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Allosteric Modulation

Synthesis of Functionalized 2-(4-Hydroxyphenyl)-3-methylbenzofuran Allosteric Modulators of Hsp90 Activity

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Dedicated to Professor Carlo Scolastico on the occasion of his 80th birthday

Abstract: Hsp90 is a molecular chaperone that plays a pivotal role in the cell life cycle. ATP-regulated internal dynamics are critical to Hsp90 function and we recently demonstrated that these dynamics can be modulated in an allosteric fashion; the protein C-terminal domain (CTD) can be effectively targeted with a family of 2-phenyl-benzofuran derivatives. Here we describe the expansion of the initial library, reporting 28 new derivatives that explore the chemical space at opposite ends of the benzofuran scaffold. Interactions of the compounds with a full-length protein homolog were explored by Saturation Transfer Difference (STD) NMR spectroscopy. In this context we also report the interaction epitope of Novobiocin, a known CTD inhibitor.

Introduction

Heat shock proteins (HSPs) are a group of chaperone proteins overexpressed by cells under stress conditions. Among these, Hsp90 has been shown to play a central role in the maturation of numerous client proteins involved in several cancer hallmarks. As such, Hsp90 represents a hub in a signaling network that controls cell cycle and apoptosis and is an established target in cancer therapy. This chaperone exists as a homodimer, each protomer consisting of four regions: an N-terminal ATP binding domain, a middle domain that completes the catalytic site, a charged region, and a C-terminal homodimerization domain.[1] A complex internal dynamics of the domains within the homodimer controls the chaperone activity of the protein and, with it, Hsp90-driven downstream signalling pathways. This dynamic process is coupled to ATP hydrolysis and competitive inhibitors of ATP binding in the Hsp90 N-terminal domain, such as geldanamycin or radicicol,[2] have shown potent antitumor activity in a wide-range of malignancies.[3] The aminocoumarin Novobiocin and its analogues[4] have been shown to bind the C-terminal domain (CTD) of Hsp90 and to lead to proteosomal degradation of its clients by inhibiting correct folding.

Recently, small molecule *activators* of Hsp90 have been reported[5] and shown to act as allosteric modulators of ATPase activity. In particular, we have described a group of functionalized 2-(4-hydroxyphenyl)-3-methylbenzofurans (**1**, Figure 1) that target a computationally predicted allosteric site in Hsp90 and able to modify its enzymatic, conformational, co-chaperone and client-binding properties.[6] The best activators were shown to stimulate Hsp90 ATPase activity while simultaneously accelerating the rate of interprotomer closure dynamics, as revealed by FRET experiments. Some of these molecules were shown to affect the viability of cancer cell lines, including cells resistant to the geldanamycin derivative 17AAG, for which proper functioning of Hsp90 is required.[5b] In the absence of X-ray structures, Molecular Dynamics (MD) simulations guided the ligand selection process and were also used to reveal the mechanisms of Hsp90 modulation by the allosteric ligands.[7] An ensemble approach was adopted to characterize chaperone-ligand interactions, with the aim of identifying the hot spots of the allosteric site where key functional groups on the ligand best complement the receptor, while taking the dynamic exchange between the binding partners explicitly into account. This process

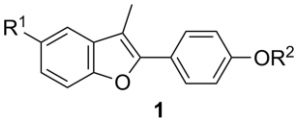

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Figure 1. General structure of the 2-(4-hydroxyphenyl)-3-methylbenzofuran modulators **1**.

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led to the definition of two regions on the ligand where functional group diversification could arguably translate into a modulated response of the chaperone: the 5-substituent of the benzofuran ring (R^1, Figure 1) and the phenol substituent (R^2, Figure 1).

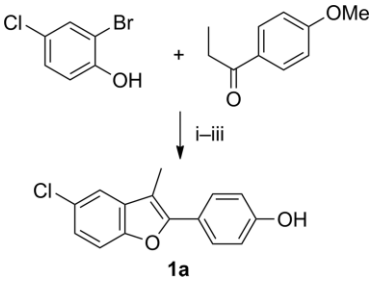
Here we describe the synthesis of 28 new derivatives in the active benzofuran series. These compounds were designed to expand the structure–activity relationship (SAR) observed in the initial generation for the R^1 and R^2 regions[7] and to explore the role played by specific structural features in determining compound potency. Hydrophilic and/or charged substituents were privileged, in an effort to increase the water solubility of the ligands. We also describe STD NMR experiments with the yeast Hsp90 isoform, Hsc82, that confirm binding of the benzofuran ligands with the full protein. In this context, we present the first STD interaction study of Novobiocin with the same protein. STD data were combined with the MD-based characterization of the structures of Hsc82/allosteric ligand complexes.[6b] The results indicate qualitative agreement between the two approaches, allowing us to identify the ligand epitopes.

Results and Discussion

Diversification at R^1

The starting material for the group of benzofuran derivatives described so far is the 5-chloro-2-(4-hydroxyphenyl)-3-methylbenzofuran (**1a**), synthesized from 2-bromo-4-chlorophenol by Pd-catalyzed enolate arylation, as described previously (Scheme 1).[8]

The introduction of substituents other than chlorine at position 5 required a different approach, based on a [3,3]-sigmatropic rearrangement of *O*-aryloximes described by Miyata et al.,[9] in the one-pot version introduced by Contiero (Scheme 2).[10] Condensation of aryloxyamine **2** with ketone **3** yields intermediate *O*-aryloxime **4**, which is heated at 60 °C in THF and with an excess of $MeSO_3H$ to induce sigmatropic rearrangement of the protonated enamine isomer. Re-aromatization of the intermediate, followed by intramolecular cyclization and ammonia elimination afford desired benzofuran **1** in 3–6 h and with satisfactory yields (Scheme 2).

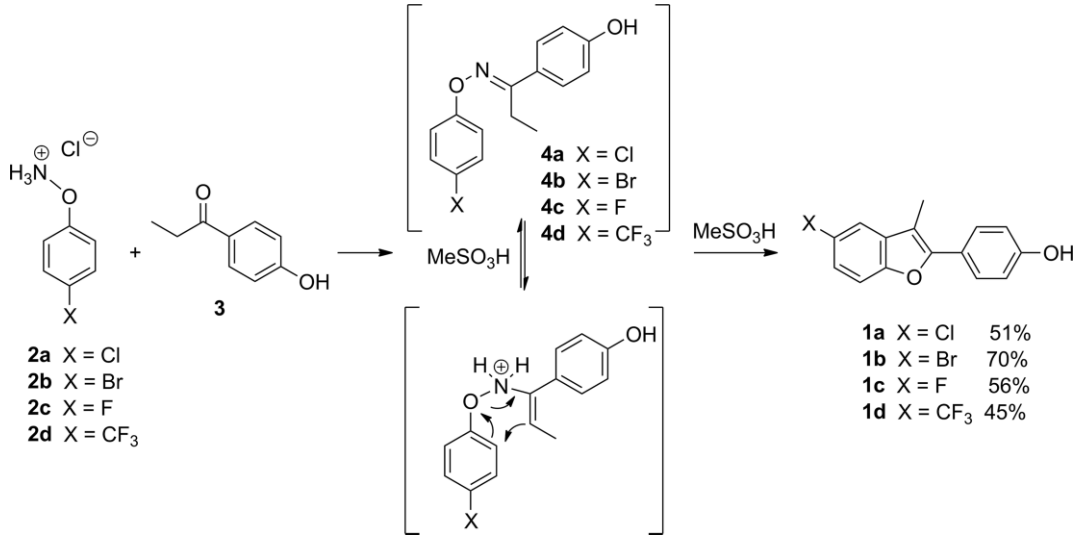


1a

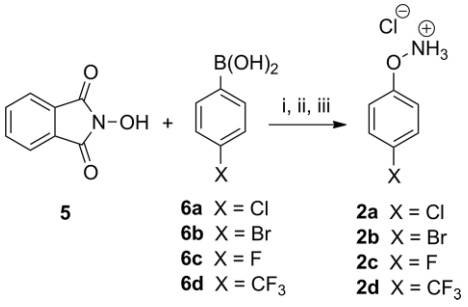
Scheme 1. Synthesis of 5-chloro-2-(4-hydroxyphenyl)-3-methylbenzofuran **1a** by enolate arylation. (i) $Pd(OAc)_2$, *rac*-2-(di-*tert*-butylphosphanyl)-1,10-binaphthyl (*rac*-DTBPB), NaO*t*Bu, toluene. (ii) TFA/DCM (iii) EtSNa, DMF 43 % over the three steps (from[8]).

Conversion of 4-trifluoromethyl derivative **4d** required harsher conditions and was achieved in 45 % yield by replacing THF with higher boiling dioxane and performing the reaction at 100 °C for 2 d. Starting aryloxyamines **2a**–**d** were conveniently synthesized from *N*-hydroxyphthalimide **5** and corresponding boronic acids **6a**–**d** (Scheme 3) using a Cu-mediated cross-coupling procedure developed by Petrassi and co-workers.[11]

It has already been shown that **1a** is a suitable substrate for Stille coupling with tributyl(1-propenyl)tin.[8] 5-Bromo-2-(4-hydroxyphenyl)-3-methylbenzofuran (**1b**) was instrumental to the exploration of additional Pd-catalyzed chemistry and to expanding the library of 5-substituents. In particular, since calculations had suggested that the Hsp90 allosteric pocket may in-

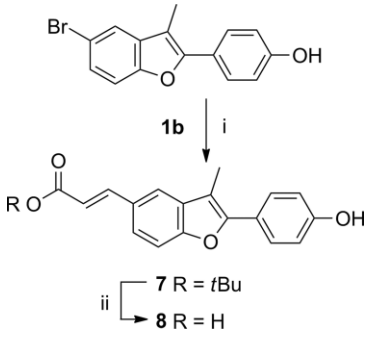


Scheme 2. Synthesis of 5-substituted 2-(4-hydroxyphenyl)-3-methylbenzofurans **1a**–**d** by [3,3]-sigmatropic rearrangment of *O*-aryloximes **2a**–**d**.



Scheme 3. Synthesis of the aryloxyamines **2a–d**. (i) CuCl, 4 Å molecular sieves, 1,2-dichloroethane, air, room temperature, 48–72 h; (ii) $H_2NNH_2{\cdot}H_2O$, 10 % MeOH in CH_2Cl_2; (iii) 4 M HCl in dioxane.

clude complementary basic sites, a Heck[12] reaction was selected as the means by which to introduce an acidic function to the benzofuran scaffold. Therefore, **1b** and *t*Bu acrylate were reacted in toluene affording 5-substituted *t*Bu ester **7** in 81 % yield and with 100 % *E* selectivity (Scheme 4). Despite the acid sensitivity of the substrate, ester deprotection could be performed using 20 % CF_3COOH in CH_2Cl_2 to afford acid **8** in quantitative yields. Double bond reduction was also successfully achieved on a set of derivatives as described below.



Scheme 4. Heck reaction of **1b**. (i) *t*Bu acrylate, $Pd(OAc)_2$, P(*o*-tol)$_3$, TEA, toluene, reflux, 6 h, 81 %; (ii) 20 % CF_3COOH in DCM, 2 h, quant.

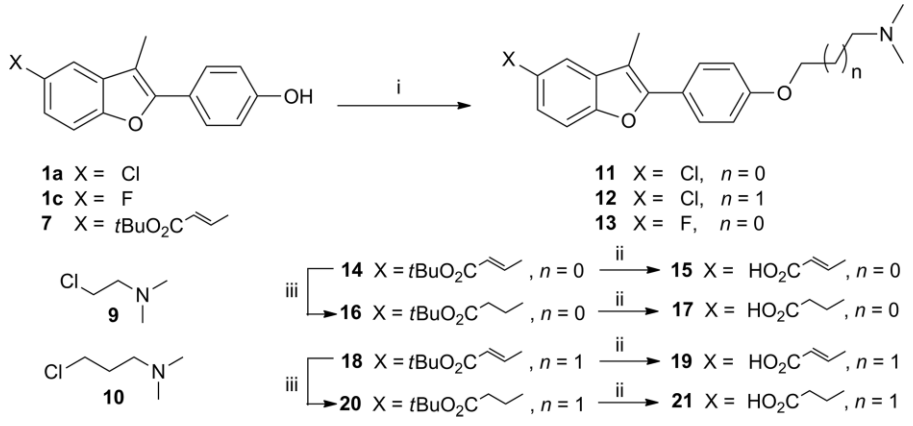
Diversification at R2

Our initial set of data for R^2 substituents had shown that basic groups at this position improve the activity of the benzofuran ligands as stimulators of Hsp90. Thus, we focused our attention on the introduction of amino groups in this region. This was accomplished by phase-transfer-catalyzed (PTC) alkylation of the phenol oxygen of **1a**, **1c** and **7** with 2-chloro-*N*,*N*-dimethylethylamine **9** or 3-chloro-*N*,*N*-dimethylpropylamine **10** (Scheme 5) to afford compounds **11**–**13** in good yields. Amino *tert*-butyl esters **14** and **18** (Scheme 5), obtained by alkylation of **7**, were either directly deprotected (20 % CF_3COOH in CH_2Cl_2) to give the corresponding *N*,*N*-dimethylamino acids **15** and **19**, or hydrolyzed after reduction of the double bond (H_2 and 10 % Pd-C) to afford **17** and **21**.

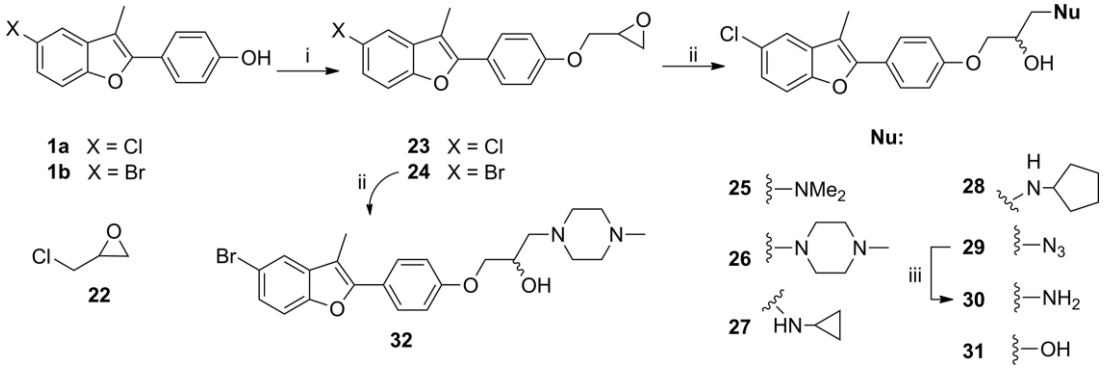
In an effort to improve the solubility of the ligands, a second group of amine derivatives was prepared from epoxides **23** and **24**, synthesized by alkylation of **1a** and **1b** with epichlorohydrin **22** (Scheme 6). Reaction of **23** with a set of four secondary amines in a 9:1 CH_2Cl_2/EtOH mixture yielded compounds **25**–**28**. Similarly, **32** was obtained by reaction of **24** with *N*-methylpiperidine (Scheme 6). The primary amine **30** was prepared by NaN_3 opening of **23** [dioxane, 80 °C, cat. Yb(OTf)$_3$, 81 % yield] and reduction of the resulting azide **29** under carefully controlled conditions (H_2, PtO_2, morpholine in MeOH, 71 % yield),[13] to avoid hydrogenolysis of the arylchloride. Finally, HCl-promoted hydrolysis of **23** in 3:1 dioxane/water mixture afforded diol **31** in 60 % yield (Scheme 6).

Two additional derivatives, **34** and **35** were prepared by activation of known acid **33**[5b] and reaction with morpholine or *N*-methylpiperazine, respectively (Scheme 7).

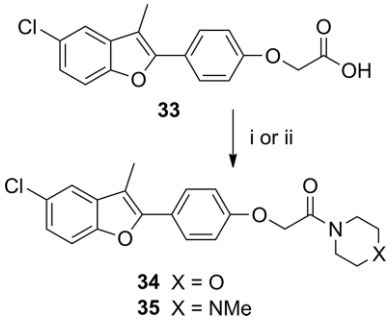
We have previously reported that a set of monoglycosides of **1a** can modulate Hsp90 activity. In particular when R^2 = α-L-Rha, α-D-Man and β-D-Gal the **1a** congeners were found to induce significant activation of Hsp90 ATPase.[5b] In order to harness the effects of both a sugar and an amino group, the synthesis of glycoconjugates of amino sugars was also attempted (Scheme 8). Glycosylation of **1a** with 6-azido-2,3,4-tri-*O*-benzoylmannose 1-trichloroacetimidate **36**[14] was executed in good yields (62 %) under standard conditions (TMSOTf, –30 °C) to afford 6-azidomannoside **37** (Scheme 8). It is worth noting that, under the same conditions, mannosylation of **1a** with 2,3,4,6-tetra-*O*-benzoylmannose 1-trichloroacetimidate afforded only a modest 20 % yield.[8] Zemplén removal of the benzoyl esters occurred uneventfully to yield **38**, which is barely



Scheme 5. PTC alkylation of the phenol with *N*,*N*-dimethylalkylamines. (i) Compounds **9·HCl**, or **10·HCl**, Bu_4NHSO_4, K_2CO_3, H_2O (5 % w/w in K_2CO_3) in $CHCl_3$. (ii) 20 % CF_3COOH in CH_2Cl_2; (iii) H_2, Pd/C, MeOH, 2 h, quant.



Scheme 6. Synthesis of epoxides **23** and **24** and nucleophilic opening reactions. (i) Compound **22**, Bu_4NHSO_4, K_2CO_3, H_2O (5 % w/w in K_2CO_3) in $CHCl_3$. (ii) Compounds **25**–**28** and **32**: secondary amine, [9:1] CH_2Cl_2/EtOH; for **29**: NaN_3 in refluxing dioxane, $Yb(OTf)_3$, 5 d, 81 %; for **31**: [3:1] dioxane/H_2O, HCl, reflux, 5 h, 60 %; (iii) H_2, PtO_2-morpholine in MeOH, 71 %.

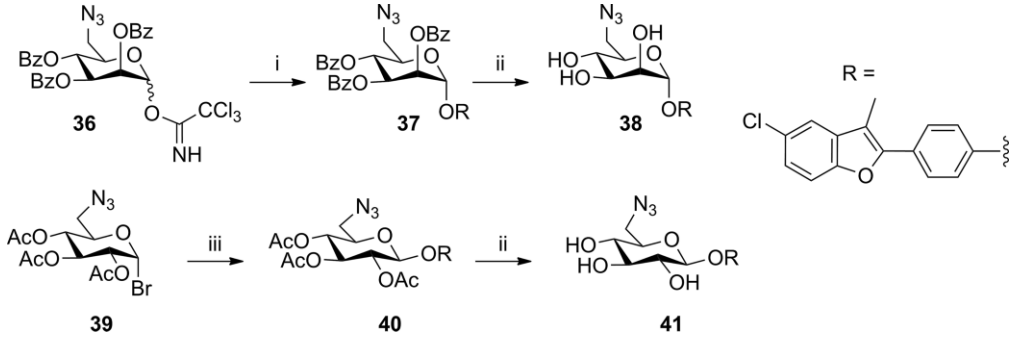


Scheme 7. Synthesis of amides **34** and **35**. (i) EDC, morpholine, THF, 20 h, 35 %; (ii) a. Oxalyl chloride, b. *N*-methylpiperazine, CH_2Cl_2, 78 %.

soluble in MeOH. Reduction of the azido group could not be achieved under a variety of conditions mainly owing to the poor solubility of **38** and of the resulting amine in most organic solvents.

Hydrogenolysis with mild catalysts, such as Lindlar-Pd, left the starting material unreacted even after 1 d. Under more severe conditions [e.g. using Pd/C (AcOEt, 1 % AcOH) or PtO_2 and morpholine] several by-products (mostly from hydrogenolysis of the aryl chloride bond) were observed by MS analysis, however, but none could be properly isolated. Similar results were obtained with the corresponding β-glucoside **41**, obtained by glycosylation of **1a** with glucosylbromide **39**[15] under PTC conditions. Zemplén removal of the acetyl groups from **40** occurred under unusually harsh conditions (MeOH, 40 °C, 2 d), due to the low solubility of the starting material in MeOH, and yielded 6-azidoglucoside **41** after precipitation from CH_2Cl_2. The compound was found to be soluble in acetone and could be fully characterized. Again, though, we were unable to obtain clean reduction of the azido group.

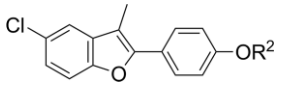
Glycosylations with other non-metabolic sugars were more successful. We focused on a limited group of commercially available monosaccharides, all characterized by the presence of an axial hydroxyl group either in position 2 or 4 of the pyranose ring, as suggested by the set of active glycosides identified in the previous campaign. The α-L-Man and the β-D-Fuc derivatives **42** and **43** (Table 1) are enantiomers of previously described derivatives[5b] and were synthesized accordingly. The L and D α-arabinosides **44** and **45** were synthesized from the corresponding bromides, as exemplified in Scheme 9 for the L enantiomer. PTC alkylation of **1a** with β-L-arabinopyranosyl bromide 2,3,4-triacetate **50**[16] followed by Zemplén hydrolysis of the acetyl groups afforded L-arabinoside **44** (60 % overall yield) exclusively in the α configuration. It is worth noting that



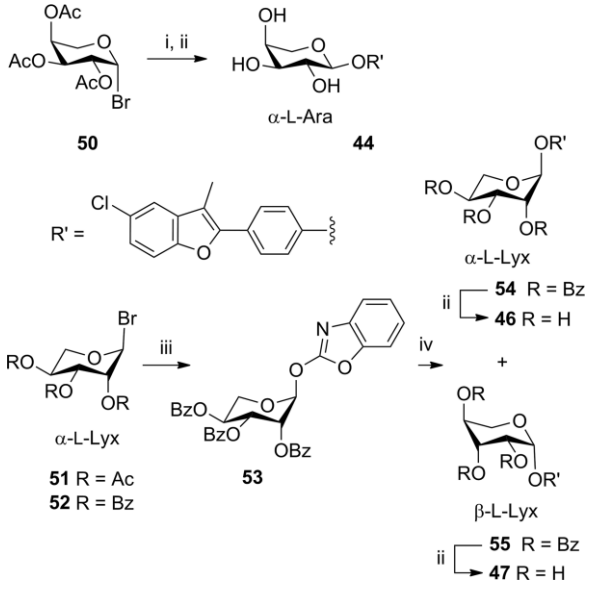
Scheme 8. Glycosylation of **1a** with 6-azidosugar donors. (i) **1a**, TMSOTf, –30 °C, 30 min, 62 %; (ii) MeONa, MeOH; (iii) **1a**, Bu_4NHSO_4, K_2CO_3, H_2O (5 % w/w in K_2CO_3) in $CHCl_3$, 40 %.

for pentapyranosides, the anomeric substituent is β(α) if in a *trans* (*cis*) orientation relative to the 4-hydroxy group[17]].

Table 1. Glycosylation of **1a** with non-metabolic sugars.



42	α-L-Man
43	β-D-Fuc
44	α-L-Ara
45	α-D-Ara
46	α-L-Lyx
47	β-L-Lyx
48	α-D-Lyx
49	β-D-Lyx



Scheme 9. Glycosylation of **1a** with non-metabolic sugars. (i) **1a**, Bu_4NHSO_4, K_2CO_3, H_2O (5 % w/w in K_2CO_3), in $CHCl_3$, 3 h, 83 %; (ii) MeONa, MeOH; (iii) AgOBox, 24 %; (iv) **1a**, TMSOTf, 1,2-dichloroethane, –78 °C, 69 % combined yield (40 % **54** and 29 % **55**).

The anomeric configuration of the compound could be established based on the 1,2 coupling constant of 7 Hz, typical of a 1,2-*trans* glycoside. Under the same conditions, glycosylation of **1a** with α-L-lyxopyranosyl bromide 2,3,4-triacetate **51**[18] (Scheme 9) afforded the desired product in less than 10 % yield. Thus, *O*-benzoxazole (O-Box) donor **53** was prepared from bromide **52** and used under Demchenko's conditions[19] to glycosylate **1a** in 69 % overall yield.

Both anomers α-L-Lyx **54** and β-L-Lyx **55** were formed in this reaction in a 56:44 ratio and were separated by flash chromatography (9:1 toluene/hexane). Their anomeric configurations and main conformations (shown in Scheme 9) were established by NMR experiments described in the Supporting Information. Benzoate removal afforded final α-L-Lyx and β-L-Lyx glycosides **46** and **47**. The D-enantiomers **48** and **49** were obtained using the same route, starting from the D-enantiomer of lyxose.

Interaction of Compounds with Hsp90: STD-NMR Experiments

Whereas full characterization of the compounds activity on Hsp90 ATPase and functional dynamics is in progress, we set out to characterize the interaction of selected library members with Hsp90 using NMR spectroscopy. Saturation Transfer Difference NMR is one of the most widespread NMR methods to study the interaction between small molecules and macromolecular receptors.[20] The technique exploits the nuclear Overhauser effect and relies on the fast exchange equilibrium for a ligand between the free and bound states, in the presence of the receptor. Selective irradiation of the protein is followed by transfer of magnetization to the ligand protons, which in turn causes a partial saturation of the ligand signals, allowing one to map the interaction epitope on the small molecule by analyzing the difference spectrum obtained in the absence or in the presence of the selective irradiation pulse. The ligand protons that are in closer contact with the protein receive a larger amount of magnetization transfer and give larger signals in the difference spectrum.

To the best of our knowledge, no STD experiments have been reported with full-length Hsp90. Thus, to test the feasibility of this experiment, we first analyzed Novobiocin **56** (Figure 2, A) in the presence of the yeast isoform of Hsp90, Hsc82. Novobiocin is the first and most studied inhibitor of the Hsp90 carboxy terminus.[21] To date, no co-crystal structure of Hsp90 bound to C-terminal ligands has been solved. Thus, information on the size and nature of the binding pocket and on ligand positioning is based exclusively on computational SAR and molecular docking studies.[22] Novobiocin affinity for Hsp90 was estimated to be in the millimolar range by SPR and other techniques,[23] which makes it ideally suitable for STD analysis. However, NMR interaction experiments had not been reported thus far.

The STD spectrum of Novobiocin **56** in the presence of Hsc82 was obtained in deuterated phosphate buffer with a 200:1 ligand:protein ratio, using as the irradiating frequency the upfield aliphatic region of the protein. The spectrum is reported in Figure 2, C, together with the ^1H spectrum of Novobiocin **56** under the same conditions (Figure 2, B). The molecule appears to be deeply embedded in the protein binding site since different degrees of magnetization transfer could be observed for each proton (Figure 2, C). A quantitative analysis of these data (Figure 2 and Supporting Information) suggests that the interaction epitope of Novobiocin strongly involves the prenylated phenol ring, the coumarin moiety and, to a lesser extent, the noviose ring. These observations are consistent with the results of MD-based studies of Hsc82/Novobiocin complexes.[6b] In the latter, extensive MD simulation of **56** docked to the putative allosteric pocket were run and characterized by means of cluster analysis. The representative structure (Figure 3, b, right panel) was largely consistent with STD data, showing the prenyl, aromatic and sugar protons within contact distance with

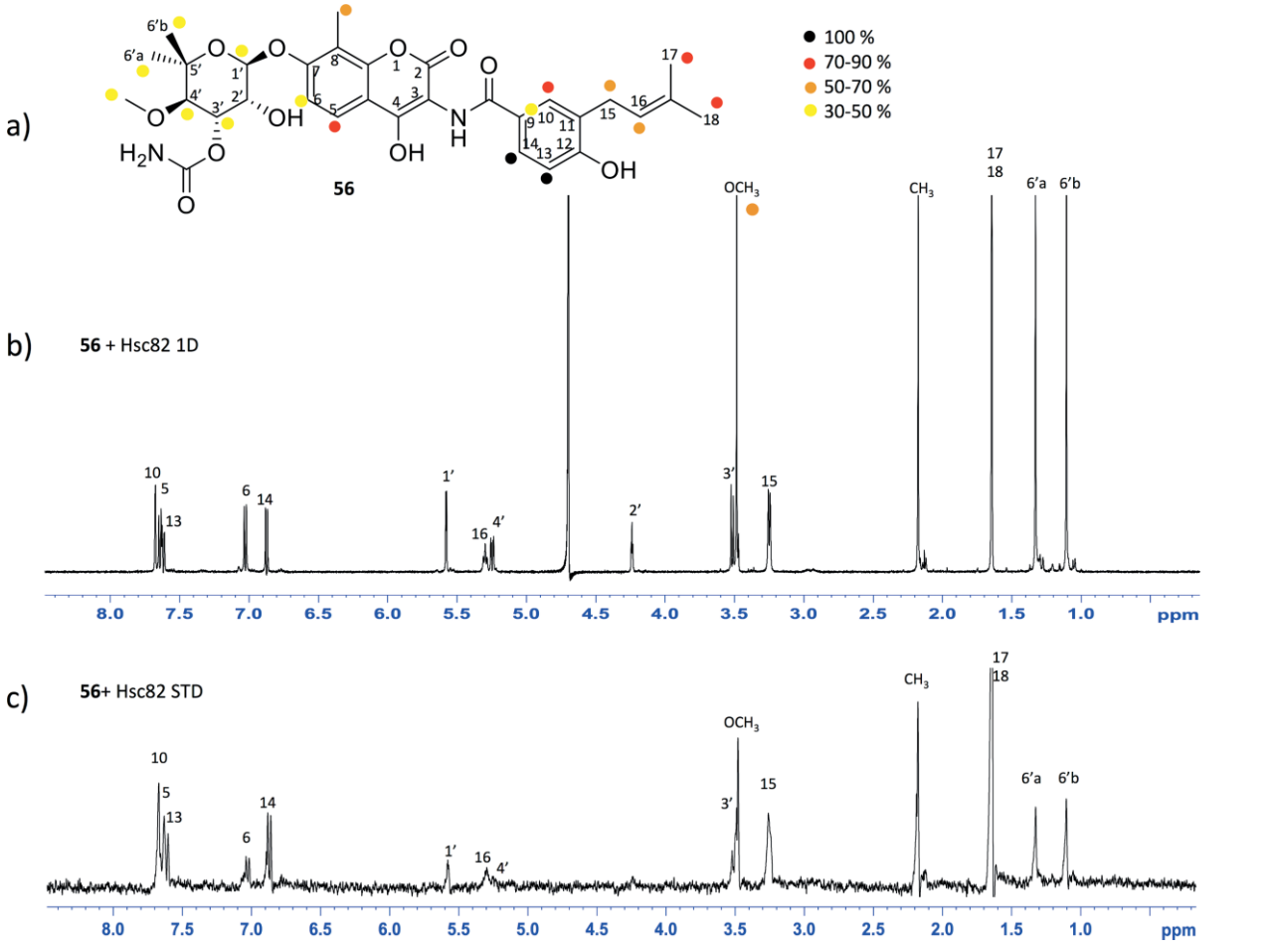


Figure 2. STD-NMR experiments with Novobiocin **56**. (a) Structure of Novobiocin **56**. (b) ^{1}H-NMR spectrum of **56** in presence of Hsc82 in a 200:1 ligand/protein ratio. (c) STD spectrum of **56** in presence of Hsc82 in a 200:1 L/P ratio. STD was obtained by irradiating the protein at –0.05 ppm with total saturation times of 0.98 s. The water suppression was achieved by Watergate 3–9-19 pulse sequence. The relative STD values, grouped in four intensity ranges, are marked with different colours and point up that the prenylated hydroxylphenyl ring is making the closest contacts with the protein in the bound state.

the protein. Additionally, the OCH_3 substituent at noviose 4′ position was also calculated to point towards the interior of the protein, consistent with the observed STD signal.

NMR analysis of the benzofuran derivatives in the presence of Hsc82 was severely impaired by the low solubility of the compounds in water. Finally, conditions were established whereby compound **11** (Figure 4, A) could be dissolved in the aqueous buffer at the appropriate concentration and maintained in solution after addition of the protein. Amine **11** has already been characterised as a powerful Hsp90 allosteric activator.[5b] The predicted binding site (Figure 3, a) is close to the region occupied by Novobiocin (Figure 3, b). However, MD simulations suggest that formation of the Hsp90:Novobiocin complex blocks the protein in a partially inactive state (Figure 3, b, left panel), whereas interaction with **11** results in higher frequency turnover of the closed-active state (Figure 3, a, left panel) and allosterically stimulates ATPase activity.

STD NMR experiments were recorded with a 200:1 ligand:protein ratio at different saturation times, using as irradiating frequency the upfield methyl region of the protein. A selected spectrum is reported in Figure 4C and the corresponding 1D spectrum is shown in Figure 4 (B).

The results confirmed that binding occurs between compound **11** and Hsc82 and that the recognition is strongly mediated by aromatic protons (belonging both to the phenol and benzofuran rings). An intense STD signal was also observed for *N*-CH_2 and *N*-methyl groups. In particular, the protons of the aromatic rings show the largest saturation transfer and the *N*-CH_3 group the lowest effect, suggesting that the region of the ligand comprising the aromatic rings makes the closest contacts with the protein binding site. A competition experiment between **11** and Novobiocin was attempted, but was frustrated by precipitation of the ligand. In good agreement with STD, the representative structures from MD simulations of the Hsc82/**11** complex (Figure 3, a, right panel) show extensive packing of the benzofuran and aromatic rings of the ligand with the protein, coupled with contacts involving both the *N*-CH_2 and *N*-methyl groups of the amine modification.[7] Within the limitations of

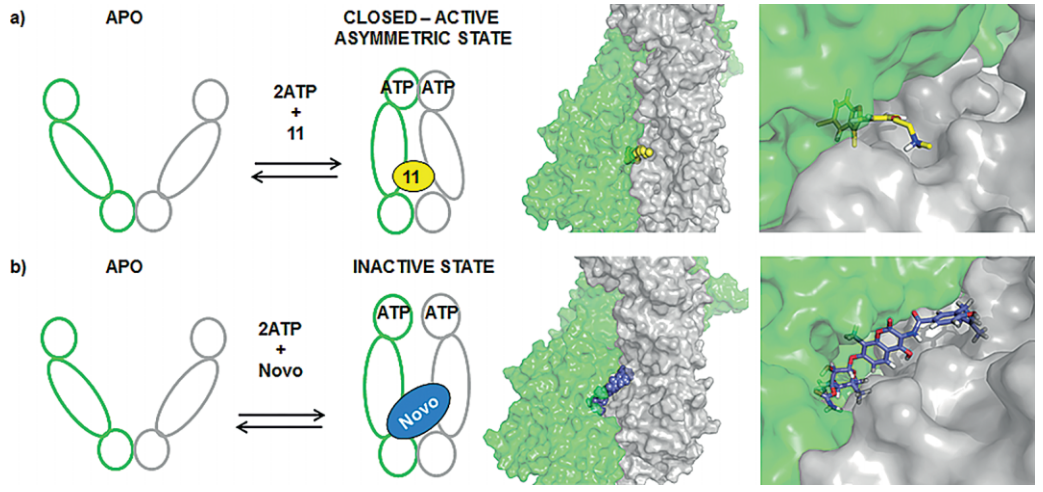


Figure 3. Hsp90 complexes of benzofuran **11** (a) and Novobiocin **56** (b). Dynamic equilibrium between open and closed Hsp90 is differentially affected by **11** (a, left panel) and Novobiocin (b, left panel) resulting in activation and inhibition of the ATPase activity, respectively. The docked complexes of Hsc82 with **11** (a) and Novobiocin (b) are shown in the right panels.

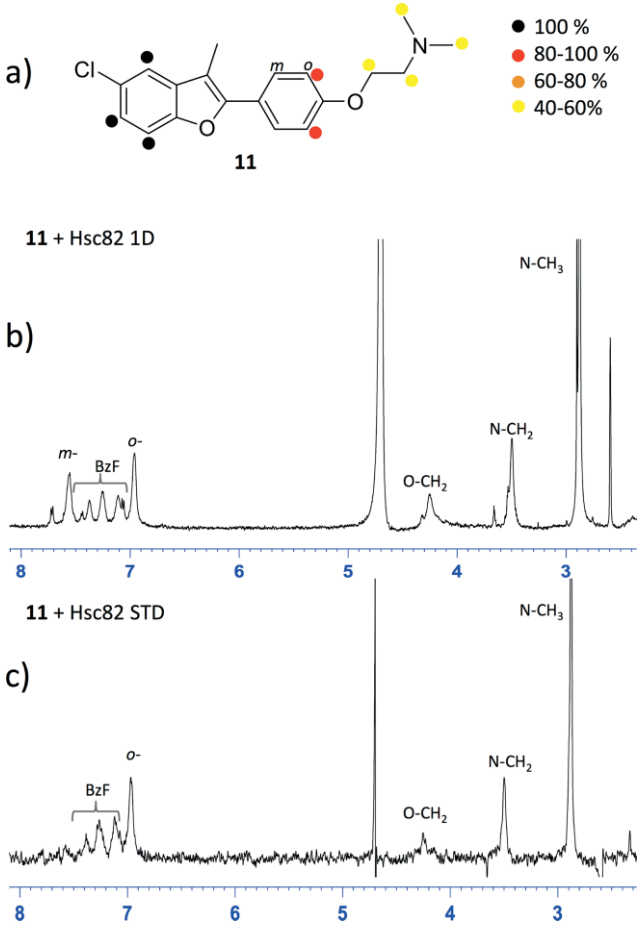


Figure 4. STD-NMR experiments with benzofuran derivative **11**. (a) Formula of **11**. (b) ^{1}H-NMR spectrum of **11** in presence of Hsc82 in a 200:1 ligand/protein ratio. (c) STD spectrum of **11** in the presence of Hsc82 in a 200:1 L/P ratio. STD was obtained by irradiating the protein at –0.05 ppm with total saturation times of 2.94 s. The water suppression was achieved by Watergate 3–9-19 pulse sequence. The relative STD values are grouped in four intensity ranges and marked with different colors.

MD sampling for such large and complex systems, and with a caveat on the qualitative nature of the comparison, comparative analysis of STD and MD results provides a consistent structural model for the complexes in solution. Moreover, it is worth noting that such knowledge has been used to guide the development of more potent derivatives, providing further support to the validity of the model.

Conclusions

A library of Hsp90 stimulators characterized by a 2-(4-hydroxyphenyl)-3-methylbenzofuran structure has been significantly expanded. Groups at position 5 of the benzofuran ring were diversified using a [3,3]-sigmatropic rearrangement of *O*-aryloximes for the synthesis of the benzofuran core and a Heck cross-coupling reaction for further modifications. The synthesis of a second set of compounds, diversified at position R^2 was achieved by alkylation of the phenol ring followed by further elaborations. Glycosylation of **1a** with amino sugars was attempted but abandoned due to low solubility of the products, although other non-metabolic sugars could be successfully introduced to the scaffold. Overall, 28 new compounds were synthesized, demonstrating the versatility of the benzofuran platform. STD-NMR analysis of the interaction of the known allosteric modulator **11** with the yeast isoform of Hsp90 (Hsc82) revealed that the ligand actually binds to the protein and confirmed the role of the benzofuran scaffold in establishing the interaction. The spectra also showed that the substituents on the amino group are in close contact with the protein, providing a viable structural model that can be used to guide the development of more potent derivatives. Full characterization of Hsp90 ATPase activity modulation by the 28 new compounds and functional dynamics studies are currently underway.

Experimental Section

Protein Expression and Purification: The Hsc82 was cloned into pET28b (Novagen, U.S.) and transformed into BL21 (DE3) cells (NEB,

U.S.). The protein expression was induced by 0.5 mM IPTG (Goldbio, U.S.) at 20 °C for 16 h. The cells were lysed using EmulsiFlex-C3 (Avestin, Canada). The lysate was purified using Ni-NTA columns (Qiagen, U.S.), monoQ ion exchange chromatography (GE, U.S.) and Superdex200 gel filtration chromatography (GE•U.S.).

STD-NMR: All NMR spectra were recorded with a Bruker Avance spectrometer operating at 600 MHz. All data were collected at 298 K. 1D, COSY, and NOESY (mixing time of 200 and 700 ms) were recorded using standard sequences from the Bruker library on Novobiocin **56** (0.23 mg, MW = 634.6, 2 mM) and Compound **11** (0.3 mg, *MW* = 366.3, 4.5 mM) in order to assign all resonances. The sample was prepared in deuterated 20 mM PBS buffer. Data were analysed using Bruker Topspin software. After NMR characterization, Hsc82 (10 mg/mL, *MW* = 80899.7) was added to each sample affording a 200:1 L/P ratio. For the acquisition of NMR Saturation Transfer Difference (STD) experiments, a 1D-pulse sequence incorporating a $T_{1\varrho}$ filter to remove disturbing protein signals was used. The STD spectra were performed with an on-resonance irradiation frequence at –0.05 ppm, whereas 200 ppm was chosen as the off-resonance frequency. Selective presaturation of the protein was achieved by a train of Gauss shaped pulses, each of 49 ms in length. STD experiments were acquired on each sample varying the total saturation times from 0.49 to 3.92 s (with 0.49 s increments). In STD experiments, water suppression was achieved by using the WATERGATE 3–9-19 pulse sequence. For both products, blank experiments in the absence of protein were performed.

Synthesis – General: Dry dichloromethane (DCM), methanol, 1,4-dioxane and triethylamine (TEA) were distilled from calcium hydride; tetrahydrofuran (THF) was distilled from sodium. Dichloroethane (DCE) was dried with molecular sieves (4 Å) and hexane (Hex) and toluene were used as purchased. Reactions requiring anhydrous conditions were performed under nitrogen, or argon where indicated. AgOBox was synthesized as reported.[19] ^{1}H and ^{13}C spectra were recorded at 400 MHz or 100 MHz, respectively, on a Bruker AVANCE-400 instrument. Chemical shifts (δ) for ^{1}H and ^{13}C spectra are expressed in ppm relative to internal standard [$CDCl_3$: 7.26 for ^{1}H and 77.16 for ^{13}C. CD_3OD: 3.31 for ^{1}H and 49.00 for ^{13}C; $(CD_3)_2CO$: 2.05 for ^{1}H and 29.84 for ^{13}C]. Signals were abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b means broad as in br. s, broad singlet. Quaternary carbon signals were abbreviated as C_q. All assignments were confirmed with the aid of two-dimensional ^{1}H-^{1}H (COSY), ^{1}H-^{13}C (HSQC) and/or ^{1}H-^{13}C (HMBC) experiments using standard pulse programs. Processing of the spectra was performed using TopSpin or MestReNova software. Sugar signals were numbered as is customary; benzofuran signals were numbered as is customary and indicated with the suffix Bf, and the substituents of benzofuran do not have any numbering, but they are clearly indicated in the characterizations. *O*Box signals were numbered as is customary and indicated with the suffix Box. In the names of the compounds the conventional numbering is used. Mass spectra were obtained with a ThermoFisher LCQ apparatus (ESI ionization), or iontrap ESI Esquire 6000 from Bruker, or Apex II ICR FTMS (ESI ionization – HR-MS). Thin layer chromatography (TLC) was carried out with pre-coated Merck F254 silica gel plates. Flash chromatography (FC) was carried out with Macherey–Nagel silica gel 60 (230–400 mesh), according to the established Still procedure.[24] Automated chromatography was performed using a Biotagelsolera Prime. Compounds **1a**, **11**, **12**, **33**,[5b] **1b**,[9] **39**[15] and **50**[16] have been described previously. Glycosides **42** and **43** were characterized based on the spectroscopic data reported for their enantiomers[8] and on the sign of their optical rotation. Boronic acids **57a**–**d** and ketone **3** are commercially available.

General Procedure I. Synthesis of the 5-Substituted 2-(4-Hydroxyphenyl)-3-methylbenzofurans (1a–c):[10] The phenyloxyamine hydrochloride **2a**–**c** (1 mmol) was suspended in THF (3 mL) under nitrogen. Freshly activated, acid washed molecular sieves (4 Å, 0.1 g) and 1-(4-hydroxyphenyl)propan-1-one **3** (1 mmol) were added. The solution was stirred for 5 min at 60 °C, then methanesulfonic acid (2 mmol) was added. The mixture was stirred for 5 h and reaction progress was followed by HP-TLC (8:2 toluene/DCM; each sample was diluted with DCM and quenched with $NaHCO_3$ before deposition on TLC). The reaction mixture was then diluted with EtOAc, the organic phase was washed with $NaHCO_3$ (2 × 5 mL), and brine (2 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography as described below.

5-Chloro-2-(4-hydroxyphenyl)-3-methylbenzofuran (1a): General procedure I performed starting from **2a**. The crude material was purified by flash chromatography (toluene/DCM gradient from 10 % to 25 % DCM) leading in 51 % yield to product **1a**, whose spectroscopic data corresponded with those reported in the literature.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.45 (d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.35 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H-7Bf), 7.20 (dd, 1 H, H-6Bf), 6.96 (d, 2 H, 2 × H-*o*-Phe-O), 2.39 (s, 3 H, CH_3-Bf) ppm.

5-Bromo-2-(4-hydroxyphenyl)-3-methylbenzofuran (1b): General procedure I performed starting from **2b**. The crude product was purified using an automated chromatography system (SiO_2, Hex/EtOAc gradient from 30 % to 100 % EtOAc), to afford compound **1b** in 70 % yield as a white solid, whose spectroscopic data corresponded with those reported in the literature.[9] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, $J_{o\text{-}m}$ = 8.3 Hz, 2 H, 2 × H-*m*-Phe-O), 7.62 (s, 1 H, H-4Bf), 7.38–7.29 (m, 2 H, H-6Bf, H-7Bf), 6.95 (d, 2 H, 2 × H-*o*-Phe-O), 2.40 (s, 3 H, CH_3Bf) ppm.

5-Fluoro-2-(4-hydroxyphenyl)-3-methylbenzofuran (1c): General procedure I performed starting from **2c**. The crude product was purified by flash chromatography (8:2 Hex/EtOAc, R_f = 0.3) leading to product **1c** in 56 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.37 (dd, $J_{7\text{-}6}$ = 8.9, $^4J_{HF}$ = 4.2 Hz, 1 H, H-7Bf), 7.15 (dd, $J_{4\text{-}6}$ = 2.6, $^3J_{H\text{-}F}$ = 8.6 Hz, 1 H, H-4Bf), 7.00–6.93 (m, 3 H, H-6Bf, 2 × H-*o*-Phe-O), 5.22 (br. s, 1 H, OH), 2.39 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5 (C_q), 156.9 (d, $^1J_{CF}$ = 240 Hz, C-F), 155.7 (C_q), 152.7 (C_q), 149.9 (C_q), 132.3 (d, $^3J_{CF}$ = 10 Hz, C_q), 128.6 (2 × C-*m*-Ph-O), 124.2 (C_q), 115.8 (2 × C-*o*-Ph-O), 111.6 (d, $^2J_{CF}$ = 12 Hz, C-6Bf), 111.4 (d, $^3J_{CF}$ = 4.4 Hz, C-7Bf), 110.1 (C_q), 104.8 (d, $^2J_{CF}$ = 30 Hz, C-4Bf), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{15}H_{10}O_2F$ $[M - H]^-$ 241.2, found 241.0.

5-Trifluoromethyl-2-(4-hydroxyphenyl)-3-methylbenzofuran (1d): Phenyloxyamine hydrochloride **2d** (1 mmol) was suspended in dioxane (3 mL) under nitrogen. Freshly activated, acid-washed 4 Å molecular sieves (0.1 g) and 1-(4-hydroxyphenyl)propan-1-one **3** (1 mmol) were added. The solution was stirred for 5 min at 40 °C, then methanesulfonic acid (2 mmol) was added and the mixture was stirred for 2 d at 100 °C. The reaction progress was followed by RP-HPLC (C18, H_2O/CH_3CN gradient from 30 % to 100 % CH_3CN; retention time of **1d** 1.36 min; retention time of the oxime intermediate **4d** 1.38 min; each sample was diluted with DCM and quenched with $NaHCO_3$ before injection). The reaction mixture was diluted with EtOAc, the organic phase was washed with $NaHCO_3$ (2 × 5 mL), and brine (2 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (8:2 Hex/EtOAc, R_f = 0.4) leading to product **1c** in 45 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (br. s, 1 H, H-4Bf), 7.71 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.55–7.48 (m, 2 H, H-7Bf,

H-6Bf), 6.97 (d, 2 H, 2 × H-*o*-Phe-O), 5.07 (br. s, 1 H, OH), 2.46 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9 (C_q), 154.0 (q, $^1J_{CF}$ = 241 Hz, CF_3), 131.5 (C_q), 128.7 (2 × C-*m*-Ph-O), 125.1 (q, $^2J_{CF}$ = 32 Hz, *C*CF_3), 123.8 (C_q), 121.1 (q, $^3J_{CF}$ = 3.7 Hz, C-6Bf), 116.8 (q, $^3J_{CF}$ = 4.1 Hz, C-4Bf), 115.9 (2 × C-*o*-Ph-O), 111.2 (C-7Bf), 110.0 (C_q), 9.4 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{16}H_{10}F_3O_2$ $[M - H]^-$ 291.064, found 291.092.

***E*-*tert*-butyl 3-[2-(4-Hydroxyphenyl)-3-methylbenzofuran-5-yl]acrylate (7):**[12] Compound **1b** (131 mg, 0.43 mmol), $Pd(OAc)_2$ (1 mg, 0.043 mmol) and (*o*-tol)$_3$P (5 mg, 0.017 mmol) were dissolved in toluene (800 μL) under nitrogen atmosphere. TEA (300 μL, 0.73 mmol) and *t*Bu-acrylate (76 μL, 0.52 mmol) were added. The mixture was warmed to reflux for 6 h (TLC 8:2 Hex/EtOAc). The reaction was cooled to room temperature and diluted with EtOAc. The mixture was washed with 1 M HCl (2 × 5 mL), water (2 × 5 mL) and brine (1 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified using an automated chromatography system (SiO_2, Hex/EtOAc gradient from 30 % to 100 % EtOAc) to afford compound **7** (122 mg, 81 % yield, 100 % *E* selectivity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (m, 3 H, 2 × H-*m*-Phe-O, =CH-Ar), 7.64 (s, 1 H, H-4Bf), 7.44 (s, 2 H, H-6Bf, H-7Bf), 6.96 (d, $J_{o\text{-}m}$ = 8.7 Hz, 2 H, 2 × H-*o*-Phe-O), 6.39 (d, J_{trans} = 15.9 Hz, 1 H, =CH-C=O), 2.44 (s, 3 H, CH_3Bf), 1.56 (s, 9 H, 3 × $CH_{3\text{-}t\text{Bu}}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9 (C=O), 155.9 (C_q-phenol), 154.9 (C_q-Bf), 152.1 (C_q-Bf), 144.5 (=CH-Ar), 132.0 (C_q-Bf), 129.5 (C_q-phenol), 128.6 (2 × C-*m*-Ph-O), 124.3 (C-6Bf), 124.0 (C_q-Bf), 119.2 (C-4Bf), 118.7 (=*CH*-C=O), 115.8 (2 × C-*o*-Ph-O), 111.3 (C-7Bf), 109.9 (C_q-Bf), 80.6 (C_q-*t*Bu), 28.4 (3 × $CH_{3\text{-}t\text{Bu}}$), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{22}H_{22}NaO_4$ $[M + Na]^+$ 373.1416, found 373.1462.

General Procedure II - Phenol Alkylation: Synthesis of 13, 14, 18, 23 and 24: The benzofuran (**1a–c** or **7**; 0.3 mmol) and the alkylating agent (**9** or **10** or **22**; 1 mmol) were dissolved in $CHCl_3$ (3 mL). Water (19 μL), K_2CO_3 (2.7 mmol) and the phase-transfer catalyst (Bu_4NHSO_4, 0.15 mmol) were added and the mixture was kept overnight at 45 °C under vigorous stirring. When the reaction was complete (TLC 95:5 $CHCl_3$/MeOH) it was diluted with chloroform and brine, the aqueous phase was extracted with chloroform (2 × 10 mL) and the organic phases were washed with water (2 × 20 mL), dried with Na_2SO_4 and concentrated in vacuo.

5-Fluoro-2-{4-[2-(dimethylamino)ethoxy]phenyl}-3-methylbenzofuran (13): Prepared from **1c** and **9**, following the general procedure II. The crude product was purified by flash chromatography ($CHCl_3$ + 1 %TEA, R_f = 0.26) leading to product **13** in 81 % yield. ^1H NMR (400 MHz, 9:1 CD_3OD/$CDCl_3$): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.40 (dd, $J_{6\text{-}7}$ = 8.9, $^4J_{HF}$ = 4.0 Hz, 1 H, H-7Bf), 7.21 (dd, $J_{4\text{-}6}$ = 2.6, $^3J_{HF}$ = 8.8 Hz, 1 H, H-4Bf), 7.08 (d, 2 H, 2 × H-o-Phe-O), 7.04–6.94 (m, 1 H, H-6Bf), 4.19 (t, J_{gem} = J_{vic} = 5.3 Hz, 2 H, CH_2-O), 2.96–2.86 (m, 2 H, CH_2-N), 2.45 (br. s, 6 H, 2 × CH_3-N), 2.40 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, 9:1 CD_3OD/$CDCl_3$): δ = 161.8 (C_q), 160.6 (d, $^1J_{CF}$ = 238 Hz, C-F), 160.0 (C_q), 153.9 (C_q), 151.1 (C_q), 129.2 (2 × C-*m*-Ph-O), 125.2 (C_q), 115.8 (2 × C-*o*-Ph-O), 112.3 (d, $^3J_{CF}$ = 5.3 Hz, C-7Bf), 112.2 (d, $^2J_{CF}$ = 11.4 Hz, C-6Bf), 105.5 ($^2J_{CF}$ = 25 Hz, C-4Bf), 66.2 (CH_2-O), 58.8 (CH_2-N), 45.6 (NMe_2), 9.4 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{19}H_{20}FNNaO_2$ $[M + Na]^+$ 336.3, found 336.0.

***tert*-Butyl (*E*)-3-(2-{4-[2-(dimethylamino)ethoxy]phenyl}-3-methylbenzofuran-5-yl)acrylate (14):** Prepared from **7** and **9**, following the general procedure II for phenol alkylation. The crude product was purified using an automated chromatography system [SiO_2, $CHCl_3$/MeOH/TEA (1 %) gradient from 0 to 20 % MeOH] to afford the product as a white foam (50 % yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 3 H, =CH-Ar, 2 × H-*m*-Phe-O), 7.65 (br. s, 1 H, H-4Bf), 7.44 (br. s, 2 H, H-6Bf, H-7Bf), 7.04 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*o*-Phe-O), 6.39 (d, J_{trans} = 15.9 Hz, 1 H, =CH-C=O), 4.13 (t, $J_{CH2\text{-}CH2}$ = 5.7 Hz, 2 H, CH_2-O), 2.77 (t, 2 H, CH_2-N), 2.44 (s, 3 H, CH_3Bf), 2.36 (s, 6 H, NMe_2), 1.55 (s, 9 H, 3 × $CH_{3\text{-}t\text{Bu}}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8 (C=O), 158.8 (C_q-phenol), 154.8 (C_q-Bf), 152.1 (C_q-Bf), 144.4 (=CH-Ar), 132.0 (C_q-Bf), 129.4 (C_q-phenol), 128.3 (2 × C-*m*-Ph-O), 124.2 (C-6Bf), 124.0 (C_q-Bf), 119.1 (C-4Bf), 118.7 (=CH-C=O), 115.0 (2 × C-*o*-Ph-O), 111.3 (C-7Bf), 109.9 (C_q-Bf), 80.4 (C_q-*t*Bu), 66.0 (CH_2-O), 58.3 (CH_2-N), 45.9 (NMe_2), 28.4 (3 × $CH_{3\text{-}t\text{Bu}}$), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{26}H_{32}NO_4$ $[M + H]^+$ 422.2331, found 422.2418.

***tert*-Butyl (*E*)-3-(2-{4-[3-(dimethylamino)propoxy]phenyl}-3-methylbenzofuran-5-yl)acrylate (18):** Prepared from **7** and **10**, following the general procedure II for phenol alkylation. The crude product was purified using an automated chromatography system [SiO_2, $CHCl_3$/MeOH/TEA (1 %) gradient from 0 to 20 % MeOH] to afford the product in 62 % yield as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 3 H, =CH-Ar, 2 × H-*m*-Phe-O), 7.64 (s, 1 H, H-4Bf), 7.43 (br. s, 2 H, H-6Bf, H-7Bf), 7.00 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*o*-Phe-O), 6.39 (d, J_{trans} = 15.9 Hz, 1 H, =CH-C=O), 4.09 (t, $J_{CH2\text{-}CH2}$ = 6.2 Hz, 2 H, CH_2-O), 2.62 (t, 2 H, CH_2-N), 2.44 (s, 3 H, CH_3Bf), 2.38 (s, 6 H, NMe_2), 2.12–2.02 (m, 2 H, CH_2-*CH*$_2$-CH_2), 1.55 (s, 9 H, 3 × $CH_{3\text{-}t\text{Bu}}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8 (C=O), 158.9 (C_q-phenol), 154.9 (C_q-Bf), 152.1 (C_q-Bf), 144.4 (=CH-Ar), 132.0 (C_q-Bf), 129.4 (C_q-phenol), 128.3 (2 × C-*m*-Ph-O), 124.3 (C-6Bf), 124.0 (C_q-Bf), 119.2 (C-4Bf), 118.7 (=CH-C=O), 114.8 (2 × C-*o*-Ph-O), 111.3 (C-7Bf), 109.9 (C_q-Bf), 80.5 (C_q-*t*Bu), 65.9 (CH_2-O), 56.3 (CH_2-N), 44.8 (NMe_2), 28.4 (3 × CH_3-*t*Bu), 26.7 (CH_2-*CH*$_2$-CH_2), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{27}H_{34}NO_4$ $[M + H]^+$ 436.2488, found 436.3021.

5-Chloro-3-methyl-2-[4-(oxiran-2-ylmethoxy)phenyl]benzofuran (23): Obtained in quantitative yield by reaction of **1a** and epichlorohydrin **22**, following the general procedure II for phenol alkylation. TLC: 6:4 Hex/DCM, R_f = 0.3. No purification required. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $J_{o\text{-}m}$ = 8.6 Hz, 2 H, 2 × H-*m*-Phe-O), 7.46 (s, 1 H, H-4Bf), 7.36 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H-7Bf), 7.21 (d, 1 H, H-6Bf), 7.03 (d, 2 H, 2 × H-*o*-Phe-O), 4.30 (dd, J_{gem} = 11.0, J_{vic} = 3.0 Hz, 1 H, CH_2-OAr), 4.02 (dd, J_{vic} = 5.7 Hz, 1 H, CH_2-OAr), 3.43–3.37 (m, 1 H, CH-O), 2.94 (t, J_{gem} = 4.9, J_{vic} = 4.5 Hz, 1 H, CH_2-O), 2.79 (dd, J_{vic} = 2.8 Hz, 1 H, CH_2-O), 2.40 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (C_q-phenol), 152.3 (C_q-Bf), 151.1 (C_q-Bf), 132.9 (C_q), 128.4 (2 × C-*m*-Ph-O), 128.1 (C_q), 124.3 (C_q), 124.1 (C-6Bf), 118.9 (C-4Bf), 115.0 (2 × C-*o*-Ph-O), 111.9 (C-7Bf), 109.7 (C_q), 69.0 (CH_2-OAr), 50.2 (CH-O), 44.8 (CH_2-O), 9.5 (CH_3Bf) ppm. ESI-MS: calcd. for $C_{18}H_{15}ClNaO_3$ $[M + Na]^+$ 337.0, found 337.0.

5-Bromo-3-methyl-2-[4-(oxiran-2-ylmethoxy)phenyl]benzofuran (24): Prepared by reaction of **1b** and epichlorohydrin **22**, following the general procedure II for phenol alkylation. TLC: 6:4 Hex/DCM, R_f = 0.4.The crude material was purified by flash chromatography (85:15 toluene/DCM, R_f = 0.3) and the product was isolated in 75 % yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 9.0 Hz, 2 H, 2 × H-*m*-Phe-O), 7.61 (d, $J_{4\text{-}6}$ = 1.8 Hz, 1 H, H-4Bf), 7.34 (dd, $J_{7\text{-}6}$ = 8.6, $J_{4\text{-}6}$ = 1.8 Hz, 2 H, H-6Bf), 7.31 (d, 1 H, H7-Bf), 7.02 (d, 2 H, 2 × H-o-Phe-O), 4.29 (dd, J_{gem} = 11.0, J_{vic} = 3.0 Hz, 1 H, CH_2-OAr), 4.00 (dd, J_{vic} = 5.9 Hz, 1 H, CH_2-OAr), 3.42–3.37 (m, 1 H, CH-O), 2.94 (dd, J_{gem} = 4.7, J_{vic} = 4.3 Hz, 1 H, CH_2-O), 2.79 (dd, J_{vic} = 3.2 Hz, 1 H, CH_2-O), 2.41 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (C_q), 152.4 (C_q), 152.0 (C_q), 133.4 (C_q), 128.3 (2 × C-*m*-Ph-O), 126.7 (C-6Bf), 124.1 (C_q), 121.8 (C-4Bf), 115.4 (C_q), 114.9 (2 × C-*o*-Ph-O), 112.3 (C-7Bf), 109.4 (C_q), 68.8 (CH_2-OAr), 50.1 (CH-O), 44.7 (CH_2-O), 9.4 (CH_3Bf) ppm. ESI-MS: calcd. for $C_{18}H_{15}BrO_3$ $[M + H]^+$ 360.2, found 360.4.

Double Bond Reduction. Synthesis of 16 and 20: To a solution of *tert*-butyl (*E*)-acrylate (**14** or **18**, 0.1 mmol) in MeOH (1 mL), Pd/C was added. The mixture was stirred for 2 h at room temperature under H_2 atmosphere. The crude reaction was filtered through celite to remove the catalyst and the filtrate concentrated in vacuo to afford the product (**16** or **20**, respectively) as a white foam.

***tert*-Butyl 3-(2-{4-[2-(Dimethylamino)ethoxy]phenyl}-3-methylbenzofuran-5-yl)propanoate (16):** Obtained from **14** in 94 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.35 (d, $J_{7\text{-}6}$ = 8.3 Hz, 1 H, H-7Bf), 7.32 (d, $J_{4\text{-}6}$ = 1.6 Hz, 1 H, H-4Bf), 7.10 (dd, 1 H, H-6Bf), 7.02 (d, J = 8.9 Hz, 2 H, 2 × H-o-Phe-O), 4.13 (t, $J_{CH2\text{-}CH2}$ = 5.7 Hz, 2 H, CH_2-O), 3.02 (t, $J_{CH2\text{-}CH2}$ = 7.8 Hz, 2 H, CH_2-Ar), 2.77 (t, 2 H, CH_2-N), 2.59 (t, 2 H, CH_2-C=O), 2.42 (s, 3 H, CH_3Bf), 2.37 (s, 6 H, NMe_2), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (C=O), 156.6 (C_q-phenol), 152.4 (C_q-Bf), 150.5 (C_q-Bf), 135.0 (C_q-Bf), 131.3 (C_q-phenol), 128.3 (2 × C-*m*-Ph-O), 124.7 (C-6Bf), 118.5 (C-4Bf), 114.8 (2 × C-*o*-Ph-O), 110.6 (C-7Bf), 110.3 (C_q-Bf), 80.3 (C_q-*t*Bu), 63.0 (CH_2-O), 56.7 (CH_2-N), 46.0 (NMe_2), 43.93, 37.9 (CH_2-C=O), 31.2 (CH_2-Ar), 28.1 (CH_3-*t*Bu), 9.4 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{26}H_{34}NO_4$ $[M + H]^+$ 424.2488, found 424.2982.

***tert*-Butyl 3-(2-{4-[3-(Dimethylamino)propoxy]phenyl}-3-methylbenzofuran-5-yl)propanoate (20):** Obtained from **18** in 82 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-m-Phe-O), 7.38–7.30 (m, 2 H, H-4Bf, H-7Bf), 7.10 (dd, $J_{6\text{-}7}$ = 8.3, $J_{6\text{-}4}$ = 1.5 Hz, 1 H, H-6Bf), 6.98 (d, 2 H, 2 × H-o-Phe-O), 4.09 (t, $J_{CH2\text{-}CH2}$ = 6.1 Hz, 2 H, CH_2-O), 3.02 (t, $J_{CH2\text{-}CH2}$ = 7.8 Hz, 2 H, CH_2-Ar), 2.83–2.77 (t, 2 H, CH_2-N), 2.59 (t, 2 H, CH_2-C=O), 2.51 (s, 6 H, NMe_2), 2.41 (s, 3 H, CH_3Bf), 2.18–2.08 (m, 2 H, CH_2-CH_2-CH_2), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (C=O), 158.4 (C_q-phenol), 152.6 (C_q-Bf), 151.1 (C_q-Bf), 135.0 (C_q-Bf), 131.5 (C_q-phenol), 128.3 (2 × C-*m*-Ph-O), 124.6 (C-6Bf), 118.6 (C-4Bf), 114.7 (2 × C-*o*-Ph-O), 110.6 (C-7Bf), 109.8 (C_q-Bf), 102 (C_q-Bf), 80.5 (C_q-*t*Bu), 65.7 (CH_2-O), 56.2 (CH_2-N), 44.5 (NMe_2), 38.0 (CH_2-C=O), 31.4 (CH_2-Ar), 29.84, 28.2 (CH_3-*t*Bu), 26.2 (CH_2-CH_2-CH_2), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{27}H_{36}NO_4$ $[M + H]^+$ 438.3, found 438.4.

Hydrolysis of *tert*-Butyl Esters: Synthesis of 8, 15, 17, 19, 21: To a DCM solution (1.8 mL) of *tert*-butyl ester (**7**, **14**, **16**, **18** or **20**; 0.1 mmol) under a flux of nitrogen, TFA (400 µL) was added dropwise. The reaction was stirred for 2 h then concentrated in vacuo. TFA was co-evaporated with toluene to afford pure product (quantitative yield) without any further purification.

(*E*)-3-[2-(4-Hydroxyphenyl)-3-methylbenzofuran-5-yl]acrylic Acid (8): ^{1}H NMR (400 MHz, CD_3OD): δ = 7.82 (d, J_{trans} = 16.0 Hz, 1 H, =CH-Ar), 7.78 (d, 1 H, H-4Bf), 7.66 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-m-Phe-O), 7.55 (dd, $J_{6\text{-}7}$ = 8.5, $J_{6\text{-}4}$ = 1.6 Hz, 1 H, H-6Bf), 7.47 (d, 1 H, H-7Bf), 6.92 (d, 2 H, 2 × H-o-Phe-O), 6.52 (d, 1 H, =CH-C=O), 2.45 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 176.1 (C=O), 159.0 (C_q-phenol), 156.2 (C_q-Bf), 153.8 (C_q-Bf), 146.9 (=CH-Ar), 133.3 (C_q-Bf), 131.0 (=CH-COOH), 130.6 (C_q-phenol), 129.4 (2 × C-*m*-Ph-O), 125.2 (C-6Bf), 123.6 (C_q-Bf), 120.4 (C-4Bf), 116.6 (2 × C-*o*-Ph-O), 112.0 (C-7Bf), 110.3 (C_q-Bf), 9.3 (CH_3-Bf) ppm. HRMS (ESI): calcd. for $C_{18}H_{13}O_4$ $[M - H]^-$ 293.08193, found 293.08172.

(*E*)-3-(2-{4-[2-(Dimethylamino)ethoxy]phenyl}-3-methylbenzofuran-5-yl)acrylic Acid (15): Isolated as the trifluoroacetate salt after *t*Bu ester removal from **14**. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.84–7.76 (m, 4 H, =CH-Ar, 2 × H-*m*-Phe-O, H-4Bf), 7.56 (dd, $J_{6\text{-}7}$ = 8.5, $J_{6\text{-}4}$ = 1.5 Hz, 1 H, H-6Bf), 7.47 (d, 1 H, H-7Bf), 7.17 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*o*-Phe-O), 6.49 (d, J_{trans} = 16.0 Hz, 1 H, =CH-C=O), 4.46–4.41 (m, 2 H, CH_2-O), 3.67–3.61 (m, 2 H, CH_2-N), 3.02 (s, 6 H, NMe_2), 2.46 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 170.7 (C=O), 159.1 (C_q-phenol), 156.2 (C_q-Bf), 152.9 (C_q-Bf), 147.0 (=CH-Ar), 133.1 (C_q-Bf), 130.7 (C_q-phenol), 129.4 (2 × C-*m*-Ph-O), 126.1 (C_q-Bf), 125.6 (C-6Bf), 120.7 (C-4Bf), 117.8 (=CH-C=O), 116.0 (2 × C-*o*-Ph-O), 112.2 (C-7Bf), 111.5 (C_q-Bf), 63.2 (CH_2-O), 57.7 (CH_2-N), 43.9 (NMe_2), 9.3 (CH_3-Bf) ppm. HRMS (ESI): calcd. for $C_{22}H_{24}NO_4^+$ $[M + H]^+$ 366.16998, found 366.17028.

3-(2-{4-[2-(Dimethylamino)ethoxy]phenyl}-3-methylbenzofuran-5-yl)propanoic Acid (17): Isolated as the trifluoroacetate salt after *t*Bu ester removal from **16**. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.74 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.37 (d, $J_{4\text{-}6}$ = 1.1 Hz, 1 H, H-4Bf), 7.33 (d, $J_{7\text{-}6}$ = 8.4 Hz, 1 H, H-7Bf), 7.15–7.10 (m, 3 H, 2 × H-*o*-Phe-O, H-6Bf), 4.40–4.36 (m, 2 H, CH_2-O), 3.64–3.58 (m, 2 H, CH_2-N), 3.03–2.97 (m, 8 H, CH_2-Ar, NMe_2), 2.64 (t, $J_{CH2\text{-}CH2}$ = 7.7 Hz, 2 H, CH_2-C=O), 2.39 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 176.8 (C=O), 158.8 (C_q-phenol), 153.8 (C_q-Bf), 151.9 (C_q-Bf), 136.4 (C_q-Bf), 132.6 (C_q-phenol), 129.2 (2 × C-*m*-Ph-O), 126.6 (C_q-Bf), 125.8 (C-6Bf), 119.5 (C-4Bf), 115.9 (2 × C-*o*-Ph-O), 111.4 (C-7Bf), 111.2 (C_q-Bf), 63.2 (CH_2-O), 57.7 (CH_2-N), 43.9 (NMe_2), 37.4 (CH_2-C=O), 32.1 (CH_2-Ar), 9.40 (CH_3-Bf) ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NO_4^+$ $[M + H]^+$ 368.18563, found 368.18594.

(*E*)-3-(2-{4-[3-(Dimethylamino)propoxy]phenyl}-3-methylbenzofuran-5-yl)acrylic Acid (19): Isolated as the trifluoroacetate salt after *t*Bu ester removal from **18**. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.83–7.71 (m, 4 H, =CH-Ar, 2 × H-*m*-Phe-O, H-4Bf), 7.55 (dd, $J_{6\text{-}7}$ = 8.6, $J_{6\text{-}4}$ = 1.5 Hz, 1 H, H-6Bf), 7.46 (d, 1 H, H-7Bf), 7.08 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*o*-Phe-O), 6.49 (d, J = 15.9 Hz, 1 H, =CH-C=O), 4.18 (t, $J_{CH2\text{-}CH2}$ = 5.7 Hz, 2 H, CH_2-O), 3.39 (t, 2 H, CH_2-N), 2.96 (s, 6 H, NMe_2), 2.44 (s, 3 H, CH_3Bf), 2.31–2.19 (m, 2 H, CH_2-CH_2-CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 170.7 (C=O), 159.9 (C_q-phenol), 156.2 (C_q-Bf), 153.1 (C_q-Bf), 147.1 (=CH-Ar), 133.2 (C_q-Bf), 130.6 (C_q-phenol), 129.2 (2 × C-*m*-Ph-O), 125.4 (C-6Bf), 125.4 (C_q-Bf), 120.6 (C-4Bf), 117.7 (=CH-C=O), 115.8 (2 × C-*o*-Ph-O), 112.1 (C-7Bf), 111.1 (C_q-Bf), 66.0 (CH_2-O), 56.8 (CH_2-N), 43.6 (NMe_2), 25.7 (CH_2-CH_2-CH_2), 9.3 (CH_3-Bf) ppm. HRMS (ESI): calcd. for $C_{23}H_{28}NO_4^+$ $[M + H]^+$ 382.20128, found 382.20177.

3-(2-{4-[3-(Dimethylamino)propoxy]phenyl}-3-methylbenzofuran-5-yl)propanoic Acid (21): Isolated as the trifluoroacetate salt after *t*Bu ester removal from **20**. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.75 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.40 (d, 1 H, H-4Bf), 7.35 (d, 1 H, H-7Bf), 7.15 (dd, $J_{6\text{-}7}$ = 8.4, $J_{6\text{-}4}$ = 1.7 Hz, 1 H, H-6Bf), 7.09 (d, 2 H, 2 × H-*o*-Phe-O), 4.19 (t, $J_{CH2\text{-}CH2}$ = 5.7 Hz, 2 H, CH_2-O), 3.39 (t, $J_{CH2\text{-}CH2}$ = 8.0 Hz, 2 H, CH_2-N), 3.03 (t, $J_{CH2\text{-}CH2}$ = 7.6 Hz, 2 H, CH_2-Ar), 2.96 (s, 6 H, NMe_2), 2.66 (t, 2 H, CH_2-C=O), 2.42 (s, 3 H, CH_3Bf), 2.31–2.21 (m, 2 H, CH_2-CH_2-CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 177.0 (C=O), 159.6 (C_q-phenol), 153.8 (C_q-Bf), 152.1 (C_q-Bf), 136.4 (C_q-Bf), 132.6 (C_q-phenol), 129.1 (2 × C-*m*-Ph-O), 125.9 (C_q-Bf), 125.7 (C-6Bf), 119.5 (C-4Bf), 115.8 (2 × C-*o*-Ph-O), 111.3 (C-7Bf), 110.9 (C_q-Bf), 66.0 (CH_2-O), 56.8 (CH_2-N), 43.7 (NMe_2), 37.5 (CH_2-C=O), 32.1 (CH_2-Ar), 25.7 (CH_2-CH_2-CH_2), 9.4 (CH_3-Bf) ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NO_4^+$ $[M + H]^+$ 382.20128, found 382.20177.

4-[5-Chloro-3-methylbenzofuran-2-yl]-phenoxy-2-hydroxy-3-dimethylaminopropane (25): Dimethylamine (33 % in EtOH, 0.1 mL, 0.56 mmol) was added to a solution of epoxide **23** (39.2 mg, 0.125 mmol) in anhydrous ethanol (2 mL) and the reaction was stirred at 80 °C for 1 h (TLC 6:4 Hex/EtOAc and 9:1 $CHCl_3$/MeOH+ 1 % TEA). The solvent and the excess of amine were evaporated at reduced pressure obtaining the crude product (44 mg) that was purified by flash chromatography (9:1 $CHCl_3$/MeOH + 1 % TEA). Desired product **25** was obtained as a white solid in 82 % yield (36.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.45 (d, $J_{4\text{-}6}$ = 2.1 Hz, 1 H, H4-Bf), 7.36 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H7-Bf), 7.20 (dd, 1 H, H6-Bf), 7.03 (d, 2 H, 2 × H-*o*-Phe-

O), 4.11 (m, 1 H, C*H*OH), 4.04 (d, J_{vic} = 4.9 Hz, 2 H, CH_2O), 2.59 (dd, J_{gem} = 12.2, J_{vic} = 9.9 Hz, 1 H, CH_2N), 2.43 (dd, J_{vic} = 3.6 Hz, 1 H, CH_2N), 2.40 (s, 3 H, CH_3-Bf), 2.36 (s, 6 H, NMe_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C_q), 152.4 (C_q), 152.1 (C_q), 132.9 (C_q), 128.3 (C-*m*-Ph-O), 128.0 (C_q), 124.1 (C6-Bf), 124.0 (C_q), 118.8 (C4-Bf), 114.9 (C-*o*-Ph-O), 111.8 (C7-Bf), 109.5 (C_q), 70.6 (CH_2O), 66.2 (CHOH), 61.9 (CH_2N), 45.7 (NMe_2), 9.5 (CH_3-Bf) ppm. MS (ESI+): calcd. for $C_{20}H_{22}ClNO_3$ $[M + H]^+$ 360.1, found 360.3.

1-[4-(5-Chloro-3-methylbenzofuran-2-yl)phenoxy]-3-(*N*-methylpiperazyl)propan-2-ol (26): To a solution of epoxide **23** (0.1 mmol) in dry EtOH (1 mL) 1-methylpiperazine (0.5 mmol) was added. The reaction was stirred for 2 h at 80 °C, monitoring by TLC (7:3 toluene/EtOAc and 9:1 $CHCl_3$/MeOH). The solvent was evaporated under vacuum and the crude purified by flash chromatography (8:2 $CHCl_3$/MeOH) to afford **26** in 58 % yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.46 (d, $J_{4\text{-}6}$ = 2.0 Hz, 1 H, H4-Bf), 7.36 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H7-Bf), 7.21 (dd, 1 H, H6-Bf), 7.03 (d, 2 H, 2 × H-*o*-Phe-O), 4.15 (m, 1 H, CHOH), 4.05 (d, J_{vic} = 4.9 Hz, 2 H, CH_2O), 2.81–2.56 (m, 10 H, CH_2N), 2.40 (s, 3 H, CH_3-Bf), 2.37 (s, 3 H, NMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C_q), 152.1 (C_q), 132.9 (C_q), 128.4 (C-*m*-Ph-O), 128.1 (C_q), 124.1 (C6-Bf), 118.9 (C4-Bf), 114.9 (C-*o*-Ph-O), 111.9 (C7-Bf), 109.6 (C_q), 70.4 (CH_2O), 65.6 (CHOH), 60.5 ($CH_2NCH_2CH_2NMe$), 55.0 ($CH_2NCH_2CH_2NMe$), 45.8 (NCH_3), 9.5 (CH_3-Bf) ppm. MS (ESI+): calcd. for $C_{23}H_{28}ClN_2O_3$ $[M + H]^+$ 415.2, found 415.5.

1-[4-(5-Chloro-3-methylbenzofuran-2-yl)phenoxy]-3-(cyclopropylamino)propan-2-ol (27): Epoxide **23** (20 mg, 63 µmol) was suspended in a solution of DCM/EtOH (0.6 mL, 9:1 ratio). Cyclopropylamine (13 µL, 0.19 mmol) was added to the reaction mixture. The reaction was stirred for 24 h at 40 °C. The reaction was followed by TLC chromatography (9:1:0.1 DCM/MeOH/TEA, R_f = 0.47). The solution was concentrated in vacuo. The crude material was purified by flash chromatography (96:4 $CHCl_3$/MeOH) leading to product **27** (13 mg, 23 µmol) in 60 % yield. ^1H NMR (400 MHz, CD_3OD): δ = 7.76 (d, $J_{o\text{-}m}$ = 8.5 Hz, 2 H, 2 × H-*m*-Phe-O), 7.53 (d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.41 (d, $J_{7\text{-}6}$ = 8.5 Hz, 2 H, H-7Bf), 7.23 (dd, 1 H, H-6Bf), 7.12 (d, 2 H, 2 × H-o-Phe-O), 4.36–4.29 (m, 1 H, CH-O), 4.15–4.06 (m, 2 H, CH_2-O), 3.88 (br. s, 1 H, NH), 3.43 (dd, J_{gem} = 12, J_{vic} = 2 Hz, 1 H, CH_2-N), 3.30–3.25 (m, 1 H, CH_2-N), 2.85–2.78 (m, 1 H, CH-N), 2.41 (s, 3 H, CH_3-Bf), 1.00–0.91 (m, 4 H, CH_2-cycle) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 160.0 (C_q), 153.5 (C_q), 153.3 (C_q), 134.0 (C_q), 129.3 (2 × C-*m*-Ph-O), 129.1 (C_q), 125.3 (C_q), 125.1 (C-6Bf), 119.7 (C-4Bf), 115.9 (2 × C-*o*-Ph-O), 112.7 (C-7Bf), 110.7 (C_q), 71.0 (CH_2-O), 66.3 (CH-O), 51.9 (CH_2-N), 31.5 (CH-N), 9.3 (CH_3-Bf), 4.3 (CH_2-cycle), 4.0 (CH_2-cycle) ppm. ESI-MS: calcd. for $C_{23}H_{27}ClNO_3$ $[M + H]^+$ 372.9, found 372.8.

1-[4-(5-Chloro-3-methylbenzofuran-2-yl)phenoxy]-3-(cyclopentylamino)propan-2-ol (28): Obtained from **23** and cyclopentylamine with the same procedure described above for **27**. The reaction was followed by TLC chromatography (6:4 Hex/EtOAc, R_f = 0.1). The solution was concentrated in vacuo. The crude reaction was purified by flash chromatography (97:3 $CHCl_3$/MeOH, R_f = 0.3) leading to product **28** (24 mg, 59 µmol) in 93 % yield. ^1H NMR (400 MHz, 9:1 CD_3OD:1,4-[D_8]dioxane): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.50 (d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.40 (d, $J_{7\text{-}6}$ = 8.8 Hz, 2 H, H-7Bf), 7.21 (dd, 1 H, H-6Bf), 7.10 (d, 2 H, 2 × H-o-Phe-O), 4.34–4.26 (m, 1 H, CH-O), 4.14–4.05 (m, 2 H, CH_2-O), 3.69–3.55 (m, 1 H, CH-N), 3.36–3.28 (m, 1 H, CH_2-N), 3.21–3.12 (m, 1 H, CH_2-N), 2.37 (s, 3 H, CH_3-Bf), 2.22–2.10 (m, 2 H, CH_2-cycle), 1.89–1.78 (m, 2 H, CH_2-cycle), 1.62 (m, 4 H, CH_2-cycle) ppm. ^{13}C NMR (100 MHz, 9:1 CD_3OD:1,4-[D_8]dioxane): δ = 160.2 (C_q), 153.6 (C_q), 153.5 (C_q), 134.2 (C_q), 129.4 (2 × C-*m*-Ph-O), 129.3 (C_q), 125.4 (C_q), 125.2 (C-6Bf), 119.9 (C-4Bf), 116.1 (2 × C-*o*-Ph-O), 112.9 (C-7Bf), 110.8 (C_q), 71.2 (CH_2-O), 67.0 (CH-O), 61.0 (CH-N), 50.6 (CH_2-N), 30.8 (CH_2-cycle), 30.7 (CH_2-cycle), 25.2 (CH_2-cycle), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{23}H_{27}ClNO_3$ $[M + H]^+$ 400.9, found 400.2.

1-Azido-3-[4-(5-chloro-3-methylbenzofuran-2-yl)phenoxy]-propan-2-ol (29): Epoxide **23** (39 mg, 0.12 mmol) was dissolved in 1,4-dioxane (0.7 mL). A solution of NaN_3 (24 mg, 0.37 mmol) and $Yb(OTf)_3$ (15.5 mg, 36 µmol) in H_2O (0.18 mL) was added and the solution was stirred for 5 d at 80 °C. The reaction was followed by TLC (7:3 Hex/EtOAc, R_f = 0.39). The reaction mixture was diluted with EtOAc, washed once with H_2O and once with brine. The organic layer was dried with Na_2SO_4 and concentrated in vacuum. The crude mixture was purified by flash chromatography (55:45 toluene/DCM, R_f = 0.3) leading to product **29** (34 mg, 97 µmol) in 81 % yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.47 (d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.37 (d, $J_{7\text{-}6}$ = 8.8 Hz, 2 H, H-7Bf), 7.21 (dd, 1 H, H-6Bf), 7.03 (d, 2 H, H-*o*-Phe-O), 4.26–4.18 (m, 1 H, CH-O), 4.08 (d, J_{vic} = 5 Hz, 2 H, CH_2-O), 3.60 (dd, J_{gem} = 12.7, J_{vic} = 4.7 Hz, 1 H, CH_2-N_3), 3.54 (dd, J_{gem} = 12.7, J_{vic} = 6.0 Hz, 1 H, CH_2-N_3), 2.41 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3 (C_q), 132.8 (C_q), 128.4 (2 × C-*m*-Ph-O), 128.1 (C_q), 124.6 (C_q), 124.2 (C-6Bf), 118.9 (C-4Bf), 114.9 (2 × C-*o*-Ph-O), 111.9 (C-7Bf), 109.8 (C_q), 69.4 (CH-O), 69.3 (CH_2-O), 53.5 (CH_2-N_3), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{18}H_{17}ClN_3O_3$ $[M + H]^+$ 358.8, found 358.4.

1-Amino-3-[4-(5-chloro-3-methylbenzofuran-2-yl)phenoxy]-propan-2-ol (30): Azide **29** (20 mg, 56 µmol) was dissolved in MeOH (0.46 mL). Morpholine (1.3 µL, 15 µmol) and PtO_2 (1.3 mg, 2 µmol) were added to the solution. The reaction mixture was stirred for 1 h under H_2 atmosphere; the reaction progress was followed by TLC (8:2:0.2 $CHCl_3$/MeOH/AcOH, R_f = 0.49). The reaction mixture was filtered through a celite pad and concentrated in vacuum. The crude product was purified by flash chromatography (75:25:0.2 $CHCl_3$/MeOH/AcOH, R_f = 0.35) leading to product **30** (13 mg, 40 µmol) in 71 % yield. ^1H NMR (400 MHz, CD_3OD): δ = 7.71 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.50 (d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.39 (d, $J_{7\text{-}6}$ = 8.8 Hz, 2 H, H-7Bf), 7.20 (dd, 1 H, H-6Bf), 7.08 (d, 2 H, H-*o*-Phe-O), 4.06–4.00 (m, 2 H, CH_2-O), 3.99–3.92 (m, 1 H, CH-O), 2.96–2.84 (m, 1 H, CH_2-NH_2), 2.84–2.72 (m, 1 H, CH_2-NH_2), 2.38 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 160.5 (C_q), 153.7 (C_q), 153.4 (C_q), 134.1 (C_q), 129.3 (2 × C-*m*-Ph-O), 129.1 (C_q), 125.0 (C-6Bf), 125.0 (C_q), 119.7 (C-4Bf), 115.9 (2 × C-*o*-Ph-O), 112.7 (C-7Bf), 110.5 (C_q), 71.6 (CH-O), 71.4 (CH_2-O), 45.1 (CH_2-NH_2), 9.3 (Cp, CH_3-Bf) ppm. ESI-MS: calcd. for $C_{18}H_{19}ClNO_3$ $[M + H]^+$ 332.1, found 332.0.

3-[4-(5-Chloro-3-methylbenzofuran-2-yl)phenoxy]propan-1,2-diol (31): Epoxide **23** (20 mg, 0.064 mmol) was dissolved in 1,4-dioxane (0.3 mL). H_2O (75 µL) and 4 M solution of HCl in dioxane (32 µL) were added to the reaction mixture. The reaction was stirred for 5 h at 80 °C and its progress was followed by TLC chromatography (7:3 Hex/EtOAc, R_f = 0.4). NaOH was added until pH = 7 was reached. The reaction mixture was diluted with EtOAc and washed with H_2O. The water layer was extracted with EtOAc three times. The organic layer was dried with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash chromatography (8:2 Hex/EtOAc, R_f = 0.28) leading to product **31** (6 mg, 38 µmol) in 60 % yield. ^1H NMR (400 MHz, CD_3OD): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.51 (d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.40 (d, $J_{7\text{-}6}$ = 8.8 Hz, 2 H, H-7Bf), 7.22 (dd, 1 H, H-6Bf), 7.09 (d, 2 H, 2 × H-o-Phe-O), 4.13 (dd, J_{gem} = 9.3, J_{vic} = 3.9 Hz, 1 H, CH_2-O), 4.06–3.97 (m, 3 H, CH_2-O, CH-O), 3.71 (dd, J_{gem} = 11.2, J_{vic} = 5.3 Hz, 1 H, CH_2-OH), 3.67 (dd, J_{vic} = 5.3 Hz, 1 H, CH_2-OH), (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR

(100 MHz, CD_3OD): δ = 160.6 (Cq), 153.8 (Cq), 134.1 (Cq), 130.2 (Cq), 129.3 (2 × CH-*m*-Phe-O), 129.1 (Cq), 125.0 (C-6Bf), 124.9 (Cq), 119.7 (C-4Bf), 115.9 (2 × C-*o*-Phe-O), 112.7 (C-7Bf), 110.5 (Cq), 71.8 (CH-O), 70.4 (CH_2-O), 64.1 (CH_2-OH), 9.3 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{18}H_{18}ClO_4$ $[M + H]^+$ 333.1, found 333.2.

1-[4-(5-Bromo-3-methylbenzofuran-2-yl)phenoxy]-3-(*N*-methylpiperazyl)propan-2-ol (32): To a solution of the epoxide **24** (0.1 mmol) in dry EtOH (1 mL) 1-methylpiperazine was added (0.5 mmol). The reaction was stirred for 2 h at 80 °C, monitoring by TLC (7:3 Toluene/EtOAc and 9:1 $CHCl_3$/MeOH). The solvent was evaporated under vacuum and the crude purified by flash chromatography (95:5 $CHCl_3$/MeOH) to afford **32** in 45 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $J_{o\text{-}m}$ = 9.2 Hz, 2 H, 2 × H-*m*-Phe-O), 7.62 (d, $J_{4\text{-}6}$ = 1.5 Hz, 1 H, H4-Bf), 7.35 (dd, $J_{6\text{-}7}$ = 8.4 Hz, 2 H, H6Bf), 7.32 (d, 1 H, H7-Bf), 7.03 (d, 2 H, 2 × H-*m*-Phe-O), 4.18–4.12 (m, 1 H, CH-O), 4.05 (d, J_{vic} = 4.9 Hz, 2 H, CH_2-O), 2.18–2.16 (br. s, 2 H, NC$H_2$$CH_2$NMe), 2.60–2.58 (m, 8 H, CH_2NCH_2CH_2NMe), 2.40 (s, 3 H, CH_3-N), 2.39 (s, 3 H, CH_3Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C_q), 152.5 (C_q), 152.2 (C_q), 133.5 (C_q), 128.4 (2 × C-*m*-Phe-O), 126.8 (C-6Bf), 124.1 (C_q), 122.0 (C-4Bf), 115.5 (C_q), 115.0 (2 × C-*m*-Phe-O), 112.4 (C-7Bf), 70.4 (CH_2-O), 65.7 (CH-OH), 60.5 (CH_2NC$H_2$$CH_2$NMe), 55.0 ($CH_2NCH_2$$CH_2$NMe), 45.7 ($CH_3$-N), 9.3 ($CH_3$Bf) ppm. ESI-MS: calcd. for $C_{23}H_{28}BrN_2O_3$ $[M + H]^+$ 460.4, found 459.9.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxyacetylmorpholine (34): To a solution of **33** (19.7 mg, 0.062 mmol) in dry THF (1.2 mL) were added EDC•HCl (15.5 mg, 0.081 mmol) and TEA (22 µL, 0.155 mmol) and the reaction was stirred at 30 °C under nitrogen atmosphere for 20 h. Morpholine (11 µL, 0.124 mmol) was added and the reaction stirred for 2 h at 45 °C. After the reaction was complete (TLC 95:5:0.1 $CHCl_3$/MeOH/HCOOH) the reaction mixture was diluted with Et_2O and washed with 0.1 M HCl. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (4:6 Hex/EtOAc) to render desired product **34** (8.4 mg) as a white solid in 35 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.0 Hz, 2 H, 2 × CH-*m*-Ph-O), 7.47 (s, 1 H, H-4Bf), 7.37 (d, $J_{7\text{-}6}$ = 8.4 Hz, 1 H, H-7Bf), 7.21 (d, 1 H, H-6Bf), 7.06 (d, 2 H, 2 × C-*o*-Ph-O), 4.76 (s, 2 H, CH_2OAr), 3.66 (m, 8 H, CH_2-Morf), 2.41 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (C=O), 157.8 (C_q), 152.2 (C_q), 132.8 (C_q), 128.5 (2 × C-*m*-Ph-O), 128.1 (C_q), 124.9 (C_q), 124.2 (C-6Bf), 118.9 (C-4Bf), 115.0 (2 × C-*o*-Ph-O), 111.9 (C-7Bf), 67.8 (CH_2OAr), 67.0 (2 × CH_2O), 46.1 (CH_2N), 42.6 (CH_2N), 9.5 (CH_3-Bf) ppm. HRMS (ESI): calcd. for $C_{21}H_{20}ClNNaO_4$ $[M + Na]^+$ 408.0979, found 408.1089.

4-[5-Chloro-3-methylbenzofuran-2-yl]-phenoxyacetyl-1-methylpiperazine (35): Oxalyl chloride (0.27 mmol, 2.0 M solution in dry DCM) was added to a solution of **33** (28.8 mg, 0.091 mmol) in dry DCM (0.9 mL) and the reaction was stirred at reflux under nitrogen atmosphere for 2 h. The solvent was co-evaporated with toluene at reduced pressure, the crude reaction was re-dissolved in dry DCM (0.1 mL) and 1-methylpiperazine (300 µL, 2.7 mmol) was added. The reaction was stirred at 40 °C overnight (TLC 9:1:0.1 $CHCl_3$/MeOH/TEA). The solvent was evaporated in vacuo and the crude product was purified using an automatic system (SiO_2, DCM/MeOH gradient from 0 to 14 % MeOH) to afford desired product **35** (28 mg) as a white solid in 78 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × CH-*m*-Ph-O), 7.46 (d, $J_{4\text{-}6}$ = 2.1 Hz, 1 H, H-4Bf), 7.36 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H-7Bf), 7.21 (dd, 1 H, H-6Bf), 7.06 (d, 2 H, 2 × CH-*o*-Ph-O), 4.75 (s, 2 H, CH_2OAr), 3.70 (m, 2 H, CH_2N), 3.66 (m, 2 H, CH_2N), 2.46 (m, 4 H, 2 × CH_2NMe), 2.40 (s, 3 H, CH_3-Bf), 2.34 (s, 3 H, NMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3 (C=O), 157.9 (C_q), 152.2 (C_q), 132.8 (C_q), 128.5 (2 × C-*m*-Ph-O), 128.1 (C_q), 124.8 (C_q), 124.2 (C-6Bf), 118.9 (C-4Bf), 115.0 (2 × C-*o*-Ph-O), 111.9 (C-7Bf), 109.9 (C_q), 67.8 (CH_2OAr), 55.1 (CH_2N), 54.6 (CH_2N), 46.0 (NCH_3), 45.1 (CH_2NMe), 41.9 (CH_2NMe), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{22}H_{24}ClN_2O_3$ $[M + H]^+$ 399.1475, found 399.1793.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl 2,3,4-Tri-*O*-benzoyl-6-azido-α-D-mannopyranoside (37): Azide **36**[14] (0.17 g, 0.25 mmol) and phenol **1a** (58 mg, 0.23 mmol) were co-evaporated three times with toluene and dissolved in dry DCM (4.6 mL) under nitrogen atmosphere. To the solution freshly activated molecular sieves (4 Å) were added. The reaction mixture was cooled to –30 °C and TMSOTf (8.3 µL, 46 µmol) was slowly added. The reaction was stirred for 30 min and followed by TLC (9:1 toluene/EtOAc, R_f = 0.91). To the solution TEA (0.13 mL) was added. The reaction was warmed to room temperature and concentrated in vacuo. The crude material was purified by flash chromatography (8:1:1 Hex/EtOAc/toluene) leading to product **37** (87 mg, 0.13 mmol) in 50 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, $J_{o\text{-}m}$ = 7.6 Hz, 2 H, 2 × *o*-CH-Bz), 7.98 (d, $J_{o\text{-}m}$ = 7.6 Hz, 2 H, 2 × *o*-CH-Bz), 7.87 (d, $J_{o\text{-}m}$ = 7.8 Hz, 2 H, 2 × *o*-CH-Bz), 7.81 (d, $J_{p\text{-}m}$ = 9.0 Hz, 2 H, 2 × *m*-CH-Bz), 7.70–7.63 (m, 1 H, *p*-CH-Bz), 7.57–7.50 (m, 3 H, *p*-CH-Bz, 2 × *m*-CH-Bz), 7.49 (d, $J_{4\text{-}6}$ = 2.2 Hz, 1 H, H-4Bf), 7.47–7.44 (m, 1 H, *p*-CH-Bz), 7.42–7.37 (m, 2 H, 2 × *m*-CH-Bz), 7.39 (d, $J_{7\text{-}6}$ = 8.5 Hz, 1 H, H-7Bf), 7.34 (d, 2 H, H-*o*-Phe-O), 7.32–7.27 (m, 2 H, 2 × *m*-CH-Bz), 7.23 (dd, 1 H, H-6Bf), 6.14 (dd, $J_{3'\text{-}4'}$ = 10.0, $J_{3'\text{-}2'}$ = 3.2 Hz, 1 H, H-3), 6.00 (dd, $J_{4'\text{-}5'}$ = 10.0 Hz, 1 H, H-4′), 5.93–5.90 (m, 1 H, H-2′), 5.9 (d, $J_{1'\text{-}2'}$ = 1.9 Hz, 1 H, H-1′), 4.43–4.37 (m, 1 H, H-5′), 3.54 (dd, $J_{5'\text{-}6'a}$ = 6, $J_{6'a\text{-}6'b}$ = 13.3 Hz, 1 H, H-6′a), 3.45 (dd, $J_{5'\text{-}6'b}$ = 2.5 Hz, 1 H, H-6′b), 2.44 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6 (C=O Bz), 165.5 (C=O), 155.6 (C_q Bf), 152.1 (C_q Bf), 151.8 (C_q Bf), 133.8 (*p*-CH-Bz), 133.7 (*p*-CH-Bz), 133.4 (*p*-CH-Bz), 132.7 (C_q), 130.0 (*o*-CH-Bz), 129.9 (*o*-CH-Bz), 129.8 (*o*-CH-Bz), 129.0 (C_qBz), 128.9 (C_qBz), 128.8 (*m*-CH-Bz), 128.7 (C_qBz), 128.6 (*m*-CH-Bz), 128.4 (C-*m*-Phe-O), 128.0 (C_q Bf), 126.0 (C_q Bf), 124.3 (C-6Bf), 118.9 (C-4Bf), 116.7 (C-*o*-Phe-O), 111.9 (C-7Bf), 110.2 (C_q Bf), 95.7 (C-1′), 71.2 (C-5′), 70.1 (C-2′), 69.5 (C-3′), 67.4 (C-4′), 51.2 (C-6), 9.4 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{42}H_{32}ClN_3NaO_9$ $[M + Na]^+$ 781.2, found 781.1.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl 6-Azido-α-D-mannopyranoside (38): Compound **37** (20 mg, 26 µmol) was dissolved in MeOH (0.26 mL) under nitrogen atmosphere. To the reaction mixture MeONa (3 mg, 53 µmol) was added. The reaction was stirred for 2.5 h and was followed by TLC (7:3 Hex/EtOAc). The solution was diluted with MeOH and treated with Amberlite IR120 to reach pH = 7. The crude product was purified by flash chromatography (96:4 DCM/MeOH, R_f = 0.28) leading to product **38** (7 mg, 17 µmol) in 79 % yield. $[\alpha]_D^{25}$ = +81 (*c* = 0.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.74 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, H-*m*-Phe-O), 7.50 (d, $J_{4\text{-}6}$ = 2.0 Hz, 1 H, H-4Bf), 7.40 (d, $J_{7\text{-}6}$ = 8.7 Hz, 1 H, H-7Bf), 7.26 (d, 2 H, H-*o*-Phe-O), 7.21 (d, 1 H, H-6Bf), 5.59 (d, $J_{1\text{-}2}$ = 1.6 Hz, 1 H, H-1′), 4.07 (dd, $J_{2'\text{-}3'}$ = 3.4 Hz, 1 H, H-2′), 3.92 (dd, $J_{3'\text{-}4'}$ = 8.8 Hz, 1 H, H-3′), 3.78–3.67 (m, 2 H, H-4′,H-5′), 3.50–3.40 (m, 2 H, H-6′), 2.44 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 157.4 (C_q), 153.2 (C_q), 133.8 (C_q), 129.1 (C-*m*-Phe-O), 129.0 (C_q), 126.1 (C_q), 125.0 (C-6Bf), 119.6 (C-4Bf), 117.5 (C-*m*-Phe-O), 112.6 (C-7Bf), 110.8 (C_q), 99.4 (C-1′), 74.5 (C-5′), 72.0 (C-3′), 71.5 (C-2′), 69.0 (C-4′), 52.6 (C-6′), 9.4 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{21}H_{21}ClN_3NaO_9$ $[M + H]^+$ 446.1, found 446.5.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl 2,3,4-Tri-*O*-acetyl-6-azido-β-D-glucopyranoside (40): 2,3,4-*O*-Acetyl-6-azido-α-D-glucopyranosyl bromide **39**[15] (189 mg, 0.48 mmol) and benzofuran **1a** (40 mg, 0.16 mmol) were diluted in $CHCl_3$ (1.6 mL). To the reaction mixture, Bu_4NHSO_4 (27 mg, 0.08 mmol) was added, followed

by K_2CO_3 (132.7 mg, 138.1 mmol) and water (6.63 μL, 18 mmol). The conversion was detected through TLC (7:3 Hex/EtOAc, R_f = 0.35). After 15 h of stirring, a change in color from yellow to brown was observed and the reaction was diluted with $CHCl_3$. 1 M HCl was added until acidic pH. The organic layer was extracted with $NaHCO_3$ (2 × 20 mL), dried with Na_2SO_4 and concentrated in vacuo. Desired product **40** (35 mg, 0.06 mmol) was purified by flash chromatography (8:2 Hex/EtOAc) and obtained in 40 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, H-*m*-Phe-O), 7.48 (d, $J_{4\text{-}6}$ = 2.0 Hz, 1 H, H-4Bf), 7.37 (d, $J_{7\text{-}6}$ = 8.8 Hz, 1 H, H-7Bf), 7.22 (d, 1 H, H-6Bf), 7.18 (d, 2 H, H-*o*-Phe-O), 5.34–5.29 (m, 2 H, H-2′, H-3′), 5.18–5.14 (m, 1 H, H-1′), 5.10–5.03 (m, 1 H, H-4′), 3.95–3.88 (m, 1 H, H-5′), 3.51 (dd, $J_{5'\text{-}6'a}$ = 2.4, $J_{6'a\text{-}6'b}$ = 11 Hz, 1 H, H-6′a), 3.43 (dd, $J_{5'\text{-}6'b}$ = 8 Hz, 1 H, H-6′b), 2.41 (s, 3 H, CH_3-Bf), 2.09 (s, 3 H, $OCOCH_3$), 2.08 (s, 3 H, $OCOCH_3$), 2.05 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (C_q=O), 169.4 (C_q=O), 169.3 (C_q=O), 156.7 (C_q), 152.1 (C_q), 151.8 (C_q), 132.7 (C_q), 128.3 (C-*m*-Ph-O), 128.1 (C_q), 126.3 (C_q), 124.3 (C-6Bf), 119.0 (C-4Bf), 117.2 (C-*o*-Ph-O), 111.9 (C-7Bf), 110.3 (C_q), 98.9 (C-1′), 74.3 (C-5′), 72.5 (C-3′), 71.3 (C-2′), 71.0 (C-4′), 30.5 (C-6′), 20.7 (3 × CH_3-Ac), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{27}H_{26}ClN_3NaO_9$ $[M + Na]^+$ 595.1, found 594.9.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl 6-Azido-β-D-glucopyranoside (41): Compound **40** (37 mg, 0.06 mmol) was suspended in MeOH (900 μL) at 40 °C under nitrogen atmosphere. A 1 M solution of MeONa in MeOH (180 μL, 0.18 mmol) was added. The reaction was followed by TLC (9:1 $CHCl_3$/MeOH, R_f = 0.37) After stirring at 40 °C for 3 d, the reaction was quenched with 1 M acetic acid in MeOH (189 μL, 0.18 mmol) and concentrated in vacuo. DCM was added to the crude and after centrifugation, the liquid phase containing all the impurities was pipetted out. The resulting pellet was re-suspended in MeOH and stirred at 50 °C for 5 min before centrifuging. Unreacted starting material (**40**, 4 mg) was recovered in the supernatant. The remaining pellet contained final product **41**, obtained in 64 % yield (17 mg, 0.038 mmol) and sufficient purity, as judged by ^{1}H NMR ([D$_6$]acetone). $[\alpha]_D^{25}$ = −58 (*c* = 0.1, acetone). ^{1}H NMR [400 MHz, $(CD_3)_2CO$]: δ = 7.79 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, H-*m*-Phe-O), 7.62 (d, $J_{4\text{-}6}$ = 2.5 Hz, 1 H, H-4Bf), 7.51 (d, $J_{7\text{-}6}$ = 8.8 Hz, 1 H, H-7Bf), 7.35–7.24 (m, 3 H, H-*o*-Phe-O, H-6Bf), 5.13 (d, $J_{1'\text{-}2'}$ = 4.6 Hz, 1 H, H-1′), 3.91 (d, $J_{5'\text{-}6'a}$ = 2.0, $J_{6'a\text{-}6'b}$ = 11.0 Hz, 1 H, H-6′a), 3.85–3.74 (m, 1 H, H-5′), 3.66–3.50 (m, 3 H, H-2′, H-3′, H-6′), 3.49–3.38 (m, 1 H, H-4′), 2.46 (s, 3 H, CH_3-Bf) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = 158.9 (C_q), 133.7 (C_q), 128.9 (C-*m*-Ph-O), 128.6 (C_q), 125.6 (2 × C_q), 125.0 (C-6Bf), 119.8 (C-4Bf), 117.8 (C-*o*-Ph-O), 112.8 (C-7Bf), 110.8 (C_q), 101.6 (C-1′), 77.5 (C-3′), 76.6 (C-5′), 74.6 (C-2′), 73.2 (C-4′), 45.5 (C-6′), 9.3 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{21}H_{20}ClNaN_3O_6$ $[M + Na]^+$ 468.9, found 468.7.

2,3,4-Tri-*O*-acetyl-β-L-arabinopyranosyl Bromide 50:[16] $La(OTf)_3$ (12 mg, 0.02 mmol) was added to a suspension of L-arabinose (1.0 g, 6.7 mmol) in acetic anhydride (2.6 mL) and the reaction was stirred at 30 °C under nitrogen atmosphere for 1 h (TLC 6:4 Hex/EtOAc). The reaction mixture was diluted with DCM, the organic phase washed with $NaHCO_3$ and brine and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product (547 mg) was purified using an automatic system (SiO_2, Hex/EtOAc gradient) obtaining the 1,2,3,4-tetra-*O*-acetyl-α/β-L-arabinopyranoside [L-Ara(OAc)$_4$] as a white solid in α:β ratio of 1:1 (1.3 g, 60 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (d, $J_{1\text{-}2}$ = 3.1 Hz, 1 H, H-1β), 5.67 (d, $J_{1\text{-}2}$ = 7.0 Hz, 1 H, H-1α), 5.41–5.35 (m, 3 H, H-2β, H-3β, H-4β), 5.33–5.27 (m, 2 H, H-2α, H-4α), 5.12 (dd, $J_{2\text{-}3}$ = 9.1, $J_{3\text{-}4}$ = 3.5 Hz, 1 H, H-3α), 4.11–4.02 (m, 2 H, H-5bα, H-5bβ), 3.87–3.75 (m, 2 H, H-5aα, H-5aβ), 2.22–2.01 (m, 24 H, $OCOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 ($OCOCH_3$), 170.3 ($OCOCH_3$), 170.2 ($OCOCH_3$), 169.9 ($OCOCH_3$), 169.9 ($OCOCH_3$), 169.4 ($OCOCH_3$), 169.1 ($OCOCH_3$), 169.1 ($OCOCH_3$), 92.1 (C-1α), 90.2 (C-1β), 69.9 (C-3α), 68.5, 68.1, 67.1, 67.01, 66.7, (C-2β, C-3β, C-4β, C-2α, C-4α), 63.9, 62.8 (C-5β, C-5α), 20.9–20.6 ($OCOCH_3$) ppm. HBr (33 % in AcOH, 21.9 mL, 12.3 mmol) was added dropwise to L-Ara(OAc)$_4$ (1.3 g, 4.1 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and after 15 min DCM was added (2.4 mL). The reaction was then stirred at room temperature for 25 min (TLC 65:35 Hex/EtOAc). The reaction was quenched adding ice and DCM at 0 °C. The organic phase was washed with cold water and cold saturated $NaHCO_3$ solution (3 × 10 mL) and finally dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product **50** (1.1 g) was obtained in 79 % yield as the single β isomer and used without further purification (the product is not stable on silica). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1 H, H-1), 5.39 (m, 2 H, H-3, H-4), 5.08 (m, 1 H, H-2), 4.20 (d, $J_{5eq\text{-}5ax}$ = 13.3 Hz, 1 H, H-5eq), 3.93 (dd, $J_{5ax\text{-}4}$ = 1.9 Hz, 1 H, H-5ax), 2.15 (s, 3 H, $OCOCH_3$), 2.11 (s, 3 H, $OCOCH_3$), 2.02 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 ($OCOCH_3$), 170.2 ($OCOCH_3$), 169.9 ($OCOCH_3$), 89.8 (C-1), 68.0, 67.9, 67.7 (C-3, C-2, C-4), 64.8 (C-5), 20.9 ($OCOCH_3$), 20.8 ($OCOCH_3$), 20.7 ($OCOCH_3$) ppm.

2,3,4-Tri-*O*-acetyl-β-D-arabinopyranosyl Bromide: Synthesized as described above for the L-enantiomer with similar yields and identical spectroscopic data.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy α-L-Arabinopyranoside (44): $TBAHSO_4$ (20 mg, 0.056 mmol), potassium carbonate (98.7 mg, 0.71 mmol) and water [5 μL, 5 % w/w in K_2CO_3] were added to a mixture of **1a** (30.7 mg, 0.12 mmol) and 2,3,4-tri-*O*-acetyl-β-L-arabinopiranosyl bromide **50** (80.5 mg, 0.24 mmol) in chloroform (0.6 mL). The reaction was vigorously stirred at room temperature for 3 h (TLC 6:4 Hex/EtOAc). The reaction mixture was diluted with chloroform, the organic phase was washed with 0.1 M HCl aq., saturated $NaHCO_3$ solution and brine. The organic phase was dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product (97.1 mg) was purified using an automatic system (SiO_2, Hex/EtOAc gradient) to render the desired product (50.8 mg) as a white solid in 83 % yield. $[\alpha]_D^{25}$ = +24 (*c* = 0.5, DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $J_{o\text{-}m}$ = 8.8 Hz, 2 H, 2 × H-*m*-Phe-O), 7.47 (d, $J_{4\text{-}6}$ = 2.1 Hz, 1 H, H-4Bf), 7.37 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H-7Bf), 7.22 (dd, 1 H, H-6Bf), 7.12 (d, 2 H, 2 × H-*o*-Phe-O), 5.46 (dd, $J_{1'\text{-}2'}$ = 8.7, $J_{3'\text{-}2'}$ = 6.3 Hz, 1 H, H-2′), 5.39–5.31 (m, 1 H, H-4′), 5.23–5.12 (m, 2 H, H-1′, H-3′), 4.15 (dd, $J_{5'ax\text{-}5'eq}$ = 12.8, $J_{4'\text{-}5'eq}$ = 4.1 Hz, 1 H, H-5′eq), 3.79 (dd, $J_{4'\text{-}5'ax}$ = 2.1 Hz, 1 H, H-5′ax), 2.41 (s, 3 H, CH_3 Bf), 2.16 (s, 3 H, $OCOCH_3$), 2.11 (s, 3 H, $OCOCH_3$), 2.10 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 ($OCOCH_3$), 170.3 ($OCOCH_3$), 169.6 ($OCOCH_3$), 156.7 (C_q), 152.2 (C_q), 151.9 (C_q), 132.7 (C_q), 128.4 (C-*m*-Ph-O), 128.1 (C_q), 126.1 (C_q), 124.4 (C-6Bf), 119.0 (C-4Bf), 117.1 (C-*o*-Ph-O), 112.0 (C-7Bf), 110.2 (C_q), 98.7 (C-1′), 69.8 (C-3′), 69.0 (C-2′), 67.2 (C-4′), 62.8 (C-5′), 21.0 ($OCOCH_3$), 20.9 ($OCOCH_3$), 20.9 ($OCOCH_3$), 9.5 (CH_3-Bf) ppm. ESI-MS: calcd. for $C_{26}H_{25}ClKO_9$ $[M + K]^+$ 555.2, found 554.9. An aliquot of 1 M MeONa in MeOH (200 μL) was added to a solution of 4-[5-chloro-3-methylbenzofuran-2-yl]phenoxy 2,3,4-triacetyl-α-L-arabinopyranoside (50.7 mg, 0.098 mmol) in MeOH (0.8 mL). The reaction was stirred under nitrogen atmosphere at room temperature for 1 h (TLC 6:4 Hex/EtOAc) and then quenched with Amberlite IR-120 H^+. The resin was filtered off, the solvent was evaporated in vacuo and the crude product (43.5 mg) was purified using an automatic system (SiO_2, DCM/MeOH gradient from 0 to 25 % MeOH) to render desired product **44** (28.1 mg) as a white solid in 73 % yield. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.74 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.53 (d, $J_{4\text{-}6}$ = 2.0 Hz, 1 H, H4-Bf), 7.42 (d, $J_{7\text{-}6}$ = 8.6 Hz, 1 H, H7-Bf), 7.25–7.18 (m, 3 H, H6-Bf, 2 × H-*o*-Phe-O), 4.94 (d, $J_{1'\text{-}2'}$ = 7.2 Hz, 1 H, H-1′), 3.96 (dd, $J_{5'eq\text{-}5'ax}$ = 12.4, $J_{5'eq\text{-}4'}$ = 2.8 Hz, 1 H, H-5′eq), 3.90 (m, 1

H, H-4′), 3.86 (dd, $J_{3'-2'}$ = 9.0 Hz, 1 H, H-2′), 3.75 (d, 1 H, H-5′ax), 3.67 (dd, $J_{3'-4'}$ = 3.5 Hz, 1 H, H-3′), 2.40 (s, 3 H, CH_3 Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.1 (C_q), 153.5 (C_q), 153.4 (C_q), 134.0 (C_q), 129.2 (C_q), 129.1 (C-*m*-Ph-O), 126.2 (C_q), 125.2 (C6-Bf), 119.8 (C4-Bf), 118.0 (C-*o*-Ph-O), 112.8 (C7-Bf), 111.0 (C_q), 102.5 (C-1′), 74.1 (C-3′), 72.2 (C-2′), 69.6 (C-4′), 67.2 (C-5′), 9.3 (CH_3 Bf) ppm. HRMS: calcd. for $C_{20}H_{19}ClNaO_6$ $[M + Na]^+$ 413.07624, found 413.07695. $[\alpha]_D^{25}$ = –9.2 (*c* = 0.1, MeOH).

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy α-D-Arabinopyranoside (45): Synthesized as described above for the L-enantiomer with similar yields and identical spectroscopic data.

1,2,3,4-Tetra-*O*-benzoyl-α/β-L-lyxopyranose:[25] Benzoyl chloride (3 mL, 26.7 mmol) was added dropwise to a solution of L-Lyxose (501.7 mg, 3.3 mmol) in pyridine (8 mL) at 0 °C under nitrogen atmosphere. DMAP (40 mg, 0.33 mmol) was added and the reaction was warmed to room temperature and stirred for 2 h (TLC 7:3 Hex/EtOAc). The reaction mixture was quenched with ice and diluted with EtOAc. The organic phase was washed with 2 M HCl (2 × 30 mL), water (1 × 30 mL), saturated $NaHCO_3$ solution (1 × 40 mL) and brine (1 × 30 mL). The organic phase was dried with anhydrous Na_2SO_4, the solvent was evaporated in vacuo and the crude product (2.5 g) was purified using an automatic system (SiO_2, Hex/EtOAc gradient from 0 to 60 % EtOAc) to render the desired product (1.8 g) as a white solid in 73:27 α:β ratio (from H^1 ^{1}H-NMR signal ratio) in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–7.27 (m, 20 H, CH-Bz), 6.66 (d, $J_{1\text{-}2}$ = 3.5 Hz, 1 H, H-1β), 6.53 (d, $J_{1\text{-}2}$ = 3.1 Hz, 1 H, H-1α), 6.07 (dd, $J_{3\alpha\text{-}4\alpha}$ = 9.3, $J_{3\alpha\text{-}2\alpha}$ = 3.5 Hz, 1 H, H-3α), 5.96–5.90 (m, 2 H, H-2β, H-3β), 5.89 (t, 1 H, H-2α), 5.81 (dt, $J_{4\alpha\text{-}5\alpha ax}$ = 9.2, $J_{4\alpha\text{-}5\alpha eq}$ = 5.0 Hz, 1 H, H-4α), 5.55 (m, 1 H, H-4β), 4.61 (dd, $J_{5\beta eq\text{-}5\beta ax}$ = 13.0, $J_{5\beta eq\text{-}4\beta}$ = 2.4 Hz, 1 H, H-5βeq), 4.37 (dd, $J_{5\alpha eq\text{-}5\alpha ax}$ = 11.5 Hz, 1 H, H-5αeq), 4.11–4.01 (m, 1 H, H-5αax, H-5βax) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 165.7, 165.5, 165.5, 165.4, 165.2, 164.4 (C=O Bz), 134.1, 133.9, 133.8, 133.7, 133.7, 133.6, 130.3, 130.3, 130.2, 130.1, 130.0, 129.9, (CH-Bz), 129.5, 129.4, 129.2, 129.1, 128.9 (C_q Bz), 128.9, 128.8, 128.7, 128.7, 128.6, 128.6 (CH-Bz), 91.7 (C-1α), 90.2 (C-1β), 69.4, 69.4 (C-2α, C-3α), 69.0 (C-4β), 67. 7 (C-2β), 67.6 (C-4α), 66.6 (C-3β), 62.5 (C-5α), 60.8 (C-5β) ppm.

2,3,4-Tri-*O*-benzoyl-α/β-L-lyxopyranosyl Bromide:[25] HBr (33 % in AcOH, 2 mL, 35.3 mmol) was added dropwise to α/β-L-Lyx(OBz)$_4$ (1.0 g, 1.4 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and after 15 min DCM was added (0.8 mL). The reaction was then stirred at room temperature for 20 min (TLC 7:3 Hex/EtOAc). The reaction was quenched adding ice and DCM at 0 °C. The organic phase was washed with cold water and cold saturated $NaHCO_3$ solution (3 × 10 mL), dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product (680 mg) was obtained in 9:1 α:β ratio (from H^1 ^{1}H-NMR signal ratio) in 73 % yield and used without further purification (the product is not stable on silica). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32–7.27 (m, 15 H, CH-Bz), 6.82 (d, $J_{1\beta\text{-}2\beta}$ = 4.1 Hz, 1 H, H-1β), 6.54 (d, $J_{1\alpha\text{-}2\alpha}$ = 1.5 Hz, 1 H, H-1α), 6.29 (dd, $J_{3\alpha\text{-}2\alpha}$ = 3.5, $J_{3\alpha\text{-}4\alpha}$ = 10.3 Hz, 1 H, H-3α), 5.89 (dd, 1 H, H-2α), 5.86 (m, 1 H, H-3β), 5.84 (td, $J_{4\alpha\text{-}5\alpha ax}$ = 10.6, $J_{4\alpha\text{-}5\alpha eq}$ = 5.7 Hz, 1 H, H-4α), 5.69 (t, *J* = 4.2 Hz, 1 H, H-2β), 5.39 (m, 1 H, H-4β), 4.60 (dd, $J_{5\beta eq\text{-}5\beta ax}$ = 13, $J_{5\beta eq\text{-}4\beta}$ = 1 Hz, 1 H, H-5βeq), 4.39 (dd, $J_{5\alpha eq\text{-}5\alpha ax}$ = 11.3, $J_{5\alpha eq\text{-}4\alpha}$ = 5.7 Hz, 1 H, H-5αeq), 4.14 (m, 1 H, H-5βax), 4.09 (t, $J_{5\alpha ax\text{-}4\alpha}$ = 11.3 Hz, 1 H, H-5αax) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 165.5, 165.3, 165.2 (C=O Bz), 134.0, 134.0, 133.9, 133.8, 133.8, 133.5 (*p*-CH-Bz), 130.5, 130.2, 130.1, 130.0, 129.9 (*o*-CH-Bz), 129.1, 129.1, 129.1, 129.0, 128.9 (C_q Bz), 128.9, 128.8, 128.8, 128.7, 128.6, 128.5 (*m*-CH-Bz), 85.4 (C-1β), 84.5 (C-1α), 73.3 (C-2α), 68.9 (C-4β), 68.3 (C-3α), 67.1 (C-4α), 66.5 (C-3β), 66.3 (C-2β), 63.5 (C-5α), 61.4 (C-5β) ppm.

2,3,4-Tri-*O*-benzoyl-α/β-L-lyxopyranosyl-O-Box (53): AgOBox (534 mg, 2.2 mmol), 2,6-lutidine (225 µL, 1.9 mmol) and TBAI (28 mg, 0.08 mmol) were added to a solution of 2,3,4-tri-*O*-benzoyl-α/β-L-lyxopyranosyl bromide (580 mg, 1.1 mmol) in dry DCM (8.6 mL) under argon atmosphere. The reaction mixture was stirred at 50 °C for 2 h (TLC 8:2 Hex/EtOAc) and then diluted with DCM. The organic phase was washed with 0.1 M NaOH (2 × 10 mL), water (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried with anhydrous Na_2SO_4, the solvent was evaporated in vacuo and the crude product (150 mg) was purified using an automatic system (SiO_2, Hex/EtOAc gradient from 0 % to 40 % EtOAc) to afford the desired product (135.7 mg) in an 84:16 α:β ratio (from H^1 ^{1}H-NMR signal ratio) as a white solid in 24 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33–7.16 (m, 19 H, CH-Bz, CH OBox), 6.75 (d, $J_{1\beta\text{-}2\beta}$ = 4 Hz, 1 H, H-1β), 6.55 (d, $J_{1\alpha\text{-}2\alpha}$ = 2.6 Hz, 1 H, H-1α), 6.09 (dd, $J_{3\alpha\text{-}4\alpha}$ = 9.6, $J_{2\alpha\text{-}3\alpha}$ = 3.4 Hz, 1 H, H-3α), 5.98 (dd, 1 H, H-2α), 5.96 (m, 1 H, H-3β), 5.89 (m, 1 H, H-2β), 5.86 (td, $J_{4\alpha\text{-}5\alpha eq}$ = 5.2 Hz, 1 H, H-4α), 5.47 (m, 1 H, H-4β), 4.62 (dd, $J_{5\beta eq\text{-}5\beta ax}$ = 13.4, $J_{5\beta eq\text{-}4\beta}$ = 1.6 Hz, 1 H, H-5βeq), 4.40 (dd, $J_{5\alpha eq\text{-}5\alpha ax}$ = 11.5 Hz, 1 H, H-5αeq), 4.12 (dd, $J_{5\alpha ax\text{-}4\alpha}$ = 10.5 Hz, 1 H, H-5αax), 4.11 (m, 1 H, H-5βax) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 165.5, 165.3 (C=O Bz), 161.3 (C_q OBox), 148.7 (C_q OBox), 140.6 (C_q OBox), 134.0, 133.9, 133.8, 133.7, 133.6, 133.6, 133.5, 130.7, 130.4, 130.2, 130.1, 130.0, 129.9 (CH-Bz), 129.0 (C_q Bz), 128.9 (C_q Bz), 128.8 (C_q Bz), 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 125.7, 124.8, 124.1, 123.7, 123.4, 118.9, 110.2 (CH Ar), 98.0 (C-1α), 96.8 (C-1β), 69.0 (C-2α, C-4β), 68.7 (C-3α), 67.1 (C-4α), 66.6 (C-3β), 66.0 (C-2β), 62.3 (C-5α) ppm. ESI-MS: calcd. for $C_{33}H_{25}NNaO_9$ [M + Na]$^+$ 602.1, found 602.2; calcd. for [2M + Na]$^+$ 1181.3, found 1180.9.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy 2,3,4-Tribenzoyl-α-L-lyxopyranoside (54) and 4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy 2,3,4-Tribenzoyl-β-L-lyxopyranoside (55): 2,3,4-Tri-*O*-benzoyl-α/β-L-lyxopyranosyl-*O*-Box (96.5 mg, 0.17 mmol) and **1a** (35.9 mg, 0.14 mmol) were dissolved in dry 1,2-dichloroethane (0.7 mL) under argon atmosphere. The solution was cooled to –78 °C and 0.1 M TMSOTf in dry 1,2-dichloroethane (170 µL, 0.017 mmol) was added dropwise to the frozen mixture. The reaction mixture was warmed to –30 °C (just above the m.p. of the solvent) and stirred for 1–2 min. After completion (TLC 9:1 toluene/EtOAc) the reaction mixture was diluted with DCM and the organic phase was washed with 0.1 $NaOH_{aq.}$ (2 × 5 mL) and water (1 × 5 mL). The organic phase was dried with anhydrous Na_2SO_4, the solvent was evaporated in vacuo and the crude product (107.6 mg) was purified using an automatic system (SiO_2, Hex/EtOAc gradient from 0 % to 20 % EtOAc) obtaining a 56:44 α:β anomeric mixture (from H^{5eq1}H-NMR signal ratio). The anomers were separated by flash chromatography (9:1 toluene/Hex) obtaining 38.6 mg of the α product **54** (R_f = 0.3, 40 % yield) and 28.1 mg of β product **55** (R_f = 0.1, 29 % yield).

α Anomer 54: $[\alpha]_D^{25}$ = –29 (*c* = 0.43, DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, $J_{o\text{-}m}$ = 7.3 Hz, 2 H, 2 × *o*-CH-Bz), 8.01 (d, $J_{o\text{-}m}$ = 7.3 Hz, 2 H, 2 × *o*-CH-Bz), 7.92 (d, $J_{o\text{-}m}$ = 7.3 Hz, 2 H, 2 × *o*-CH-Bz), 7.77 (d, $J_{p\text{-}m}$ = 8.8 Hz, 2 H, 2 × *m*-CH-Bz), 7.69–7.19 (m, 14 H, CH-Bz, H-4Bf, H-6Bf, H7-Bf, H-*m*-Phe-O, H-*o*-Phe-O), 6.16 (dd, $J_{3'-4'}$ = 9.9, $J_{3'-2'}$ = 3.4 Hz, 1 H, H-3′), 5.90 (dd, 1 H, H-2′), 5.86 (dd, 1 H, H-4′), 5.82 (br. d, $J_{1'-2'}$ = 2.1 Hz, 1 H, H-1′), 4.28 (dd, $J_{5'eq\text{-}5'ax}$ = 11.2, $J_{5'eq\text{-}4'}$ = 5.5 Hz, 1 H, H-5′eq), 4.02 (br. t, $J_{5'ax\text{-}4'}$ = 10.7 Hz, 1 H, H-5′ax), 2.43 (s, 3 H, CH_3 Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (C=O Bz), 165.7 (2 × C=O Bz), 155.9 (C_q Bf), 152.2 (C_q Bf), 152.0 (C_q Bf), 133.9 (*p*-CH-Bz), 133.7 (*p*-CH-Bz), 133.5 (*p*-CH-Bz), 132.8 (C_q), 130.1 (2 × *o*-CH-Bz), 130.0 (2 × *o*-CH-Bz), 129.9 (2 × *o*-CH-Bz), 129.3 (C_q Bz), 129.2 (C_q Bz), 129.2 (C_q Bz), 128.8 (C-*m*-Ph-O), 128.6 (2 × *m*-CH-Bz), 128.6 (2 × *m*-CH-Bz), 128.4 (2 × *m*-CH-Bz), 128.1 (C_q Bf), 125.9 (C_q Bf), 124.3 (C6-Bf), 119.0 (C4-Bf), 116.9 (C-*o*-Ph-O), 112.0 (C7-Bf),

110.2 (C_q Bf), 96.1 (C-1′), 70.4 (C-2′), 69.2 (C-3′), 67.7 (C-4′), 60.8 (C-5′), 9.5 (CH_3 Bf) ppm. ESI-MS: calcd. for $C_{41}H_{31}ClNaO_9$ $[M + Na]^+$ 725.2, found 725.1; calcd. for $[2M + Na]^+$ 1427.3, found 1426.7.

β Anomer (55): $[\alpha]_D^{25}$ = +66 (*c* = 0.3, DCM) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (br. d, $J_{o\text{-}m}$ = 7.7 Hz, 2 H, 2 × *o*-CH-Bz), 8.15 (br. d, $J_{o\text{-}m}$ = 7.4 Hz, 2 H, 2 × *o*-CH-Bz), 7.95 (br. d, $J_{o\text{-}m}$ = 7.2 Hz, 2 H, 2 × *o*-CH-Bz), 7.74 (br. d, 2 H, 2 × *m*-CH-Bz), 7.69–7.19 (m, 14 H, CH-Bz, H-4Bf, H-6Bf, H7-Bf, H-*m*-Phe-O, H-*o*-Phe-O), 5.95 (m, 2 H, H-1′, H-3′), 5.82 (br. t, *J* = 3.7 Hz, 1 H, H-2′), 5.46 (m, 1 H, H-4′), 4.58 (br. dd, $J_{5'eq\text{-}5'ax}$ = 13.2, $J_{5'eq\text{-}4'}$ = 1.7 Hz, 1 H, H-5′eq), 4.01 (br. dd, $J_{5'ax\text{-}4'}$ = 2.0 Hz, 1 H, H-5′ax), 2.41 (s, 3 H, CH_3 Bf) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6 (C=O Bz), 165.3 (2 × C=O Bz), 157.2 (C_q Bf), 152.1 (C_q Bf), 151.9 (C_q Bf), 133.7 (*p*-CH-Bz), 133.6 (*p*-CH-Bz), 133.5 (*p*-CH-Bz), 132.6 (C_q), 130.1 (2 × *o*-CH-Bz), 130.0 (2 × *o*-CH-Bz), 129.9 (2 × *o*-CH-Bz), 129.6 (C_q Bz), 129.2 (C_q Bz), 129.1 (C_q Bz), 128.6 (2 × *m*-CH-Bz), 128.6 (2 × *m*-CH-Bz), 128.5 (2 × *m*-CH-Bz), 128.4 (C-*m*-Ph-O), 128.0 (C_q Bf), 125.6 (C_q Bf), 124.2 (C6-Bf), 118.9 (C4-Bf), 116.9 (C-*o*-Ph-O), 111.8 (C7-Bf), 110.0 (C_q Bf), 95.0 (C-1′), 69.4 (C-4′), 67.3 (C-3′), 67.2 (C-2′), 59.1 (C-5′), 9.4 (CH_3 Bf) ppm.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy α-L-Lyxopyranoside (46): An aliquot of 1 M MeONa in MeOH (85 μL) was added to a solution of 4-[5-chloro-3-methylbenzofuran-2-yl]phenoxy 2,3,4-tribenzoyl-α-L-lyxopyranoside (30 mg, 0.043 mmol) in MeOH (350 μL). The reaction was stirred under nitrogen atmosphere at room temperature for 1 h (TLC 7:3 Hex/EtOAc) and then quenched with Amberlite IR-120 H^+. The resin was filtered off, the solvent was evaporated in vacuo and the crude product (16.8 mg, quantitative yield) was used without further purifications. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.71 (d, $J_{o\text{-}m}$ = 8.9 Hz, 2 H, 2 × H-*m*-Phe-O), 7.46 (br. d, $J_{4\text{-}6}$ = 2 Hz, 1 H, H-4Bf), 7.36 (d, $J_{7\text{-}6}$ = 8.8 Hz, 1 H, H-7Bf), 7.21–7.14 (m, 3 H, H-6Bf, 2 × H-*o*-Phe-O), 5.48 (d, $J_{1'\text{-}2'}$ = 2.9 Hz, 1 H, H-1′), 4.03 (m, 1 H, H-2′), 3.93–3.86 (m, 2 H, H-3′, H-4′), 3.78 (br. dd, $J_{5'eq\text{-}5'ax}$ = 11.4 Hz, $J_{5'eq\text{-}4'}$ = 3.9 Hz, 1 H, H-5′eq), 3.59–3.50 (m, 1 H, H-5′ax), 2.39 (s, 3 H, CH_3 Bf) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 157.3 (C_q), 152.9 (C_q), 133.4 (C_q), 128.8 (C-*m*-Ph-O), 128.7 (C_q), 125.7 (C_q), 124.7 (C-6Bf), 119.3 (C-4Bf), 117.3 (C-*o*-Ph-O), 112.3 (C-7Bf), 110.4 (C_q), 99.3 (C-1′), 72.0 (C-4′), 70.7 (C-2′), 67.8 (C-3′), 64.3 (C-5′), 9.5 (CH_3 Bf) ppm. ESI-MS: calcd. for $C_{20}H_{19}ClNaO_6$ $[M + Na]^+$ 413.1, found 413.0. HR-MS: calcd. for $C_{20}H_{19}ClNaO_6$ $[M + Na]^+$ 413.07624, found 413.07817.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy β-L-Lyxopyranoside (47): An aliquot of 1 M MeONa in MeOH (43 μL) was added to a solution of 4-[5-chloro-3-methylbenzofuran-2-yl]phenoxy 2,3,4-tribenzoyl-α-L-lyxopyranoside (15 mg, 0.021 mmol) in MeOH (160 μL). The reaction was stirred under nitrogen atmosphere at room temperature for 1 h (TLC 7:3 Hex/EtOAc) and then quenched with Amberlite IR-120 H^+. The resin was filtered off, the solvent was evaporated in vacuo and the crude product (10.4 mg, quantitative yield) was used without further purifications. ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$): δ = 7.74–7.70 (m, 2 H, 2 × H-*m*-Phe-O), 7.47 (d, $J_{4\text{-}6}$ = 2.0 Hz, 1 H, H-4Bf), 7.37 (d, $J_{7\text{-}6}$ = 8.7 Hz, 1 H, H-7Bf), 7.23–7.18 (m, 3 H, H-6Bf, 2 × H-*o*-Phe-O), 5.37 (d, $J_{1'\text{-}2'}$ = 2.6 Hz, 1 H, H-1′), 4.12–4.07 (m, 2 H, H-2′, H-5′eq), 3.89–3.84 (m, 1 H, H-4′), 3.79 (dd, $J_{3'\text{-}2'}$ = 6.2, $J_{3'\text{-}4'}$ = 3.5 Hz, 1 H, H-3′), 3.43 (dd, $J_{5'eq\text{-}5'ax}$ = 11.9, $J_{5'ax\text{-}4'}$ = 5.5 Hz, 1 H, H-5′ax), 2.40 (s, 3 H, CH_3 Bf) ppm. ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ = 158.2 (C_q), 153.0, 153.0 (C_q), 133.6 (C_q), 128.9 (C-*m*-Ph-O), 128.8 (C_q), 126.0 (C_q), 124.8 (C-6Bf), 119.5 (C-4Bf), 117.7 (C-*o*-Ph-O), 112.5 (C-7Bf), 110.6 (C_q), 99.2 (C-1′), 72.8 (C-3′), 69.2 (C-4′), 68.3 (C-2′), 63.2 (C-5′), 9.4 (CH_3 Bf) ppm. HRMS: calcd. for $C_{20}H_{19}ClNaO_6$ $[M + Na]^+$ 413.07624, found 413.07813.

4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy α-D-Lyxopyranoside (48) and 4-[5-Chloro-3-methylbenzofuran-2-yl]phenoxy β-D-Lyxopyranoside (49): Synthesized as described above for the L-enantiomer with similar yields and identical spectroscopic data.

Supporting Information (see footnote on the first page of this article): Procedures for the synthesis of **2a**–**d** and **58a**–**d**; NMR spectra of all new compounds; STD-NMR quantitative analysis; configurational assignment of **42**–**49**.

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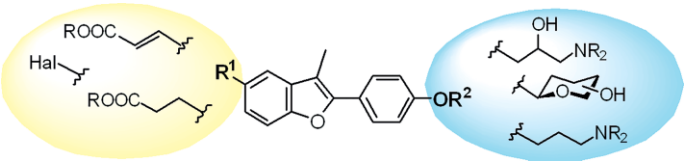
Allosteric Modulation



Hsp90 ATP-regulated internal dynamics can be modulated in an allosteric fashion, targeting the protein C-terminal domain (CTD) with a family of 2-phenylbenzofuran derivatives. Here we report 28 new derivatives that explore chemical space at opposite ends of the benzofuran scaffold. Compound interactions with Hsc82, a yeast isoform of full-length Hsp90, were explored using STD-NMR spectroscopy.

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