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(±)-*trans*-2-phenyl-2,3-dihydrobenzofurans as leishmanicidal agents: synthesis, *in vitro* evaluation and SAR analysis

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Abstract

Leishmaniasis, a neglected tropical disease caused by parasites of the genus *Leishmania*, causes a serious burden of disease around the world, represents a threat to the life of millions of people, and therefore is a major public health problem. More effective and non-toxic new treatments are required, especially for visceral leishmaniasis, the most severe form of the disease. On the backdrop that dihydrobenzofurans have previously shown antileishmanial activity, we present here the synthesis of a set of seventy *trans*-2-phenyl-2,3-dihydrobenzofurans and evaluation of their *in vitro* activity against *Leishmania donovani* as well as a discussion of structure-activity relationships. Compounds **8m-o** and **8r** displayed the highest potency (IC_{50} < 2 µmol/L) and interesting selectivity of the antileishmanial activity over cytotoxicity against mammalian cells (SI > 4.6). Nonetheless, structural optimization as further requirement was inferred from the high clearance of the most potent compound (**8m**) observed during determination *in vitro* of its metabolic stability. On the other hand, chiral separation of **8m** and subsequent biological evaluation of its enantiomers demonstrated no effect of chirality on activity and cytotoxicity. Holistic analysis of *in silico* ADME-like properties and ligand efficiency metrics by a simple scoring function estimating druglikeness highlighted compounds **16c**, **18** and **23** as promising candidates for further development. Overall, the potential of *trans*-2-phenyl-2,3-dihydrobenzofurans as leishmanicidal agents was confirmed.

Keywords: 2-phenyl-2,3-dihydrobenzofurans; antileishmanial agents; structure-activity relationships; *Leishmania donovani*; neolignan analogues.

1. Introduction

Visceral leishmaniasis (VL) threatens the life of millions of people around the world, mainly in tropical and subtropical regions, where poverty and lack of good sanitary conditions are common characteristic issues. The different forms of leishmaniasis (VL as well as the other clinical forms, cutaneous and mucocutaneous leishmaniasis) are part of the so-called neglected tropical diseases, as

currently defined by WHO [1]. Leishmaniasis causes the third-highest burden of disease among parasitic diseases [2], which reflects its high relevance as a public health problem.

Leishmaniasis is a vector-borne disease transmitted by hematophagous female sand flies, mainly from the genera *Phlebotomus* and *Lutzomyia*, in the Old and New World, respectively [3,4]. Although there are approximately 20 *Leishmania* species that are able to parasitize humans [3,5], only two of them are responsible for VL, the most severe form of leishmaniasis [6]: *L. donovani* and *L. infantum*. Typical symptoms of VL include anemia, progressive cachexia, intermittent fever, hepatomegaly and splenomegaly, but most importantly, it can lead to death if it remains untreated [6,7].

The number of currently available treatments for leishmaniasis is quite limited, pentavalent antimonials, amphotericin B, paromomycin and miltefosine being those employed as first-line drugs [7–9]. Unfortunately, these drugs suffer from several disadvantages, including poor efficacy and major side effects, as well as increasing resistance. Moreover, many of them require parenteral administration, which is often not suitable or even impossible in the setting of remote rural areas in low-income countries where the highest burden of disease is found. Additionally, the number of compounds entering clinical trials is still low despite increasing efforts in recent years [8]. Thus, the search for new effective antileishmanial agents remains as a fundamental need.

A group of synthetic analogues of dihydrobenzofuran neolignans (formally *trans*-(*E*)-2-phenyl-5-propenyl-2,3-dihydrobenzofurans; Fig. 1) has previously demonstrated potential as antitumoral and antileishmanial agents [10,11]. Furthermore, the antileishmanial activity for such compounds was related to structural features using a Quasar model (quasi-atomistic receptor surface modelling) [11], as summarized in simplified form in Fig. 1. On this background, the present paper describes the synthesis and biological evaluation of seventy *trans*-2-phenyl-2,3-dihydrobenzofurans with varying substitution patterns, in order to generate a better understanding of the structural requirements for improving the antileishmanial activity of this kind of compounds. Structure-activity relationships are discussed in a qualitative manner. Results of an investigation on the *in vitro* metabolism of the congener with the most potent antileishmanial activity, compound **8m**, as well as the chiral separation and activity testing of its pure enantiomers, are reported. A comprehensive *in silico* evaluation of bioavailability and pharmacokinetic properties in this set of compounds is also presented to provide a rationale for further optimization of such neolignan analogues.

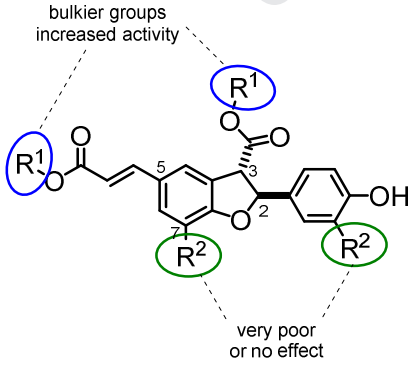
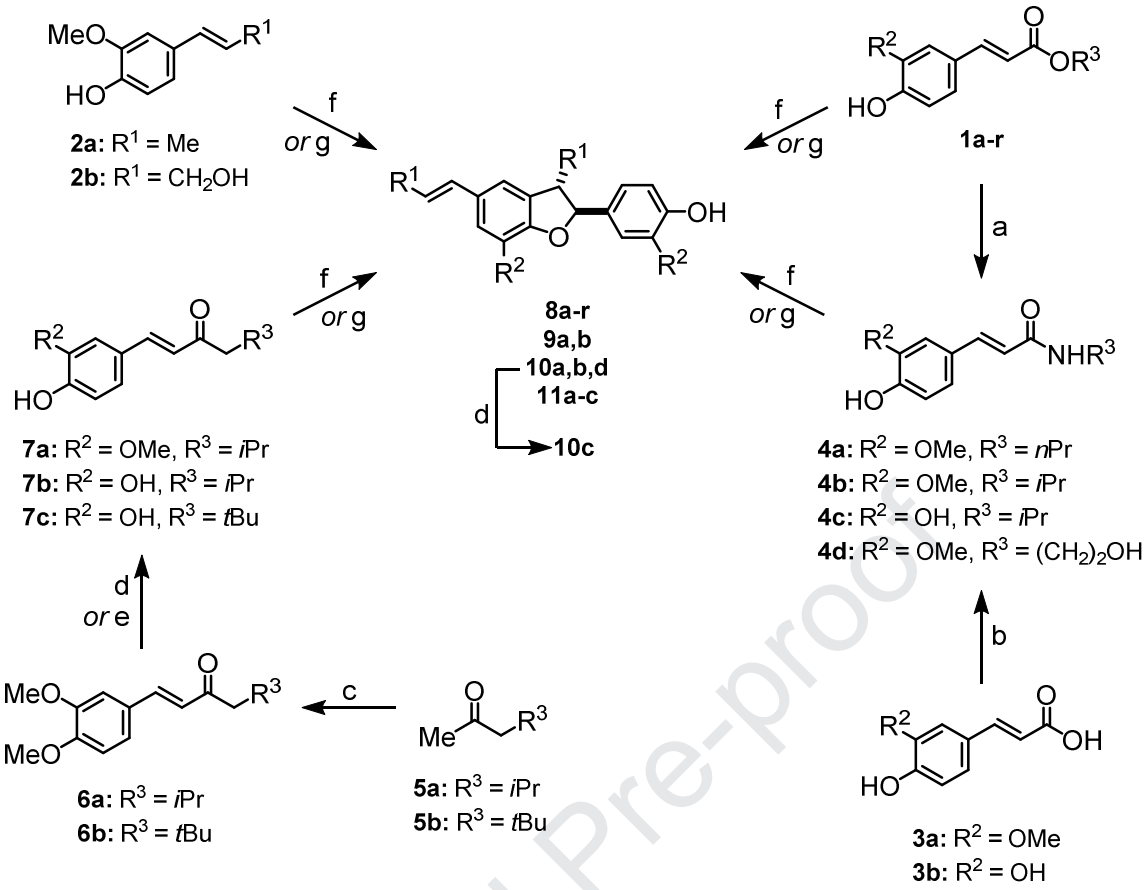


Fig. 1. General chemical structure of previously reported synthetic dihydrobenzofuran neolignans and key structural features for antileishmanial activity [11].

2. Results and Discussion

2.1. Chemistry

The preparation of the 2,3-dihydrobenzofurans has been reported using several synthetic strategies [12]. Two main approaches were chosen here for most of the products based on the previously reported findings and aiming furthermore at changes on C-3 and C-5 (Fig. 1), as shown in Schemes 1 and 2. Oxidative coupling of cinnamate ester analogues **1a-r** using Ag_2O [13–15] or H_2O_2/Horseradish peroxidase (HRP) [16,17] afforded compounds **8a-r** (Scheme 1). The same coupling using H_2O_2/HRP on the simple phenylpropenes **2a,b** led to **9a,b**. This dehydrodimerization reaction was further extended to amides **4a-d** and ketones **7a-c** to obtain the 2-phenyl-2,3-dihydrobenzofurans **10a-d** and **11a-c**, respectively. Amides **4a-c** were readily prepared from the corresponding cinnamic acid derivatives **3a,b** using BOP as coupling agent [18], while **4d** was obtained from **1f** by direct amidation with 2-aminoethanol [19]. Ketones **7a-c** were prepared by aldol condensation [20,21] between the aliphatic ketones **5a,b** and 3,4-dimethoxybenzaldehyde, with subsequent total [22] or partial demethylation [23]. The oxidative coupling follows a radical pathway [12,14,16,24–26], affording complex mixtures of products with different polymerization degrees. The purification of the 2-phenyl-2,3-dihydrobenzofurans was therefore typically challenging, resulting in overall low yields. On the other hand, the non-dimeric compounds **13a-l** were synthesized by Heck oxyarylation [27] between the corresponding diazonium salts prepared *in situ* from *o*-aminophenols **12a-c** and the phenylpropene analogues **2a-h** (Scheme 2). These alkene derivatives were mainly obtained by reduction of the corresponding ethyl esters **1b,s-u** with DIBAL-H [28]. The use of 3-phenylprop-2-en-1-ols (**2b,d-f,h**) as substrates for Heck oxyarylation is herein presented for the first time. In general, the reaction yields were comparable to those for simple phenylpropenes like **2a** (used for development of the general reaction [27] and its enantioselective version [29]), but formation of 4-phenyl-chroman-2-ols as side products was evidenced. The obtained 2-phenyl-2,3-dihydrobenzofurans **13a-l** were then further structurally modified by halogenation with the corresponding halosuccinimides to afford **14a-d,m**, bearing a halogen atom on C-5, and **15a-d,m-s** as products of substitution on the 2-phenyl ring (typically side products; Scheme 2). Compounds **14c,d** and **13k** were submitted to Heck reaction for introduction of a *tert*-butyl acrylate unit on C-5 affording **16c,d,k** (Scheme 2). Moreover, compounds **14b,c** gave **17b,c** by demethylation. The same demethylation procedure on **16c** was accompanied by hydrolysis of the ester to give **18** (Scheme 2).

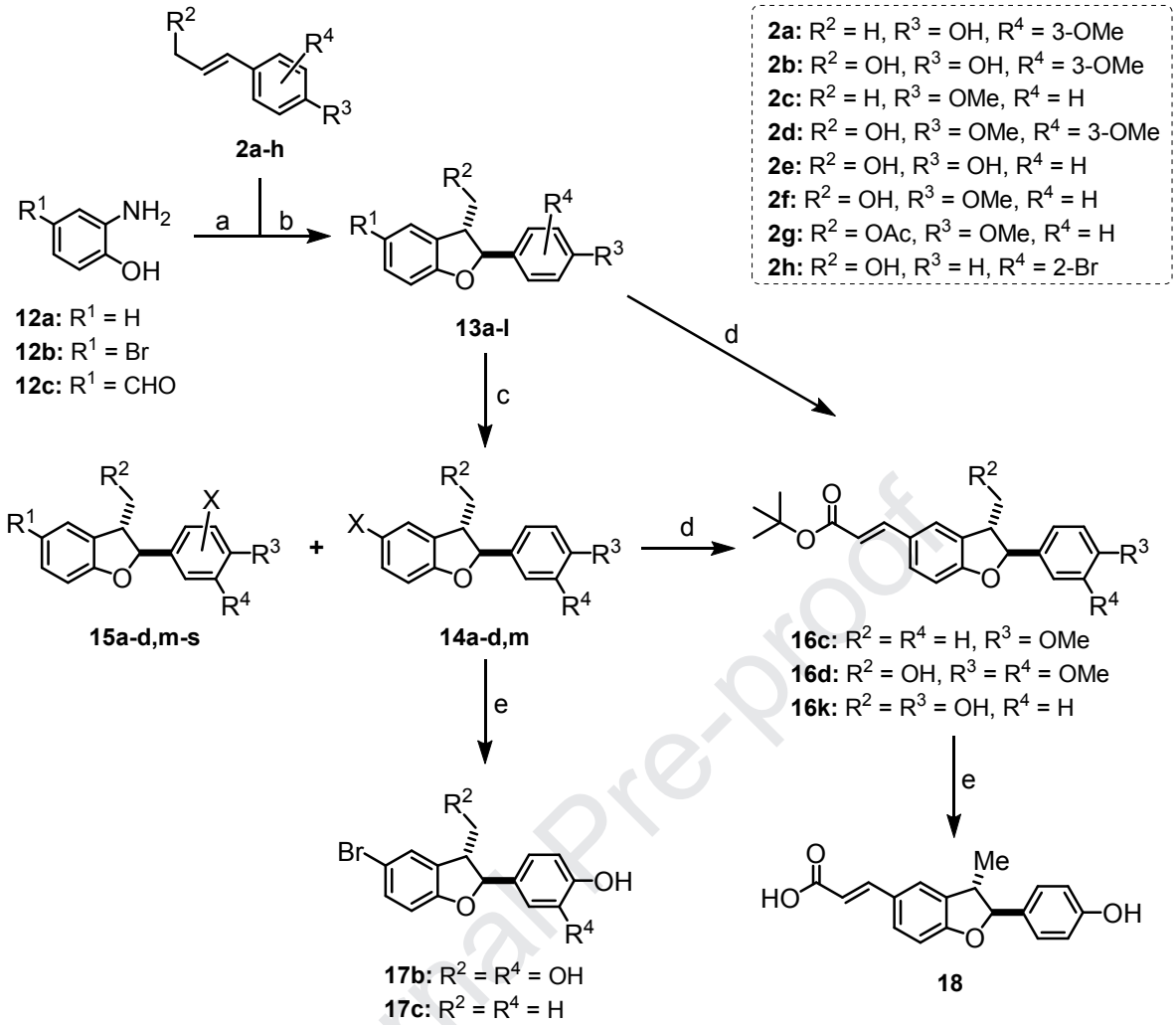


1a: R^2 = H, R^3 = Me	**1g:** R^2 = OMe, R^3 = Et	**1m:** R^2 = OH, R^3 = *i*Pr
1b: R^2 = H, R^3 = Et	**1h:** R^2 = OMe, R^3 = *i*Pr	**1n:** R^2 = OH, R^3 = *n*Bu
1c: R^2 = H, R^3 = *i*Pr	**1i:** R^2 = OMe, R^3 = *n*Bu	**1o:** R^2 = OH, R^3 = *t*Bu
1d: R^2 = H, R^3 = *n*Bu	**1j:** R^2 = OMe, R^3 = *t*Bu	**1p:** R^2 = OH, R^3 = $(CH_2)_7CH_3$
1e: R^2 = H, R^3 = *t*Bu	**1k:** R^2 = OH, R^3 = Me	**1q:** R^2 = OH, R^3 = $CHCH{=}CH_2$
1f: R^2 = OMe, R^3 = Me	**1l:** R^2 = OH, R^3 = Et	**1r:** R^2 = F, R^3 = *t*Bu

8a: $R^1 = CO_2Me$, R^2 = H	**8g:** $R^1 = CO_2Et$, R^2 = OMe	**8m:** $R^1 = CO_2iPr$, R^2 = OH
8b: $R^1 = CO_2Et$, R^2 = H	**8h:** $R^1 = CO_2iPr$, R^2 = OMe	**8n:** $R^1 = CO_2nBu$, R^2 = OH
8c: $R^1 = CO_2iPr$, R^2 = H	**8i:** $R^1 = CO_2nBu$, R^2 = OMe	**8o:** $R^1 = CO_2tBu$, R^2 = OH
8d: $R^1 = CO_2nBu$, R^2 = H	**8j:** $R^1 = CO_2tBu$, R^2 = OMe	**8p:** $R^1 = CO_2(CH_2)_7CH_3$, R^2 = OH
8e: $R^1 = CO_2tBu$, R^2 = H	**8k:** $R^1 = CO_2Me$, R^2 = OH	**8q:** $R^1 = CO_2CHCH{=}CH_2$, R^2 = OH
8f: $R^1 = CO_2Me$, R^2 = OMe	**8l:** $R^1 = CO_2Et$, R^2 = OH	**8r:** $R^1 = CO_2tBu$, R^2 = F

9a: R^1 = Me, R^2 = OMe	**10a:** $R^1 = CONHnPr$, R^2 = OMe
9b: $R^1 = CH_2OH$, R^2 = OMe	**10b:** $R^1 = CONHiPr$, R^2 = OMe
11a: $R^1 = COCH_2CH(CH_3)_2$, R^2 = OMe	**10c:** $R^1 = CONHiPr$, R^2 = OH
11b: $R^1 = COCH_2CH(CH_3)_2$, R^2 = OH	**10d:** $R^1 = CONH(CH_2)_2OH$, R^2 = OMe
11c: $R^1 = COCH_2C(CH_3)_3$, R^2 = OH	

Scheme 1. Synthesis of *trans*-2-phenyl-2,3-dihydrobenzofurans by oxidative coupling (dimeric products). Reagents and conditions: a) ethanolamine, Na_2CO_3, MeOH, 80 °C, 46 h; b) R^3NH_2, BOP, Et_3N, DCM, DMF, 0 °C, 3 h; c) 3,4-dimethoxybenzaldehyde, NaOH, EtOH, rt, 24 h; d) BBr_3, DCM, 0 °C, 2 h; e) $AlCl_3$, DCM, 0 °C to rt, 23 h; f) Ag_2O, toluene/acetone (2:1), rt, 28 h; g) HRP, H_2O_2, phosphate/citrate buffer (pH 3.1), MeOH, rt, 3 h.



2a: R^2 = H, R^3 = OH, R^4 = 3-OMe
2b: R^2 = OH, R^3 = OH, R^4 = 3-OMe
2c: R^2 = H, R^3 = OMe, R^4 = H
2d: R^2 = OH, R^3 = OMe, R^4 = 3-OMe
2e: R^2 = OH, R^3 = OH, R^4 = H
2f: R^2 = OH, R^3 = OMe, R^4 = H
2g: R^2 = OAc, R^3 = OMe, R^4 = H
2h: R^2 = OH, R^3 = H, R^4 = 2-Br

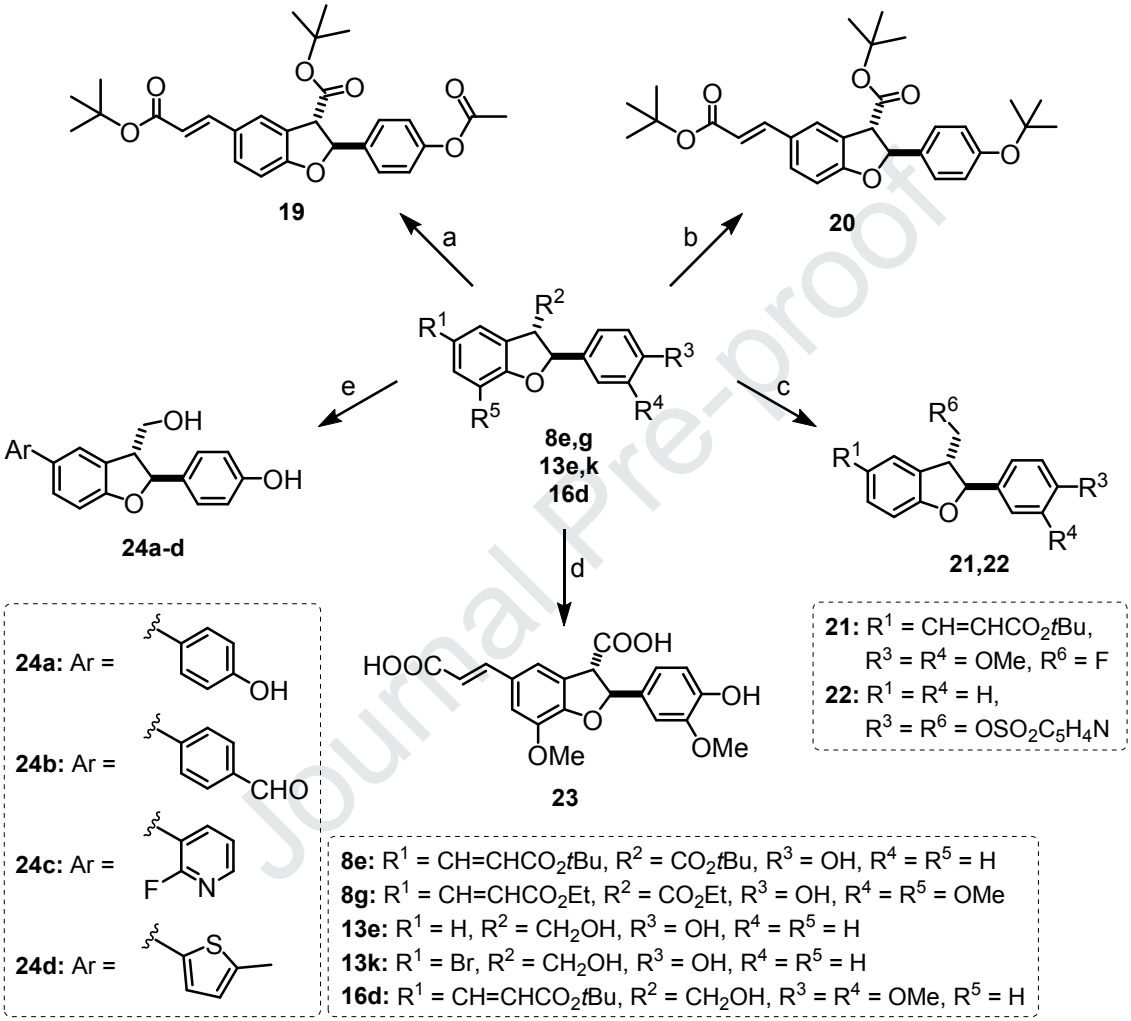
13a: R^1 = R^2 = H, R^3 = OH, R^4 = 3-OMe
13b: R^1 = H, R^2 = R^3 = OH, R^4 = 3-OMe
13c: R^1 = R^2 = R^4 = H, R^3 = OMe
13d: R^1 = H, R^2 = OH, R^3 = OMe, R^4 = 3-OMe
13e: R^1 = R^4 = H, R^2 = R^3 = OH
13f: R^1 = R^4 = H, R^2 = OH, R^3 = OMe
13g: R^1 = R^4 = H, R^2 = OAc, R^3 = OMe
13h: R^1 = R^3 = H, R^2 = OH, R^4 = 2-Br
13i: R^1 = CHO, R^2 = R^4 = H, R^3 = OMe
13j: R^1 = CH=CHCOMe, R^2 = R^4 = H, R^3 = OMe
13k: R^1 = Br, R^2 = R^3 = OH, R^4 = H
13l: R^1 = Br, R^2 = OAc, R^3 = OH, R^4 = H

14a: X = Br, R^2 = H, R^3 = OH, R^4 = OMe
14b: X = Br, R^2 = R^3 = OH, R^4 = OMe
14c: X = Br, R^2 = R^4 = H, R^3 = OMe
14d: X = Br, R^2 = OH, R^3 = R^4 = OMe
14m: X = Cl, R^2 = H, R^3 = OH, R^4 = OMe

15a: R^1 = Br, R^2 = H, R^3 = OH, R^4 = OMe, X = 2-Br
15b: R^1 = Br, R^2 = R^3 = OH, R^4 = OMe, X = 2-Br
15c: R^1 = Br, R^2 = R^4 = H, R^3 = OMe, X = 3-Br
15d: R^1 = Br, R^2 = OH, R^3 = R^4 = OMe, X = 2-Br
15m: R^1 = Cl, R^2 = H, R^3 = OH, R^4 = OMe, X = 3-Cl
15n: R^1 = Br, R^2 = R^3 = OH, R^4 = H, X = 3-Br
15o: R^1 = Br, R^2 = H, R^3 = OH, R^4 = OMe, X = 3-Br
15p: R^1 = Br, R^2 = R^3 = OH, R^4 = OMe, X = 3-Br
15q: R^1 = H, R^2 = R^3 = OH, R^4 = Br, X = 5-Br
15r: R^1 = H, R^2 = R^3 = OH, R^4 = H, X = 3-Br
15s: R^1 = R^2 = H, R^3 = OH, R^4 = OMe, X = 3-I

Scheme 2. Synthesis of *trans*-2-phenyl-2,3-dihydrobenzofurans by Heck oxyarylation (non-dimeric products) and derivatization. Reagents and conditions: a) $NOPF_6$, ACN, rt, 2 h; b) $Pd_2(dba)_3$, $ZnCO_3$, rt, 20 h; c) *N*-halosuccinimide, ACN, rt, overnight; d) $PdCl_2$, PPh_3 or P(*o*-tol)$_3$, *tert*-butyl acrylate, K_2CO_3, DMF, 100 °C, 24 h; e) BBr_3, DCM, 0 °C, 2 h.

Further derivatization attempts were carried out as depicted in Scheme 3. Acetylation and *tert*-butyl ether formation were successfully accomplished on **8e**, affording **19** and **20**, respectively. Deoxyfluorination [30] attempts were mainly unsuccessful, leading only to traces of **21** (from **16d**) and the undesired intermediate **22** (from **13e**). Hydrolysis of **8g** produced **23**. In addition, compounds **24a-d** were obtained from **13k** by Suzuki reaction.



Scheme 3. Further derivatization of *trans*-2-phenyl-2,3-dihydrobenzofurans. Reagents and conditions: a) Ac_2O, $NaHCO_3$, toluene, rt, 24 h; b) $Sc(OTf)_3$, Boc_2O, DCM, rt, 48 h; c) PyFluor, DBU, toluene, rt or 0 °C, 6-24 h; d) NaOH, EtOH, rt, overnight; e) $PdCl_2$, PPh_3, $ArB(OH)_2$, H_2O/toluene/DMF (1:4:2), 100 °C, 24 h.

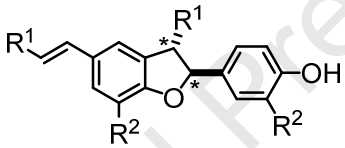
All the isolated products from the reactions shown in Schemes 1-3 were effectively characterized as *trans*-configured compounds using NMR spectroscopy. Although it is well known that the coupling constant between 2-H and 3-H is not sufficient to distinguish *trans*- from *cis*-dihydrobenzofurans [31], the chemical shifts of the carbon and hydrogen atoms in 2-position and those from the substituent on 3-position (e.g. methyl/hydroxymethyl in non-dimeric compounds **13a-l** and alkoxy groups in dimeric compounds **8a-r**) have demonstrated significant differences among isomers [31–35] and were therefore used here as a viable means of identification. The relative configuration

assignment agreed with the typically observed and reported diastereoselectivity for both synthetic pathways (i.e. oxidative coupling and Heck oxyarylation) [12,14,16,17,27,29,36–39]. However, the employed reactions do not offer any enantioselectivity and thus, all synthesized compounds were obtained as racemates.

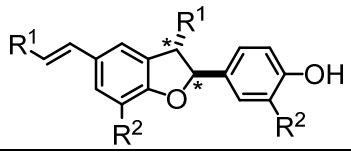
2.2. Biological activity and structure-activity relationships

All compounds obtained as described in the previous section were evaluated for their antileishmanial potential against axenically grown amastigotes of *L. donovani* and toxicity against rat skeletal myoblasts (L-6 cell line). The results are shown in Table 1 and 2. The corresponding confidence intervals for the activity values are compiled in the Supporting Information. Overall, 34% of the compounds demonstrated to be active against the parasite with IC_{50} values below 10 µmol/L. Moreover, around half of those active compounds were found to be selective against the parasite as compared to mammalian cells (selectivity index, SI > 5).

Table 1. Antileishmanial and cytotoxic activity of dimeric compounds (all compounds tested as racemic mixtures unless stated otherwise).



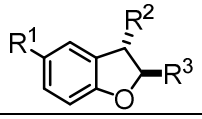
Compound	R^1	R^2	IC_{50} (µmol/L)		SI
			Ld	L-6	
8a	$COOCH_3$	H	7.84	23.2	3.0
8b	$COOCH_2CH_3$	H	7.45	26.3	3.5
8c	$COOCH(CH_3)_2$	H	4.21	14.3	3.4
8d	$COO(CH_2)_3CH_3$	H	10.8	14.3	1.3
8e	$COOC(CH_3)_3$	H	6.07	13.3	2.2
8f	$COOCH_3$	OCH_3	10.6	2.43	0.2
8g	$COOCH_2CH_3$	OCH_3	9.10	4.42	0.5
8h	$COOCH(CH_3)_2$	OCH_3	3.95	10.3	2.6
8i	$COO(CH_2)_3CH_3$	OCH_3	3.11	8.18	2.6
8j	$COOC(CH_3)_3$	OCH_3	2.10	11.4	5.4
8k	$COOCH_3$	OH	12.6	0.37	0.03
8l	$COOCH_2CH_3$	OH	3.87	9.99	2.6
8m	$COOCH(CH_3)_2$	OH	0.54	10.2	18.9
(2*R*,3*R*)-**8m**†	$COOCH(CH_3)_2$	OH	0.65	10.6	16.4
(2*S*,3*S*)-**8m**†	$COOCH(CH_3)_2$	OH	0.53	10.2	19.3
8n	$COO(CH_2)_3CH_3$	OH	1.66	9.34	5.6
8o	$COOC(CH_3)_3$	OH	1.66	9.05	5.5
8p	$COO(CH_2)_7CH_3$	OH	23.5	19.1	0.8
8q	$CH_2CH{=}CH_2$	OH	6.32	6.41	1.0
8r	$COOC(CH_3)_3$	F	1.97	9.22	4.7
9a	CH_3	OCH_3	6.45	6.21	1.0

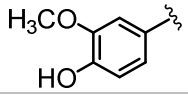
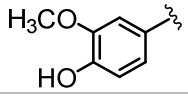
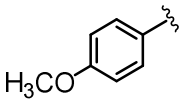
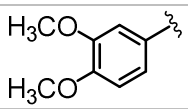
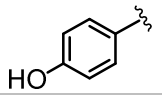
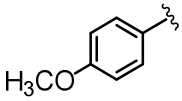


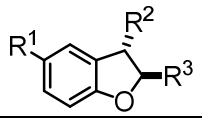
Compound	R^1	R^2	IC_{50} (µmol/L)		SI
			Ld	L-6	
9b	CH_2OH	OCH_3	160	74.2	0.5
10a	$CONH(CH_2)_2CH_3$	OCH_3	8.88	73.8	8.3
10b	$CONHCH(CH_3)_2$	OCH_3	53.6	77.2	1.4
10c	$CONHCH(CH_3)_2$	OH	82.3	55.5	0.7
10d	$CONH(CH_2)_2OH$	OCH_3	212	212	1.0
11a	$COCH_2CH(CH_3)_2$	OCH_3	3.81	5.29	1.4
11b	$COCH_2CH(CH_3)_2$	OH	4.42	5.00	1.1
11c	$COCH_2C(CH_3)_3$	OH	3.42	2.45	0.7
23	COOH	OCH_3	6.89	259	37.6
Miltefosine			0.77		
Podophyllotoxin				0.017	

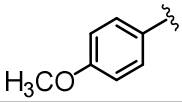
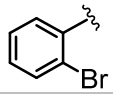
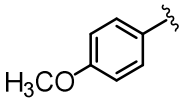
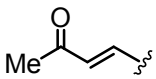
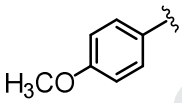
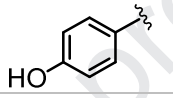
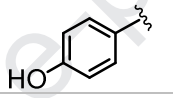
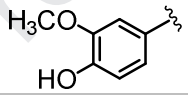
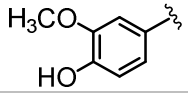
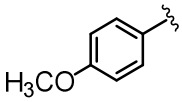
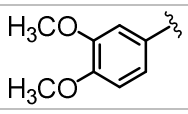
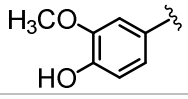
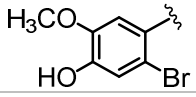
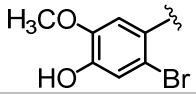
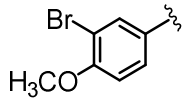
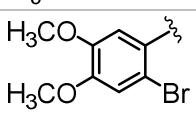
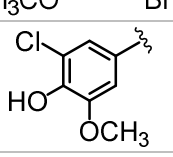
† Data from a separate determination scaled by the relative IC_{50} value of the positive control, miltefosine. Absolute values for miltefosine and the tested compounds in this experiment were higher by factor 6.6.

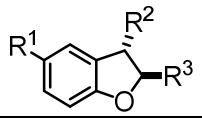
Table 2. Antileishmanial and cytotoxic activity of non-dimeric compounds (all compounds tested as racemic mixtures).

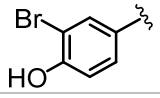
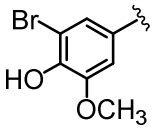
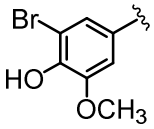
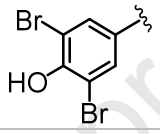
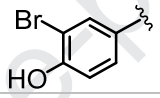
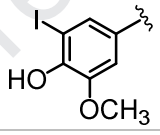
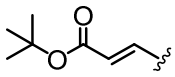
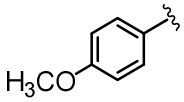
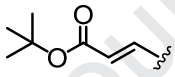
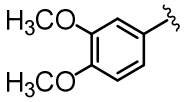
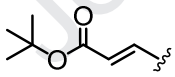
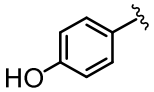
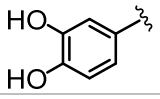
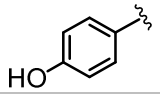
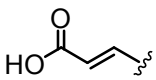
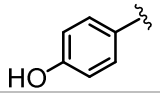
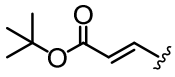
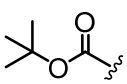
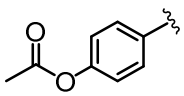
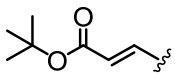
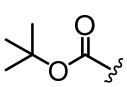
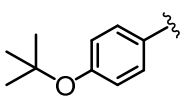
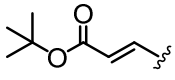
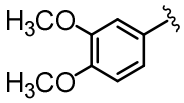


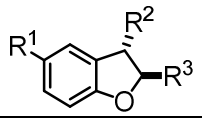
Compound	R^1	R^2	R^3	IC_{50} (µmol/L)		SI
				Ld	L-6	
13a	H	CH_3		59.0	84.4	1.4
13b	H	CH_2OH		185	58.0	0.3
13c	H	CH_3		99.9	154	1.6
13d	H	CH_2OH		136	53.7	0.4
13e	H	CH_2OH		158	217	1.4
13f	H	CH_2OH		70.3	43.6	0.6

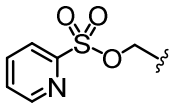
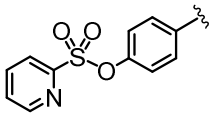
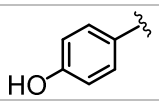
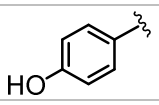
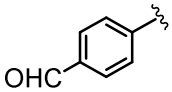
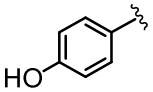
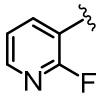
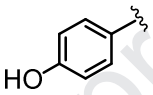
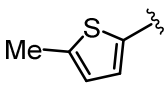
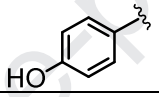


Compound	R^1	R^2	R^3	IC_{50} (μmol/L)		SI
				Ld	L-6	
13g	H	CH_2OAc		58.4	43.9	0.8
13h	H	CH_2OH		21.7	25.4	1.2
13i	CHO	CH_3		30.5	43.8	1.4
13j		CH_3		17.4	9.35	0.5
13k	Br	CH_2OH		18.8	22.0	1.2
13l	Br	CH_2OAc		13.7	55.5	4.0
14a	Br	CH_3		24.8	13.1	0.5
14b	Br	CH_2OH		30.5	32.3	1.1
14c	Br	CH_3		31.8	60.3	1.9
14d	Br	CH_2OH		33.8	21.2	0.6
14m	Cl	CH_3		16.1	55.4	3.4
15a	Br	CH_3		15.0	18.2	1.2
15b	Br	CH_2OH		10.7	40.6	3.8
15c	Br	CH_3		29.7	39.7	1.3
15d	Br	CH_2OH		11.4	21.0	1.8
15m	Cl	CH_3		13.4	64.2	4.8



Compound	R^1	R^2	R^3	IC_{50} (μmol/L)		SI
				Ld	L-6	
15n	Br	CH_2OH		21.8	64.8	3.0
15o	Br	CH_3		17.2	44.8	2.6
15p	Br	CH_2OH		12.1	45.4	3.8
15q	H	CH_2OH		10.1	109	10.8
15r	H	CH_2OH		43.8	115	2.6
15s	H	CH_3		13.4	46.9	3.5
16c		CH_3		4.01	40.1	10.0
16d		CH_2OH		10.7	22.9	2.1
16k		CH_2OH		17.1	33.8	2.0
17b	Br	CH_2OH		17.8	3.93	0.2
17c	Br	CH_3		32.5	56.6	1.7
18		CH_3		5.64	73.9	13.1
19				2.06	11.8	5.7
20				13.1	202	15.5
21		CH_2F		13.0	34.0	2.6



Compound	R^1	R^2	R^3	IC_{50} (µmol/L)		SI
				Ld	L-6	
22	H			6.31	189	29.9
24a		CH_2OH		16.5	44.5	2.7
24b		CH_2OH		37.7	55.9	1.5
24c		CH_2OH		18.8	52.4	2.8
24d		CH_2OH		16.1	15.8	1.0
Miltefosine				0.77		
Podophyllotoxin					0.017	

Structure-activity relationships (SARs) were separately analyzed for the dimeric (Table 1) and the non-dimeric (Table 2) compounds as disclosed below. Within the former group (Table 1), the antileishmanial activity showed dependence on the lateral chain of the esters **8a-p**. Thus, larger and bulkier lateral chains typically led to higher activities, isopropyl and *tert*-butyl being those conferring better leishmanicidal potential (compounds **8c,j,m-o**). Further increase of length of the alkyl chain (**8p**), however, led to marked loss of activity accompanied by toxicity (SI < 1). Unsaturation on the lateral chain seemed not to benefit the activity (**8q**). Hydroxy groups on the aromatic rings (R^2 = OH, Table 1; **8k-o**) provided significantly better activity values than both the corresponding methoxy derivatives (**8f-j**) and the non-substituted compounds (**8a-e**). Despite compound **8m** showed the best activity among the whole set of products, **8n** and **8o** displayed comparable values. Their SIs were lower than that of **8m**, though. Replacement of OH by F (**8o** vs **8r**) led to similar antileishmanial and cytotoxic activities. Surprisingly, the amide analogues **10b-d** were inactive against the parasite. Only **10a** exhibited some activity, indicating that the general trends observed for the esters are no longer valid for the amides (e.g. OH did not improve the activity; **10b** vs **10c**). Although the presence of OH groups for the ketone **11b** seemed not appear to play a role as important as for the esters (when compared to **11a** bearing OMe groups instead), all the ketones (**11a-c**) were actually active against *L. donovani*. Unfortunately, those compounds showed higher toxicity against the mammalian cells than the corresponding esters (**8h,m,o**), which resulted in significantly lower SIs. On the other hand, the carboxylic acid **23** displayed antileishmanial activity lower than the most active esters and ketones. Yet its almost inexistent toxicity against the L-6 cells rendered it the most selective compound within this group. Compound **9b**, the alcohol corresponding to the carboxylic acid **23**, was totally inactive. Additionally, the less polar **9a**, bearing a methyl group instead of the hydroxymethyl group of **9b**, was as active as the acid **23**. However, the replacement of COOH by CH_3 was not useful in terms of cytotoxicity, **9a** being quite toxic and non-selective.

In general, most of the non-dimeric 2-phenyl-2,3-dihydrobenzofurans were significantly less active than the dimers as clearly observed in Table 2. Substitution on C-5 was found to be essential for the leishmanicidal potential as inferred from the lack of activity in all the compounds without any substitution on this position (**13a-g**). Although introduction of Br on C-5 (**13k,l** and **14a-d**) led to improved antileishmanial activity (three- to four-fold more active than unsubstituted congeners), the IC_{50} values for those compounds were still too high to be considered interesting candidates (only three of them have IC_{50} < 20 μmol/L). For these brominated compounds, changes from methyl to hydroxymethyl on C-3 did not lead to any significant difference. Acetylation of the hydroxymethyl moiety of **13k** did not lead to higher activity (**13l**) but improved selectivity. Moreover, only 4-hydroxyphenyl groups on C-2 seemed to confer better activity (**13k,l**). However, this was not a defined rule, as **17c** was not more active than its respective congeners **14a,c**. Interestingly, the presence of a second OH group on the pending phenyl ring (3,4-dihydroxyphenyl) did not increase the activity in this series (**17b** vs **13k**) as would be expected by comparison with the dimeric products, where catechol units led to improved activity (**8l-o**). Use of Cl instead of Br (**14m** vs **14a**) provided not only slightly better potency but also a marked reduction in cytotoxicity (increasing the SI 6.5 times). Introduction of another halogen atom on the 2-phenyl ring afforded products with variable antileishmanial potential (**15a-d,m-s**). While the second halogen caused only slight changes in activity for compounds with methyl groups on C-3 (**15a,c,m,o** vs **14a,c,m,a**, respectively), this modification typically improved the activity by a factor of about 2 for those substances bearing a hydroxymethyl moiety on C-3 (with exception of **15n**; **15b,d,p** vs **14b,d,b**, respectively). Regardless of the group on C-3, a clear improvement in selectivity was observed in most of dihalogenated cases. A marked increase in antileishmanial activity was also found for compounds with halogen substituents only on the 2-phenyl ring (**15q-s**). This was accompanied by a rise of selectivity, as highlighted by the significant SI of **15q**. This compound was not as active as many of the dimeric ones in Table 1 but its selectivity was far better than that of most dimers.

No difference in activity was observed when Br (**14c**) was replaced by CHO (**13i**; Table 2), whereas the presence of an α,β-unsaturated carbonyl moiety (**13j**) enhanced the activity. A similar effect was generally observed when an acrylate unit was introduced on C-5. Thus, compound **16c** was eight times more active than the corresponding brominated analogue **14c**, making it part of the group of most active compounds. The acrylate moiety in **16c** also rendered it 5.2-fold more selective than **14c**. A similar improvement of activity and selectivity was also observed with **16d** in comparison with **14d**, although at lesser extent. Surprisingly, introduction of the acrylate moiety on **13k** showed little effect on either activity or selectivity (**16k**). Direct comparison of **16k** (Table 2) with **8e** (Table 1) would indicate that the presence of a *tert*-butylcarboxylate on C-3 might be important for the activity. Nevertheless, only an insignificant difference in selectivity was observed between these two compounds. It should be noted that **16k** did not follow the trend described above for **16c,d** so that a clear conclusion cannot be drawn. Regarding changes on C-3, replacement of OH by F from **16d** to **21** did not improve the activity (Table 2). Presence of a free acrylic acid moiety instead of Br led to a 5.8-fold increase of activity and a more than seven-fold improvement of selectivity (**18** vs **17c**; SI = 1.74 and 13.10, respectively). Insertion of a third aromatic ring on C-5 (**24a-d**) instead of the acrylate moiety (**16k**) did not lead to an improvement but rather a decrease of the leishmanicidal potential. However, **24a,c** were less cytotoxic than **16k** and **13k**. The undesired product **22**, obtained after an unsuccessful deoxyfluorination attempt, was found to be the only compound without substitution on C-5 with an IC_{50} value below 10 μmol/L, which also showed one of the best SI values among the analyzed compounds.

Additional interesting findings were obtained from blocking the phenol group on **8e** (Table 1). Etherification with a *tert*-butyl group led to **20** (Table 2), which was only half as potent but seven

times more selective than **8e**. In contrast, acetylation of **8e** gave the three-fold more potent **19**, the most potent within the series of non-dimeric compounds, whose selectivity was also improved.

*2.3. Effect of chirality on the bioactivity of **8m***

The compound with the highest antileishmanial potency also showing promising selectivity, **8m**, was investigated in more detail. As mentioned above, all compounds of this study were synthesized in racemic form, so that it was of special interest to investigate whether the two enantiomers of **8m** would differ in activity. To study the effect of chirality at C-2 and C-3 on the biological activity, **8m** was subjected to preparative chiral HPLC separation (Fig. 2A). Measurement of the electronic circular dichroism (ECD) spectra for both pure enantiomers (2*R,3R*)-**8m** and (2*S,3S*)-**8m**, and subsequent comparison with the corresponding calculated spectra obtained by time-dependent density functional theory (TDDFT) computation (Fig. 2B) allowed to establish their absolute configuration. Thus, the first eluted enantiomer was defined as (2*R*,3*R*)-**8m**. Conversely, the second eluted enantiomer corresponded to (2*S*,3*S*)-**8m**. These results were in agreement with previously reported CD assignments [10,15]. Moreover, all the conformers for (2*R*,3*R*)-**8m** optimized at DFT level effectively showed *M* helicity (Fig. 2C), following the empirical rule proposed by Antus et al. [40], which is connected to a negative Cotton effect for the $^{1}L_{b}$ band (appearing over 280 nm).

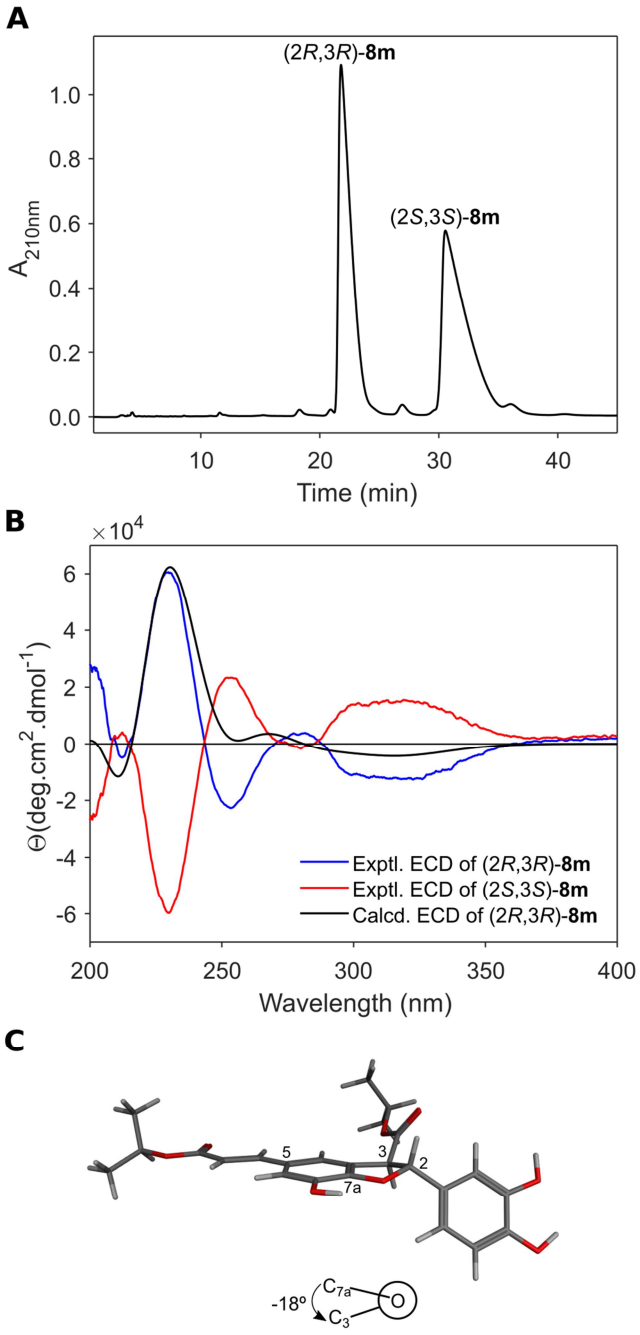


Fig. 2. Chiral HPLC profile for **8m** (A), calculated ECD spectra for (2*R*,3*R*)-**8m** and experimental ECD for both (2*R,3R*)-**8m** and (2*S,3S*)-**8m** (B), and lowest energy conformer for (2*R*,3*R*)-**8m** showing *M* helicity (C). The racemic mixture was separated on a Chiralpak IA column (5 µm, 250 mm × 20 mm) eluted at a flow rate of 10 mL/min with isohexane-EtOH (9:1). TDDFT calculated ECD spectrum for the weighted ensemble of five conformers at B3LYP/6-31G(d,p) level of theory.

Both pure enantiomers were tested for antileishmanial and cytotoxic activity as shown in Table 1. Although the antileishmanial activity of (2*R*,3*R*)-**8m** seems slightly lower than that for its enantiomer, statistically significant differences were not observed as indicated by ANOVA (p = 0.569 from triplicates). This result might be seen as an advantage, offering then the possibility of avoiding chiral separations or enantioselective synthetic routes.

263

264 *2.4. In vitro metabolism of **8m** in mouse liver microsomes*

265 The usefulness of liver microsomes for *in vitro* studies of metabolic stability of potential drugs has
266 been demonstrated [41]. Therefore, the metabolism of the most active neolignan analogue, **8m**, was
267 studied using a method previously described and optimized [42]. After 90 min of incubation of
268 compound **8m** (25 µmol/L) with mouse liver microsomes at 37 °C, quantification of the amount of
269 residual parent compound was conducted by LC-MS. Only 41.8% (±1.1%) of **8m** remained unchanged
270 after treatment under phase I conditions. Combination of phase I + II conditions led to 31.4% (±0.2%)
271 of residual **8m**. These results indicated that **8m** is easily transformed when incubated with the
272 microsomes, which represents an important limitation for further development as leishmanicidal
273 agent.

274 Extensive analysis of the LC-MS profiles using higher concentration of **8m** (100 µmol/L) revealed that
275 its high *in vitro* metabolization rate was mainly due to hydrolysis of one ester group (early hydrolysis
276 under phase I conditions) and glucuronidation (under phase II). Thus, the major metabolites detected
277 were the glucuronidated **8m-A**, and the two partially hydrolyzed **8m-B** and **8m-C** (Fig. 3). The exact
278 position of the glucuronic acid unit in **8m-A** as well for the residual isopropyl group in **8m-B** and **8m-C**
279 were not determined so the structures are shown only for illustrative purposes. Additionally, the
280 minor metabolite **8m-D** was also found. It could come from hydrolysis of **8m-A** or glucuronidation of
281 **8m-B** or **8m-C**.

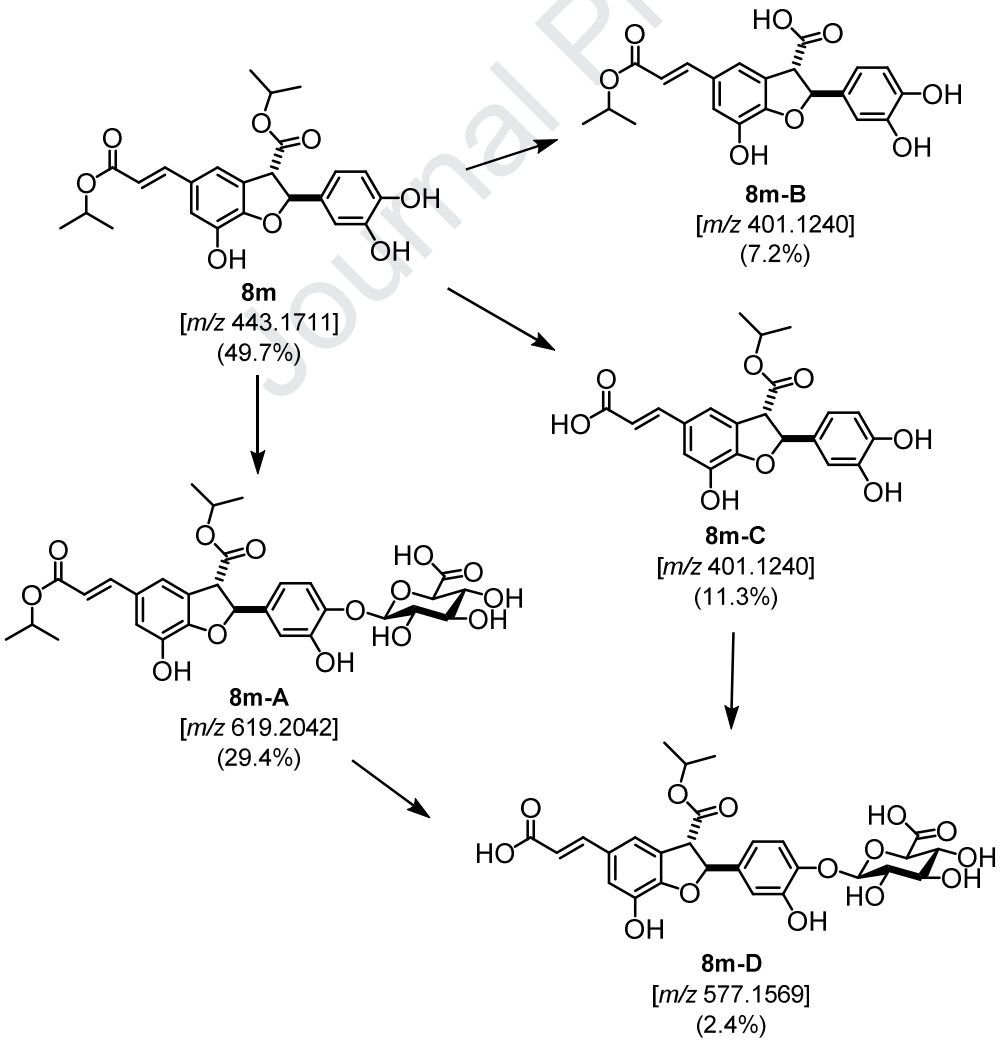


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Fig. 3. Proposed metabolism pathway for **8m** under *in vitro* conditions using mouse liver microsomes. Numbers in parenthesis represent the relative percentage of each metabolite in the profile.

2.5. Efficiency metrics and in silico ADME

The low metabolic stability of **8m** suggested that it might be useful to assess the potential of the more selective compounds from our set of synthesized 2-phenyl-2,3-dihydrobenzofurans as possible candidates for further development using theoretical predictions of their ADME properties with established computational methods. To this end, topological descriptors related to ADME properties were calculated for the more selective compounds of our series (SI ≥ 3; Table 3). Two calculated water/octanol distribution coefficient (cLogP) values were independently obtained and included (one representing the consensus calculation of five different methods employed by the SwissADME webtool [43] and another calculated by the Molecular Software Environment, MOE [44]). Furthermore, calculated ligand efficiency metrics are known to be useful in drug discovery pipelines [45–48]. Therefore, the ligand efficiency (LE), lipophilic efficiency (LipE), binding efficiency index (BEI), and surface efficiency index (SEI) were also calculated using the number of Hydrogen bond acceptors (HBA), cLogP, molecular weight (MW), and the topological polar surface area (TPSA), respectively [46,48]. The latter was also obtained from MOE. The results obtained for these theoretical descriptors are shown together with the activity and selectivity data in Table 3. As can be seen, the most selective compounds covered a narrow activity range compared to the whole range of activity found (Table 1 and 2). The table entries are traffic light color-coded using different thresholds, with green representing a suitable property, yellow for acceptable values, and red in cases where the value is unfavorable for drug development. In case of MW, HBA, Hydrogen bond donors (HBD), and cLogP, compliance with the rule of five (Ro5; compliance: green) [49] and the rule of three (Ro3; compliance: yellow) [50] were used to delimit them. The thresholds for the ligand efficiency metrics were arbitrarily defined taking into account that representative values for such metrics are typically calculated rather using pK_i (for target-specific drugs). SI and activity values were also ranked using arbitrarily selected cutoffs. The use of these metrics and ranges were considered to give an easy overview to the compounds' characteristics, and to represent a tool to rank interesting candidates beyond a purely potency-based criterion. From the selected group of compounds, only four (**8r**, **19**, **20**, and **22**) violated the Ro5. Those compounds exceeded the threshold for cLogP (> 5 in both cases for **8r** and **20** and in one case for **19** and **22**). In case of **22**, it has also a MW exceeding the Ro5 threshold.

Table 3. Ligand efficiency metrics and *in silico* ADME-related properties for selected compounds.

Compound	IC_{50} *Ld* (µmol/L)	SI	MW (Da)	HBA	HBD	cLogP 1[a]	cLogP 2[b]	LE[c]	BEI[d]	SEI[e]	LipE 1[f]	LipE 2[g]	Score[h]
8b	7.45	3.5	382.412	6	1	3.41	3.75	0.25	13.4	6.2	1.72	1.38	9
8c	4.21	3.4	410.466	6	1	4.01	4.27	0.25	13.1	6.6	1.37	1.11	10
8j	2.10	5.4	498.572	8	1	4.53	4.69	0.22	11.4	5.6	1.15	0.99	11
8m	0.54	18.9	442.464	8	3	3.28	3.32	0.27	14.2	5.1	2.99	2.94	16
8n	1.66	5.6	470.518	8	3	3.88	4.36	0.23	12.3	4.7	1.90	1.42	9
8o	1.66	5.5	470.518	8	3	3.77	3.85	0.23	12.3	4.7	2.01	1.93	11
8r	1.97	4.7	474.500	8	1	5.14	5.13	0.23	12.0	7.0	0.57	0.57	6
10a	8.88	8.3	468.550	6	3	3.33	3.58	0.20	10.8	4.8	1.72	1.47	8
13l	13.7	4.0	363.207	4	1	3.34	3.52	0.30	13.4	8.7	1.52	1.34	8
14m	16.1	3.4	290.746	3	1	3.60	3.45	0.33	16.5	12.4	1.19	1.34	11
15b	10.7	3.8	430.092	4	2	3.56	3.90	0.31	11.6	8.4	1.41	1.07	8
15m	13.4	4.8	325.191	3	1	4.11	4.18	0.32	15.0	12.6	0.76	0.69	11
15p	12.1	3.8	430.092	4	2	3.47	3.92	0.31	11.4	8.3	1.45	1.00	8
15q	10.1	10.8	400.066	3	2	3.48	4.04	0.34	12.5	10.0	1.51	0.95	11
15s	13.4	3.5	382.197	3	1	3.72	3.90	0.33	12.8	12.6	1.15	0.97	10
16c	4.01	10.0	366.457	4	0	4.59	4.67	0.27	14.7	12.1	0.81	0.73	13
18	5.64	13.1	296.322	4	2	2.92	3.00	0.33	17.7	7.9	2.33	2.24	19
19	2.06	5.7	480.557	7	0	4.84	5.45	0.22	11.8	6.5	0.85	0.24	9
20	13.1	15.5	494.628	6	0	5.72	5.95	0.19	9.9	6.9	-0.84	-1.07	0
22	6.31	29.9	524.574	9	0	3.43	5.37	0.20	9.9	4.3	1.77	-0.17	2
23	6.89	37.6	386.356	8	3	1.97	2.13	0.25	13.4	4.2	3.19	3.03	15

[a] Consensus from SwissADME; [b] from MOE; [c] $LE \approx 1.37\ pIC_{50}/HA$; [d] $BEI = pIC_{50}/MW$; [e] $SEI = \frac{pIC_{50}}{PSA/100Å^2}$; [f] $LipE = pIC_{50} - cLogP\ 1$; [g] $LipE = pIC_{50} - cLogP\ 2$;

[h] green = +2 points, yellow = +1 point, red = - 2 points

Aiming at a simple ranking of the compounds based on the properties presented in Table 3 and considering the "desirability" criteria published by Bickerton [51] as fundamental guide, the qualitative analysis represented by the color code in Table 3 was employed to afford a quality score. It was arbitrarily defined assigning two points for each parameter in green, one point for each parameter in yellow and penalizing with two points any parameter in red. The quality score of each compound is presented in the rightmost column of Table 3. High scores indicate low incidence of parameters within the unfavorable red-colored range and prevalence of good or acceptable parameters (green and yellow, respectively), which would represent an overall estimate of better candidates. A look at the score for the selected compounds makes clear the extremely poor quality of **20** and **22** as possible candidates for further development. Many of the other compounds were ranked in an intermediate range. However, four compounds (**8m**, **16c**, **18**, and **23**) were indicated to be the best candidates through this estimation of quality. These compounds were structurally rather dissimilar so that, besides **8m** (with the limitations mentioned above), **16c**, **18** and **23** would appear interesting candidates for further optimization despite their somewhat lower activity. Based on its highest score value in this assessment, **18** could be considered as the best candidate. Due to its low MW and cLogP (fulfilling the Ro3), structural optimization of **18** appears more than feasible. The four mentioned compounds were moreover predicted to be able to pass the gastrointestinal barrier according to the brain or intestinal estimated permeation method implemented in the SwissADME [43]. However, **18** was anticipated by the SwissADME calculations to inhibit two out of five major CYP isoenzymes, CYP1A2 and CYP2C9. Thus, attempts to optimize this compound should not only pursue an increase of antileishmanial potency but also strive to avoid this interaction. In this regard, **23**, even though somewhat less active and presenting a lower score in the above-mentioned investigation, might be similarly suitable for optimization since it was not predicted to inhibit any of the CYP enzymes included in the calculations.

3. Conclusion

In the present research, a medium size set of structurally diverse *trans*-2-phenyl-2,3-dihydrobenzofurans was successfully prepared and evaluated against *L. donovani*. The reasonably high activity (IC_{50} < 10 µmol/L) of more than 30% of the analyzed compounds demonstrated their potential as leishmanicidal agents. Furthermore, the wide range of activity values observed indicates that the desired biological activity strongly depends on the molecular structure. Qualitative SAR analysis, even though rather complex, confirmed the previously reported importance of the lateral chain for the antileishmanial activity of dehydrodimers bearing ester functionalities. Structurally related ketones, synthesized to avoid possible instability due to ester hydrolysis, were less active and more toxic than the corresponding esters, while amide analogues resulted to be inactive. In general, dehydrodimers were significantly more active than the corresponding non-dimeric congeners, highlighting the fundamental role of acrylate moieties on C-5 for the antileishmanial activity. Double halogenation on non-dimeric compounds usually increased activity and selectivity. It was also found that the presence of catechol moieties represented an activity-improving unit in case of dehydrodimers. Biological testing of both enantiomers of **8m** revealed no effect of chirality on activity. The limited metabolic stability of **8m** (evaluated *in vitro* with the racemate) represents an impediment for further development. However, a ranking of the more selective compounds (SI > 3) using a simple quality approach based on *in silico* determined properties, such as compliance with Ro5 and Ro3, as well as activity, selectivity and ligand efficiency metrics, pointed towards compounds **16c**, **18** and **23** as interesting candidates for future attempts at structural optimization.

4. Experimental

4.1. Chemistry: General methods and instrumentation

All the solvents and chemicals were used as obtained from Merck, Sigma-Aldrich, Thermofisher Acros Organics, and Fluorochem. NMR spectra were recorded on an Agilent DD2 400 MHz and an Agilent DD2 600 MHz spectrometers (the latter equipped with a cryo-probe). Exact mass determinations were accomplished by UHPLC/+ESI-QqTOF-MS as follows: Chromatographic separations were performed on a Dionex Ultimate 3000 RS Liquid Chromatography System (UHPLC) on a Dionex Acclaim RSLC 120, C18 column (2.1 x 100 mm, 2.2 µm) at 40 °C with a binary gradient (A: water with 0.1% formic acid; B: acetonitrile with 0.1% formic acid) at 0.8 mL/min: 0 to 0.4 min: isocratic at 5% B; 0.4 to 9.9 min: linear from 5% B to 100% B; 9.9 to 15.0 min: isocratic at 100% B; 15.0 to 15.1 min: linear from 100% B to 5% B; 15.1 to 20 min: isocratic at 5% B. The injection volume was 2 µL. Eluted compounds were detected using a Dionex Ultimate DAD-3000 RS over a wavelength range of 200-400 nm and a Bruker Daltonics micrOTOF-QII time-of-flight mass spectrometer equipped with an Apolo electrospray ionization source in positive mode at 3 Hz over a mass range of *m/z* 50-1500 using the following instrument settings: nebulizer gas nitrogen, 4 bar; dry gas nitrogen, 9 L/min, 220 °C; capillary voltage 4500 V; end plate offset -500 V; transfer time 100 µs; collision gas nitrogen; collision energy and collision RF settings were combined to each single spectrum of 1250 summations as follows: 624 summations with 80 eV collision energy and 130 Vpp + 313 summations with 16 eV collision energy and 200 Vpp + 313 summations with 16 eV collision energy and 200 Vpp. Internal dataset calibration (HPC mode) was performed for each analysis using the mass spectrum of a 10 mmol/L solution of sodium formiate in 50% isopropyl alcohol that was infused during LC re-equilibration using a divert valve equipped with a 20 µL sample loop. The purity of all compounds was assessed by this method. With exception of **11b**, the purity of all compounds was at least 95%. The preparation of the intermediate cinnamate ester analogues **1a-u** and **2b** was carried out as recently described [52]. The synthesis of **8a,f,g,k-o**, **9a,b**, **13a,c**, **14c**, and **17c** has been published before [10,11,15,16,27,29,39].

4.2. Synthetic procedures

4.2.1. Synthesis of cinnamic amides (General procedure A)

The procedure was adapted from literature [18]. To a solution of ferulic or caffeic acid (**3a,b**; 1 mmol) in dry DMF (2.0 mL), Et_3N (1 mmol) was added and the mixture cooled to 0 °C. The corresponding amine (1 mmol) was added to the solution, followed by addition of solution of BOP (1 mmol) in dry CH_2Cl_2 (2.0 mL) over a period of 30 min. The mixture was stirred (from 0 °C to rt) until full conversion by TLC was observed. Afterwards, the volatile solvent was evaporated, and the residue was diluted with H_2O (15 mL) and extracted with EtOAc (3x). The combined organic layers were successively washed with 1 mol/L HCl (2x), 1 mol/L $NaHCO_3$ (2x), H_2O (3x), and afterwards dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the product purified as indicated.

4.2.2. Synthesis of cinnamic ketones (General procedure B)

The procedure was based on previous reports in aldol condensation of benzaldehyde derivatives [20,21]. 3,4-dimethoxybenzaldehyde (9 mmol), EtOH (15.0 mL), and the appropriate ketone

derivative (27 mmol) were mixed. A 5% NaOH aqueous solution (720 µL) was then slowly added to the mixture over a period of 15 min. The resulting solution was stirred at rt until full conversion observed by TLC. Afterwards, the solvent was evaporated under reduced pressure and the resulting yellow resin was taken up in H_2O (75 mL) and extracted EtOAc (3x). The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The pure product was obtained by chromatographic separation as indicated.

4.2.3. Demethylation of cinnamic ketones (General procedure C)

The procedure was adapted from literature [23]. To a solution of the corresponding compound **6a,b** (1.5 mmol) in dry CH_2Cl_2 (9.0 mL) at 0 °C, a dilution of 1 mol/L BBr_3 (6.0 mL, 6.0 mmol) in CH_2Cl_2 (12.0 mL) was dropwise added. The resulting mixture was stirred at rt for 2 h and then carefully quenched with cold water. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The product was purified as indicated.

4.2.4. Oxidative coupling with Ag_2O (General procedure D)

The protocol was adapted from literature [15]. The corresponding cinnamate analogue (0.5 mmol), silver(I) oxide (0.25 mmol), dry toluene (1.7 mL) and dry acetone (1.0 mL) were mixed together under nitrogen. The mixture was stirred for 28 h at rt in absence of light. The inorganic material was then filtered off and the organic solvent removed under reduced pressure. The product was purified out of the residue by chromatography as indicated.

4.2.5. Oxidative coupling with HRP (General procedure E)

The procedure was carried out according to literature [16]. The corresponding cinnamate analogue (0.5 mmol) was dissolved in acetone (2.5 mL) and diluted under stirring with citrate-phosphate buffer (19 mmol/L, pH 3.1, 22.5 mL). Horseradish peroxidase in buffer (1.48 mg/mL, 707 µL, ≙210 U) and 1 mol/L H_2O_2 (250 µL, 0.25 mmol) were portion-wise added over a period of 20 min. The reaction was stirred for 3 h at rt. Afterwards 5% NaCl (5 mL) was added and the organic solvent carefully removed. The residual mixture was extracted with EtOAc (3x) and the product purified as indicated.

4.2.6. Synthesis of *o*-aminophenols (General procedure F)

The *o*-aminophenols **12b,c** were prepared by nitration of the corresponding phenol [53] and subsequent reduction [54]. The corresponding phenol (10 mmol) was dissolved in acetone (35 mL) and $Bi(NO_3)_3 \bullet 5H_2O$ (5 mmol) was added. The mixture was stirred at 50 °C. Afterwards, the inorganic material was filtered off over a Celite® pad and the solvent removed under reduced pressure. The residue was chromatographed as indicated to afford the respective nitrophenol.

Tin(II) chloride dihydrate (20 mmol) was dissolved in MeOH (17.2 mL) with conc. HCl (9.2 mL) and the resulting solution cooled to 0 °C. The corresponding purified nitrophenol (4 mmol) was then added in one portion and the mixture stirred at rt overnight to end with a colorless solution. The mixture was diluted with EtOAc and neutralized with saturated $NaHCO_3$ solution. The inorganic material was removed by filtration and the residue washed with EtOAc. Filtrates were combined and phases separated. The residual aqueous phase was further extracted with EtOAc (3x). The combined organic layers were dried over magnesium sulfate and the organic solvent removed under reduced pressure. The product was used without additional purification.

4.2.7. Synthesis of 3-phenylprop-2-en-1-ols (General procedure G)

Prepared following a procedure adapted from literature [28,55]. The corresponding cinnamate ester (1 mmol) was dissolved in dry toluene (10 mL) under nitrogen. The solution was cooled to 0 °C and 1.2 mol/L DIBAL-H (in toluene, 3.3 mL, 4 mmol) was dropwise added (via syringe). Afterwards, the stirring was continued for 15 min at 0 °C and for 2 h more at rt. The reaction was then quenched by carefully adding EtOH. The organic solvent was partially removed under reduced pressure. Water was then added, and the gelatinous precipitate was filtered off. The precipitate was washed with EtOAc. The filtrate was extracted with EtOAc (3x). All the organic layers were combined and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the product was purified as indicated.

4.2.8. Heck oxyarylation (General procedure H)

One-pot diazotization and Heck oxyarylation between **12a-c** and **2a-h** was performed using optimized reaction conditions reported in literature [27,56]. In brief, the corresponding *o*-aminophenol (1 mmol) was dissolved in ACN (9 mL) and cooled to 0 °C. Then, $NOPF_6$ (1 mmol) was added in one portion. Immediate formation of brown gas was observed. After 2 h of stirring at that temperature, $ZnCO_3$ (2 mmol), $Pd_2(dba)_3$ (5 mol%) and phenylpropene derivative (1.2 mmol) were added. The resulting darkened mixture was stirred at rt for 20 h and then 10% $NaHCO_3$ (30 mL) was added. The mixture was filtered over a Celite® pad and the filtrate extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The product was purified by chromatography as indicated.

4.2.9. Halogenation (General procedure I)

A solution of the corresponding compound (0.5 mmol) in ACN (1.8 mL) was cooled to 0 °C and NBS, NCS, or NIS (0.5 mmol) was then added in one portion. The mixture was stirred overnight. The product was purified as indicated.

4.2.10. Heck coupling (General procedure J)

The corresponding bromide (0.3 mmol) was dissolved in dry DMF (0.9 mL) under nitrogen. *Tert*-butyl acrylate (0.6 mmol), anhydrous potassium carbonate (0.6 mmol), palladium dichloride (1 mol%) and PPh_3 or P(*o*-tol)$_3$ (2 mol%) were added. The mixture was heated at 100 °C under nitrogen for 24 h. After that period, the mixture was cooled down and filtered over a Celite® pad. The pad was washed several times with ethyl acetate and the layers separated. The organic one was washed with 1 mol/L HCl (2x), 10% NaCl (2x), and water (3x), and afterwards dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product purified as indicated.

4.2.11. Demethylation of 2-phenyl-2,3-dihydrobenzofurans (General procedure K)

To a solution of the corresponding 2-phenyl-2,3-dihydrobenzofurans (0.2 mmol) in dry CH_2Cl_2 (1.28 mL) at 0 °C, a dilution of 1 mol/L BBr_3 (0.43 mL, 0.4 mmol) in CH_2Cl_2 (0.85 mL) was dropwise added. The resulting mixture was stirred at rt for 2 h and then carefully quenched with cold water. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The product was purified as indicated.

4.2.12. Attempts of deoxyfluorination (General procedure L)

The procedure was adopted from the original report [30]. In an HPLC vial the corresponding compound (0.1 mmol), toluene (0.1 mL), DBU (0.2 mmol) and PyFluor (0.11 mmol) were added. PyFluor was dispensed as liquid. The mixture was stirred at rt or 0 °C for 24-36 h. The product was purified as indicated.

4.2.13. Suzuki-Miyaura coupling (General procedure M)

A mixture of compound **13k** (0.32 mmol), $PdCl_2$ (5 mol%), PPh_3 (20 mol%), the corresponding boronic acid (0.53 mmol), water (0.5 mL), toluene (2 mL), and DMF (1 mL) was heated at 100 °C under nitrogen for 24 h. The resulting mixture was diluted with EtOAc and filtered over a Celite® pad. The filtrate was washed with water, dried over anhydrous Na_2SO_4 and the solvent was then removed under reduced pressure. The product was purified as indicated.

4.2.14. (*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**2d**)

Prepared according to the general procedure G from ethyl (*E*)-3-(3,4-dimethoxyphenyl)acrylate (**1t**, 236 mg, 1 mmol); isolated by column chromatography (31 g silica gel, hexane/EtOAc 65:35); colorless liquid; yield: 144 mg (74%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.94 (d, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.55 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.24 (dt, *J* = 15.8, 5.9 Hz, 1H), 4.30 (dd, *J* = 6.0, 1.6 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 149.2, 149.0, 131.3, 129.9, 126.7, 119.8, 111.2, 109.0, 64.0, 56.0, 55.9. HRMS (ESI): *m/z* calcd. for $C_{11}H_{14}NaO_3$: 217.0835 $[M+Na]^+$; found: 217.0821.

4.2.15. (*E*)-4-(3-hydroxyprop-1-en-1-yl)phenol (**2e**)

Prepared according to the general procedure G from ethyl 4-hydroxycinnamate (**1b**, 192 mg, 1 mmol); isolated by flash chromatography (30 g silica gel, CH_2Cl_2/EtOAc 85:15). White solid; yield: 120 mg (98%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.34 (br s, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.51 (dt, *J* = 15.8, 1.7 Hz, 1H), 6.20 (dt, *J* = 15.9, 5.6 Hz, 1H), 5.61 (s, 1H), 4.19 (dd, *J* = 5.7, 1.8 Hz, 2H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 157.8, 130.2, 129.8, 128.4, 127.9, 116.2, 63.5. HRMS (ESI): *m/z* calcd. for $C_9H_{10}NaO_2$: 173.0573 $[M+Na]^+$; found: 173.0585.

4.2.16. (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (**2f**)

Prepared according to the general procedure G from ethyl (*E*)-3-(4-methoxyphenyl)acrylate (**1s**, 206 mg, 1 mmol); isolated by column chromatography (16 g silica gel, hexane/EtOAc 9:1 → 7:3); colorless liquid; yield: 80 mg (48%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.55 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.0 Hz, 1H), 4.29 (dd, *J* = 6.0, 1.6 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.4, 131.1, 129.5, 127.8, 126.4, 114.1, 64.0, 55.4. HRMS (ESI): *m/z* calcd. for $C_{10}H_{12}NaO_2$: 187.0730 $[M+Na]^+$; found: 187.0752.

4.2.17. (*E*)-3-(4-methoxyphenyl)allyl acetate (**2g**)

Obtained as side product by the reaction of synthesis of compound **13f** and purified therefore out of the same chromatographic separation; colorless liquid; yield: 49 mg (24%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.60 (dd, *J* = 15.9, 1.5 Hz, 1H), 6.15 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.70 (dd, *J* = 6.7, 1.3 Hz, 2H), 3.81 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.0, 159.7, 134.2, 129.1, 128.0, 121.0, 114.1, 65.5, 55.4, 21.2. HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}NaO_3$: 229.0835 $[M+Na]^+$; found: 229.0861.

4.2.18. (*E*)-3-(2-bromophenyl)prop-2-en-1-ol (**2h**)

Prepared according to the general procedure G from ethyl (*E*)-3-(2-bromophenyl)acrylate (**1u**, 255 mg, 1 mmol); isolated by flash chromatography (23 g silica gel, hexane/EtOAc 85:15); colorless liquid; yield: 188 mg (88%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.10 (td, *J* = 7.6, 1.7 Hz, 1H), 6.96 (dt, *J* = 15.8, 1.7 Hz, 1H), 6.31 (dt, *J* = 15.8, 5.6 Hz, 1H), 4.36 (dd, *J* = 5.7, 1.7 Hz, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 136.7,

133.1, 131.8, 129.9, 129.1, 127.7, 127.3, 123.8, 63.7. HRMS (ESI): *m/z* calcd. for C_9H_9BrNaO: 234.9729 $[M+Na]^+$; found: 234.9726.

4.2.19. (*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-propylacrylamide (**4a**)

Prepared according to general procedure A from ferulic acid (**3a**, 194 mg, 1 mmol) and propylamine (85 µL, 1 mmol); isolated by column chromatography (60 g silica gel, hexane/EtOAc/MeOH 1:1:0.1); yellow oil; yield: 135 mg (58%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.42 (d, *J* = 15.7 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 3.87 (s, 3H), 3.24 (t, *J* = 7.1 Hz, 2H), 1.60 – 1.53 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 170.4, 151.1, 150.5, 143.2, 129.5, 124.4, 120.0, 117.7, 112.8, 57.6, 43.6, 25.0, 13.0. HRMS (ESI): *m/z* calcd. for $C_{13}H_{18}NO_3$: 236.1208 $[M+H]^+$; found: 236.1311.

4.2.20. (*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-isopropylacrylamide (**4b**)

Prepared according to general procedure A from ferulic acid (**3a**, 194 mg, 1 mmol) and isopropylamine (85 µL, 1 mmol); isolated by column chromatography (60 g silica gel, hexane/EtOAc/MeOH 1:1:0.1); yellow oil; yield: 172 mg (73%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.41 (d, *J* = 15.7 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.39 (d, *J* = 15.7 Hz, 1H), 4.07 (hept, *J* = 6.6 Hz, 1H), 3.86 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 169.5, 151.0, 150.5, 143.1, 129.6, 124.3, 120.3, 117.7, 112.8, 57.6, 43.8, 24.0. HRMS (ESI): *m/z* calcd. for $C_{13}H_{18}NO_3$: 236.1242 $[M+H]^+$; found: 236.1270.

4.2.21. (*E*)-3-(3,4-dihydroxyphenyl)-*N*-isopropylacrylamide (**4c**)

Prepared according to general procedure A from caffeic acid (**3b**, 180 mg, 1 mmol) and isopropylamine (85 µL, 1 mmol); isolated by column chromatography (60 g silica gel, hexane/EtOAc/MeOH 1:1:0.1); yellow oil; yield: 86 mg (39%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.38 (d, *J* = 15.7 Hz, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.91 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 4.08 (hept, *J* = 6.6 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 168.3, 148.7, 146.7, 142.0, 128.4, 122.0, 118.7, 116.4, 115.0, 42.5, 22.7. HRMS (ESI): *m/z* calcd. for $C_{12}H_{16}NO_3$: 222.1085 $[M+H]^+$; found 222.1148.

4.2.22. (*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(2-hydroxyethyl)acrylamide (**4d**)

The procedure was adapted from literature [19]. To a solution of methyl ferulate (**1f**, 536 mg, 2.6 mmol) in MeOH (3 mL), ethanolamine (780 µL, 12.9 mmol) and Na_2CO_3 (272 mg, 2.6 mmol) were added. The mixture was heated at 80 °C for 46 h. The resulting mixture was then diluted with MeOH and filtered. The filtrate was concentrated under reduced pressure. The product was purified by flash chromatography (60 g silica gel, $CHCl_3$/MeOH 9:1); white solid; yield: 255 mg (42%). ^{1}H NMR (600 MHz, Methanol-d_4) δ = 7.45 (d, *J* = 15.7 Hz, 1H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.03 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 3.88 (s, 3H), 3.66 (t, *J* = 5.8 Hz, 2H), 3.42 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 169.5, 149.9, 149.3, 142.2, 128.2, 123.2, 118.7, 116.5, 111.6, 61.7, 56.4, 43.1. HRMS (ESI): m/z calcd. for $C_{12}H_{16}NO_4$: 238.1074 $[M+H]^+$; found: 238.1113.

4.2.23. (*E*)-1-(3,4-dimethoxyphenyl)-5-methylhex-1-en-3-one (**6a**)

Prepared according to general procedure B using 4-methylpentan-2-one (3.4 mL, 27 mmol); the resulting yellow resin was used without further purification; yield: 2.26 g (quantitative). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 16.1 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 16.1 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.52 (d, *J* = 7.1 Hz, 2H), 2.24 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 200.4, 151.4, 149.4, 142.6,

127.6, 124.9, 123.1, 111.2, 109.8, 56.1, 56.0, 49.8, 25.5, 22.9. HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}O_3$: 249.1446 $[M+H]^+$; found: 249.1454.

4.2.24. (*E*)-1-(3,4-dimethoxyphenyl)-5,5-dimethylhex-1-en-3-one (**6b**)

Prepared according to general procedure B using 4,4-dimethylpentan-2-one (3.8 mL, 27 mmol); yellow needles crystalized over time and were used without further purification; yield: 2.36 g (quantitative). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 16.0 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.53 (s, 2H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.3, 151.4, 149.4, 142.3, 127.7, 126.0, 123.1, 111.2, 109.9, 56.1, 56.0, 53.6, 31.7, 30.2. HRMS (ESI): *m/z* calcd. for $C_{16}H_{23}O_3$: 263.1602 $[M+H]^+$; found: 263.1640.

4.2.25. (*E*)-1-(4-hydroxy-3-methoxyphenyl)-5-methylhex-1-en-3-one (**7a**)

The procedure was adapted from literature [23]. Anhydrous $AlCl_3$ (3.19 g, 27.7 mmol) was added carefully to a solution of **6a** (1.96 g, 7.9 mmol) in dry CH_2Cl_2 (20 mL), and the resulting mixture stirred at rt. After full conversion as indicated by TLC, the mixture was quenched by H_2O (40 mL) and the solvent removed under reduced pressure. The residue was then extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The mixture of regioisomers was separated by column chromatography (100 g silica gel, hexane/EtOAc/MeOH 80:20:2.5); yellow oil; yield: 557 mg (30%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 16.1 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 16.1 Hz, 1H), 3.91 (s, 3H), 2.51 (d, *J* = 7.0 Hz, 2H), 2.28 – 2.26 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.6, 148.4, 147.0, 142.9, 127.1, 124.5, 123.5, 115.0, 109.6, 56.0, 49.7, 25.5, 22.8. HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}O_3$: 235.1289 $[M+H]^+$; found: 235.1396.

4.2.26. (*E*)-1-(3,4-dihydroxyphenyl)-5-methylhex-1-en-3-one (**7b**)

Prepared according to general procedure C from **6a** (374 mg, 1.51 mmol); isolated by column chromatography (50 g silica gel, hexane/EtOAc 6:4); greenish crystals; yield: 96 mg (29%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 (d, *J* = 16.0 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 16.1 Hz, 1H), 2.53 (d, *J* = 7.0 Hz, 2H), 2.22 – 2.09 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 203.4, 149.9, 146.9, 145.6, 127.8, 124.3, 123.5, 116.6, 115.3, 50.2, 26.7, 23.0. HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}O_3$: 221.1133 $[M+H]^+$; found: 221.1179.

4.2.27. (*E*)-1-(3,4-dihydroxyphenyl)-5,5-dimethylhex-1-en-3-one (**7c**)

Prepared according to general procedure C from **6b** (397 mg, 1.51 mmol); isolated by column chromatography (50 g silica gel, $CHCl_3$/MeOH 93:7); yellow crystals; yield: 258 mg (73%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.46 (d, *J* = 16.0 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 2.55 (s, 2H), 1.05 (s, 9H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 203.1, 149.9, 146.9, 145.3, 127.9, 125.6, 123.5, 116.6, 115.3, 53.9, 32.4, 30.4. HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}O_3$: 235.1289 $[M+H]^+$; found: 235.1382.

4.2.28. (±)-Methyl *trans*-(*E*)-2-(4-hydroxyphenyl)-5-(-3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (**8a**)

Prepared according to the general procedure E from methyl 4-hydroxycinnamate (**1a**, 89 mg, 0.5 mmol); isolated by column chromatography (16 g silica gel, hexane/EtOAc 7:3); white solid; yield: 19 mg (10%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.52 (br s, 1H), 7.71 (t, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.60 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.6

Hz, 2H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.03 (d, *J* = 7.4 Hz, 1H), 4.39 (d, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 171.7, 167.8, 162.3, 158.8, 145.2, 132.0, 131.8, 128.8, 128.6, 126.9, 126.2, 116.4, 116.2, 110.9, 87.9, 55.7, 53.1, 51.7. HRMS (ESI): *m/z* calcd. for $C_{20}H_{19}O_6$: 355.1176 $[M+H]^+$; found: 355.1204.

4.2.29. (±)-Ethyl *trans*-(*E*)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-(4-hydroxyphenyl)-2,3-di-hydro-benzofuran-3-carboxylate (**8b**)

Prepared according to the general procedure E from ethyl 4-hydroxycinnamate (**1b**, 96 mg, 0.5 mmol); isolated by column chromatography (16 g silica gel, hexane/EtOAc 7:3); white solid; yield: 23 mg (12%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.56 (br s, 1H), 7.71 (br s, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.60 (br d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.03 (d, *J* = 7.5 Hz, 1H), 4.36 (d, *J* = 7.5 Hz, 1H), 4.34 – 4.21 (m, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 171.1, 167.3, 162.2, 158.7, 145.0, 132.0, 131.6, 128.8, 128.6, 126.9, 126.1, 116.5, 116.4, 110.9, 87.8, 62.3, 60.7, 55.8, 14.7, 14.6. HRMS (ESI): *m/z* calcd. for $C_{22}H_{23}O_6$: 383.1489 $[M+H]^+$; found: 383.1494.

4.2.30. (±)-Isopropyl *trans*-(*E*)-2-(4-hydroxyphenyl)-5-(3-isopropoxy-3-oxoprop-1-en-1-yl)-2,3-di-hydrobenzofuran-3-carboxylate (**8c**)

Prepared according to the general procedure E from isopropyl 4-hydroxycinnamate (**1c**, 103 mg, 0.5 mmol); isolated by column chromatography (31 g silica gel, hexane/Et_2O 6:4); white solid; yield: 20 mg (10%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.57 (br s, 1H), 7.70 (t, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 15.9 Hz, 1H), 7.61 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 5.16 – 5.04 (m, 1H), 5.09 – 4.99 (m, 1H), 4.32 (d, *J* = 7.5 Hz, 1H), 1.30 (d, *J* = 6.3 Hz, 6H), 1.27 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 170.7, 166.9, 162.2, 158.8, 144.9, 132.0, 131.5, 128.8, 128.6, 127.0, 126.0, 117.0, 116.4, 110.9, 87.9, 70.0, 68.0, 56.0, 22.2, 22.1, 22.0. HRMS (ESI): *m/z* calcd. for $C_{24}H_{27}O_6$: 411.1802 $[M+H]^+$; found: 411.1800.

4.2.31. (±)-Butyl *trans*-(*E*)-5-(3-butoxy-3-oxoprop-1-en-1-yl)-2-(4-hydroxyphenyl)-2,3-dihydro-benzofuran-3-carboxylate (**8d**)

Prepared according to the general procedure E from butyl 4-hydroxycinnamate (**1d**, 110 mg, 0.5 mmol); isolated by flash chromatography (SVF D26-RP18 column, 25-40 µm, gradient MeOH/H_2O, 9 mL/min flow); white solid; yield: 10 mg (5%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.57 (br s, 1H), 7.72 (t, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.04 (d, *J* = 7.4 Hz, 1H), 4.39 (d, *J* = 7.4 Hz, 1H), 4.29 – 4.18 (m, 2H), 4.16 (t, *J* = 6.4 Hz, 2H), 1.74 – 1.62 (m, 4H), 1.47 – 1.39 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 171.2, 167.4, 162.2, 158.8, 145.0, 132.0, 131.8, 130.2, 128.8, 128.6, 127.0, 126.0, 116.5, 116.4, 110.9, 87.8, 66.1, 64.6, 55.8, 31.7, 31.5, 19.9, 14.1, 14.0. HRMS (ESI): *m/z* calcd. for $C_{26}H_{31}O_6$: 439.2115 $[M+H]^+$; found: 439.2110.

4.2.32. (±)-*tert*-butyl *trans*-(*E*)-5-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-2-(4-hydroxyphen-yl)-2,3-dihydrobenzofuran-3-carboxylate (**8e**)

Prepared according to the general procedure E from *tert*-butyl 4-hydroxycinnamate (**1e**, 110 mg, 0.5 mmol); isolated by preparative RP-HPLC (gradient MeOH/H_2O, 10 mL/min flow); white solid; yield: 20 mg (9%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.49 (s, 1H), 7.67 (br s, 1H), 7.64 – 7.54 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.98 (d, *J* = 7.5 Hz, 1H), 4.26 (d, *J* = 7.5, 1H), 1.52 (s, 9H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 170.4, 166.9,

162.2, 158.8, 144.3, 132.3, 131.3, 128.9, 128.6, 127.2, 126.0, 118.3, 116.5, 110.9, 87.8, 82.7, 80.4, 56.8, 28.5, 28.3. HRMS (ESI): *m/z* calcd. for $C_{26}H_{31}O_6$: 439.2115 $[M+H]^+$; found: 439.2139.

4.2.33. (±)-Methyl *trans*-(*E*)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (**8f**)

Prepared according to the general procedure D from methyl ferulate (**1f**, 105 mg, 0.50 mmol); isolated by column chromatography (15 g silica gel, hexane/EtOAc 7:3); white solid; yield: 34 mg (16%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 7.72 (s, 1H), 7.63 (d, *J* = 16.0 Hz, 1H), 7.33 (d, *J* = 1.5 Hz, 1H), 7.29 (br s, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.04 (d, *J* = 7.9 Hz, 1H), 4.47 (d, *J* = 7.9 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 171.8, 167.9, 151.2, 148.7, 148.2, 146.0, 145.6, 132.2, 129.6, 127.5, 120.4, 119.1, 116.5, 116.0, 113.7, 110.9, 88.5, 56.7, 56.5, 56.1, 53.2, 51.7. HRMS (ESI): *m/z* calcd. for $C_{22}H_{23}O_8$: 415.1387 $[M+H]^+$; found: 415.1366.

4.2.34. (±)-Ethyl *trans*-(*E*)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-(4-hydroxy-3-methoxyphen-yl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate (**8g**)

Prepared according to the general procedure E from ethyl ferulate (**1g**, 112 mg, 0.5 mmol); isolated by column chromatography (24 g silica gel, hexane/EtOAc 7:3); white solid; yield: 40 mg (18%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 7.76 (s, 1H), 7.63 (d, *J* = 15.9 Hz, 1H), 7.34 (d, *J* = 1.6 Hz, 1H), 7.29 (t, *J* = 1.3 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.42 (d, *J* = 15.9 Hz, 1H), 6.04 (d, *J* = 8.0 Hz, 1H), 4.44 (d, *J* = 7.9 Hz, 1H), 4.36 – 4.20 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 171.2, 167.4, 151.1, 148.7, 148.1, 145.9, 145.3, 132.2, 129.6, 127.5, 120.3, 119.0, 116.8, 115.9, 113.3, 110.8, 88.5, 62.3, 60.7, 56.6, 56.4, 56.2, 14.8, 14.6. HRMS (ESI): *m/z* calcd. for $C_{24}H_{27}O_8$: 443.1700 $[M+H]^+$; found: 443.1709.

4.2.35. (±)-Isopropyl *trans*-(*E*)-2-(4-hydroxy-3-methoxyphenyl)-5-(3-isopropoxy-3-oxo-prop-1-en-1-yl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate (**8h**)

Prepared according to the general procedure E from isopropyl ferulate (**1h**, 118 mg, 0.5 mmol); isolated by column chromatography (22 g silica gel, hexane/EtOAc 7:3); white solid; yield: 33 mg (14%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 7.75 (s, 1H, OH), 7.62 (d, *J* = 15.9 Hz, 1H, H-1''), 7.34 (d, *J* = 1.6 Hz, 1H, H-6), 7.27 (t, *J* = 1.4 Hz, 1H, H-4), 7.09 (d, *J* = 2.0 Hz, 1H, H-2'), 6.92 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6'), 6.85 (d, *J* = 8.1 Hz, 1H, H-5'), 6.39 (d, *J* = 15.9 Hz, 1H, H-2''), 6.03 (d, *J* = 8.1 Hz, 1H, H-2), 5.09 (hept, *J* = 6.3 Hz, 1H, $OCH_{carboxylate}$), 5.06 (hept, *J* = 6.3 Hz, 1H, $OCH_{acrylate}$), 4.40 (d, *J* = 8.1 Hz, 1H, H-3), 3.93 (s, 3H, 7-OCH_3), 3.84 (s, 3H, 3'-OCH_3), 1.30 (d, *J* = 6.3 Hz, 3H, CH_3), 1.30 (d, *J* = 6.3 Hz, 3H, CH_3), 1.27 (d, *J* = 6.3 Hz, 6H, 2xCH_3). ^{13}C NMR (151 MHz, Acetone-d_6) δ 170.7 (3-C=O), 167.0 (C-3''), 151.1 (C-7a), 148.7 (C-3'), 148.1 (C-4'), 146.0 (C-7), 145.2 (C-1''), 132.2 (C-1'), 129.6 (C-5), 127.6 (C-3a), 120.3 (C-6'), 119.0 (C-4), 117.2 (C-2''), 115.9 (C-5'), 113.2 (C-6), 110.8 (C-2'), 88.5 (C-2), 70.0 ($OCH_{carboxylate}$), 67.9 ($OCH_{acrylate}$), 56.6 (7-OCH_3), 56.4 (3'-OCH_3), 56.3 (C-3), 22.3 (2xCH_3), 22.1 (CH_3), 22.0 (CH_3). HRMS (ESI): *m/z* calcd. for $C_{26}H_{31}O_8$: 471.2013 $[M+H]^+$; found: 471.2023.

4.2.36. (±)-Butyl *trans*-(*E*)-5-(3-butoxy-3-oxoprop-1-en-1-yl)-2-(4-hydroxy-3-methoxyphen-yl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate (**8i**)

Prepared according to the general procedure E from butyl ferulate (**1i**, 125 mg, 0.5 mmol); isolated by column chromatography (21 g silica gel, hexane/EtOAc 8:2 → 7:3); white solid; yield: 26 mg (10%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 7.75 (s, 1H), 7.63 (d, *J* = 15.9 Hz, 1H), 7.33 (br s, 1H), 7.29 (br s, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.42 (d, *J* = 15.9 Hz, 1H), 6.04 (d, *J* = 7.9 Hz, 1H), 4.46 (d, *J* = 7.9 Hz, 1H), 4.25 (dt, *J* = 10.8, 6.6 Hz, 1H), 4.20 (dt, *J* = 10.8, 6.5 Hz,

1H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 1.72 – 1.62 (m, 4H), 1.47 – 1.38 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 171.2, 167.4, 151.1, 148.7, 148.1, 145.9, 145.3, 132.2, 129.5, 127.5, 120.3, 119.0, 116.8, 115.9, 113.5, 110.8, 88.4, 66.1, 64.6, 56.6, 56.4, 56.2, 31.7, 31.5, 20.0, 19.9, 14.1, 14.0. HRMS (ESI): *m/z* calcd. for $C_{28}H_{35}O_8$: 499.2326 $[M+H]^+$; found: 499.2349.

4.2.37. (±)-*tert*-butyl *trans*-(*E*)-5-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate (**8j**)

Prepared according to the general procedure E from *tert*-butyl ferulate (**1j**, 125 mg, 0.5 mmol); isolated by flash chromatography (24 g silica gel, hexane/EtOAc 85:15 → 80:20); white solid; yield: 27 mg (11%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 15.9 Hz, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 7.02 (d, *J* = 1.5 Hz, 1H), 6.91 – 6.89 (m, 3H), 6.23 (d, *J* = 15.8 Hz, 1H), 6.05 (d, *J* = 8.4 Hz, 1H), 5.65 (br s, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 1.54 (s, 9H), 1.51 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.4, 166.8, 149.9, 146.8, 146.1, 144.8, 143.8, 131.9, 128.8, 126.4, 119.7, 118.2, 117.8, 114.6, 111.5, 108.9, 87.6, 82.6, 80.5, 56.5, 56.2, 56.1, 28.4, 28.3. HRMS (ESI): *m/z* calcd. for $C_{28}H_{35}O_8$: 499.2326 $[M+H]^+$; found: 499.2350.

4.2.38. (±)-Methyl *trans*-(*E*)-2-(3,4-dihydroxyphenyl)-7-hydroxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (**8k**)

Prepared according to the general procedure D from methyl caffeate (**1k**, 97 mg, 0.5 mmol); isolated by column chromatography (9.8 g silica gel, hexane/acetone 7:3); white foam; yield: 33 mg (17%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.15 (br s, 3H), 7.58 (d, *J* = 15.9 Hz, 1H), 7.21 (t, *J* = 1.4 Hz, 1H), 7.15 (d, *J* = 1.7 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 5.98 (d, *J* = 7.3 Hz, 1H), 4.36 (d, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 170.8, 166.8, 149.2, 145.5, 145.3, 144.5, 141.7, 131.8, 128.5, 126.5, 117.8, 116.9, 116.5, 115.3, 115.2, 113.0, 87.0, 55.4, 52.1, 50.7. HRMS (ESI): *m/z* calcd. for $C_{20}H_{19}O_8$: 387.1074 $[M+H]^+$; found: 387.1063.

4.2.39. (±)-Ethyl *trans*-(*E*)-2-(3,4-dihydroxyphenyl)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-7-hydroxy-2,3-dihydrobenzofuran-3-carboxylate (**8l**)

Prepared according to the general procedure D from ethyl caffeate (**1l**, 104 mg, 0.5 mmol); isolated by flash chromatography (20 g silica gel, CH_2Cl_2/acetone 9:1 → 8:2); white solid; yield: 29 mg (14%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.16 (s, 3H), 7.58 (d, *J* = 15.9 Hz, 1H), 7.21 (t, *J* = 1.5 Hz, 1H), 7.15 (d, *J* = 1.6 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 5.98 (d, *J* = 7.4 Hz, 1H), 4.33 (d, *J* = 7.4 Hz, 1H), 4.30 – 4.23 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 171.3, 167.4, 150.1, 146.5, 146.3, 145.4, 142.7, 132.9, 129.6, 127.6, 118.9, 117.8, 117.4, 116.6, 116.3, 114.1, 88.0, 62.3, 60.7, 56.6, 14.8, 14.6. HRMS (ESI): *m/z* calcd. for $C_{22}H_{23}O_8$: 415.1387 $[M+H]^+$; found: 415.1403.

4.2.40. (±)-Isopropyl *trans*-(*E*)-2-(3,4-dihydroxyphenyl)-7-hydroxy-5-(3-isopropoxy-3-oxo-prop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (**8m**)

Prepared according to the general procedure D from isopropyl caffeate (**1m**, 111 mg, 0.5 mmol); isolated by flash chromatography (15 g silica gel, hexane/acetone 7:3); yellowish oil; yield: 13 mg (6%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.16 (br s, 3H, 3xOH), 7.57 (d, *J* = 15.9 Hz, 1H, H-1''), 7.19 (t, *J* = 1.4 Hz, 1H, H-4), 7.15 (d, *J* = 1.7 Hz, 1H, H-6), 6.90 (d, *J* = 2.1 Hz, 1H, H-2'), 6.84 (d, *J* = 8.1 Hz, 1H, H-5'), 6.80 (dd, *J* = 8.1, 2.1 Hz, 1H, H-6'), 6.29 (d, *J* = 15.9 Hz, 1H, H-2''), 5.97 (d, *J* = 7.4 Hz, 1H, H-2), 5.09 (hept, *J* = 6.3 Hz, 1H, $OCH_{carboxylate}$), 5.05 (hept, *J* = 6.4 Hz, 1H, $OCH_{acrylate}$), 4.29 (d, *J* = 7.5 Hz, 1H, H-3), 1.30 (d, *J* = 6.2 Hz, 6H, $CH_{3,carboxylate}$), 1.27 (d, *J* = 6.3 Hz, 6H, $CH_{3,acrylate}$). ^{13}C NMR (151 MHz, Acetone-d_6)

δ 170.8 (3-C=O), 167.0 (C-3''), 150.2 (C-7a), 146.6 (C-4'), 146.3 (C-3'), 145.2 (C-1''), 142.8 (C-7), 133.0 (C-1'), 129.7 (C-5), 127.8 (C-3a), 118.9 (C-6'), 117.7 (C-4), 117.3 (C-6), 117.1 (C-2''), 116.3 (C-5'), 114.1 (C-2'), 88.1 (C-2), 70.0 ($OCH_{carboxylate}$), 68.0 ($OCH_{acrylate}$), 56.8 (C-3), 22.3 (2xCH_3), 22.1 (CH_3), 22.1 (CH_3). HRMS (ESI): *m/z* calcd. for $C_{24}H_{27}O_8$: 443.1700 $[M+H]^+$; found: 443.1723.

4.2.41. (±)-Butyl *trans*-(*E*)-5-(3-butoxy-3-oxoprop-1-en-1-yl)-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydrobenzofuran-3-carboxylate (**8n**)

Prepared according to the general procedure D from butyl caffeate (**1n**, 118 mg, 0.5 mmol); isolated by flash chromatography (30 g silica gel, CH_2Cl_2/acetone 10:0 → 9:1); white solid; yield: 19 mg (8%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56 (d, *J* = 15.9 Hz, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 5.95 (d, *J* = 7.2 Hz, 1H), 4.28 (d, *J* = 7.2 Hz, 1H), 4.30 – 4.17 (m, 2H), 4.18 (t, *J* = 6.5 Hz, 2H), 1.76 – 1.60 (m, 4H), 1.52 – 1.34 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.4, 169.2, 150.7, 146.9, 146.7, 146.3, 143.2, 133.1, 129.8, 127.7, 118.7, 117.8, 117.4, 116.4, 116.1, 113.9, 88.5, 66.6, 65.4, 57.1, 32.0, 31.8, 20.2, 14.1, 14.0. HRMS (ESI): *m/z* calcd. for $C_{26}H_{31}O_8$: 471.2013 $[M+H]^+$; found: 471.1982.

4.2.42. (±)-*tert*-butyl *trans*-(*E*)-5-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-2-(3,4-dihydroxy-phenyl)-7-hydroxy-2,3-dihydrobenzofuran-3-carboxylate (**8o**)

Prepared according to the general procedure D from *tert*-butyl caffeate (**1o**, 118 mg, 0.5 mmol); isolated by flash chromatography (31 g silica gel, hexane/acetone 8:2 → 7:3); further purification by preparative RP-HPLC; colorless oil; yield: 29 mg (12%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.47 (d, *J* = 15.9 Hz, 1H), 7.07 (t, *J* = 1.4 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.20 (d, *J* = 15.8 Hz, 1H), 5.90 (d, *J* = 7.3 Hz, 1H), 4.16 (d, *J* = 7.4 Hz, 1H), 1.53 (s, 9H), 1.51 (s, 9H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 171.4, 168.6, 150.6, 146.9, 146.7, 145.4, 143.1, 133.2, 129.8, 128.0, 118.7, 117.9, 117.7, 117.0, 116.4, 113.9, 88.5, 83.4, 81.6, 58.1, 28.5, 28.3. HRMS (ESI): *m/z* calcd. for $C_{26}H_{31}O_8$: 471.2013 $[M+H]^+$; found: 471.2049.

4.2.43. (±)-Octyl *trans*-(*E*)-2-(3,4-dihydroxyphenyl)-7-hydroxy-5-(3-(octyloxy)-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (**8p**)

Prepared according to the general procedure D from octyl caffeate (**1p**, 146 mg, 0.35 mmol); isolated by flash chromatography (50 g silica gel, $CHCl_3$/MeOH 97:3); white solid; yield: 27 mg (9%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 15.9 Hz, 1H), 7.07 (br s, 1H), 6.98 (d, *J* = 1.5 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 6.11 (br s, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 5.95 (br s, 1H), 5.84 (br s, 1H), 4.26 (d, *J* = 7.4 Hz, 1H), 4.24 – 4.13 (m, 4H), 1.72 – 1.63 (m, 4H), 1.44 – 1.18 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.8, 168.1, 148.5, 144.9, 144.5, 144.1, 140.5, 132.4, 129.0, 125.7, 119.0, 117.6, 116.5, 116.0, 115.7, 113.2, 87.4, 66.4, 65.1, 55.9, 31.9, 31.9, 29.4, 29.3, 29.3, 29.3, 28.9, 28.7, 26.1, 26.0, 22.8, 22.7, 14.2, 14.2. HRMS (ESI): *m/z* calcd. for $C_{34}H_{47}O_8$: 583.3265 $[M+H]^+$; found: 583.3256.

4.2.44. (±)-Allyl *trans*-(*E*)-5-(3-(allyloxy)-3-oxoprop-1-en-1-yl)-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydrobenzofuran-3-carboxylate (**8q**)

Prepared according to the general procedure D from allyl caffeate (**1q**, 110 mg, 0.5 mmol); isolated by flash chromatography (31 g silica gel, hexane/acetone 7:3 → 6:4); white solid; yield: 11 mg (5%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.58 (d, *J* = 15.9 Hz, 1H), 7.11 (br s, 1H), 7.04 (d, *J* = 1.7 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 6.04 – 5.94 (m, 2H), 5.97 (d, *J* = 7.1 Hz, 1H), 5.34 (ddd, *J* = 17.2, 11.2, 1.6 Hz, 2H), 5.27 – 5.22 (m, 2H),

4.77 – 4.67 (m, 2H), 4.69 – 4.65 (m, 2H), 4.32 (dd, *J* = 7.2, 1.0 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 171.9, 168.6, 150.8, 146.9, 146.7, 146.6, 143.1, 133.9, 133.3, 133.0, 129.7, 127.5, 119.0, 118.7, 118.3, 118.1, 117.3, 116.4, 115.8, 113.9, 88.5, 67.2, 66.1, 57.0. HRMS (ESI): *m/z* calcd. for $C_{24}H_{23}O_8$: 439.1387 $[M+H]^+$; found: 439.1417.

4.2.45. (±)-*tert*-butyl *trans*-(*E*)-5-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-7-fluoro-2-(3-fluoro-4-hydroxyphenyl)-2,3-dihydrobenzofuran-3-carboxylate (**8r**)

Prepared according to the general procedure E from *tert*-butyl (*E*)-3-(3-fluoro-4-hydroxyphenyl)acrylate (**1r**, 119 mg, 0.5 mmol); isolated by flash chromatography (25 g silica gel, hexane/EtOAc 85:15); white solid; yield: 14 mg (6%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 15.9 Hz, 1H), 7.29 (t, *J* = 1.5 Hz, 1H), 7.22 (dd, *J* = 11.0, 1.6 Hz, 1H), 7.15 (dd, *J* = 11.1, 2.1 Hz, 1H), 7.09 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.01 (t, *J* = 8.5 Hz, 1H), 6.22 (d, *J* = 15.9 Hz, 1H), 6.09 (d, *J* = 8.0 Hz, 1H), 4.18 (d, *J* = 7.9 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.8, 166.5, 151.1 (d, *J* = 238.7 Hz), 147.7 (d, *J* = 11.6 Hz), 147.4 (d, *J* = 247.9 Hz), 144.1 (d, *J* = 14.4 Hz), 142.5 (d, *J* = 2.2 Hz), 132.6 (d, *J* = 5.7 Hz), 129.2 (d, *J* = 5.2 Hz), 128.4 (d, *J* = 3.4 Hz), 122.7 (d, *J* = 3.3 Hz), 120.8 (d, *J* = 2.9 Hz), 119.2, 117.7 (d, *J* = 2.3 Hz), 116.1 (d, *J* = 17.3 Hz), 113.6 (d, *J* = 19.6 Hz), 87.2 (d, *J* = 1.6 Hz), 83.2, 80.8, 56.4 (d, *J* = 2.2 Hz), 28.3, 28.2. ^{19}F NMR (376 MHz, Chloroform-*d*) δ –137.1 (d, *J* = 11.1 Hz), –139.7 (dd, *J* = 11.2, 8.6 Hz). HRMS (ESI): *m/z* calcd. for $C_{26}H_{29}F_2O_6$: 475.1927 $[M+H]^+$; found: 475.1944.

4.2.46. (±)-*trans*-(*E*)-2-methoxy-4-(7-methoxy-3-methyl-5-(prop-1-en-1-yl)-2,3-dihydro-benzo-furan-2-yl)phenol (**9a**)

Prepared according to the general procedure E from isoeugenol (**2a**, 82 mg, 0.5 mmol); isolated by column chromatography (25 g silica gel, hexane/EtOAc 8:2); white solid; yield: 31 mg (19%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.98 (d, *J* = 1.7 Hz, 1H), 6.92 – 6.88 (m, 2H), 6.80 (d, *J* = 1.6 Hz, 1H), 6.77 (d, *J* = 1.4 Hz, 1H), 6.37 (dd, *J* = 15.7, 1.8 Hz, 1H), 6.11 (dq, *J* = 15.6, 6.6 Hz, 1H), 5.67 (d, *J* = 1.4 Hz, 1H), 5.11 (d, *J* = 9.5 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.50 – 3.42 (m, 1H), 1.88 (dd, *J* = 6.7, 1.8 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 146.8, 146.7, 145.9, 144.3, 133.4, 132.3, 132.2, 131.0, 123.6, 120.1, 114.2, 113.4, 109.3, 109.0, 93.9, 56.1, 56.0, 45.7, 18.5, 17.7. HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}O_4$: 327.1591 $[M+H]^+$; found: 327.1621.

4.2.47. (±)-*trans*-(*E*)-4-(3-(hydroxymethyl)-5-(3-hydroxyprop-1-en-1-yl)-7-methoxy-2,3-di-hydro-benzofuran-2-yl)-2-methoxyphenol (**9b**)

Prepared according to the general procedure E from coniferyl alcohol (**2b**, 90 mg, 0.5 mmol); isolated by preparative RP-HPLC (gradient H_2O/MeOH) and further purification by column chromatography (Sephadex LH-20, MeOH); white solid; yield: 24 mg (13%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 6.96 (t, *J* = 1.2 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.54 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.22 (dt, *J* = 15.8, 5.9 Hz, 1H), 5.52 (d, *J* = 6.3 Hz, 1H), 4.20 (dd, *J* = 5.9, 1.6 Hz, 2H), 3.87 (s, 3H), 3.90 – 3.75 (m, 2H), 3.81 (s, 3H), 3.49 (q, *J* = 6.2 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 149.2, 149.1, 147.6, 145.5, 134.5, 132.6, 132.0, 130.3, 127.5, 119.8, 116.5, 116.2, 112.1, 110.5, 89.3, 64.8, 63.9, 56.7, 56.4, 55.1. HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}O_6$: 359.1489 $[M+H]^+$; found: 359.1491.

4.2.48. (±)-*trans*-(*E*)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-(3-oxo-3-(propylamino)prop-1-en-1-yl)-*N*-propyl-2,3-dihydrobenzofuran-3-carboxamide (**10a**)

Prepared according to general procedure E from **4a** (118 mg, 0.5 mmol); isolated by column chromatography (50 g aluminium oxide, $CHCl_3$/MeOH 97:3) and subsequent purification by HPLC; white solid; yield: 8 mg (14%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 (d, *J* = 15.7 Hz, 1H), 7.14 (d, *J* =

1.6 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 6.85 – 6.76 (m, 2H), 6.45 (d, *J* = 15.7 Hz, 1H), 5.94 (d, *J* = 8.3 Hz, 1H), 4.21 (d, *J* = 8.3, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.24 (q, *J* = 6.8 Hz, 4H), 1.64 – 1.50 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 173.0, 168.9, 151.2, 149.3, 148.2, 146.1, 141.5, 132.7, 130.6, 129.6, 119.9, 119.7, 117.7, 116.4, 113.4, 110.5, 90.0, 58.8, 56.8, 56.4, 42.6, 42.4, 23.7, 11.8, 11.7. HRMS (ESI): *m/z* calcd. for $C_{26}H_{33}N_2O_6$: 469.2294 $[M+H]^+$; found: 469.2370.

4.2.49. (±)-*trans*-(*E*)-2-(4-hydroxy-3-methoxyphenyl)-*N*-isopropyl-5-(3-(isopropyl-amino)-3-oxoprop-1-en-1-yl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxamide (**10b**)

Prepared according to general procedure E from **4b** (118 mg, 0.5 mmol); isolated by column chromatography (30 g silica gel, hexane/EtOAc/MeOH 1:1:0.1) and subsequent HPLC purification; white solid; yield: 21 mg (16%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.45 (d, *J* = 15.7 Hz, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 6.98 (br s, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 6.81 (d, *J* = 1.5 Hz, 2H), 6.43 (d, *J* = 15.7 Hz, 1H), 5.95 (d, *J* = 8.5 Hz, 1H), 4.18 (d, *J* = 8.4 Hz, 1H), 4.12 – 4.01 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 6H), 1.17 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 171.9, 168.0, 151.2, 149.3, 148.1, 146.1, 141.4, 132.7, 130.5, 129.8, 119.9, 119.8, 117.4, 116.4, 113.4, 110.5, 89.8, 58.7, 56.8, 56.4, 43.1, 42.6, 22.8, 22.7, 22.6. HRMS (ESI): *m/z* calcd. for $C_{26}H_{33}N_2O_6$: 469.2260 $[M+H]^+$; found: 469.2308.

4.2.50. (±)-*trans*-(*E*)-2-(3,4-dihydroxyphenyl)-7-hydroxy-*N*-isopropyl-5-(3-(isopropylamino)-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxamide (**10c**)

A 1M BBr_3 solution (CH_2Cl_2, 0.680 mL, 0.68 mmol) was dropwise added to a solution of **10b** (40 mg, 0.085 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. The solution was stirred at rt for 69 h. Afterwards, the mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4, the solvent removed under reduced pressure, and the product isolated by HPLC; colorless oil; yield: 10 mg (55%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 (d, *J* = 15.7 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 6.89 (br s, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.39 (d, *J* = 15.6 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 4.14 (d, *J* = 8.1, 1H), 4.12 – 4.01 (m, 2H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 6H), 1.20 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.2, 168.1, 150.4, 146.8, 146.7, 142.9, 141.7, 133.2, 130.4, 129.7, 119.4, 118.6, 116.6, 116.4, 116.3, 114.0, 89.5, 59.0, 43.0, 42.6, 22.8, 22.7, 22.5. HRMS (ESI): *m/z* calcd. for $C_{24}H_{29}N_2O_6$: 441.1981 $[M+H]^+$; found: 441.2053.

4.2.51. (±)-*trans*-(*E*)-2-(4-hydroxy-3-methoxyphenyl)-*N*-(2-hydroxyethyl)-5-(3-((2-hydroxy-ethyl)-amino)-3-oxoprop-1-en-1-yl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxamide (**10d**)

Prepared according to the general procedure E from compound **4d** (119 mg, 0.5 mmol); isolated by preparative RP-HPLC (gradient H_2O/MeOH) and further purification by flash chromatography (16 g silica gel, $CHCl_3$/MeOH 85:15); white solid; yield: 21 mg (12%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.47 (d, *J* = 15.6 Hz, 1H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.10 (t, *J* = 1.2 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 5.96 (d, *J* = 8.2 Hz, 1H), 4.26 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.66 (td, *J* = 5.7, 1.7 Hz, 4H), 3.48 – 3.34 (m, 4H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 173.3, 169.3, 151.2, 149.3, 148.1, 146.0, 141.8, 132.7, 130.5, 129.6, 120.0, 119.5, 117.8, 116.3, 113.6, 110.6, 89.8, 61.7, 61.5, 58.6, 56.8, 56.4, 43.3, 43.2. HRMS (ESI): *m/z* calcd. for $C_{24}H_{29}N_2O_8$: 473.1918 $[M+H]^+$; found: 473.1945.

4.2.52. (±)-*trans*-(*E*)-1-(2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-(3-methylbutanoyl)-2,3-dihydrobenzofuran-5-yl)-5-methylhex-1-en-3-one (**11a**)

Prepared according to general procedure D from **7a** (122 mg, 0.5 mmol); isolated by HPLC; white solid; yield: 13 mg (27%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (d, *J* = 16.1 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.93 (br s, 1H), 6.82 – 6.76 (m, 3H), 6.03 (d, *J* = 6.2 Hz, 1H), 4.51 (d, *J* = 6.3 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 2.72 – 2.58 (m, 4H), 2.28 – 2.12 (m, 2H), 1.01 (d, *J* = 7.6 Hz, 6H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 208.1, 203.2, 152.0, 149.3, 148.2, 146.3, 144.9, 133.0, 130.1, 128.1, 125.5, 119.9, 119.5, 116.4, 114.1, 110.6, 88.4, 64.2, 56.8, 56.4, 51.6, 50.5, 26.6, 25.3, 23.0, 23.0, 22.8, 22.7. HRMS (ESI): *m/z* calcd. for $C_{28}H_{35}O_6$: 467.2389 $[M+H]^+$; found: 467.2428.

4.2.53. (±)-*trans*-(*E*)-1-(2-(3,4-dihydroxyphenyl)-7-hydroxy-3-(3-methylbutanoyl)-2,3-dihydrobenzofuran-5-yl)-5-methylhex-1-en-3-one (**11b**)

Prepared according to general procedure D from **7b** (110 mg, 0.5 mmol), but extending the stirring period to 65 h; isolated by column chromatography (40 g silica gel, $CHCl_3$/MeOH 95:5); colorless oil; yield: 2 mg (2%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.55 (d, *J* = 16.1 Hz, 1H), 7.15 (br s, 1H), 7.08 (d, *J* = 1.8 Hz, 1H), 6.77 – 6.74 (m, 2H), 6.70 – 6.65 (m, 2H), 5.94 (d, *J* = 5.8 Hz, 1H), 4.39 (d, *J* = 5.8 Hz, 1H), 2.64 – 2.60 (m, 2H), 2.59 – 2.53 (m, 2H), 2.22 – 2.11 (m, 2H), 1.02 – 0.96 (m, 12H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 208.3, 203.2, 151.3, 149.6, 146.9, 145.1, 143.3, 133.5, 129.9, 128.1, 126.7, 125.1, 118.6, 118.4, 116.4, 113.8, 88.0, 64.7, 51.5, 50.3, 26.6, 25.4, 23.0, 23.0, 22.8. HRMS (ESI): *m/z* calcd. for $C_{26}H_{31}O_6$: 439.2076 $[M+H]^+$; found: 439.2116.

4.2.54. (±)-*trans*-(*E*)-1-(2-(3,4-dihydroxyphenyl)-3-(3,3-dimethylbutanoyl)-7-hydroxy-2,3-dihydrobenzofuran-5-yl)-5,5-dimethylhex-1-en-3-one (**11c**)

Prepared according to general procedure D from **7c** (117 mg, 0.5 mmol), but extending the stirring period to 65 h; isolated by column chromatography (40 g silica gel, $CHCl_3$/MeOH 94:6) and subsequent purification by HPLC; white solid; yield: 3 mg (3%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.52 (d, *J* = 16.1 Hz, 1H), 7.16 (br s, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.94 (d, *J* = 5.9 Hz, 1H), 4.41 (d, *J* = 5.8, 1H), 2.66 (s, 2H), 2.58 (s, 2H), 1.07 (s, 9H), 1.02 (s, 9H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 208.0, 203.1, 151.3, 146.9, 146.7, 144.8, 143.3, 133.5, 129.9, 128.2, 126.3, 118.6, 118.3, 117.4, 116.4, 113.8, 88.0, 65.7, 54.7, 54.0, 32.4, 32.0, 30.4, 30.0. HRMS (ESI): *m/z* calcd. for $C_{28}H_{35}O_6$: 467.2389 $[M+H]^+$; found: 467.2459.

4.2.55. 2-amino-4-bromophenol (**12b**)

Prepared according to the general procedure F from 4-bromophenol (1.73 g, 10 mmol); 4-bromo-2-nitrophenol was isolated by column chromatography (166 g silica gel, hexane/EtOAc 98:2); yellow crystals; yield: 1.94 g (89%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 10.49 (d, *J* = 0.9 Hz, 1H, OH), 8.25 (dd, *J* = 2.5, 0.9 Hz, 1H, H-3), 7.67 (dd, *J* = 8.9, 2.4 Hz, 1H, H-5), 7.08 (d, *J* = 9.0 Hz, 1H, H-6). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.3 (C-1), 140.5, 134.2 (C-2), 127.5, 121.9, 111.8 (C-4). HRMS (ESI): *m/z* calcd. for $C_6H_3BrNO_3$: 215.9302 $[M-H]^-$; found: 215.9286. Reduction of 4-bromo-2-nitrophenol (0.87 g, 4 mmol) afforded **12b**; red crystals; yield: 0.71 g (94%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.25 (s, 1H, OH), 6.71 (d, *J* = 2.4 Hz, 1H, H-3), 6.55 (d, *J* = 8.3 Hz, 1H, H-6), 6.48 (dd, *J* = 8.3, 2.4 Hz, 1H, H-5), 4.78 (s, 2H, NH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 143.3 (C-1), 138.9 (C-2), 118.0 (C-5), 116.0 (C-3), 115.6 (C-6), 110.6 (C-4). HRMS (ESI): *m/z* calcd. for C_6H_7BrNO: 187.9706 $[M+H]^+$; found: 187.9692.

4.2.56. 3-amino-4-hydroxybenzaldehyde (**12c**)

Prepared according to the general procedure F from 4-hydroxybenzaldehyde (1.22 g, 10 mmol); 4-hydroxy-3-nitro-benzaldehyde was isolated by column chromatography (102 g silica gel, CH_2Cl_2); yellow crystals; yield: 0.69 g (41%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 11.02 (s, 1H), 9.94 (d, *J* = 0.7

Hz, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 8.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 188.7, 159.4, 136.5, 133.7, 129.4, 128.7, 121.4. HRMS (ESI): m/z calcd. for $C_7H_6NO_4$: 168.0291 $[M+H]^+$; found: 168.0302. Reduction of 4-hydroxy-3-nitro-benzaldehyde (0.67 g, 4 mmol) afforded **12c**; red-brownish solid; yield: 0.15 g (27%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 191.6, 150.6, 137.6, 129.2, 122.2, 113.9, 112.4. HRMS (ESI): m/z calcd. for $C_7H_8NO_2$: 138.0550 $[M+H]^+$; found: 138.0547.

4.2.57. (±)-*trans*-2-methoxy-4-(3-methyl-2,3-dihydrobenzofuran-2-yl)phenol (**13a**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and isoeugenol (**2a**, 197 mg, 1.2 mmol); isolated by flash chromatography (32 g silica gel, hexane/Et_2O 8:2); yellowish oil; yield: 154 mg (60%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.19 (tdd, *J* = 7.9, 7.4, 2.3, 1.2 Hz, 1H), 7.15 (dd, *J* = 7.3, 1.4 Hz, 1H), 6.98 (d, *J* = 1.2 Hz, 1H), 6.94 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 1.1 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.64 (d, *J* = 2.1 Hz, 1H), 5.08 (d, *J* = 9.2 Hz, 1H), 3.89 (s, 3H), 3.49 – 3.41 (m, 1H), 1.41 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.3, 146.9, 145.9, 132.5, 132.2, 128.4, 123.7, 120.9, 119.8, 114.4, 109.7, 108.7, 92.9, 56.1, 45.5, 17.7. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}O_3$: 257.1172 $[M+H]^+$; found: 257.1168.

4.2.58. (±)-*trans*-4-(3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)-2-methoxyphenol (**13b**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and (*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol (**2b**, 216 mg, 1.2 mmol); isolated by column chromatography (112 g silica gel, hexane/EtOAc 8:2 → 6:4); yellowish oil; yield: 154 mg (56%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.24 – 7.20 (m, 2H), 6.95 – 6.87 (m, 5H), 5.68 (br s, 1H), 5.53 (d, *J* = 6.8 Hz, 1H), 3.97 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.92 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.86 (s, 3H), 3.62 – 3.56 (m, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.1, 146.8, 145.7, 133.5, 129.2, 126.7, 124.5, 120.9, 119.2, 114.5, 109.9, 108.6, 87.2, 64.3, 56.1, 53.4. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}O_4$: 273.1121 $[M+H]^+$; found: 273.1140.

4.2.59. (±)-*trans*-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (**13c**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and anethole (**2c**, 178 mg, 1.2 mmol); isolated by flash chromatography (26 g silica gel, hexane/CH_2Cl_2 9:1 → 8:2); yellowish oil; yield: 95 mg (39%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.7 Hz, 2H), 7.18 (tdd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.15 (dt, *J* = 7.4, 1.4 Hz, 1H), 6.94 – 6.90 (m, 3H), 6.86 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.11 (d, *J* = 9.0 Hz, 1H), 3.82 (s, 3H), 3.48 – 3.41 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.8, 159.3, 132.9, 132.2, 128.4, 127.8, 123.7, 120.8, 114.1, 109.6, 92.5, 55.5, 45.4, 17.9. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}O_2$: 241.1223 $[M+H]^+$; found: 241.1230.

4.2.60. (±)-*trans*-(2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl)methanol (**13d**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and **2d** (233 mg, 1.2 mmol); isolated by column chromatography (73 g silica gel, hexane/EtOAc 3:1 → 3:2); yellowish oil; yield: 96 mg (33%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.22 (ddt, *J* = 7.7, 6.8, 1.2 Hz, 2H), 6.95 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.93 – 6.92 (m, 2H), 6.90 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 5.55 (d, *J* = 6.8 Hz, 1H), 4.00 – 3.89 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.59 (q, *J* = 6.1 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.1, 149.3, 149.1, 134.1, 129.2, 126.7, 124.5, 120.9, 118.5, 111.2, 109.8, 109.1, 87.0, 64.3, 56.1, 56.0, 53.4. HRMS (ESI): *m/z* calcd. for $C_{17}H_{19}O_4$: 287.1278 $[M+H]^+$; found: 287.1291.

4.2.61. (±)-*trans*-4-(3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)phenol (**13e**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and **2e** (180 mg, 1.2 mmol); isolated by column chromatography (83 g silica gel, hexane/EtOAc 7:3); yellowish oil; yield: 119 mg (49%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.24 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.15 (tdd, *J* = 8.2, 1.4, 0.6 Hz, 1H), 6.86 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.46 (d, *J* = 6.0 Hz, 1H), 3.82 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.75 (dd, *J* = 11.0, 7.2 Hz, 1H), 3.46 (q, *J* = 6.1 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 161.2, 158.4, 134.4, 129.7, 128.8, 128.2, 125.9, 121.6, 116.2, 110.1, 88.2, 65.2, 54.9. HRMS (ESI): *m/z* calcd. for $C_{15}H_{15}O_3$: 243.1016 $[M+H]^+$; found: 243.1022.

4.2.62. (±)-*trans*-(2-(4-methoxyphenyl)-2,3-dihydrobenzofuran-3-yl)methanol (**13f**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and **2f** (198 mg, 1.2 mmol); isolated by flash chromatography (51 g silica gel, $CHCl_3$/EtOAc 100:0 → 97:3); yellowish oil; yield: 78 mg (31%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 8.8 Hz, 2H), 7.24 – 7.19 (m, 2H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 6.90 – 6.85 (m, 3H), 5.56 (d, *J* = 6.4 Hz, 1H), 4.01 – 3.89 (m, 2H), 3.80 (s, 3H), 3.58 (dt, *J* = 7.4, 5.5 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.2, 159.6, 133.8, 129.2, 127.4, 126.7, 124.6, 120.8, 114.2, 114.2, 109.8, 64.5, 55.4, 53.5. HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}O_3$: 257.1172 $[M+H]^+$; found: 257.1190.

4.2.63. (±)-*trans*-(2-(4-methoxyphenyl)-2,3-dihydrobenzofuran-3-yl)methyl acetate (**13g**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and **2g** (248 mg, 1.2 mmol); isolated by column chromatography (120 g silica gel, hexane/EtOAc 95:5); yellowish oil; yield: 45 mg (15%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.6 Hz, 2H), 7.24 – 7.19 (m, 2H), 6.93 – 6.86 (m, 4H), 5.45 (d, *J* = 6.7 Hz, 1H), 4.43 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.31 (dd, *J* = 11.0, 7.8 Hz, 1H), 3.81 (s, 3H), 3.74 (dtt, *J* = 7.6, 6.6, 0.9 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.0, 159.8, 159.8, 133.2, 129.4, 127.4, 126.3, 124.8, 121.0, 114.2, 109.9, 87.3, 65.9, 55.5, 50.2, 21.0. HRMS (ESI): *m/z* calcd. for $C_{18}H_{18}NaO_4$: 321.1097 $[M+Na]^+$; found: 321.1125.

4.2.64. (±)-*trans*-(2-(2-bromophenyl)-2,3-dihydrobenzofuran-3-yl)methanol (**13h**)

Prepared according to the general procedure H from *o*-aminophenol (**12a**, 109 mg, 1 mmol) and **2h** (255 mg, 1.2 mmol); isolated by flash chromatography (38 g silica gel, hexane/EtOAc 9:1 → 8:2); yellowish oil; yield: 4 mg (1%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.25 – 7.20 (m, 1H), 7.14 (td, *J* = 7.6, 1.8 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.93 (td, *J* = 7.4, 1.0 Hz, 1H), 5.91 (d, *J* = 4.4 Hz, 1H), 4.13 (dd, *J* = 11.0, 4.8 Hz, 1H), 4.04 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.50 (q, *J* = 4.9 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.3, 140.9, 133.1, 129.5, 129.4, 127.9, 127.4, 126.4, 125.2, 121.4, 121.2, 109.8, 85.2, 65.3, 53.3. HRMS (ESI): *m/z* calcd. for $C_{15}H_{14}BrO_2$: 305.0172 $[M+H]^+$; found: 305.0174.

4.2.65. (±)-*trans*-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran-5-carbaldehyde (**13i**)

Prepared according to the general procedure H from **12c** (137 mg, 1 mmol) and anethole (**2c**, 177 mg, 1.2 mmol); isolated by flash chromatography (75 g silica gel, hexane/Et_2O 9:1 → 8:2); yellowish oil; yield: 21 mg (8%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.87 (s, 1H), 7.75 – 7.70 (m, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.23 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.52 – 3.44 (m, 1H), 1.45 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 190.8, 164.8, 160.1, 133.8, 133.6, 131.8, 130.9, 127.8, 124.7, 114.3, 109.9, 94.0, 55.5, 44.5, 18.0. HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}O_3$: 269.1172 $[M+H]^+$; found: 269.1174.

4.2.66. (±)-*trans*-(*E*)-4-(2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran-5-yl)but-3-en-2-one (**13j**)

Obtained as side product by the reaction of synthesis of compound **13i** and purified therefore out of the same chromatographic separation; yellowish oil; yield: 12 mg (4%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 16.2 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 16.2 Hz, 1H), 5.17 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 3.50 – 3.41 (m, 1H), 2.36 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 198.5, 161.8, 160.0, 143.9, 133.5, 132.1, 130.4, 127.8, 127.7, 124.7, 123.4, 114.3, 110.1, 93.4, 55.5, 44.9, 27.6, 18.0. HRMS (ESI): *m/z* calcd. for $C_{20}H_{21}O_3$: 309.1485 $[M+H]^+$; found: 309.1497.

4.2.67. (±)-*trans*-4-(5-bromo-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)phenol (**13k**)

Prepared according to the general procedure H from **12b** (188 mg, 1 mmol) and **2e** (180 mg, 1.2 mmol); isolated by column chromatography (67 g silica gel, CH_2Cl_2/EtOAc 95:5); brownish oil; yield: 124 mg (39%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.32 (dd, *J* = 2.2, 1.0 Hz, 1H, H-4), 7.30 (ddd, *J* = 8.5, 2.2, 0.7 Hz, 1H, H-6), 7.22 (d, *J* = 8.5 Hz, 2H, H-2'/H-6'), 6.78 (d, *J* = 8.6 Hz, 2H, H-3',H-5'), 6.75 (d, *J* = 8.4 Hz, 1H, H-7), 5.53 (d, *J* = 6.4 Hz, 1H, H-2), 3.93 (dd, J = 10.9, 6.3 Hz, 1H, CH_2-a), 3.89 (dd, J = 10.9, 5.3 Hz, 1H, CH_2-b), 3.61 – 3.52 (m, 1H, H-3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.2, 155.9, 133.3, 132.0, 129.4, 127.7, 127.6, 115.7, 112.6, 111.4, 87.5, 64.4, 53.2. HRMS (ESI): *m/z* calcd. for $C_{15}H_{14}BrO_3$: 321.0121 $[M+H]^+$; found: 321.0135.

4.2.68. (±)-*trans*-(5-bromo-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-3-yl)methyl acetate (**13l**)

Obtained as side product by reaction of **12b** and **2e** according to the general procedure H but stirring over a period of 40 h; isolated by column chromatography (56 g silica gel, CH_2Cl_2/EtOAc 95:5); brownish solid; yield: 46 mg (14%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.31 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 1H), 5.43 (d, *J* = 6.8 Hz, 1H), 4.38 (dd, *J* = 11.1, 5.9 Hz, 1H), 4.30 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.71 (q, *J* = 6.9 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.1, 158.9, 156.0, 132.7, 132.2, 128.9, 127.9, 127.6, 115.8, 112.7, 111.5, 87.8, 65.5, 50.1, 20.9. HRMS (ESI): *m/z* calcd. for $C_{17}H_{15}BrNaO_4$: 385.0046 $[M+Na]^+$; found: 385.0064.

4.2.69. (±)-*trans*-4-(5-bromo-3-methyl-2,3-dihydrobenzofuran-2-yl)-2-methoxyphenol (**14a**)

Prepared according to the general procedure I from compound **13a** (128 mg, 0.78 mmol) and NBS; isolated by successive flash chromatography (32 g silica gel, hexane/EtOAc 85:15; 50 g silica gel, hexane/CH_2Cl_2 3:7); white solid; yield: 109 mg (65%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 – 7.26 (m, 1H), 7.23 (dd, *J* = 2.2, 1.3 Hz, 1H), 6.93 – 6.91 (m, 2H), 6.89 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.67 (s, 1H), 5.09 (d, *J* = 9.2 Hz, 1H), 3.89 (s, 3H), 3.47 – 3.40 (m, 1H), 1.39 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.4, 146.9, 146.1, 134.7, 131.9, 131.1, 126.9, 119.8, 114.4, 112.7, 111.2, 108.6, 93.4, 56.1, 45.4, 17.7. HRMS (ESI): *m/z* calcd. for $C_{16}H_{16}BrO_3$: 335.0277 $[M+H]^+$; found: 335.0275.

4.2.70. (±)-*trans*-4-(5-bromo-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)-2-methoxy-phenol (**14b**)

Prepared according to the general procedure I from compound **13b** (136 mg, 0.5 mmol) and NBS; isolated by preparative RP-HPLC (C18, gradient H_2O/MeOH); white solid; yield: 97 mg (55%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.34 – 7.32 (m, 1H), 7.30 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.69 (br s, 1H), 5.52 (d, *J* = 6.8 Hz, 1H), 3.94 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.89 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.86 (s, 3H), 3.57 (q, *J* = 6.0 Hz, 1H), 1.69 (br s, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.2, 146.9, 145.9, 132.9, 132.0, 129.5, 127.6, 119.2, 114.6, 112.6, 111.4, 108.5, 87.7, 64.1, 56.1, 53.2. HRMS (ESI): *m/z* calcd. for $C_{16}H_{16}BrO_4$: 351.0226 $[M+H]^+$; found: 351.0236.

4.2.71. (±)-*trans*-5-bromo-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (**14c**)

Prepared according to the general procedure I from **13c** (120 mg, 0.5 mmol) and NBS; isolated by flash chromatography (53 g silica gel, hexane/EtOAc 10:0 → 8:2); colorless oil; yield: 141 mg (88%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.9 Hz, 2H, H-2'/H-6'), 7.26 (dd, *J* = 8.3, 2.1 Hz, 1H, H-6), 7.23 (d, *J* = 2.2 Hz, 1H, H-4), 6.92 (d, *J* = 8.7 Hz, 2H, H-3'/H-5'), 6.72 (d, *J* = 8.4 Hz, 1H, H-7), 5.12 (d, *J* = 8.9 Hz, 1H, H-2), 3.82 (s, 3H, OCH_3), 3.47 – 3.40 (m, 1H, H-3), 1.38 (d, *J* = 6.8 Hz, 3H, 3-CH_3). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.0 (C-4'), 158.5 (C-7a), 134.7 (C-3a), 132.2 (C-1'), 131.1 (C-6), 127.8 (C-2'/C-6'), 126.9 (C-4), 114.2 (C-3'/C-5'), 112.6 (C-5), 111.2 (C-7), 93.0 (C-2), 55.5 (OCH_3), 45.4 (C-3), 17.9 (3-CH_3). HRMS (ESI): *m/z* calcd. for $C_{16}H_{16}BrO_2$: 319.0328 $[M+H]^+$; found: 319.0303.

4.2.72. (±)-*trans*-(5-bromo-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl)methanol (**14d**)

Prepared according to the general procedure I from compound **13d** (143 mg, 0.5 mmol) and NBS; isolated by flash chromatography (108 g silica gel, hexane/EtOAc 8:2); white solid; yield: 126 mg (69%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.40 – 7.37 (m, 1H, H-4), 7.28 (dd, *J* = 8.5, 2.1 Hz, 1H, H-6), 6.95 (br s, 1H, H-6'), 6.91 (m, 2H, H-2'/H-5'), 6.74 (d, *J* = 8.5 Hz, 1H, H-7), 5.51 (d, *J* = 6.3 Hz, 1H, H-2), 3.81 (s, 3H, 4'-OCH_3), 3.81 – 3.79 (m, 2H, CH_2), 3.79 (s, 3H, 3'-OCH_3), 3.49 (q, *J* = 6.2 Hz, 1H, H-3). ^{13}C NMR (151 MHz, Methanol-d_4) δ 160.5 (C-7a), 150.6 (C-3'), 150.4 (C-4'), 135.7 (C-1'), 132.5 (C-6), 131.8 (C-3a), 129.0 (C-4), 119.4, 113.2 (C-5), 112.9, 111.9 (C-7), 110.6 (C-6'), 88.7 (C-2), 64.6 (CH_2), 56.5 (4'-OCH_3), 56.4 (3'-OCH_3), 54.8 (C-3). HRMS (ESI): *m/z* calcd. for $C_{17}H_{18}BrO_4$: 365.0383 $[M+H]^+$; found: 365.0380.

4.2.73. (±)-*trans*-4-(5-chloro-3-methyl-2,3-dihydrobenzofuran-2-yl)-2-methoxyphenol (**14m**)

Prepared according to the general procedure I from compound **13a** (128 mg, 0.5 mmol) and NCS; isolated by flash chromatography (34 g silica gel, hexane/CH_2Cl_2 3:7) and purified by preparative RP-HPLC (gradient H_2O/MeOH); white solid; yield: 43 mg (30%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.14 – 7.12 (m, 1H), 7.10 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.07 (d, *J* = 8.9 Hz, 1H), 3.82 (s, 3H), 3.44 – 3.36 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 159.3, 149.2, 147.9, 135.8, 133.0, 129.0, 126.4, 124.9, 120.4, 116.1, 111.2, 110.8, 94.7, 56.4, 46.5, 17.9. HRMS (ESI): *m/z* calcd. for $C_{16}H_{16}ClO_3$: 291.0782 $[M+H]^+$; found: 291.0808.

4.2.74. (±)-*trans*-5-bromo-4-(5-bromo-3-methyl-2,3-dihydrobenzofuran-2-yl)-2-methoxy-phenol (**15a**)

Obtained during bromination of **13a** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **14a**; white solid; yield: 21 mg (10%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.22 (dd, *J* = 2.1, 1.0 Hz, 1H), 7.13 (s, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 5.63 (s, 1H), 5.60 (d, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 3.45 – 3.31 (m, 1H), 1.50 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.3, 146.4, 146.2, 134.4, 131.5, 131.3, 127.3, 118.7, 113.0, 112.6, 111.1, 109.2, 90.8, 56.2, 46.1, 19.5. HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}Br_2O_3$: 412.9382 $[M+H]^+$; found: 412.9375.

4.2.75. (±)-*trans*-5-bromo-4-(5-bromo-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)-2-meth-oxyphenol (**15b**)

Obtained during bromination of **13b** according to the general procedure I and purified out of the mixture by the same chromatographic separation as **14b**; white solid; yield: 14 mg (6%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 2.2 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.13 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 5.65 (br s, 1H), 4.10 (dd, *J* = 10.9, 4.7 Hz, 1H), 4.00 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.78 (s, 3H), 3.48 (q, *J* = 5.4 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.3, 146.5, 146.3, 132.1, 131.5, 129.6, 128.2, 118.8, 113.1, 112.0, 111.2, 109.2, 86.0, 64.5, 56.2, 53.4. HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}Br_2O_4$: 428.9332 $[M+H]^+$; found: 428.9360.

4.2.76. (±)-*trans*-5-bromo-2-(3-bromo-4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (**15c**)

Obtained during bromination of **13c** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **14c**; white solid; yield: 10 mg (5%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.27 (ddd, *J* = 8.2, 2.0, 0.7 Hz, 1H), 7.23 (dd, *J* = 2.2, 1.2 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 5.09 (d, *J* = 8.7 Hz, 1H), 3.91 (s, 3H), 3.44 – 3.37 (m, 1H), 1.40 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.3, 156.1, 134.3, 133.9, 131.3, 131.3, 127.0, 126.6, 112.9, 112.1, 112.0, 111.3, 92.1, 56.5, 45.6, 18.0. HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}Br_2O_2$: 396.9433 $[M+H]^+$; found: 396.9383.

4.2.77. (±)-*trans*-(5-bromo-2-(2-bromo-4,5-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl)methanol (**15d**)

Obtained bromination of **13d** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **14d**; yellowish oil; yield: 46 mg (21%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.41 (d, *J* = 1.1 Hz, 1H, H-4), 7.31 (dd, *J* = 8.5, 1.8 Hz, 1H, H-6), 7.13 (s, 1H, H-5'), 6.84 (s, 1H, H-2'), 6.80 (d, *J* = 8.4 Hz, 1H, H-7), 5.80 (d, *J* = 5.4 Hz, 1H, H-2), 4.00 (dd, *J* = 11.0, 4.7 Hz, 1H, CH_2-a), 3.86 (dd, *J* = 10.9, 6.4 Hz, 1H, CH_2-b), 3.81 (s, 3H, 4'-OCH_3), 3.68 (s, 3H, 3'-OCH_3), 3.45 (q, *J* = 5.6 Hz, 1H, H-3). ^{13}C NMR (151 MHz, Methanol-d_4) δ 160.6 (C-7a), 151.0 (C-4'), 150.3 (C-3'), 133.8 (C-1'), 132.7 (C-6), 132.0 (C-3a), 129.4 (C-4), 117.2 (C-5'), 113.6 (C-5), 112.6 (C-6'), 111.8 (C-7), 111.6 (C-2'), 87.1 (C-2), 64.7 (CH_2), 56.7 (4'-OCH_3), 56.5 (3'-OCH_3), 54.4 (C-3). HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}Br_2O_4$: 442.9488 $[M+H]^+$; found: 442.9499.

4.2.78. (±)-*trans*-2-chloro-4-(5-chloro-3-methyl-2,3-dihydrobenzofuran-2-yl)-6-methoxy-phenol (**15m**)

Obtained during bromination of **13a** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **14m**; white solid; yield: 12 mg (7%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.15 (dd, *J* = 2.3, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.4, 2.3, 0.9 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 8.6 Hz, 1H), 3.86 (s, 3H), 3.42 – 3.36 (m, 1H), 1.39 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 159.2, 150.2, 144.4, 135.5, 133.2, 129.1, 126.6, 125.0, 121.3, 120.6, 111.3, 108.8, 93.8, 56.8, 46.7, 18.2. HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}Cl_2O_3$: 325.0393 $[M+H]^+$; found: 325.0404.

4.2.79. (±)-*trans*-2-bromo-4-(5-bromo-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)phenol (**15n**)

Obtained during bromination of **13e** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **15q**; white solid; yield: 17 mg (8%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.45 (d, *J* = 2.2 Hz, 1H), 7.39 (dd, *J* = 2.3, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.5, 2.2, 0.8 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 5.48 (d, *J* = 6.1 Hz, 1H), 3.81 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.77 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.48 – 3.44 (m, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 160.4, 155.4, 135.5, 132.6, 131.6, 131.5, 129.0, 127.1, 117.3, 113.3, 111.9, 110.8, 87.9, 64.7, 54.8. HRMS (ESI): *m/z* calcd. for $C_{15}H_{13}Br_2O_3$: 398.9226 $[M+H]^+$; found: 398.9257.

4.2.80. (±)-*trans*-2-bromo-4-(5-bromo-3-methyl-2,3-dihydrobenzofuran-2-yl)-6-methoxy-phenol (**15o**)

Obtained during bromination of **13a** according to the general procedure I and purified out of the crude mixture by the first chromatographic separation of **14a**; white solid; yield: 5 mg (3%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (ddd, *J* = 8.4, 2.2, 0.9 Hz, 1H), 7.23 (dd, *J* = 2.1, 1.2 Hz, 1H), 7.13 (d, *J* = 1.8 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 5.95 (s, 1H), 5.05 (d, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 3.44 – 3.38 (m, 1H), 1.40 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.2, 147.6,

143.4, 134.3, 133.0, 131.3, 127.0, 122.8, 113.0, 111.3, 108.3, 107.8, 92.5, 56.6, 45.6, 17.9. HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}Br_2O_3$: 412.9382 $[M+H]^+$; found: 412.9339.

4.2.81. (±)-*trans*-2-bromo-4-(5-bromo-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)-6-methoxyphenol (**15p**)

Obtained during bromination of **13b** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **14b**; white solid; yield: 7 mg (3%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.34 – 7.30 (m, 2H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 1.9 Hz, 1H), 6.78 (d, *J* = 9.1 Hz, 1H), 5.93 (s, 1H), 5.52 (d, *J* = 6.5 Hz, 1H), 3.94 (dd, *J* = 5.8, 3.0 Hz, 2H), 3.88 (s, 3H), 3.58 – 3.52 (m, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.1, 147.5, 143.2, 134.0, 132.1, 129.0, 127.7, 122.2, 112.9, 111.5, 108.4, 107.6, 86.9, 64.2, 56.6, 53.4. HRMS (ESI): *m/z* calcd. for $C_{16}H_{15}Br_2O_4$: 428.9332 $[M+H]^+$; found: 428.9339.

4.2.82. (±)-*trans*-2,6-dibromo-4-(3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)phenol (**15q**)

Obtained by bromination of compound **13e** (121 mg, 0.5 mmol) according to the general procedure I; isolated by flash chromatography (35 g silica gel, CH_2Cl_2/EtOAc 10:0 → 9:1); white solid; yield: 18 mg (9%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.50 (s, 2H), 7.24 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.19 (dt, *J* = 7.5, 1.3 Hz, 1H), 6.94 (td, *J* = 7.4, 1.0 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.90 (s, 1H), 5.54 (d, *J* = 6.0 Hz, 1H), 3.97 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.92 (dd, *J* = 10.8, 6.9 Hz, 1H), 3.56 – 3.51 (m, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.7, 149.2, 136.7, 129.5, 129.5, 125.8, 124.7, 121.3, 110.2, 110.0, 85.2, 64.6, 53.7. HRMS (ESI): *m/z* calcd. for $C_{15}H_{13}Br_2O_3$: 398.9226 $[M+H]^+$; found: 398.9243.

4.2.83. (±)-*trans*-2-bromo-4-(3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)phenol (**15r**)

Obtained during bromination of **13e** according to the general procedure I and purified out of the crude mixture by the same chromatographic separation as **15q**; white solid; yield: 6 mg (4%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 2.2 Hz, 1H), 7.25 (dd, J = 8.4, 2.2 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.21 – 7.19 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91 – 6.89 (m, 1H), 5.59 (s, 1H), 5.54 (d, *J* = 6.2 Hz, 1H), 3.94 (d, *J* = 5.8 Hz, 2H), 3.55 (q, *J* = 6.0 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.9, 152.2, 135.6, 129.6, 129.4, 126.9, 126.2, 124.6, 121.1, 116.4, 110.5, 109.9, 85.9, 64.6, 53.6. HRMS (ESI): *m/z* calcd. for $C_{15}H_{14}BrO_3$: 321.0121 $[M+H]^+$; found: 321.0137.

4.2.84. (±)-*trans*-2-iodo-6-methoxy-4-(3-methyl-2,3-dihydrobenzofuran-2-yl)phenol (**15s**)

Prepared according to the general procedure I from compound **13a** (128 mg, 0.44 mmol) and NIS; isolated by flash chromatography (34 g silica gel, hexane/CH_2Cl_2 3:7) and purified by preparative RP-HPLC (gradient H_2O/MeOH); white solid; yield: 23 mg (12%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.29 (d, *J* = 1.9 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.96 (d, *J* = 1.9 Hz, 1H), 6.89 (td, *J* = 7.4, 1.0 Hz, 1H), 6.79 (dt, *J* = 7.8, 0.7 Hz, 1H), 5.01 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 3.41 – 3.33 (m, 1H), 1.39 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 160.3, 148.5, 148.0, 135.2, 133.2, 129.4, 129.3, 124.8, 122.0, 110.2, 110.1, 92.9, 83.3, 56.6, 46.8, 18.4. HRMS (ESI): *m/z* calcd. for $C_{16}H_{16}IO_3$: 383.0139 $[M+H]^+$; found: 383.0159.

4.2.85. (±)-*tert*-butyl *trans*-(*E*)-3-(2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran-5-yl)-acrylate (**16c**)

Prepared according to the general procedure J from compound **14c** (99 mg, 0.31 mmol) using P(*o*-tol)$_3$; isolated by flash chromatography (22 g silica gel, hexane/EtOAc 95:5); colorless oil; yield: 107 mg (94%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 15.9 Hz, 1H), 7.36 – 7.31 (m, 4H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.24 (d, *J* = 15.9 Hz, 1H), 5.15 (d, *J* = 8.9 Hz, 1H), 3.82 (s, 3H), 3.43 (dddd, *J* = 9.8, 8.1, 6.8, 5.8 Hz, 1H), 1.53 (s, 9H), 1.41 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz,

Chloroform-*d*) δ 166.9, 161.2, 159.9, 143.8, 133.2, 132.3, 129.8, 128.0, 127.8, 123.1, 117.3, 114.2, 109.9, 93.3, 80.3, 55.5, 45.0, 28.4, 17.9. HRMS (ESI): *m/z* calcd. for $C_{23}H_{27}O_4$: 367.1904 $[M+H]^+$; found: 367.1918.

4.2.86. (±)-*tert*-butyl *trans*-(*E*)-3-(2-(3,4-dimethoxyphenyl)-3-(hydroxymethyl)-2,3-dihydrobenzofuran-5-yl)acrylate (**16d**)

Prepared according to the general procedure J from compound **14d** (114 mg, 0.31 mmol) using P(*o*-tol)$_3$; isolated by preparative RP-HPLC (gradient H_2O/MeOH); colorless oil; yield: 59 mg (46%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 15.9 Hz, 1H), 7.41 (d, *J* = 1.7 Hz, 1H) , 7.37 (br d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 5.59 (d, *J* = 6.7 Hz, 1H), 3.97 (dd, *J* = 10.8, 6.3 Hz, 1H), 3.93 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.59 (q, *J* = 6.1 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.9, 161.9, 149.4, 149.2, 143.5, 133.6, 130.4, 128.1, 128.1, 124.0, 118.5, 117.5, 111.3, 110.1, 109.1, 88.0, 80.4, 64.2, 56.1, 56.1, 52.9, 28.4. HRMS (ESI): *m/z* calcd. for $C_{24}H_{29}O_6$: 413.1959 $[M+H]^+$; found: 413.1959.

4.2.87. (±)-*tert*-butyl *trans*-(*E*)-3-(3-(hydroxymethyl)-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-5-yl)acrylate (**16k**)

Prepared according to the general procedure J from compound **13k** (100 mg, 0.31 mmol) using PPh_3; isolated by flash chromatography (27 g silica gel, hexane/CH_2Cl_2 1:9 → 0:10) and subsequent purification by preparative RP-HPLC (gradient H_2O/MeOH); yellowish oil; yield: 8 mg (7%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.42 (br s, 1H, OH_{phenol}), 7.65 (t, *J* = 1.5 Hz, 1H), 7.55 (d, *J* = 15.9 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 5.62 (d, *J* = 6.2 Hz, 1H), 4.20 (br t, *J* = 5.4 Hz, 1H, $OH_{alcohol}$), 3.98 – 3.83 (m, 2H), 3.54 (q, *J* = 6.2 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 166.9, 163.0, 158.3, 144.6, 133.7, 131.1, 130.4, 128.5, 128.2, 125.5, 117.8, 116.3, 110.2, 88.8, 80.2, 64.6, 54.2, 28.5. HRMS (ESI): *m/z* calcd. for $C_{22}H_{25}O_5$: 369.1697 $[M+H]^+$; found: 369.1686.

4.2.88. (±)-*trans*-4-(5-bromo-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)benzene-1,2-diol (**17b**)

Prepared according to the general procedure K from compound **14b** (70 mg, 0.2 mmol); isolated by column chromatography (19 g silica gel, hexane/EtOAc 6:4); white solid; yield: 49 mg (73%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.38 (br s, 1H), 7.27 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.40 (d, *J* = 6.1 Hz, 1H), 3.77 (d, *J* = 5.9 Hz, 2H), 3.46 (q, *J* = 6.1 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 160.6, 146.5, 146.4, 134.5, 132.4, 132.0, 129.0, 118.5, 116.2, 113.8, 113.0, 111.8, 88.8, 64.7, 54.7. HRMS (ESI): *m/z* calcd. for $C_{15}H_{14}BrO_4$: 337.0070 $[M+H]^+$; found: 337.0060.

4.2.89. (±)-*trans*-4-(5-bromo-3-methyl-2,3-dihydrobenzofuran-2-yl)phenol (**17c**)

Prepared according to the general procedure K from compound **14c** (64 mg, 0.2 mmol); isolated by flash chromatography (11 g silica gel, hexane/EtOAc 9:1); white solid; yield: 43 mg (71%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.25 (m, 1H), 7.23 (dd, *J* = 2.1, 1.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.20 – 5.13 (br s, 1H), 5.11 (d, *J* = 8.9 Hz, 1H), 3.46 – 3.39 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.3, 155.9, 134.6, 132.4, 131.1, 128.0, 126.9, 115.7, 112.7, 111.2, 93.0, 45.4, 17.9. HRMS (ESI): *m/z* calcd. for $C_{15}H_{14}BrO_2$: 305.0172 $[M+H]^+$; found: 305.0172.

4.2.90. (±)-*trans*-(*E*)-3-(2-(4-hydroxyphenyl)-3-methyl-2,3-dihydrobenzofuran-5-yl)acrylic acid (**18**)

Prepared according to the general procedure K from compound **16c** (72 mg, 0.2 mmol); isolated by column chromatography (18 g silica gel, CH_2Cl_2/MeOH 95:5); white solid; yield: 31 mg (53%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (d, *J* = 15.9 Hz, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.39 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 5.11 (d, *J* = 8.7 Hz, 1H), 3.38 (quint, *J* = 7.0 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 171.0, 162.8, 158.8, 146.7, 134.8, 132.4, 131.0, 128.9, 128.8, 124.5, 116.4, 116.0, 110.5, 94.7, 46.1, 18.2. HRMS (ESI): *m/z* calcd. for $C_{18}H_{17}O_4$: 297.1121 $[M+H]^+$; found: 297.1154.

4.2.91. (±)-*tert*-butyl *trans*-(*E*)-2-(4-acetoxyphenyl)-5-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-2,3-dihydro-benzofuran-3-carboxylate (**19**)

The procedure was adapted from literature [57]. In a small vial a mixture of compound **8e** (14 mg, 0.032 mmol), Ac_2O (16 µL, 0.17 mmol), $NaHCO_3$ (6 mg, 0.071 mmol), and toluene (400 µL) was stirred at rt for 24 h. Afterwards the mixture was filtered and concentrated under reduced pressure. The residue was partitioned between water and CH_2Cl_2; the layers were separated and the aqueous one was further extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash chromatography (5 g silica gel, hexane/EtOAc 9:1); white solid; yield: 14 mg (88%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 15.9 Hz, 1H), 7.53 (t, *J* = 1.6 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 6.10 (d, *J* = 7.6 Hz, 1H), 4.16 (d, *J* = 7.6 Hz, 1H), 2.30 (s, 3H), 1.53 (s, 9H), 1.53 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.6, 169.4, 166.8, 161.0, 150.8, 143.5, 138.2, 130.3, 128.3, 127.1, 125.4, 125.1, 122.1, 117.7, 110.3, 85.9, 82.8, 80.5, 56.2, 28.4, 28.3, 21.3. HRMS (ESI): *m/z* calcd. for $C_{28}H_{33}O_7$: 481.2221 $[M+H]^+$; found: 481.2232.

4.2.92. (±)-*tert*-butyl *trans*-(*E*)-5-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-2-(4-(*tert*-butoxy)-phenyl)-2,3-dihydrobenzofuran-3-carboxylate (**20**)

The procedure was adopted from literature [58]. In a small vial $Sc(OTf)_3$ (1.6 mg, 5.1 mol%) and compound **8e** (28 mg, 0.064 mmol) were mixed in CH_2Cl_2 (1 mL). Then, Boc_2O (60 mg, 0.27 mmol) was added and the mixture stirred at rt for 48 h after which the maximum amount of product remained constant as indicated by TLC. The crude was therefore quenched with water and the product extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash chromatography (6.5 g silica gel, hexane/EtOAc 95:5 → 85:15); white solid; yield: 12 mg (39%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 15.9 Hz, 1H), 7.53 (t, *J* = 1.6 Hz, 1H), 7.41 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 6.06 (d, *J* = 7.6 Hz, 1H), 4.18 (d, *J* = 7.6 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.5, 166.9, 161.1, 155.8, 143.6, 135.2, 130.3, 128.1, 126.7, 125.7, 125.1, 124.4, 117.6, 110.3, 86.5, 82.6, 80.4, 78.9, 56.1, 29.0, 28.4, 28.3. HRMS (ESI): *m/z* calcd. for $C_{30}H_{37}O_6$: 493.2596 $[M-H]^-$; found: 493.2610.

4.2.93. (±)-*tert*-butyl *trans*-(*E*)-3-(2-(3,4-dimethoxyphenyl)-3-(fluoromethyl)-2,3-dihydrobenzofuran-5-yl)acrylate (**21**)

Obtained as a minor product from the reaction of compound **16d** (45 mg, 0.1 mmol) according to the general procedure L at rt; isolated by flash chromatography (28 g silica gel, hexane/EtOAc 85:15); colorless oil; yield: 4 mg (9%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 15.9 Hz, 1H), 7.42 – 7.39 (m, 2H), 6.92 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.24 (d, *J* = 15.9 Hz, 1H), 5.58 (d, *J* = 6.6 Hz, 1H), 4.70 (ddd, *J* = 46.9, 9.3, 5.5 Hz, 1H), 4.66 (ddd, *J* = 47.1, 9.3, 7.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.79 (dq, *J* = 16.7, 6.4 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.8, 161.6, 149.5, 149.4, 143.3, 132.9, 130.7, 128.4, 126.4 (d, *J* =

7.1 Hz), 124.3, 118.4, 117.9, 111.3, 110.3, 108.9, 87.3 (d, *J* = 4.6 Hz), 84.0 (d, *J* = 174.4 Hz), 80.5, 56.1, 56.1, 51.4 (d, *J* = 20.2 Hz), 28.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -220.90 (td, *J* = 47.0, 16.7 Hz). ^{1}H NMR decoupled (400 MHz, Chloroform-*d*) δ 4.73 (qd, *J* = 9.2, 6.3 Hz, 1H), 4.62 (qd, *J* = 9.3, 6.3 Hz, 1H). HRMS (ESI): *m/z* calcd. for $C_{24}H_{28}FO_5$: 415.1915 $[M+H]^+$; found: 415.1930.

4.2.94. (±)-*trans*-4-(3-(((pyridin-2-ylsulfonyl)oxy)methyl)-2,3-dihydrobenzofuran-2-yl)phenyl pyridine-2-sulfonate (**22**)

Obtained by reaction of compound **13e** (23 mg, 0.1 mmol) according to the general procedure L at 0 °C; isolated by flash chromatography (12 g silica gel, $CHCl_3$/EtOAc 95:5 → 80:20); yellow solid; yield: 8 mg (16%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.70 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.02 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.99 – 7.90 (m, 3H), 7.62 – 7.55 (m, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.21 (dddd, *J* = 8.0, 7.4, 1.4, 0.7 Hz, 1H), 7.14 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.91 – 6.85 (m, 2H), 5.57 (d, *J* = 5.2 Hz, 1H), 4.72 (dd, *J* = 10.3, 5.1 Hz, 1H), 4.53 (dd, *J* = 10.3, 9.1 Hz, 1H), 3.73 (dt, *J* = 9.7, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.7, 154.7, 153.7, 150.7, 150.5, 149.5, 140.2, 138.5, 138.3, 130.0, 128.2, 128.0, 127.0, 125.2, 124.4, 123.8, 123.3, 122.7, 121.4, 110.1, 85.6, 73.5, 51.0. HRMS (ESI): *m/z* calcd. for $C_{25}H_{20}N_2NaO_7S_2$: 547.0604 $[M+Na]^+$; found: 547.0651.

4.2.95. (±)-*trans*-5-((*E*)-2-carboxyvinyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydro-benzofuran-3-carboxylic acid (**23**)

To a strongly stirred suspension of compound **8g** (29 mg, 0.065 mmol) in EtOH (310 µL), 1 M NaOH (390 µL, 0.043 mmol) solution was dropwise added. Stirring was kept overnight at rt. The resulting mixture was acidified with 1 M HCl and diluted with water. The product was extracted with EtOAc (3x) and purified by flash chromatography (14 g silica gel, $CHCl_3$/MeOH/formic acid 47:3:0.1); white solid; yield: 10 mg (40%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.63 (d, *J* = 15.9 Hz, 1H), 7.27 (d, *J* = 1.3 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.03 (d, *J* = 7.7 Hz, 1H), 4.27 (d, *J* = 7.7 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 174.6, 170.8, 151.4, 149.2, 148.0, 146.5, 146.0, 133.1, 129.9, 128.7, 119.9, 119.1, 116.8, 116.3, 113.8, 110.6, 89.4, 57.5, 56.8, 56.4. HRMS (ESI): *m/z* calcd. for $C_{20}H_{19}O_8$: 387.1074 $[M+H]^+$; found: 387.1100.

4.2.96. (±)-*trans*-4,4'-(3-(hydroxymethyl)-2,3-dihydrobenzofuran-2,5-diyl)diphenol (**24a**)

Prepared according to the general procedure M using (4-hydroxyphenyl)boronic acid; isolated by flash chromatography (25 g silica gel, hexane/acetone 8:2 → 6:4) and further purified by column chromatography (Sephadex LH-20, MeOH); yellowish oil; yield: 40 mg (38%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.37 (br s, 2H), 7.52 – 7.47 (m, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.36 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.86 – 6.82 (m, 3H), 5.58 (d, *J* = 6.1 Hz, 1H), 3.93 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.87 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.55 (q, *J* = 6.2 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 159.9, 157.9, 157.2, 134.6, 134.1, 133.5, 129.5, 128.4, 128.0, 127.5, 123.9, 116.3, 116.0, 109.8, 87.9, 64.8, 54.6. HRMS (ESI): *m/z* calcd. for $C_{21}H_{19}O_4$: 335.1278 $[M+H]^+$; found: 335.1266.

4.2.97. (±)-*trans*-4-(3-(hydroxymethyl)-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-5-yl)-benzal-dehyde (**24b**)

Prepared according to the general procedure M using (4-formylphenyl)boronic acid; isolated by flash chromatography (43 g silica gel, CH_2Cl_2/Et_2O 90:10 → 85:15) and further purified by column chromatography (Sephadex LH-20, MeOH); yellowish oil; yield: 33 mg (30%). ^{1}H NMR (600 MHz, Acetone-d_6) δ 10.05 (s, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.74 – 7.70 (m, 1H), 7.60 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.64 (d,

J = 6.1 Hz, 1H), 3.95 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.91 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.60 (q, *J* = 6.2 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 192.4, 161.7, 158.2, 147.8, 135.8, 133.9, 132.9, 130.9, 130.4, 128.9, 128.2, 127.8, 125.0, 116.2, 110.3, 88.4, 64.7, 54.4. HRMS (ESI): *m/z* calcd. for $C_{22}H_{19}O_4$: 347.1278 $[M+H]^+$; found: 347.1283.

4.2.98. (±)-*trans*-4-(5-(2-fluoropyridin-3-yl)-3-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)phenol (**24c**)

Prepared according to the general procedure M using (2-fluoropyridin-3-yl)boronic acid; isolated by flash chromatography (30 g silica gel, $CHCl_3$/acetone 93:7 → 80:20); yellowish oil; yield: 27 mg (25%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.10 (dt, *J* = 4.9, 1.0 Hz, 1H), 8.04 – 7.96 (m, 1H), 7.50 (d, *J* = 1.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.54 (d, *J* = 6.0 Hz, 1H), 3.86 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.83 (dd, *J* = 11.0, 6.5 Hz, 1H), 3.54 (q, *J* = 6.2 Hz, 1H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 161.8, 161.6 (d, *J* = 239.7 Hz), 158.5, 146.2 (d, *J* = 13.8 Hz), 142.4 (d, *J* = 4.7 Hz), 134.0, 130.8 (d, *J* = 3.3 Hz), 130.0, 128.3, 127.4 (d, *J* = 4.9 Hz), 126.6 (d, *J* = 3.1 Hz), 125.5 (d, *J* = 27.4 Hz), 123.4 (d, *J* = 4.3 Hz), 116.3, 110.4, 88.9, 65.0, 54.6. ^{19}F NMR (376 MHz, Methanol-d_4) δ -74.19 (d, *J* = 9.9 Hz). HRMS (ESI): *m/z* calcd. for $C_{20}H_{17}FNO_3$: 338.1187 $[M+H]^+$; found: 338.1207.

4.2.99. (±)-*trans*-4-(3-(hydroxymethyl)-5-(5-methylthiophen-2-yl)-2,3-dihydrobenzofuran-2-yl)-phenol (**24d**)

Prepared according to the general procedure M using (5-methylthiophen-2-yl)boronic acid; isolated by flash chromatography (SVF D-26-RP18 30 g column, gradient H_2O/MeOH); yellowish oil; yield: 33 mg (31%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.48 – 7.43 (m, 1H), 7.36 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 3.6 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.67 (dt, *J* = 3.6, 1.2 Hz, 1H), 5.48 (d, *J* = 6.1 Hz, 1H), 3.82 (qd, *J* = 11.0, 6.2 Hz, 2H), 3.48 (q, *J* = 6.4 Hz, 1H), 2.45 (t, *J* = 1.0 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 160.7, 158.5, 143.6, 139.1, 134.1, 129.8, 129.3, 128.3, 127.3, 127.1, 123.2, 122.7, 116.3, 110.3, 88.7, 65.0, 54.7, 15.2. HRMS (ESI): *m/z* calcd. for $C_{20}H_{19}O_3S$: 339.1049 $[M+H]^+$; found: 339.1057.

*4.3. Chiral separation of **8m** and circular dichroism spectroscopy*

The preparative chiral separation was performed on a Merck-Hitachi (Darmstadt, Germany) HPLC system (pump: L-7150; autosampler: L-7200; interface: D-7000; UV-detector: L-7400; sample injection loop: 2000 µL) using a Chiralpak IA column (5 µm, 250 mm × 20 mm, Daicel, Osaka, Japan) and isocratic elution with isohexane-EtOH (9:1). The chromatograms were recorded at 210 nm. Electronic circular dichroism spectra were recorded on a Jasco (Pfungstadt, Germany) J-815 spectropolarimeter in the range 190 – 400 nm in methanol (0.3 – 0.5 mmol/L) using quartz cells with path length of 0.1 cm.

4.4. Biological activity

In vitro determinations of antileishmanial activity and cytotoxicity for all the synthesized compounds against *L. donovani* axenic amastigotes (MHOM/ET/67/L82) and mammalian cells (L-6 cell line, rat skeletal myoblasts), respectively, were accomplished under well-established protocols at the Swiss TPH (Basel, Switzerland) as previously described [52]. All data are reported as geometric means of three independent measurements. Confidence intervals are shown in Supporting Information.

*4.5. In vitro metabolic stability of **8m***

4.5.1. General

In case of *in vitro* metabolic stability determinations, a UPLC-UV/MS Agilent Technologies system was used [pump: 1260 Bin Pump (G1212B); MS-Detector: 6120 Single Quadrupole (G1978B); precolumn: Zorbax Eclipse Plus-C18 (5 µm, 2.1 mm x 12.5 mm); column: Zorbax SB-C18 (1.8 µm, 2.1 mm x 50 mm); column oven: 1290 TCC (G1316C), 30 °C; degasser: 1260 HiP (G4225A); autosampler: 1260 HiP ALS (G1367E)]; For MS verification: MS source: multimode source; injection volume: 1 µL; MS parameter: vaporizer temperature: 200 °C, drying gas: 12 L/min, nebulizer pressure: 35 psi, VCap: 3000 V, fragmentor voltage: 100 V, drying gas temperature: 250 °C; solvent A: water/acetonitrile 95:5 + 0.1% HCO_2H; solvent B: acetonitrile/water 95:5 + 0.1% HCO_2H; Specifically for compound **8m**, the following conditions were set: SIM negative mode *m/z*: 443; flow rate: 0.4 mL/min; gradient elution: (A%): 0 – 3.0 min: gradient from 60% to 0%, 2.0 – 3.0 min: 0%, 3.0 – 3.5 min: gradient from 0% to 60%, 3.5 – 8.0 min: 100%.

4.5.2. Determination of metabolic stability

A previously optimized and reported protocol [42] was used. A suspension of mouse liver microsomes (27 µL, 3.7 mg protein/mL) was added to an Eppendorf cup filled with sodium phosphate buffer pH 7.4 (PBS, 21.5 µL, 0.1 mol/L, pH 7.4), $MgCl_2$ solution (50 µL, 0.05 mol/L), NADPH solution (50 µL, 2 mg/mL in PBS), UDPGA solution (50 µL, 2 mg/mL in PBS) and DMSO stock solution of compound **8m** (1.5 µL, 3.33 mmol/L). In case of phase I stability, PBS (50 µL, 0.1 mol/L, pH 7.4) was added instead of UDPGA solution. Final concentrations for the incubations were 0.075 mol/L PBS, 0.6 mmol/L NADPH, 0.77 mmol/L UDPGA, 0.5 mg/mL microsomal protein, 25.0 µmol/L of the respective compound, 12.5 mmol/L $MgCl_2$ and 0.75% DMSO. The suspension was mixed vigorously and shaken for 90 min at 37 °C (900 rpm). The incubation was stopped by addition of acetonitrile/methanol (1:1, 400 µL). The suspension was cooled down to 0 °C for 10 min using a water/ice bath and the precipitated proteins were separated by centrifugation (15 min, 16000 rpm, 4 °C). Afterwards, a convenient dilution of the supernatant was analyzed via LC-MS. With the same procedure, the blank value (without compound **8m**) was prepared. The external calibration was carried out by the same procedure as described above with the change, that the DMSO stock solution (1.5 µL) was added after the calibration samples were treated with acetonitrile/methanol (100% sample). This procedure led to the same final DMSO and matrix concentration for the calibration. The incubation samples and the 100% samples were prepared three times (n = 3) and the stability was calculated as the ratio of the peak areas. The resulting solution of the same experiment using a four-fold higher concentration of **8m** was analyzed by UHPLC/+ESI-QqTOF-MS in order to establish the metabolites formed.

4.6. Computational Methods

4.6.1. General

Conformational searches and basic force field energy minimizations were performed with the Molecular Operating Environment (MOE) software (version 2018.0101) [44]. Semi-empirical and quantum chemical calculations (geometry optimizations, and ECD spectra calculations at DFT level of theory) were performed with Gaussian 03 software [59] with default grids and convergence criteria. ADME-like properties were retrieved from the SwissADME website [43].

4.6.2. Preparation of structures

A basic preparation of the data set was carried out for all the computational methods employed and presented herein, as follows: 2D structures of the *trans*-2-phenyl-2,3-dihydrobenzofurans were converted into 3D models in MOE assuring a (2*R*)-configuration. Each structure was then energy minimized using the Amber10:EHT molecular force field and subsequently submitted to a conformational search using the low mode molecular dynamics (LowMD) method as implemented in MOE, with the same force field as above (energy window of 5 kcal/mol and RMSD limit of 0.75Å).

4.6.3. Calculation of ECD spectra for **8m** enantiomers

The structure of each conformer of **8m** obtained as described above was firstly optimized using the AM1 semi-empirical method, and then using the B3LYP density functional and a 6-31G(d,p) basis set (DFT) in Gaussian 03 [59]. The population of the resulting conformers were estimated from their final total DFT energies by a Boltzmann distribution. Time-dependent density functional theory (TDDFT) was employed to calculate the ECD spectrum [60–62] for the five lowest energy conformers (representing 97% of the population), using the same density functional and basis set as above, and considering the first 30 excited states (the lowest energy conformer was used to evaluate the effect of the functional/basis set combination on the calculated ECD [62], allowing to define the reliability of the combination used). All calculations were run in vacuo. The ECD curve, expressed as the differential molar extinction, Δε (in $L.mol^{-1}cm^{-1}$), as function of the energy, E (in eV), was obtained by applying a Gaussian-type function [63] in Microsoft Excel over the corresponding dipole-length rotatory strength vectors. A band width at 1/e height of 0.3 eV was chosen. The final ECD spectrum was obtained as a weighted average of the spectra of the five relevant conformers according to the calculated Boltzmann distribution, and then transformed to Molar Ellipticity (Θ). Neither intensity scaling nor energy shift were needed for good fit.

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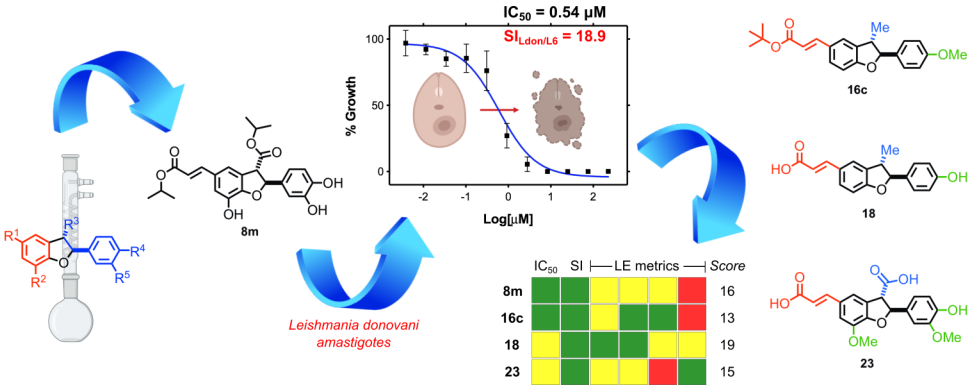

Highlights

- 2-phenyl-2,3-dihydrobenzofurans possess activity against *Leishmania donovani*.
- 70 structurally diverse compounds of this type were synthesized.
- More than 30% of the synthetic analogues showed IC_{50} < 10 µM and low cytotoxicity.
- IC_{50} values between 0.54 - >200 µM indicate strong structure-dependence of activity.
- SAR, in vitro metabolism, ADME and ligand efficiency metrics were investigated.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: