Bioorganic & Medicinal Chemistry 17 (2009) 4160–4184

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Insecticidal heterolignans—Tubuline polymerization inhibitors with activity against chewing pests

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ARTICLE INFO

Article history:
Received 23 October 2008
Revised 14 January 2009
Accepted 20 January 2009
Available online 24 January 2009

Keywords:
Heterolignan
Dihydropyridine
Tubuline polymerization inhibitor
Insecticide

ABSTRACT

Starting from natural product podophyllotoxin **1** substituted heterolignans were identified with promising insecticidal in vivo activity. The impact of substitution in each segment of the core structure was investigated in a detailed SAR study, and variation of substituents in both aromatic moieties afforded derivatives **5** and **43** with broad insecticidal activity against lepidopteran and coleopteran species. In vitro measurements supported by modeling studies indicate that heterolignans **3–134** act as tubuline polymerization inhibitors interacting with the colchicine-binding site. Insect specific structure–activity effects were observed showing that the insecticidal SAR described herein differs from reported cytotoxicity studies.

1. Introduction

Phytopathogenic microorganisms, weeds and insects cause significant damage to agriculture. Where insect pests are not systematically controlled, significant amounts of a typical crop are lost pre- and postharvest. Much of the increase in agricultural productivity over recent decades stems from the successful control of these pests with synthetic chemical pesticides. However, agrochemical and insecticidal research in particular are driven by a constant need to identify alternative chemical classes and new modes of action due to development of resistance to current active ingredients.[1] Investigating natural products from terrestrial and marine sources not only enhances diversity in the search for new prototype insecticides, but may lead to new market products as the prominent examples of spinosyns and avermectins underline.[2] Natural products and their closely related analogs are thus an important resource for new agrochemical agents and are regularly tested in our initial in vivo screening. In a test sequence of a large set of natural products from diverse sources, two lignans exhibited good initial activity against chewing insects with podophyllotoxin **1** being the most potent compound, in accordance with previous reports.[3] Podophyllotoxin **1** is a naturally occurring tetralin lignan that has been found in a variety of plants, including *Podophyllum peltatum* and *Juniperus sabina*.[4] Meanwhile, in medicinal chemistry, the corresponding glycosides of podophyllotoxin and related natural products have raised strong interest in total synthesis approaches or semi-synthetic variations[5] since etoposide and teniposide are widely used as anti-cancer drugs.

Although structure anti-tumour activity relationships of podophyllotoxin analogues were extensively investigated,[6] only few investigations have been published so far focusing on the impact of structural variations of podophyllotoxin on its insecticidal activity. In first approaches podophyllotoxin **1** has been transformed at its hydroxyl function into the corresponding esters,[7] halides and aryl amines,[8] and into acylated amino derivatives.[9] Most compounds prepared also exhibited insecticidal activity in various initial test systems. In our approach we tried to identify analogues of **1** with reduced chemical complexity which could be accessed via short and reliable synthetic routes. Taking natural product podophyllotoxin **1** with its reported and internally confirmed insecticidal potential as a starting point, we sought to reduce structural complexity initially by selecting deoxypodophyllotoxin **2** as test compound (Scheme 1). Deoxypodophyllotoxin **2** retains full

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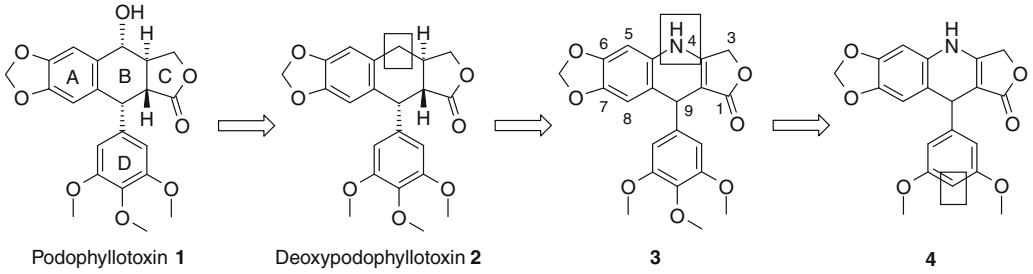
doi:10.1016/j.bmc.2009.01.042



Scheme 1. Pathway towards heterolignan lead structure **4**.

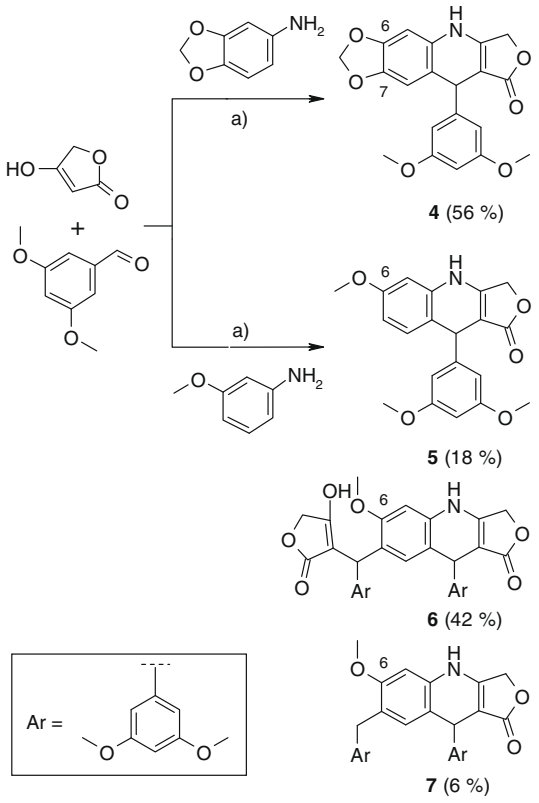
biological activity despite the missing hydroxy group. This observation prompted us to search for other tolerated structural simplifications. Inspired by a concise review concerning heterocyclic podophyllotoxin analogues[10] and recent literature[11–13] we also simplified the synthetic approach by replacing carbocyclic ring B with a dihydropyridine moiety. The resulting prototype **3** still exhibited promising activity against mustard beetle *Phaedon cochleariae*. A slight variation of the substituents in aryl ring D from 3,4,5-trimethoxy to 3,5-dimethoxy afforded derivative **4** with surprisingly good activity against *P. cochleariae* and fall armyworm *Spodoptera frugiperda* at a level of 20 g/ha. Heterolignan **4** was identified as a lead compound and a broad SAR study was started.

2. Results and discussion

2.1. Chemistry

In contrast to podophyllotoxin derivatives which are accessible only in challenging multi-step syntheses aza-analogues **3** and **4** could be prepared using a well described one-pot reaction of the corresponding aldehyde, tetronic acid and 3,4-methylenedioxy aniline.[11–13] The major advantages of this methodology are the relatively mild conditions without further activation (EtOH, reflux), acceptable reaction times (<2 h) and reported tolerance for structural diversity. Although heterocyclic amines were recently found to be tolerated,[11] initial synthetic studies of this multi component reaction were only performed with polysubstituted aldehydes and anilines carrying strongly electron-donating groups,[12] for example, 3,4,5-trimethoxy benzaldehyde and 3,4-methylenedioxy- or 3,4-dimethoxyaniline. A related three-step procedure has also been studied with alkoxy substituents.[13] As we wanted to a carry out a detailed SAR-study including substitution patterns relevant for agrochemistry, for example, halogen, haloalkyl and haloalkoxy groups,[14] we investigated the reported one-pot dihydropyridine synthesis[11–13] with selected substituents first in order to identify potential limitations. Target molecule **4**, with a 6,7-methylenedioxy substitution pattern, was prepared in good yield and high purity via initial formation of an intermediate Knoevenagel adduct. However, the corresponding 6-methoxy derivative **5** was synthesized in much lower yield (18%) and a double addition product **6** (Scheme 2) was formed as the major product (42%). Due to the activated position at C7 dihydropyridine **5** could react with intermediate benzylidene 2,4-furandione to afford **6**. Furthermore, benzyl derivative **7** was observed as second side product.

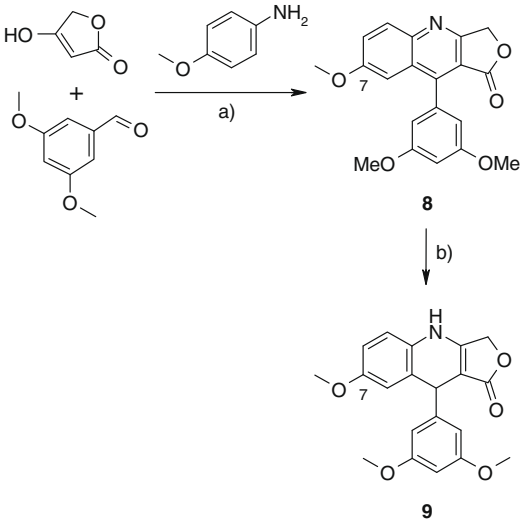
We thus carefully varied temperature, solvent and concentration to improve the yield of desired heterolignan **5**. High boiling protic solvents such as 2-pentanol, 3-pentanol or 3-methyl-1-butanol proved to be beneficial for high and stable yields (Table 1), but isolation was hampered as **5** did not precipitate readily from those solvents. The use of acetonitrile and 2-methoxyethanol afforded **5** in slightly enhanced medium yield (20–30%), but in high purity due to clean precipitation. On the other hand, MeOH and water



Scheme 2. Formation of heterolignans with electron-donating groups in ring A by a three-component reaction. Reagents and conditions: (a) EtOH, 2 h, reflux.

Table 1
Variation of conditions for the one-pot synthesis of **5**

Entry	Solvent	Time (h)	Temp (°C)	Concn (mol)	Yield (%)
1	EtOH	2	78	0.25	18
2	EtOH	2	40	0.01	9
3	EtOH	1	78	0.5	26
4	MeOH	4	40	0.01	6
5	MeOH	2	40	0.5	12
6	2-Methoxy-ethanol	1	120	0.01	31
7	2-Methoxy-ethanol	4	120	0.5	45
8	MeCN	1	40	0.01	11
9	MeCN	1	80	0.25	16
10	MeCN	4	80	0.5	28
11	2-BuOH	1	40	0.25	26
12	2-BuOH	2	98	0.5	49
13	3-Methyl-1-butanol	2	120	0.01	42
14	3-Methyl-1-butanol	1	120	0.5	50
15	2-Pentanol	1	120	0.01	53
16	2-Pentanol	2	120	0.25	61
17	3-Pentanol	1	80	0.5	47
18	3-Pentanol	1	120	0.5	62

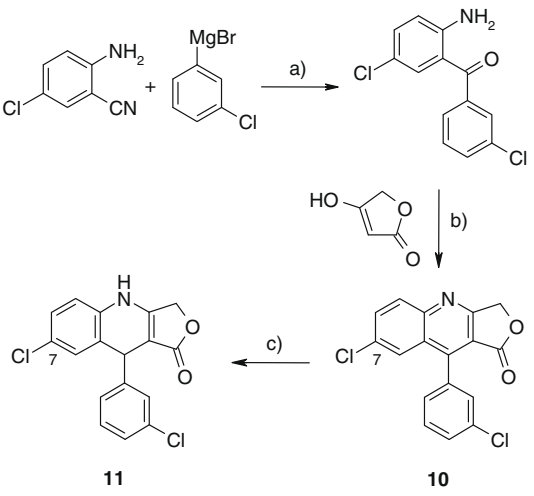


Scheme 3. Stepwise synthesis of heterolignans with electron-donating substituents in ring A. Reagents and conditions: (a) EtOH, 2 h, reflux; (b) $NaBH_3CN$, HOAc, 3 h, rt.

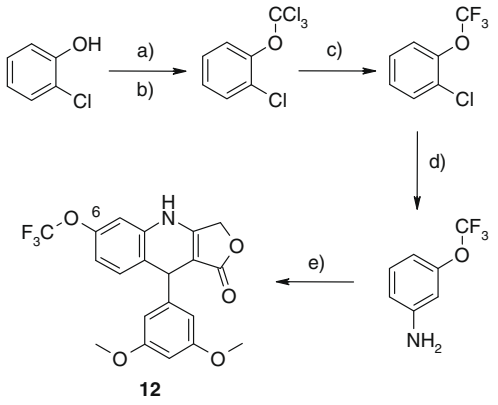
gave the lowest yield. In general, high concentrations and high temperatures led to increased yields of **5** and side reactions were suppressed. The use of microwave conditions did not have a significant impact on resulting yields and purity, but could be used to shorten reaction times. Due to the promising initial yields further reactions were carried out in 2- and 3-pentanol showing that 2-pentanol was the best solvent evaluated. Selected experiments carried out to optimize the formation of **5** are summarized in Table 1.

In contrast to 6-alkoxy-monosubstituted heterolignans, corresponding 7-alkoxy-substituted analogs were mostly obtained as pyridines. Thus, with *p*-methoxyaniline as coupling partner the three-component reaction yielded pyridine derivative **8** as single product which could be reduced with $NaBH_3CN$ in acetic acid affording desired 7-methoxy substituted dihydropyridine **9** (Scheme 3). In other cases related pyridines were only obtained as easily separable side products. Furthermore, the three-component reaction could also be applied to acetophenones yielding corresponding 9-methyl-substituted dihydropyridines in fair yield.

Although benzaldehydes and acetophenones with a wide variety of electron-withdrawing and electron-donating substituents



Scheme 4. Synthesis of analogues with electron-withdrawing groups in ring A. Reagents and conditions: (a) (1) THF, 1 h, reflux; (2) aq HCl, 2 h, 30 °C; (c) $NaBH_3CN$, HOAc, 3 h, rt.

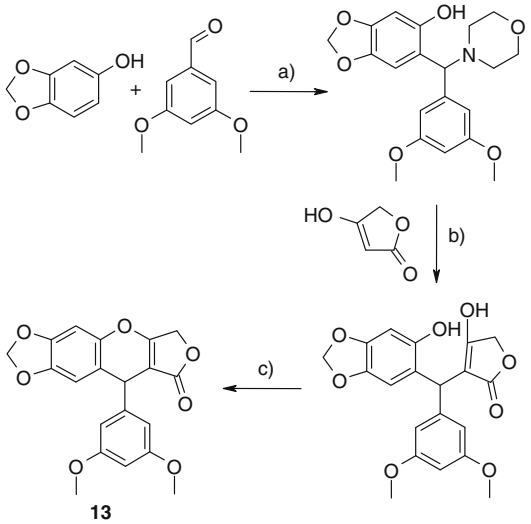


Scheme 5. Heterolignans with agrolike aniline precursors. Reagents and conditions: (a) Me_2SO_4, NaOH, H_2O; (b) Cl_2, CCl_4, *hν*; (c) HF; (d) NH_3, $NaNH_2$; (e) EtOH, 1 h, reflux.

were tolerated in the one-pot approach, heterolignans with electron-withdrawing groups in ring A had to be prepared following an alternative pathway. 2-amino-4-chloro-benzonitrile was thus transformed via Grignard reaction into a bis-arylated ketone which readily formed quinoline intermediate **10** upon condensation with tetronic acid in toluene. The desired dihydropyridine **11** was obtained after $NaBH_3CN$-mediated reduction. The three-step procedure (Scheme 4) proceeded in high yield and good purity. Alternatively, heterolignan **11** could also be synthesized via reduction of the ketone intermediate with $NaBH_4$ followed by condensation of the resulting alcohol with tetronic acid.

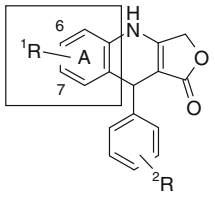
Some aniline building blocks were not readily available from commercial sources and were thus prepared following literature procedures to complement our SAR-study. 3-Trifluoromethoxy aniline, for example, could be prepared from 2-chlorophenol with a regiospecific arynic amination of 2-chloro-trifluoromethoxybenzene as key step[15] to afford 6-OCF_3-substituted heterolignan **12** in the three-component reaction described above. Selected 3-alkoxy- or 2,3-bisalkoxy anilines were synthesized via Curtius rearrangement or Hofmann degradation of corresponding benzoic acids or starting from suitable nitrophenol precursors[16] (Scheme 5).

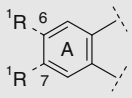
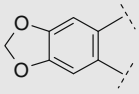
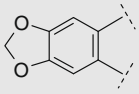
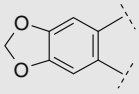
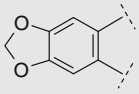
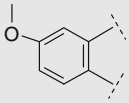
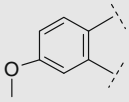
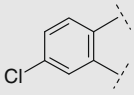
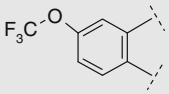
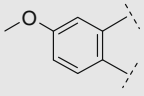
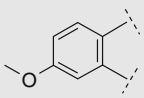
To further complement the structural variations of the dihydropyridine ring B selected oxy-analogues were synthesized via



Scheme 6. Synthetic approach towards oxa-Heterolignans. Reagents and conditions: (a) morpholine, MeOH; (b) tetronic acid, AcOH–H_2O; (c) H_2SO_4, AcOH.

Table 2
In vivo SAR—variation of ring A at positions C6 and C7



Compound		R_2	*Phaedon Cochl.* In vivo activity[a]	*Spod. Frugip.* In vivo activity[a]
1[b]		3,4,5-$(OMe)_3$	++	n.a.
2[b]		3,4,5-$(OMe)_3$	++	+
3		3,4,5-$(OMe)_3$	+++	n.a.
4		3,5-$(OMe)_2$	+++	+++
5		3,5-$(OMe)_2$	+++	++++
9		3,5-$(OMe)_2$	+++	++
11		3-Cl	n.a.	n.a.
12		3,5-$(OMe)_2$	n.a.	n.a.
14		3,4,5-$(OMe)_3$	+	+++
15		3,4,5-$(OMe)_3$	+++	n.a.

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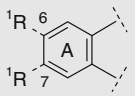
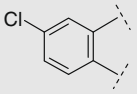
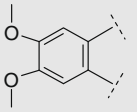
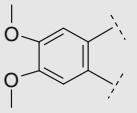
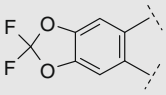
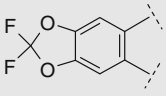
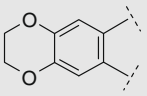
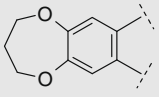
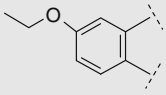
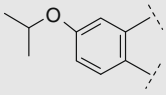
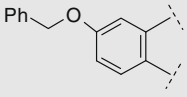
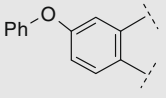
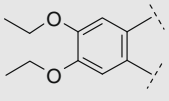
Compound		R_2	*Phaedon Cochl.* In vivo activity[a]	*Spod. Frugip.* In vivo activity[a]
16		3,4,5-$(OMe)_3$	n.a.	n.a.
17		3,5-$(OMe)_2$	+	+
18		3,4,5-$(OMe)_3$	n.a.	n.a.
19		3,5-$(OMe)_2$	+	n.a.
20		3,4,5-$(OMe)_3$	++	n.a.
21		3,5-$(OMe)_2$	+	++
22		3,5-$(OMe)_2$	+	++
23		3,5-$(OMe)_2$	+	++++
24		3,5-$(OMe)_2$	n.a.	+
25		3,5-$(OMe)_2$	n.a.	n.a.
26		3,5-$(OMe)_2$	n.a.	n.a.
27		3,5-$(OMe)_2$	n.a.	n.a.

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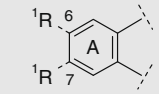
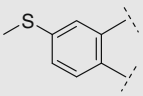
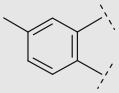
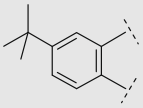
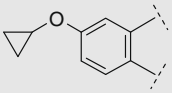
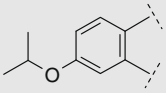
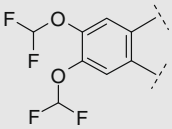
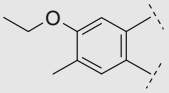
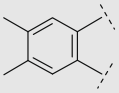
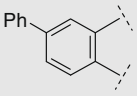
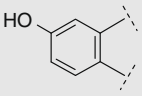
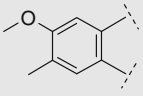
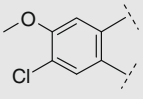
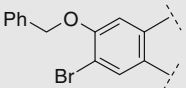
Table 2 (*continued*)

Compound		R_2	*Phaedon Cochl.*	*Spod. Frugip.*
			In vivo activity[a]	In vivo activity[a]
28		3,5-$(OMe)_2$	+	++
29		3,5-$(OMe)_2$	+	+++
30		3,5-$(OMe)_2$	n.a.	n.a.
31		3,5-$(OMe)_2$	+	++
32		3,5-$(OMe)_2$	n.a.	n.a.
33		3,5-$(OMe)_2$	n.a.	n.a.
34		3,5-$(OMe)_2$	++	n.a.
35		3,5-$(OMe)_2$	n.a.	n.a.
36		3,5-$(OMe)_2$	n.a.	n.a.
37		3,5-$(OMe)_2$	n.a.	n.a.
38		3,5-$(OMe)_2$	+++	+
39		3,5-$(OMe)_2$	n.a.	n.a.
40		3,5-$(OMe)_2$	n.a.	n.a.

[a] ++++ = activity at 4 g/ha; +++ = activity at 20 g/ha; ++ = activity at 100 g/ha; + = activity at 500 g/ha; n.a. = no activity in the test systems.

[b] Natural products **1** and **2** contain a tetraline core instead of the dihydroquinoline moiety shown above.

Mannich-reaction of substituted benzaldehydes with electron-rich phenols in the presence of morpholine. Subsequent addition to tetronic acid and ring closure afforded desired oxa-heterolignans in good yield, for example, furochromenone **13**.[17] (Scheme 6).

2.2. In vivo SAR-study

In view of our goal to identify a heterolignan with broad activity against chewing pests, all four ring segments of initial lead structure **4** were varied thoroughly. All derivatives described below possessing one chiral centre were tested as racemates. The impact of stereochemistry at position C9 was investigated and will be described in detail in Section 2.3. Keeping substitution in ring D constant in most cases we first introduced alternative substituents at positions C6 and C7 in ring A to replace the methylenedioxy group. We tested all analogues prepared against two representative chewing insects, mustard beetle *P. cochleariae* and the fall armyworm *S. frugiperda*. With these initial results in hand we could directly deduce that ring A was highly sensitive to minor structural changes. While 6-methoxy derivative **5** showed improved activity against *S. frugiperda* down to a level of 4 g/ha the corresponding 7-methoxy isomer **9** exhibited good activity against *P. cochleariae*, but performed significantly weaker against *S. frugiperda*. This effect could also be observed clearly with related isomeric methoxy-pair **14** and **15** both carrying a 3,4,5-trimethoxy-phenyl moiety (ring D) (Table 2). Again, **14** (6-OMe) showed good activity against *S. frugiperda*, whereas **15** (7-OMe) was only active against *P. cochleariae*. In good accordance, 6-ethoxy substituted derivative **23** showed excellent selective efficacy against *S. frugiperda*.

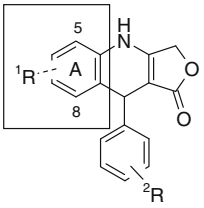
We then tested whether larger 6-alkoxy groups might further improve activity against *S. frugiperda*, but we soon reached the limits of steric tolerance with cyclo-propyl and isopropyl analogues **31, 24** and **32** being less active. Furthermore, corresponding benzyloxy and phenoxy derivatives **25**, **26** as well as non-cyclized 6,7-bis alkoxy-substituted compounds **17**, **18**, **27** performed poorly or were inactive. Introducing fluorine in the methylenedioxy group (**19, 20**, Table 2) and enlarging the ring size (**21**, **22**) of this privileged naturally occurring substituent also decreased the biological efficacy sharply. Interestingly, the latter observation was in clear contrast to the cytotoxic SAR established in recent years. In those studies larger alkoxy and alkyl groups were tolerated without loss of activity, and electronic effects were claimed not to be important.[13]

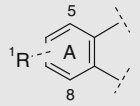
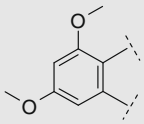
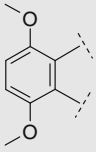
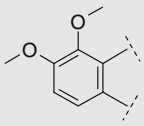
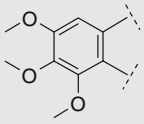
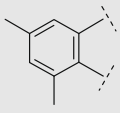
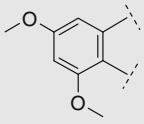
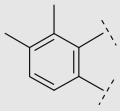
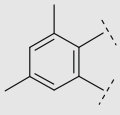
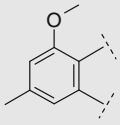
Disappointingly, introducing halogen or fluoroalkoxy substituents, for example, 6-Cl (**16**), 7-Cl (**11**), 6-OMe-7-Cl (**39**), 6-OCF_3 (**12**) and bis-6,7-$OCHF_2$ (**33**) led to a complete loss of activity. The best non-alkoxy substituted analogues were thioether **28** and methyl derivative **29** but their efficacy was lower than that of the initial lead structure **4**.

Introducing alkoxy and alkyl substituents at position C5 gave rise to surprisingly good insecticidal activities (Table 3). 5,7-Dimethoxy and related 5-methoxy-7-methyl heterolignans **41** and **49** exhibited strong efficacy against *P. cochleariae*, whereas 5,6-dimethoxy derivative **43** showed the strongest performance of all analogues **3–49** with high activity against both test organisms. Also 5,6-dimethyl-substituted heterolignan **47** was active against both *P. cochleariae* and *S. frugiperda* underlining the positive effect of C5 substitution.

In summary, only small electron-donating alkoxy substituents are well tolerated in ring A, preferably at positions 5, 6 and 7. Sterically more demanding and less electron-donating substituents afforded reduced efficacies with isopropoxy being at the limit of steric tolerance. Likewise, halogen and most fluoroalkoxy analogues as well as large alkoxy, phenoxy and alkyl groups proved to be inactive. Promising efficacies were obtained with the 5,6-dimethoxy and 6-methoxy group affording **5** and **43** as most potent derivatives. Activity against the two test organisms could

Table 3
In vivo SAR—variation of ring A involving positions C5 and C8



Compound		R_2	*Phaedon Cochl.*	*Spod. Frugip.*
			In vivo activity[a]	In vivo activity[a]
41		3,5-$(OMe)_2$	++++	+
42		3,5-$(OMe)_2$	n.a.	n.a.
43		3,5-$(OMe)_2$	+++	++++
44		3,5-$(OMe)_2$	n.a.	n.a.
45		3,5-$(OMe)_2$	n.a.	n.a.
46		3,5-$(OMe)_2$	++	+
47		3,5-$(OMe)_2$	++	++
48		3,5-$(OMe)_2$	n.a.	n.a.
49		3,5-$(OMe)_2$	+++	+

[a] ++++ = activity at 4 g/ha; +++ = activity at 20 g/ha; ++ = activity at 100 g/ha; + = activity at 500 g/ha; n.a. = no activity in the test systems.

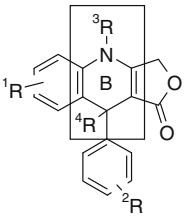
be discriminated with the help of derivatives carrying one alkoxy substituent either at C6 or C7. Substituents at position C8 (e.g., in **42**, **44** and **45**) were not beneficial for biological in vivo activity, whereas most compounds carrying a substituent at C5 were active.

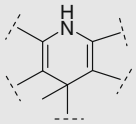
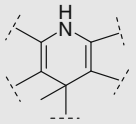
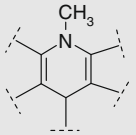
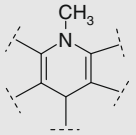
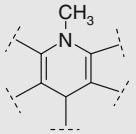
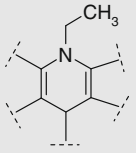
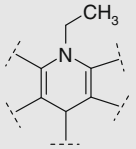
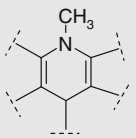
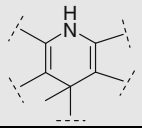
We turned our attention next to variations in other parts of the core structure. Although promising cytotoxic and antiproliferative activity combined with a simple synthetic access makes heterolignans an attractive target for detailed SAR studies few efforts have been described exploring structural changes in rings B and C (Scheme 1). To our knowledge, lactone moiety C of the heterolignan core structure has been varied in two recent studies only by structurally related analogs also leaving the dihydropyridine part unchanged.[13,18] In our insecticidal in vivo SAR study, introducing substituents in the dihydropyridine moiety (ring B) showed that N-alkylation is tolerated in some cases affording derivatives with in vivo activity, for example, **52** and **55**, whereas alkylation at C9 totally erased biological activity (e.g., **58**, Table 4). Nevertheless, all compounds modified in ring B exhibited weaker activity than initial lead structure **4**.

A similar trend could be observed for variations of the lactone moiety in ring C where only few minor structural changes were tolerated. Although a highly diverse set of heterolignans with lactone-replacing groups including ketones, lactams, oxazinones and cyclic sulfonates and sulfones was synthesized, in vivo activity against both target organisms was preserved only in methyl lactone **79**, ketone **87**, lactam **74** and the 6-membered lactones **65** and **76**. Activity of these five derivatives did not exceed a level of 100 g/ha. All other structural analogs exhibited only weak, for example, partial activity at 500 g/ha for **66**, **67**, **69**, **83** and **84**, or no activity at all. Interestingly, most free lactams (e.g., **72**, **82**, **91**) showed in vivo efficacy, whereas alkylated or Boc-protected analogues were inactive. To make sure that these effects might not be different with other substituents in rings A and D, some analogues were prepared with a *m*-chlorine substituent in ring D. Results were comparable with unsubstituted lactam **74** and 6-membered lactone **65** being more potent than their analogues carrying a 3,5-dimethoxy-substituted phenyl ring D. Hence, an unsubstituted 5-membered lactone, originating from tetronic acid, remained the subunit of choice for ring C and was not replaced in the broad variations of rings A and D. Our observations are in line with results obtained in the course of the two cytotoxicity studies mentioned above[13,17] where only a ketone similar to **87** exhibited submicromolar affinity (Table 5).

In contrast to the concurring biological results for rings B and C, insecticidal and anti-cancer SAR differ with respect to the impact of variations in ring D. In our work alkoxy and halogen substituents in the *para*-position led to significantly reduced activity as examples **93** (*p*-OMe), **94** (*m,p*-$(OMe)_2$), **97** (*p*-Cl), **109** (difluoro-methylenedioxy) and **127** (*m*-OMe-*p*-Cl) underline (Table 6). Related analogues from the pharmacological studies, however, show moderate to good activity against cancer cell lines still reaching nanomolar levels. Important exceptions in our insecticidal SAR are 3,4,5-trisubstituted derivatives with alkoxy groups similar to the natural product podophyllotoxin **1** and *p*-fluorine containing compounds. Analogues such as **121**, **123**, **124**, **125** and **130** show good efficacy against *P. cochleariae* as is observed for natural products **1** and **2**, but are not effective to control *S. frugiperda*. 3,4-disubstituted derivatives **128** and **131** with fluorine in the *para*-position exhibit moderate activity. Furthermore, substituents in the *ortho*-position were generally not tolerated affording inactive compounds, for example, **95** (2-Cl), **110** (2,3,5-Cl_3), **112** (2,3-Cl_2), **124** (2,5-Cl_2), except for fluorinated heterolignan **115** with a special 2-F-3-Cl-5-CF_3 substitution pattern. This particular derivative was more active than natural products **1** and **2**, and parent compound **3**, respectively. It nearly reached the level of activity of initial lead structure **4** indicating that there is space in our insecticidal study for variations of substituents in ring D beyond well described

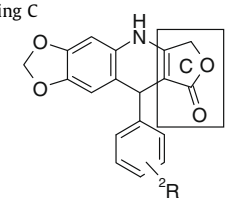
Table 4
In vivo SAR—variation of ring B



Compound		R_1	R_2	*Phaed. Cochl.*	*Spod. Frugip.*
				In vivo activity[a]	In vivo activity[a]
50		6-Cl	3,4,5-$(OMe)_3$	n.a.	n.a.
51		7-Cl	3-Cl	n.a.	n.a.
52			3,4,5-$(OMe)_3$	++	n.a.
53		6,7-$(OMe)_2$	3,4,5-$(OMe)_3$	n.a.	n.a.
54		6-Me	4-Cl	n.a.	n.a.
55			3,5-$(OMe)_2$	+	+
56		6,7-$(OMe)_2$	3,5-$(OMe)_2$	n.a.	n.a.
57		6-OMe	3,5-$(OMe)_2$	n.a.	++
58			3,5-$(OMe)_2$	n.a.	n.a.

[a] ++++ = activity at 4 g/ha; +++ = activity at 20 g/ha; ++ = activity at 100 g/ha; + = activity at 500 g/ha; n.a. = no activity in the test systems.

Table 5
In vivo SAR—variation of ring C



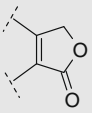
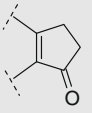
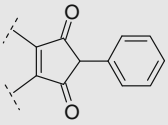
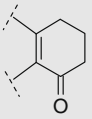
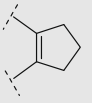
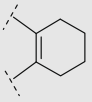
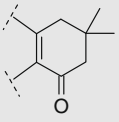
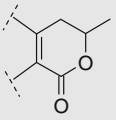
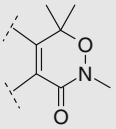
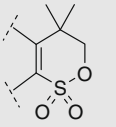
Compound		R_2	*Phaedon Cochl.*	*Spod. Frugip.*
			In vivo activity[a]	In vivo activity[a]
4		3,5-$(OMe)_2$	+++	+++
59		3-Cl	n.a.	n.a.
60		3-Cl	n.a.	n.a.
61		3-Cl	n.a.	n.a.
62		3-Cl	n.a.	n.a.
63		3-Cl	n.a.	n.a.
64		3-Cl	n.a.	n.a.
65		3-Cl	++	++
66		3-Cl	n.a.	+
67		3-Cl	+	n.a.

Table 5 (*continued*)

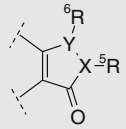
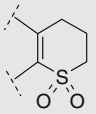
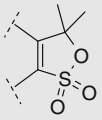
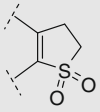
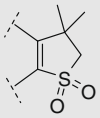
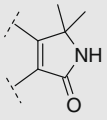
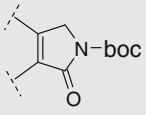
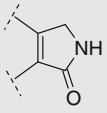
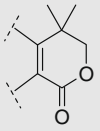
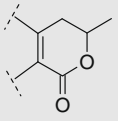
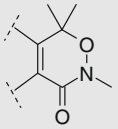
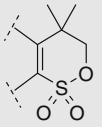
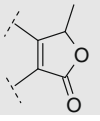
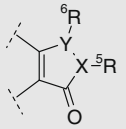
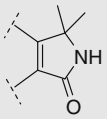
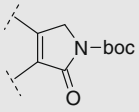
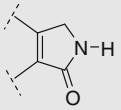
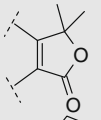
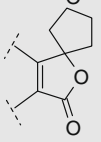
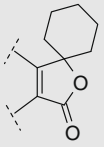
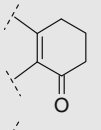
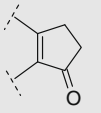
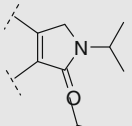
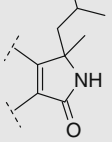
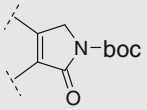
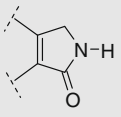
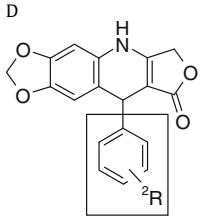
Compound		R_2	*Phaedon Cochl.*	*Spod. Frugip.*
			In vivo activity[a]	In vivo activity[a]
68		3-Cl	n.a.	n.a.
69		3-Cl	+	n.a.
70		3-Cl	n.a.	n.a.
71		3-Cl	n.a.	n.a.
72		3-Cl	+	n.a.
73		3-Cl	n.a.	n.a.
74		3-Cl	+	++
75		3,5-$(OMe)_2$	n.a.	n.a.
76		3,5-$(OMe)_2$	+	+
77		3,5-$(OMe)_2$	n.a.	n.a.
78		3,5-$(OMe)_2$	n.a.	n.a.
79		3,5-$(OMe)_2$	++	+

Table 5 (*continued*)

Compound		R_2	*Phaedon Cochl.*	*Spod. Frugip.*
			In vivo activity[a]	In vivo activity[a]
80		3,5-$(OMe)_2$	n.a.	n.a.
81		3,5-$(OMe)_2$	n.a.	n.a.
82		3,5-$(OMe)_2$	+	n.a.
83		3-Cl	+	n.a.
84		3-Cl	+	n.a.
85		3-Cl	n.a.	n.a.
86		3,5-$(OMe)_2$	n.a.	n.a.
87		3,5-$(OMe)_2$	+	++
88		3,5-$(OMe)_2$	n.a.	n.a.
89		3,5-$(OMe)_2$	n.a.	n.a.
90		3,4,5-$(OMe)_3$	n.a.	n.a.
91		3,4,5-$(OMe)_3$	+	n.a.

[a] ++++ = activity at 4 g/ha; +++ = activity at 20 g/ha; ++ = activity at 100 g/ha; + = activity at 500 g/ha; n.a. = no activity in the test systems.

Table 6
In vivo SAR—variation of ring D



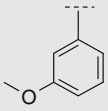
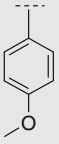
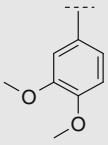
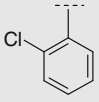
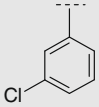
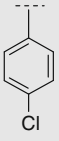
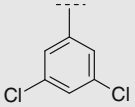
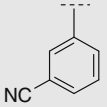
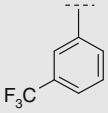
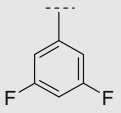
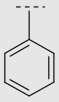
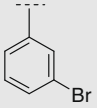
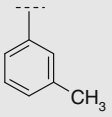
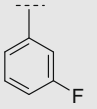
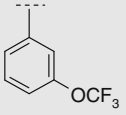
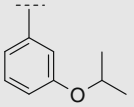
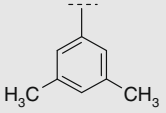
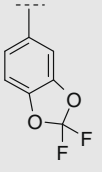
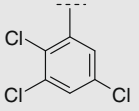
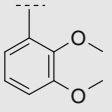
Compound		*Phaedon Cochl.*	*Spod. Frugip.*
		In vivo activity[a]	In vivo activity[a]
92		n.a.	++
93		n.a.	n.a.
94		n.a.	n.a.
95		n.a.	n.a.
96		+	++
97		n.a.	n.a.
98		++	+++
99		n.a.	+
100		++	++

Table 6 (*continued*)

Compound		*Phaedon Cochl.*	*Spod. Frugip.*
		In vivo activity[a]	In vivo activity[a]
101		++	+++
102		n.a.	+++
103		++	+++
104		n.a.	++
105		++	+++
106		++	+++
107		n.a.	+
108		++	+++
109		n.a.	n.a.
110		n.a.	n.a.
111		n.a.	n.a.

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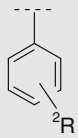
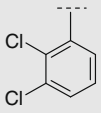
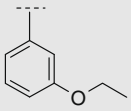
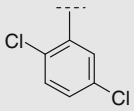
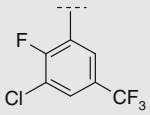
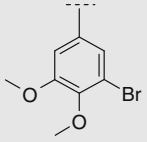
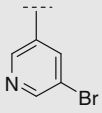
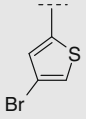
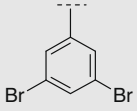
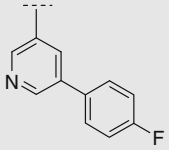
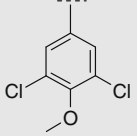
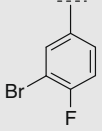
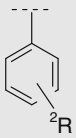
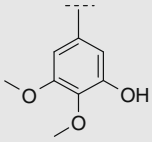
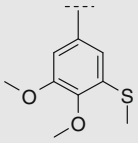
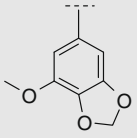
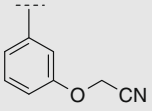
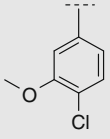
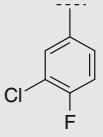
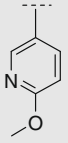
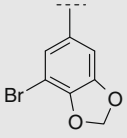
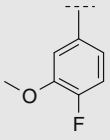
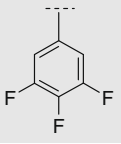
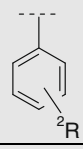
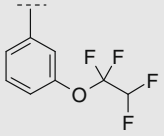
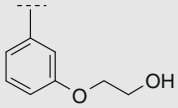
Compound		*Phaedon Cochl.* In vivo activity[a]	*Spod. Frugip.* In vivo activity[a]
112		n.a.	n.a.
113		++	++
114		n.a.	n.a.
115		+++	++
116		++	n.a.
117		n.a.	++
118		n.a.	+
119		n.a.	++
120		++	+
121		++	++
122		+	+++

Table 6 (*continued*)

Compound		*Phaedon Cochl.* In vivo activity[a]	*Spod. Frugip.* In vivo activity[a]
123		++	n.a.
124		++	n.a.
125		+++	+
126		+	++
127		+	+
128		n.a.	++
129		+	+
130		++	+
131		+	++
132		n.a.	+

(*continued on next page*)

Table 6 (*continued*)

Compound		*Phaedon Cochl.*	*Spod. Frugip.*
		In vivo activity[a]	In vivo activity[a]
133		++	++
134		n.a.	+++

[a] ++++ = activity at 4 g/ha; +++ = activity at 20 g/ha; ++ = activity at 100 g/ha; + = activity at 500 g/ha; n.a. = no activity in the test systems.

methoxy and methylenedioxy groups. Likewise, the aryl D-ring could be replaced by pyridines with *meta*-substituted derivatives **117** and **120** (Table 6) showing the best in vivo results. As can preliminarily be deduced from the selected examples discussed above, substituents in the *meta*-position turned out to be beneficial for insecticidal activity. *m*-Cl-Substituted heterolignan **96**, as well as monosubstituted closely related analogues **100** (*m*-CF_3), **103** (*m*-Br), **105** (*m*-F) and **106** (*m*-OCF_3) showed good activity against both target organisms down to 20 g/ha. Similarly strong results were obtained with 3,5-disubstituted analogues, for example, with **98** (3,5-Cl_2), **101** (3,5-F_2) and **108** (3,5-Me_2). Among all derivatives listed in Table 6 highest efficacies were in fact achieved with halogen-disubstituted heterolignans **98** and **101**. Electron-donating alkoxy groups in ring D are thus not crucial for high in vivo efficacy, contrary to what has been observed for ring A.

Furthermore, some sterically more demanding alkoxy substituents are also tolerated in the *meta*-position with isopropoxy-derivative **107** being at the upper limit. Ethoxy (**113**), tetrafluoroethoxy (**133**), and cyano methyleneoxy (**126**) groups afforded heterolignans with fair activity against both species. Interestingly, the additional hydroxyl group in **134** further enhanced the efficacy against *S. frugiperda*.

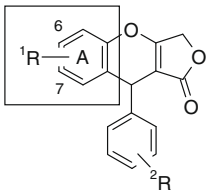
Replacing the dihydropyridine unit by a pyran, however, led to a sharp decrease in biological activity. Only the closest analogue of lead structure **4**, methylenedioxy-substituted furochromenone **13**, showed in vivo activity against both target organisms, albeit at a high concentration (Table 7). Other pyran derivatives prepared were mostly inactive.

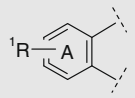
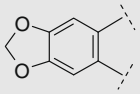
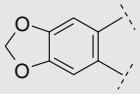
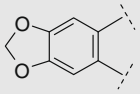
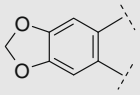
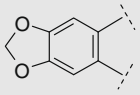
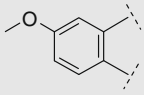
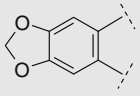
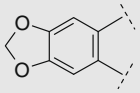
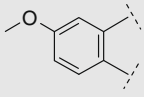
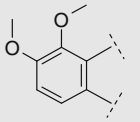
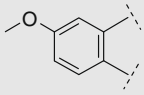
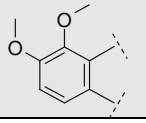
In summary, a wide variety of substituents can be introduced in the *meta*-positions with insecticidal activity being preserved or enhanced. Nevertheless, the most potent insecticidal heterolignans identified in the course of our initial SAR study are derivatives **5, 23** and **43** with modified alkoxy groups in ring A. By combining the best substituents emerging from variations of rings A and D we have identified further highly potent analogues which are disclosed in a patent.[18] Presenting all results obtained so far would go far beyond the scope of our work outlined herein.

2.3. Mode of action studies

A number of experiments using permanent insect cell cultures were carried out to determine the mode of action of the heterolignans. Insect Sf9 cell cultures were incubated and analysed with fluorescent markers under a fluorescence microscope for viabil-

Table 7
In vivo SAR—oxa-analogues



Compound		R_2	*Phaedon Cochl.*	*Spod. Frugip.*
			In vivo activity[a]	In vivo activity[a]
13		3,5-$(OMe)_2$	+	+
135		3,5-Cl_2	n.a.	n.a.
136		3-Cl	n.a.	n.a.
137		3-Br	n.a.	n.a.
138		3-OCF_3	n.a.	n.a.
139		3-Cl	n.a.	n.a.
140		3-Br-4,5-$(OMe)_2$	+	n.a.
141		3-$OCHF_2$	n.a.	n.a.
142		3,5-$(OMe)_2$	n.a.	n.a.
143		3,5-$(OMe)_2$	n.a.	n.a.
144		3,5-Cl_2	n.a.	+
145		3,5-Cl_2	n.a.	+

[a] ++++ = activity at 4 g/ha; +++ = activity at 20 g/ha; ++ = activity at 100 g/ha; + = activity at 500 g/ha; n.a. = no activity in the test systems.

ity/cytotoxicity, changes in cell shape/cell membrane, chromatin, cytoskeleton, or mitochondrial membrane potential.

First, a set of representative compounds selected on the basis of different levels of in vivo activities was analysed in the toxicity/viability test using the *Spodoptera* Sf9 cell line and a related mammalian CHO cell line. It turned out that activities in vitro in SF9 cells correlated very well to the activities observed in vivo, as those compounds which were toxic to *S. frugiperda* in vivo (e.g., most promising derivatives **23** and **43**) also showed strong cytotoxic activity in the insect Sf9 cell line at the same level as colchicine (Entries 5 and 7, Table 8). The moderate in vitro activity of heterolignans **17** and **55** correlated with weak in vivo activity. Likewise, heterolignans with weak in vitro effects, for example, **94** and **59**, were inactive in our in vivo tests.

After 24 and 48 h heterolignans produced symptoms in CHO and Sf9 cells which looked very similar to those induced by colchicine. These cellular symptoms included a stop in cell division, the induction of polyploid cells with abnormal bubble-like chromatin and enhancement of cell volume (Fig. 1). From these observations the hypothesis was formulated that the mode of action of the heterolignans is by inhibition of the polymerization of the microtubular system.

To strengthen the hypothesis that heterolignans are interfering with tubulin polymerization, a tubulin polymerization assay with purified bovine tubulin was performed.[19] Similar to colchicine, in vivo active heterolignan **43** was able to inhibit the in vitro polymerization of tubulin in clear contrast to taxol which strongly enhanced polymerization (Fig. 2).

Most striking were the activities of the enantiomeric pair *S*-**5** and *R*-**5**, where in vivo active enantiomer *R*-**5** not only was cytotoxic in vitro in Sf9 cells (Table 8), but also showed the typical changes in chromatin/cell nucleus phenotype seen with colchicine, whereas the in vivo inactive enantiomer *S*-**5** was also inactive in vitro on Sf9 cells and did not show any cellular symptoms typical for interfering with microtubules. Absolute stereochemistry at carbon C9 was determined by X-ray analysis using Cu-Kα radiation. The measurement was performed at 100 K to produce more

Table 8
In vitro–in vivo correlation of selected heterolignans

Entry	Compound	*Spod. Frugip. SF9 cells* In vitro toxicity[a]	*Spod. Frugip.* In vivo activity[b]
1	**94**	++	n.a.
2	**95**	+	n.a.
3	**59**	++	n.a.
4	**17**	+++	+
5	**23**	++++	++++
6	**24**	++	+
7	**43**	++++	++++
8	**55**	+++	+
9	***S*-5**	o	n.a.
10	***R*-5**	++++	++++
12	Colchicine	++++	

[a] ++++ = activity at 0.14 ppm; +++ = activity at 1 ppm; ++ = activity at 3 ppm; + = activity at 10 ppm; o = activity at concentrations >10 ppm.
[b] ++++ = activity at 4 ppm; +++ = activity at 20 ppm; ++ = activity at 100 ppm; + = activity at 500 ppm; n.a. = no activity in the test systems.

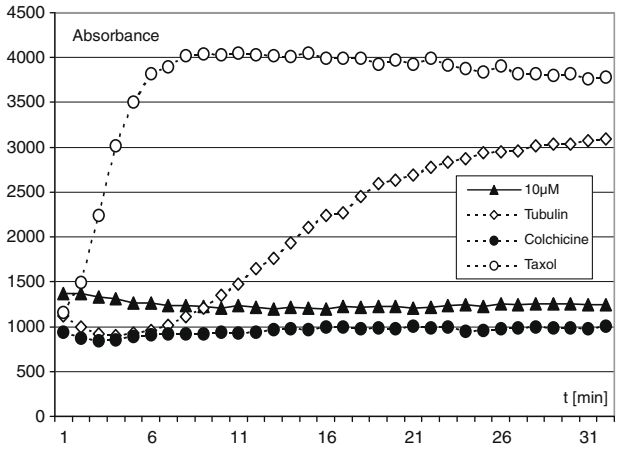


Figure 2. Inhibition of tubulin polymerisation in the presence of heterolignan **43** (–▲–).

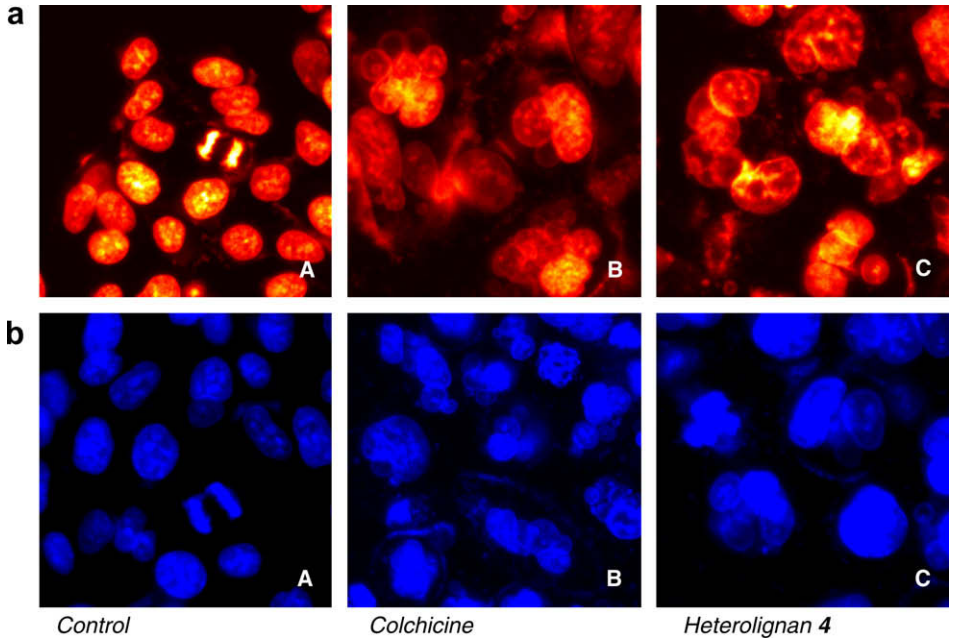


Figure 1. Analysis of subcellular changes in chromatin structure; (a) nuclear staining after 48 h of incubation with colchicine (B) or heterolignan **4** (C) in CHO cells; (b) nuclear staining of Sf9 cells after 48 h of incubation with colchicine (B) and heterolignan **4** (C). Normal dividing cells cultured without compounds were stained in A.

accurate data for the measurement. Both enantiomers of heterolignan **5** were carefully separated by chiral HPLC before. As the biologically inactive enantiomer was more prone to crystallize its X-ray structure was thoroughly analyzed first showing that substituents at carbon C9 carried an *S* configuration (Fig. 3). Interestingly, the most important interactions within the crystal lattice are hydrogen bonds between the NH group of dihydropyridine ring B and the lactone carbonyl group of ring C.

Taking all results together it can be concluded that heterolignans inhibit the polymerization of microtubules analogous to the activity of colchicine.

Based upon the co-crystal structure of tubuline with the closely related inhibitor molecule podophyllotoxin (PDB 1SA1, derived from Protein Data Bank),[20] modeling studies were undertaken to augment the chemical optimization procedure of the heterolignan compound class. Tubuline is composed of two non-identical (α/β) chains, each about 450 residues in length. The so-called 'Colchicine Site' is located at the β subunit, right at the interface between a and b chains. In the crystal structure of rat tubuline (1SA1) the trimethoxyphenyl moiety is deeply buried within a hydrophobic pocket of β-tubuline, while the hydroxyl group from ring B forms a hydrogen bond to the backbone carbonyl group of Thr179 from the α-tubuline chain laying adjacent to the colchicine binding site. As crystal structures of bound and unbound tubulines are currently available only for mammals but not for insects, protein homology techniques were applied to construct a model of the colchicine binding site of Heliothis. Therefore, a sequence alignment was carried out for the β-tubuline subunits from rat (X-ray) and Heliothis, showing an overall identity level of more than 90%. Despite the high overall identity two mutations could be identified next to the colchicine binding site, which may influence the biological activity of the heterolignans. Both residues are positioned around the hydrophobic binding pocket surrounding the trimethoxyphenyl moiety. Differences between our insect SAR and preceding medicinal chemistry studies observed for substituent effects of heterolignan ring D can thus be explained. In line with in vivo results described above only a small set of variations in *m*-position is favourable in our models. A close look at the binding model shown in Figure 4 also rationalises the striking impact of stereochemistry on activity as only one enantiomer fits into the T-like binding pocket. Due to a conserved part of the colchicine binding pocket, structural changes in ring A have a strong impact on the fit of heterolignans, also in accord with in vivo results (cf. Tables 2 and 3).

However, the important role of the lactone moiety (ring C) for in vivo activity remains unclear; although vital for high insecticidal activity, neither the carbonyl group nor the oxygen atom seem to be involved in any (polar) interactions.

3. Conclusion

More than 140 heterolignan derivatives have been prepared in the course of our study covering all major parts of the core structure.[21] The three-component reaction used to prepare target molecules turned out to be highly sensitive to solvent, temperature and concentration effects with ethanol, 2-pentanol and MeCN giving the best yields. Various unprecedented substituents have been introduced to investigate the structure–insecticidal activity relationship in detail. Variations in ring A had a high impact on biological activity with small alkoxy substituents at positions 5 and 6, for example, **5**, **23** and **43**, affording promising improved activity against *coleopteran* and *lepdiopteran* target organisms. Activity against the two test insects could be discriminated with the help of derivatives carrying one alkoxy substituent either at C6 or C7.

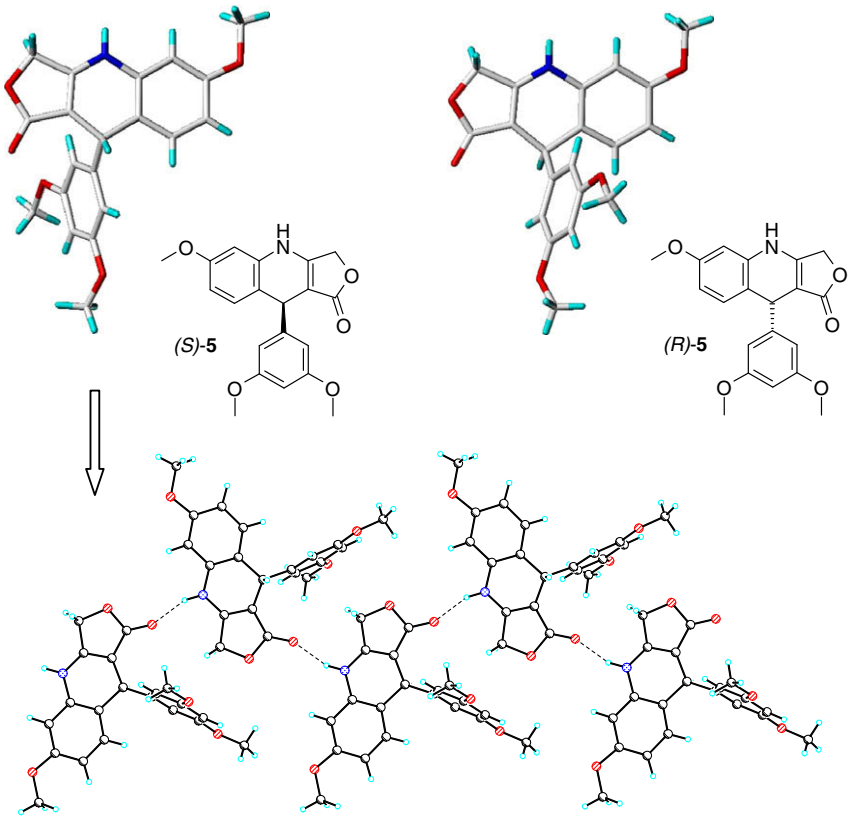


Figure 3. X-ray crystal structures of (*S*)-**5** and (*R*)-**5**.

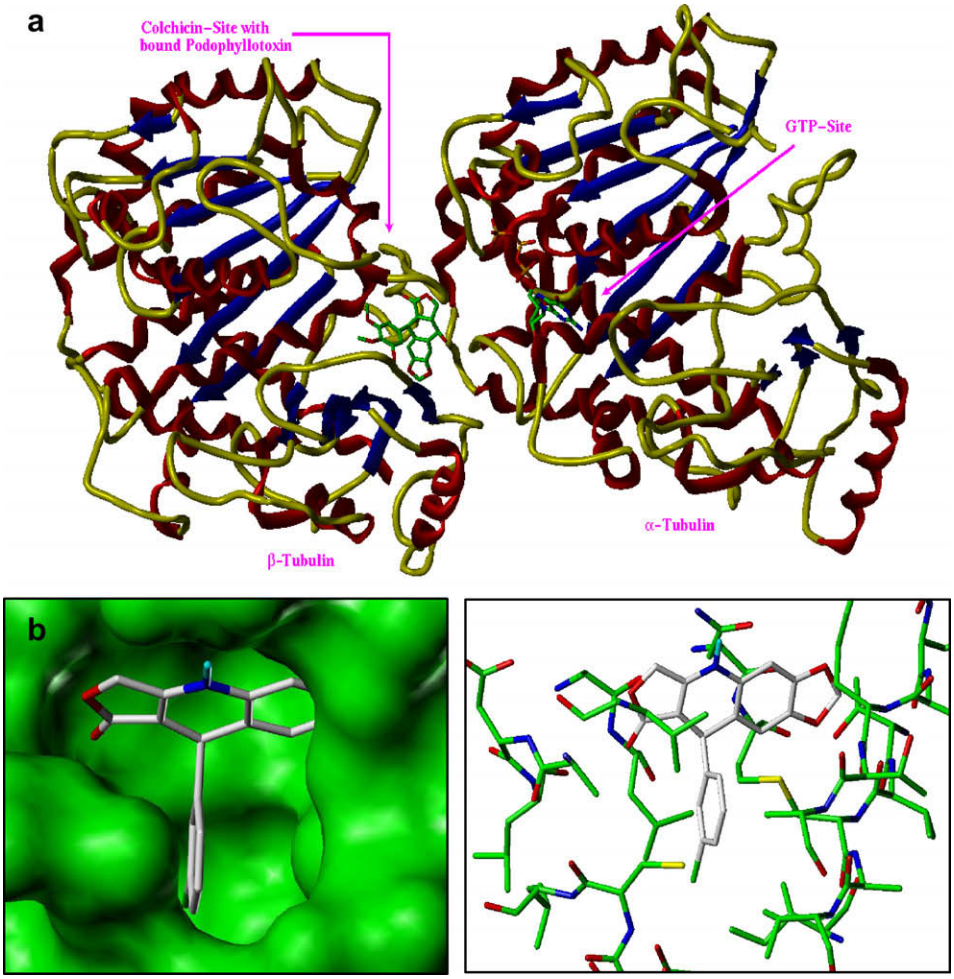


Figure 4. Receptor binding of heterolignans; (a) crystal structure of α,β-tubulin dimer from rat bound with podophyllotoxin **1** (colchicine site) and GTP; (b) docking pose for **96** in the colchicine binding site of tubulin.

All structural changes in rings B and C, however, led to decreased efficacy compared with initial lead structure **4**. This observation is in good accordance with molecular modeling studies indicating the interaction of rings B and C with a highly conservative binding site. In the case of substituent effects of ring D, groups in *meta*-substitution enhanced biological activity, while *ortho*- and *para*-substituents (except for fluorine) reduced the corresponding activity. With the help of in vitro experiments it was clearly shown that the heterolignans described herein act as insecticides by inhibiting the polymerisation of the microtubular system.

4. Experimental

4.1. Chemistry

4.1.1. General

Unless otherwise stated, all reagents and building blocks were purchased from commercial sources. Solvents were distilled prior to use or purchased in reagent-grade quality. All melting points where given, were determined in open capillary tubes using a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with either a 400 MHz Varian Unity Inova instrument or a 300 MHz Varian Mercury *Vx* instrument in $CDCl_3$ or DMSO using tetramethylsilane as an internal standard. Chemical shifts are given in delta (δ) values and coupling constants (J) in Hertz (Hz). The following peak multiplicity abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. LC–MS spectra were recorded using either a Shimadzu LC–MS-QP8000α system (EI/CI, pH 2 or pH 7, UVλ = 230 nm) or an Agilent Series 1100 system (ES, pH 2.4, UVλ = 230 nm and 254 nm). Microwave reactions were carried out using a Biotage (Personal Chemistry) Smith Synthesiser, operating at 300 W. Unless otherwise stated, silica gel chromatography was performed using an Isco Combiflash® parallel system with Teledyne Isco RediSep® 12 g or 40 g column cartridges at a flow rate of approximately 10 ml/min.

4.1.2. Single crystal X-ray structure analysis

The Crystal structure determination was carried out using a diffractometer (Oxford Diffraction, Xcalibur series) equipped with a CCD area detector (model Ruby), a sealed tube with Cu Kα radiation, osmic mirrors as monochromator and a Cryojet low temperature device (T = 100 K), as well as fullsphere data collection with omega and phi scans. Programs used: Data collection and reduction Crysalis (Oxford Diffraction 2007). Crystal structure solution was achieved using direct methods as implemented in SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany), 2000) and visualized using XP program. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F^2 using all measured intensities was carried out using the program SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany), 2000). All non-hydrogen atoms were refined including anisotropic displacement parameters. Fur-

Table 9
Crystal data and structure refinement for (*S*)-**5**

	Data for (*S*)-**5**
Empirical formula	$C_{20}H_{19}NO_5$
Formula weight	353.36
Temperature (K)	100
Wavelength (Å)	1.54178
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
Unit cell dimensions	
a (Å)	6.23860(10)
b (Å)	12.86480(10)
c (Å)	21.2606(2)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å)	1706.34(3)
Z	4
D_{calcd} (Mg/m^3)	1.376
Absorption coefficient (mm^{-1})	0.821
F(000)	744
Crystal size (mm^3)	0.20 × 0.15 × 0.13
Theta range for data collection (°)	4.02–66.93
Index ranges	$-7 \leqslant h \leqslant 3$, $-15 \leqslant k \leqslant 14$, $-24 \leqslant l \leqslant 24$
Reflections collected	9010
Independent reflections	2869 [*R*(int) = 0.0164]
Completeness to theta = 66.93°	95.6%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2869/0/311
Goodness-of-fit on F^2	1.065
Final *R* indices [*I* > 2sigma(*I*)]	R_1 = 0.0255, wR_2 = 0.0653
R indices (all data)	R_1 = 0.0267, wR_2 = 0.0660
Absolute structure parameter	−0.05(15)
Largest diff. peak and hole (e Å^{-3})	0.123 and −0.136

ther details are given in Table 9, and complete crystal structure data were deposited at the Cambridge Crystallographic Data Centre (ref. no. to be announced).

4.2. Biology

4.2.1. *P.* cochleariae larvae test (spray treatment)

Seventy eight parts by weight of acetone and 1.5 parts by weight of dimethylformamide were used as solvents with 0.5 part by weight of alkyl polyglycol ether added as emulsifier. An appropriate preparation of active compound is prepared by mixing 1 part by weight of active compound with the stated amounts of solvent and emulsifier and diluting the concentrate with emulsifier-containing water to the desired concentration. Disks of Chinese cabbage leaf (*Brassica pekinensis*) are sprayed with a preparation of active compound in the desired concentration and, after they have dried, are populated with larvae of the mustard beetle (*P. cochleariae*). After the desired time the activity is determined. Good activity indicated by '+' here means that at least 80% of the beetle larvae have been killed at the given concentration; 'n.a.' here means that no beetle larvae have been killed.

4.2.2. *S.* frugiperda larvae test (spray treatment)

Seventy eight parts by weight of acetone and 1.5 parts by weight of dimethylformamide were used as solvents with 0.5 part by weight of alkyl polyglycol ether added as emulsifier. An appropriate preparation of active compound is prepared by mixing 1 part by weight of active compound with the stated amounts of solvent and emulsifier and diluting the concentrate with emulsifier-containing water to the desired concentration. Disks of maize leaf (*Zea mays*) are sprayed with a preparation of active compound in the desired concentration and, after they have dried, are populated with larvae of the army worm (*S. frugiperda*). After the desired time the activity is determined. Good activity indicated by '+' here means that at least 80% of the larvae have been killed at the given concentration; 'n.a.' here means that no larvae have been killed.

4.3. Biochemistry

4.3.1. Analysis of in vitro microtubule polymerization

The CytoDYNA-MIX ScreenTM3 (CDS-03) kits purchased from Cytoskeleton Inc. (Denver, CO) were used for the detection of in vitro polymerization of tubulin.[19] Tubulin proteins (>99% purity) were suspended (300 μg/sample) in 100 μl of G-PEM buffer (80 mM PIPES, 2 mM $MgCl_2$, 0.5 mM EGTA, 1.0 mM GTP, pH 6.9) with 5% of glycerol added in the absence or presence of the test compounds including standard compounds colchicine and taxol at 4 °C. Then, the sample mixture was transferred to the pre-warmed 96-well plate, and the polymerization of tubulin was measured by the change in absorbance at 340 nm every 1 min for up to 60 min at 37 °C (Tecan Spectrafluor Plus).

4.3.2. Measurement of chromatin condensation by fluorescence microscopy

All selected test compounds were analysed on *S. frugiperda* (Sf9) and Chinese Hamster Ovary (CHO) cells. The cells were seeded into an 8-well slide chamber the day before treatment. In brief, after the cells were incubated with compounds for 48 h, they were washed twice with phosphate-buffered saline (PBS). Then, cells were fixed with ice-cold methanol for 10 min on ice followed by two short washes with acetone. After rehydrating the cells with PBS, the cells were incubated with Dapi solution (2 μM) for 30 min and subsequently analysed under a Zeiss Axiovert fluorescence microscope using a ×40 objective to detect the presence of chromatin condensation/fragmentation.

4.4. Chemistry—experimental procedures

4.4.1. General procedure 1 for the three-component reaction with electron-rich anilines

Tetronic acid (1 equiv), the corresponding aldehyde (1 equiv) and an aniline with electron-donating substituents (1 equiv) were added to a suitable polar solvent (e.g., ethanol, 2-pentanol, 3-pentanol or acetonitrile) and refluxed under Ar. After cooling to room temperature the precipitate formed was filtered off, dried and purified if necessary. When no precipitate was formed, the resulting crude reaction mixture was concentrated under reduced pressure and purified by preparative HPLC to afford desired heterolignan. In most cases, the three-component reaction was carried out on millimolar scale (i.e., 1–4 mmol).

4.4.2. General procedure 2 for the conversion of quinolines into desired dihydroquinoline target compounds

The quinoline derivative (1 equiv) or its corresponding mixture with desired dihydroquinoline was dissolved in glacial acetic acid (5 ml/mmol). Subsequent to 15 min stirring at rt under Ar $NaBH_3CN$ (2 equiv) was added and stirring was continued for 3 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography.

4.4.3. General procedure 3 for the synthesis of heterolignans with electron-withdrawing substituents in ring A

If the suitable Grignard reagent was not available from commercial sources it was freshly prepared as follows: Magnesium turnings (2 equiv) and some drops of the aryl bromide were added to abs tetrahydrofuran (1 ml/mmol), and the resulting reaction

mixture was heated to reflux. Then, the major portion of the aryl bromide (2 equiv in total) was added and refluxing was continued for 2 h. After cooling to rt the corresponding amino-chlorobenzonitrile (1 equiv, dissolved in abs tetrahydrofuran) was added dropwise. The reaction mixture was refluxed again for 1 h, and subsequent to cooling to rt aq HCl (2 N) was added carefully, and stirring was continued for 2 h at a temperature of 30 °C. After the reaction mixture had been neutralized with aq NaOH (2 N), the aqueous layer was extracted thoroughly with methyl-*t*-butyl ether. The combined organic layer was dried, filtered and concentrated under reduced pressure to afford the crude ketone intermediate which was purified by flash chromatography. In the following step intermediate ketone (1 equiv) was dissolved in abs toluene and tetronic acid (1 equiv) and *p*-toluenesulfonic acid (0.1 equiv) were added. The resulting reaction mixture was refluxed for 1 h. After cooling to rt the precipitate obtained was filtered off and washed with toluene to yield a substituted quinoline. Without purification the quinoline was further reduced with sodium cyanoborohydride following procedure 2 to afford desired heterolignan with electron-withdrawing substituents.

4.4.4. General procedure 4 for the synthesis of heterolignans with electron-withdrawing groups in ring A and further substituents in ring B

If the suitable Grignard reagent was not available from commercial sources it was freshly prepared as follows: Magnesium turnings (2 equiv) and some drops of the aryl bromide were added to abs tetrahydrofuran (1 ml/mmol), and the resulting reaction mixture was heated to reflux. Then, the major portion of the aryl bromide (2 equiv in total) was added and refluxing was continued for 2 h. After cooling to rt the corresponding amino-chlorobenzonitrile (1 equiv, dissolved in abs tetrahydrofuran) was added dropwise. The reaction mixture was refluxed again for 1 h, and subsequent to cooling to rt aq HCl (2 N) was added carefully, and stirring was continued for 2 h at a temperature of 30 °C. After the reaction mixture had been neutralized with aq NaOH (2 N), the aqueous layer was extracted thoroughly with methyl-*t*-butyl ether. The combined organic layer was dried, filtered and concentrated under reduced pressure to afford the crude ketone intermediate which was purified by flash chromatography. In the following step the aryl substituted ketone was suspended in diethyl ether, cooled to 0 °C and mixed dropwise with 1.3 ml of a 3 M solution of methyl magnesium bromide in diethyl ether (3 equiv). After the mixture had been stirred at room temperature for 5 h, ice was added cautiously, and with ice cooling, and then the mixture was adjusted to a pH of 6 using 1 N hydrochloric acid. The organic layer was extracted by shaking with saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to yield the corresponding tertiary alcohol. Then, the intermediate alcohol (1 equiv) was dissolved in abs toluene, and tetronic acid (1 equiv) and *p*-toluenesulfonic acid (0.1 equiv) were added. The resulting reaction mixture was refluxed for 1 h. After cooling to rt the precipitate obtained was filtered off and washed with toluene to yield desired heterolignan with alkyl substituent in ring B.

4.4.5. General procedure 5 for the synthesis of oxa-heterolignans

5 mmol of each a substituted benzaldehyde, a substituted phenol and morpholine are heated in methanol (5 ml) for 2 h under reflux and stirred over night at room temperature. The solvent is removed and the residue is treated with 2-propanol, the solid obtained is filtered with suction and dried. Resulting crystals and tetronic acid (1.5 equiv) are heated in a mixture of each 3 ml of water and acetic acid. After some minutes the product precipitates. The cooled mixture is triturated with 2-propanol, the crystals are filtered with suction, washed with 2-propanol and dried. The crude intermediate (1 mmol) is then suspended in 3 ml of acetic acid, two drops of concd sulfuric acid are added and the mixture is heated to 110 °C until all crystals are dissolved. After cooling the reaction mixture to room temperature water is added, and the resulting crystals are removed by filtration, washed with 2-propanol and dried to afford desired oxa-heterolignans.

4.4.6. 9-(3,4,5-Trimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (3)

Following general procedure 1 heterolignan **3** was isolated as a colourless solid (1536 mg, 77%). ^{1}H NMR (DMF-d_7) (δ): 6.73 (s, 1H), 6.65 (s, 2H), 6.62 (s, 1H), 5.98 (d, 2H), 5.05 (d, 1H), 4.98 (s, 1H), 4.92 (d, 1H), 3.78 (s, 6H), 3.66 (s, 3H).

4.4.7. 9-(3,5-Dimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (4)

Following general procedure 1 heterolignan **4** was obtained as colourless solid (980 mg, 73%); mp >310 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.85 (s, NH), 6.64 (s, 1H), 6.52 (s, 1H), 6.33 (m, 3H), 5.97 (s, 1H), 5.90 (s, 1H), 4.97 (d, 1H), 4.86 (d, 1H), 4.82 (s, 1H), 3.70 (s, 6H). MS (ES+) *m/z*: 368 (M^++1, 100).

4.4.8. 9-(3,5-Dimethoxyphenyl)-6-methoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (5)

Following general procedure 1 with 2-pentanol as solvent heterolignan **5** was obtained as colourless solid (400 mg, 66%) after HPLC purification; mp 254 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.92 (br s, NH), 6.98 (d, 1H), 6.50 (dd, 1H), 6.43 (d, 1H), 6.29 (m, 3H), 4.95 (d, 1H), 4.84 (s, 1H), 4.82 (d, 1H), 3.69 (s, 3H), 3.67 (s, 6H). MS (ES+) *m/z*: 353 (M^+), 351 (M^+-2H); MS (CI) *m/z*: 354 (M^++1, 100).

4.4.9. 9-(3,5-Dimethoxyphenyl)-7-[(3,5-dimethoxyphenyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl]-6-methoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (6)

Heterolignan **6** was isolated as side product upon HPLC purification of crude **5** (40 mg); mp 296 °C. ^{1}H NMR (DMSO-d_6) (δ): 11.80 (br s, OH), 9.94 (br s, NH), 7.09 (m, 1H), 6.44 (s, 1H), 6.22 (m, 1H), 6.19 (m, 3H), 6.12 (m, 2H), 5.19 (s, 1H), 4.94 (d, 1H), 4.80 (d, 1H), 4.76 (s, 1H), 4.59 (m, 2H), 3.69 (s, 3H), 3.64 (s, 6H), 3.51 (s, 6H). MS (ES+) *m/z*: 602 (M^+), 600 (M^+-2H); MS (CI) *m/z*: 603 (M^++1, 100).

4.4.10. 9-(3,5-Dimethoxyphenyl)-7-methoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (9)

Following general procedures 1 and 2 heterolignan **9** was obtained as colourless solid (21 mg, 3%) after HPLC purification; mp 235 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.88 (br s, NH), 6.86 (d, 1H), 6.74 (dd, 1H), 6.65 (d, 1H), 6.34 (m, 2H), 6.30 (m, 1H), 4.94 (d, 1H), 4.90 (s, 1H), 4.83 (d, 1H), 3.67 (s, 6H), 3.63 (s, 3H). MS (ES+) *m/z*: 353 (M^+), 351 (M^+-2H); MS (CI) *m/z*: 354 (M^++1, 100).

4.4.11. 9-(3,5-Dimethoxyphenyl)-6-(trifluoromethoxy)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (12)

Following general procedure 1 heterolignan **12** was purified by preparative HPLC and isolated as colourless solid (30 mg, 4%); mp 231 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.20 (br s, NH), 7.21 (d, 1H), 7.05 (dd, 1H), 6.86 (d, 1H), 6.38 (m, 3H), 5.02 (d, 1H), 4.99 (s, 1H), 4.87 (d, 1H), 3.68 (s, 6H). MS (ES+) *m/z*: 408 (M^++1), 405 (M^+-2H); MS (CI) *m/z*: 408 (M^++1, 100).

4.4.12. 9-(3,5-Dimethoxyphenyl)-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (13)

Following general procedure 5 heterolignan **13** was isolated as colourless solid (60 mg, 19%). ^{1}H NMR (CH_3CN-d_3) (δ): 6.70 (s,

1H), 6.55 (s, 1H), 6.40 (m, 2H), 6.36 (m, 1H), 5.95 (m, 2H), 4.83 (m, 3H). MS (ES+) *m/z*: 369 (MH^+).

4.4.13. 6-Methoxy-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (14)

Following general procedure 1 heterolignan **14** was obtained as colourless solid (300 mg, 19%); mp 284–286 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.75 (br s, NH), 7.01 (d, 1H), 6.53 (dd, 1H), 6.48 (d, 1H), 6.47 (s, 2H), 4.92 (d, 1H), 4.88 (s, 1H), 4.81 (d, 1H), 3.71 (s, 3H), 3.70 (s, 6H), 3.62 (s, 3H). MS (ES+) *m/z*: 384 (M^++1, 90), 216 (100).

4.4.14. 7-Methoxy-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (15)

Following general procedure 2 heterolignan **15** was obtained as colourless solid (240 mg, 92%); mp 217–218 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.90 (s, NH), 6.90 (d, 1H), 6.77 (dd, 1H), 6.73 (d, 1H), 6.52 (s, 2H), 5.02 (d, 1H), 4.95 (s, 1H), 4.87 (d, 1H), 3.70 (s, 6H), 3.65 (s, 3H), 3.61 (s, 3H). MS (ES+) *m/z*: 384 (M^++1, 100), 216 (98).

4.4.15. 6-Chloro-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (16)

Following general procedures 2 and 3 heterolignan **16** was isolated by simple filtration as a colourless solid (25 mg, 68%); mp 249 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.16 (br s, NH), 7.19 (m, 2H), 6.96 (d, 1H), 6.52 (s, 2H), 5.01 (s, 1H), 4.99 (d, 1H), 4.85 (d, 1H), 3.72 (s, 6H), 3.61 (s, 3H). MS (ES+) *m/z*: 388 (M^+), 386 (M^+−2H).

4.4.16. 9-(3,5-Dimethoxyphenyl)-6,7-dimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (17)

Following general procedure 1 heterolignan **17** was obtained as colourless solid (200 mg, 40%); mp 259 °C. ^{1}H NMR ($CDCl_3$) (δ): 6.64 (br s, NH), 6.56 (s, 1H), 6.40 (m, 2H), 6.36 (s, 1H), 6.28 (m, 1H), 5.02 (s, 1H), 4.78 (d, 1H), 4.68 (d, 1H), 3.85 (s, 3H), 3.74 (s, 9H). MS (ES+) *m/z*: 383 (M^+), 381 (M^+−2H), 246.

4.4.17. 6,7-Dimethoxy-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (18)

Following general procedure 2 heterolignan **18** was isolated by simple filtration as a colourless solid (78 mg, 94%). ^{1}H NMR (MeOD) (δ): 6.58 (s, 1H), 6.52 (s, 1H), 6.48 (s, 2H), 4.98 (s, 1H), 4.88 (d, 1H), 4.80 (d, 1H), 3.85 (s, 3H), 3.78 (s, 6H), 3.75 (s, 3H), 3.70 (s, 3H).

4.4.18. 2,2-Difluoro-9-(3,5-dimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (19)

Following general procedure 1 heterolignan **19** was afforded as colourless solid (250 mg, 53%); mp >300 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.18 (br s, NH), 7.17 (s, 1H), 6.96 (s, 1H), 6.36 (m, 3H), 5.01 (d, 1H), 4.95 (s, 1H), 4.84 (d, 1H), 3.69 (s, 6H). MS (ES+) *m/z*: 404 (M^++1), 401 (M^+−2H), 266; MS (CI) *m/z*: 404 (M^++1, 100).

4.4.19. 2,2-Difluoro-9-(3,4,5-trimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (20)

Following general procedure 1 heterolignan **20** was isolated by flash chromatography as a colourless solid (287 mg, 33%). ^{1}H NMR (MeOD) (δ): 6.83 (s, 1H), 6.75 (s, 1H), 6.50 (s, 2H), 5.02 (s, 1H), 4.92 (d, 1H), 4.84 (d, 1H), 3.80 (s, 6H), 3.73 (s, 3H).

4.4.20. 10-(3,5-Dimethoxyphenyl)-2,3,7,10-tetrahydro[1,4]dioxino[2,3-*g*]furo[3,4-*b*]quinolin-9(6*H*)-one (21)

Following general procedure 1 heterolignan **21** was afforded as colourless solid (150 mg, 29%); mp >300 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.82 (br s, NH), 6.58 (s, 1H), 6.42 (s, 1H), 6.31 (m, 3H), 4.94 (d, 1H), 4.81 (d, 1H), 4.80 (s, 1H), 4.19 (m, 2H), 4.12 (m, 2H), 3.68 (s, 6H). MS (ES+) *m/z*: 382 (M^++1), 379 (M^+−2H), 244; MS (CI) *m/z*: 382 (M^++1, 100).

4.4.21. 11-(3,5-Dimethoxyphenyl)-3,4,8,11-tetrahydro-2*H*-[1,4]dioxepino[2,3-*g*]furo[3,4-*b*]quinolin-10(7*H*)-one (22)

Following general procedure 1 heterolignan **22** was obtained as colourless solid (160 mg, 33%); mp 289 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.89 (br s, NH), 6.71 (s, 1H), 6.54 (s, 1H), 6.32 (m, 3H), 4.96 (d, 1H), 4.83 (d, 1H), 4.81 (s, 1H), 4.06 (m, 2H), 3.97 (m, 2H), 3.66 (s, 6H), 2.02 (m, 2H). MS (ES+) *m/z*: 395 (M^+), 393 (M^+−2H), 258; MS (CI) *m/z*: 396 (M^++1, 100),

4.4.22. 9-(3,5-Dimethoxyphenyl)-6-ethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (23)

Following general procedure 1 heterolignan **23** was obtained as colourless solid (160 mg, 27%); mp 259 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.96 (br s, NH), 6.97 (d, 1H), 6.48 (dd, 1H), 6.42 (d, 1H), 6.30 (m, 3H), 4.95 (d, 1H), 4.84 (s, 1H), 4.82 (d, 1H), 3.94 (q, 2H), 3.67 (s, 6H), 1.28 (t, 3H). MS (ES+) *m/z*: 367 (M^+), 365 (M^+−2H), 230; MS (CI) *m/z*: 368 (M^++1, 100).

4.4.23. 9-(3,5-Dimethoxyphenyl)-6-(propan-2-yloxy)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (24)

Following general procedure 1 heterolignan **24** was isolated as colourless solid (70 mg, 14%); mp 267 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.88 (br s, NH), 6.96 (d, 1H), 6.46 (dd, 1H), 6.41 (d, 1H), 6.29 (m, 3H), 4.96 (d, 1H), 4.83 (s, 1H), 4.82 (d, 1H), 4.47 (sept, 1H), 3.67 (s, 6H), 1.25 (d, 3H), 1.22 (d, 3H). MS (ES+) *m/z*: 381 (M^+), 379 (M^+−2H), 244, 202; MS (CI) *m/z*: 382 (M^++1, 100).

4.4.24. 6-(Benzyloxy)-9-(3,5-dimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (25)

Following general procedures 1 and 2 heterolignan **25** was obtained as colourless solid after HPLC purification (20 mg, 5%); mp 277 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.94 (br s, NH), 7.35 (m, 5H), 6.98 (d, 1H), 6.57 (dd, 1H), 6.49 (d, 1H), 6.28 (m, 3H), 5.05 (s, 2H), 4.94 (d, 1H), 4.83 (s, 1H), 4.81 (d, 1H), 3.66 (s, 6H). MS (ES+) *m/z*: 429 (M^+), 427 (M^+−2H); MS (CI) *m/z*: 431 (M^++1, 100).

4.4.25. 9-(3,5-Dimethoxyphenyl)-6-(phenoxy)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (26)

Following general procedures 1 and 2 heterolignan **26** was isolated as colourless solid after HPLC purification (40 mg, 9%); mp 281 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.98 (br s, NH), 7.36 (m, 2H), 7.12 (m, 1H), 7.06 (d, 1H), 6.99 (m, 2H), 6.55 (dd, 1H), 6.48 (d, 1H), 6.33 (m, 2H), 6.29 (m, 1H), 4.93 (d, 1H), 4.89 (s, 1H), 4.80 (d, 1H), 3.66 (s, 6H). MS (ES+) *m/z*: 415 (M^+), 413 (M^+−2H), 278; MS (CI) *m/z*: 416 (M^++1, 100).

4.4.26. 9-(3,5-Dimethoxyphenyl)-6,7-diethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (27)

Following general procedure 1 heterolignan **27** was isolated as colourless solid (210 mg, 53%); mp 285 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.77 (br s, NH), 6.65 (s, 1H), 6.48 (s, 1H), 6.32 (m, 2H), 6.28 (m, 1H), 4.93 (d, 1H), 4.82 (s, 1H), 4.80 (d, 1H), 3.94 (q, 2H), 3.79 (q, 2H), 3.67 (s, 6H), 1.28 (t, 3H), 1.20 (t, 3H). MS (ES+) *m/z*: 411 (M^+), 409 (M^+−2H); MS (CI) *m/z*: 412 (M^++1, 100).

4.4.27. 9-(3,5-Dimethoxyphenyl)-6-(methylsulfanyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (28)

Following general procedure 1 heterolignan **28** was isolated as colourless solid (66 mg, 12%); mp 283 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.98 (br s, NH), 7.01 (d, 1H), 6.78 (dd, 1H), 6.75 (d, 1H), 6.29 (m, 3H), 4.96 (d, 1H), 4.87 (s, 1H), 4.82 (d, 1H), 3.66 (s, 6H), 2.42 (s, 3H). MS (ES+) *m/z*: 369 (M^+), 367 (M^+−2H); MS (CI) *m/z*: 370 (M^++1, 100).

4.4.28. 9-(3,5-Dimethoxyphenyl)-6-methyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (29)

Following general procedure 1 heterolignan **29** was isolated as colourless solid (140 mg, 21%); mp 269 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.93 (br s, NH), 6.97 (d, 1H), 6.70 (m, 2H), 6.29 (m, 3H), 4.97 (d, 1H), 4.87 (s, 1H), 4.82 (d, 1H), 3.67 (s, 6H), 2.22 (s, 3H). MS (ES+) *m/z*: 337 (M^+), 335 (M^+-2H); MS (CI) *m/z*: 338 (M^++1, 100).

4.4.29. 9-(3,5-Dimethoxyphenyl)-6-(methylsulfanyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (30)

Following general procedure 1 heterolignan **30** was obtained as colourless solid (200 mg, 39%); mp 243 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.98 (br s, NH), 7.02 (d, 1H), 6.92 (dd, 1H), 6.88 (d, 1H), 6.31 (m, 3H), 4.98 (d, 1H), 4.86 (s, 1H), 4.82 (d, 1H), 3.68 (s, 6H), 1.22 (s, 9H). MS (ES+) *m/z*: 379 (M^+), 377 (M^+-2H); MS (CI) *m/z*: 380 (M^++1, 100).

4.4.30. 6-(Cyclopropyloxy)-9-(3,5-dimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (31)

Following general procedure 1 heterolignan **31** was obtained as colourless solid (60 mg, 10%) after HPLC purification; mp 244 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.98 (br s, NH), 6.88 (d, 1H), 6.60 (m, 1H), 6.30 (m, 2H), 6.21 (m, 1H), 6.14 (d, 1H), 4.96 (d, 1H), 4.86 (s, 1H), 4.74 (d, 1H), 4.58 (m, 1H), 3.68 (s, 6H), 0.74 (m, 2H), 0.65 (m, 2H). MS (ES+) *m/z*: 379 (M^+), 377 (M^+-2H); MS (CI) *m/z*: 380 (M^++1, 100).

4.4.31. 9-(3,5-Dimethoxyphenyl)-7-(propan-2-yloxy)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (32)

Following general procedure 1 heterolignan **32** was obtained as colourless solid (39 mg, 8%) after HPLC purification; mp 244 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.86 (br s, NH), 6.84 (d, 1H), 6.70 (dd, 1H), 6.65 (d, 1H), 6.36 (m, 2H), 6.31 (m, 1H), 4.95 (d, 1H), 4.89 (s, 1H), 4.82 (d, 1H), 4.39 (sept, 1H), 3.67 (s, 6H), 1.18 (d, 3H), 1.15 (d, 3H). MS (ES+) *m/z*: 381 (M^+), 379 (M^+-2H); MS (CI) *m/z*: 382 (M^++1, 100).

4.4.32. 6,7-Bis(difluoromethoxy)-9-(3,5-dimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (33)

Following general procedure 1 heterolignan **33** was obtained as colourless solid (39 mg, 8%) after HPLC purification; mp 244 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.18 (br s, NH), 7.13 (s, 1H), 7.00 (t, 1H), 6.86 (s, 1H), 6.73 (t, 1H), 6.38 (m, 2H), 6.35 (m, 1H), 5.04 (d, 1H), 4.95 (s, 1H), 4.86 (d, 1H), 3.68 (s, 6H). MS (ES+) *m/z*: 455 (M^+), 453 (M^+-2H); MS (CI) *m/z*: 456 (M^++1, 100).

4.4.33. 9-(3,5-Dimethoxyphenyl)-6-ethoxy-7-methyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (34)

Following general procedure 2 heterolignan **34** was obtained as colourless solid (110 mg, 95%); mp 182 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.84 (br s, NH), 6.80 (s, 1H), 6.44 (s, 1H), 6.30 (m, 3H), 4.94 (d, 1H), 4.81 (s, 1H), 4.80 (d, 1H), 3.95 (q, 2H), 3.66 (s, 6H), 1.99 (s, 3H), 1.33 (t, 3H). MS (ES+) *m/z*: 381 (M^+), 379 (M^+-2H); MS (CI) *m/z*: 382 (M^++1, 100).

4.4.34. 9-(3,5-Dimethoxyphenyl)-6,7-dimethyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (35)

Following general procedure 1 heterolignan **35** was obtained as colourless solid (150 mg, 25%) after HPLC purification; mp 268 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.82 (br s, NH), 6.83 (s, 1H), 6.69 (s, 1H), 6.31 (m, 3H), 4.95 (d, 1H), 4.83 (s, 1H), 4.81 (d, 1H), 3.66 (s, 6H), 2.14 (s, 3H), 2.07 (s, 3H). MS (ES+) *m/z*: 351 (M^+), 349 (M^+-2H), 214; MS (CI) *m/z*: 352 (M^++1, 100).

4.4.35. 9-(3,5-Dimethoxyphenyl)-6-phenyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (36)

Following general procedure 1 heterolignan **36** was isolated as colourless solid (110 mg, 22%); mp 275 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.09 (br s, NH), 7.58 (m, 2H), 7.44 (m, 2H), 7.37 (d, 1H), 7.20 (m, 2H), 7.16 (m, 1H), 6.40 (m, 2H), 6.34 (m, 1H), 5.03 (d, 1H), 4.98 (s, 1H), 4.86 (d, 1H), 3.68 (s, 6H). MS (ES+) *m/z*: 399 (M^+), 397 (M^+-2H), 262; MS (CI) *m/z*: 400 (M^++1, 100).

4.4.36. 9-(3,5-Dimethoxyphenyl)-6-hydroxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (37)

Following general procedure 1 heterolignan **37** was obtained as colourless solid (110 mg, 33%); mp 251 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.83 (br s, NH), 9.40 (br s, OH), 6.84 (d, 1H), 6.29 (m, 5H), 4.93 (d, 1H), 4.82 (d, 1H), 4.79 (s, 1H), 3.66 (s, 6H). MS (ES+) *m/z*: 339 (M^+), 337 (M^+-2H); MS (CI) *m/z*: 340 (M^++1, 100).

4.4.37. 9-(3,5-Dimethoxyphenyl)-6-methoxy-7-methyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (38)

Following general procedure 1 heterolignan **38** was obtained as colourless solid (220 mg, 40%); mp 234 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.84 (br s, NH), 6.81 (s, 1H), 6.45 (s, 1H), 6.29 (m, 3H), 4.96 (d, 1H), 4.81 (d, 1H), 4.80 (s, 1H), 3.76 (s, 3H), 3.67 (s, 6H), 1.99 (s, 3H). MS (ES+) *m/z*: 367 (M^+), 365 (M^+-2H), 230; MS (CI) *m/z*: 368 (M^++1, 100).

4.4.38. 7-Chloro-9-(3,5-dimethoxyphenyl)-6-methoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (39)

Following general procedure 1 heterolignan **39** was obtained as colourless solid (38 mg, 7%); mp 273 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.09 (br s, NH), 7.11 (s, 1H), 6.62 (s, 1H), 6.33 (m, 3H), 4.99 (d, 1H), 4.87 (s, 1H), 4.84 (d, 1H), 3.82 (s, 3H), 3.68 (s, 6H). MS (ES+) *m/z*: 387 (M^+), 385 (M^+-2H); MS (CI) *m/z*: 388 (M^++1, 100).

4.4.39. 6-Benzyloxy-7-bromo-9-(3,5-dimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (40)

Following general procedure 1 heterolignan **40** was obtained as colourless solid (100 mg, 26%); mp 235 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.06 (br s, NH), 7.32 (m, 5H), 7.25 (s, 1H), 6.65 (s, 1H), 6.36 (m, 3H), 5.19 (s, 2H), 4.98 (d, 1H), 4.88 (s, 1H), 4.82 (d, 1H), 3.68 (s, 6H). MS (ES+) *m/z*: 508 (M^+), 506 (M^+-2H); MS (CI) *m/z*: 509 (M^++1, 100).

4.4.40. 9-(3,5-Dimethoxyphenyl)-5,7-dimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (41)

Following general procedure 1 heterolignan **41** was obtained as colourless solid (70 mg, 94%); mp 204 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.48 (br s, NH), 6.49 (d, 1H), 6.31 (m, 3H), 6.26 (d, 1H), 4.88 (d, 1H), 4.87 (s, 1H), 4.77 (d, 1H), 3.84 (s, 3H), 3.67 (s, 6H), 3.64 (s, 3H). MS (ES+) *m/z*: 383 (M^+), 381 (M^+-2H); MS (CI) *m/z*: 384 (M^++1, 100).

4.4.41. 9-(3,5-Dimethoxyphenyl)-5,8-dimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (42)

Following general procedure 1 heterolignan **42** was isolated as colourless solid (30 mg, 6%) after HPLC purified by HPLC; mp 228 °C. ^{1}H NMR ($CDCl_3$) (δ): 7.14 (br s, NH), 6.74 (d, 1H), 6.44 (d, 1H), 6.42 (m, 2H), 6.25 (m, 1H), 5.24 (s, 1H), 4.80 (d, 1H), 4.72 (d, 1H), 3.88 (s, 3H), 3.76 (s, 6H), 3.62 (s, 3H). MS (ES+) *m/z*: 383 (M^+), 381 (M^+-2H); MS (CI) *m/z*: 384 (M^++1, 100).

4.4.42. 9-(3,5-Dimethoxyphenyl)-5,6-dimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (43)

Following general procedure 1 heterolignan **43** was isolated as colourless solid (180 mg, 34%); mp 278 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.73 (br s, NH), 6.78 (d, 1H), 6.62 (d, 1H), 6.30 (m, 3H), 4.92 (d, 1H), 4.84 (s, 1H), 4.80 (d, 1H), 3.78 (s, 6H), 3.68 (s, 6H). MS (ES+) *m/z*: 383 (M^+), 381 (M^+-2H), 244, 202; MS (CI) *m/z*: 384 (M^++1, 100).

4.4.43. 9-(3,5-Dimethoxyphenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (44)

Following general procedure 1 using 2-pentanol as solvent heterolignan **44** was isolated as colourless solid (290 mg, 63%); mp 201 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.84 (br s, NH), 6.38 (s, 1H), 6.27 (m, 1H), 6.22 (m, 2H), 4.87 (s, 1H), 4.84 (d, 1H), 4.75 (d, 1H), 3.90 (s, 3H), 3.65 (s, 6H), 3.63 (s, 3H), 3.43 (s, 3H). MS (ES+) *m/z*: 413 (M^+), 411 (M^+-2H), 276; MS (CI) *m/z*: 414 (M^++1, 100).

4.4.44. 9-(3,5-Dimethoxyphenyl)-6,8-dimethyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (45)

Following general procedure 1 heterolignan **45** was obtained as colourless solid (100 mg, 17%); mp 232 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.82 (br s, NH), 6.62 (s, 2H), 6.29 (m, 1H), 6.20 (m, 2H), 4.91 (s, 1H), 4.83 (d, 1H), 4.76 (d, 1H), 3.64 (s, 6H), 2.22 (s, 3H), 1.98 (s, 3H). MS (ES+) *m/z*: 351 (M^+), 349 (M^+-2H), 214; MS (CI) *m/z*: 352 (M^++1, 100).

4.4.45. 9-(3,5-Dimethoxyphenyl)-6,8-dimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (46)

Following general procedure 1 heterolignan **46** was obtained as colourless solid (150 mg, 28%); mp >300 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.91 (br s, NH), 6.32 (d, 1H), 6.26 (m, 1H), 6.22 (m, 1H), 6.14 (dd, 1H), 5.82 (dd, 1H), 4.88 (d, 1H), 4.85 (s, 1H), 4.78 (d, 1H), 3.75 (s, 3H), 3.64 (s, 6H), 3.62 (s, 3H). MS (ES+) *m/z*: 383 (M^+), 381 (M^+-2H); MS (CI) *m/z*: 384 (M^++1, 100).

4.4.46. 9-(3,5-Dimethoxyphenyl)-5,6-dimethyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (47)

Following general procedure 1 heterolignan **47** was obtained as colourless solid (100 mg, 16%); mp 259 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.28 (br s, NH), 6.82 (d, 1H), 6.73 (d, 1H), 6.30 (m, 3H), 4.95 (d, 1H), 4.88 (s, 1H), 4.82 (d, 1H), 3.66 (s, 6H), 2.19 (s, 3H), 2.17 (s, 3H). MS (ES+) *m/z*: 351 (M^+), 349 (M^+-2H); MS (CI) *m/z*: 352 (M^++1, 100).

4.4.47. 9-(3,5-Dimethoxyphenyl)-5,7-dimethyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (48)

Following general procedure 2 heterolignan **48** was obtained as colourless solid (100 mg, 65%); mp 284 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.31 (br s, NH), 6.82 (s, 1H), 6.75 (s, 1H), 6.31 (m, 3H), 4.92 (d, 1H), 4.85 (s, 1H), 4.80 (d, 1H), 3.66 (s, 6H), 2.22 (s, 3H), 2.12 (s, 3H). MS (ES+) *m/z*: 351 (M^+), 349 (M^+-2H); MS (CI) *m/z*: 352 (M^++1, 100).

4.4.48. 9-(3,5-Dimethoxyphenyl)-5-methoxy-7-methyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (49)

Following general procedure 2 heterolignan **49** was obtained as colourless solid (80 mg, 14%); mp >300 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.52 (br s, NH), 6.66 (m, 1H), 6.45 (m, 1H), 6.28 (m, 3H), 4.85 (d, 1H), 4.83 (s, 1H), 4.76 (d, 1H), 3.83 (s, 3H), 3.66 (s, 6H), 2.16 (s, 3H). MS (ES+) *m/z*: 367 (M^+), 365 (M^+-2H); MS (CI) *m/z*: 368 (M^++1, 100).

4.4.49. 6-Chloro-9-methyl-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (50)

Following general procedure 4 heterolignan **50** was obtained as colourless solid (280 mg, 94%); mp 240–242 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.95 (br s, NH), 7.10 (d, 1H), 6.91 (m, 2H), 6.54 (s, 2H), 4.90 (d, 1H), 4.82 (d, 1H), 3.70 (s, 6H), 3.64 (s, 3H), 1.90 (s, 3H). MS (ES+) *m/z*: 402 (M^++1, 45), 234 (100).

4.4.50. 5-Methyl-9-(3,4,5-trimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (52)

K_2CO_3 (1 equiv) and MeI (3 equiv) were successively added to a solution of heteolignan **3** (0.5 mmol, 1 equiv) in dry THF. The reaction mixture was refluxed overnight and then evaporated. The crude product was purified by flash chromatography. Heterolignan **52** was isolated as a colourless solid (39 mg, 11%). ^{1}H NMR ($CDCl_3$) (δ): 6.60 (s, 1H), 6.58 (s, 1H), 6.40 (s, 2H), 5.95 (dd, 2H), 5.0 (s, 1H), 4.87 (d, 1H), 4.80 (d, 1H), 3.80 (s, 9H), 3.20 (s, 3H).

4.4.51. 6,7-Dimethoxy-5-methyl-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (53)

Following general procedure 1 heterolignan **53** was isolated as a colourless solid (44 mg, 12%). ^{1}H NMR (DMSO-d_6) (δ): 6.75 (s, 2H), 6.41 (s, 2H), 5.16 (d, 1H), 4.99 (d, 1H), 4.85 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.64 (s, 9H), 3.60 (s, 3H). MS (ES+) *m/z*: 427 (M^+), 425 (M^+-2H); MS (CI) *m/z*: 428 (M^++1, 100).

4.4.52. 9-(4-Chlorophenyl)-4,6-dimethyl-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (54)

Following general procedure 1 heterolignan **54** was isolated as a colourless solid (90 mg, 13%). ^{1}H NMR ($CDCl_3$) (δ): 7.20 (d, 2H), 7.12 (d, 2H), 6.94 (d, 1H), 6.85 (d, 1H), 6.80 (s, 1H), 5.10 (s, 1H), 4.90 (d, 1H), 4.82 (d, 1H), 3.25 (s, 3H), 2.36 (s, 3H).

4.4.53. 9-(3,5-Dimethoxyphenyl)-5-ethyl-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (55)

Following general procedure 1 heterolignan **55** was isolated as a colourless solid (80 mg, 16%); mp 238 °C. ^{1}H NMR (DMSO-d_6) (δ): 6.96 (s, 1H), 6.71 (s, 1H), 6.30 (m, 3H), 5.99 (d, 1H), 5.92 (d, 1H), 5.14 (d, 1H), 5.98 (d, 1H), 4.82 (s, 1H), 3.70 (q, 2H), 3.67 (s, 6H), 1.19 (t, 3H). MS (ES+) *m/z*: 395 (M^+), 393 (M^+-2H); MS (CI) *m/z*: 396 (M^++1, 100).

4.4.54. 9-(3,5-Dimethoxyphenyl)-4-ethyl-6,7-dimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (56)

Following general procedure 1 heterolignan **56** was isolated as a colourless solid (200 mg, 39%); mp 200 °C. ^{1}H NMR (DMSO-d_6) (δ): 6.75 (s, 2H), 6.28 (m, 3H), 5.16 (d, 1H), 4.99 (d, 1H), 4.85 (s, 1H), 3.82 (s, 3H), 3.77 (q, 2H), 3.66 (s, 6H), 3.62 (s, 3H), 1.23 (t, 3H). MS (ES+) *m/z*: 411 (M^+), 409 (M^+-2H); MS (CI) *m/z*: 412 (M^++1, 100).

4.4.55. 9-(3,5-Dimethoxyphenyl)-4-methyl-6-methoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (57)

Following general procedure 1 heterolignan **57** was isolated as a colourless solid (15 mg, 12%); mp 216 °C. ^{1}H NMR ($CDCl_3$) (δ): 7.06 (d, 1H), 6.58 (dd, 1H), 6.52 (d, 1H), 6.37 (m, 1H), 6.30 (m, 1H), 6.27 (m, 1H), 5.04 (s, 1H), 4.86 (d, 1H), 4.78 (d, 1H), 3.82 (s, 3H), 3.74 (s, 6H), 3.21 (s, 3H). MS (ES+) *m/z*: 367 (M^+), 365 (M^+-2H); MS (CI) *m/z*: 368 (M^++1, 100).

4.4.56. 9-(3,5-Dimethoxyphenyl)-9-methyl-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (58)

Following general procedure 1 using a benzophenone precursor instead of a benzaldehyde heterolignan **4** was obtained as colourless solid (41 mg, 21%). ^{1}H NMR (DMSO-d_6) (δ): 9.88 (s, NH), 6.60 (s, 1H), 6.47 (s, 1H), 6.43 (m, 2H), 6.33 (m, 1H), 5.94 (s, 1H), 5.92 (s, 1H), 4.92 (d, 1H), 4.83 (d, 1H), 3.70 (s, 6H), 1.88 (s, 3H). MS (ES+) *m/z*: 382 (M^++1, 100).

4.4.57. 9-(3-Chlorophenyl)-5,6,7,9-tetrahydro-8*H*-cyclopenta[*b*]-[1,3]dioxolo[4,5-*g*]quinolin-8-one (59)

Following general procedure 1 heterolignan **59** was obtained as colourless solid (900 mg, 72%); mp 285–290 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.03 (s, NH), 7.27 (dd, 1H), 7.18 (m, 2H), 7.12 (d, 1H), 6.62 (s, 1H), 6.57 (s, 1H), 5.96 (s, 1H), 5.90 (s, 1H), 4.92 (s, 1H), 2.68 (m, 2H), 2.28 (m, 2H). MS (ES+) *m/z*: 340 (M^++1, 100).

4.4.58. 9-(3-Chlorophenyl)-7-phenyl-5*H*-cyclopenta[b][1,3]dioxolo[4,5-*g*]quinoline-6,8(7*H*,9*H*)-dione (60)

Following general procedure 1 heterolignan **60** was obtained as colourless solid (940 mg, 60%); mp 205–207 °C. MS (ES+) *m/z*: 431 (M^++1, 100).

4.4.59. 10-(3-Chlorophenyl)-6,7,8,10-tetrahydro[1,3]dioxolo[4,5-*b*]acridin-9(5*H*)-one (61)

Following general procedure 1 heterolignan **61** was obtained as colourless solid (78 mg, 6%) after HPLC purification; mp 280–285 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.18 (br s, NH), 7.12 (m, 3H), 6.69 (s, 1H), 6.55 (s, 1H), 5.90 (s, 1H), 5.86 (s, 1H), 5.05 (s, 1H), 2.55 (m, 2H), 2.19 (m, 2H), 1.92 (m, 1H), 1.83 (m, 1H). MS (ES+) *m/z*: 354 (M^++1, 100).

4.4.60. 9-(3-Chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclopenta[*b*]-[1,3]dioxolo[4,5-*g*]quinoline (62)

Following general procedure 1 heterolignan **62** was obtained as colourless solid (90 mg, 7%) after HPLC purification; mp 106–110 °C. MS (ES+) *m/z*: 326 (M^++1, 100).

4.4.61. 10-(3-Chlorophenyl)-5,6,7,8,9,10-hexahydro[1,3]dioxolo-[4,5-*b*]acridine (63)

Following general procedure 1 heterolignan **63** was obtained as colourless solid (190 mg, 15%); mp 173–175 °C. ^{1}H NMR (DMSO-d_6) (δ): 7.47 (m, 1H), 7.39 (m, 3H), 6.98 (s, 1H), 6.26 (s, 1H), 6.02 (br s, NH), 5.87 (s, 1H), 5.82 (s, 1H), 3.80 (d, 1H), 2.38 (m, 1H), 2.15 (m, 2H), 1.68 (m, 1H), 1.37 (m, 1H), 1.15 (m, 1H), 1.01 (m, 1H). MS (ES+) *m/z*: 340 (M^++1, 100), 216 (98).

4.4.62. 10-(3-Chlorophenyl)-7,7-dimethyl-6,7,8,10-tetrahydro[1,3]dioxolo[4,5-*b*]acridin-9(5*H*)-one (64)

Following general procedure 1 heterolignan **64** was obtained as colourless solid (1080 mg, 77%); mp 144–147 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.34 (s, NH) 7.22 (m, 2H), 7.13 (m, 2H), 6.75 (s, 1H), 6.54 (s, 1H), 5.94 (s, 1H), 5.88 (s, 1H), 5.01 (s, 1H), 2.43 (d, 1H), 2.35 (dd, 1H), 2.18 (d, 1H), 1.99 (d, 1H), 1.03 (s, 3H), 0.94 (s, 3H). MS (ES+) *m/z*: 382 (M^++1, 100).

4.4.63. 10-(3-Chlorophenyl)-7-methyl-5,6,7,10-tetrahydro-9*H*-[1,3]dioxolo[4,5-*g*]pyrano-[4,3-*b*]quinolin-9-one (65)

Following general procedure 1 heterolignan **65** (2:1 mixture of diastereomers) was obtained as colourless solid (1200 mg, 89%); mp 288–290 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.49 (2s, NH) 7.20 (m, 4H), 6.75 + 6.70 (2s, 1H), 6.50 (s, 1H), 5.96 (s, 1H), 5.89 + 5.88 (2s, 1H), 5.05 + 4.85 (2s, 1H), 4.53 + 4.38 (2m, 1H), 2.60 (m, 2H), 1.31 + 1.31 (2d, 3H). MS (ES+) *m/z*: 370 (M^++1, 100).

4.4.64. 10-(3-Chlorophenyl)-6,6,8-trimethyl-6,10-dihydro-5*H*-[1,3]dioxolo[4,5-*g*][1,2]-oxazino[5,4-*b*]quinolin-9(8*H*)-one (66)

Following general procedure 1 heterolignan **66** was obtained as colourless solid (780 mg, 53%); mp 300–303 °C. ^{1}H NMR (DMSO-d_6) (δ): 8.69 (s, NH) 7.25 (t, 1H), 7.17 (m, 2H), 7.10 (m, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 5.92 (s, 1H), 5.88 (s, 1H), 5.08 (s, 1H), 2.97 (s, 3H), 1.57 (s, 3H), 1.48 (s, 3H). MS (ES+) *m/z*: 399 (M^++1, 100).

4.4.65. 11-(3-Chlorophenyl)-4,4-dimethyl-3,4,5,11-tetrahydro[1,3]dioxolo[4,5-*g*][1,2]-oxathiino[4,3-*b*]quinoline 1,1-dioxide (67)

Following general procedure 1 heterolignan **67** was obtained as colourless solid (570 mg, 37%); mp 250–252 °C. ^{1}H NMR (DMSO-d_6) (δ): 8.69 (s, NH) 7.28 (m, 2H), 7.18 (m, 2H), 6.85 (s, 1H), 6.75 (s, 1H), 5.94 (s, 1H), 5.89 (s, 1H), 5.07 (s, 1H), 4.47 (d, 1H), 4.36 (d, 1H), 1.35 (s, 6H). MS (ES+) *m/z*: 420 (M^++1, 100).

4.4.66. 10-(3-Chlorophenyl)-6,7,8,10-tetrahydro-5*H*-[1,3]dioxolo[4,5-*g*]thiopyrano[3,2-*b*]-quinoline 9,9-dioxide (68)

Following general procedure 1 heterolignan **68** was obtained as colourless solid (200 mg, 18%); mp 268–270 °C. MS (ES+) *m/z*: 390 (M^++1, 100).

4.4.67. 10-(3-Chlorophenyl)-3,3-dimethyl-4,10-dihydro-3*H*-[1,3]dioxolo[4,5-*g*][1,2]oxathiolo[4,3-*b*]quinoline 1,1-dioxide (69)

Following general procedure 1 heterolignan **69** was obtained as colourless solid (910 mg, 61%); mp 240–243 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.63 (s, NH) 7.29 (m, 3H), 7.20 (m, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.97 (s, 1H), 5.91 (s, 1H), 5.23 (s, 1H), 1.72 (s, 3H), 1.66 (s, 3H). MS (ES+) *m/z*: 406 (M^++1, 100).

4.4.68. 9-(3-Chlorophenyl)-5,6,7,9-tetrahydro[1,3]dioxolo[4,5-*g*]thieno[3,2-*b*]quinoline 8,8-dioxide (70)

Following general procedure 1 heterolignan **70** was obtained as colourless solid (330 mg, 40%); mp 240–243 °C. MS (ES+) *m/z*: 376 (M^++1, 100).

4.4.69. 9-(3-Chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro[1,3]dioxolo[4,5-*g*]thieno[3,2-*b*]quinoline 8,8-dioxide (71)

Following general procedure 1 heterolignan **71** was obtained as colourless solid (510 mg, 57.7%); mp 280–283 °C. MS (ES+) *m/z*: 404 (M^++1, 100).

4.4.70. 9-(3-Chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinolin-8-one (72)

Following general procedure 1 heterolignan **72** was obtained as colourless solid (810 mg, 60%); mp 297–302 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.22 (s, NH) 7.32 (s, NH), 7.28 (t, 1H), 7.19 (m, 2H), 7.12 (d, 1H), 6.62 (s, 1H), 6.52 (s, 1H), 5.93 (s, 1H), 5.87 (s, 1H), 4.88 (s, 1H), 1.38 (s, 3H), 1.33 (s, 3H). MS (ES+) *m/z*: 369 (M^++1, 100).

4.4.71. *tert*-Butyl 9-(3-chlorophenyl)-8-oxo-5,6,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*g*]-pyrrolo[3,4-*b*]quinoline-7-carboxylate (73)

Following general procedure 1 heterolignan **73** was obtained as colourless solid (600 mg, 60%); mp 220–222 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.60 (s, NH) 7.20 (m, 4H), 6.52 (d, 1H), 5.90 (d, 1H), 4.92 (s, 1H), 4.41 (d, 1H), 4.28 (d, 1H), 1.44 (s, 9H). MS (ES+) *m/z*: 439 (M^++1, 100).

4.4.72. 9-(3-Chlorophenyl)-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]-quinolin-8-one (74)

250 mg (0.57 mmol) of *tert*-butyl 9-(3-chlorophenyl)-8-oxo-5,6,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*g*]-pyrrolo[3,4-*b*]quinoline-7-carboxylate **73** and 0.14 ml of 4 M hydrogen chloride solution in dioxane were stirred for 24 h at 50 °C. The solvent was removed and the solid triturated with 2-propanol, filtered and dried to yield **74** as colourless solid (180 mg, 83%); mp 218–222 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.19 (s, NH) 7.24 (t, 1H), 7.14 (m, 3H), 6.52 (d, 1H), 5.88 (d, 1H), 4.92 (s, 1H), 4.00 (d, 1H), 3.83 (d, 1H), 3.57 (s, 6H). MS (ES+) *m/z*: 341 (M^++1, 100).

4.4.73. 10-(3,5-Dimethoxyphenyl)-6,6-dimethyl-5,6,7,10-tetrahydro-9*H*-[1,3]dioxolo[4,5-*g*]pyrano[4,3-*b*]quinolin-9-one (75)

Following general procedure 1 heterolignan **75** was obtained as colourless solid 830 mg, 55%); mp 302–305 °C. ^{1}H NMR (DMSO-d_6) (δ): 8.81 (s, NH), 6.78 (s, 1H), 6.76 (s, 1H), 6.36 (m, 2H), 6.26 (m, 1H), 5.93 (s, 1H), 5.88 (s, 1H), 4.88 (s, 1H), 3.93 (m, 2H), 3.67 (s, 6H), 1.29 (s, 3H), 1.23 (s, 3H). MS (ES+) *m/z*: 410 (M^++1, 100).

4.4.74. 10-(3,5-Dimethoxyphenyl)-7-methyl-5,6,7,10-tetrahydro-9*H*-[1,3]dioxolo[4,5-*g*]pyrano[4,3-*b*]quinolin-9-one (76)

Following general procedure 1 heterolignan **76** (1:1 mixture of diastereomers) was obtained as colourless solid (1220 mg, 84%); mp 304–306 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.18 (br s, NH), 6.69 + 6.68 (2s, 1H), 6.50 (s, 1H), 6.35 (m, 2H), 6.25 (m, 1H), 5.90 (s, 1H), 5.85 + 5.84 (2s, 1H), 4.92 + 4.75 (2s, 1H), 4.53 + 4.38 (2m, 1H), 3.67 (s, 6H), 2.60 (m, 2H), 1.32 + 1.31 (2d, 3H). MS (ES+) *m/z*: 396 (M^++1, 100).

4.4.75. 10-(3,5-Dimethoxyphenyl)-6,6,8-trimethyl-6,10-dihydro-5*H*-[1,3]dioxolo[4,5-*g*][1,2]oxazino[5,4-*b*]quinolin-9(8*H*)-one (77)

Following general procedure 1 heterolignan **77** was obtained as colourless solid 1200 mg, 78%); mp 295–297 °C. ^{1}H NMR (DMSO-d_6) (δ): 8.70 (s, NH), 6.79 (s, 1H), 6.66 (s, 1H), 6.34 (m, 2H), 6.25 (m, 1H), 5.93 (s, 1H), 5.88 (s, 1H), 4.96 (s, 1H), 3.67 (s, 6H), 2.97 (s, 3H), 1.57 (s, 3H), 1.47 (s, 3H). MS (ES+) *m/z*: 425 (M^++1, 100).

4.4.76. 11-(3,5-Dimethoxyphenyl)-4,4-dimethyl-3,4,5,11-tetrahydro[1,3]dioxolo[4,5-*g*][1,2]oxathiino[4,3-*b*]quinoline 1,1-dioxide (78)

Following general procedure 1 heterolignan **78** was obtained as colourless solid (340 mg, 20%); mp 290–292 °C. ^{1}H NMR (DMSO-d_6) (δ): 8.70 (s, NH) 6.89 (s, 1H), 6.71 (s, 1H), 6.41 (m, 2H), 6.28 (m, 1H), 5.93 (s, 1H), 5.87 (s, 1H), 4.90 (s, 1H), 4.47 (d, 1H), 4.36 (d, 1H), 3.67 (s, 6H), 1.32 (s, 6H). MS (ES+) *m/z*: 446 (M^++1, 100).

4.4.77. 9-(3,5-Dimethoxyphenyl)-6-methyl-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (79)

Following general procedure 1 heterolignan **79** (1:1 mixture of diastereomers) was obtained as colourless solid (760 mg, 54%); mp 295–296 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.63 + 9.60 (s, NH), 6.62–6.52 (4s, 2H), 6.33 (m, 2H), 6.30 (m, 1H), 5.92 (s, 1H), 5.88 (s, 1H), 5.12 + 5.05 (2q, 1H), 4.81 (s, 1H), 3.68 (s, 6H), 1.49 + 1.47 (2d, 3H). MS (ES+) *m/z*: 382 (M^++1, 100).

4.4.78. 9-(3,5-Dimethoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinolin-8-one (80)

Following general procedure 1 heterolignan **80** was obtained as colourless solid (460 mg, 31%); mp 290–292 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.14 (s, NH), 7.30 (s, NH), 6.67 (s, 1H), 6.50 (s, 1H), 6.34 (m, 2H), 6.27 (m, 1H), 5.93 (s, 1H), 5.87 (s, 1H), 4.74 (s, 1H), 3.67 (s, 6H), 1.39 (s, 3H), 1.34 (s, 3H). MS (ES+) *m/z*: 395 (M^++1, 100).

4.4.79. *tert*-Butyl 9-(3,5-dimethoxyphenyl)-8-oxo-5,6,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinoline-7-carboxylate (81)

Following general procedure 1 heterolignan **81** was obtained as colourless solid (630 mg, 58%). MS (ES+) *m/z*: 411 (M^++1−C_4H_8, 50), 367 (M^++1−$COOC_4H_9$, 100).

4.4.80. 9-(3,5-Dimethoxyphenyl)-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]-quinolin-8-one (82)

300 mg (0.64 mmol) of *tert*-Butyl 9-(3,5-dimethoxy-phenyl)-8-oxo-5,6,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinoline-7-carboxylate **81** and 0.14 ml of 4 M hydrogen chloride solution in dioxane were stirred for 24 h at 50 °C. The solvent was removed and the solid triturated with 2-propanol, filtered and dried to afford **82** as colourless solid (200 mg, 80%); mp >300 °C. MS (ES+) *m/z*: 367 (M^++1, 100).

4.4.81. 9-(3-Chlorophenyl)-6,6-dimethyl-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (83)

Following general procedure 1 heterolignan **83** was obtained as colourless solid (210 mg, 15%); mp 273–277 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.88 (s, NH) 7.32 (t, 1H), 7.24 (m, 2H), 7.13 (d, 1H), 6.60 (s, 1H), 6.56 (s, 1H), 5.97 (s, 1H), 5.90 (s, 1H), 4.95 (s, 1H), 1.52 (s, 3H), 1.50 (s, 3H). MS (ES+) *m/z*: 370 (M^++1, 100).

4.4.82. 9′-(3-Chlorophenyl)-5′,9′-dihydro-8′*H*-spiro[cyclopentane-1,6′-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin]-8′-one (84)

Following general procedure 1 heterolignan **84** was obtained as colourless solid (370 mg, 25%); mp 257–259 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.83 (s, NH) 7.30 (t, 1H), 7.22 (m, 2H), 7.12 (d, 1H), 6.60 (s, 1H), 6.56 (s, 1H), 5.97 (s, 1H), 5.91 (s, 1H), 4.97 (s, 1H), 2.10 (m, 2H), 1.80 (m, 6H). MS (ES+) *m/z*: 396 (M^++1, 100).

4.4.83. 9′-(3-Chlorophenyl)-5′,9′-dihydro-8′*H*-spiro[cyclohexane-1,6′-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin]-8′-one (85)

Following general procedure 1 heterolignan **77** was obtained as colourless solid (470 mg, 38%); mp 323–325 °C. ^{1}H NMR (DMSO-d_6) (δ): 10.18 (s, NH) 7.30 (t, 1H), 7.22 (m, 2H), 7.12 (d, 1H), 6.67 (s, 1H), 6.60 (s, 1H), 5.97 (s, 1H), 5.90 (s, 1H), 4.94 (s, 1H), 1.97 (m, 2H), 1.70 (m, 2H), 1.55 (m, 4H), 1.25 (m, 2H). MS (ES+) *m/z*: 410 (M^++1, 100).

4.4.84. 10-(3,5-Dimethoxyphenyl)-6,7,8,10-tetrahydro[1,3]dioxolo[4,5-*b*]acridin-9(5*H*)-one (86)

Following general procedure 1 heterolignan **86** was obtained as colourless solid (870 mg, 62%); mp 269–272 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.30 (s, NH), 6.79 (s, 1H), 6.51 (s, 1H), 6.32 (m, 2H), 6.22 (m, 1H), 5.93 (s, 1H), 5.87 (s, 1H), 4.93 (s, 1H), 3.66 (s, 6H), 2.55 (m, 2H), 2.19 (m, 2H), 1.92 (m, 1H), 1.83 (m, 1H). MS (ES+) *m/z*: 380 (M^++1, 100).

4.4.85. 9-(3,5-Dimethoxyphenyl)-5,6,7,9-tetrahydro-8*H*-cyclopenta[*b*][1,3]dioxolo[4,5-*g*]quinolin-8-one (87)

Following general procedure 1 heterolignan **87** was obtained as colourless solid (224 mg, 16%); mp 277–280 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.88 (s, NH), 6.66 (s, 1H), 6.53 (s, 1H), 6.29 (m, 2H), 6.27 (m, 1H), 5.96 (s, 1H), 5.89 (s, 1H), 4.78 (s, 1H), 3.67 (s, 6H), 2.71 (dt, 1H), 2.60 (dt, 1H), 2.27 (m, 2H). MS (ES+) *m/z*: 366 (M^++1, 100).

4.4.86. 9-(3,5-Dimethoxyphenyl)-7-(propan-2-yl)-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinolin-8-one (88)

Following general procedure 1 heterolignan **88** was obtained as colourless solid (150 mg, 12%); mp 270–273 °C. MS (ES+) *m/z*: 409 (M^++1, 100).

4.4.87. 9-(3,5-Dimethoxyphenyl)-6-methyl-6-(2-methylpropyl)-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinolin-8-one (89)

Following general procedure 1 heterolignan **89** was obtained as colourless solid (360 mg, 46%); mp 300–303 °C. MS (ES+) *m/z*: 437 (M^++1, 100).

4.4.88. *tert*-Butyl 8-oxo-9-(3,4,5-trimethoxyphenyl)-5,6,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinoline-7-carboxylate (90)

Following general procedure 1 heterolignan **90** was obtained as colourless solid (690 mg, 54%). ^{1}H NMR (DMSO-d_6) (δ): 7.65 (s, NH), 6.54 (s, 1H), 6.50 (2, 2H), 6.44 (s, 1H), 5.86 (s, 1H), 5.84 (s, 1H), 4.83 (s, 1H), 4.36 (d, 1H), 4.24 (d, 1H), 3.75 (s, 6H), 3.67 (s, 3H), 1.48 (s, 9H). MS (ES+) *m/z*: 441 (M^++1−C_4H_8, 100).

4.4.89. 9-(3,4,5-Trimethoxyphenyl)-5,6,7,9-tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinolin-8-one (91)

300 mg (0.6 mmol) of *tert*-butyl 8-oxo-9-(3,4,5-trimethoxyphenyl)-5,6,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[3,4-*b*]quinoline-7-carboxylate **90** and 0.15 ml of 4 M hydrogen chloride solution in dioxane were stirred for 24 h at 50 °C. The solvent was removed and the solid triturated with 2-propanol, filtered and dried to yield free lactam **91** as colourless solid (210 mg, 90%). MS (ES+) *m/z*: 397 (M^++1, 100).

4.4.90. 9-(3-Methoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (92)

Following general procedure 1 heterolignan **92** was obtained as colourless solid (1130 mg, 91%); mp >310 °C. ^{1}H NMR (DMSO-d_6)

(δ): 9.89 (s, NH), 7.18 (t, 1H), 6.75 (m, 3H), 6.62 (s, 1H), 6.54 (s, 1H), 5.97 (s, 1H), 5.90 (s, 1H), 4.97 (d, 1H), 4.88 (s, 1H), 4.86 (d, 1H), 3.72 (s, 3H). MS (ES+) *m/z*: 338 (M^++1, 100).

4.4.91. 9-(4-Methoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (93)

Following general procedure 1 heterolignan **93** was obtained as colourless solid (1200 mg, 97%); mp 295–297 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.63 (br s, NH), 7.09 (d, 2H), 6.80 (d, 2H), 6.51 (s, 2H), 5.92 (s, 1H), 5.88 (s, 1H), 4.87 (d, 1H), 4.85 (s, 1H), 4.78 (d, 1H), 3.70 (s, 3H). MS (ES+) *m/z*: 338 (M^++1, 48), 230 (100).

4.4.92 9-(3,4-Dimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (94)

Following general procedure 1 heterolignan **94** was obtained as colourless solid (900 mg, 67%); mp 305–310 °C. ^{1}H NMR (DMF-d_7) (δ): 9.90 (br s, NH), 7.01 (d, 1H), 6.89 (d, 1H), 6.72 (dd, 1H), 6.69 (s, 1H), 6.62 (s, 1H), 6.01 (s, 1H), 5.97 (s, 1H), 5.00 (d, 1H), 4.96 (s, 1H), 4.90 (d, 1H), 3.70–3.85 (2s, 6H). MS (ES+) *m/z*: 368 (M^++1, 43), 230 (100).

4.4.93. 9-(2-Chlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (95)

Following general procedure 1 heterolignan **95** was obtained as colourless solid (155 mg, 11%); mp >320 °C. ^{1}H NMR (DMF-d_7) (δ): 10.05 (br s, NH), 7.42 (dd, 1H), 7.35 (dd, 1H), 7.25 (m, 2H), 6.63 (s, 1H), 6.52 (s, 1H), 6.01 (s, 1H), 5.97 (s, 1H), 5.57 (s, 1H), 5.02 (d, 1H), 4.95 (d, 1H). MS (ES+) *m/z*: 342 (M^++1, 100).

4.4.94. 9-(3-Chlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (96)

Following general procedure 1 heterolignan **96** was obtained as colourless solid (340 mg, 27%); mp 290–294 °C. ^{1}H NMR (DMF-d_7) (δ): 10.05 (br s, NH), 7.35 (m, 2H), 7.26 (m, 2H), 6.67 (s, 1H), 6.65 (s, 1H), 6.03 (s, 1H), 5.99 (s, 1H), 5.09 (s, 1H), 5.03 (d, 1H), 4.92 (d, 1H). MS (ES+) *m/z*: 342 (M^++1, 100).

4.4.95. 9-(4-Chlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (97)

Following general procedure 1 heterolignan **97** was obtained as colourless solid (290 mg, 23%); mp >310 °C. ^{1}H NMR (DMF-d_7) (δ): 10.00 (s, NH), 7.35 (m, 4H), 6.65 (s, 1H), 6.63 (s, 1H), 6.02 (s, 1H), 5.98 (s, 1H), 5.06 (s, 1H), 4.99 (d, 1H), 4.91 (d, 1H). MS (ES+) *m/z*: 342 (M^++1, 100).

4.4.96. 9-(3,5-Dichlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (98)

Following general procedure 1 heterolignan **98** was obtained as colourless solid (770 mg, 56%); mp 308–312 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.79 (br s, NH), 7.35 (m, 1H), 7.21 (d, 2H), 6.58 (s, 1H), 6.56 (s, 1H), 5.95 (s, 1H), 5.92 (s, 1H), 5.02 (s, 1H), 4.96 (d, 1H), 4.82 (d, 1H). MS (ES+) *m/z*: 376 (M^++1, 100).

4.4.97. 3-(8-Oxo-5,6,8,9-tetrahydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-9-yl)benzonitrile (99)

Following general procedure 1 heterolignan **99** was obtained as colourless solid (730 mg, 60%); mp 305–310 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.78 (br s, NH), 7.60 (m, 2H), 7.50 (m, 2H), 6.56 (s, 1H), 6.55 (s, 1H), 5.94 (s, 1H), 5.90 (s, 1H), 5.05 (s, 1H), 4.92 (d, 1H), 4.82 (d, 1H). MS (ES+) *m/z*: 333 (M^++1, 100).

4.4.98. 9-[3-(Trifluoromethyl)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (100)

Following general procedure 1 heterolignan **100** was obtained as colourless solid (510 mg, 37%); mp 303–306 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.75 (br s, NH), 7.49 (m, 4H), 6.55 (s, 1H), 6.54 (s, 1H), 5.93 (s, 1H), 5.89 (s, 1H), 5.10 (s, 1H), 4.92 (d, 1H), 4.82 (d, 1H). MS (ES+) *m/z*: 376 (M^++1, 100).

4.4.99. 9-(3,5-Difluorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (101)

Following general procedure 1 heterolignan **101** was obtained as colourless solid (540 mg, 41%); mp 296–299 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.78 (br s, NH), 6.90 (m, 3H), 6.61 (s, 1H), 6.55 (s, 1H), 5.95 (s, 1H), 5.91 (s, 1H), 5.01 (s, 1H), 4.95 (d, 1H), 4.82 (d, 1H). MS (ES+) *m/z*: 344 (M^++1, 100).

4.4.100. 9-Phenyl-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (102)

Following general procedure 1 heterolignan **102** was obtained as colourless solid (770 mg, 66%); mp 295–298 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.67 (br s, NH), 7.19 (m, 5H), 6.52 (s, 2H), 5.92 (s, 1H), 5.88 (s, 1H), 4.90 (s, 1H), 4.89 (d, 1H), 4.80 (d, 1H). MS (ES+) *m/z*: 308 (M^++1, 100).

4.4.101. 9-(3-Bromophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (103)

Following general procedure 1 heterolignan **103** was obtained as colourless solid (800 mg, 56%); mp 305–307 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.67 (br s, NH), 7.34 (m, 2H), 7.20 (m, 2H), 6.55 (s, 1H), 6.53 (s, 1H), 5.93 (s, 1H), 5.90 (s, 1H), 4.96 (s, 1H), 4.92 (d, 1H), 4.81 (d, 1H). MS (ES+) *m/z*: 388 (100), 386 (M^++1, 99).

4.4.102. 9-(3-Methylphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (104)

Following general procedure 1 heterolignan **104** was obtained as colourless solid (780 mg, 66%); mp 308–312 °C. ^{1}H NMR (DMSO-d_6) (δ): ^{1}H NMR (DMSO-d_6) (δ): 9.85 (s, NH), 7.15 (m, 1H), 6.97 (m, 3H), 6.55 (s, 1H), 6.52 (s, 1H), 5.95 (s, 1H), 5.89 (s, 1H), 4.96 (d, 1H), 4.87 (s, 1H), 4.85 (d, 1H), 2.24 (s, 3H). MS (ES+) *m/z*: 322 (M^++1, 100).

4.4.103. 9-(3-Fluorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (105)

Following general procedure 1 heterolignan **105** was obtained as colourless solid (490 mg, 41%); mp 295–298 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.72 (br s, NH), 7.28 (m, 2H), 6.95 (m, 2H), 6.56 (s, 1H), 6.53 (s, 1H), 5.93 (s, 1H), 5.89 (s, 1H), 4.97 (s, 1H), 4.91 (d, 1H), 4.80 (d, 1H). MS (ES+) *m/z*: 326 (M^++1, 100).

4.4.104. 9-[3-(Trifluoromethoxy)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (106)

Following general procedure 1 heterolignan **106** was obtained as colourless solid (530 mg, 37%); mp 277–283 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.75 (br s, NH), 7.38 (t, 1H), 7.15 (m, 3H), 6.57 (s, 1H), 6.54 (s, 1H), 5.93 (s, 1H), 5.90 (s, 1H), 5.03 (s, 1H), 4.91 (d, 1H), 4.81 (d, 1H). MS (ES+) *m/z*: 392 (M^++1, 100).

4.4.105. 9-[3-(Propan-2-yloxy)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (107)

Following general procedure 1 heterolignan **107** was obtained as colourless solid (890 mg, 66%); mp 279–282 °C. ^{1}H NMR (DMSO-d_6) (δ): 9.65 (br s, NH), 7.12 (t, 1H), 6.68 (m, 3H), 6.57 (s, 1H), 6.53 (s, 1H), 5.93 (s, 1H), 5.89 (s, 1H), 4.89 (d, 1H), 4.87 (s, 1H), 4.79 (d, 1H), 4.51 (m, 1H), 1.24 (d, 6H). MS (ES+) *m/z*: 366 (M^++1, 100).

4.4.106. 9-(3,5-Dimethylphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (108)

Following general procedure 1 heterolignan **108** was obtained as colourless solid (800 mg, 65%). ^{1}H NMR (DMSO-d_6) (δ): ^{1}H

NMR (DMSO-d_6) (δ): 9.81 (s, NH), 6.78 (s, 3H), 6.53 (s, 1H), 6.51 (s, 1H), 5.94 (s, 1H), 5.89 (s, 1H), 4.96 (d, 1H), 4.85 (d, 1H), 4.81 (s, 1H), 2.20 (s, 6H). MS (ES+) *m/z*: 336 (M^++1, 100).

4.4.107. 9-(2,2-Difluoro-1,3-benzodioxol-5-yl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (109)

Following general procedure 1 heterolignan **109** was isolated as a colourless solid (1.46 g, 75%). ^{1}H NMR (MeOD) (δ): 7.1–7.0 (m, 3H), 6.46 (s, 2H), 5.88 (dd, 2H), 5.02 (s, 1H), 4.94–4.82 (m, 2H).

4.4.108. 9-(2,3,5-Trichlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (110)

Following general procedure 1 heterolignan **110** was obtained as colourless solid (292 mg, 47%). ^{1}H NMR (DMSO-d_6) (δ): 10.05 (br s, NH), 7.72 (s, 1H), 7.32 (br s, 1H), 6.56 (s, 1H), 6.39 (s, 1H), 5.98 (s, 1H), 5.92 (s, 1H), 5.52 (s, 1H), 4.97 (d, 1H), 4.88 (d, 1H). MS (ES+) *m/z*: 412 (98), 410 (M^++1, 100).

4.4.109. 9-(2,3-Dimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (111)

Following general procedure 1 heterolignan **111** was obtained as colourless solid (290 mg, 52%). ^{1}H NMR (DMSO-d_6) (δ): 9.82 (s, NH), 6.95 (t, 1H), 6.85 (d, 1H), 6.65 (d, 1H), 6.49 (s, 1H), 6.41 (s, 1H), 5.93 (s, 1H), 5.87 (s, 1H), 5.23 (s, 1H), 4.95 (d, 1H), 4.85 (d, 1H), 3.79 (s, 3H), 3.75 (s, 3H). MS (ES+) *m/z*: 368 (M^++1, 100).

4.4.110. 9-(2,3-Dichlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (112)

Following general procedure 1 heterolignan **112** was obtained as colourless solid (295 mg, 52%). ^{1}H NMR (DMSO-d_6) (δ): 10.05 (s, NH), 7.49 (d, 1H), 7.28 (m, 2H), 6.55 (s, 1H), 6.39 (s, 1H), 5.97 (s, 1H), 5.90 (s, 1H), 5.52 (s, 1H), 4.94 (d, 1H), 4.88 (d, 1H). MS (ES+) *m/z*: 376 (M^++1, 100).

4.4.111. 9-(3-Ethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (113)

Following general procedure 1 heterolignan **113** was obtained as colourless solid (366 mg, 69%). ^{1}H NMR (DMSO-d_6) (δ): 9.87 (br s, NH), 7.16 (t, 1H), 6.73 (m, 3H), 6.60 (s, 1H), 6.54 (s, 1H), 5.96 (s, 1H), 5.89 (s, 1H), 4.96 (d, 1H), 4.87 (s, 1H), 4.85 (d, 1H), 3.97 (m, 2H), 1.28 (t, 3H). MS (ES+) *m/z*: 352 (M^++1, 100).

4.4.112. 9-(2,5-Dichlorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (114)

Following general procedure 1 heterolignan **114** was obtained as colourless solid (374 mg, 66%). ^{1}H NMR (DMSO-d_6) (δ): 10.05 (br s, NH), 7.46 (d, 1H), 7.28 (m, 1H), 6.57 (s, 1H), 6.40 (s, 1H), 5.97 (s, 1H), 5.91 (s, 1H), 5.43 (s, 1H), 4.97 (d, 1H), 4.88 (d, 1H). MS (ES+) *m/z*: 376 (M^++1, 100).

4.4.113. 9-[3-Chloro-2-fluoro-5-(trifluoromethyl)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (115)

Following general procedure 1 heterolignan **115** was obtained as colourless solid (260 mg, 40%). ^{1}H NMR (DMSO-d_6) (δ): 10.08 (s, NH), 7.97 (m, 1H), 7.63 (m, 1H), 6.57 (s, 1H), 6.51 (s, 1H), 5.98 (s, 1H), 5.93 (s, 1H), 5.38 (s, 1H), 4.97 (d, 1H), 4.88 (d, 1H). MS (ES+) *m/z*: 428 (M^++1, 100).

4.4.114. 9-(3-Bromo-4,5-dimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (116)

Following general procedure 1 heterolignan **116** was obtained as colourless solid (470 mg, 70%). ^{1}H NMR (DMSO-d_6) (δ): 9.90 (s, NH), 7.03 (s, 1H), 6.83 (s, 1H), 6.67 (s, 1H), 6.55 (s, 1H), 5.98 (s, 1H), 5.93 (s, 1H), 5.00 (d, 1H), 4.92 (s, 1H), 4.87 (d, 1H), 3.81 (s, 3H), 3.69 (s, 3H). MS (ES+) *m/z*: 448 (80), 446 (M^++1, 100), 230 (50).

4.4.115. 9-(5-Bromopyridin-3-yl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (117)

Following general procedure 1 heterolignan **117** was obtained as colourless solid (319 mg, 54%). ^{1}H NMR (DMSO-d_6) (δ): 10.04 (s, NH), 8.53 (s, 1H), 8.48 (s, 1H), 7.80 (s, 1H), 6.63 (s, 1H), 6.57 (s, 1H), 5.98 (s, 1H), 5.92 (s, 1H), 5.07 (s, 1H), 4.98 (d, 1H), 4.87 (d, 1H). MS (ES+) *m/z*: 389 (100), 387 (M^++1, 98).

4.4.116. 9-(4-Bromothiophen-2-yl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (118)

Following general procedure 1 heterolignan **118** was obtained as colourless solid (436 mg, 74%). ^{1}H NMR ($CDCl_3$) (δ): 9.70 (s, NH), 7.71 (s, 1H), 6.84 (s, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 5.95 (s, 1H), 5.93 (s, 1H), 5.25 (s, 1H), 4.83 (d, 1H), 4.75 (d, 1H). MS (ES+) *m/z*: 394 (35), 392 (M^++1, 35), 230 (100).

4.4.117. 9-(3,5-Dibromophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (119)

Following general procedure 1 heterolignan **119** was obtained as colourless solid (280 mg, 40%). ^{1}H NMR (DMSO-d_6) (δ): 10.00 (br s, NH), 7.64 (s, 1H), 7.40 (s, 2H), 6.62 (s, 1H), 6.57 (s, 1H), 5.97 (s, 1H), 5.93 (s, 1H), 5.01 (s, 1H), 5.01 (d, 1H), 4.87 (d, 1H). MS (ES+) *m/z*: 468 (57), 466 (100), 464 (M^++1, 55).

4.4.118. 9-[5-(4-Fluorophenyl)pyridin-3-yl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (120)

Following general procedure 1 heterolignan **120** was obtained as colourless solid (206 mg, 38%). ^{1}H NMR (DMSO-d_6) (δ): 10.00 (br s, NH), 8.72 (d, 1H), 8.45 (d, 1H), 7.89 (s, 1H), 7.75 (m, 2H), 7.36 (m, 2H), 6.71 (s, 1H), 6.59 (s, 1H), 6.00 (s, 1H), 5.93 (s, 1H), 5.13 (s, 1H), 5.02 (d, 1H), 4.90 (d, 1H). MS (ES+) *m/z*: 403 (M^++1, 100).

4.4.119. 9-(3,5-Dichloro-4-methoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (121)

Following general procedure 1 heterolignan **121** was obtained as colourless solid (234 mg, 38%). ^{1}H NMR (DMSO-d_6) (δ): 10.00 (br s, NH), 7.30 (s, 2H), 6.66 (s, 1H), 6.58 (s, 1H), 5.99 (s, 1H), 5.95 (s, 1H), 5.01 (d, 1H), 5.00 (s, 1H), 4.88 (d, 1H), 3.80 (s, 3H). MS (ES+) *m/z*: 406 (M^++1, 100).

4.4.120. 9-(3-Bromo-4-fluorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (122)

Following general procedure 1 heterolignan **122** was obtained as colourless solid (374 mg, 61%). ^{1}H NMR (DMSO-d_6) (δ): 9.98 (br s, NH), 7.53 (dd, 1H), 7.25 (m, 2H), 6.60 (s, 1H), 6.54 (s, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.00 (s, 1H), 4.97 (d, 1H), 4.86 (d, 1H). MS (ES+) *m/z*: 406 (85), 404 (M^++1, 100).

4.4.121. 9-(3-Hydroxy-4,5-dimethoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (123)

Following general procedure 1 heterolignan **123** was obtained as colourless solid (404 mg, 70%). ^{1}H NMR (DMSO-d_6) (δ): 9.86 (br s, NH), 6.63 (s, 1H), 6.52 (s, 1H), 6.46 (d, 1H), 6.17 (d, 1H), 5.97 (s, 1H), 5.91 (s, 1H), 4.94 (d, 1H), 4.85 (d, 1H), 4.76 (s, 1H), 3.73 (s, 3H), 3.60 (s, 3H). MS (ES+) *m/z*: 384 (M^++1, 100), 230 (46).

4.4.122. 9-[3,4-Dimethoxy-5-(methylsulfanyl)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (124)

Following general procedure 1 heterolignan **124** was obtained as colourless solid (436 mg, 70%). ^{1}H NMR (DMSO-d_6) (δ): 9.88 (s, NH), 6.69 (s, 1H), 6.68 (s, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.97 (s, 1H), 5.91 (s, 1H), 4.98 (d, 1H), 4.89 (s, 1H), 4.87 (d, 1H), 3.74 (s, 3H), 3.66 (s, 3H). MS (ES+) *m/z*: 414 (M^++1, 50), 230 (100).

4.4.123. 9-(7-Methoxy-1,3-benzodioxol-5-yl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (125)

Following general procedure 1 heterolignan **125** was obtained as colourless solid (463 mg, 78%). ^{1}H NMR (DMSO-d_6) (δ): 9.88 (s, NH), 6.65 (s, 1H), 6.56 (s, 1H), 6.52 (s, 1H), 6.34 (s, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.91 (s, 2H), 4.97 (d, 1H), 4.93 (d, 1H), 4.92 (s, 1H), 3.81 (s, 3H). MS (ES+) *m/z*: 382 (M^++1, 100), 230 (87).

4.4.124. [3-(8-Oxo-5,6,8,9-tetrahydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-9-yl)-phenoxy]acetonitrile (126)

Following general procedure 1 heterolignan **126** was obtained as colourless solid (220 mg, 40%). ^{1}H NMR (DMSO-d_6) (δ): 9.92 (br s, NH), 7.28 (t, 1H), 6.90 (m, 3H), 6.65 (s, 1H), 6.56 (s, 1H), 5.98 (s, 1H), 5.91 (s, 1H), 5.14 (s, 2H), 4.97 (d, 1H), 4.92 (s, 1H), 4.87 (d, 1H). MS (ES+) *m/z*: 363 (M^++1, 100).

4.4.125. 9-(4-Chloro-3-methoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (127)

Following general procedure 1 heterolignan **127** was obtained as colourless solid (146 mg, 26%). ^{1}H NMR (DMSO-d_6) (δ): 9.92 (s, NH), 7.30 (d, 1H), 7.11 (s, 1H), 6.68 (d, 1H), 6.67 (s, 1H), 6.55 (s, 1H), 5.98 (s, 1H), 5.91 (s, 1H), 4.96 (d, 1H), 4.95 (s, 1H), 4.88 (d, 1H), 3.86 (s, 3H). MS (ES+) *m/z*: 372 (M^++1, 100).

4.4.126. 9-(3-Chloro-4-fluorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (128)

Following general procedure 1 heterolignan **128** was obtained as colourless solid (325 mg, 60%). ^{1}H NMR (DMSO-d_6) (δ): 10.00 (br s, NH), 7.40 (dd, 1H), 7.34 (t, 1H), 7.21 (m, 1H), 6.63 (s, 1H), 6.58 (s, 1H), 6.00 (s, 1H), 5.95 (s, 1H), 5.02 (s, 1H), 4.98 (d, 1H), 4.88 (d, 1H). MS (ES+) *m/z*: 360 (M^++1, 100).

4.4.127. 9-(6-Methoxypyridin-3-yl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (129)

Following general procedure 1 heterolignan **129** was obtained as colourless solid (354 mg, 69%). ^{1}H NMR (DMSO-d_6) (δ): 9.90 (s, NH), 8.06 (d, 1H), 7.44 (dd, 1H), 6.74 (d, 1H), 6.59 (s, 1H), 6.55 (s, 1H), 5.98 (s, 1H), 5.92 (s, 1H), 4.96 (s, 1H), 4.96 (d, 1H), 4.87 (d, 1H), 3.82 (s, 3H). MS (ES+) *m/z*: 339 (M^++1, 100).

4.4.1289-(7-Bromo-1,3-benzodioxol-5-yl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (130)

Following general procedure 1 heterolignan **130** was obtained as colourless solid (476 mg, 73%). ^{1}H NMR (DMSO-d_6) (δ): 9.95 (s, NH), 6.87 (s, 1H), 6.77 (s, 1H), 6.64 (s, 1H), 6.55 (s, 1H), 6.09 (s, 1H), 6.08 (s, 1H), 5.98 (s, 1H), 5.93 (s, 1H), 4.98 (d, 1H), 4.89 (s, 1H), 4.87 (d, 1H). MS (ES+) *m/z*: 432 (85), 430 (M^++1, 100).

4.4.129. 9-(4-Fluoro-3-methoxyphenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (131)

Following general procedure 1 heterolignan **131** was obtained as colourless solid (391 mg, 73%). ^{1}H NMR (DMSO-d_6) (δ): 9.90 (s, NH), 7.08 (m, 2H), 6.66 (m, 1H), 6.66 (s, 1H), 6.55 (s, 1H), 5.98 (s, 1H), 5.92 (s, 1H), 4.97 (d, 1H), 4.94 (s, 1H), 4.87 (d, 1H), 3.83 (s, 3H). MS (ES+) *m/z*: 356 (M^++1, 100).

4.4.130. 9-(3,4,5-Trifluorophenyl)-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (132)

Following general procedure 1 heterolignan **132** was obtained as colourless solid (361 mg, 66%). ^{1}H NMR (DMSO-d_6) (δ): 10.00 (br s, NH), 7.17 (m, 2H), 6.67 (s, 1H), 6.56 (s, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.00 (s, 1H), 4.97 (d, 1H), 4.87 (d, 1H). MS (ES+) *m/z*: 362 (M^++1, 100).

4.4.131. 9-[3-(1,1,2,2-Tetrafluoroethoxy)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (133)

Following general procedure 1 heterolignan **133** was obtained as colourless solid (417 mg, 65%). ^{1}H NMR (DMSO-d_6) (δ): 9.94 (br s, NH), 7.38 (t, 1H), 7.17 (d, 1H), 7.08 (m, 2H), 6.77 (tt, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 5.97 (s, 1H), 5.91 (s, 1H), 5.03 (s, 1H), 4.96 (d, 1H), 4.87 (d, 1H). MS (ES+) *m/z*: 424 (M^++1, 100).

4.4.132. 9-[3-(2-Hydroxyethoxy)phenyl]-6,9-dihydro[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(5*H*)-one (134)

Following general procedure 1 heterolignan **134** was obtained as colourless solid (374 mg, 68%). ^{1}H NMR (DMSO-d_6) (δ): 9.88 (br s, NH), 7.16 (t, 1H), 6.74 (m, 3H), 6.60 (s, 1H), 6.54 (s, 1H), 5.95 (s, 1H), 5.88 (s, 1H), 4.96 (d, 1H), 4.87 (s, 1H), 4.85 (d, 1H), 4.84 (br s, OH), 3.92 (m, 2H), 3.69 (m, 2H). MS (ES+) *m/z*: 368 (M^++1, 100).

4.4.133. 9-(3,5-Dichlorophenyl)-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (135)

Following general procedure 5 heterolignan **135** was isolated as colourless solid (144 mg, 34%); mp 166 °C. ^{1}H NMR (CH_3CN-d_3) (δ): 7.33 (s, 1H), 7.24 (s, 2H), 6.74 (s, 1H), 6.49 (s, 1H), 5.95 (m, 2H), 4.83 (m, 3H). MS (ES+) *m/z*: 377 (MH^+).

4.4.134. 9-(3-Chlorophenyl)-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (136)

Following general procedure 5 heterolignan **136** was obtained as colourless solid (253 mg, 35%). ^{1}H NMR (CH_3CN-d_3) (δ): 7.26 (m, 4H), 6.73 (s, 1H), 6.48 (s, 1H), 5.95 (m, 2H), 4.86 (m, 3H). MS (ES+) *m/z*: 343 (MH^+).

4.4.135. 9-(3-Bromophenyl)-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (137)

Following general procedure 5 heterolignan **137** was isolated as colourless solid (270 mg, 29%); mp 228 °C. ^{1}H NMR (CH_3CN-d_3) (δ): 7.40 (m, 2H), 7.23 (m, 2H), 6.73 (s, 1H), 6.48 (s, 1H), 5.94 (m, 2H), 4.85 (m, 3H). MS (ES+) *m/z*: 387 (MH^+), 389 (MH^+).

4.4.136. 9-[3-(Trifluoromethoxy)phenyl]-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (138)

Following general procedure 5 heterolignan **138** was isolated as slightly greenish solid (270 mg, 59%); mp 130 °C. ^{1}H NMR (CH_3CN-d_3) (δ): 7.28 (m, 4H), 6.73 (s, 1H), 6.48 (s, 1H), 5.94 (m, 2H), 4.87 (m, 3H). MS (ES+) *m/z*: 393 (MH^+).

4.4.137. 9-(3-Chlorophenyl)-6-methoxy-3,9-dihydro-1*H*-furo[3,4-*b*]chromen-1-one (139)

Following general procedure 5 heterolignan **139** was obtained as colourless solid (30 mg, 5%) after flash chromatography. ^{1}H NMR (CH_3CN-d_3) (δ): 7.25 (m, 4H), 6.99 (m, 1H), 6.74 (m, 2H), 4.88 (m, 3H), 3.79 (s, 3H). MS (ES+) *m/z*: 329 (MH^+).

4.4.138. 9-(3-Bromo-4,5-dimethoxyphenyl)-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (140)

Following general procedure 5 heterolignan **140** was isolated as colourless solid (90 mg, 14%) after flash chromatography. ^{1}H NMR (CH_3CN-d_3) (δ): 6.98 (m, 1H), 6.92 (m, 1H), 6.72 (s, 1H), 6.53 (s, 1H), 5.95 (m, 2H), 4.85 (m, 3H), 3.82 (s, 3H), 3.76 (s, 3H). MS (ES+) *m/z*: 447 (MH^+), 449 (MH^+).

4.4.139. 9-[3-(Difluoromethoxy)phenyl]-6,9-dihydro-8*H*-[1,3]dioxolo[4,5-*g*]furo[3,4-*b*]chromen-8-one (141)

Following general procedure 5 heterolignan **141** was isolated as colourless solid (100 mg, 23%) after flash chromatography; mp 193–195 °C. ^{1}H NMR (CH_3CN-d_3) (δ): 7.35 (t, 1H), 7.14 (d, 1H),

7.01 (m, 2H), 6.73 (s, 1H), 6.72 (t, 1H), 6.49 (s, 1H), 5.94 (m, 2H), 4.87 (m, 3H). MS (ES+) *m/z*: 375 (MH^+).

4.4.140. 9-(3,5-Dimethoxyphenyl)-6-methoxy-3,9-dihydro-1*H*-furo[3,4-*b*]chromen-1-one (142)

Following general procedure 5 heterolignan **142** was obtained as colourless solid (58 mg, 14%) after flash chromatography. ^1H NMR (CH_3CN-d_3) (δ): 7.04 (m, 1H), 6.72 (m, 2H), 6.37 (m, 3H), 4.87 (m, 3H), 3.78 (s, 3H), 3.73 (s, 6H). MS (ES+) *m/z*: 355 (MH^+).

4.4.141. 9-(3,5-dimethoxyphenyl)-5,6-dimethoxy-3,9-dihydro-1*H*-furo[3,4-*b*]chromen-1-one (143)

Following general procedure 5 heterolignan **143** was obtained as colourless solid (40 mg, 14%) after flash chromatography. ^1H NMR (CH_3CN-d_3) (δ): 6.81 (m, 2H), 6.38 (m, 3H), 4.90 (m, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (s, 6H). MS (ES+) *m/z*: 385 (MH^+).

4.4.142. 9-(3,5-Dichlorophenyl)-6-methoxy-3,9-dihydro-1*H*-furo[3,4-*b*]chromen-1-one (144)

Following general procedure 5 heterolignan **144** was obtained as colourless solid (69 mg, 38%). ^1H NMR (CH_3CN-d_3) (δ): 7.32 (m, 1H), 7.23 (m, 2H), 7.00 (m, 1H), 6.75 (m, 2H), 4.88 (m, 3H), 3.80 (s, 3H). MS (ES+) *m/z*: 363 (MH^+).

4.4.143. 9-(3,5-Dichlorophenyl)-5,6-dimethoxy-3,9-dihydro-1*H*-furo[3,4-*b*]chromen-1-one (145)

Following general procedure 5 heterolignan **145** was isolated as colourless solid (60 mg, 32%). ^1H NMR (CH_3CN-d_3) (δ): 7.32 (m, 1H), 7.24 (m, 2H), 6.82 (m, 1H), 6.76 (m, 1H), 4.91 (m, 3H), 3.87 (s, 3H), 3.83 (s, 3H). MS (ES+) *m/z*: 393 (MH^+).

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