Published in final edited form as:

Tetrahedron Lett. 2013 August 7; 54(32): . doi:10.1016/j.tetlet.2013.06.003.

Libraries from Libraries: A Series of Sulfonamide Linked Heterocycles Derived from the Same Scaffold

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Abstract

A libraries from libraries approach is described for the synthesis of five different sulfonamide linked scaffolds. Four of the scaffolds are sulfonamides linked to heterocycles; piperazine, thiourea, cyclic guanidine, and dimethyl cyclic guanidine. The fifth scaffold is a polyamine linked sulfonamide. Three different diversity positions were effectively incorporated into each scaffold providing a number of different compounds with good yields and purity.

Keywords

piperazine; positional scanning; sulfonamide; urea; guanidine; libraries from libraries

The innovation of mixture-based combinatorial chemistry has proven to be a valuable tool in drug discovery. In particular positional scanning synthetic combinatorial libraries (PS-SCL) allow for the rapid biological evaluation of thousands to trillions of compounds from hundreds of samples in order to identify active compounds for a variety of biological targets¹⁻³. PS-SCL that are comprised of oligonucleotides, peptides, low molecular weight acyclic and heterocyclic compounds offer a diversity of structures for high-throughput screening while simultaneously requiring exponentially fewer samples to screen⁴⁻⁵.

In nature, heterocyclic structures play an essential role as structural and reactive components in many biologically relevant ligands. In particular, the heterocyclic ring offers medicinally relevant properties that can increase hydrogen bonding possibilities and polarity, and generate ligands for specific biological targets⁶. A number of heterocyclic motifs show efficacy as therapeutics and are found incorporated into approved drugs. Heterocyclic thioureas have shown activity in growth inhibition of pathogenic bacteria⁷, while a number of marketed drugs contain piperazines such as imatinib, quetiapine, and eszopiclone and are used to treat cancer, behavioral disorders, and insomnia.

In medicinal chemistry, the sulfonamide moiety is widely used because of its widespread biological activity. Marketed drugs containing a sulfonamide group can be divided into two

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classes: nonantibiotic and antibiotic. Antibiotics containing a sulfonamide have a long history, starting with Prontosil in the 1930's. Additionally, there are many other marketed drugs not used as antimicrobials in the United States that contain the sulfonamide moiety, including acetazolamide, bumetanide, valdecoxib, celecoxib, dorzolamide, glyburide, sumatriptan, sultiame, and celecoxib. These drugs are used for such diverse applications as diuretics, anti-inflammatories, anti-glaucoma, anti-diabetics, anti-migraines, anticonvulsants, and COX-2 inhibitors⁸. Research indicates that compounds that include a sulfonamide structure could be a powerful tool in combating the progression of Alzheimer's disease by potentially inhibiting the BACE1 enzyme, which is a key enzyme in the progression of the disease⁹. Sulfonamides have shown anticancer potential by being effective against human tumor cells as well¹⁰.

A library in which the core scaffold includes these two biologically active motifs thus holds great promise for drug discovery efforts. In our continuing endeavor to synthesize biological relevant libraries and utilizing the proven "libraries from libraries" approach¹¹, five scaffolds were synthesized. This method allows the modification of existing libraries to create diverse libraries that have different physical and chemical characteristics. Herein we report the efficient solid phase synthetic approach used to obtain these diverse libraries.

Multiple sequences that contained a variety of amino acids and sulfonyl chlorides were first selected for synthesis. In order to be further utilized for a synthetic mixture library, the method must be robust to sequences with diverse chemical properties. The core sulfonamide product **3** from which the libraries are derived is generated by the solid phase synthetic scheme described below (scheme 1). Starting with MBHA resin, Boc protected amino acids were coupled to the resin using standard DIC/HOBt protocol for 2 hours at room temperature, followed by washes DMF (2X) and DCM (2X). After removal of the Boc protecting group using 55% trifluoroacetic acid in DCM for 30 minutes, followed by washes with DCM(2X), IPA(2X), and DCM (2X) the amino acid coupling was repeated to obtain a resin bound dipeptide **1**. After Boc removal sulfonyl chlorides at 8 eq in 0.1M anhydrous DCM were coupled to the resin bound dipeptide using DIEA (10 eq) overnight to obtain the sulfonamide structure **2**. Each coupling reaction was monitored by the use of the ninhydrin test to ensure the coupling was complete. Resin bound **2** was reduced by exhaustive borane reduction followed by piperidine treatment to yield **3**. The resin bound thiourea heterocyclic sulfonamide product **5** was obtained by cyclization with thiocarbonyldiimidazole in 0.1M anhydrous DCM overnight at room temperature followed by cleavage from the resin with HF (1.5 hours). Reacting **3** with phosgeniminium chloride (3 eq in 0.1M anhydrous DCM, 3 eq DIEA) for 4 hours at room temperature followed by removal from the solid support with HF yielded a dimethyl cyclic guanidine attached to the sulfonamide **6**. A similar scaffold **7**, a cyclic guanidine sulfonamide, was achieved by cyclization using 5 eq cyanogen bromide in 0.1M anhydrous DCM overnight at room temperature followed by treatment with HF. The piperazine ring attached to the sulfonamide was obtained with similar ease; however it did require extra steps. The 2-Oxopiperazine ring structure **8** is first achieved by reaction of **3** with bromoacetic acid at 5eq in 0.1M anhydrous DCM overnight at room temperature. Next **8** underwent an exhaustive borane reduction followed by treatment with piperidine producing the resin bound piperazine attached to a sulfonamide **9**. The desired product **10** is released from the resin by HF cleavage (7 hours). In all cases before analysis the final products were extracted from their HF vessels with 95% acetic acid and then underwent three successive rounds of freezing, lyophilizing, and resuspending with 50% acetonitrile/water. The samples were analyzed by reverse phase LCMS. Diverse sequences were obtained which showed good purity and yields. The results are presenting in Table 1. Additionally selected compounds were purified and characterized by H1 NMR¹².

In a continuing effort to create diverse mixture libraries and utilizing the libraries from library approach the synthetic methodologies described above have been expanded to include a wide range of substituents in the R₁, R₂ and R₃ position. The work done to establish the positional scanning libraries for the cyclic guanidine sulfonamide (**7**) and piperazine sulfonamide (**10**) has already been completed and is the subject of a previous publication¹³. We are currently applying this same methodology to produce positional scanning libraries for **4**, **5**, and **6** that will each contain 18,360 compounds. These libraries will be immediately used in work directed at the identification of novel antinociceptives and efflux pump inhibitors. In summary, this is an efficient approach to create five distinct sulfonamide scaffolds through the use of solid phase chemistry.

Acknowledgments

This work was supported by NIH Grant 1R01DA031370, DOD Contract HDTRA1-13-C-005, Arthritis & Chronic Pain Research Institute, and the State of Florida, Executive Office of the Governor's Department of Economic Opportunity.

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12. H1 NMR of sample **4f** (S)-3-phenyl-N²-(((S)-1-(phenylsulfonyl)pyrrolidin-2-yl)methyl)propane-1,2-diamine (400Hz, CDCl₃): δ 7.83(2H,d) 7.56(3H,sex) 7.32-7.18(5H, m) 3.66 (1H,s) 3.20 (1H,quin) 2.95-2.89 (8H,m) 2.81 (3H,quin) 1.73 – 1.4 (4H, m). H1 NMR of sample **5f** (S)-5-benzyl-1-(((S)-1-(phenylsulfonyl)pyrrolidin-2-yl)methyl)imidazolidine-2-thione (400MHz, DMSO): δ 7.70(2H,d) 7.66-7.62 (3H, m) 7.26-7.23 (5H, m) 4.37 -3.59 (4H, m) 3.41 (1H, quin) 3.28 – 3.27 (4H, m) 2.63 (1H, q) 2.51 (1H, s) 1.90-1.33 (4H, m). H1NMR of sample **6j** N-(1-(5-benzyl-2-(dimethylamino)-4,5-dihydro-1H-imidazol-1-yl)-3-phenylpropan-2-yl)-4-bromobenzenesulfonamide (400MHz, DMSO): δ 8.46 (1H, s) 7.58 (4H, q) 7.49-7.48 (5H, m) 7.25 (3H, quin) 6.91 (2H, d) 4.06 (1H, q) 3.73 (2H, t) 3.27 (2H, quin) 2.93 (6H, s) 2.93-2.76 (3H,m) 2.52 -2.28 (2H, m). H1NMR of sample **7j** N-((S)-1-((S)-5-benzyl-2-iminoimidazolidin-1-yl)-3-phenylpropan-2-yl)-4-bromobenzenesulfonamide (400MHz, DMSO): δ 8.46 (1H,s) 7.50 (2H,d) 7.39 – 7.27 (5H,m) 7.22-7.01 (6H, m) 4.22 (1H,s) 3.68 (2H, t) 3.32 (1H, d) 3.26 (2H, q) 2.94(1H, q) 2.67 -2.50 (3H, m) spectrum previously reported¹³. H¹NMR of sample **10h** N-((S)-1-((S)-2-benzylpiperazin-1-yl)-3-(4-hydroxyphenyl)propan-2-yl)benzenesulfonamide H1 NMR of **10h** (400MHz, DMSO): δ 7.69 (2h, t) 7.55 – 7.43 (4H, m) 7.27- 6.92 (10H, m) 3.37 (3H, q) 2.80 (2H, q) 2.78-2.51 (4H, m) 2.49 – 2.18 (6H, m) spectrum previously reported¹³.

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Scheme 1.

Reagents and conditions (a) 55% TFA/DCM (30min); 3×5% DIEA (b) Sulfonyl chloride (8 equiv 0.1M anhydrous DCM), DIEA (10 equiv) rt overnight; (c) BH₃ – THF, 65°C 100 hours; (d) piperidine, 65°C 24hours; (e) Thiocarbonyldiimidazole (5 equiv in 0.1M anhydrous DCM) overnight rt; (f) HF, 0°C 1.5hours; (g) Phosgeniumminium chloride (3 equiv in 0.1M anhydrous DCM) rt 4 hours; (h) cyanogen bromide (5 equiv in 0.1M DCM) rt overnight; (i) HF, 0°C 7 hours; (j) bromoacetic acid (5 equiv in 0.1M anhydrous DCM) rt overnight.

Table 1

Individual compound purities and yields for compounds from scaffolds **4**, **5**, **6**, **7** and **10**.

ID	R1	R2	R3	4		5		6		7		10	
				Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'	Purity %
A				38	97	2.95	70	N/A	N/A	114	99	3.90	95
B				43	98	3.02	46	30	5	107	90	3.70	90
C				48	98	3.50	79	20	25	113	98	4.00	90
D				52	85	4.30	75	23	10	109	95	4.55	60
E				43	98	3.70	69	42	90	114	95	4.32	90

ID	R1	R2	R3	4			5			6			7			10		
				Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'
F				68	99	3.35	104	80	6.43	30	90	4.10	106	95	4.10	109	90	3.95
G				40	99	3.05	86	75	5.50	61	50	3.64	127	85	3.75	119	92	3.50
H				42	99	3.97	51	80%	6.81	N/A	N/A	N/A	82	95	4.38	107	98	4.24
I				47	75	3.95	56	85	6.80	54	75	4.35	75	95	4.25	104	75	4.25
J				55	99	4.20	51	75	7.15	55	95	4.65	100	98	4.55	92	95	4.45
K				60	97	4.30	61	75	7.22	49	95	4.75	94	98	4.50	81	75	4.50

ID	R1	R2	R3	4			5			6			7			10		
				Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'	Yield %	Purity %	K'
L				55	99	4.45	53	65	7.37	50	90	4.87	95	95	4.70	89	98	4.70

^aCrude yields

^bPurity of crude product before purification based on the UV peak at 214nm.

N/A: not available

K': Samples analyzed on Shimadzu Prominence liquid chromatograph (Solvent A: water with 0.1% formic acid, solvent B: acetonitrile with 0.1% formic acid), Shimadzu Prominence UV Detector (wavelength 214 and 254nm) and Shimadzu LCMS-2010 (positive mode scanning 175–1000 m/z). Samples are run in reverse phase mode with a flow rate of 0.5mL/min and a gradient of 5–95% over 6 minutes on a Phenomenex Luna C18 5μ 100A 50 × 4.60mm column.