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Efficient Routes to a Diverse Array of Amino Alcohol-Derived Chiral Fragments

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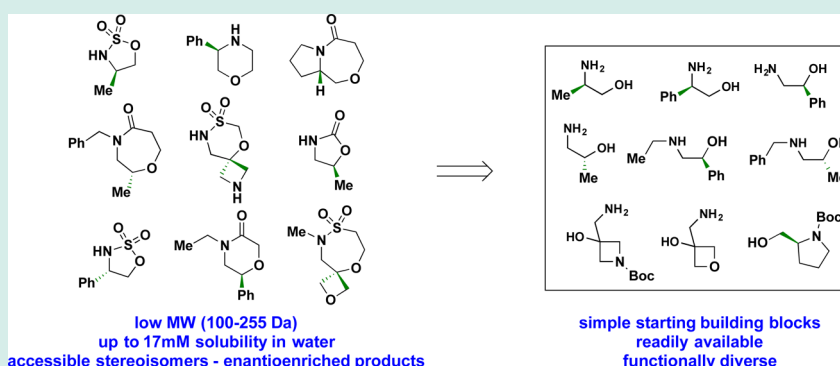
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S Supporting Information



ABSTRACT: Efficient syntheses of chiral fragments derived from chiral amino alcohols are described. Several unique scaffolds were readily accessed in 1–5 synthetic steps leading to 45 chiral fragments, including oxazolidinones, morpholinones, lactams, and sultams. These fragments have molecular weights ranging from 100 to 255 Da and are soluble in water (0.085 to >15 mM).

KEYWORDS: amino alcohols, fragment-based lead discovery, chiral fragments, drug discovery

INTRODUCTION

Fragment-based ligand discovery (FBLD) has emerged as a valuable complement to high-throughput screening over the past decade and has produced clinical-stage candidates (Figure 1), as well as the FDA-approved drugs vemurafenib and venetoclax.^{1–3} The rise of FBLD has been underpinned by methodological advances in the discovery of fragments hits by biophysical screening methods such as nuclear magnetic resonance (NMR), surface plasmon resonance (SPR), calorimetry, mass-spectrometry (MS) and X-ray crystallography. In contrast, the chemical features and optimal properties of fragments remain an area of debate and unresolved challenges.² For instance, some fragments available from commercial vendors are limited by their poor solubility in water and lack of appropriate functionality for rapid fragment growth. Many commercial fragment collections are enriched in aromatic and heteroaromatic compounds, therefore expanding existing fragment chemical space by making compounds with a higher

proportion of sp^3 -hybridized atoms may be beneficial.^{3,4} Here, we describe initial efforts to access sp^3 -rich chiral fragments from chiral amino alcohols, a class of starting materials advantaged by commercial availability, diversity of additional functional groups, and well-understood reactivity with electrophiles.

RESULTS AND DISCUSSION

We synthesized low molecular weight 5-, 6- and 7-membered cyclic scaffolds from 1,2-amino alcohols and measured their aqueous solubilities to evaluate their potential for use in FBLD. Since thousands of enantioenriched 1,2-amino alcohols are already commercially available or easily obtained through modern asymmetric synthesis,^{5–9} chemical pathways and

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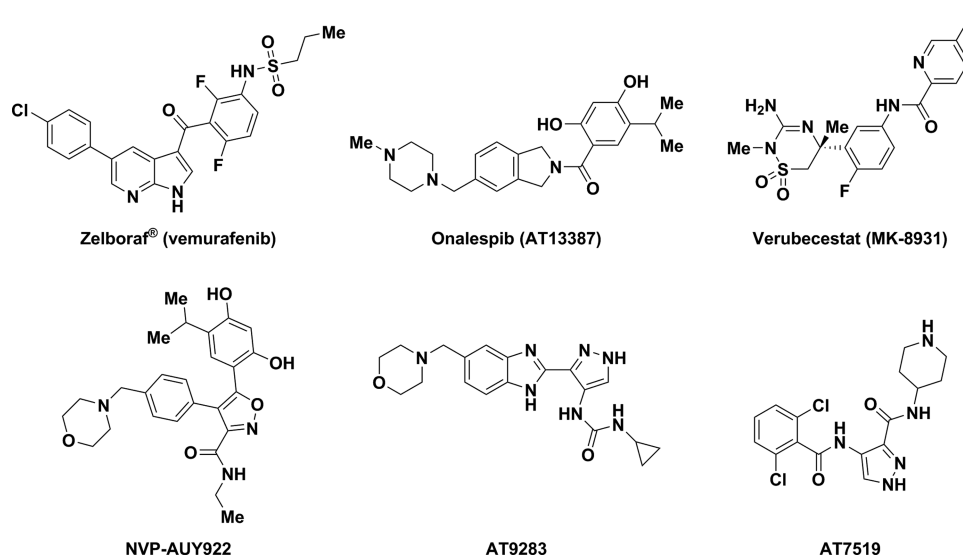


Figure 1. Representative examples of clinical-stage and approved compounds originating from FBLD.

solubility data reported in this article will encourage the production of more diverse and larger sub-libraries.

A representative selection of nine amino alcohols (Figure 2) were selected to pilot the synthesis of diverse skeletons. Amino

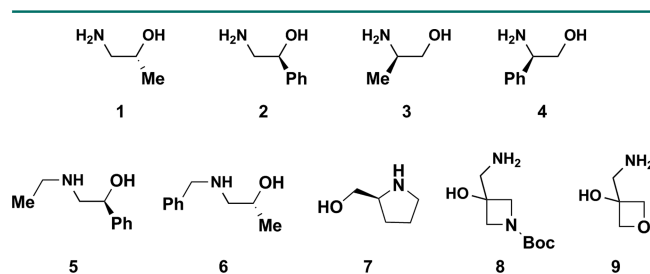
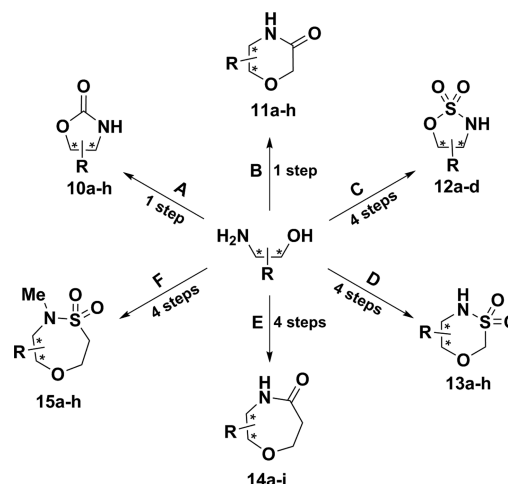


Figure 2. Structures of the representative chiral (or spiro) amino alcohol building blocks.

alcohols 1–4 were chosen to explore the effects of both aliphatic and aromatic substituents on the carbon atom alpha to the amine or alcohol across all scaffolds. Amino alcohols 5–7¹⁰ explore the role of secondary amines while 8 and 9¹¹ represent simple amino alcohols that can result in polar spirocyclic fragments with additional heteroatoms. The goal of this study was to “de-risk” the chemistry involved in accessing various scaffolds with a limited set of amino alcohols and to evaluate the suitability of the resulting fragments for FBLD by experimentally determining their aqueous solubilities.

Oxazolidinones 10a–g (Scheme 1) were straightforward to prepare by previously reported approaches or modifications thereof.^{12–18} In general, amino alcohols could be treated with carbonyldiimidazole and triethylamine (Et₃N), followed by heating at 60 °C overnight to afford the desired compounds in low to high yields (28–85%). Alternatively, oxazolidinones 10a and 10b were obtained in high yields (84%) by treatment of the neat amino alcohol with diethylcarbonate and a substoichiometric amount of sodium ethoxide at temperatures between 135 and 150 °C. Morpholinones 11a–f were synthesized by a similarly direct process in which the amino alcohols were treated with sodium hydride and ethyl chloroacetate at room temperature overnight to afford the morpholinone analogs in variable yields (19–82%).¹⁹ Morpholinones 11g and 11h were

Scheme 1^a



^aReaction conditions: (A) CDI, Et₃N, THF, 60 °C, 24 h, 27–85%; (B) NaH; ethyl chloroacetate, THF, rt, 24 h, 19–82%; (C) (i) Boc₂O, Et₃N, DCM, 0 °C, rt, 24 h, 83–99%; (ii) SOCl₂, imidazole, Et₃N, DCM, –40 °C, 2 h; then at rt for 2 h, 55–94%; (iii) RuCl₃, NaIO₄, MeCN:H₂O (1:1), 0 °C to rt, 3 h, 31–95%; (iv) TFA, DCM, rt, 24 h, 66–90%; (D) (i) ClCH₂SO₂Cl, Et₃N, DCM, 0 °C to rt, 6 h, 34–84%; (ii) PMB-Br, K₂CO₃, DMF, rt, 1 h, 17–89%; (iii) Cs₂CO₃, DMF, 80 °C, 24 h, 55–78%; (iv) CAN, MeCN:H₂O (9:1), rt, 24 h, 24–78%; (E) (i) Boc₂O, Et₃N, DCM, 0 °C, rt, 24 h, 83–99%; (ii) *t*-butyl acrylate, Cs₂CO₃, *t*-BuOH, 24 h, 75–99%; (iii) 4.0 M HCl in dioxane, 24 h, 97–99%; (iv) T3P, Et₃N, dioxane, 24 h, rt, 33–86%; (F) (i) TBS-Cl, Et₃N, DCM, 0 °C to rt, 24 h, 71–95%; (ii) chloroethane sulfonyl chloride, Et₃N, 0 °C to rt, 2 h, 75–95%; (iii) MeI, K₂CO₃, MeCN, 72 h, 70–90%; (iv) TBAF, THF, 2 h, 38–91%.

prepared using an alternative methodology in which the amino alcohols were treated with chloroacetyl chloride at room temperature, followed by intramolecular cyclization with sodium hydride at temperatures between 65 and 80 °C (18–22%).²⁰ Conveniently, morpholinones 11c, 11d, 11f, and 11g, were transformed to morpholines 11i–l in low to good yields (23–75%) by direct reduction of the lactam with lithium aluminum hydride at room temperature (those not shown were not attempted or were readily commercially available).^{21,22}

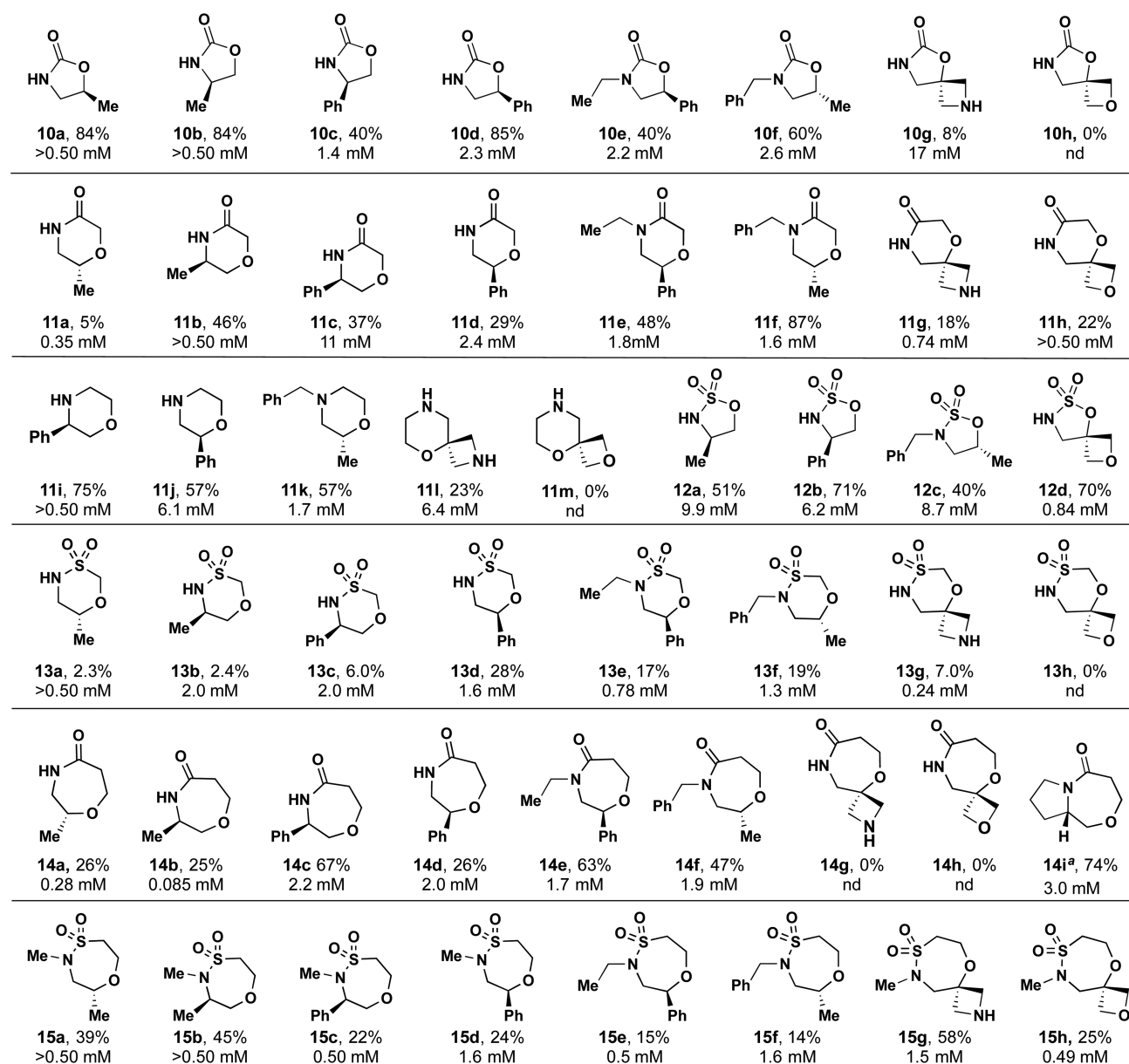
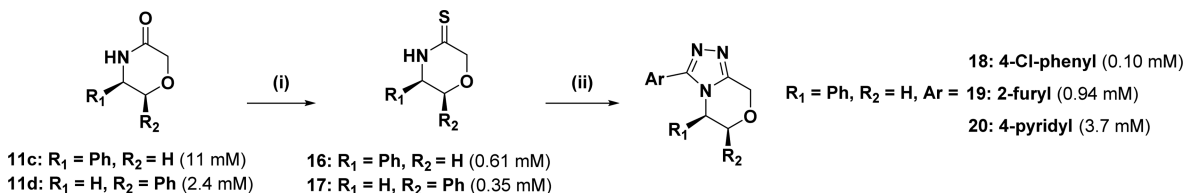


Figure 3. Readily prepared pilot collection of 45 chiral amino alcohol-derived fragments presented with overall yields and solubility data (nd = not determined). Compounds with >0.50 mM solubilities were exposed to an assay with a 0.50 mM upper limit (see [Supporting Information](#)). (a) Amino alcohol 7 was explored solely for the 7-membered lactam family of compounds.

Sulfamidates **12a**, **12b**, and **12d** were obtained by a four step sequence as outlined in [Scheme 1](#).^{23,24} Protection of the amine as the *t*-butoxycarbonyl (Boc) carbamate and reaction with thionyl chloride in the presence of imidazole and triethylamine at $-40\text{ }^{\circ}\text{C}$ afforded the desired cyclic sulfamidite in modest to high yields (55–94%). The sulfamidite was subsequently oxidized using catalytic ruthenium(III) chloride and an excess of sodium periodate in acetonitrile to afford the protected sulfamidates. Removal of the Boc protecting group with trifluoroacetic acid afforded the desired sulfamidates (**12a**, **12b**, and **12d**) in good to high yields (66–90%). The *N*-benzylated sulfamidate **12c** was prepared with an analogous approach in modest yields (40%) by treatment of the *N*-benzyl amino alcohol with thionyl chloride, imidazole, and triethylamine at $-40\text{ }^{\circ}\text{C}$, followed by oxidation with catalytic ruthenium(III) chloride and sodium periodate in acetonitrile

(products derived from amino alcohols **1**, **2**, **7**, **8**, and **5** were not investigated).

Our initial efforts to synthesize low molecular weight sultams commenced with the straightforward preparation of the α -chlorosulfonamide by treatment of amino alcohols with chloromethanesulfonyl chloride under basic conditions (20–84%). In accordance with previous observations on analogous systems by Borcard and colleagues,²⁵ we observed that direct cyclization attempts from this intermediate were ineffective and resulted in poor conversion and polymeric products. These synthetic challenges were readily overcome by selective protection of the sulfonamide nitrogen with a *p*-methoxybenzyl (PMB) group (17–98%) and subsequent cyclization under basic conditions (55–87%). The PMB protecting group was readily removed by ceric ammonium nitrate (CAN) in a 9:1 mixture of acetonitrile and water to produce **13a-g** in low to

Scheme 2. Synthetic Route to Expanded Product Library Derived from 11c as a Representative Example^a

^aReaction conditions: (i) Lawesson's reagent, THF, 55 °C, 3 h, 78%; (ii) RCONHNH₂, *t*-BuOH, 135 °C, 24 h, 39–63%. Aqueous solubility data is shown in parentheses.

good yields (24–78%); 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was wholly ineffective for this deprotection.

Limited literature precedent exists for the synthesis of 7-membered chiral lactams from amino alcohols.²⁶ Treatment of amino alcohols with acryloyl chloride followed by intramolecular oxa-conjugate addition has been studied for accessing 7-membered lactams but this approach is plagued by ineffective cyclizations and poor yields.^{27,28} Here, we report an efficient route that furnishes the desired analogues, **14a–f**, **14h**, and **14i** in four-steps. After *N*-Boc protection of the amino alcohols, treatment with *t*-butyl acrylate and cesium carbonate (Cs₂CO₃) in *t*-butanol (*t*-BuOH) at 50 °C yielded the desired conjugate addition products in good to high yields (75–99%). Next, a global deprotection was performed using hydrochloric acid (HCl) in dioxane to afford the amine hydrochloride salts in high yields (97–100%). The intermediate salts were surveyed for optimal intramolecular amidation conditions which were achieved upon treatment with propylphosphonic anhydride (T3P) in dioxane and stirring at room temperature for 24 h. As such, analogs **14a–f**, **14h**, and **14i** were prepared in modest to high yields (33–83%). Compared to existing methods for accessing these 7-membered rings that require high heat and pressure,²⁹ the T3P-mediated cyclization reported here proceeds at ambient conditions and hence represents an advance. Given the mild conditions, we anticipate broader substrate scope for the T3P-mediated access to 7-membered ring lactams.

The 7-membered sultams (Scheme 1, **15a–h**) were synthesized by a modified protocol in accord with the precedent of Zhou and colleagues.^{30,31} After protection of the alcohol as the *t*-butyldimethylsilyl (TBS) ether, treatment with 2-chloroethanesulfonyl chloride in the presence of excess Et₃N yielded the vinyl sulfonamide intermediates in good to high yields (60–98%). In order to promote intramolecular cyclization, all secondary vinyl sulfonamides were methylated to afford *N*-Me-sulfonamides (70–90%). Lastly, intramolecular cyclizations were achieved in a one-pot fashion via tetra-*n*-butylammonium fluoride (TBAF) promoted TBS cleavage, followed by hetero-conjugate addition to afford the desired sultams **15a–h** in low to high yields (37–97%). No reaction was observed with secondary sulfonamides. We postulate the favorable *s-trans* conformation of the secondary sulfonamides hinders the cyclization reaction.

Overall, we prepared a library of 50 (Figure 3, Schemes 1 and 2) chiral amino alcohol-derived fragments using the methodologies described above and amino alcohols chosen from the set shown in Figure 1. All of the prepared compounds were evaluated in an aqueous solubility assay using either LC-MS/MS or UV for quantification.³² As displayed in Figure 3 and Scheme 2, the aqueous solubilities ranged from 0.085 to >15 mM.

We then investigated the utility of our chiral fragments as starting points for further diversification. For example, compound **11c** was transformed into an array of extended triazole products via thiolactam intermediates (Scheme 2). Following a modified procedure from Wishka and Walker,³³ two thiolactams **16** and **17** were obtained in 78 and 48% yield, respectively, upon treatment with Lawesson's reagent. Conversion of **16** into triazoles **18–20** was accomplished by heating in an excess of the appropriate hydrazide in *t*-BuOH for 24 h (39–63%).³⁴

CONCLUSION

In conclusion, we have developed facile and convenient synthetic routes to several families of unique and water-soluble amino alcohol-derived chiral fragments. A total of 45 compounds including chiral morpholines, lactams, sultams, and sulfamidates were synthesized in 1–5 synthetic steps. These chiral fragments are characterized by low molecular weights (100–255 Da) and aqueous solubilities in the range of 0.085 to >15 mM which are important criteria among compounds useful for FBLD.³⁵

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00050.

Information on compound synthesis, characterization, detailed results, experimental procedures, and spectra (PDF)

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S.H. and S.D.N. contributed equally. The manuscript was written through contributions of all authors.

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Notes

The authors declare no competing financial interest.

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