Published in final edited form as:

ACS Comb Sci. 2013 April 8; 15(4): 193–201. doi:10.1021/co300159g.

SOLUTION PHASE SYNTHESIS OF A DIVERSE LIBRARY OF BENZISOXAZOLES UTILIZING THE [3 + 2] CYCLOADDITION OF *IN SITU* GENERATED NITRILE OXIDES AND ARYNES

Anton V. Dubrovskiy^{†,‡}, Prashi Jain^{§,‡}, Feng Shi[†], Gerald H. Lushington[§], Conrad Santini[§], Patrick Porubusky[§], and Richard C. Larock^{†,*}

[†]Department of Chemistry, Iowa State University, Ames, Iowa 50011

[§]University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development, Lawrence, Kansas 66047

Abstract

A library of benzisoxazoles has been synthesized by the [3 + 2] cycloaddition of nitrile oxides with arynes and further diversified by acylation/sulfonylation and palladium-catalyzed coupling processes. The eight key intermediate benzisoxazoles have been prepared by the reaction of *o*-(trimethylsilyl)aryl triflates and chlorooximes in the presence of CsF in good to excellent yields under mild reaction conditions. These building blocks have been used as the key components of a diverse set of 3,5,6-trisubstituted benzisoxazoles.

Introduction

Low molecular weight heterocycles are among the most highly recognized pharmacophores.¹ Among them, the benzisoxazole scaffold has evolved as a convenient bioisosteric replacement for the benzoyl functionality of some biologically active molecules.² Benzisoxazoles, particularly their 3-alkyl and 3-aryl substituted derivatives, have displayed a broad range of biological activities, such as antipsychotic,^{2a,3} antitumor,⁴ anticonvulsant,⁵ antimicrobial,⁶ antibacterial,⁷ diuretic,⁸ antithrombotic,^{2c} and acetylcholinesterase-inhibition^{2b,9} (Alzheimer's disease treatment) activities (Figure 1).

Various routes to 3-alkyl/aryl benzisoxazoles have been reported. Most of the syntheses are 3 to 4 steps in length, usually involving formation of the carbon-oxygen bond (through S_NAr ,^{8b,10} or Pd-¹¹ or CuI¹²-catalyzed reactions) or the oxygen-nitrogen bond (through

*Corresponding Author: larock@iastate.edu. Phone: (515) 294-4660. Fax: (515) 294-0105..

[‡]AVD and PJ should be considered equal contributors to this work.

Supporting Information. Experimental details and characterization of a representative 20 library members, including full ¹H and ¹³C NMR spectra and conditions for their high throughput liquid chromatography purification. This material is available free of charge via the Internet at <http://pubs.acs.org>.

base-mediated cyclizations¹³ or intramolecular Mitsunobu¹⁴ reactions) *via* intermediate *o*-halo- or *o*-hydroxyaryl ketoximes during the final steps. The syntheses of the corresponding *o*-halo- or *o*-hydroxyaryl ketones often involve a strongly acidic Friedel-Craft's reaction and the use of one of the substrates as a solvent, or in other cases require the use of strongly basic organometallics.

Because of the extensive biological activity of benzisoxazoles, it is likely that libraries of low molecular weight benzisoxazoles will serve as valuable tools for drug discovery. However, the limitations of present convergent literature syntheses of these heterocycles have been an obstacle to expedient evaluation of diverse benzisoxazoles for biological activity. It should be noted that amino-containing benzisoxazoles have been produced and simple alkylation/acylation derivatization steps have been used to prepare and evaluate up to 36 members from a single scaffold in a divergent manner.¹⁵

We have previously reported an efficient method leading to 3-alkyl- and 3-arylbisoxazoles by the [3 + 2] cycloaddition of nitrile oxides and arynes.¹⁶ Both highly reactive components have been generated *in situ* by fluoride anion from commercially available aryne precursors and readily prepared chlorooximes (Scheme 1).

In an extension of our previous studies, we hereby report the synthesis of a solution-phase library using this methodology, which includes preparation of benzisoxazole-containing blocks **4-6**, followed by: a) their acylation/sulfonylation if the building block possesses an amino functionality, such as the piperidinyl-containing substrates **4** (their derivatives are prevalent in the literature)¹⁷ or the *L*-proline-derived substrates **5**; b) elaboration using Pd-catalyzed coupling processes if the building block possesses a Br/I handle, such as the 3-haloaryl-substituted benzisoxazoles **6** (Scheme 2).

As such, we set out to construct a diverse 72-membered library of benzisoxazoles to be screened for biological activity. This is the first example of the use of aryne chemistry for constructing a benzisoxazole library.

Results and Discussion

To synthesize a library with greater chances for biological activity, the substituted derivatives **4-6** have been evaluated computationally for their drug-like properties using SYBYL,¹⁸ plus Lipinski's "rule of five" and Veber's rule as additional guidelines for the prediction of oral bioavailability.¹⁹ Lipinski calculations have been performed based on the commercial availability of the aryne precursors [the *o*-(trimethylsilyl)aryl triflates],²⁰ acylating/sulfonylating agents, boronic acids (for Suzuki-Miyaura coupling), amines and hydrazines (for Buchwald-Hartwig amination), and terminal alkynes (for Sonogashira coupling).²¹ Four benzyne precursors, 52 acylating/sulfonylating agents, 21 boronic acids, 10 amines and hydrazines, and 10 terminal alkynes have been used to generate a 2440-membered virtual library. *In silico* analysis of this virtual set revealed 71 members with diversity scores²² <1.0 along with one having a slightly higher score, allowing the synthesis of the target compounds from only eight building blocks (Figure 2). The distributions of the Lipinski and Veber parameters (molecular weight, cLogP, number of rotatable bonds, *H*-bond donors and acceptors) are shown in Figure 3. All compounds follow Lipinski's and Veber's rules with no violations.

Synthesis of the Building Blocks

For practical purposes, relatively stable benzisoxazole blocks were needed. Thus, we chose to synthesize amine-containing starting benzisoxazoles as their corresponding Boc-urethanes **7-12**. The amounts of the eight building blocks required were estimated assuming a 60%

yield in the final diversification step and our goal of preparing 35 mg of each compound for screening.

Despite the scalability issues inherent in the heterogeneous CsF-promoted benzyne-mediated chemistry,²³ running the reactions in parallel at increased loadings (up to 4x) furnished starting materials **9-14** in sufficient amounts for further diversification (Table 1). Using our methodology, *N*-Boc-piperidine-derived chlorooxime **15** afforded the desired benzisoxazoles **7** and **8** in 88% and 59% yields respectively with different aryne precursors when performed on a 0.25 mmol scale (entries 1 and 3).

The coupling of the chiral proline-derived chlorooxime **16** with an array of symmetrical benzyne afforded the desired chiral benzisoxazoles **9-12** in 33-88% yields (entries 5-10). The substituted benzyne provided slightly lower yields than the parent system, with the dimethoxybenzyne being the best of the three (73% yield of the corresponding benzisoxazole **10**, entry 7). The dimethylbenzyne and the symmetrical naphthalene provided the desired benzisoxazoles **11** and **12** in 51% and 50% yields, respectively when allowed to react on a 0.50 mmol scale (entries 8 and 10). The electron-rich dimethoxyiodo-substituted chlorooxime **17** led to formation of the desired benzisoxazole **13** in a 76% yield on a standard 0.25 mmol scale (entry 11). The yield was significantly lower (56%) when the reaction was run on a 0.50 mmol scale. The more electron-deficient chlorooxime **18** afforded the benzisoxazole **14** in a lower 57% yield, when run on a 0.25 mmol scale (compared to 54% on a 0.50 mmol scale, entry 14). With the benzisoxazole building blocks **9-14** in hand, a 72-member library was designed. The library was constructed by diversification of the 3-substituted benzisoxazole core scaffold using acylation, sulfonylation and metal-catalyzed cross-coupling reactions as outlined in Scheme 2. This method permits the introduction of functional diversity to generate benzisoxazoles with potential biological activity using parallel synthesis.

Diversifications

Acylation/Sulfonylation

Our diversification sequence involved TFA-mediated Boc-deprotection of the cycloadducts **7-12** and subsequent *N*-acylation/sulfonylation with various acyl/sulfonyl chlorides. This deprotection-acylation procedure²⁴ was best carried out in one pot: TFA deprotection in DCM, parallel concentration, addition of fresh DCM followed by basification using triethylamine (5.0 equiv), and finally the addition of an acyl/sulfonyl chloride (1.5 equiv). The reactions were carried out in 1-dram vials using Mettler-Toledo Miniblocks® in which the crude final reaction mixtures were concentrated and purified *via* automated mass-directed (MDF) LC/MS. Table 2 shows the chemset diversity inputs for the substituted 3-(4-piperidinyl)benzisoxazoles. Amide/sulfonamide products **23**{ *1-17* } (Figure 4) derived from the starting blocks **7** and **8** were obtained in 34-95% yields and excellent purities (88 to >99%) after MDF purification.

A series of 3-(pyrrolidin-2-yl)-benzisoxazoles (Table 3) was prepared using the same procedure utilized for the synthesis of the 3-(4-piperidinyl)benzisoxazoles. The yields of *N*-acylated and *N*-sulfonylated benzisoxazoles **24**{ *1-41* } (Figure 5) ranged from 1 to 57% with 60 to >99% purities obtained after MDF purification. In the case of sulfinylamides **24**{ *19*, *27*, *35* and *40* }, mixtures of diastereomers were obtained, which were separable by MDF separation. The relative stereochemical assignments of the diastereomers were not determined.

Pd/Cu Catalyzed Cross-Couplings

To prepare libraries derived from 3-(3-iodo-4,5-dimethoxyphenyl)benzoxazole (**13**) and 3-(2-fluoro-5-iodophenyl)benzoxazole (**14**), we utilized various Pd/Cu-catalyzed cross-coupling reaction sequences, such as Suzuki-Miyaura coupling with aryl boronic acids, Hartwig-Buchwald coupling with alkyl hydrazines, and Sonogashira coupling with terminal alkynes. The data for the compounds (Figure 6) obtained through these diversification procedures are combined in Table 4.

Hartwig-Buchwald coupling²⁵ of 3-(3-iodo-4,5-dimethoxyphenyl)benzoxazole (**13**) with morpholin-4-amine afforded the desired product **25**{ 1} in a 41% yield (Scheme 3). With optimized conditions in hand, we employed this method for coupling of 3-(2-fluoro-5-iodophenyl)benzoxazole (**14**) with appropriate alkyl hydrazines. While we were unable to isolate any of the desired compounds after MDF purification, we were able to obtain **25**{ 2} in a 14% yield after purification using normal phase chromatography.

Scheme 4 describes the synthesis of 4 analogues of 3-(2-fluoro-5-iodophenyl)benzoxazole (**14**) using a Sonogashira coupling²⁶ with 16-39% yields for successful entries in 90 to >99% purities after MDF chromatography. The generation of 3 analogues based on Sonogashira couplings of 3-(3-iodo-4,5-dimethoxyphenyl)benzoxazole (**13**) with terminal alkynes provided unfavorable results and we were not able to isolate the desired products.

The Suzuki-Miyaura coupling²⁷ of 3-(2-fluoro-5-iodophenyl)benzoxazole (**14**) with aryl boronic acids afforded the desired products **25**{ 7-9} in 7-32% yields in excellent purities *via* preparative MDF purification (Scheme 5).

Conclusions

The aryne-mediated preparation and subsequent acylation/sulfonylation and palladium-catalyzed reactions of benzoxazoles with various cross-coupling partners has enabled the construction of a 72-member library of diverse 3-substituted benzoxazoles with potential biological activity. We anticipate that this methodology will be applicable in future diversity-oriented parallel synthesis for discovery purposes. The overall success rate for the library was 83% and the average purity after preparative MDF-HPLC was 99%.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

We are grateful to the National Institute of General Medical Sciences for their generous financial support through grants GM079593 and GM070620 to RCL and to the NIH Chemical Methodologies and Library Development Center at the University of Kansas (P50 GM069663).

References

- (1). (a) Horton DA, Bourne GT, Smythe ML. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.* 2003; 103:893–930. [PubMed: 12630855] (b) Dolle RE. Comprehensive survey of combinatorial library synthesis. 2002. *J. Comb. Chem.* 2003; 5:693–753. (c) D'Souza DM, Müller TJ. Multi-component syntheses of heterocycles by transition-metal catalysis. *J. Chem. Soc. Rev.* 2007; 36:1095–1108.

- (2). (a) Strupczewski JT, Allen RC, Gardner BA, Schmid BL, Stache U, Glamkowski EJ, Jones MC, Ellis DB, Huger FP, Dunn RW. Synthesis and neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. *J. Med. Chem.* 1985; 28:761–769. [PubMed: 2861286] (b) Villalobos A, Blake JF, Biggers CK, Butler TW, Chapin DS, Chen YL, Ives JL, Jones SB, Liston DR, Nagel AA, Nason DM, Nielsen JA, Shalaby IA, White WF. Novel benzisoxazole derivatives as potent and selective inhibitors of acetylcholinesterase. *J. Med. Chem.* 1994; 37:2721–2734. [PubMed: 8064800] (c) Nuhlich A, Varache-Lembege M, Renard P, Devaux G. Synthesis and inhibitory effects on platelet aggregation of 3-(2-thienyl)- and 3-(1-imidazolyl)-1,2-benzisoxazole derivatives. *Eur. J. Med. Chem.* 1994; 29:75–83.
- (3). (a) Davis L, Effland RC, Klein JT, Dunn RW, Geyer HM III, Petko WM. 3-Substituted-1,2-benzisoxazoles: novel antipsychotic agents. *Drug Design and Discovery.* 1992; 8:225–239. [PubMed: 1356026] (b) Janssen PAJ, Niemegeers CJE, Awouters F, Schellekens KHL, Megens AAHP, Meert TF. Biochemical profile of Risperidone, a new antipsychotic. *J. Pharmacol. Exp. Ther.* 1988; 244:661–670. [PubMed: 2460616] (c) Strupczewski JT, Bordeau KJ, Chiang Y, Glamkowski EJ, Conway PG, Corbett R, Hartman HB, Szewczak MR, Wilmot CA, Helsley GC. 3-[[Aryloxy]alkyl]piperidinyl-1,2-benzisoxazoles as D2/5-HT2 antagonists with potential atypical antipsychotic activity: antipsychotic profile of Iloperidone (HP 873). *J. Med. Chem.* 1995; 38:1119–1131. [PubMed: 7707315]
- (4). (a) Gopalsamy A, Shi M, Golas J, Vogan E, Jacob J, Johnson M, Lee F, Nilakantan R, Petersen R, Svenson K, Chopra R, Tam MS, Wen Y, Ellingboe J, Arndt K, Boschelli F. Discovery of benzisoxazoles as potent inhibitors of Chaperone heat shock protein 90. *J. Med. Chem.* 2008; 51:373–375. [PubMed: 18197612] (b) Jain M, Kwon C-H. 1,2-Benzisoxazole phosphorodiamidates as novel anticancer prodrugs requiring bioreductive activation. *J. Med. Chem.* 2003; 46:5428–5436. [PubMed: 14640551] (c) Benaka Prasad SB, Vinaya K, Ananda Kumar CS, Swarup S, Rangappa KS. Synthesis of novel 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole derivatives as antiproliferative agents: a structure–activity relationship study. *Invest. New Drugs.* 2009; 27:534–542. [PubMed: 19066725]
- (5). (a) Stiff DD, Zemaitis MA. Metabolism of the anticonvulsant agent Zonisamide in the rat. *Drug Metab. Dispos.* 1990; 18:888–894. [PubMed: 1981533] (b) Masuda Y, Nishimura H. Studies on 3-substituted 1,2-benzisoxazole derivatives. 6 Syntheses of 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives and their anticonvulsant activities. *J. Med. Chem.* 1979; 22:180–183. [PubMed: 423197]
- (6). (a) Priya BS, Basappa, Swamy SN, Rangappa KS. Synthesis and characterization of novel 6-fluoro-4-piperidinyl-1,2-benzisoxazole amides and 6-fluoro-chroman-2-carboxamides: antimicrobial studies. *Bioorg. Med. Chem.* 2005; 13:2623–2628. [PubMed: 15846867] (b) Suhas R, Chandrashekar S, Gowda DC. Synthesis of elastin based peptides conjugated to benzisoxazole as a new class of potent antimicrobials – a novel approach to enhance biocompatibility. *Eur. J. Med. Chem.* 2011; 46:704–711. [PubMed: 21211872]
- (7). Vaidya SD, Kumar BVS, Kumar RV, Bhise UN, Mashelkar UC. Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel *N*-substituted-2-(benzo[d]isoxazol-3-ylmethyl)-1*H*-benzimidazoles. *J. Heterocycl. Chem.* 2007; 44:685–691.
- (8). (a) Shutske GM, Setescak LL, Allen RC, Davis L, Effland RC, Ranbom K, Kitzen JM, Wilker JC, Novick WJ. [(3-Aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids. A new diuretic series. *J. Med. Chem.* 1982; 25:36–44. [PubMed: 7086820] (b) Plattner JJ, Fung AKL, Parks JA, Pariza RJ, Crowley SR, Pernet AG, Bunnell PR, Dodge PW. Substituted 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acids: high-ceiling diuretics with uricosuric activity. *J. Med. Chem.* 1984; 27:1016–1026. [PubMed: 6431103] (c) Sato H, Dan T, Onuma E, Tanaka H, Aoki B, Koga H. Studies on uricosuric diuretics. III. Substituted 1,3-dioxolo[4,5-*f*]-1,2-benzisoxazole-6-carboxylic acids and 1,3-dioxolo[4,5-*g*]-1,2-benzisoxazole-7-carboxylic acids. *Chem. Pharm. Bull.* 1992; 40:109–116. [PubMed: 1576661]
- (9). Rangappa KS, Basappa. New cholinesterase inhibitors: synthesis and structure–activity relationship studies of 1,2-benzisoxazole series and novel imidazolyl-*d*²-isoxazolines. *J. Phys. Chem.* 2005; 18:773–778.
- (10). Bunnet JF, Yih SY. Kinetics of cyclization of *o*-halobenzophenone oximes to 3-phenyl-1,2-benzisoxazole. *J. Am. Chem. Soc.* 1961; 83:3805–3807.

- (11). Inamoto K, Katsuno M, Yoshino T, Arai Y, Hiroya K, Sakamoto T. Synthesis of 3-substituted indazoles and benzisoxazoles *via* Pd-catalyzed cyclization reactions: application to the synthesis of nigellicine. *Tetrahedron*. 2007; 63:2695–2711.
- (12). De P, Nonappa, Pandurangan K, Maitra U, Wailes S. CuI-Mediated cross-coupling of aryl halides with oximes: a direct access to *o*-aryloximes. *Org. Lett.* 2007; 9:2767–2770. [PubMed: 17580882]
- (13). (a) Roman G, Comanita E, Comanita B. Synthesis and reactivity of Mannich bases. Part 15: synthesis of 3-(2-(1-pyrazolyl)ethyl)-1,2-benzisoxazoles. *Tetrahedron*. 2002; 58:1617–1622.(b) Shelke KF, Sapkal SB, Shitole NV, Shingate BB, Shingare MS. Microwave-assisted synthesis of 1,2-benzisoxazole derivatives in ionic liquid. *Org. Commun.* 2009; 2:72–78.(c) Dale TJ, Sather AC, Rebek J. Synthesis of novel aryl-1,2-oxazoles from *ortho*-hydroxyaryloximes. *Tetrahedron Lett.* 2009; 50:6173–6175.
- (14). Poissonnet G. A simple and convenient synthesis of 1,2-benzisoxazoles *via* intramolecular Mitsunobu reaction from salicylaldoximes and *ortho*-hydroxyarylketoimes. *Synth. Commun.* 1997; 27:3839–3846.
- (15). See refs. 2a, 3c, 4c, 6a, and 9b.
- (16). Dubrovskiy AV, Larock RC. Synthesis of benzisoxazoles by the [3 + 2] cycloaddition of *in situ* generated nitrile oxides and arynes. *Org. Lett.* 2010; 12:1180–1183. [PubMed: 20184347]
- (17). See refs. 2a, 2b, 3c, 4c, 6, and 9.
- (18). SYBYL 8.0, Tripos International, 1699 South Hanley Rd. St. Louis, Missouri; p. 63144USA
- (19). (a) Lipinski CA, Lombardo F, Dominay BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* 1997; 23:3–25.(b) Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* 2002; 45:2615–2623. [PubMed: 12036371]
- (20). Himeshima Y, Sonoda T, Kobayashi H. Fluoride-induced 1,2-elimination of *o*-trimethylsilylphenyl triflate to benzyne under mild conditions. *Chem. Lett.* 1983:1211–1214.
- (21). See examples of the use of these procedures for the synthesis of combinatorial libraries in: Dubrovskiy AV, Markina NA, Larock RC. Iodocyclization, followed by palladium-catalyzed coupling: a versatile strategy for heterocyclic library construction. *Comb. Chem. High Throughput Screening*. 2012; 15:451–472.
- (22). (a) Pearlman RS, Smith KM. Novel software tools for chemical diversity. *Perspectives in Drug Discovery and Design*. 1998:339–353.(b) Pearlman RS, Smith KM. Metric validation and the receptor-relevant subspace concept. *J. Chem. Inf. Comput. Sci.* 1999; 39:28–35.(c) Schnur D. Design and diversity analysis of large combinatorial libraries using cell-based methods. *J. Chem. Inf. Comp. Sci.* 1999; 39:36–45.(d) Menard PR, Mason JS, Morize I, Bauerschmidt S. Chemistry space metrics in diversity analysis, library design, and compound selection. *J. Chem. Inf. Comp. Sci.* 1998; 38:1204–1213.
- (23). See, for example: Shi F, Larock RC. Synthesis of substituted indazoles *via* [3+2] cycloaddition of benzyne and diazo compounds. [*1H*-Indazole-3-carboxylic acid, ethyl ester]. *Org. Syn.* 2010; 87:95.
- (24). Adapted from: Carpenter RD, DeBerdt PB, Holden JB, Milinkevich KA, Min T, Willenbring D, Fettinger JC, Tantillo DJ, Kurth MJ. Design and synthesis of propeller-shaped dispiroisoxazolinopiperidinochromanones. *J. Comb. Chem.* 2008; 10:225–229. [PubMed: 18232646]
- (25). Cacchi S, Fabrizi G, Goggiamani A, Licandro E, Maiorana S, Perdicchia D. Synthesis of *N,N*-dialkyl-*N'*-arylhydrazines *via* palladium-catalyzed *N*-arylation by using *N,N*-dialkylhydrazines/2LiCl adducts. *Org. Lett.* 2005; 7:1497–1500. [PubMed: 15816736]
- (26). a) Markina NA, Mancuso R, Neuenswander B, Lushington GH, Larock RC. Solution-phase parallel synthesis of a diverse library of 1,2-dihydroisquinolines. *ACS Comb. Sci.* 2011; 13:265–271. [PubMed: 21410207] b) Tret'yakov EV, Tkachev AV, Rybalova TV, Gatilov YV, Knight DW, Vasilevsky SF. Reaction of arylpropargyl aldehydes with 2,3-bis-hydroxylamino-2,3-dimethylbutane: synthesis of 2-(1-hydroxy-4,4,5,5-tetramethylimidazolidin-2-ylidene)-1-arylethanones. *Tetrahedron*. 2000; 56:10075–10080.c) Revesz L, Blum E, Di Padova FE, Buhl T, Feifel R, Gram H, Hiestand P, Manning U, Neumann

- U, Rucklin G. Pyrazoloheteroaryls: novel p38 α MAP kinase inhibiting scaffolds with oral activity. *Bioorg. Med. Chem. Lett.* 2006; 16:262–266. [PubMed: 16249085]
- (27). Marchais-Oberwinkler S, Wetzel M, Ziegler E, Kruchten P, Werth R, Henn C, Hartmann RW, Frotscher M. New drug-like hydroxyphenylnaphthol steroidomimetics as potent and selective 17 β -hydroxysteroid dehydrogenase type 1 inhibitors for the treatment of estrogen-dependent diseases. *J. Med. Chem.* 2011; 54:534–547. [PubMed: 21189020]

Figure 1.
Examples of medicinally relevant benzisoxazoles.

Note: numbers in parentheses represent the number of the anticipated diversification products of each particular type.

Figure 2.
Desired Benzisoxazole Building Blocks.

Figure 3.
Distribution of the Physicochemical and Structural Properties of our Library Entries.

Figure 4.
Derivatized 3-(4-Piperidinyl)benzoxazoles.

Figure 5.
Derivatized 3-(2-Pyrrolidinyl)benzoxazoles.

Figure 6.
Benzisoxazoles Derivatized through Pd/Cu-Catalyzed Coupling.

Scheme 1.
Aryne Methodology for the Synthesis of Benzisoxazoles.

Scheme 2.
Parent Benzisoxazole Scaffolds and Derivatization Methodology.

Scheme 3.
Hartwig-Buchwald Amination of **13** and **14**.

Scheme 4.
Sonogashira coupling of **14**.

Scheme 5.
Suzuki-Miyaura coupling of **14**.

Table 1

Preparation of the Benzisoxazole Building Blocks 7-14.

Entry	Chloro-oxime	R'	Benzoyne Precursor	R	Reaction Scale (mmol) ^a	Product	Yield (%) ^b
1	15	4-(N-Boc-piperidinyl)	19	H	0.25	7	88
2	15	"	19	H	0.50	7	78
3	15	"	20	OMe	0.25	8	59
4	15	"	20	OMe	0.75	8	40
5	16	(S)-2-(N-Boc-pyrrolidinyl)	19	H	0.25	9	85
6	16	"	19	H	0.50	9	88
7	16	"	20	OMe	0.50	10	73
8	16	"	21	Me	0.50	11	51
9	16	"	21	Me	1.00	11	33
10	16	"	22	C ₆ H ₄	0.50	12	50
11	17	3-iodo-4,5-dimethoxyphenyl	19	H	0.25	13	76
12	17	"	19	H	0.50	13	56
13	18	5-bromo-2-fluorophenyl	19	H	0.25	14	57
14	18	"	19	H	0.50	14	54

^aThe amount of chloro-oxime used.

^bIsolated yields after normal phase column chromatography.

Table 2

Data for library compounds **21** {1-17}.

Product	R	HRMS (calcd)	HRMS (found) ^a	Purity (%) ^b	Yield (%) ^c
23 {1}	H	298.0929	299.1051	99	24
23 {2}	H	296.1161	297.1249	>99	35
23 {3}	H	272.1525	273.1619	>99	52
23 {4}	H	315.1583	316.1671	>99	31
23 {5}	H	313.1790	314.1880	>99	36
23 {6}	H	312.0932	313.1023	88	(3)
23 {7}	H	306.1402	307.1512	95	21
23 {8}	H	342.1038	343.1134	>99	32
23 {9}	H	348.0602	349.0710	99	26
23 {10}	H	346.1100	347.1189	>99	52
23 {11}	H	347.0940	348.1025	97	48
23 {12}	H	343.0991	344.1068	95	29
23 {13}	H	497.9248	498.9355	96	62 ^d
23 {14}	H	366.1579	367.1654	99	95 ^d
23 {15}	OMe	358.1140	359.1227	88	(4)
23 {16}	OMe	366.1613	367.1704	>99	33
23 {17}	OMe	346.1892	347.1986	94	23

Reactions were performed on a 0.25 mmol scale. TFA deprotection: 0.5 mL of TFA and 1 mL of DCM were used. Acylation: Et₃N (5 equiv), acyl/sulfonyl chloride (1.5 equiv) and anhydrous CH₂Cl₂ were used.

^afor [M+H]⁺

^bUV purity determined at 214 nm after preparative HPLC.

^cIsolated yields after MDF column chromatography. Yields in parentheses are considered failed entries (<90% purity and/or <5 mg quantity).

^dPurified by normal phase column chromatography.

Product	R	HRMS (calcd)	HRMS (found) ^a	Purity (%) ^b	Yield (%) ^c
24 {20}	H		Not found	-	(nd)
24 {21}	OMe	430.0528	431.0629	99	28
24 {22}	OMe	332.1736	333.1831	>99	30
24 {23}	OMe	344.0984	345.1090	>99	34
24 {24}	OMe	388.1093	389.1180	>99	(5)
24 {25}	OMe	432.0991	433.1060	99	(3)
24 {26}	OMe	406.0999	407.1081	>99	34
24 {27.1}	OMe	352.1457	353.1548	>99	28 ^e
24 {27.2}	OMe	352.1457	353.1553	>99	28 ^e
24 {28}	Me	312.1085	313.1180	>99	(3)
24 {29}	Me	300.1837	301.1925	>99	40
24 {30}	Me	327.1946	328.2033	>99	43
24 {31}	Me	300.1837	301.1941	92	(7)
24 {32}	Me	328.1535	329.1629	60	(1)
24 {33}	Me	329.1739	330.1854	>99	32
24 {34}	Me	362.0758	363.0855	94	27
24 {35.1}	Me	320.1558	321.1657	>99	46 ^e
24 {35.2}	Me	320.1558	321.1650	95	46 ^e
24 {36}	Me	365.1375	366.1476	92	39
24 {37}	Me	361.1096	362.1197	96	36
24 {38}	C ₄ H ₄	387.1219	388.1332	>99	29
24 {39}	C ₄ H ₄	334.0929	335.1029	>99	36
24 {40.1}	C ₄ H ₄	342.1402	343.1505	>99	37 ^e
24 {40.2}	C ₄ H ₄	342.1402	343.1513	92	(37) ^e
24 {41}	C ₄ H ₄	350.1319	351.1490	>99	10

Reactions were performed on a 0.25 mmol scale. TFA deprotection: 0.5 mL of TFA and 1 mL of DCM were used. Acylation: Et₃N (5 equiv), acyl/sulfonyl chloride (1.5 equiv) and anhydrous CH₂Cl₂ were used.

^a for [M+H]⁺

^b UV purity determined at 214 nm after preparative HPLC.

^c Isolated yields after MDF column chromatography. Yields in parentheses are considered failed entries (<90% purity and/or <5 mg quantity).

^d Purified by normal phase column chromatography.

^e Combined yield for the two diastereomers formed.

Table 4

Data for library compounds **25** {1-9}.

Product	Reaction	HRMS (calcd)	HRMS (found) ^a	Purity (%) ^b	Yield (%) ^c
25 {1}	Amination ^d	355.1532	356.1635	>99	41
25 {2}	"	313.1226	314.1322	97	14 ^e
25 {3}	Sonogashira ^f	335.1322	336.1407	98	39
25 {4}	"	334.1481	335.1555	90	30
25 {5}	"		Not found	-	(nd)
25 {6}	"	281.0852	282.0927	>99	16
25 {7}	Suzuki-Miyaura ^g	290.0855	291.0941	>99	32
25 {8}	"	291.0808	292.0885	>99	25
25 {9}	"	279.0696	280.0992	>99	7

Reactions were performed on a 0.25 mmol scale.

^afor [M+H]⁺.^bYield/Purities as in ^a. Yields in parentheses are considered failed entries (<90% purity and/or <5 mg quantity).^cYield/Purities as in ^a. Yields in parentheses are considered failed entries (<90% purity and/or <5 mg quantity).^dFor Hartwig-Buchwald coupling: alkyl hydrazine (2.0 equiv), LiCl (4.0 equiv), Pd₂(dba)₃ (2.5 mol%), Xantphos (5 mol%), NaO^tBu (2.0 equiv), dioxane, 85 °C, 33 h.^ePurified by normal phase column chromatography.^fFor Sonogashira coupling: CuI (3 mol%), PdCl₂(PPh₃)₂ (2 mol%), terminal alkyne (1.5 equiv), Et₃N (1 mL), DMF, 80 °C.^gFor Suzuki-Miyaura coupling: aryl boronic acid (1.5 equiv), Pd(PPh₃)₄ (5 mol%), K₂CO₃ (2.5 equiv), Tol/EtOH/H₂O (20:5:1), 80 °C, 18 h.