEt$, K_2CO_3, DMF.



Scheme 3. Reaction conditions: (a) **43a**, EDCI, HOBT, DIPEA, DMF for **17**, **24**; **43b**–**d**, DCC, DMAP, DMF for **25**–**27**; **44**, TEA, CH_2Cl_2 for **18**, **28**; (b) Pd/C, H_2, MeOH; (c) R'B$(OH)_2$, $(PPh_3)_4Pd$, $NaHCO_3$, H_2O/DME.

importance of the furan ring moiety in enhancing activity. Similarly, the role of the furan ring has been investigated in analogues of (±)-moracin P. In these analogues we tried a diverse variety of substituents on the 2-aryl unit, but all our attempts to improve activity were in vain. Thus, the results of series 2 and 3 highlighted the significance of the furan moiety in anti-HIF-1 activity while the results of series 1 revealed the importance of substituents on the D-ring.

In regard to the results described in Tables 1 and 2, the most active analogue was the para-hydroxy group substituted product **5** as the racemate. However, it was important to further evaluate the inhibitory activity of the pure enantiomer **5**. Having demonstrated that the (*R*)-stereoisomer had a more effective configuration, as previously reported in recent work by us, we performed an asymmetric synthesis of (*R*)-(−)-**5**. The (*R*)-configured compound (*R*)-(−)-**5** was more potent than the racemic compound (±)-**5**. From this result, it is proved that the (*R*)-configuration more potently affects biological functions.

To further confirm their inhibition of HIF-1 activation, compounds **1**, **5** and (*R*)-(−)-**5**, which showed strong HIF-1 inhibitory effects in cell-based HRE assays, were evaluated by western blot analysis for their effects on hypoxia-induced HIF-1α accumulation. As shown in Fig. 3, all three of these inhibitors blocked HIF-1α accumulation under hypoxia in a dose dependent manner. Of the three compounds (*R*)-(−)-**5** significantly suppressed the accumulation of HIF-1α protein in the presence of 10 μM.

HIF-1α responds to hypoxia by binding to the HRE of target genes, including *VEGF* and *EPO*. In particular, *VEGF* stimulates new blood vessel formation, tumour growth and metastasis. Therefore, to confirm that inhibition of HIF-1α decreased expression of *VEGF*, compounds **1** and **5** were analyzed for their effect on secreted levels of *VEGF* in Hep3B cell culture media using an ELISA assay (Fig. 4). Of particular interest, **5** significantly and dose-dependently inhibited hypoxia-induced *VEGF* production.

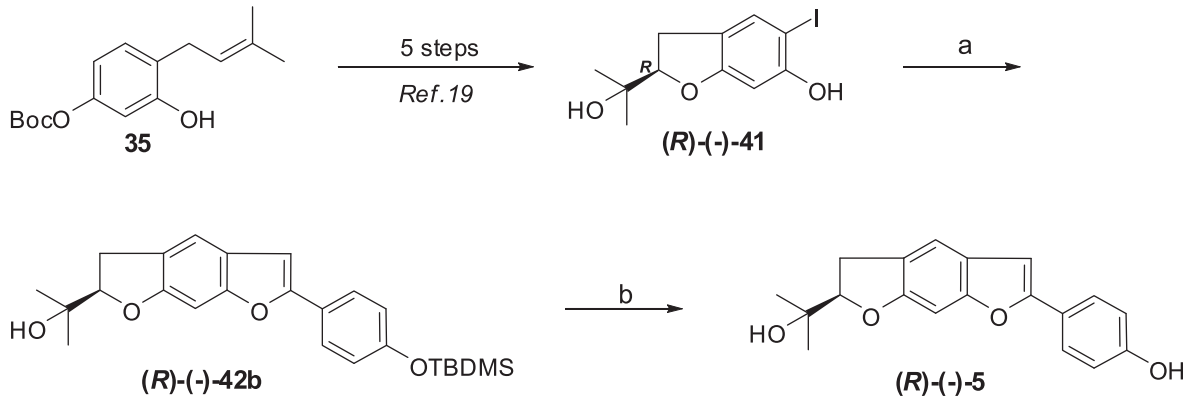
4. Conclusion

In summary, we showed structure-activity relationships for moracin O and P derivatives, and demonstrated that the 2-arylbenzofuran and (*R*)-configuration are critical to the HIF-1α inhibition of moracin derivatives. Among these analogues, analogue **5** had a potent inhibitory effect on hypoxia-induced HIF-1α protein accumulation and on secreted *VEGF* levels. Studies investigating more detailed mechanisms for the effects of **5** and (*R*)-(−)-**5** on HIF-1α -mediated tumour progression and angiogenesis are in progress and the results will be reported in due course. This study may provide valuable information for further designing and developing more potent anticancer agents.

5. Experimental

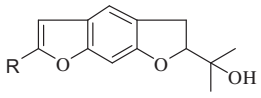
5.1. Chemistry

All of the commercial chemicals and solvents were of reagent grade and were used without further purification. 2,4-Dihydroxybenzaldehyde, Di-*tert*-butyl dicarbonate, 2-Methyl-1-propenyl

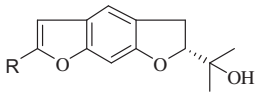


Scheme 4. Reaction conditions: (a) **40c**, $Pd(PPh_3)_2Cl_2$, CuI, TEA, dioxane, 85 °C; (b) HF/pyridine.

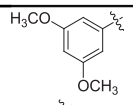
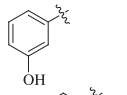
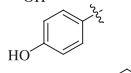
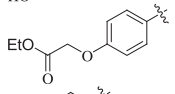
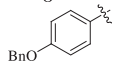
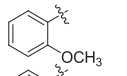
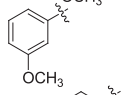
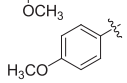
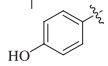
Table 1
In vitro HIF-1 inhibitory activity for series 1.



3-15

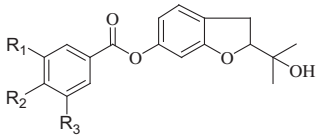


(*R*)-(-)-5

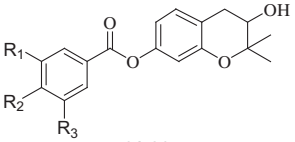
Compound	R	HRE-Luc IC_{50} (nM)	Cell viability IC_{50} (μM)
3		10	>30
4		46	>30
5		4.2	>30
6		54	>30
7		490	>30
8		580	>30
9		7	>30
10		110	>30
11		54	>30
12		310	>30
13		360	>30
14		1100	>30
15		>30	>30
(*R*)-(−)-**5**		1.0	>30
(±)-**1**		6.76	>30

Values were obtained as described in supplementary data.

Table 2
In vitro HIF-1 inhibitory activity for series 2 and 3.



16-20



21-32

Compound (*Open ring*)	R_1	R_2	R_3	HRE-Luc IC_{50} (μM)	Cell viability IC_{50} (μM)
16	OH	H	OH	>30	>30
17	OBn	H	OBn	26.2	>30
18	H	Br	H	>30	>30
19	H	*m*-OMePh	H	>30	>30
20	H	*m*-NO_2Ph	H	>30	>30
21	OH	H	OH	>30	>30
22	OH	OH	H	>30	>30
23	H	OH	H	>30	>30
24	OBn	H	OBn	2.6	>30
25	OBn	OBn	H	7.3	>30
26	H	OBn	H	12.9	>30
27	OBn	H	H	5.3	>30
28	H	Br	H	16.8	>30
29	H	*m*-OMePh	H	17.2	>30
30	H	*m*-NO_2Ph	H	17.5	>30
31	H	*m*-CNPh	H	>30	>30
32	H	*o,p*-F_2Ph	H	17.6	>30
(±)-**1**				6.76	>30
(±)-**2**				10.7	>30

Values were obtained as described in supplementary data.

magnesium bromide, *m*-Chloroperbenzoic acid, *p*-Toluenesulphonic acid, 3,5-Dibenzyloxybenzoic acid, Iodine monochloride, *tert*-Butyldimethylsilyl chloride (TBDMSCl), 3-Hydroxy benzoic acid, 4-Hydroxy benzoic acid, 3,4-Dihydroxy benzoic acid, 4-Bromo-benzoyl chloride, 3-Nitrophenyl boronic acid, 3-Cyanophenyl boronic acid, 2,4-Difluorophenyl boronic acid, 3,5-Dihydroxybenzaldehyde, 3-Hydroxybenzaldehyde, 4-Hydroxybenzaldehyde, 2-Ethynylanisole, 3-Ethynylanisole, 4-Ethynylanisole, Ethynylbenzene, 4-Ethynyltoluene,1-Ethynyl-3,5-difluorobenzene, 4-Ethynylpyridine, 5-Ethynyl-1-methyl-1H-imidazole, Triphenylphosphine (PPh_3), Lithium diisopropylamide solution (2 M in heptane/THF/ethylbenzene) *N,N*-Dicyclohexylcarbodiimide (DCC), Triethyl amine (TEA), Tetrakis(triphenylphosphine)palladium [Pd(PPh_3)$_4$], *N,N*-Diisopropylethylamine(DIPEA), 1-Hydroxybenzotriazol (HOBT), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), and Dichlorobis(triphenylphosphine) palladium (II) ($Pd(Ph_3P)_2Cl_2$) were purchased from commercial sources. All reactions were carried out under an atmosphere of dried argon, in flame-dried glassware. Melting points were recorded using a Thermo Fisher Scientific Melting Point Apparatus Model-IA9200 capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Varian (300 MHz) spectrometer. ^{13}C-NMR spectra were recorded on Bruker Avance-500 (500 MHz) spectrometer. Chemical shifts are provided in parts per million (ppm) downfield from tetramethylsilane (internal standard) with coupling constants in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), pseudo triplet (ps-t), quartet (q), multiplet (m), broad (br). Mass spectra were recorded on a Finnigan ESI mass spectrometer and HRMS (EI-MS) was obtained on a JMS-700 (Jeol, Japan). Products from all reactions were purified to a minimum purity of 96% as determined by HPLC, either by flash column chromatography using silica gel 60 (230–400 mesh Kieselgel 60) or by preparative thin-layer chromatography using glass-backed silica gel plates (1 mm thickness) unless otherwise indicated. Additionally, thin-layer chromatography on 0.25 mm silica plates (E. Merck, silica gel 60 F254) was used to monitor reactions. The chromatograms were visualized using ultraviolet illumination, exposure to iodine vapours, dipping in PMA, or Hanessian's solution. The purity of the products was checked by reversed phase high-pressure liquid chromatography (RP-HPLC), which was performed on a Waters Corp. HPLC system with a UV detector set at 254 nm. The mobile phases used were A: H_2O containing 0.05% TFA, and B: CH_3CN. The HPLC employed a YMC Hydrosphere C18 (HS-302) column (5 μ particle size, 12 nm pore size), 4.6 mm dia. × 150 mm with a flow rate of 1.0 mL/min. Compound purity was assessed using one of the following methods. Method A: gradient 20% B to 100% B in 30 min then 100% B over 10 min; Method B: gradient 25% B to 100% B in 30 min then 100% B over 10 min. A table listing HPLC retention times and purities in two different systems for **3-32**, and (*R*)-(−)-**5** are shown in the Supplementary data.

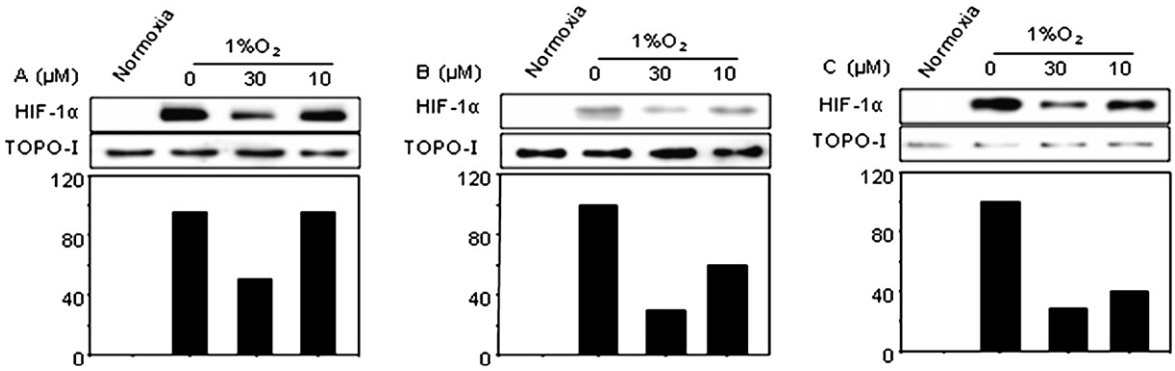


Fig. 3. Effect of compounds on the expression of HIF-1α protein. Hep3B cells were incubated under normoxia, or hypoxia for 12 h, in the absence or presence of the indicated concentration of compounds **1** (A), **5** (B), and (*R*)-(−)-**5** (C). Nuclear extracts for HIF-1α were analyzed by western blotting. The same blot was reprobed with an anti-topoisomerase-I antibody as a loading control. The amount of HIF-1α estimated by image scanning is expressed in arbitrary units. Western blot analysis was done to determine the effects of compounds **1**, **5**, and (*R*)-(−)-**5** on the accumulation of HIF-1α in Hep3B cells under hypoxic conditions. TOPO-I was used as loading control.

5.2. 2-(1-Hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-ol (**37**)

A solution of *m*-chloroperbenzoic acid (800 mg, 4.65 mmol) in EtOAc (25 mL) was added dropwise to a solution of prenylated derivative **35** (500 mg, 1.80 mmol) in EtOAc (15 mL) at 0 °C. The reaction was stirred for 4 h at 0 °C and then quenched by slow addition of an aqueous solution of $NaHSO_3$ (1 g in 100 mL of water). The mixture was stirred for 20 min and then the layers were separated. The organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was taken up in MeOH (25 mL) and LiOH (150 mg, 3.57 mmol) was added to the solution. The solution was stirred at room temperature overnight. The MeOH was evaporated; the crude residue was diluted with water, acidified with 10% HCl and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (*n*-Hexane: Et_2O = 40:60) gave compound **37** as a white solid (191 mg 56.7%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (1H, d, J = 9.0 Hz, aromatic-H), 6.31 (2H, m, aromatic-H), 4.79 (1H, bs, OH), 4.62 (1H, t, J = 8.7 Hz, CH), 3.06 (2H, d, J = 8.7 Hz, CH_2), 1.33 (3H, s, CH_3), 1.20 (3H, s, CH_3).

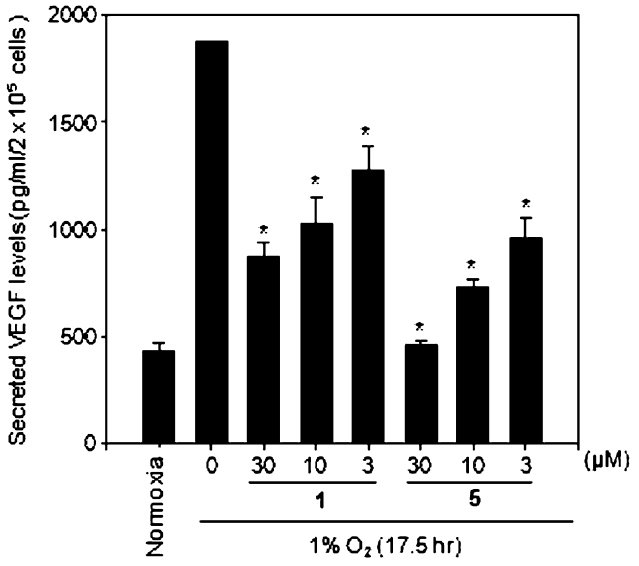


Fig. 4. Effect of representative compounds on secreted VEGF levels. Secreted VEGF levels were evaluated by ELISA in culture supernatant of Hep3B cells after exposure to normoxia or hypoxia for 17.5 h in the presence or absence of the indicated concentrations of **1** and **5**. Mean values from four independent experiments are shown; the *bar* indicates the S.D. Statistical significance ($p < 0.01$) judged by a paired Student's t test is marked with an *asterisk*.

5.3. Carbonic acid tert-butyl ester 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**38**)

The solution of prenylated derivative **35** (100 mg, 0.36 mmol) in CH_2Cl_2 (1 mL) was added dropwise to pre-cooled solutions of *m*-chloroperbenzoic acid (97 mg, 0.43 mmol) and *p*-toluenesulphonic acid (4 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The solution was stirred for 1 h at 0 °C, gradually warmed to room temperature, and stirred overnight. The solution was washed with dilute aqueous $NaHCO_3$ and water, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (*n*-Hexane: EtoAc = 85:15) to afford the desired compound **38** as a white solid (52 mg, 49% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (1H, d, J = 8.1 Hz, aromatic-H), 6.65–6.71 (2H, m, aromatic-H), 3.79 (1H, m, CH), 3.04 (1H, dd, J = 5.1 & 16.8 Hz, CH_2), 2.75 (1H, dd, J = 6.0 & 16.8 Hz, CH_2), 1.55 (9H, s, $C(CH_3)_3$), 1.35 (3H, s, CH_3), 1.31 (3H, s, CH_3).

5.4. 2,2-Dimethyl-chroman-3,7-diol (**39**)

To a solution of carbonic acid *tert*-butyl ester 3-hydroxy-2,2-dimethyl-chroman-7-yl ester **38** (1.18 g, 4.02 mmol) in MeOH (50 mL) was added 4 M HCl solution (in dioxane, 8.2 mL) at room temperature and stirred until completion as indicated by TLC. The reaction mixture was quenched in ice cold water, neutralized with aqueous sodium bicarbonate solution and diluted with a mixture of MeOH:MC (10%). The separated organic layer was washed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (*n*-Hexane:EtOAc:MeOH = 15:3:1) yielded compound **39** as a white solid (780 mg, 100% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.07 (1H, s, OH), 6.80 (1H, d, J = 7.8 Hz, aromatic-H), 6.23 (1H, dd, J = 2.4 & 8.1 Hz, aromatic-H), 6.08 (1H, d, J = 2.4 Hz, aromatic-H), 5.05 (1H, d, J = 4.8 Hz, $C(CH_3)O\underline{H}$), 3.56 (1H, m, CH), 2.75 (1H, dd, J = 5.4 & 16.2 Hz, CH_2), 2.75 (1H, m, CH_2), 1.25 (3H, s, CH_3), 1.10 (3H, s, CH_3).

5.5. General procedure for preparation of compounds (**42a,b**, **3**–**15**)

To a well-stirred mixture of the 2-iodophenol derivative **41** (1 equiv), $Pd(Ph_3P)_2Cl_2$ (0.01 equiv), CuI (0.02 equiv) and Et_3N (8 equiv) in dioxane and an appropriate terminal alkyne **40a-l**

(2 equiv) were added under an argon atmosphere. The mixture was stirred at 85 °C for 20 h. After removal of the solvent under reduced pressure, the mixture was cooled, diluted with EtOAc, and washed sequentially with dilute HCl, aqueous $NaHCO_3$ and water. The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified through silica gel column chromatography or by Prep-TLC.

*5.5.1. 2-[6-(3,5-Dimethoxy-phenyl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**3**)*

Yield: 14 mg (24.8%) of **3** as yellow oil. R_f = 0.31 (*n*-Hexane:EtOAc = 3:1); mp 138.3–138.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (1H, s, aromatic-H), 6.89–6.96 (3H, m, aromatic-H), 6.89 (1H, s, aromatic-H), 6.43 (1H, m, aromatic-H), 4.89 (1H, t, J = 8.7 Hz, CH), 3.87 (6H, s, OCH_3), 3.21–3.24 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 354 (M^+); HRMS (EI) *m/z* calcd for $C_{21}H_{22}O_5$ [M^+] 354.1467, found: 354.1466; Purity >99% (as determined by RP-HPLC, method B, t_R = 20.7 min).

*5.5.2. 2-{6-[3-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-2,3-dihydro-benzo[1,2-b;5,4-b']difuran-2-yl}-propan-2-ol (**42a**)*

Yield: 66 mg (27.5%) of **42a** as yellow oil. R_f = 0.27 (*n*-Hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (1H, d, J = 8.1 Hz, aromatic-H), 7.24–7.29 (3H, m, aromatic-H), 6.94 (1H, s, aromatic-H), 6.87 (1H, s, aromatic-H), 6.76–6.80 (1H, m, aromatic-H), 4.68 (1H, t, J = 9.3 Hz, CH), 3.20–3.24 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.02 (9H, s, $C(CH_3)_3$), 0.25 (6H, s, Si-$(CH_3)_2$); MS (EI) *m/z* 424 (M^+).

*5.5.3. 2-{6-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-2,3-dihydro-benzo[1,2-b;5,4-b']difuran-2-yl}-propan-2-ol (**42b**)*

Yield: 73 mg (30.7%) of **42b** as yellow oil. R_f = 0.20 (*n*-Hexane:EtOAc = 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (2H, d, J = 8.7 Hz, aromatic), 7.23 (1H, s, aromatic), 6.92–6.98 (3H, m, aromatic), 6.78 (1H, s, aromatic), 4.68 (1H, t, J = 9.3 Hz, CH), 3.20–3.24 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.02 (9H, s, $C(CH_3)_3$), 0.25 (6H, s, Si-$(CH_3)_2$); MS (EI) *m/z* 424 (M^+).

*5.5.4. 2-[6-(4-Benzyloxy-phenyl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**7**)*

Yield: 2.5 mg (1.3%) of **7** as yellow oil. R_f = 0.21 (*n*-Hexane:EtOAc = 3:1); mp 190–191.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J = 8.7 Hz, Aromatic), 7.33–7.47 (6H, m, aromatic), 7.03 (2H, d, J = 8.7 Hz, aromatic), 6.92 (1H, s, aromatic), 6.76 (1H, s, aromatic), 5.11 (2H, s, CH_2), 4.68 (1H, t, J = 8.7 Hz, CH), 3.21–3.23 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 400 (M^+); HRMS (EI) *m/z* calcd for $C_{26}H_{24}O_4$ [M^+] 400.1675, found: 400.1671; Purity >99% (as determined by RP-HPLC, method B, t_R = 21.6 min).

*5.5.5. 2-[6-(2-Methoxy-phenyl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**8**)*

Yield: 8 mg (15.4%) of **8** as a yellow solid. R_f = 0.31 (*n*-Hexane: EtOAc = 3:1); mp 135.9–136.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98–8.02 (1H, m, aromatic-H), 7.30 (2H, m, Aromatic), 7.23 (1H, s, aromatic-H), 7.06 (1H, t, J = 7.2 Hz, aromatic-H), 6.99 (1H, d, J = 8.1 Hz, aromatic-H), 6.93 (1H, s, aromatic-H), 4.68 (1H, t, J = 8.7 Hz, CH), 3.99 (3H, s, OCH_3), 3.22 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 324 (M^+); HRMS (EI) *m/z* calcd for $C_{20}H_{20}O_4$ [M^+] 324.1362, found: 324.1362.

*5.5.6. 2-[6-(3-Methoxy-phenyl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**9**)*

Yield: 14 mg (27.0%) of **9** as a yellow solid. R_f = 0.22 (*n*-Hexane:EtOAc = 3:1); mp 88.4–88.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.39 (4H, m, aromatic-H), 6.94 (1H, s, aromatic-H), 6.90 (1H, s, aromatic-H), 6.85–6.87 (1H, m, aromatic-H), 4.69 (1H, t, J = 8.7 Hz, CH), 3.89 (3H, s, OCH_3), 3.20–3.24 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 324 (M^+); HRMS (EI) *m/z* calcd for $C_{20}H_{20}O_4$ [M^+] 324.1362, found: 324.1361.

*5.5.7. 2-[6-(4-Methoxy-phenyl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**10**)*

Yield: 26 mg (50.1%) of **10** as a yellow solid. R_f = 0.23 (*n*-Hexane:EtOAc = 3:1); mp 180.8–181.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (2H, d, J = 7.5 Hz, aromatic-H), 7.26 (1H, s, aromatic-H), 6.93–6.97 (3H, m, aromatic-H), 6.77 (1H, s, aromatic-H), 4.69 (1H, t, J = 8.1 Hz, CH), 3.86 (3H, s, OCH_3), 3.22 (2H, d, J = 8.7 Hz, CH_2), 1.38 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 324 (M^+); HRMS (EI) *m/z* calcd for $C_{20}H_{20}O_4$ [M^+] 324.1362, found: 324.1366.

*5.5.8. 2-(6-Phenyl-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl)-propan-2-ol (**11**)*

Yield: 13 mg (27.6%) of **11** as a yellow solid. R_f = 0.55 (*n*-Hexane:EtOAc = 1:1); mp 158.0–160.3 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (2H, d, J = 8.1 Hz, aromatic-H), 7.42 (2H, t, J = 8.1 Hz, aromatic-H), 7.30 (2H, m, aromatic-H), 6.94 (1H, s, aromatic-H), 6.91 (1H, s, aromatic-H), 4.69 (1H, t, J = 8.7 Hz, CH), 3.21–3.24 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 294 (M^+); HRMS (EI) *m/z* calcd for $C_{19}H_{18}O_3$ [M^+] 294.1256, found: 294.1255.

*5.5.9. 2-(6-p-Tolyl-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl)-propan-2-ol (**12**)*

Yield: 13 mg (26.3%) of **12** as a yellow solid. R_f = 0.60 (*n*-Hexane:EtOAc = 1:1); mp 150.3–153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (2H, d, J = 8.1 Hz, aromatic-H), 7.24 (3H, m, aromatic-H), 6.93 (1H, s, aromatic-H), 6.84 (1H, s, aromatic-H), 4.68 (1H, t, CH, J = 9.0 Hz), 3.21–3.23 (2H, m, CH_2), 2.38 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 308 (M^+); HRMS (EI) *m/z* calcd for $C_{19}H_{18}O_3$ [M^+] 308.1412, found: 308.1409.

*5.5.10. 2-[6-(3,5-Difluoro-phenyl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**13**)*

Yield: 4 mg (7.6%) of **13** as a yellow solid. R_f = 0.21 (*n*-Hexane:EtOAc = 3:1); mp 133.5–135.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.30 (3H, m, Aromatic), 6.94 (1H, s, aromatic), 6.93 (1H, s, aromatic), 6.73 (1H, m, aromatic), 4.70 (1H, t, J = 9.0 Hz, CH), 3.21–3.25 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 330 (M^+); HRMS (EI) *m/z* calcd for $C_{19}H_{18}O_3$ [M^+] 330.1068, found: 330.1069.

*5.5.11. 2-(6-Pyridin-4-yl-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl)-propan-2-ol (**14**)*

Yield: 8 mg (17.0%) of **14** as a yellow solid. R_f = 0.15 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 182.9–183.6 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.53 (2H, m, aromatic), 7.79 (2H, d, J = 6.3 Hz, aromatic), 7.42 (1H, s, aromatic), 7.40 (1H, s, aromatic), 6.93 (1H, s, aromatic), 4.68 (1H, t, J = 9.0 Hz, CH), 3.24–3.27 (2H, m, CH_2), 1.28 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 295 (M^+); HRMS (EI) *m/z* calcd for $C_{18}H_{17}NO_3$ [M^+] 295.1208, found: 295.1207.

*5.5.12. 2-[6-(3-Methyl-3H-imidazol-4-yl)-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-propan-2-ol (**15**)*

Yield: 10 mg (21.0%) of **15** as a yellow solid. R_f = 0.10 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 241.9–243.3 °C (dec); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (1H, s, aromatic), 7.32–7.34 (2H, m, aromatic), 6.89 (1H, s, aromatic), 6.88 (1H, s, aromatic), 4.66 (1H, t, J = 8.7 Hz, CH), 3.23–3.27 (2H, m, CH_2), 1.27 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (EI) *m/z* 298 (M^+); HRMS (EI) *m/z* calcd for $C_{17}H_{18}N_2O_3$ [M^+] 298.1317, found: 298.1315.

5.6. 3-[6-(1-Hydroxy-1-methyl-ethyl)-5,6-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-phenol (**4**)

To a solution of 2-{6-[3-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl}-propan-2-ol **42a** (30 mg, 0.07 mmol) in THF/Pyridine (4 : 1, 3.5 mL) in a teflon bottle was added 70% HF/Pyridine solution (0.15 mL) with a Teflon syringe at 0 °C. The reaction was gradually warmed to room temperature and stirred for 2 h. The reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with dil. HCl and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then purified by Prep-TLC (*n*-Hexane:EtOAc = 3:2) to afford compound **4** as a white solid (4 mg, 18.4% yield). R_f = 0.33 (*n*-Hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.19–7.30 (4H, m, aromatic), 6.96 (1H, s, aromatic), 6.87 (1H, s, aromatic), 6.70–6.74 (1H, m, aromatic), 4.65 (1H, t, CH, J = 8.7 Hz), 3.21–3.24 (2H, m, CH_2), 1.27 (3H, s, CH_3), 1.23 (3H, s, CH_3); MS (EI) m/z 310 (M^+); HRMS (EI) m/z calcd for $C_{19}H_{18}O_4$ [M^+] 310.1205, found: 310.1207.

5.7. 4-[6-(1-Hydroxy-1-methyl-ethyl)-5,6-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-phenol (**5**)

To a solution of 2-{6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-2,3-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl}-propan-2-ol **42b** (100 mg, 0.24 mmol) in THF/Pyridine (4:1, 5 mL) in a teflon bottle was added 70% HF/Pyridine solution (0.5 mL) with a Teflon syringe at 0 °C. The reaction was gradually warmed to room temperature and stirred for 2 h. The reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with dil. HCl and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then purified by Prep-TLC (*n*-Hexane:EtOAc = 3:2) to afford compound **5** as a white solid (62 mg, 83.0% yield). R_f = 0.35 (*n*-Hexane:EtOAc:MeOH = 15:3:1); mp 229.3–230.5 °C (dec); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.62 (2H, d, J = 8.7 Hz, aromatic), 7.28 (1H, s, aromatic), 6.83 (2H, d, J = 7.8 Hz, aromatic), 6.74 (1H, s, aromatic), 6.71 (1H, s, aromatic), 4.64 (1H, t, J = 9.0 Hz, CH), 3.20–3.23 (2H, m, CH_2), 1.27 (3H, s, CH_3), 1.23 (3H, s, CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 159.3, 158.6, 156.0, 155.8, 126.7, 125.0, 123.8, 123.6, 116.7, 116.6, 100.3, 93.1, 91.3, 71.6, 30.8, 26.2, 25.6; MS (EI) m/z 310 (M^+); HRMS (EI) m/z calcd for $C_{19}H_{18}O_4$ [M^+] 310.1205, found: 310.1208.

5.8. {4-[6-(1-Hydroxy-1-methyl-ethyl)-5,6-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-phenoxy}-acetic acid ethyl ester (**6**)

To a suspension of 4-[6-(1-hydroxy-1-methyl-ethyl)-5,6-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-phenol **5** (37.1 mg, 0.12 mmol) and anhydrous potassium carbonate (100.9 mg, 0.73 mmol) in DMF (2 mL) was added ethyl chloroacetate (60.1 mg, 0.55 mmol) dropwise at room temperature. The resulting mixture was stirred for 12 h. The reaction mixture was diluted with EtOAc and sequentially washed with aqueous sodium bicarbonate, brine and water, and dried over anhydrous $MgSO_4$. The solvent was filtered and evaporated under reduced pressure to afford a crude solid, which was purified by column chromatography on silica gel (*n*-Hexane:EtOAc = 3:1) to afford **6** as a white solid (40 mg, 84.2% yield). R_f = 0.35 (*n*-Hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J = 8.7 Hz, aromatic), 7.26 (1H, s, aromatic), 6.92–6.98 (3H, m, aromatic), 6.78 (1H, s, aromatic), 4.68 (1H, t, J = 9.0 Hz, CH), 4.66 (2H, s, OCH_2CO_2), 4.29 (2H, q, J = 7.5 Hz, CH_2), 3.20–3.23 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.31 (3H, t, J = 6.6 Hz, CH_3),1.24 (3H, s, CH_3); MS (EI) m/z 396 (M^+); HRMS (EI) m/z calcd for $C_{23}H_{24}O_6$ [M^+] 396.1573, found: 396.1573.

5.9. General method for synthesis of compounds (**17**, **25**–**27**)

A mixture of appropriate benzoic acid (1.2 equiv), 2-(1-Hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-ol **37** or 2,2-dimethyl-chroman-3,7-diol **39** (1 equiv), DCC (3 equiv) and 4-dimethylaminopyridine (DMAP) (0.2 equiv) in DMF was stirred overnight at room temperature. Then the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$ anh), and concentrated. The residue was purified by silica gel flash column chromatography.

5.9.1. 3,5-Bis-benzyloxy-benzoic acid 2-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-yl ester (**17**)

Yield: 40 mg (15.1%) of **17** as a white solid. R_f = 0.47 (*n*-Hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.25–7.42 (12H, m, aromatic-H), 7.13 (1H, d, J = 7.8 Hz, aromatic-H), 6.88 (1H, t, J = 1.8 Hz, aromatic-H), 6.58–6.61 (2H, m, aromatic-H), 5.05 (4H, s, CH_2), 4.63 (1H, t, J = 9.0 Hz, $CH_2\underline{CH}OH$), 3.12–3.16 (2H, m, $\underline{CH_2}CHOH$), 1.25 (3H, s, CH_3), 1.21 (3H, s, CH_3); MS (EI) m/z 510 (M^+); HRMS (EI) m/z calcd for $C_{32}H_{30}O_6$ [M^+] 510.2042, found: 510.2044.

5.9.2. 3,4-Bis-benzyloxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**25**)

Yield: 57 mg (22.2%) of **25** as a white solid. R_f = 0.44 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 115.8–116.9 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.68–7.73 (2H, m, aromatic-H), 7.30–7.49 (10H, m, aromatic-H), 7.25 (1H, d, J = 8.4 Hz, aromatic-H), 7.11 (1H, d, J = 8.7 Hz, aromatic-H), 6.68 (1H, dd, J = 2.4 & 7.8 Hz, aromatic-H), 6.58 (1H, m, aromatic-H), 5.28 (2H, s, CH_2), 5.22 (2H, s, CH_2), 3.63–3.69 (1H, m, $CH_2\underline{CH}OH$), 2.93 (1H, dd, J = 4.8 & 16.8 Hz, $\underline{CH_2}CHOH$), 2.62 (1H, dd, J = 7.5 & 16.5 Hz, $\underline{CH_2}CHOH$), 1.28 (3H, s, CH_3), 1.19 (3H, s, CH_3); MS (EI) m/z 510 (M^+); HRMS (EI) m/z calcd for $C_{32}H_{30}O_6$ [M^+] 510.2042, found: 510.2045.

5.9.3. 4-Benzyloxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**26**)

Yield: 33 mg (15.9%) of **26** as a white solid. R_f = 0.45 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 158.5–160.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11–8.14 (2H, m, aromatic-H), 7.33–7.46 (5H, m, aromatic-H), 7.03–7.10 (3H, m, aromatic-H), 6.68–6.76 (2H, m, aromatic-H), 5.16 (2H, s, CH_2), 3.82 (1H, t, J = 5.4 Hz, $CH_2\underline{CH}OH$), 3.07 (1H, dd, J = 5.4 & 16.8 Hz, $\underline{CH_2}CHOH$), 2.79 (1H, dd, J = 5.4 & 16.8 Hz, $\underline{CH_2}CHOH$), 1.37 (3H, s, CH_3), 1.33 (3H, s, CH_3); MS (EI) m/z 404 (M^+); HRMS (EI) m/z calcd for $C_{25}H_{24}O_5$ [M^+] 404.1624, found: 404.1634.

5.9.4. 3-Benzyloxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**27**)

Yield: 16 mg (14.1%) of **27** as a white solid. R_f = 0.43 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 111.3–112.8 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.78–7.81 (2H, m, aromatic-H), 7.32–7.48 (6H, m, aromatic-H), 7.22–7.25 (1H, m, aromatic-H), 7.10 (1H, d, J = 8.4 Hz, aromatic-H), 6.70–6.76 (2H, m, aromatic-H), 5.14 (2H, s, CH_2), 3.81 (1H, t, J = 5.7 Hz, $CH_2\underline{CH}OH$), 3.07 (1H, dd, J = 4.8 & 16.5 Hz, $C\underline{H_2}CHOH$), 2.79 (1H, dd, J = 5.4 & 17.7 Hz, $C\underline{H_2}CHOH$), 1.37 (3H, s, CH_3), 1.34 (3H, s, CH_3); MS (EI) m/z 404 (M^+); HRMS (EI) m/z calcd for $C_{25}H_{24}O_5$ [M^+] 404.1624, found: 404.1623.

5.10. 3,5-Bis-benzyloxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**24**)

To a mixture of 3,5-Bis-benzyloxy-benzoic acid (364.7 mg, 1.09 mmol), 2,2-Dimethyl-chroman-3,7-diol **39** (176.5 mg, 0.91 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethyl carbodiimide·HCl (EDC) (260.7 mg, 1.36 mmol) and 1-hydroxybenzotriazole (HOBt) (185.1 mg, 1.36 mmol) in DMF (7 mL) was added redistilled *N*, *N*-

diisopropylethylamine (DIPEA) (170.3 mg, 0.23 mL, 1.36 mmol). The mixture was stirred overnight, and then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$ anh), and concentrated. The residue was purified by silica gel flash column chromatography (*n*-Hexane:EtOAc:MeOH = 6:3:1) to give **24** as a white solid (89 mg, 19.2% yield). R_f = 0.46 (*n*-Hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.45 (12H, m, aromatic-H), 7.10 (1H, d, J = 8.4 Hz, aromatic-H), 6.87 (1H, t, J = 2.4 Hz, aromatic-H), 6.63–6.75 (2H, m, aromatic-H), 5.10 (4H, s, CH_2), 3.82 (1H, t, J = 4.8 Hz, $CH_2\underline{CH}OH$), 3.07 (1H, dd, J = 4.8 & 17.1 Hz, $\underline{CH_2}CHOH$), 2.79 (1H, dd, J = 5.7 & 16.8 Hz, $\underline{CH_2}CHOH$), 1.37 (3H, s, CH_3), 1.34 (3H, s, CH_3); MS (EI) m/z 510 (M^+); HRMS (EI) m/z calcd for $C_{32}H_{30}O_6$ [M^+] 510.2042, found: 510.2039.

5.11. General method for preparation of compounds (**16**, **21**–**23**)

The appropriate benzyloxy-benzoic acid compound **17**, **24**–**26** was taken up? in methanol and treated with 5% Pd-carbon (5% w/w), and stirred at room temperature under hydrogen gas. After completion of the reaction as monitored by TLC, the mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography.

5.11.1. 3,5-Dihydroxy-benzoic acid 2-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-yl ester (**16**)

Yield: 12 mg (51.3%) of **16** as yellow foam. R_f = 0.13 (*n*-Hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.17 (1H, d, J = 7.2 Hz, aromatic-H), 7.04 (2H, d, J = 2.7 Hz, aromatic-H), 6.57–6.62 (2H, m, aromatic-H), 6.53 (1H, t, J = 2.4 Hz, aromatic-H), 4.66 (1H, t, J = 9.3 Hz, $CH_2\underline{CH}OH$), 3.15–3.19 (2H, m, $\underline{CH_2}CHOH$), 1.27 (3H, s, CH_3), 1.22 (3H, s, $\overline{CH_3}$); MS (ESI) m/z 353 ($\overline{M + Na}$)$^+$, 329 ($M - H$)$^-$; HRMS (EI) m/z calcd for $C_{18}H_{18}O_6$ [M^+] 330.1103, found: 330.1099.

5.11.2. 3,5-Dihydroxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**21**)

Yield: 25 mg (45.0%) of **21** a white solid. R_f = 0.21 (CH_2Cl_2:MeOH = 15:1); ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ 6.85–6.93 (3H, m, aromatic-H), 6.37–6.47 (3H, m, aromatic-H), 3.57 (1H, m, $CH_2\underline{CH}OH$), 2.81 (1H, dd, J = 5.4 & 16.8 Hz, $\underline{CH_2}CHOH$), 2.53 (1H, dd, J = 7.2 & 16.8 Hz, $\underline{CH_2}CHOH$), 1.14 (3H, s, CH_3), 1.08 (3H, s, CH_3); MS (ESI) m/z 353 ($\overline{M + Na}$)$^+$, 329 ($M - H$)$^-$; HRMS (EI) m/z calcd for $C_{18}H_{18}O_6$ [M^+] 330.1103, found: 330.1104.

5.11.3. 3,4-Dihydroxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**22**)

Yield: 10 mg (33.6%) of **22** a white solid. R_f = 0.24 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 190.0–192.5 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.53–7.56 (2H, m, aromatic-H), 7.09 (1H, d, J = 8.1 Hz, aromatic-H), 6.85 (1H, d, J = 7.8 Hz, aromatic-H), 6.64 (1H, dd, J = 2.4 & 6.9 Hz, aromatic-H), 6.56 (1H, d, J = 2.4 Hz, aromatic-H), 3.75–3.79 (1H, m, $CH_2\underline{CH}OH$), 3.02 (1H, dd, J = 5.7 & 16.7 Hz, $\underline{CH_2}CHOH$), 2.72 (1H, dd, J = 7.5 & 16.4 Hz, $\underline{CH_2}CHOH$), 1.33 (3H, s, $\overline{CH_3}$), 1.27 (3H, s, CH_3); MS (ESI) m/z 329 ($\overline{M + Na}$)$^+$, 353 ($M - H$)$^-$; HRMS (EI) m/z calcd for $C_{18}H_{18}O_6$ [M^+] 330.1103, found: 330.1103.

5.11.4. 4-Hydroxy-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**23**)

Yield: 9.5 mg (40.8%) of **23** as a white solid. R_f = 0.19 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 208.1–209.2 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.97–8.02 (2H, m, aromatic-H), 7.09 (1H, d, J = 8.7 Hz, aromatic-H), 6.85–6.90 (2H, m, aromatic-H), 6.66 (1H, dd, J = 2.4 & 8.4 Hz, aromatic-H), 6.57 (1H, d, J = 2.4 Hz, aromatic-H), 3.75–3.79 (1H, m, $CH_2\underline{CH}OH$), 3.02 (1H, dd, J = 5.4 & 16.5 Hz, $\underline{CH_2}CHOH$), 2.73 (1H, dd, J = 7.5 & 16.5 Hz, $\underline{CH_2}CHOH$), 1.34 (3H, s, $\overline{CH_3}$), 1.27 (3H, s, CH_3); MS (ESI) m/z 337 ($\overline{M + Na}$)$^+$, 313 ($M - H$)$^-$; HRMS (EI) m/z calcd for $C_{18}H_{18}O_5$ [M^+] 314.1154, found: 314.1155.

5.12. 4-Bromo-benzoic acid 2-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-yl ester (**18**)

A solution of 2-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-ol **37** (200 mg, 1.13 mmol) was dissolved in dry CH_2Cl_2 (6 mL) and treated with TEA (0.29 mL. 2.06 mmol) under Ar. A solution of the 4-bromo-benzoyl chloride **44** (248.3 mg, 1.13 mmol) in dry CH_2Cl_2 (6 mL) was added at 0 °C. After completion of the reaction as monitored by TLC, the mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (*n*-Hexane:EtOAc:MeOH = 15:3:1) to give **18** as a white solid (376 mg, 88.1% yield). R_f = 0.53 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 119.3–119.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (2H, d, J = 8.7 Hz, aromatic-H), 7.64 (2H, d, J = 8.7 Hz, aromatic-H), 7.16 (1H, d, J = 8.1 Hz, aromatic-H), 6.63–6.68 (2H, m, aromatic-H), 4.68 (1H, t, J = 9.3 Hz, $CH_2\underline{CH}OH$), 3.14–3.18 (2H, m, $\underline{CH_2}CHOH$), 1.35 (3H, s, CH_3), 1.23 (3H, s, CH_3); MS (ESI) m/z 394 ($\overline{M + Na}$)$^+$, 375 ($M - H$)$^-$; HRMS (EI) m/z calcd for $C_{18}H_{17}BrO_4$ [M^+] 376.0310, found: 376.0313.

5.13. 4-Bromo-benzoic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**28**)

A solution of 2,2-dimethyl-chroman-3,7-diol **39** (116.4 mg, 0.60 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and treated with TEA (0.17 mL, 1.2 mmol) under Ar. A solution of the 4-bromo-benzoyl chloride **44** (144.9 mg, 0.66 mmol) in dry CH_2Cl_2 (3 mL) was added at 0 °C. After completion of the reaction as monitored by TLC, the mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (*n*-Hexane:EtOAc:MeOH = 15:3:1) to give **28** as a white solid (217 mg, 95.8% yield). R_f = 0.59 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 151.3–152.3 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.04 (2H, d, J = 8.4 Hz, aromatic-H), 7.72 (2H, d, J = 8.7 Hz, aromatic-H), 7.11 (1H, d, J = 8.7 Hz, aromatic-H), 6.69 (1H, dd, J = 2.4 & 8.1 Hz, aromatic-H), 6.61 (1H, d, J = 2.4 Hz, aromatic-H), 3.75–3.80 (1H, m, $CH_2\underline{CH}OH$), 3.03 (1H, dd, J = 5.4 & 16.8 Hz, $\underline{CH_2}CHOH$), 2.73 (1H, dd, J = 7.5 & 16.4 Hz, $\underline{CH_2}CHOH$), 1.34 (3H, s, $\overline{CH_3}$), 1.27 (3H, s, CH_3); MS (ESI) m/z 399 ($\overline{M + Na}$)$^+$, 375 ($M - H$)$^-$; HRMS (EI) m/z calcd for $C_{18}H_{17}BrO_4$ [M^+] 376.0310, found: 376.0307.

5.14. General method for synthesis of compounds (**19**,**20**,**29**–**32**)

A mixture of 4-bromo-benzoic acid **18** or **28** (1 equiv) and Pd(PPh_3)$_4$ (0.05 equiv) in 1,2-dimethoxyethane was heated overnight at 110 °C. The solution was cooled to ambient temperature and we sequentially added the appropriate amount of boronic acid (2 equiv), and a solution of sodium hydrogen carbonate (2 equiv, 1 M in H_2O). The mixture was reheated for 5 h at 110 °C with vigorous stirring, then cooled and extracted with ethyl acetate. The combined extracts were washed using brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated under vacuo. The residue was purified by silica gel flash column chromatography.

5.14.1. 3′-Methoxy-biphenyl-4-carboxylic acid 2-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-yl ester (**19**)

Yield: 5.0 mg (15.4%) of **19** as yellow foam. R_f = 0.46 (*n*-Hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (2H, d, J = 8.4 Hz, aromatic-H), 7.72 (2H, d, J = 8.4 Hz, aromatic-H), 7.40 (1H, t, J = 8.1 Hz, aromatic-H), 7.17–7.26 (3H, m, aromatic-H), 6.95–6.98 (1H, m, aromatic-H), 6.68–6.73 (2H, m, aromatic-H), 4.69 (1H, t, J = 9.0 Hz, $CH_2\underline{CH}OH$), 3.89 (3H, s, OCH_3), 3.15–3.20 (2H,

m, $\underline{CH_2}CHOH$), 1.34 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (ESI) *m/z* 427 $(M + Na)^+$, 403 $(M - H)^-$; HRMS (EI) *m/z* calcd for $C_{25}H_{24}O_5$ $[M^+]$ 404.1624, found: 404.1623.

*5.14.2. 3′-Nitro-biphenyl-4-carboxylic acid 2-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-benzofuran-6-yl ester (**20**)*

Yield: 9.6 mg (28.6%) of **20** as a white solid. R_f = 0.40 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 110–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (1H, m, aromatic-H), 8.26–8.32 (3H, m, aromatic-H), 7.98 (1H, d, J = 8.1 Hz, aromatic-H), 7.77 (2H, d, J = 7.8 Hz, aromatic-H), 7.68 (1H, t, J = 8.1 Hz, aromatic-H), 7.18 (1H, d, J = 7.5 Hz, aromatic-H), 6.69–6.72 (2H, m, aromatic-H), 4.70 (1H, t, J = 9.0 Hz, $CH_2\underline{CH}OH$), 3.16–3.20 (2H, m, $\underline{CH_2}CHOH$), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); MS (ESI) *m/z* 442 $(M + Na)^+$, 418 $(M - H)^-$; HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO_6$ $[M^+]$ 419.1369, found: 419.1370.

*5.14.3. 3′-Methoxy-biphenyl-4-carboxylic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**29**)*

Yield: 17 mg (81.3%) of **29** as yellow foam. R_f = 0.43 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 96.5–97.5 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.19 (2H, d, J = 8.1 Hz, aromatic-H), 7.77 (2H, d, J = 8.4 Hz, aromatic-H), 7.38 (1H, t, J = 8.1 Hz, aromatic-H), 7.21–7.26 (2H, m, aromatic-H), 7.11 (1H, d, J = 8.7 Hz, aromatic-H), 6.95–6.99 (1H, m, aromatic-H), 6.70 (1H, dd, J = 2.4 & 8.0 Hz, aromatic-H), 6.63 (1H, d, J = 2.4 Hz, aromatic-H), 3.85 (3H, s, CH_3), 3.77 (1H, t, J = 5.4 Hz, $CH_2\underline{CH}OH$), 3.03 (1H, dd, J = 5.4 & 16.8 Hz, $\underline{CH_2}CHOH$), 2.74 (1H, dd, J = 7.2 & 16.5 Hz, $\underline{CH_2}CHOH$), 1.34 (3H, s, CH_3), 1.28 (3H, s, CH_3); MS (ESI) *m/z* 427 $(M + Na)^+$, 403 $(M - H)^-$; HRMS (EI) *m/z* calcd for $C_{25}H_{24}O_5$ $[M^+]$ 404.1624, found: 404.1623.

*5.14.4. 3′-Nitro-biphenyl-4-carboxylic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**30**)*

Yield: 5.1 mg (22.5%) of **30** as yellow foam. R_f = 0.16 (*n*-Hexane:EtOAc:MeOH = 15:3:1); mp 147.1–149 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.55 (1H, m, aromatic-H), 8.26–8.30 (3H, m, aromatic-H), 8.13 (1H, d, J = 8.1 Hz, aromatic-H), 7.90 (2H, d, J = 8.7 Hz, aromatic-H), 7.75 (1H, t, J = 7.8 Hz, aromatic-H), 7.13 (1H, d, J = 7.8 Hz, aromatic-H), 6.72 (1H, dd, J = 2.4 & 8.4 Hz, aromatic-H), 6.64 (1H, d, J = 2.4 Hz, aromatic-H), 3.76–3.80 (1H, m, $CH_2\underline{CH}OH$), 3.04 (1H, dd, J = 5.4 & 16.8 Hz, $\underline{CH_2}CHOH$), 2.74 (1H, dd, J = 7.2 & 17.1 Hz, $\underline{CH_2}CHOH$), 1.35 (3H, s, CH_3), 1.28 (3H, s, CH_3); MS (ESI) *m/z* 442 $(M + Na)^+$, 418 $(M - H)^-$; HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO_6$ $[M^+]$ 419.1369, found: 419.1370.

*5.14.5. 3′-Cyano-biphenyl-4-carboxylic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**31**)*

Yield: 5.3 mg (10.0%) of **31** as yellow foam. R_f = 0.34 (*n*-Hexane:EtOAc:MeOH = 6:3:1); mp 139.7–141.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (2H, d, J = 8.1 Hz, aromatic-H), 7.86–7.92 (2H, m, aromatic-H), 7.68–7.71 (3H, m, aromatic-H), 7.60 (1H, t, J = 8.1 Hz, aromatic-H), 7.12 (1H, d, J = 8.7 Hz, aromatic-H), 6.72–6.79 (2H, m, aromatic-H), 3.83 (1H, m, $CH_2\underline{CH}OH$), 3.01 (1H, dd, J = 5.1 & 17.0 Hz, $\underline{CH_2}CHOH$), 2.80 (1H, dd, J = 2.83 & 16.8 Hz, $\underline{CH_2}CHOH$), 1.38 (3H, s, CH_3), 1.34 (3H, s, CH_3); MS (EI) *m/z* 399 (M^+); HRMS (EI) *m/z* calcd for $C_{25}H_{21}NO_4$ $[M^+]$ 399.1471, found: 399.1472.

*5.14.6. 2′,4′-Difluoro-biphenyl-4-carboxylic acid 3-hydroxy-2,2-dimethyl-chroman-7-yl ester (**32**)*

Yield: 15 mg (31.7%) of **32** as a yellow solid. R_f = 0.61 (*n*-Hexane:EtOAc:MeOH = 12:3:1); mp 132.8–133.3 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.25 (2H, d, J = 8.1 Hz, aromatic-H), 7.62–7.65 (2H, m, aromatic-H), 7.42–7.50 (1H, m, aromatic-H), 7.11 (1H, d, J = 8.1 Hz, aromatic-H), 6.92–7.03 (2H, m, aromatic-H), 6.72–6.78 (2H, m, aromatic-H), 3.81–3.86 (1H, m, $CH_2\underline{CH}OH$), 3.09 (1H, dd, J = 5.1 & 17.0 Hz, $\underline{CH_2}CHOH$), 2.80 (1H, dd, J = 5.4 & 16.5 Hz, $\underline{CH_2}CHOH$), 1.38 (3H, s, CH_3), 1.34 (3H, s, CH_3); MS (ESI) *m/z* 433 $(M + Na)^+$, 409 $(M - H)^-$; HRMS (EI) *m/z* calcd for $C_{24}H_{20}F_2O_4$ $[M^+]$ 410.1330, found: 410.1330.

*5.15. (R)-2-{6-[4-(tert-butyl-dimethyl-silanyloxy)phenyl]-2,3-dihydrobenzo[1,2-b;5,4-b']difuran-2-yl}-propan-2-ol [(R)-(−)-**42b**]*

To a well-stirred mixture of the 2-iodophenol derivative (*R*)-(−)-**41** (230 mg, 0.72 mmol), $Pd(pph_3)_2Cl_2$ (50 mg, 0.07 mmol), CuI (27 mg, 0.14 mmol) and Et_3N (582 mg, 5.75 mmol) in dioxane (10 mL) and a terminal alkyne (334 mg, 1.44 mmol) **40c** were added under an argon atmosphere. The mixture was stirred at 85 °C for 20 h. After removal of the solvent under reduced pressure the mixture was cooled, diluted with ethyl acetate, and washed sequentially with diluted HCl, aqueous $NaHCO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography to afford compound (*R*)-(−)-**42b** as a yellow solid (80 mg, 26%); mp 115.4–116.5 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (2H, d, J = 8.7 Hz), 7.26 (1H, s), 6.87–6.91 (3H, m), 6.76 (1H, s), 4.68 (1H, t, J = 9.3 Hz), 3.20–3.23 (2H, m), 1.37 (3H, s), 1.24 (3H, s), 1.00 (9H, s), 0.23 (6H, s); MS (EI) *m/z* 424 (M^+).

5.16. (R)-4-[6-(1-hydroxy-1-methyl-ethyl)-5,6-dihydro-benzo[1,2-b; 5,4-b']difuran-2-yl]-phenol [(R)-(−)-5]

To a solution of compound (*R*)-(−)-**42b** (80 mg, 0.19 mmol) in THF/pyridine (4:1, 5 mL) in a Teflon bottle was added a 70% HF/pyridine solution (0.5 mL) with a Teflon syringe at 0 °C. The reaction was gradually warmed to room temperature and stirred for 2 h. The reaction was quenched slowly with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with diluted HCl and water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was then purified by column chromatography to obtain (*R*)-(−)-**5** as a white solid (49 mg, 84% yield); mp 227.6–230.6 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.62 (2H, d, J = 8.4 Hz), 7.26 (1H, s), 6.82 (4H, m), 4.63 (1H, t, J = 8.4 Hz), 3.20–3.23 (2H, m), 1.27 (3H, s), 1.24 (3H, s); MS (EI) *m/z* 310 (M^+); HRMS (EI) *m/z* calcd for $C_{19}H_{18}O_4$ $[M^+]$ 310.1205, found: 310.1208.

Acknowledgements

This study was supported by the National Research Foundation of Korea (NRF) grant (2010-0024391) and KRIBB/KRCF grant funded by the Korean Government.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.03.022.

References

[1] G.L. Wang, B.H. Jiang, E.A. Rue, G.L. Semenza, Proc. Natl. Acad. Sci. U.S.A. 92 (1995) 5510–5514.
[2] B.H. Jiang, E. Rue, G.L. Wang, R. Roe, G.L. Semenza, J. Biol. Chem. 271 (1996) 17771–17778.
[3] I.B. Zhulin, B.L. Taylor, R. Dixon, Trends Biochem. Sci. 22 (1997) 331–333.
[4] C.P. Ponting, L. Aravind, Curr. Biol. 7 (1997) R674–R677.
[5] J. Yang, L. Zhang, P.J. Erbel, K.H. Gardner, K. Ding, J.A. Garcia, R.K. Bruick, J. Biol. Chem. 280 (2005) 36047–36054.
[6] (a) G.L. Wang, B. Jiang, E.A. Rue, G.L. Semenza, Proc. Natl. Acad. Sci. U.S.A. 92 (1995) 5510–5514;
(b) G. Michel, E. Minet, I. Ernest, I. Roland, F. Durant, J. Remacle, C.A. Michiels, J. Biomol. Struct. Dyn. 18 (2000) 169–180;
(c) A. Zagorska, J. Dulak, Acta Biochim. Pol. 51 (2004) 563–585;
(d) L. Poellinger, R.S. Johnson, Curr. Opin. Genet. Dev. 14 (2004) 81–85;

(e) M.K. Jones, I.L. Szabo, H. Kawanaka, S.S. Husain, A.S. Tarnawski, FASEB J. 16 (2002) 264–266;
(f) P.H. Maxwell, G.U. Dachs, J.M. Gleadle, L.G. Nicholls, A.L. Harris, I.J. Stratford, O. Hankinson, C.W. Pugh, P.J. Ratcliffe, Proc. Natl. Acad. Sci. U.S.A. 94 (1997) 8104–8109;
(g) G.L. Semenza, Annu. Rev. Cell Dev. Biol. 15 (1999) 551–578.
[7] G.L. Semenza, Trends Mol. Med. 8 (2002) S62–S67.
[8] P. Birner, M. Schindl, A. Obermair, C. Plank, G. Breitenecker, G. Oberhuber, Cancer Res. 60 (2000) 4693–4696.
[9] (a) A. Giaccia, B.G. Siim, R.S. Johnson, Nat. Rev. Drug Discov. 2 (2003) 803–811;
(b) G.L. Semenza, Nat. Rev. Cancer 3 (2003) 721–732.
[10] (a) K. Lee, J.H. Lee, S.K. Boovanahalli, Y. Jin, M. Lee, X. Jin, J.H. Kim, Y.S. Hong, J.J. Lee, J. Med. Chem. 50 (2007) 1675–1684;
(b) K.A. Mohammed, R.C. Jadulco, T.S. Bugni, M.K. Harper, M. Sturdy, C.M. Ireland, J. Med. Chem. 51 (2008) 1402–1405;
(c) M.E. Jung, G.Y. Im, Tetrahedron Lett. 49 (2008) 4962–4964.
[11] (a) V.E. Belozerov, E.G. Van Meir, Anticancer Drugs 16 (2005) 901–909;
(b) C. Tan, R.G. de Norcholson, A.J. Roecker, B. Pyrzynska, F. Khwaja, Z. Zhang, H. Zhang, Q. Teng, A.C. Nicholson, P. Giannakakou, W. Zhou, J.J. Olson, M.M. Pereira, K.C. Nicolaou, E.G. Van Meir, Cancer Res. 65 (2005) 605–612;
(c) N.M. Chau, P. Rogers, W. Aherne, V. Carroll, I. Collins, E. McDonald, P. Workman, M. Ashcroft, Cancer Res. 65 (2005) 4918–4928.
[12] D.R. Mole, I. Schlemminger, L.A. McNeill, K.S. Hewitson, C.W. Pugh, P.J. Ratcliffe, C.J. Schofield, Bioorg. Med. Chem. Lett. 13 (2003) 2677–2680.
[13] A.C.R. Epstein, J.M. Gleadle, L.A. McNeill, K.S. Hewitson, J. O'Rourke, D.R. Mole, M. Mukherji, E. Metzen, M.I. Wilson, A. Dhanda, Y.M. Tian, N. Masson, D.L. Hamilton, P. Jaakkola, R. Barstead, J. Hodgkin, P.H. Maxwell, C.W. Pugh, C.J. Schofield, P.J.C. Ratcliffe, Cellule 107 (2001) 43–54.
[14] J.M. Elkins, K.S. Hewitson, L.A. McNeill, J.F. Seibel, I. Schlemminger, C.W. Pugh, P.J. Ratcliffe, C.J. Schofield, J. Biol. Chem. 278 (2003) 1802–1806.
[15] I. Schlemminger, D.R. Mole, L.A. McNeill, A. Dhanda, K.S. Hewitson, Y.M. Tian, P.J. Ratcliffe, C.W. Pugh, C.J. Schofield, Bioorg. Med. Chem. Lett. 13 (2003) 1451–1454.
[16] K.S. Hewitson, C.J. Schofield, Drug Discov. Today 9 (2004) 704–711.
[17] E.J. Yeo, Y.S. Chun, J.W. Park, Biochem. Pharmacol. 68 (2004) 1061–1069.
[18] N.T. Dat, X. Jin, K. Lee, Y.S. Hong, Y.H. Kim, J.J. Lee, J. Nat. Prod. 72 (2009) 39–43.
[19] N. Kaur, Y. Xia, Y. Jin, N.T. Dat, K. Gajulapati, Y. Choi, Y.S. Hong, J.J. Lee, K. Lee, Chem. Commun. (2009) 1879–1881.
[20] T. Gibtner, F. Hampel, J.P. Gisselbrecht, A. Hirsch, Chem. Eur. J. 8 (2002) 408–432.
[21] X.F. Cai, X. Jin, D. Lee, Y.T. Yang, K. Lee, Y.S. Hong, J.H. Lee, J.J. Lee, J. Nat. Prod. 69 (2006) 1095–1097.