

Synthesis of functionalized 2-(4-hydroxyphenyl)-3-methylbenzofuran allosteric modulators of Hsp90 activity

Sara Sattin,^{*[a]} Matteo Panza,^[a] Francesca Vasile,^[a] Francesca Berni,^[a] Giulio Goti,^[a] Jiahui Tao,^[b] Elisabetta Moroni,^[c,d] David Agard,^[b] Giorgio Colombo,^[c] Anna Bernardi^[a]

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

Abstract: Hsp90 is a molecular chaperone playing a pivotal role in the cell life cycle. ATP-regulated internal dynamics are critical for its function and we recently demonstrated that they can be modulated in an allosteric fashion, targeting the protein C-terminal domain (CTD) 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. Interaction of the compounds with the full-length protein was explored by Saturation Transfer Difference (STD) NMR. In this context we report also 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 them, 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 it is established as a 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, the downstream signalling pathways. This dynamic process is coupled to ATP hydrolysis and competitive inhibitors of ATP binding in Hsp90 N-terminal domain, such as geldanamycin or radicicol,^[2] have shown potent antitumor activity in a wide-range of malignancies.^[3] The amino-coumarin Novobiocin and its analogues^[4] have been shown to bind the C-terminal domain (CTD) of Hsp90 and to lead to proteosomal degradation of the 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) targeted against 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.^[6b] 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 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).

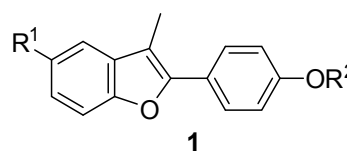


Figure 1. General structure of the 2-(4-hydroxyphenyl)-3-methylbenzofurans modulators **1**.

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 Saturation Transfer Difference (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 to the MD-based characterization of the structures of Hsc82/allosteric ligand complexes.^[6b] The results indicate

[a] Department of Chemistry, Università degli Studi di Milano, via Golgi, 19, 20133 - Milano, Italy
E-mail: sara.sattin@unimi.it

[b] Howard Hughes Medical Institute and Dept. of Biochemistry & Biophysics, University of California, San Francisco, 94158 USA

[c] ICRM-CNR, via Mario Bianco, 9, 20131 - Milano, Italy

[d] IRCCS MultiMedica, via Fantoli 16/15, 20138 - Milano, Italy

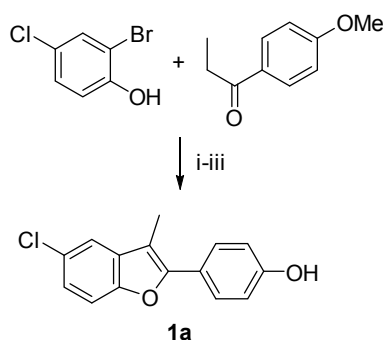
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <http://dx.doi.org/>

qualitative agreement between the two approaches, allowing to identify the ligand epitopes.

Results and Discussion

Diversification at R¹

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



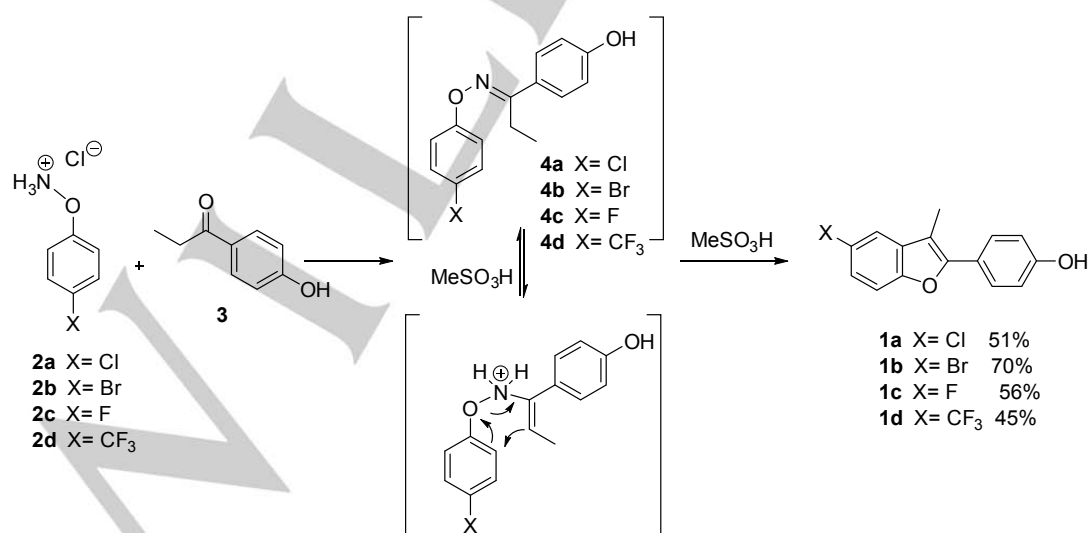
Scheme 1. Synthesis of 5-chloro-2-(4-hydroxyphenyl)-3-methylbenzofuran **1a** by enolate arylation. (i) Pd(OAc)₂, *rac*-2-(di-*tert*-butylphosphino)-1,10-binaphthyl (*rac*-DTBPB), NaOtBu, toluene. (ii) TFA/DCM (iii) Et₃SnNa, DMF 43% over the three steps (from^[8]).

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]

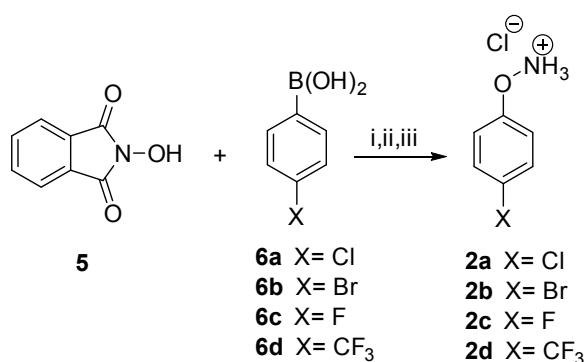
Condensation of an aryloxyamine **2** with ketone **3** yields the intermediate *O*-aryloxime **4**, which is heated at 60 °C in THF and with an excess of MeSO₃H to induce sigmatropic rearrangement of the protonated enamine isomer. Re-aromatization of the intermediate, followed by intramolecular cyclization and ammonia elimination afford the desired benzofuran **1** in 3-6 h and satisfactory yields (Scheme 2).

Conversion of the 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 days. The starting aryloxyamines **2a-d** were conveniently synthesized from *N*-hydroxyphthalimide **5** and the corresponding boronic acids **6a-d** (Scheme 3) using a Cu-mediated cross-coupling procedure developed by Petrassi *et al.*^[11]

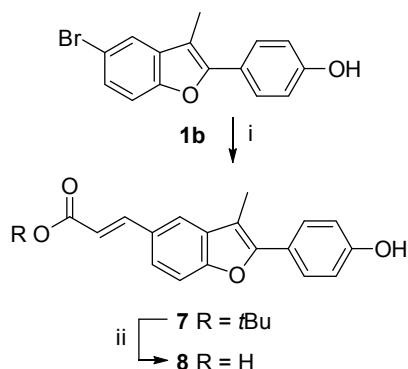
It has already been shown that **1a** is a suitable substrate for Stille coupling reaction with tributyl(1-propenyl)tin.^[8] The 5-bromo-2-(4-hydroxyphenyl)-3-methylbenzofuran **1b** was instrumental to explore additional Pd catalyzed chemistry and to expand the library of 5-substituents. In particular, since calculations had suggested that the Hsp90 allosteric pocket may include complementary basic sites, a Heck^[12] reaction was selected to introduce an acidic function to the benzofuran scaffold. Therefore, **1b** and *t*Bu acrylate were reacted in toluene affording the 5-substituted *t*Bu ester **7** in 81% yields and 100% *E* selectivity (Scheme 4). Despite the acid sensitivity of the substrate, ester deprotection could be performed using 20% CF₃COOH in CH₂Cl₂ to afford acid **8** in quantitative yields. Double bond reduction was also successfully achieved on a set of derivatives and will be described below.



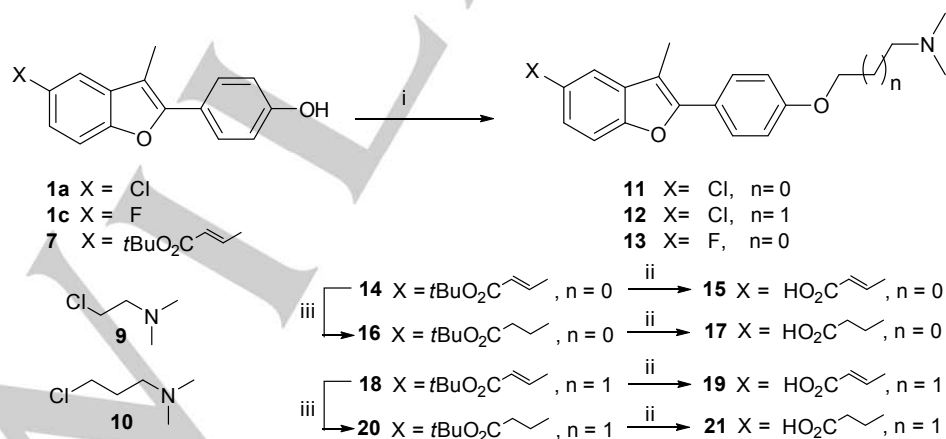
Scheme 2. Synthesis of 5-substituted-2-(4-hydroxyphenyl)-3-methylbenzofurans **1a-d** by [3,3]-sigmatropic of *O*-aryloximes **2a-d**.



Scheme 3. Synthesis of the aryloxyamines **2a-d**. (i) CuCl, 4 Å molecular sieves, 1,2-dichloroethane, air, room temperature, 48 – 72 h; (ii) H₂NNH₂·H₂O, 10% MeOH in CH₂Cl₂; (iii) 4 M HCl in dioxane.



Scheme 4. Heck reaction of **1b** (i) *t*Bu acrylate, Pd(OAc)₂, P(*o*-tol)₃, TEA, toluene, reflux, 6h, 81%; (ii) 20% CF₃COOH in DCM, 2h, quant.

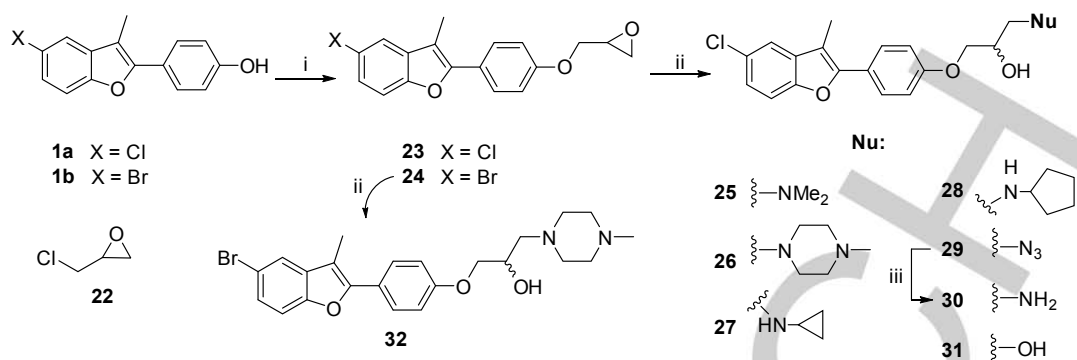


Scheme 5. PTC alkylation of the phenol with *N,N*-dimethylalkylamines. (i) **9**·HCl, or **10**·HCl, Bu₄NHSO₄, K₂CO₃, H₂O 5% w/w_{K₂CO₃}, CHCl₃; (ii) 20% CF₃COOH in CH₂Cl₂; (iii) H₂, Pd/C, MeOH, 2h, quant.

Diversification at R²

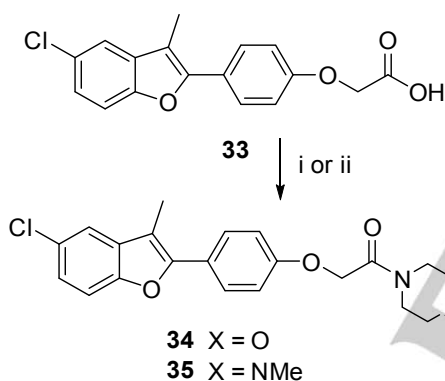
Our initial set of data for R² substituents had shown that basic groups at this position improve the activity of the benzofuran ligands as stimulators of Hsp90. Thus, we focused our attention on the introduction of amino groups in this region. This was accomplished by phase transfer catalyzed (PTC) alkylation 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) that allowed to obtain compounds **11-13** in good yields. The amino *t*-butylesters **14** and **18** (Scheme 5), obtained by alkylation of **7**, were either directly deprotected (20% CF₃COOH in CH₂Cl₂) to give the corresponding *N,N*-dimethylamino acids **15** and **19**, or hydrolyzed after reduction of the double bond (H₂ 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 9:1 CH₂Cl₂: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 NaN₃ opening of **23** (dioxane, 80°C, cat. Yb(OTf)₃, 81% yield) and reduction of the resulting azide **29** under carefully controlled conditions (H₂, PtO₂, 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 the diol **31** in 60% yields (Scheme 6).



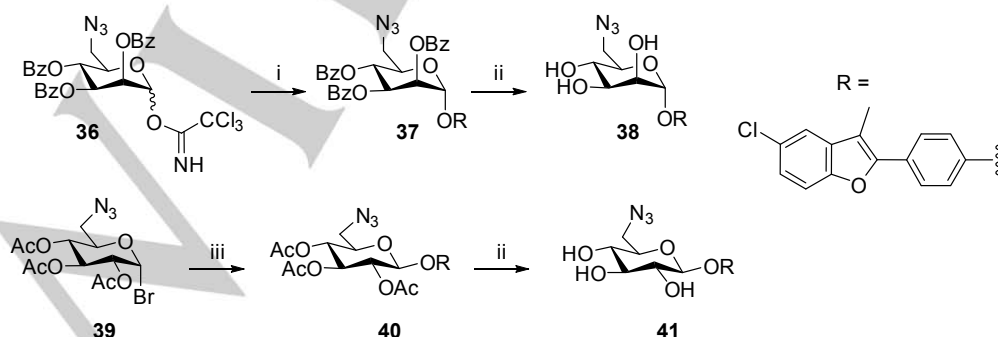
Scheme 6. Synthesis of epoxides **23** and **24** and nucleophilic opening reactions. (i) **22**, Bu_4NHSO_4 , K_2CO_3 , H_2O 5% 5% w/w K_2CO_3 , CHCl_3 ; (ii) for **25-28** and **32**: secondary amine, $[\text{9/1}] \text{CH}_2\text{Cl}_2/\text{EtOH}$; for **29**: NaN_3 in refluxing dioxane, $\text{Yb}(\text{OTf})_3$, 5 d, 81%; for **31**: $[\text{3/1}] \text{dioxane}/\text{H}_2\text{O}$, HCl , reflux, 5 h, 60%; (iii) H_2 , PtO_2 -morpholine in MeOH , 71%.

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



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%.

We have previously reported that a set of monoglycosides of **1a** can modulate Hsp90 activity. In particular $\text{R}^2 = \alpha\text{-L-Rha}$, $\alpha\text{-D-Man}$ and $\beta\text{-D-Gal}$ were found to induce significant activation of Hsp90 ATPase.^[5b] In order to harness the effect 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] occurred in good yields (62%) under standard conditions (TMSOTf , -30°C) to afford the 6-azidomannoside **37** (Scheme 8). It is worth noting that, in 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 soluble in MeOH . Reduction of the azido group could not be achieved, under a variety of conditions, mainly owing to poor solubility of **38** and of the resulting amine in most organic solvents.



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 K_2CO_3 , CHCl_3 , 40%.

Hydrogenolysis with mild catalysts, such as Lindlar-Pd, left the starting material unreacted even after 1 day. Under more severe conditions, e.g. using Pd/C (AcOEt, 1% AcOH) or PtO₂ and morpholine, several by-products (mostly from hydrogenolysis of the aryl-chloride bond) were observed by MS analysis, 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 the 6-azidoglucoside **41** after precipitation from CH₂Cl₂. The compound was found to be soluble in acetone and could be fully characterized, but again we were unable to obtain clean reduction of the azido group.

Glycosylation with other non-metabolic sugars was 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 (note: for pentapyranosides, the anomeric substituent is $\beta(\alpha)$ if in *trans* (*cis*) relative to the 4-hydroxy group^[17]).

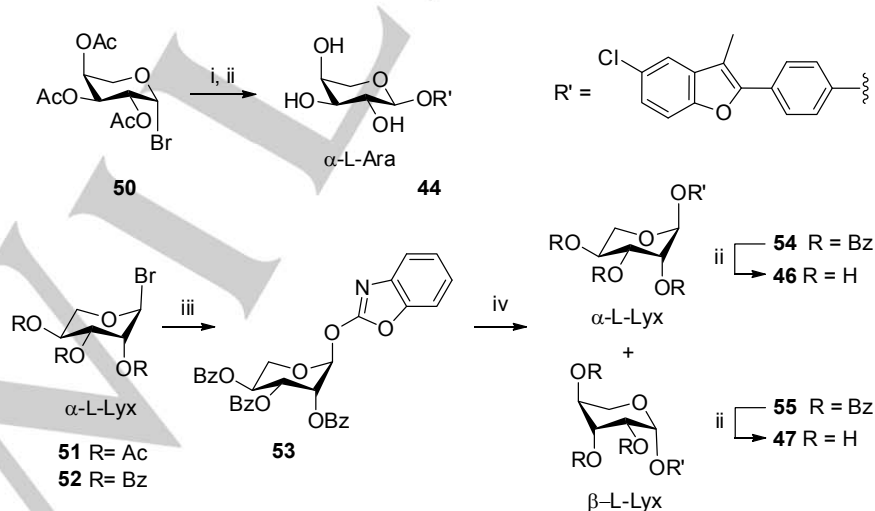
The anomeric configuration of the compound could be established based on the 1,2 coupling constant of 7 Hz, typical of a 1,2-*trans* glycoside. Under the same conditions, glycosylation of **1a** with the α -L-lyxopyranosyl bromide 2,3,4-triacetate **51**^[18] (Scheme 9) afforded the desired product in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

prepared from bromide **52** and used under Demchenko's conditions^[19] to glycosylate **1a** in overall 69% yields.

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

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

	R ²
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**, Bu₄NHSO₄, K₂CO₃, H₂O 5% w/w_{K₂CO₃}, CHCl₃, 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**).

Interaction of the compounds with Hsp90: STD-NMR experiments

While 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 (STD) 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 state, 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 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 2A) 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, so that information on the size and nature of the binding pocket and on ligands 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 have never been reported, so far.

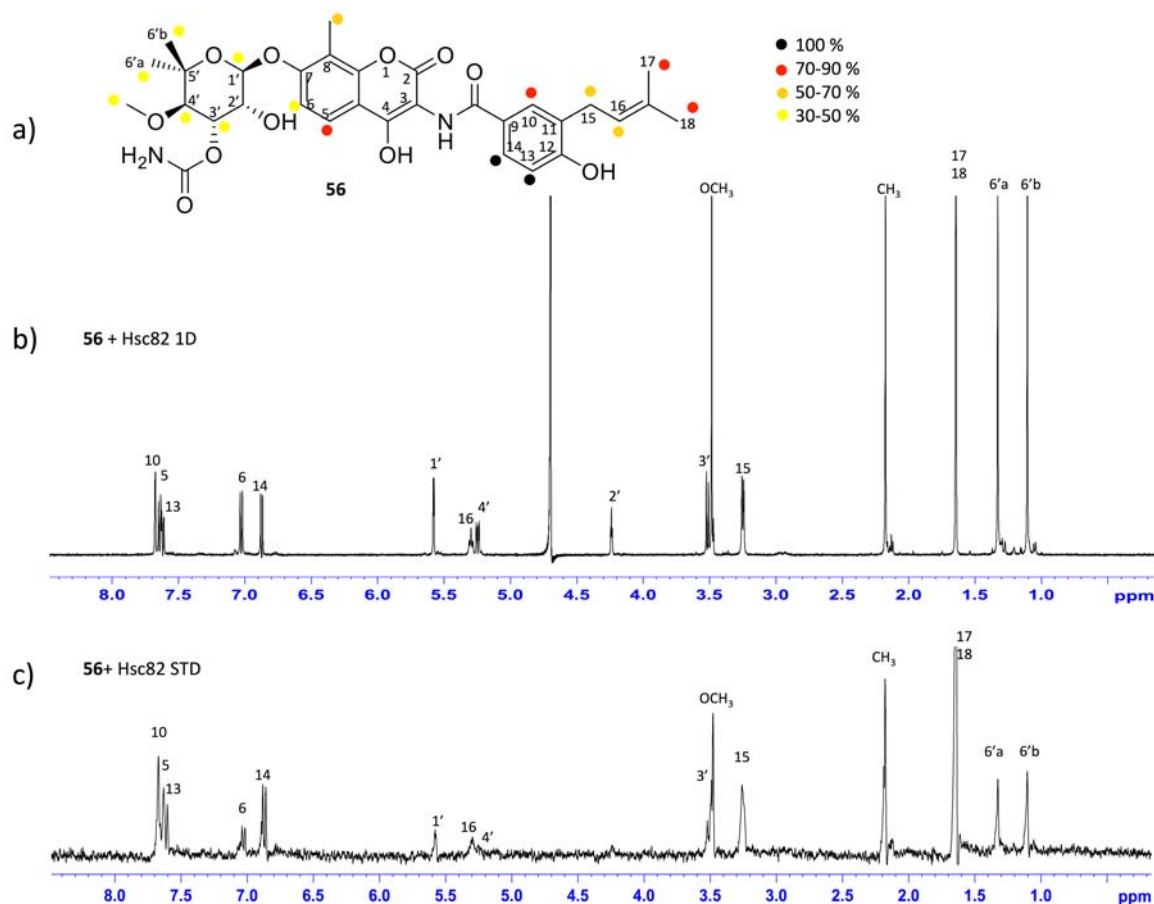


Figure 2. STD-NMR experiments with Novobiocin **56**. (a) Formula of Novobiocin **56**. (b) ^1H -NMR spectrum of **56** in presence of Hsc82 in a 200:1 Ligand/Protein ratio. (c) STD spectrum of **56** in presence of Hsc82 in a 200:1 L/P ratio. STD was obtained by irradiating the protein at **-0.05 ppm** 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 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 irradiating frequency the upfield aliphatic region of the protein. The spectrum is reported in Figure 2C, together with the ^1H spectrum of Novobiocin **56** in the same conditions (Figure 2B). 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 2C). 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 (Figures 3b, right panel) was largely consistent with STD, showing the prenyl, aromatic and sugar protons at contact distance with the protein. Additionally, the OCH_3 substituent at noviose 4' position was also calculated to point towards the interior of the protein, as consistent with the observed STD signal.

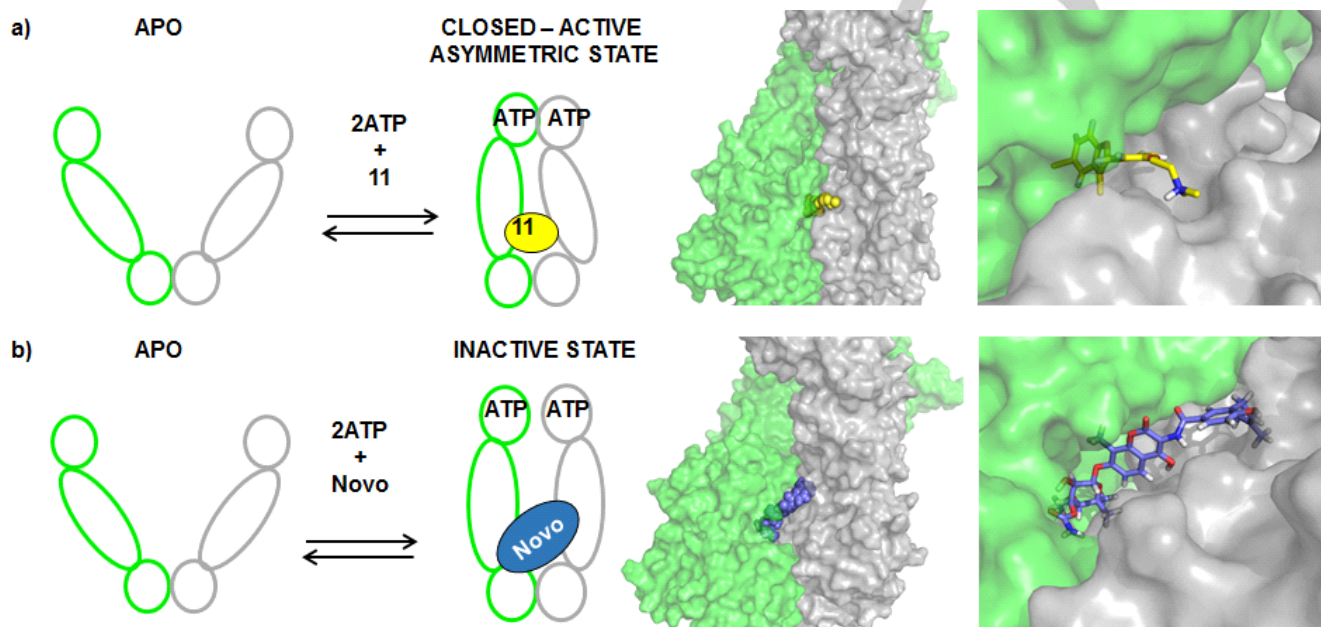


Figure 3. Hsp90 complexes of benzofuran **11** (a) and Novobiocin **56** (b). Dynamic equilibrium between open and closed Hsp90 is differentially affected by **11** (a, left panel) and Novobiocin (b, left panel) resulting in activation and inhibition of the ATPase activity, respectively. The docked complexes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

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 4A) could be dissolved in the aqueous buffer at the appropriate concentration and maintained in solution after addition of the protein. The amine **11** has already been characterised as a powerful Hsp90 allosteric activator.^[5b] The predicted binding site (Figure 3a) is close to the region occupied by Novobiocin (Figure 3b). However, MD simulations suggest that formation of the Hsp90:Novobiocin complex blocks the protein in a partially inactive state (Fig 3b, left panel), whereas interaction with **11** results in higher frequency turnover of the closed-active state (Fig. 3a, 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 4B.

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-CH₂ and N-methyl groups. In particular, the protons of the aromatic rings show the largest saturation transfer and the N-CH₃ group the lowest effect, suggesting that the region of the ligand comprising the aromatic rings is making the closest contacts with the protein binding site. A competition experiment between **11** and Novobiocin was attempted, but it was frustrated by precipitation of the ligand. In good agreement with STD, the representative structures from MD simulations of the Hsc82/**11** complex (Figure 3a, right panel) show extensive packing of the benzofuran and aromatic rings of the ligand with the protein, coupled to contacts involving both the N-CH₂ and N-methyl groups of the amine modification.^[7] Within the limitations of 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. It is worth noting, moreover, that such knowledge has been used to guide the development of more potent derivatives, providing further support to the validity of the model.

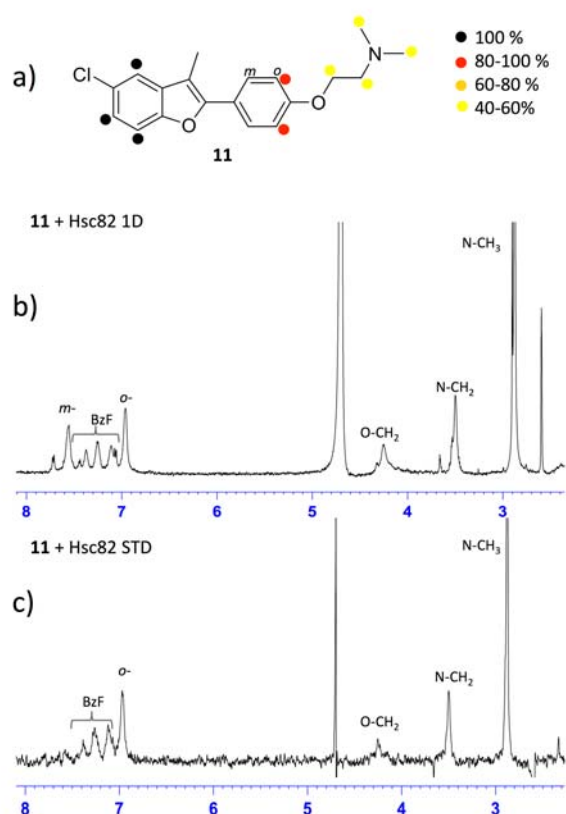


Figure 4. STD-NMR experiments with benzofuran derivative **11**. (a) Formula of **11**. (b) ¹H-NMR spectrum of **11** in presence of Hsc82 in a 200:1 Ligand/Protein ratio. (c) STD spectrum of **11** in presence of Hsc82 in a 200:1 L/P ratio. STD was obtained by irradiating the protein at -0.05 ppm with total saturation times of 2.94s. 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.

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 R² 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, while other non-metabolic sugars could be successfully introduced. 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) proved that the ligand actually binds to the protein and confirmed the role of the benzofuran scaffold in establishing the interaction. The spectra showed that also the substituents of 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 the 28 new compounds activity on Hsp90 ATPase and functional dynamics is underway.

Experimental Section

Protein expression and purification: The Hsc82 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 hours. The cells were lysed using EmulsiFlex-C3 (Avestin, Canada). The lysate was purified using Ni-NTA column (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 on 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 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 the resonances. The sample was prepared in deuterated 20 mM PBS buffer. Data were analysed using Bruker Topspin software. After NMR characterization, 30 μ L of the Hsc82 solution (10 mg/mL, MW=80899.7) was added to each sample, giving to a 200:1 L/P ratio. For the acquisition of NMR Saturation Transfer Difference (STD) experiments, a 1D-pulse sequence incorporating a $T_{1\rho}$ filter to remove disturbing protein signals was used. The STD spectra were performed with an on-resonance irradiation frequency at -0.05 ppm, while 200 ppm was chosen as 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 0.49s increments). In STD experiments, water suppression was achieved by using the WATERGATE 3-9-19 pulse sequence. For both product blank experiments in absence of protein were performed.

Synthesis – general: Dry dichloromethane (DCM), methanol, 1,4-dioxane and triethylamine (TEA) were distilled over calcium hydride; tetrahydrofuran (THF) was distilled over sodium. Dichloroethane (DCE) was dried over 4 Å molecular sieves 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] ¹H and ¹³C spectra were recorded at 400 MHz or 100 MHz, respectively, on a Bruker AVANCE-400 instrument. Chemical shifts (δ) for ¹H and ¹³C spectra are expressed in ppm relative to internal standard (CDCl₃: 7.26 for ¹H and 77.16 for ¹³C; CD₃OD: 3.31 for ¹H and 49.00 for ¹³C; (CD₃)₂CO: 2.05 for ¹H and 29.84 for ¹³C). Signals were abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b means broad as in bs, broad singlet. Quaternary carbon signals were abbreviated as C_q. All assignments were confirmed with the aid of two-dimensional ¹H-¹H (COSY), ¹H-¹³C (HSQC) and/or ¹H-¹³C (HMBC) experiments using standard pulse programs. Processing of the spectra was performed using TopSpin or MestReNova software. Sugar signals were numbered as customary; benzofuran signals were numbered as 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; OBox signals were numbered as 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 Still's procedure.^[24] Automated chromatography was performed using

a Biotagsolera 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 spectral 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-methyl-benzofurans (1a-c):^[10] The phenyloxyamine hydrochloride **2a-c** (1 mmol) was suspended in THF (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 60 °C, then methanesulfonic acid (2 mmol) was added. The mixture was stirred for 5 h and the progress was followed by HP-TLC (8:2 Toluene:DCM, each sample was diluted with DCM and quenched with NaHCO₃ before deposition on TLC). The reaction mixture was then diluted with EtOAc, the organic phase was washed with NaHCO₃ (2x5 mL), and brine (2x5 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude was purified by chromatography as described below.

5-chloro-2-(4-hydroxyphenyl)-3-methylbenzofuran (1a): General procedure I performed starting from **2a**. The crude was purified by flash chromatography (Toluene:DCM gradient from 10% to 25% DCM) leading in 51% yield to product **1a**, whose spectral data corresponded with those reported in the literature^[9]. ¹H-NMR (400 MHz, CDCl₃): δ = 7.67 (d, *J*_{o-m} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.45 (d, *J*₄₋₆ = 2 Hz, 1 H, H-4Bf), 7.35 (d, *J*₇₋₆ = 8.6 Hz, 1 H, H-7Bf), 7.20 (dd, 1 H, H-6Bf), 6.96 (d, 2 H, 2 x H-*o*-Phe-O), 2.39 (s, 3 H, CH₃-Bf) ppm.

5-bromo-2-(4-hydroxyphenyl)-3-methylbenzofuran (1b): General procedure I performed starting from **2b**. The crude was purified using an automated chromatography system (SiO₂, Hex:EtOAc gradient from 30% to 100% EtOAc), to afford compound **1b** in 70% yield as a white solid, whose spectral data corresponded with those reported in the literature.^[9] ¹H-NMR (400 MHz, CDCl₃): δ = 7.68 (d, *J*_{o-m} = 8.3 Hz, 2 H, 2 x 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 x H-*o*-Phe-O), 2.40 (s, 3 H, CH₃-Bf) ppm.

5-fluoro-2-(4-hydroxyphenyl)-3-methylbenzofuran (1c): General procedure I performed starting from **2c**. The crude was purified by flash chromatography (8:2 Hex:EtOAc, R_f=0.3) leading to product **1c** in 56% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.68 (d, *J*_{o-m} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.37 (dd, *J*₇₋₆ = 8.9 Hz, ⁴*J*_{HF} = 4.2 Hz, 1 H, H-7Bf), 7.15 (dd, *J*₄₋₆ = 2.6 Hz, ³*J*_{HF} = 8.6 Hz, 1 H, H-4Bf), 7.00-6.93 (m, 3 H, H-6Bf, 2 x H-*o*-Phe-O), 5.22 (bs, 1 H, OH), 2.39 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 160.5 (C_q), 156.9 (d, ¹*J*_{CF} = 240 Hz, C-F), 155.7 (C_q), 152.7 (C_q), 149.9 (C_q), 132.3 (d, ³*J*_{CF} = 10 Hz, C_q), 128.6 (2 x C-*m*-Ph-O), 124.2 (C_q), 115.8 (2 x C-*o*-Ph-O), 111.6 (d, ²*J*_{CF} = 12 Hz, C-6Bf), 111.4 (d, ³*J*_{CF} = 4.4 Hz, C-7Bf), 110.1 (C_q), 104.8 (d, ²*J*_{CF} = 30 Hz, C-4Bf), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₁₅H₁₀O₂F [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 days at 100 °C. The reaction progress was followed by RP-HPLC (C18, H₂O:CH₃CN gradient from 30% to 100% CH₃CN; 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 NaHCO₃ before injection). The reaction mixture was diluted with EtOAc, the organic phase was washed with NaHCO₃ (2x5 mL), and brine (2x5 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude was purified by flash chromatography (8:2 Hex:EtOAc, R_f=0.4) leading to product **1c** in 45% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.79 (bs, 1 H, H-4Bf), 7.71 (d, *J*_{o-m} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.55-7.48 (m, 2 H, H-7Bf, H-6Bf), 6.97 (d, 2 H, 2 x H-*o*-Phe-O), 5.07 (bs, 1 H, OH), 2.46 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 155.9 (C_q), 154.0 (q, ¹*J*_{CF} = 241 Hz, CF₃), 131.5 (C_q), 128.7 (2 x C-*m*-Ph-O), 125.1 (q, ²*J*_{CF} = 32 Hz, CCF₃), 123.8 (C_q), 121.1 (q, ³*J*_{CF} = 3.7 Hz, C-6Bf), 116.8 (q, ³*J*_{CF} = 4.1

Hz, C-4Bf), 115.9 (2 x C-*o*-Ph-O), 111.2 (C-7Bf), 110.0 (C_q), 9.4 (CH₃-Bf) ppm. ESI-MS: calcd for C₁₆H₁₀F₃O₂ [M-H]⁻ 291.064, found 291.092.

E-t-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)₃P (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 (2x5 mL), water (2x5 mL) and brine (1x5 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude was purified using an automated chromatography system (SiO₂, 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, CDCl₃): δ = 7.71 (m, 3 H, 2 x 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-m} = 8.7 Hz, 2 H, 2 x H-*o*-Phe-O), 6.39 (d, *J*_{trans} = 15.9 Hz, 1 H, =CH-C=O), 2.44 (s, 3 H, CH₃-Bf), 1.56 (s, 9 H, 3 x CH₃-*t*Bu) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 x 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 x C-*o*-Ph-O), 111.3 (C-7Bf), 109.9 (C_q-Bf), 80.6 (C_q-*t*Bu), 28.4 (3 x CH₃-*t*Bu), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₂H₂₂NaO₄ [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 CHCl₃ (3 mL). Water (19 μL), K₂CO₃ (2.7 mmol) and the phase transfer catalyst (Bu₄NHSO₄, 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 CHCl₃:MeOH) it was diluted with chloroform and brine, the aqueous phase was extracted with chloroform (2x10 mL) and the organic phases were washed with water (2x20 mL), dried over Na₂SO₄ 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 was purified by flash chromatography (CHCl₃ + 1%TEA, R_f=0.26) leading to product **13** in 81% yield. ¹H-NMR (400 MHz, 9:1 CD₃OD:CDCl₃): δ = 7.73 (d, *J*_{o-m} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.40 (dd, *J*₆₋₇ = 8.9 Hz, ⁴*J*_{HF} = 4.0 Hz, 1 H, H-7Bf), 7.21 (dd, *J*₄₋₆ = 2.6 Hz, ³*J*_{HF} = 8.8 Hz, 1 H, H-4Bf), 7.08 (d, 2 H, 2 x 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, CH₂-O), 2.96-2.86 (m, 2 H, CH₂-N), 2.45 (bs, 6 H, 2xCH₃-N), 2.40 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, 9:1 CD₃OD:CDCl₃): δ = 161.8 (C_q), 160.6 (d, ¹*J*_{CF} = 238 Hz, C-F), 160.0 (C_q), 153.9 (C_q), 151.1 (C_q), 129.2 (2 x C-*m*-Ph-O), 125.2 (C_q), 115.8 (2 x C-*o*-Ph-O), 112.3 (d, ³*J*_{CF} = 5.3 Hz, C-7Bf), 112.2 (d, ²*J*_{CF} = 11.4 Hz, C-6Bf), 105.5 (C-4Bf, ²*J*_{CF} = 25 Hz), 66.2 (CH₂-O), 58.8 (CH₂-N), 45.6 (NMe₂), 9.4 (CH₃-Bf) ppm. ESI-MS: calcd for C₁₉H₂₀FNNaO₂ [M+Na]⁺ 336.3, found 336.0

E-t-butyl-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 was purified using an automated chromatography system (SiO₂, CHCl₃:MeOH:TEA (1%) gradient from 0 to 20% MeOH) to afford the product as a white foam (50% yield). ¹H-NMR (400 MHz, CDCl₃): δ = 7.75-7.69 (m, 3 H, =CH-Ar, 2 x 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-m} = 8.9 Hz, 2 H, 2 x H-*o*-Phe-O), 6.39 (d, *J*_{trans} = 15.9 Hz, 1 H, =CH-C=O), 4.13 (t, *J*_{CH₂-CH₂} = 5.7 Hz, 2 H, CH₂-O), 2.77 (t, 2 H, CH₂-N), 2.44 (s, 3 H, CH₃-Bf), 2.36 (s, 6 H, NMe₂), 1.55 (s, 9 H, 3xCH₃-*t*Bu) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 x 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 x C-*o*-Ph-O), 111.3 (C-7Bf), 109.9 (C_q-Bf), 80.4 (C_q-*t*Bu), 66.0 (CH₂-O), 58.3 (CH₂-N), 45.9 (NMe₂), 28.4 (3 x CH₃-*t*Bu), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₆H₃₂NO₄ [M+H]⁺ 422.2331, found 422.2418.

***E*-*t*-butyl-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 was purified using an automated chromatography system (SiO₂, CHCl₃:MeOH:TEA (1%) gradient from 0 to 20% MeOH) to afford the product in 62% yield as a white foam. ¹H-NMR (400 MHz, CDCl₃): δ = 7.75-7.68 (m, 3 H, =CH-Ar, 2 x 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-m} = 8.8 Hz, 2 H, 2 x H-*o*-Phe-O), 6.39 (d, *J*_{trans} = 15.9 Hz, 1 H, =CH-C=O), 4.09 (t, *J*_{CH₂-CH₂} = 6.2 Hz, 2 H, CH₂-O), 2.62 (t, 2 H, CH₂-N), 2.44 (s, 3 H, CH₃Bf), 2.38 (s, 6 H, NMe₂), 2.12-2.02 (m, 2 H, CH₂-CH₂-CH₂), 1.55 (s, 9 H, 3 x CH₃-*t*Bu) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 x 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 x C-*o*-Ph-O), 111.3 (C-7Bf), 109.9 (C_q-Bf), 80.5 (C_q-*t*Bu), 65.9 (CH₂-O), 56.3 (CH₂-N), 44.8 (NMe₂), 28.4 (3 x CH₃-*t*Bu), 26.7 (CH₂-CH₂-CH₂), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₇H₃₄NO₄ [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, CDCl₃): δ = 7.72 (d, *J*_{o-m} = 8.6 Hz, 2 H, 2 x H-*m*-Phe-O), 7.46 (s, 1 H, H-4Bf), 7.36 (d, *J*₇₋₆ = 8.6 Hz, 1 H, H-7Bf), 7.21 (d, 1 H, H-6Bf), 7.03 (d, 2 H, 2 x H-*o*-Phe-O), 4.30 (dd, *J*_{gem} = 11.0 Hz, *J*_{vic} = 3.0 Hz, 1 H, CH₂-OAr), 4.02 (dd, *J*_{vic} = 5.7 Hz, 1 H, CH₂-OAr), 3.43-3.37 (m, 1 H, CH-O), 2.94 (t, *J*_{gem} = 4.9 Hz, *J*_{vic} = 4.5 Hz, 1 H, CH₂-O), 2.79 (dd, *J*_{vic} = 2.8 Hz, 1 H, CH₂-O), 2.40 (s, 3 H, CH₃Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 158.6 (C_q-phenol), 152.3 (C_q-Bf), 151.1 (C_q-Bf), 132.9 (C_q), 128.4 (2 x C-*m*-Ph-O), 128.1 (C_q), 124.3 (C_q), 124.1 (C-6Bf), 118.9 (C-4Bf), 115.0 (2 x C-*o*-Ph-O), 111.9 (C-7Bf), 109.7 (C_q), 69.0 (CH₂-OAr), 50.2 (CH-O), 44.8 (CH₂-O), 9.5 (CH₃Bf) ppm. ESI-MS: calculated for C₁₈H₁₅ClNO₃ [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 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, CDCl₃): δ = 7.71 (d, *J* = 9.0 Hz, 2 H, 2 x H-*m*-Phe-O), 7.61 (d, *J*₄₋₆ = 1.8 Hz, 1 H, H-4Bf), 7.34 (dd, *J*₇₋₆ = 8.6 Hz, *J*₄₋₆ = 1.8 Hz, 2 H, H-6Bf), 7.31 (d, 1 H, H-7Bf), 7.02 (d, 2 H, 2 x H-*o*-Phe-O), 4.29 (dd, *J*_{gem} = 11.0 Hz, *J*_{vic} = 3.0 Hz, 1 H, CH₂-OAr), 4.00 (dd, *J*_{vic} = 5.9 Hz, 1 H, CH₂-OAr), 3.42-3.37 (m, 1 H, CH-O), 2.94 (dd, *J*_{gem} = 4.7, *J*_{vic} = 4.3 Hz, 1 H, CH₂-O), 2.79 (dd, *J*_{vic} = 3.2 Hz, 1 H, CH₂-O), 2.41 (s, 3 H, CH₃Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 158.5 (C_q), 152.4 (C_q), 152.0 (C_q), 133.4 (C_q), 128.3 (2 x C-*m*-Ph-O), 126.7 (C-6Bf), 124.1 (C_q), 121.8 (C-4Bf), 115.4 (C_q), 114.9 (2 x C-*o*-Ph-O), 112.3 (C-7Bf), 109.4 (C_q), 68.8 (CH₂-OAr), 50.1 (CH-O), 44.7 (CH₂-O), 9.4 (CH₃Bf) ppm. ESI-MS: calcd for C₁₈H₁₅BrO₃ [M+H]⁺ 360.2, found 360.4

Double bond reduction. Synthesis of 16 and 20: To a solution of *E*-*t*-butylacrylate (**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 H₂ atmosphere. The crude 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.

***t*-butyl 3-(2-(4-(2-(dimethylamino)ethoxy)phenyl)-3-methylbenzofuran-5-yl)propanoate (16):** Obtained from **14** in 94% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.72 (d, *J*_{o-m} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.35 (d, *J*₇₋₆ = 8.3 Hz, 1 H, H-7Bf), 7.32 (d, *J*₄₋₆ = 1.6 Hz, 1 H, H-4Bf), 7.10 (dd, 1 H, H-6Bf), 7.02 (d, *J* = 8.9 Hz, 2 H, 2 x H-*o*-Phe-O), 4.13 (t, *J*_{CH₂-CH₂} = 5.7 Hz, 2 H, CH₂-O), 3.02 (t, *J*_{CH₂-CH₂} = 7.8 Hz, 2 H, CH₂-Ar), 2.77 (t, 2 H, CH₂-N), 2.59 (t, 2 H, CH₂-C=O), 2.42 (s, 3 H, CH₃Bf), 2.37 (s, 6 H, NMe₂), 1.43 (s, 9 H, *t*Bu) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 x C-*m*-Ph-O), 124.7 (C-6Bf), 118.5 (C-4Bf), 114.8 (2 x C-*o*-Ph-O), 110.6 (C-7Bf), 110.3 (C_q-Bf), 80.3 (C_q-*t*Bu), 63.0 (CH₂-O), 56.7 (CH₂-N), 46.0 (NMe₂), 43.93, 37.9 (CH₂-C=O), 31.2 (CH₂-

Ar), 28.1 (CH₃-*t*Bu), 9.4 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₆H₃₄NO₄ [M+H]⁺ 424.2488, found 424.2982.

***t*-butyl 3-(2-(4-(3-(dimethylamino)propoxy)phenyl)-3-methylbenzofuran-5-yl)propanoate (20):** Obtained from **18** in 82% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.71 (d, *J*_{o-m} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.38-7.30 (m, 2 H, H-4Bf, H-7Bf), 7.10 (dd, *J*₆₋₇ = 8.3 Hz, *J*₆₋₄ = 1.5 Hz, 1 H, H-6Bf), 6.98 (d, 2 H, 2 x H-*o*-Phe-O), 4.09 (t, *J*_{CH₂-CH₂} = 6.1 Hz, 2 H, CH₂-O), 3.02 (t, *J*_{CH₂-CH₂} = 7.8 Hz, 2 H, CH₂-Ar), 2.83-2.77 (t, 2 H, CH₂-N), 2.59 (t, 2 H, CH₂-C=O), 2.51 (s, 6 H, NMe₂), 2.41 (s, 3 H, CH₃Bf), 2.18-2.08 (m, 2 H, CH₂-CH₂-CH₂), 1.43 (s, 9 H, *t*Bu) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 x C-*m*-Ph-O), 124.6 (C-6Bf), 118.6 (C-4Bf), 114.7 (2 x 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 (CH₂-O), 56.2 (CH₂-N), 44.5 (NMe₂), 38.0 (CH₂-C=O), 31.4 (CH₂-Ar), 29.84, 28.2 (CH₃-*t*Bu), 26.2 (CH₂-CH₂-CH₂), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₇H₃₆NO₄ [M+H]⁺ 438.3, found 438.4

Hydrolysis of *t*-butyl esters. Synthesis of 8, 15, 17, 19, 21: To a DCM solution (1.8 mL) of the *t*-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):** ¹H-NMR (400 MHz, CD₃OD): 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-m} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.55 (dd, *J*₆₋₇ = 8.5 Hz, *J*₆₋₄ = 1.6 Hz, 1 H, H-6Bf), 7.47 (d, 1 H, H-7Bf), 6.92 (d, 2 H, 2 x H-*o*-Phe-O), 6.52 (d, 1 H, =CH-C=O), 2.45 (s, 3 H, CH₃Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 x C-*m*-Ph-O), 125.2 (C-6Bf), 123.6 (C_q-Bf), 120.4 (C-4Bf), 116.6 (2 x C-*o*-Ph-O), 112.0 (C-7Bf), 110.3 (C_q-Bf), 9.3 (CH₃-Bf) ppm. HRMS (ESI): calcd for C₁₈H₁₃O₄ [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**. ¹H-NMR (400 MHz, CD₃OD): δ = 7.84-7.76 (m, 4 H, =CH-Ar, 2 x H-*m*-Phe-O, H-4Bf), 7.56 (dd, *J*₆₋₇ = 8.5, *J*₆₋₄ = 1.5 Hz, 1 H, H-6Bf), 7.47 (d, 1 H, H-7Bf), 7.17 (d, *J*_{o-m} = 8.9 Hz, 2 H, 2 x H-*o*-Phe-O), 6.49 (d, *J*_{trans} = 16.0 Hz, 1 H, =CH-C=O), 4.46-4.41 (m, 2 H, CH₂-O), 3.67-3.61 (m, 2 H, CH₂-N), 3.02 (s, 6 H, NMe₂), 2.46 (s, 3 H, CH₃Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 x 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 x C-*o*-Ph-O), 112.2 (C-7Bf), 111.5 (C_q-Bf), 63.2 (CH₂-O), 57.7 (CH₂-N), 43.9 (NMe₂), 9.3 (CH₃-Bf) ppm. HRMS (ESI): calcd for C₂₂H₂₄NO₄⁺ [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**. ¹H-NMR (400 MHz, CD₃OD): δ = 7.74 (d, *J*_{o-m} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.37 (d, *J*₄₋₆ = 1.1 Hz, 1 H, H-4Bf), 7.33 (d, *J*₇₋₆ = 8.4 Hz, 1 H, H-7Bf), 7.15-7.10 (m, 3 H, 2 x H-*o*-Phe-O, H-6Bf), 4.40-4.36 (m, 2 H, CH₂-O), 3.64-3.58 (m, 2 H, CH₂-N), 3.03-2.97 (m, 8 H, CH₂-Ar, NMe₂), 2.64 (t, *J*_{CH₂-CH₂} = 7.7 Hz, 2 H, CH₂-C=O), 2.39 (s, 3 H, CH₃Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 x C-*m*-Ph-O), 126.6 (C_q-Bf), 125.8 (C-6Bf), 119.5 (C-4Bf), 115.9 (2 x C-*o*-Ph-O), 111.4 (C-7Bf), 111.2 (C_q-Bf), 63.2 (CH₂-O), 57.7 (CH₂-N), 43.9 (NMe₂), 37.4 (CH₂-C=O), 32.1 (CH₂-Ar), 9.40 (CH₃-Bf) ppm. HRMS (ESI): calcd for C₂₂H₂₆NO₄⁺ [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**. ¹H-NMR (400 MHz, CD₃OD): δ = 7.83-7.71 (m, 4 H, =CH-Ar, 2 x H-*m*-Phe-O, H-4Bf), 7.55 (dd, *J*₆₋₇ = 8.6, *J*₆₋₄ = 1.5 Hz, 1 H, H-6Bf), 7.46 (d, 1 H, H-7Bf), 7.08 (d, *J*_{o-m} = 8.9 Hz, 2 H, 2 x H-*o*-Phe-O), 6.49 (d, *J* = 15.9 Hz, 1 H, =CH-C=O), 4.18 (t, *J*_{CH₂-CH₂} = 5.7 Hz, 2 H, CH₂-

O), 3.39 (t, 2 H, CH₂-N), 2.96 (s, 6 H, NMe₂), 2.44 (s, 3 H, CH₃Bf), 2.31-2.19 (m, 2 H, CH₂-CH₂-CH₂) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 x 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 x C-*o*-Ph-O), 112.1 (C-7Bf), 111.1 (C_q-Bf), 66.0 (CH₂-O), 56.8 (CH₂-N), 43.6 (NMe₂), 25.7 (CH₂-CH₂-CH₂), 9.3 (CH₃-Bf) ppm. HRMS (ESI): calcd for C₂₃H₂₈NO₄⁺ [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**. ¹H-NMR (400 MHz, CD₃OD): δ = 7.75 (d, *J*_{*o-m*} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.40 (d, 1 H, H-4Bf), 7.35 (d, 1 H, H-7Bf), 7.15 (dd, *J*_{*6-7*} = 8.4, *J*_{*6-4*} = 1.7 Hz, 1 H, H-6Bf), 7.09 (d, 2 H, 2 x H-*o*-Phe-O), 4.19 (t, *J*_{CH₂-CH₂} = 5.7 Hz, 2 H, CH₂-O), 3.39 (t, *J*_{CH₂-CH₂} = 8.0 Hz, 2 H, CH₂-N), 3.03 (t, *J*_{CH₂-CH₂} = 7.6 Hz, 2 H, CH₂-Ar), 2.96 (s, 6 H, NMe₂), 2.66 (t, 2 H, CH₂-C=O), 2.42 (s, 3H, CH₃Bf), 2.31-2.21 (m, 2 H, CH₂-CH₂-CH₂) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 x C-*m*-Ph-O), 125.9 (C_q-Bf), 125.7 (C-6Bf), 119.5 (C-4Bf), 115.8 (2 x C-*o*-Ph-O), 111.3 (C-7Bf), 110.9 (C_q-Bf), 66.0 (CH₂-O), 56.8 (CH₂-N), 43.7 (NMe₂), 37.5 (CH₂-C=O), 32.1 (CH₂-Ar), 25.7 (CH₂-CH₂-CH₂), 9.4 (CH₃-Bf) ppm. HRMS (ESI): calcd for C₂₂H₂₆NO₄⁺ [M+H]⁺ 382.20128, found 382.20177.

4-[5-chloro-3-methylbenzofuran-2-yl]-phenoxy-2-hydroxy-3-dimethylamino propane (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 CHCl₃: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 CHCl₃:MeOH + 1% TEA). The desired product **25** was obtained as a white solid in 82 % yield (36.7 mg). ¹H-NMR (400 MHz, CDCl₃): δ = 7.71 (d, *J*_{*o-m*} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.45 (d, *J*_{*4-6*} = 2.1 Hz, 1 H, H-4Bf), 7.36 (d, *J*_{*7-6*} = 8.6 Hz, 1 H, H-7Bf), 7.20 (dd, 1 H, H-6Bf), 7.03 (d, 2 H, 2 x H-*o*-Phe-O), 4.11 (m, 1 H, CHOH), 4.04 (d, *J*_{*vic*} = 4.9 Hz, 2 H, CH₂O), 2.59 (dd, *J*_{*gem*} = 12.2 Hz, *J*_{*vic*} = 9.9 Hz, 1 H, CH₂N), 2.43 (dd, *J*_{*vic*} = 3.6 Hz, 1 H, CH₂N), 2.40 (s, 3 H, CH₃-Bf), 2.36 (s, 6 H, NMe₂) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 (C-6Bf), 124.0 (C_q), 118.8 (C-4Bf), 114.9 (C-*o*-Ph-O), 111.8 (C-7Bf), 109.5 (C_q), 70.6 (CH₂O), 66.2 (CHOH), 61.9 (CH₂N), 45.7 (NMe₂), 9.5 (CH₃-Bf) ppm. MS (ESI+): Calculated for C₂₀H₂₂ClNO₃ [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 the 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 CHCl₃:MeOH). The solvent was evaporated under vacuum and the crude purified by flash chromatography (8:2 CHCl₃:MeOH) to afford **26** in 58% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.72 (d, *J*_{*o-m*} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.46 (d, *J*_{*4-6*} = 2.0 Hz, 1 H, H-4Bf), 7.36 (d, *J*_{*7-6*} = 8.6 Hz, 1 H, H-7Bf), 7.21 (dd, 1 H, H-6Bf), 7.03 (d, 2 H, 2 x H-*o*-Phe-O), 4.15 (m, 1 H, CHOH), 4.05 (d, *J*_{*vic*} = 4.9 Hz, 2 H, CH₂O), 2.81-2.56 (m, 10 H, CH₂N), 2.40 (s, 3 H, CH₃-Bf), 2.37 (s, 3 H, NMe) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 (C-6Bf), 118.9 (C-4Bf), 114.9 (C-*o*-Ph-O), 111.9 (C-7Bf), 109.6 (C_q), 70.4 (CH₂O), 65.6 (CHOH), 60.5 (CH₂NCH₂CH₂NMe), 55.0 (CH₂NCH₂CH₂NMe), 45.8 (NCH₃), 9.5 (CH₃-Bf) ppm. MS (ESI+): Calculated for C₂₃H₂₈ClN₂O₃ [M+H]⁺ 415.2, Found 415.5.

1-(4-(5-chloro-3-methylbenzofuran-2-yl)phenoxy)-3-(cyclopropylamino) propan-2-ol (27): The 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 was purified by flash chromatography (96:4 CHCl₃:MeOH) leading to product **27** (13 mg, 23

μmol) in 60% yield. ¹H-NMR (400 MHz, CD₃OD): δ = 7.76 (d, *J*_{*o-m*} = 8.5 Hz, 2 H, 2 x H-*m*-Phe-O), 7.53 (d, *J*_{*4-6*} = 2 Hz, 1 H, H-4Bf), 7.41 (d, *J*_{*7-6*} = 8.5 Hz, 2 H, H-7Bf), 7.23 (dd, 1 H, H-6Bf), 7.12 (d, 2 H, 2 x H-*o*-Phe-O), 4.36-4.29 (m, 1 H, CH-O), 4.15-4.06 (m, 2 H, CH₂-O), 3.88 (bs, 1 H, NH), 3.43 (dd, *J*_{*gem*} = 12 Hz, *J*_{*vic*} = 2 Hz, 1 H, CH₂-N), 3.30-3.25 (m, 1 H, CH₂-N), 2.85-2.78 (m, 1 H, CH-N), 2.41 (s, 3 H, CH₃-Bf), 1.00-0.91 (m, 4 H, CH₂-cycle) ppm. ¹³C-NMR (100 MHz, CD₃OD): δ = 160.0 (C_q), 153.5 (C_q), 153.3 (C_q), 134.0 (C_q), 129.3 (2 x C-*m*-Ph-O), 129.1 (C_q), 125.3 (C_q), 125.1 (C-6Bf), 119.7 (C-4Bf), 115.9 (2 x C-*o*-Ph-O), 112.7 (C-7Bf), 110.7 (C_q), 71.0 (CH₂-O), 66.3 (CH-O), 51.9 (CH₂-N), 31.5 (CH-N), 9.3 (CH₃-Bf), 4.3 (CH₂-cycle), 4.0 (CH₂-cycle) ppm. ESI-MS: calcd for C₂₃H₂₇ClNO₃ [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 was purified by flash chromatography (97:3 CHCl₃:MeOH, R_f=0.3) leading to product **28** (24 mg, 59 μmol) in 93% yield. ¹H-NMR (400 MHz, 9:1 CD₃OD:1,4-dioxane-d8): δ = 7.73 (d, *J*_{*o-m*} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.50 (d, *J*_{*4-6*} = 2 Hz, 1 H, H-4Bf), 7.40 (d, *J*_{*7-6*} = 8.8 Hz, 2 H, H-7Bf), 7.21 (dd, 1 H, H-6Bf), 7.10 (d, 2 H, 2 x H-*o*-Phe-O), 4.34-4.26 (m, 1 H, CH-O), 4.14-4.05 (m, 2 H, CH₂-O), 3.69-3.55 (m, 1 H, CH-N), 3.36-3.28 (m, 1 H, CH₂-N), 3.21-3.12 (m, 1 H, CH₂-N), 2.37 (s, 3 H, CH₃-Bf), 2.22-2.10 (m, 2 H, CH₂-cycle), 1.89-1.78 (m, 2 H, CH₂-cycle), 1.62 (m, 4 H, CH₂-cycle) ppm. ¹³C-NMR (100 MHz, 9:1 CD₃OD:1,4-dioxane-d8): δ = 160.2 (C_q), 153.6 (C_q), 153.5 (C_q), 134.2 (C_q), 129.4 (2 x C-*m*-Ph-O), 129.3 (C_q), 125.4 (C_q), 125.2 (C-6Bf), 119.9 (C-4Bf), 116.1 (2 x C-*o*-Ph-O), 112.9 (C-7Bf), 110.8 (C_q), 71.2 (CH₂-O), 67.0 (CH-O), 61.0 (CH-N), 50.6 (CH₂-N), 30.8 (CH₂-cycle), 30.7 (CH₂-cycle), 25.2 (CH₂-cycle), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₃H₂₇ClNO₃ [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 NaN₃ (24 mg, 0.37 mmol) and Yb(OTf)₃ (15.5 mg, 36 μmol) in H₂O (0.18 mL) was added and the solution was stirred for 5 days 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 H₂O and once with brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude 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, CDCl₃): δ = 7.73 (d, *J*_{*o-m*} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.47 (d, *J*_{*4-6*} = 2 Hz, 1 H, H-4Bf), 7.37 (d, *J*_{*7-6*} = 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, CH₂-O), 3.60 (dd, *J*_{*gem*} = 12.7 Hz, *J*_{*vic*} = 4.7 Hz, 1 H, CH₂-N₃), 3.54 (dd, *J*_{*gem*} = 12.7 Hz, *J*_{*vic*} = 6.0 Hz, 1 H, CH₂-N₃), 2.41 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 158.3 (C_q), 132.8 (C_q), 128.4 (2 x C-*m*-Ph-O), 128.1 (C_q), 124.6 (C_q), 124.2 (C-6Bf), 118.9 (C-4Bf), 114.9 (2 x C-*o*-Ph-O), 111.9 (C-7Bf), 109.8 (C_q), 69.4 (CH-O), 69.3 (CH₂-O), 53.5 (CH₂-N₃), 9.5 (CH₃-Bf) ppm. ESI-MS: calcd for C₁₈H₁₇ClN₃O₃ [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 PtO₂ (1.3 mg, 2 μmol) were added to the solution. The reaction mixture was stirred for 1 h under H₂ atmosphere; the reaction progress was followed by TLC (8:2:0.2 CHCl₃:MeOH:AcOH, R_f=0.49). The reaction mixture was filtered on a celite pad and concentrated *in vacuo*. The crude was purified by flash chromatography (75:25:0.2 CHCl₃:MeOH:AcOH, R_f=0.35) leading to product **30** (13 mg, 40 μmol) in 71% yield. ¹H-NMR (400 MHz, CD₃OD): δ = 7.71 (d, *J*_{*o-m*} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.50 (d, *J*_{*4-6*} = 2 Hz, 1 H, H-4Bf), 7.39 (d, *J*_{*7-6*} = 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, CH₂-O), 3.99-3.92 (m, 1 H, CH-O), 2.96-2.84 (m, 1 H, CH₂-NH₂), 2.84-2.72 (m, 1 H, CH₂-NH₂), 2.38 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): δ = 160.5 (C_q), 153.7 (C_q), 153.4 (C_q), 134.1 (C_q), 129.3 (2 x C-*m*-Ph-O), 129.1 (C_q), 125.0 (C-6Bf), 125.0 (C_q), 119.7 (C-4Bf), 115.9 (2 x C-*o*-Ph-O), 112.7 (C-7Bf), 110.5

(C_q), 71.6 (CH-O), 71.4 (CH₂-O), 45.1 (CH₂-NH₂), 9.3 (Cp, CH₃-Bf) ppm. ESI-MS: calcd for C₁₈H₁₉ClNO₃ [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). H₂O (75 μ L) and 4 M solution of HCl in dioxane (32 μ L) 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 H₂O. The water layer was extracted with EtOAc three times. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by flash chromatography (8:2 Hex:EtOAc, R_f=0.28) leading to product **31** (6 mg, 38 μ mol) in 60% yield. ¹H-NMR (400 MHz, CD₃OD): δ = 7.73 (d, J_{o-m} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.51 (d, J₄₋₆ = 2 Hz, 1 H, H-4Bf), 7.40 (d, J₇₋₆ = 8.8 Hz, 2 H, H-7Bf), 7.22 (dd, 1 H, H-6Bf), 7.09 (d, 2 H, 2 x H-*o*-Phe-O), 4.13 (dd, J_{gem} = 9.3 Hz, J_{vic} = 3.9 Hz, 1 H, CH₂-O), 4.06-3.97 (m, 3 H, CH₂-O, CH-O), 3.71 (dd, J_{gem} = 11.2 Hz, J_{vic} = 5.3 Hz, 1 H, CH₂-OH), 3.67 (dd, J_{vic} = 5.3 Hz, 1 H, CH₂-OH), (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): δ = 160.6 (C_q), 153.8 (C_q), 134.1 (C_q), 130.2 (C_q), 129.3 (2 x CH-*m*-Phe-O), 129.1 (C_q), 125.0 (C-6Bf), 124.9 (C_q), 119.7 (C-4Bf), 115.9 (2 x C-*o*-Phe-O), 112.7 (C-7Bf), 110.5 (C_q), 71.8 (CH-O), 70.4 (CH₂-O), 64.1 (CH₂-OH), 9.3 (CH₃-Bf). ESI-MS: calculated for C₁₈H₁₈ClO₄ [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 CHCl₃:MeOH). The solvent was evaporated under vacuum and the crude purified by flash chromatography (95:5 CHCl₃:MeOH) to afford **32** in 45% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.72 (d, J_{o-m} = 9.2 Hz, 2 H, 2xH-*m*-Phe-O), 7.62 (d, J₄₋₆ = 1.5 Hz, 1 H, H-4Bf), 7.35 (dd, J₆₋₇ = 8.4 Hz, 2 H, H-6Bf), 7.32 (d, 1 H, H-7Bf), 7.03 (d, 2 H, 2xH-*m*-Phe-O), 4.18-4.12 (m, 1 H, CH-O), 4.05 (d, J_{vic} = 4.9 Hz, 2 H, CH₂-O), 2.18-2.16 (bs, 2 H, NCH₂CH₂NMe), 2.60-2.58 (m, 8 H, CH₂NCH₂CH₂NMe), 2.40 (s, 3 H, CH₃-N), 2.39 (s, 3 H, CH₃Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 158.9 (C_q), 152.5 (C_q), 152.2 (C_q), 133.5 (C_q), 128.4 (2 x C-*m*-Phe-O), 126.8 (C-6Bf), 124.1 (C_q), 122.0 (C-4Bf), 115.5 (C_q), 115.0 (2 x C-*m*-Phe-O), 112.4 (C-7Bf), 70.4 (CH₂-O), 65.7 (CH-OH), 60.5 (CH₂NCH₂CH₂NMe), 55.0 (CH₂NCH₂CH₂NMe), 45.7 (CH₃-N), 9.3 (CH₃Bf) ppm. ESI-MS: calcd for C₂₃H₂₈BrN₂O₃ [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 μ L, 0.155 mmol) and the reaction was stirred at 30 °C under nitrogen atmosphere for 20 h. Morpholine (11 μ L, 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 CHCl₃:MeOH:HCOOH) the reaction mixture was diluted with Et₂O and washed with 0.1 M HCl. The organic phase was dried over anhydrous Na₂SO₄ and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (4:6 Hex:EtOAc) obtaining the desired product **34** (8.4 mg) as a white solid in 35% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.73 (d, J_{o-m} = 8.0 Hz, 2 H, 2 x CH-*m*-Ph-O), 7.47 (s, 1 H, H-4Bf), 7.37 (d, J₇₋₆ = 8.4 Hz, 1 H, H-7Bf), 7.21 (d, 1 H, H-6Bf), 7.06 (d, 2 H, 2 x C-*o*-Ph-O), 4.76 (s, 2 H, CH₂OAr), 3.66 (m, 8 H, CH₂-Morf), 2.41 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 166.5 (C=O), 157.8 (C_q), 152.2 (C_q), 132.8 (C_q), 128.5 (2 x C-*m*-Ph-O), 128.1 (C_q), 124.9 (C_q), 124.2 (C-6Bf), 118.9 (C-4Bf), 115.0 (2 x C-*o*-Ph-O), 111.9 (C-7Bf), 67.8 (CH₂OAr), 67.0 (2xCH₂O), 46.1 (CH₂N), 42.6 (CH₂N), 9.5 (CH₃-Bf) ppm. HRMS (ESI): Calcd for C₂₁H₂₀ClNNO₄ [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 was re-dissolved in dry DCM (0.1 mL) and 1-methylpiperazine

(300 μ L, 2.7 mmol) was added. The reaction was stirred at 40 °C overnight (TLC 9:1:0.1 CHCl₃:MeOH:TEA). The solvent was evaporated *in vacuo* and the crude was purified using an automatic system (SiO₂, DCM:MeOH gradient from 0 to 14% MeOH) obtaining the desired product **35** (28 mg) as a white solid in 78% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 7.73 (d, J_{o-m} = 8.9 Hz, 2 H, 2 x CH-*m*-Ph-O), 7.46 (d, J₄₋₆ = 2.1 Hz, 1 H, H-4Bf), 7.36 (d, J₇₋₆ = 8.6 Hz, 1 H, H-7Bf), 7.21 (dd, 1 H, H-6Bf), 7.06 (d, 2 H, 2 x CH-*o*-Ph-O), 4.75 (s, 2 H, CH₂OAr), 3.70 (m, 2 H, CH₂N), 3.66 (m, 2 H, CH₂N), 2.46 (m, 4 H, 2 x CH₂NMe), 2.40 (s, 3 H, CH₃-Bf), 2.34 (s, 3 H, NMe) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 166.3 (C=O), 157.9 (C_q), 152.2 (C_q), 132.8 (C_q), 128.5 (2 x C-*m*-Ph-O), 128.1 (C_q), 124.8 (C_q), 124.2 (C-6Bf), 118.9 (C-4Bf), 115.0 (2 x C-*o*-Ph-O), 111.9 (C-7Bf), 109.9 (C_q), 67.8 (CH₂OAr), 55.1 (CH₂N), 54.6 (CH₂N), 46.0 (NCH₃), 45.1 (CH₂NMe), 41.9 (CH₂NMe), 9.5 (CH₃-Bf) ppm. ESI-MS: Calculated for C₂₂H₂₄ClN₂O₃ [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 4 Å molecular sieves were added. The reaction mixture was cooled at -30 °C and TMSOTf (8.3 μ L, 46 μ mol) 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 was purified by flash chromatography (8:1:1 Hex:EtOAc:toluene) leading to product **37** (87 mg, 0.13 mmol) in 50% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 8.16 (d, J_{o-m} = 7.6 Hz, 2 H, 2x *o*-CH-Bz), 7.98 (d, J_{o-m} = 7.6 Hz 2 H, 2x *o*-CH-Bz), 7.87 (d, J_{o-m} = 7.8 Hz, 2 H, 2x *o*-CH-Bz), 7.81 (d, J_{p-m} = 9.0 Hz, 2 H, 2x *m*-CH-Bz), 7.70-7.63 (m, 1 H, *p*-CH-Bz), 7.57-7.50 (m, 3 H, *p*-CH-Bz, 2 x *m*-CH-Bz), 7.49 (d, J₄₋₆ = 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 x *m*-CH-Bz), 7.39 (d, J₇₋₆ = 8.5 Hz, 1 H, H-7Bf), 7.34 (d, 2 H, H-*o*-Phe-O), 7.32-7.27 (m, 2 H, 2 x *m*-CH-Bz), 7.23 (dd, 1 H, H-6Bf), 6.14 (dd, J₃₋₄ = 10.0 Hz, J₃₋₂ = 3.2 Hz, 1 H, H₃), 6.00 (dd, J₄₋₅ = 10.0 Hz, 1 H, H₄), 5.93-5.90 (m, 1 H, H₂), 5.9 (d, J_{1-2'} = 1.9 Hz, 1 H, H₁), 4.43-4.37 (m, 1 H, H₅), 3.54 (dd, J_{5-6'a} = 6 Hz, J_{6'a-6'b} = 13.3 Hz, 1 H, H_{6'a}), 3.45 (dd, J_{5-6'b} = 2.5 Hz, 1 H, H_{6'b}), 2.44 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 (C₁), 71.2 (C₅), 70.1 (C₂), 69.5 (C₃), 67.4 (C₄), 51.2 (C₆), 9.4 (CH₃-Bf) ppm. ESI-MS: calcd for C₄₂H₃₂ClN₃NaO₉ [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 μ mol) was dissolved in MeOH (0.26 mL) under nitrogen atmosphere. To the reaction mixture MeONa (3 mg, 53 μ mol) 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 was purified by flash chromatography (96:4 DCM:MeOH, R_f=0.28) leading to product **38** (7 mg, 17 μ mol) in 79% yield. [α]_D²⁵ = +81 (c=0.1, MeOH). ¹H-NMR (400 MHz, CD₃OD): δ = 7.74 (d, J_{o-m} = 8.8 Hz, 2 H, H-*m*-Phe-O), 7.50 (d, J₄₋₆ = 2.0 Hz, 1 H, H-4Bf), 7.40 (d, J₇₋₆ = 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, J₁₋₂ = 1.6 Hz, 1 H, H₁), 4.07 (dd, J₂₋₃ = 3.4 Hz, 1 H, H₂), 3.92 (dd, J₃₋₄ = 8.8 Hz, 1 H, H₃), 3.78-3.67 (m, 2 H, H₄, H₅), 3.50-3.40 (m, 2 H, H₆), 2.44 (s, 3 H, CH₃-Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 (C₁), 74.5 (C₅), 72.0 (C₃), 71.5 (C₂), 69.0 (C₄), 52.6 (C₆), 9.4 (CH₃-Bf) ppm. ESI-MS: calcd for C₂₁H₂₁ClN₃NaO₉ [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 CHCl₃ (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 (2x20 mL), dried over Na_2SO_4 and concentrated in vacuum. The desired product **40** (35 mg, 0.06 mmol) was purified by flash chromatography (8:2 Hex:EtOAc) and obtained in 40% yield. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.74 (d, J_{o-m} = 8.8 Hz, 2 H, H-*m*-Phe-O), 7.48 (d, J_{4-6} = 2.0 Hz, 1 H, H-4Bf), 7.37 (d, J_{7-6} = 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_{5-6a} = 2.4 Hz, J_{6a-6b} = 11 Hz, 1 H, H_{6a}), 3.43 (dd, J_{5-6b} = 8 Hz, 1 H, H_{6b}), 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. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 169.6 ($\text{C}_q=\text{O}$), 169.4 ($\text{C}_q=\text{O}$), 169.3 ($\text{C}_q=\text{O}$), 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 (3x CH_3 -Ac), 9.5 (CH_3 -Bf) ppm. ESI-MS: calcd for $\text{C}_{27}\text{H}_{26}\text{ClN}_3\text{NaO}_9$ [$\text{M}+\text{Na}$] $^+$ 595.1, found 594.9

4-[5-chloro-3-methylbenzofuran-2-yl]phenyl-6-azido- β -D-glucofuranoside (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 days, 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 the final product **41**, obtained in 64% yield (17 mg, 0.038 mmol) and sufficient purity, as judged by $^1\text{H-NMR}$ (d_6 -acetone). $[\alpha]_D^{25} = -58$ (c=0.1, Acetone). $^1\text{H-NMR}$ (400 MHz, $(\text{CD}_3)_2\text{CO}$): δ = 7.79 (d, J_{o-m} = 8.8 Hz, 2 H, H-*m*-Phe-O), 7.62 (d, J_{4-6} = 2.5 Hz, 1 H, H-4Bf), 7.51 (d, J_{7-6} = 8.8 Hz, 1 H, H-7Bf), 7.35-7.24 (m, 3 H, H-*o*-Phe-O, H-6Bf), 5.13 (d, J_{1-2} = 4.6 Hz, 1 H, H_1), 3.91 (d, J_{5-6a} = 2.0 Hz, J_{6a-6b} = 11.0 Hz, 1 H, H_{6a}), 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. $^{13}\text{C-NMR}$ (100 MHz, $(\text{CD}_3)_2\text{CO}$): δ = 158.9 (C_q), 133.7 (C_q), 128.9 (C-*m*-Ph-O), 128.6 (C_q), 125.6 (2x 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 $\text{C}_{21}\text{H}_{20}\text{ClN}_3\text{Na}_3\text{O}_6$ [$\text{M}+\text{Na}$] $^+$ 468.9, found 468.7

2,3,4-tri-O-acetyl- β -L-arabinopyranosyl bromide 50:^[16] $\text{La}(\text{OTf})_3$ (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 over 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 $\alpha:\beta$ ratio of 1:1 (1.3 g, 60% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 6.36 (d, J_{1-2} = 3.1 Hz, 1 H, $\text{H}_{1\beta}$), 5.67 (d, J_{1-2} = 7.0 Hz, 1 H, $\text{H}_{1\alpha}$), 5.41-5.35 (m, 3 H, $\text{H}_{2\beta}$, $\text{H}_{3\beta}$, $\text{H}_{4\beta}$), 5.33-5.27 (m, 2 H, $\text{H}_{2\alpha}$, $\text{H}_{4\alpha}$), 5.12 (dd, J_{2-3} = 9.1 Hz, J_{3-4} = 3.5 Hz, 1 H, $\text{H}_{3\alpha}$), 4.11-4.02 (m, 2 H, $\text{H}_{5\alpha}$, $\text{H}_{5\beta}$), 3.87-3.75 (m, 2 H, $\text{H}_{5\alpha}$, $\text{H}_{5\beta}$), 2.22-2.01 (m, 24 H, OCOCH_3) ppm. $^{13}\text{C-NMR}$ (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 ($\text{C}_{1\alpha}$), 90.2 ($\text{C}_{1\beta}$), 69.9 ($\text{C}_{3\alpha}$), 68.5, 68.1, 67.1, 67.01, 66.7, ($\text{C}_{2\beta}$, $\text{C}_{3\beta}$, $\text{C}_{4\beta}$, $\text{C}_{2\alpha}$, $\text{C}_{4\alpha}$), 63.9, 62.8 ($\text{C}_{5\beta}$, $\text{C}_{5\alpha}$), 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 (3x10 mL) and finally dried over 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). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 6.69 (d, J_{1-2} = 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, $J_{5\text{eq}-5\text{ax}}$ = 13.3 Hz, 1 H, $\text{H}_{5\text{eq}}$), 3.93 (dd, $J_{5\text{ax}-4}$ = 1.9 Hz, 1 H, $\text{H}_{5\text{ax}}$), 2.15 (s, 3 H, OCOCH_3), 2.11 (s, 3 H, OCOCH_3), 2.02 (s, 3 H, OCOCH_3) ppm. $^{13}\text{C-NMR}$ (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 spectral 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(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-arabinopyranosyl 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 0.1M HCl aq., saturated NaHCO_3 solution and brine. The organic phase was dried over 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) obtaining the desired product (50.8 mg) as a white solid in 83% yield. $[\alpha]_D^{25} = +24$ (c 0.5, DCM). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.73 (d, J_{o-m} = 8.8 Hz, 2 H, 2 x H-*m*-Phe-O), 7.47 (d, J_{4-6} = 2.1 Hz, 1 H, H-4Bf), 7.37 (d, J_{7-6} = 8.6 Hz, 1 H, H-7Bf), 7.22 (dd, 1 H, H-6Bf), 7.12 (d, 2 H, 2 x H-*o*-Phe-O), 5.46 (dd, J_{1-2} = 8.7, J_{3-2} = 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, $J_{5\text{ax}-5\text{eq}}$ = 12.8, $J_{4'-5'\text{eq}}$ = 4.1 Hz, 1 H, $\text{H}_{5'\text{eq}}$), 3.79 (dd, $J_{4'-5'\text{ax}}$ = 2.1 Hz, 1 H, $\text{H}_{5'\text{ax}}$), 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. $^{13}\text{C-NMR}$ (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: Calculated for $\text{C}_{26}\text{H}_{25}\text{ClK}_2\text{O}_9$ [$\text{M}+\text{K}$] $^+$ 555.2 found 554.9. 1M 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) obtaining the desired product **44** (28.1 mg) as a white solid in 73% yield. $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ = 7.74 (d, J_{o-m} = 8.9 Hz, 2 H, 2 x H-*m*-Phe-O), 7.53 (d, J_{4-6} = 2.0 Hz, 1 H, H-4Bf), 7.42 (d, J_{7-6} = 8.6 Hz, 1 H, H-7Bf), 7.25-7.18 (m, 3 H, H-6Bf, 2 x H-*o*-Phe-O), 4.94 (d, J_{1-2} = 7.2 Hz, 1 H, H_1), 3.96 (dd, $J_{5\text{eq}-5\text{ax}}$ = 12.4 Hz, $J_{5\text{ax}-4}$ = 2.8 Hz, 1 H, $\text{H}_{5\text{eq}}$), 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, $\text{H}_{5\text{ax}}$), 3.67 (dd, J_{3-4} = 3.5 Hz, 1 H, H_3), 2.40 (s, 3 H, CH_3 Bf) ppm. $^{13}\text{C-NMR}$ (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 (C-6Bf), 119.8 (C-4Bf), 118.0 (C-*o*-Ph-O), 112.8 (C-7Bf), 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: Calculated for $\text{C}_{20}\text{H}_{19}\text{ClNaO}_6$ [$\text{M}+\text{Na}$] $^+$ 413.07624 Found 413.07695. $[\alpha]_D^{25} = -9.2$ (c0.1, 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 spectral 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 (2x30 mL), water (1x30 mL), saturated NaHCO₃ solution (1x40 mL) and brine (1x30 mL). The organic phase was dried over anhydrous Na₂SO₄, the solvent was evaporated *in vacuo* and the crude product (2.5 g) was purified using an automatic system (SiO₂, Hex:EtOAc gradient from 0 to 60% EtOAc) obtaining the desired product (1.8 g) as a white solid in 73:27 α:β ratio (from H₁¹H-NMR signal ratio) in quantitative yield. ¹H-NMR (400 MHz, CDCl₃): δ = 8.20-7.27 (m, 20 H, CH-Bz), 6.66 (d, J₁₋₂ = 3.5 Hz, 1 H, H_{1β}), 6.53 (d, J₁₋₂ = 3.1 Hz, 1 H, H_{1α}), 6.07 (dd, J_{3α-4α} = 9.3 Hz, J_{3α-2α} = 3.5 Hz, 1 H, H_{3α}), 5.96-5.90 (m, 2 H, H_{2β}, H_{3β}), 5.89 (t, 1H, H_{2α}), 5.81 (dt, J_{4α-5αax} = 9.2 Hz, J_{4α-5αeq} = 5.0 Hz, 1 H, H_{4α}), 5.55 (m, 1 H, H_{4β}), 4.61 (dd, J_{5βeq-5βax} = 13.0 Hz, J_{5βeq-4β} = 2.4 Hz, 1 H, H_{5βeq}), 4.37 (dd, J_{5αeq-5αax} = 11.5 Hz, 1 H, H_{5αeq}), 4.11-4.01 (m, 1 H, H_{5αax}, H_{5βax}) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 minutes (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 NaHCO₃ solution (3x10 mL), dried over anhydrous Na₂SO₄. The solvent was evaporated *in vacuo* and the crude product (680 mg) was obtained in 9:1 α:β ratio (from H₁¹H-NMR signal ratio) in 73% yield and used without further purification (the product is not stable on silica). ¹H-NMR (400 MHz, CDCl₃): δ = 8.32-7.27 (m, 15 H, CH-Bz), 6.82 (d, J_{1β-2β} = 4.1 Hz, 1 H, H_{1β}), 6.54 (d, J_{1α-2α} = 1.5 Hz, 1 H, H_{1α}), 6.29 (dd, J_{3α-4α} = 3.5 Hz, J_{3α-4α} = 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_{4α-5αax} = 10.6 Hz, J_{4α-5αeq} = 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_{5βeq-5βax} = 13 Hz, J_{5βeq-4β} = 1 Hz, 1 H, H_{5βeq}), 4.39 (dd, J_{5αeq-5αax} = 11.3 Hz, J_{5αeq-4α} = 5.7 Hz, 1 H, H_{5αeq}), 4.14 (m, 1 H, H_{5βax}), 4.09 (t, J_{5αax-4α} = 11.3 Hz, 1 H, H_{5αax}) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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 TBAl (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 (2x10 mL), water (2x10 mL) and brine (1x10 mL). The organic phase was dried over anhydrous Na₂SO₄, the solvent was evaporated *in vacuo* and the crude product (150 mg) was purified using an automatic system (SiO₂, Hex:EtOAc gradient from 0% to 40% EtOAc) obtaining the desired product (135.7 mg) in 84:16 α:β ratio (from H₁¹H-NMR signal ratio) as a white solid in 24% yield. ¹H-NMR (400 MHz, CDCl₃): δ = 8.33-7.16 (m, 19 H, CH-Bz, CH OBox), 6.75 (d, J_{1β-2β} = 4 Hz, 1 H, H_{1β}), 6.55 (d, J_{1α-2α} = 2.6 Hz, 1 H, H_{1α}), 6.09 (dd, J_{3α-4α} = 9.6 Hz, J_{2α-3α} = 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_{4α-5αeq} = 5.2 Hz, 1 H, H_{4α}), 5.47 (m, 1 H, H_{4β}), 4.62 (dd, J_{5βeq-5βax} = 13.4 Hz, J_{5βeq-4β} = 1.6 Hz, 1 H, H_{5βeq}), 4.40 (dd, J_{5αeq-5αax} = 11.5 Hz, 1 H, H_{5αeq}), 4.12 (dd, J_{5αax-4α} = 10.5 Hz, 1 H, H_{5αax}), 4.11 (m, 1 H, H_{5βax}) ppm. ¹³C-NMR (100 MHz, CDCl₃): 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, 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: Calculated for C₃₃H₂₅NNaO₉ [M+Na]⁺ 602.1 Found 602.2 Calculated 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 minutes. 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} (2x5 mL) and water (1x5 mL). The organic phase was dried over anhydrous Na₂SO₄, the solvent was evaporated *in vacuo* and the crude product (107.6 mg) was purified using an automatic system (SiO₂, Hex:EtOAc gradient from 0% to 20% EtOAc) obtaining a 56:44 α:β anomeric mixture (from H_{5eq}¹H-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)** [α]_D²⁵ = -29 (c=0.43, DCM). ¹H-NMR (400 MHz, CDCl₃): δ = 8.15 (d, J_{o-m} = 7.3 Hz, 2 H, 2x o-CH-Bz), 8.01 (d, J_{o-m} = 7.3 Hz, 2 H, 2x o-CH-Bz), 7.92 (d, J_{o-m} = 7.3 Hz, 2 H, 2x o-CH-Bz), 7.77 (d, J_{p-m} = 8.8 Hz, 2 H, 2x m-CH-Bz), 7.69-7.19 (m, 14 H, CH-Bz, H-4Bf, H-6Bf, H-7Bf, H-m-Phe-O, H-o-Phe-O), 6.16 (dd, J_{4'-3'} = 9.9 Hz, J_{2'-3'} = 3.4 Hz, 1 H, H_{3'}), 5.90 (m, 1 H, H₂), 5.86 (m, 1 H, H₄), 5.82 (br d, J_{1'-2'} = 2.1 Hz, 1 H, H_{1'}), 4.28 (dd, J_{5eq-5ax} = 11.2 Hz, J_{5eq-4'} = 5.5 Hz, 1 H, H_{5eq}), 4.02 (br t, J_{5ax-4'} = 10.7 Hz, 1 H, H_{5ax}), 2.43 (s, 3 H, CH₃ Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 165.9 (C=O Bz), 165.7 (2x 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 (2x o-CH-Bz), 130.0 (2x o-CH-Bz), 129.9 (2x 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 (2x m-CH-Bz), 128.6 (2x m-CH-Bz), 128.4 (2x 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 (C₁), 70.4 (C₂), 69.2 (C₃), 67.7 (C₄), 60.8 (C₅), 9.5 (CH₃ Bf) ppm. ESI-MS: Calculated for C₄₁H₃₁ClNaO₉ [M+Na]⁺ 725.2 Found 725.1 Calcd for [2M+Na]⁺ 1427.3 Found 1426.7. **β anomer (55)** [α]_D²⁵ = +66 (c=0.3, DCM) ¹H-NMR (400 MHz, CDCl₃): δ = 8.27 (bd, J_{o-m} = 7.7 Hz, 2 H, 2x o-CH-Bz), 8.15 (bd, J_{o-m} = 7.4 Hz, 2 H, 2x o-CH-Bz), 7.95 (bd, J_{o-m} = 7.2 Hz, 2 H, 2x o-CH-Bz), 7.74 (bd, 2 H, 2x m-CH-Bz), 7.69-7.19 (m, 14 H, CH-Bz, H-4Bf, H-6Bf, H-7Bf, H-m-Phe-O, H-o-Phe-O), 5.95 (m, 2 H, H₁, H₃), 5.82 (bt, J = 3.7 Hz, 1 H, H₂), 5.46 (m, 1 H, H₄), 4.58 (bdd, J_{5eq-5ax} = 13.2 Hz, J_{5eq-4'} = 1.7 Hz, 1 H, H_{5eq}), 4.01 (bdd, J_{5ax-4'} = 2.0 Hz, 1 H, H_{5ax}), 2.41 (s, 3 H, CH₃ Bf) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 165.6 (C=O Bz), 165.3 (2x 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 (2x o-CH-Bz), 130.0 (2x o-CH-Bz), 129.9 (2x o-CH-Bz), 129.6 (C_q Bz), 129.2 (C_q Bz), 129.1 (C_q Bz), 128.6 (2x m-CH-Bz), 128.6 (2x m-CH-Bz), 128.5 (2x 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 (C₁), 69.4 (C₄), 67.3 (C₃), 67.2 (C₂), 59.1 (C₅), 9.4 (CH₃ Bf) ppm.

4-[5-chloro-3-methylbenzofuran-2-yl]-phenoxy-α-L-lyxopyranoside (46): 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. ¹H-NMR (400 MHz, CD₃OD): δ = 7.71 (d, J_{o-m} = 8.9 Hz, 2 H, 2x H-m-Phe-O), 7.46 (bd, J₄₋₆ = 2 Hz, 1 H, H4-Bf), 7.36 (d, J₇₋₆ = 8.8 Hz, 1 H, H7-Bf), 7.21-7.14 (m, 3 H, H6-Bf, 2x H-o-Phe-O), 5.48 (d, J₁₋₂ = 2.9 Hz, 1 H, H₁), 4.03 (m, 1 H, H₂), 3.93-3.86 (m, 2 H, H₃, H₄), 3.78 (bdd, J_{5eq-5ax} = 11.4 Hz, J_{5eq-4'} = 3.9 Hz, 1 H, H_{5eq}), 3.59-3.50 (m, 1 H, H_{5ax}), 2.39 (s, 3 H, CH₃ Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD): 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 (C6-Bf), 119.3 (C4-Bf), 117.3 (C-o-Ph-O), 112.3 (C7-Bf), 110.4 (C_q), 99.3

(C₁), 72.0 (C₄), 70.7 (C₂), 67.8 (C₃), 64.3 (C₅), 9.5 (CH₃ Bf) ppm. ESI-MS: Calculated for C₂₀H₁₉ClNaO₆ [M+Na]⁺ 413.1 Found 413.0 HR-MS Calculated for C₂₀H₁₉ClNaO₆ [M+Na]⁺ 413.07624 Found 413.07817

4-[5-chloro-3-methylbenzofuran-2-yl]-phenoxy-β-L-lyxopyranoside

(47): 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. ¹H-NMR (400 MHz, CD₃OD/CDCl₃): δ = 7.74-7.70 (m, 2 H, 2 x H-*m*-Phe-O), 7.47 (d, J₄₋₆ = 2.0 Hz, 1 H, H₄-Bf), 7.37 (d, J₇₋₆ = 8.7 Hz, 1 H, H₇-Bf), 7.23-7.18 (m, 3 H, H₆-Bf, 2 x H-*o*-Phe-O), 5.37 (d, J_{1-2'} = 2.6 Hz, 1 H, H₁), 4.12-4.07 (m, 2 H, H₂, H_{5eq}), 3.89-3.84 (m, 1 H, H₄), 3.79 (dd, J_{3-2'} = 6.2 Hz, J₃₋₄ = 3.5 Hz, 1 H, H₃), 3.43 (dd, J_{5eq-5ax} = 11.9 Hz, J_{5ax-4'} = 5.5 Hz, 1 H, H_{5ax}), 2.40 (s, 3 H, CH₃ Bf) ppm. ¹³C-NMR (100 MHz, CD₃OD/CDCl₃): 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 (C₆-Bf), 119.5 (C₄-Bf), 117.7 (C-*o*-Ph-O), 112.5 (C₇-Bf), 110.6 (C_q), 99.2 (C₁), 72.8 (C₃), 69.2 (C₄), 68.3 (C₂), 63.2 (C₅), 9.4 (CH₃ Bf) ppm. HRMS: Calculated for C₂₀H₁₉ClNaO₆ [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 spectral 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**.

Acknowledgements

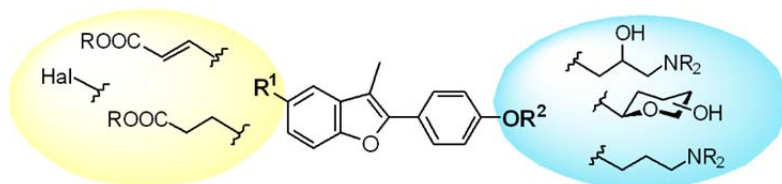
This work was supported by Premio Fondazione Cariplo-Ricerca di frontiera 2011 (Project: Chemical control of signalling pathways by modulation of hub proteins, CheCOSP). We thank L. Sedda for help with the synthesis of non-metabolic sugar derivatives. S.S. was supported by a post-doctoral fellowship from Univeristà degli Studi di Milano (Assegno di tipo A). G.C. was supported by the Associazione Italiana Ricerca sul Cancro (AIRC) through grant IG 15420. The HRMS spectra have been obtained from CIGA (Centro Interdipartimentale Grandi Apparecchiature, Università degli Studi di Milano).

Keywords: Hsp90 • benzofuran • STD-NMR • Novobiocin • allosteric modulators

- [1] L. H. Pearl, C. Prodromou, *Curr. Opin. Struct. Biol.* **2000**, *10*, 46-51.
 [2] R. R. A. Kitson, C. J. Moody, *J. Org. Chem.* **2013**, *78*, 5117-5141.
 [3] T. Taldone, A. Gozman, R. Maharaj, G. Chiosis, *Curr. Opin. Pharmacol.* **2008**, *8*, 370-374.
 [4] a) X. M. Yu, G. Shen, L. Neckers, H. Blake, J. Holzbeierlein, B. Cronk, B. S. J. Blagg, *J. Am. Chem. Soc.* **2005**, *127*, 12778-12779; b) J. A. Burlison, C. Avila, G. Vielhauer, D. J. Lubbers, J. Holzbeierlein, B. S. J. Blagg, *J. Org. Chem.* **2008**, *73*, 2130-2137.
 [5] a) B. K. Zierer, M. Weiwad, M. Rubbelke, L. Freiburger, G. Fischer, O. R. Lorenz, M. Sattler, K. Richter, J. Buchner, *Angew. Chem. Int. Ed.* **2014**, *53*, 12257-12262; b) S. Sattin, J. Tao, G. Vettoretti, E. Moroni, M. Pennati, A. Loperigolo, L. Morelli, A. Bugatti, A. Zuehlke, M. Moses, T. Prince, T. Kijima, K. Beebe, M. Rusnati, L. Neckers, N. Zaffaroni, D. A. Agard, A. Bernardi, G. Colombo, *Chem. Eur. J.* **2015**, *21*, 13598-13608.
 [6] a) G. Morra, M. A. C. Neves, C. J. Plescia, S. Tsustsumi, L. Neckers, G. Verkhivker, D. C. Altieri, G. Colombo, *J. Chem. Theory Comput.* **2010**, *6*, 2978-2989; b) E. Moroni, H. Zhao, B. S. Blagg, G. Colombo, *J. Chem. Inf. Model.* **2014**, *54*, 195-208.
 [7] G. Vettoretti, E. Moroni, S. Sattin, J. Tao, D. A. Agard, A. Bernardi, G. Colombo, *Sci Rep* **2016**, *6*, 23830.
 [8] L. Morelli, A. Bernardi, S. Sattin, *Carbohydr Res* **2014**, *390C*, 33-41.
 [9] O. Miyata, N. Takeda, T. Naito, *Org. Lett.* **2004**, *6*, 1761-1763.
 [10] N. Tomkinson, F. Contiero, K. Jones, E. Matts, A. Porzelle, *Synlett* **2009**, *2009*, 3003-3006.
 [11] H. M. Petrassi, K. B. Sharpless, J. W. Kelly, *Org. Lett.* **2001**, *3*, 139-142.
 [12] R. F. Heck, in *Organic Reactions*, John Wiley & Sons, Inc., **2004**.
 [13] M. Scharenberg, O. Schwardt, S. Rabbani, B. Ernst, *J. Med. Chem.* **2012**, *55*, 9810-9816.
 [14] S. Ordanini, Doctoral thesis, Università degli Studi di Milano **2014**.
 [15] C. Bullock, L. Hough, A. C. Richardson, *Carbohydr. Res.* **1990**, *197*, 131-138.
 [16] S. C. Timmons, D. L. Jakeman, *Carbohydr. Res.* **2008**, *343*, 865-874.
 [17] A. D. McNaught, *Carbohydr. Res.* **1997**, *297*, 1-92.
 [18] P. L. Durette, D. Horton, *Carbohydr. Res.* **1971**, *18*, 57-80.
 [19] S. S. Nigudkar, A. R. Parameswar, P. Pornsuriyasak, K. J. Stine, A. V. Demchenko, *Org. Biomol. Chem.* **2013**, *11*, 4068-4076.
 [20] a) M. Mayer, B. Meyer, *Angew. Chem. Int. Ed.* **1999**, *38*, 1784-1788; b) M. Mayer, B. Meyer, *J. Am. Chem. Soc.* **2001**, *123*, 6108-6117.
 [21] M. G. Marcu, T. W. Schulte, L. Neckers, *J. Natl. Cancer I.* **2000**, *92*, 242-248.
 [22] a) X. Y. Huang, Z. J. Shan, H. L. Zhai, L. N. Li, X. Y. Zhang, *J. Chem. Inf. Model.* **2011**, *51*, 1999-2006; b) R. L. Matts, A. Dixit, L. B. Peterson, L. Sun, S. Voruganti, P. Kalyanaraman, S. D. Hartson, G. M. Verkhivker, B. S. J. Blagg, *ACS Chem Biol* **2011**, *6*, 800-807; c) G. Garg, H. Zhao, B. S. J. Blagg, *ACS Med. Chem. Lett.* **2014**.
 [23] a) A. Donnelly, B. Blagg, S. J., *Curr. Med. Chem.* **2008**, *15*, 2702-2717; b) S. N. Shelton, M. E. Shawgo, S. B. Matthews, Y. Lu, A. C. Donnelly, K. Szabla, M. Tanol, G. A. Vielhauer, R. A. Rajewski, R. L. Matts, B. S. Blagg, J. D. Robertson, *Mol. Pharmacol.* **2009**, *76*, 1314-1322.
 [24] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.
 [25] H. G. Fletcher, R. K. Ness, C. S. Hudson, *J Am Chem Soc* **1951**, *73*, 3698-3699.

Entry for the Table of Contents

FULL PAPER

**Key Topic: Allosteric modulation**

Sara Sattin,* Matteo Panza, Francesca Vasile, Francesca Berni, Giulio Goti, Jiahui Tao, Elisabetta Moroni, David Agard, Giorgio Colombo, Anna Bernardi

Page No. – Page No.

Synthesis of functionalized 2-(4-hydroxyphenyl)-3-methylbenzofuran allosteric modulators of Hsp90 activity

Hsp90. ATP-regulated internal dynamics can be modulated in an allosteric fashion, targeting the protein C-terminal domain (CTD) with a family of 2-phenyl-benzofuran derivatives. Here we report 28 new derivatives that explore the chemical space at opposite ends of the benzofuran scaffold. Interaction of the compounds with the full-length protein was explored by STD-NMR.