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Diversity-oriented Synthesis of Libraries Based on Benzofuran and 2,3-Dihydrobenzofuran Scaffolds

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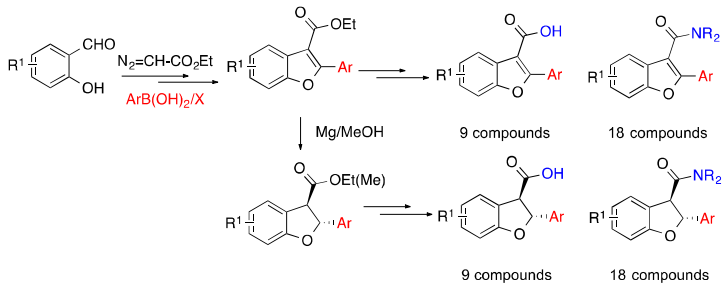
Abstract

Benzofuran and 2,3-dihydrobenzofuran scaffolds are core components in a large number of biologically active natural and synthetic compounds including approved drugs. Herein, we report efficient synthetic protocols for preparation of libraries based on 3-carboxy 2-aryl benzofuran and 3-carboxy 2-aryl *trans*-2,3-dihydrobenzofuran scaffolds using commercially available salicylaldehydes, aryl boronic acids or halides and primary or secondary amines. The building blocks were selected to achieve variation in physicochemical properties and statistical molecular design and subsequent synthesis resulted in 54 lead-like compounds with molecular weights of 299-421 and calculated octanol/water partition coefficients of 1.9-4.7.

TOC graphic



Keywords

diversity oriented synthesis, benzofuran, 2,3-dihydrobenzofuran

Introduction

Benzofuran and 2,3-dihydrobenzofuran scaffolds are ubiquitous structural motifs found in a vast number of natural products and synthetic compounds of which many display a wide range of activities including antiviral, antibacterial, anti-inflammatory, antiangiogenic and antimitotic activities (Figure 1).[1] Our own interest in these scaffolds originates from the finding that the resveratrol tetramer (-)-hopeaphenol, a complex plant stilbenoid isolated from the Papua Guinean species *Anisoptera thurifera* and *Anisoptera polyandra*, blocks type III secretion (T3S) of toxins in the gram-negative bacteria *Yersinia pseudotuberculosis* and *Pseudomonas aeruginosa* (Figure 1).[2] We have therefore initiated studies to expand our knowledge on the chemistry and biology of these scaffolds and recently we published total syntheses of (+/-)-ε-viniferin[3], (+/-)-ampelopsin[3], viniferifuran, a resveratrol-picetannol hybrid and anigopreissin A[4]. However, compared with complex natural products, successful lead compounds are typically smaller and simpler and have more drug-like properties.[5] To address this, we have directed our attention towards preparation of libraries suitable for screening and identification of novel bioactive structures based on benzofuran and 2,3-dihydrobenzofuran scaffolds.

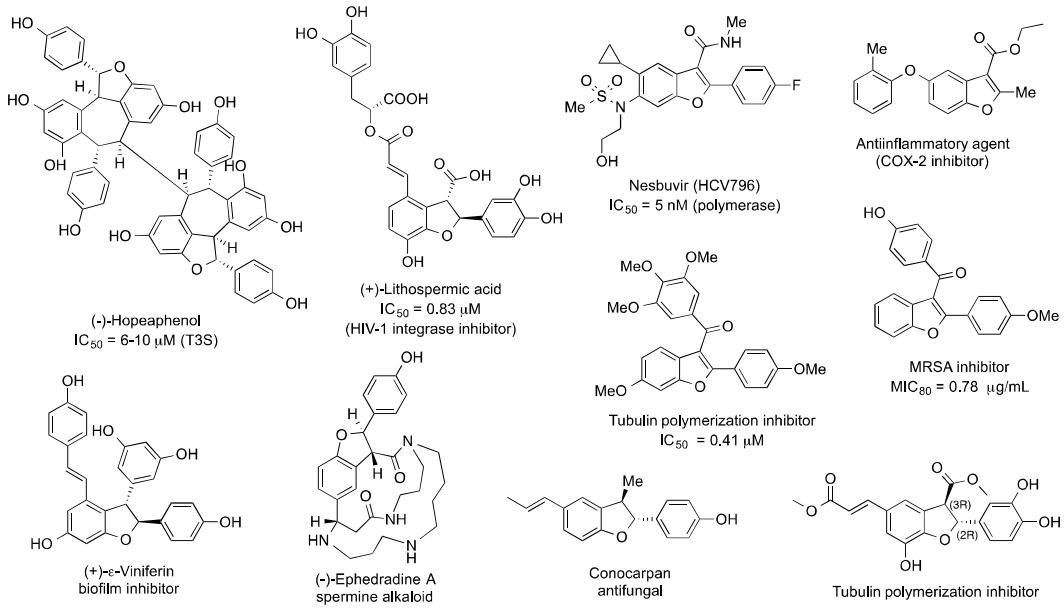


Figure 1. Examples of compounds based on benzofuran and 2,3-dihydrobenzofuran scaffolds. Natural compounds: (-)-hopeaphenol[2], (+)-lithospermic acid[6], (+)-ε-viniferin[7], conocarpan[8] and (-)-ephedradine[9]. Synthetic compounds: nesbuvir[10], a COX-2 inhibitor[11], two inhibitors of tubulin polymerization[12], and an inhibitor of methicillin resistant *Staphylococcuccus aureus*[13].

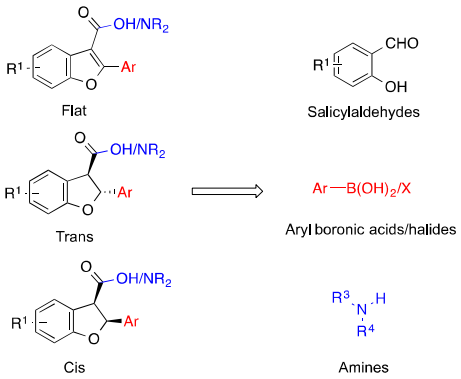
Building on Larock's publications describing palladium catalyzed heteroannulation of alkynes for indole synthesis[14], a number of methods for preparation of 2-arylbenzofuran-3-carboxylates by palladium catalyzed carbonylative heteroannulation of *o*-hydroxylarylacetylenes have been decribed[15] (reference 19 and publications cited therein). However, these methods require extra steps for preparation of o-hydroxylarylacetylenes by Sonogashira couplings and the us of alkynes as starting material also limits the scope by excluding heterocycle substrates. Preparation of 2,3-trans disubstituted 2,3-dihydrobenzofurans is however less straightforward[16] and most efforts have been directed towards total synthesis of resveratrol-based natural products. To the best of our knowledge, designed libraries of 2-arylbenzofuran-3-carboxylates and 2,3-trans disubstituted dihydrobenzofurans have not been reported. Herein we describe the design and synthesis of

lead-like libraries based on 3-carboxy 2-aryl benzofuran and 3-carboxy 2-aryl *trans*-2,3-dihydrobenzofuran scaffolds.

Results and discussion

We designed the libraries of 2-arylbenzofuran-3-carboxamides and 2,3-dihydro-2-aryl-benzofuran-3-carboxamides based on the analysis outlined in Scheme 1. By using readily available salicylaldehydes, aryl boronic acids or aryl halides and amines as building blocks, diverse target compounds can be achieved based on the flat benzofuran scaffold as well as the topographically distinct *cis*- and *trans*-substituted 2,3-dihydrobenzofuran scaffolds. The salicylaldehydes can be reacted with ethyl 2-diazoacetate to form the 3-carboxyfunctionalized benzofurans. Subsequent arylation furnishes the 2,3-disubstituded benzofuran that can be reduced to the *cis*-2,3-dihydrobenzofuran by catalytic hydrogenation. Reduction with NH_4Cl/Mg would on the other hand produce the corresponding *trans*-2,3-dihydrobenzofurans. Ester hydrolysis and amide coupling would eventually provide the flat, *cis* and *trans* target series. The benzofuran and 2,3-dihydrobenzofuran scaffolds were decorated with substituent originating from the building blocks shown in Figure 2. A statistical molecular design (SMD)[17] was performed to select a subset of compounds to be synthesized from the pool of possible building block combinations. In effect, SMD predisposes a set of compounds for a robust structure-activity relationship analysis after biological testing by making sure that the building blocks systematically appear in several molecules but in different combinations. This gives a more robust basis for identification of combination effects and avoids a situation where two building blocks always appear together in the molecules, thus making it impossible to elucidate the effect of the individual structural features. The building blocks in Figure 2 giving rise to the compounds in Figure 3 were selected to vary in their physicochemical features. The salicylaldehydes and the arylboronic acids contained both electron withdrawing

(fluorine) and electron donating (methoxy) substituents, and for the arylboronic acids, heteroaromatic features affect size, polarity and basicity. The amines were varied even more in size, and basicity with both aromatic and aliphatic ring structures and aliphatic chains affecting flexibility.



Scheme 1. Synthetic strategy to achieve 3-carboxy 2-aryl benzofuran and 3-carboxy 2-aryl *trans*-2,3-dihydrobenzofuran scaffolds starting from salicylaldehydes, arylboronic acids or arylhalides and amines.

The designed compounds were analyzed for their physicochemical properties and they were generally drug-like (80 of 81 compounds) and lead-like (77 of 81 compounds) according to definitions of Lipinski[18] and Oprea,[19] respectively. The molecular weights were in the range 228.2—421.5 (median of 299.8) and a calculated octanol/water partition coefficient between 1.9 and 5.3 (median of 3.0). Calculation details are provided in the Supporting Information.

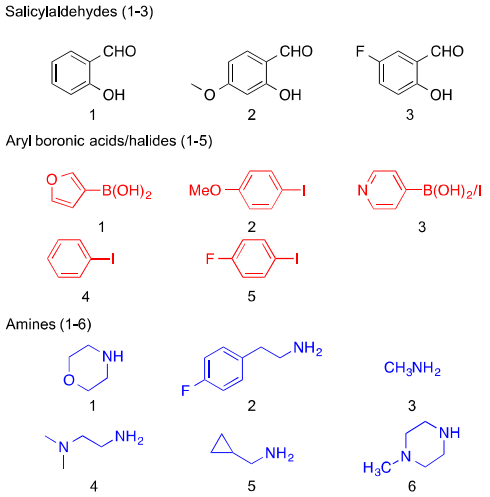
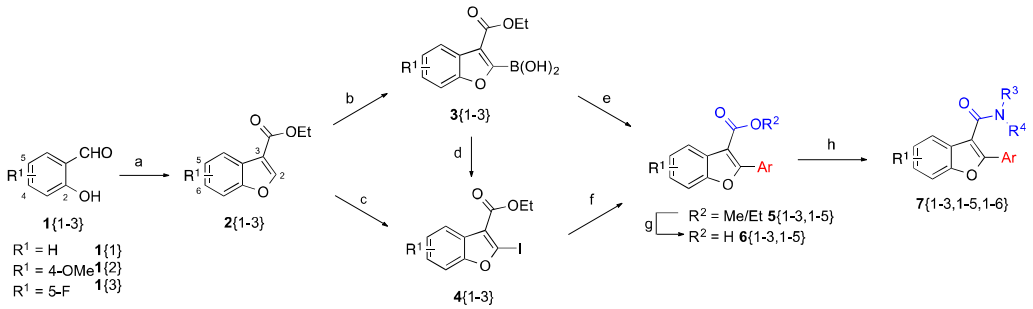


Figure 2. Selected salicylic aldehydes, arylboronic acids or arylhalides and amines.

The concise synthetic route for 2-arylbenzofuran-3-carboxamide derivatives is described in Scheme 2. Despite numerous efforts to synthesize benzofuran core structures, routes to benzofuran-3-carboxylate are rare. We applied a recently developed method described by Hossain and co-workers.[20] Starting from the salicylaldehyde and derivatives **1***{1-3}* we first constructed the 3-carboxylate benzofurans via reaction with ethyl 2-diazoacetate under catalysis by $HBF_4{\cdot}OEt_2$ followed by dehydratation in concentrated H_2SO_4 to furnish **2***{1-3}* in 66, 20 and 73% yield, respectively. These were then transformed into benzofuran-2-boronic acid derivatives **3***{1-3}* in excellent yields (88-98%) using trimethyl borate and lithium diisopropylamide (LDA) at -78 °C for 15 min. The boronic acid **3***{1-3}* were then submitted to a Suzuki couplings using $PdCl_2(dppf){\cdot}DCM$ (5 mol %) as catalyst. Coupling of **3***{1}* with 4-iodoanisole and 4-iodopyridine gave **5***{1,2}* and **5***{1,3}* in 70% and 50% yield respectively. However, when reacting 4-iodopyridine with **3***{2}* and **3***{3}* no or <10% coupling product was obtained, respectively. The second heteroaryl coupling partner 3-bromofuran followed this pattern and only **3***{3}* reacted to give **5***{3,1}* in 11% yield. To overcome the low efficiency of Suzuki couplings with the heteroaromatic coupling partners, we used a reversed strategy and prepared the 2-iodobenzofuran derivatives **4***{1-3}* by treatment of **2***{1-3}*, iodine and LDA in

43, 39 and 16% yield, respectively. Transformation of the boronic acids **3***{1-3}* into the corresponding iodo derivatives **4***{1-3}* did not result in improved yields. Applying Suzuki couplings on the iodo derivatives **4***{1-3}* with 4-pyridine boronic acid and 3-furan boronic acid gratifyingly produced **5***{1-3,1-5}* in 45-92% yield. Subsequent hydrolysis of the ester coupling products **5***{1-3,1-5}* under basic condition gave carboxylic acid derivatives **6***{1-3,1-5}* in 64-100% yield. Amide couplings applied on **6***{1-3,1-5}* using *N,N,N′,N′*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) as coupling reagent gave the target compounds **7***{1-3,1-5,1-6}* in 14-88% yield (Figure 3). *N,N*-dimethylethylenediamine proved to be the most challenging amine and the target compounds were only isolated in 14-28% yield.



Scheme 2. Synthetic route to 2-arylbenzofuran-3-carboxamide derivatives. Reagents and conditions: a) ethyl 2-diazoacetate (1.6-2.0 *equiv.*), $HBF_4 \cdot OEt_2$ (0.1 *equiv.*), rt, 1 h then conc. H_2SO_4, 15 min, rt, 23-73%; b) trimethylborate (2.2 *equiv.*), LDA solution (2.2 *equiv.*), THF, -78 °C, 15 min, 88-98%; c) I_2 (2.5 *equiv.*), LDA (3.5 *equiv.*), THF, -78 °C - rt, 24 h, 16-43%; d) NIS (1 *equiv.*), CH_3CN, rt, 24 h, 13%. e) iodo derivatives (1.0 -2.0 *equiv.*), $PdCl_2$(dppf)·DCM (5 mol%), DME/H_2O (1:1), Na_2CO_3 (4 *equiv.*), 70 °C, 30-80%; f) boronic acid (1.5-2.0 *equiv.*), $PdCl_2$(dppf)·DCM (5 mol%), DME/H_2O (1:1), Na_2CO_3 (4.0 *equiv.*), 70 °C, 45-92%; g) NaOH (4.0 *equiv.*), THF/MeOH/H_2O (1:1:1), 70 °C, 64-100%; h) amine (1.5-2.5 *equiv.*), TBTU (1.2 *equiv.*), DMF, rt, 24 h, 14-88%. DCM = dichloromethane; DME = 1,2-

dimethoxyethane; dppf = 1,1′-Bis(diphenylphosphino)ferrocene; NIS = N-iodosuccinimide; rt = room temperature; THF = tetrahydrofuran.

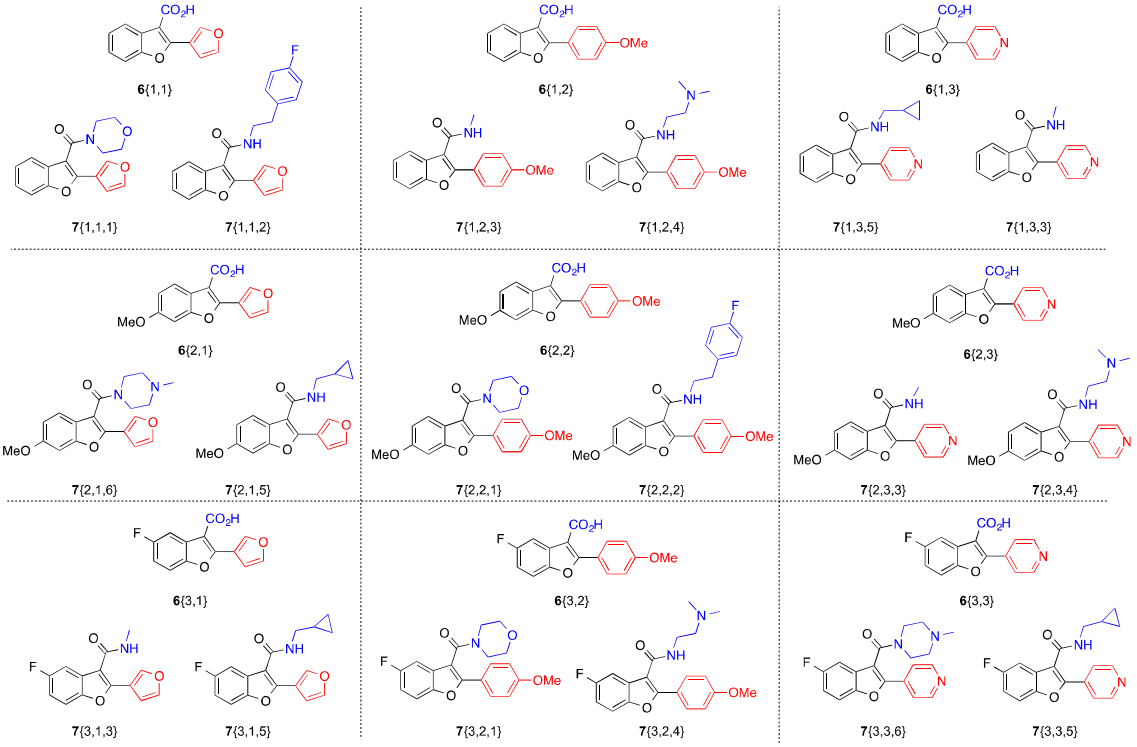
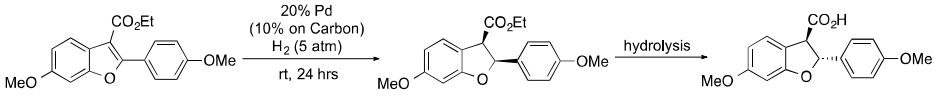


Figure 3. Synthesized and characterized compounds in the benzofuran series.

We then turned our attention to preparation of the *cis* series. Enantio- and diastereo-selective synthesis of *cis*-2,3-dihydrobenzofuran can be achieved by rhodium-catalyzed intramolecular C−H insertion reaction of aryldiazoacetates or donor-donor carbenoid chemistry.[16, 21] However, synthesis of products carrying a 3-carboxamide functional group have not been reported using these efficient protocols. Only one example of rhodium-catalyzed enantio-selective synthesis of *cis*-2-amide-3-aryl-2,3-dihydrobenzofuran have been reported and the synthetic sequence involves a multistep procedure to prepare the carbenoid precursor[22]. Instead we attempted to synthesize the *cis*-2,3-dihydrobenzofuran series by reducing the 2-

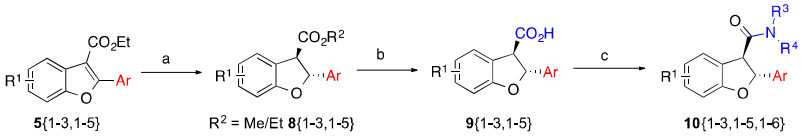
aryl-3-ethoxycarbonyl benzofuran by hydrogen catalyzed by palladium on carbon. The *cis*-ester could be isolated but the subsequent ester hydrolysis resulted in epimerization under both acidic and basic conditions (Scheme 3). In an alternative approach, we attempted to reduce the benzofuran ring after ester hydrolysis. However, in our hands this strategy failed to provide the target compounds. Based on these results we concluded that current methodology does not provide general procedures and we decided abandon our efforts towards the *cis* series.



Scheme 3. Attempts to synthesize the *cis*-2,3-dihydrobenzofuran series.

Instead we focused our efforts on preparation of the *trans* series employing NH_4Cl/Mg in methanol that predominantly produces *trans* 2,3-dihydrobenzofurans. The *trans* series was thus obtained by reduction followed by ester hydrolysis and amide formation as outlined in Scheme 4 to give the target **9***{1-3,1-5}* and **10***{1-3,1-5,1-6}* (Figure 4). The reduction typically resulted in a mixture of the desired trans isomer together with the cis-isomer as minor side-product. By performing the subsequent ester hydrolysis of the mixture at 70 °C the cis isomer was epimerized to the target *trans*-dihydrobenzofuran-3-carboxylic acid derivatives **9***{1-3,1-5}* as racemates in 25-80% yield over two steps. Next, coupling of **9***{1-3,1-5}* with corresponding amines using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate/triethyl amine (TBTU/Et_3N) as coupling reagent afforded the target amides **10***{1-3,1-5,1-6}* in moderate to good yields (41-88%). However, in the case of amide couplings with *N,N*-dimethylethylenediamine the yields were modest (14-28%). The *trans*

configuration was verified by comparing *J* coupling constants of the compounds with selected examples of *cis* and *trans* 2,3-dihydrobenzofurans[22-23].



Scheme 4. Synthetic sequence leading to the *trans* series consisting of compounds **9***{1-3,1-5}* and **10***{1-3,1-5,1-6}*. Reagents and conditions: a) Magnesium crumbles (10-30 *equiv.*), NH_4Cl (2.0 *equiv.*), THF-MeOH, 0 °C to rt; b) NaOH (2 M, 4.0 *equiv.*), THF-MeOH-H_2O, rt; c) amine (1.5 *equiv.*), TBTU (1.2 *equiv.*), triethyl amine (2.0 *equiv.*), *N*,*N*-dimethylformamide, rt. All chiral compounds were prepared and isolated as racemates.

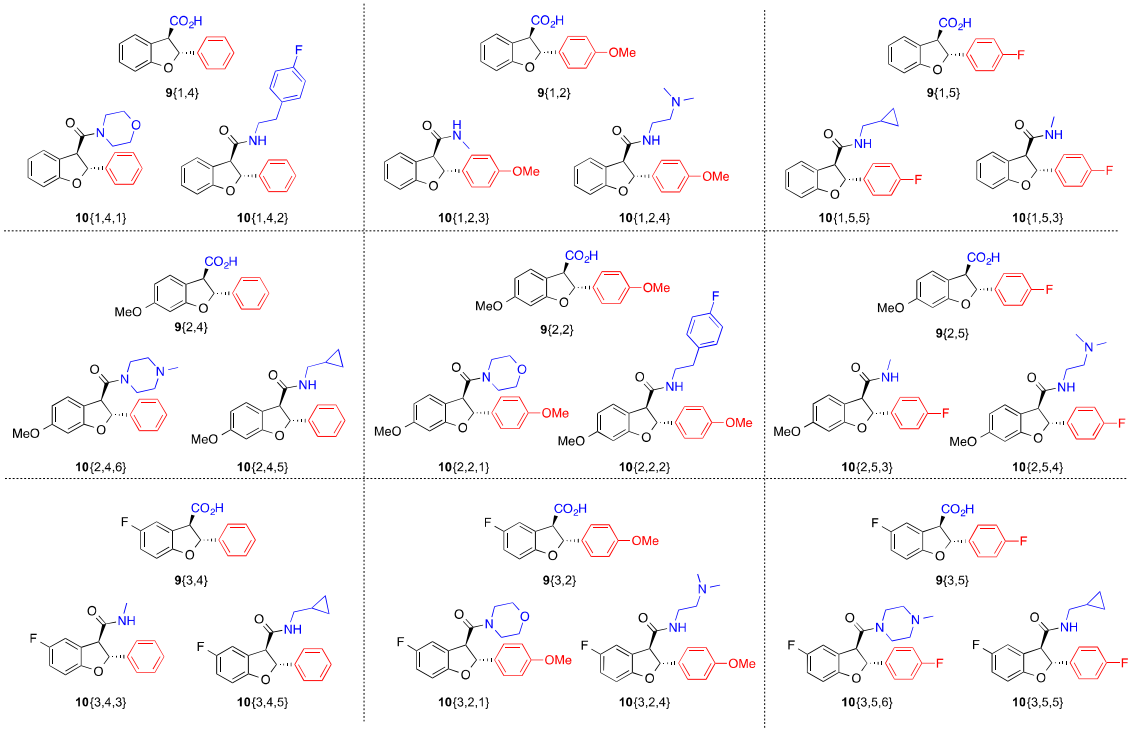


Figure 4. Synthesized and characterized compounds in the trans 2,3-dihydrobenzofuran series.

In conclusion, we applied statistical molecular design and prepared lead-like libraries based on 3-carboxy-2-aryl-benzofuran and 3-carboxy-2-aryl-*trans*-2,3-dihydrobenzofuran scaffolds using commercially available salicylaldehydes, aryl boronic acids or halides and primary or secondary amines. The approach is flexible and allows variation of structural features and physicochemical properties. The current compounds fall into the definition of lead- and drug-likeness with respect to molecular weights and calculated octanol/water partition coefficients. The compounds are thus well suited for incorporation in screening collection and the robust chemistry allow post screening medicinal chemistry to elucidate structure-activity relationships.

Experimental procedures

General procedure for preparation of intermediate 2 represented by the synthesis of ethyl benzofuran-3-carboxylate 2*{1}*. The compound was synthesized according to a reported procedure[20]. To a solution of salicylaldehyde (1.00 g, 8.2 mmol, 1.0 *equiv.*) in dichloromethane (7 mL) was added $HBF_4 \cdot OEt_2$ (132.6 mg, 0.819 mmol, 0.1 *equiv.*) at rt with stirring, to give a dark red mixture. The solution of ethyl diazoacetate (1.50 g, 13.2 mmol, 1.6 *equiv.*) in dichloromethane (5 mL) was added dropwise to the stirring mixture during a period of 10 min, resulting a steady release of nitrogen. The mixture was stirred for an extra h before removing the solvent on rotary evaporator. To the mixture was added concentrated sulfuric acid (0.4 mL); and the mixture was stirred for 10 min before neutralized with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (50 mL) and washed with water (25 mL) and brine (25 mL) consecutively. The desired product was purified by silica gel chromatography (heptane/ethyl acetate 97:3) and obtained as slightly yellow viscous oil (1.00 g, 66% yield).

General procedure for preparation of intermediate 3 represented by the synthesis of (3-(ethoxycarbonyl)-benzofuran-2-yl)boronic acid 3*{1}*. The compound was prepared according to a reported procedure[24]. A mixture of ethyl benzofuran-3-carboxylate **2***{1}* (1.57 g, 8.3 mmol, 1.0 *equiv.*) and trimethyl borate (1.91 g, 18.4 mmol, 2.2 *equiv.*) dissolved in dry THF (25 mL) was precooled at -78 °C in dry ice-acetone bath under the protection of nitrogen. LDA (9.2 mL, 2 M in THF/heptane/ethylbenzene, 2.2 *equiv.*) was added via syringe to the solution with stirring; and the resulting mixture was kept stirring at the same temperature for additional 15 min before quenched with HCl solution (30 mL, 4 M in H_2O). The reaction mixture was then allowed to stir at rt for 10 min before extraction with ethyl acetate (150 mL). The organic phase was washed with water (50 mL) and brine (50 mL) consecutively. The desired product was obtained after removal of solvents under reduced pressure as white solid (1.89 g, 98 % yield) and used for next step without further purification.

General procedure for preparation of intermediate 4 represented by the synthesis of ethyl 2-iodo-benzofuran-3-carboxylate 4*{1}*. The compound was prepared according to a reported procedure[25]. To a mixture of ethyl benzofuran-3-carboxylate **2***{1}* (1.54 g, 8.1 mmol, 1.0 *equiv.*) and iodine (5.13 g, 20.2 mmol, 2.5 *equiv.*) in THF (30 mL) at -78 °C in dry ice-acetone bath under the protection of nitrogen, was added LDA (14.2 mL, 2 M in THF/heptane/ethylbenzene, 3.5 *equiv.*). The mixture was allowed to warm up to room temperature and stirred overnight; and then quenched with saturated NH_4Cl solution (50 mL). The mixture was extracted with ethyl acetate (150 mL); and the organic phase was washed with water (50 mL) and brine (50 mL) consecutively. The solvents were evaporated under reduced pressure to give a resin-like residue (1.66 g), which was suspended in cold

cyclohexane (5 mL). The solid formed was triturated and kept cold at 0 °C for 15 min and then filtered to give desired product as a white solid (1.10 g, 43% yield).

General procedure for Suzuki coupling represented by the synthesis of ethyl 2-(4-methoxyphenyl)benzofuran-3-carboxylate 5*{1,2}* and ethyl 2-(furan-3-yl)benzofuran-3-carboxylate 5*{1,1}*. Compound 5*{1,2}*: A mixture of (3-(ethoxycarbonyl)-benzofuran-2-yl)boronic acid **3***{1}* (300 mg, 1.28 mmol. 1.0 *equiv.*), 4-idodoanisole (330 mg, 1.41 mmol, 1.1 *equiv.*), $PdCl_2$(dppf)·DCM (53.3 mg, 0.064 mmol, 0.05 *equiv.*) and sodium carbonate (544 mg, 5.13 mmol, 4.0 *equiv.*) were placed in a sealed tube with rubber septum. The reaction tube was evacuated under vacuum and refilled with nitrogen three times using schlenk line. Milli-Q water (6 mL) and 1,2-dimethoxyethane (6 mL) were degassed under nitrogen gas before adding to the reaction tube via syringe. The reaction mixture was stirred at 70 °C overnight; and monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was flushed through a pad of silica gel with ethyl acetate to remove some insoluble salts. The desired product was obtained by silica gel chromatography (heptane/ethyl acetate 97:3) as yellowish viscous oil (267 mg, 70% yield). **Compound 5*{1,1}*:** A mixture of ethyl 2-iodo-benzofuran-3-carboxylate **4***{1}* (67.0 mg, 0.21 mmol. 1.0 *equiv.*), 3-furan boronic acid (35.9 mg, 0.32 mmol, 1.5 *equiv.*), $PdCl_2$(dppf)·DCM (8.9 mg, 0.011 mmol, 0.05 *equiv.*) and sodium carbonate (90.6 mg, 0.85 mmol, 4 *equiv.*) were placed in a sealed tube with rubber septum. The reaction tube was evacuated under vacuum and refilled with nitrogen three times using schlenk line. Milli-Q water (1 mL) and 1,2-dimethoxyethane (1 mL) were degassed under nitrogen gas before adding to the reaction tube via syringe. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, the mixture was diluted with ethyl acetate (10 mL). The organic phase was washed with water

(3 mL) and brine (3 mL) consecutively. Silica gel chromatography (heptane/ethyl acetate 99:1) furnished the desired product as white solid (39 mg, 71% yield).

General procedure of ester hydrolysis for preparation of 2-arylbenzofuran-3-carboxylic acids 6*{1-3,1-5}*. To the solution of corresponding ethyl benzofuran-3-carboxylate (0.2 mmol, 1.0 *equiv.*) dissolved in a mixed solvent of tetrahydrofuran, methanol and water (1 mL each) was added NaOH (2 M in H_2O, 0.8 mmol, 4 *equiv.*). The resulting solution was stirred at 70 °C overnight under the protection of nitrogen. The reaction mixture was acidified with HCl (1 M, aq.) to pH 1 and the most of the product directly precipitated as a solid. Removal of the organic solvent under reduced pressure increased formation of product precipitation. The product was subsequently washed with water, filtered and dried under vacuum; and used for next step without further purification.

General procedure of amide coupling for preparation of compound 7*{1-3,1-5,1-6}*. To a reaction tube was added the corresponding 2-arylbenzofuran-3-carboxylic acid (0.175 mmol, 1.0 *equiv.*), free amine (0.262 mmol, 1.5 *equiv.*), TBTU (62.0 mg, 0.193 mmol, 1.1 *equiv.*), triethyl amine (35.4 mg, 0.350 mmol, 2.0 *equiv.*) and DMF (1 mL). The reaction mixture was stirred at rt overnight. The completion of reaction was monitored by TLC and liquid chromatography mass spectrometry (LCMS). DMF was removed under reduced pressure. Dichloromethane (15 mL) was added to the residue; and the resulting solution was washed with water (5 mL) and brine (5 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The desired product was obtained by silica gel chromatography (typically dichloromethane/MeOH).

General procedure for reducing 2-arylbenzofuran-3-carboxylate 5*{1-3,1-5}* to *trans*-2-aryl-2, 3-dihydrobenzofuran-3-carboxylate 8*{1-3,1-5}* followed by hydrolysis to generate *trans*-2-aryl-2,3-dihydrobenzofuran-3-carboxylic acid 9*{1-3,1-5}*. The *trans*-2-aryl-2, 3-dihydrobenzofuran-3-carboxylate **8***{1-3,1-5}* was prepared according to a reported procedure[26]. To a solution of 2-arylbenzofuran-3-carboxylate **5***{1-3,1-5}* (0.34 mmol, 1.0 *equiv.*) dissolved in a mixture solvent of THF-MeOH (8 mL, 1:1 ratio) precooled at -15 °C under nitrogen atmosphere, magnesium crumbles (10.10 mmol, 30.0 *equiv.*) were added followed by the addition of ammonium chloride (0.68 mmol, 2 *equiv.*) The reaction mixture was stirred at the same temperature for 90 min and then allowed to warm up to rt and stirred for additional 30 min. The reaction mixture was quenched with saturated ammonium chloride solution (aq., 30 mL) at -15 °C, before dilution with water (30 mL) and extraction with dichloromethane (30 mL). The aqueous phase was extracted with dichloromethane (30 mL x 2). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (heptane/ethyl acetate) to provide *trans*-2-aryl-2,3-dihydrobenzofuran-3-carboxylate **8***{1-3,1-5}*. The corresponding methyl ester was identified as side product due to the fact that the reduction was performed in methanol. To the solution of corresponding *trans*-2-aryl-2, 3-dihydrobenzofuran-3-carboxylate **8***{1-3,1-5}* (0.15 mmol, 1.0 *equiv.*) dissolved in a mixture solvent of tetrahydrofuran, methanol and water (2 mL each) was added NaOH (2M in H_2O, 0.6 mmol, 4.0 *equiv.*). The resulting solution was stirred in 70 °C overnight under the protection of nitrogen. The reaction mixture was acidified with HCl (1M in H_2O) to pH 1. The mixture was extracted with ethyl acetate (15 mL x 3), dried over sodium sulfate, filtered and concentrated. The product of *trans*-2-aryl-2, 3-dihydrobenzofuran-3-carboxylic acid **9***{1-3,1-5}* was obtained and used for next step without further purification.

General procedure of amide couplings to prepare compound 10*{1-3,1-5,1-6}*. To a reaction tube was added the corresponding 2-arylbenzofuran-3-carboxylic acid (0.10 mmol, 1.0 *equiv.*), amine (0.15 mmol, 1.5 *equiv.*), TBTU (38.5 mg, 0.12 mmol, 1.2 *equiv.*), triethyl amine (30.3 mg, 0.30 mmol, 3.0 *equiv.*) and DMF (1 mL). The reaction mixture was stirred at rt overnight. Completion of the reaction was monitored by TLC and LCMS. DMF was removed under reduced pressure. Dichloromethane (15 mL) was added to the residue; and the resulting solution was washed with water (5 mL) and brine (5 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The desired product was obtained by silica gel chromatography (heptane/ethyl acetate or dichloromethane/MeOH).

Supporting information

Details on the statistical molecular design, calculated physicochemical properties, analytical data for compounds and copies of NMR spectra for all final compounds.

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