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Sulfonyl Fluorides as Alternative to Sulfonyl Chlorides in Parallel Synthesis of Aliphatic Sulfonamides

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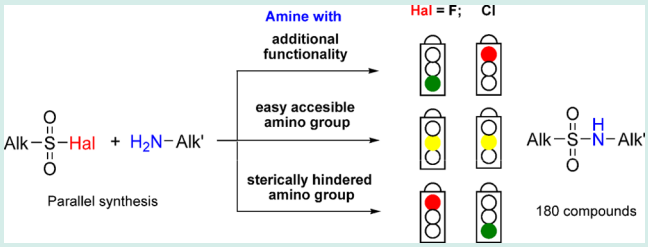
Supporting Information

ABSTRACT: Two types of aliphatic sulfonyl halides (Cl versus F) were compared in parallel synthesis of sulfonamides derived from aliphatic amines. Aliphatic sulfonyl fluorides showed good results with amines bearing an additional functionality, while the corresponding chlorides failed. Both sulfonyl halides were effective in the reactions with amines having an easily accessible amino group. Aliphatic sulfonyl chlorides reacted efficiently with amines bearing sterically hindered amino group while the corresponding fluorides showed low activity.



KEYWORDS: *sulfonamides, sulfonyl fluorides, sulfonyl chlorides, saturated compounds, parallel synthesis*

INTRODUCTION

Sulfonamides play a role in medicinal chemistry: many antimicrobial, antipsychotic, and anticancer drugs contain the sulfonamide bond (−SO_2N−) (Figure 1).[1−4] Most of these

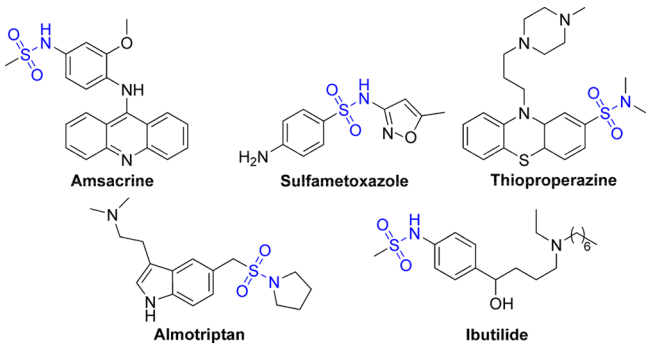
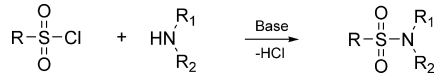


Figure 1. Representative sulfonamide drugs.

compounds, however, comprise the residues of aromatic and heteroaromatic amines, while recent studies have demonstrated that bioactivity increases with growing the number of sp^3-hybridized carbon atoms in the molecule.[5,6] The saturated "skeleton" provides better fitness to a three-dimensional protein binding pocket, higher water solubility and lower toxicity compared with the "flat" aromatic fragments.[7,8] In contrast to the aromatic sulfonamides (Ar−SO_2−NAr′R), the aliphatic analogues (Alk−SO_2−NAlk′R) are still rare: in the drug-like database of bioactive molecules (ChEMBL)[9] the corresponding ratio is ∼20:1. We assume that the lack of a general practical approach to aliphatic sulfonamides has caused their underestimation in drug discovery.

The "classical" approach to sulfonamides relies on a reaction between sulfonyl chlorides and amines in the presence of a base (Scheme 1).[10] Given the importance of saturated compounds

Scheme 1. Classical Synthesis of Sulfonamides



in medicinal applications,[5,6,11,12] we decided to prepare a library of diverse aliphatic sulfonamides by parallel synthesis. In this project, however, we observed that aliphatic sulfonyl chlorides afforded complex mixtures with functionalized aliphatic amines under conditions of parallel synthesis. Eventually, we solved these problems by using the more stable and less active aliphatic sulfonyl fluorides. Indeed, sulfonyl fluorides have been utilized before in the synthesis of sulfonamides,[13−22] but in these nonsystematic studies, researchers mostly obtained the aromatic derivatives: Ar−SO_2−NR_2. In many cases, commercial unavailability of the required halides has caused their rare

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employment in drug discovery, for example, 54 alkyl sulfonyl fluorides are listed in our internal database compared with 346 alkyl sulfonyl chlorides. Moreover, no detailed comparison between sulfonyl chlorides and sulfonyl fluorides in the synthesis of sulfonamides has been performed so far. In this context, herein we report our results on comparing the aliphatic sulfonyl halides (Cl versus F) in the parallel synthesis of aliphatic sulfonamides (Alk−SO_2−NAlk′R).

RESULTS AND DISCUSSION

We began our study by selecting seven pairs of diverse alkyl sulfonyl halides, chemset **1**, with: methyl {1*a*/*b*}, *n*-propyl {2*a*/*b*}, 2-methoxyethyl {4*a*/*b*}, cyclohexyl {3*a*/*b*}, benzyl {5*a*/*b*}, substituted benzyl {6*a*/*b*}, and heterocyclic {7*a*/*b*} groups (where *a* = sulfonyl chloride, *b* = sulfonyl fluoride, Figure 2).

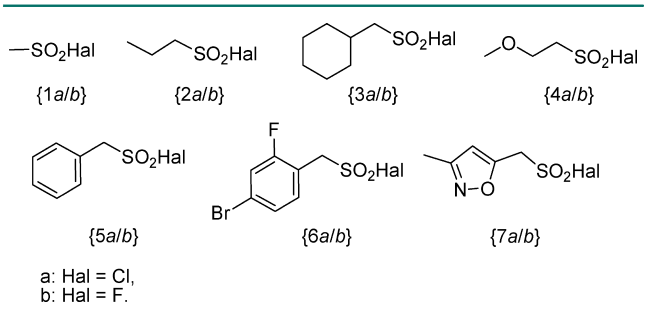
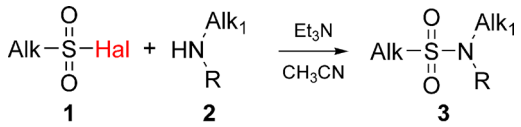


Figure 2. Aliphatic sulfonyl halides **1** utilized in the study.

Next, we chose three groups of aliphatic amines, chemset **2**: (I) with the additional functional group, **2**{*1*−*25*}; (II) with the easily accessible amino group, **2**{*26*−*31*}; and (III) with the sterically hindered amino group, **2**{*32*−*38*}.

We synthesized a collection of the corresponding sulfonamides, chemset **3** (Figures S2−S6, in the Supporting Information), by parallel synthesis according to Scheme 2.

Scheme 2. Parallel Synthesis of Aliphatic Sulfonamides



Our purpose was to generate a diverse library of compounds based on a variety of aliphatic motifs but not a full set with all possible variants. After the synthesis and subsequent chloroform extraction, each crude sample was analyzed by LC-MS and ^{1}H NMR spectroscopy to check the initial product purity (Figures S7−S36, in the Supporting Information). The products were further purified by column chromatography. We did not, however, purify the mixtures having small mass or less than 5% of the product by LC-MS and ^{1}H NMR. The structure and purity of the obtained sulfonamides were confirmed by ^{1}H and ^{13}C NMR spectroscopy and LC-MS analysis.

Aliphatic Amines with Additional Functional Group. The common feature of these substrates is an additional nucleophilic center capable to react with electrophiles, such as sulfonyl chlorides, to form the side products. We further divided these amines into three subgroups based on the functionality.

Aliphatic Alcohols. The first subgroup contains primary **2**{*1*−*5*} and secondary **2**{*6*−*10*} amino alcohols (Figure 3). In

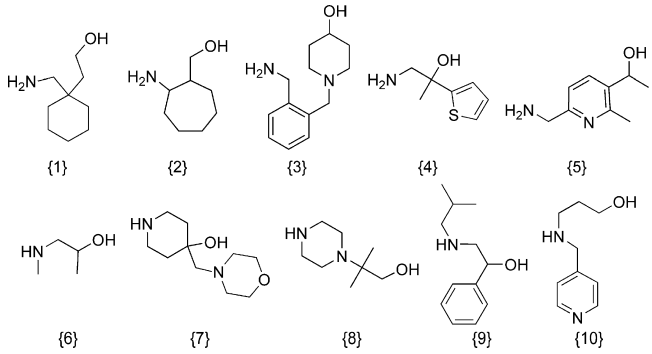


Figure 3. Aliphatic amines **2** with the aliphatic hydroxyl group (subgroup **Ia**).

more than 90% of experiments (in 23 out of 25) sulfonyl fluorides gave significantly higher yields of products compared with the chlorides (Table 1). Sulfonyl fluorides selectively reacted at the amino function tolerating the less nucleophilic hydroxyl group. In most experiments with sulfonyl chlorides, however, we obtained the products in very low yields, only in 4

Table 1. Comparison of Aliphatic Sulfonyl Halides in the Parallel Synthesis with Aliphatic Amino Alcohols (Subgroup Ia Figure 3)

entry	sulfonyl halide **1**	amine **2**	sulfonamide **3**	yield[a] (%) for *a*/*b*[b]
1	{1*a*/*b*}	{*2*}	{*1*,*2*}	<5%[c]: 42
2		{*4*}	{*1*,*4*}	62: 55
3		{*8*}	{*1*,*8*}	<5%: 51
4	{2*a*/*b*}	{*1*}	{*2*,*1*}	<5%: 27
5		{*2*}	{*2*,*2*}	<5%: 22
6		{*3*}	{*2*,*3*}	12: 15
7		{*4*}	{*2*,*4*}	<5%: 70
8		{*5*}	{*2*,*5*}	<5%: 12
9		{*6*}	{*2*,*6*}	<5%: 44
10		{*7*}	{*2*,*7*}	56: 63
11		{*8*}	{*2*,*8*}	<5%: 68
12	{3*a*/*b*}	{*2*}	{*3*,*2*}	<5%: 38
13		{*4*}	{*3*,*4*}	<5%: 64
14		{*8*}	{*3*,*8*}	<5%: 31
15	{4*a*/*b*}	{*2*}	{*4*,*2*}	<5%: 12
16		{*4*}	{*4*,*4*}	<5%: 71
17	{5*a*/*b*}	{*1*}	{*5*,*1*}	<5%: 17
18		{*3*}	{*5*,*3*}	<5%: 31
19		{*4*}	{*5*,*4*}	<5%: 86
20		{*6*}	{*5*,*6*}	40: 35
21		{*7*}	{*5*,*6*}	<5%: 71
22		{*8*}	{*5*,*8*}	<5%: 8
23		{*9*}	{*5*,*9*}	<5%: 33
24		{*10*}	{*5*,*10*}	<5%: 34
25	{7*a*/*b*}	{*8*}	{*7*,*8*}	<5%: 58

[a]Isolated yield. [b]*a* = yield in experiments with sulfonyl chloride; *b* = yield in experiments with sulfonyl fluorides. [c]Yield of the product in the crude mixture determined by LC-MS or ^{1}H NMR was below 5% or complex mixture of product-byproducts made separation impossible.

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experiments (entries 2, 6, 10, and 20, in Table 1) the yields were comparable to those for the fluorides. Active sulfonyl chlorides reacted nonselectively resulting side products of trisulfonylation (Figure S8 and S9 in the Supporting Information), elimination of H_2O (Figure S10 in the Supporting Information), *O*-sulfonylation (Figure S12 in the Supporting Information), and chlorination (Figure S18 in the Supporting Information), thus leading to more complex mixtures (Figures S7−S13, S27−S34, in the Supporting Information).

Phenols and NH-Heteroaromatics. The second subgroup of aliphatic amines contains fairly acidic X−H group (X = O, N) that may act as a strong nucleophile under basic conditions (Figure 4). Again, the less active sulfonyl fluorides showed

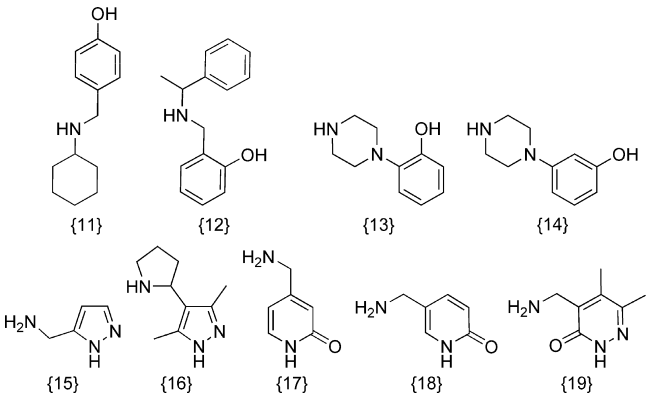

Figure 4. Aliphatic amines **2** with additional phenol or NH-heteroaromatic groups (subgroup **Ib**).

higher efficiency in the synthesis of sulfonamides over the chlorides (Table 2). In ∼75% of experiments the active sulfonyl chlorides noneselectively reacted at the both nucleophilic centers affording in many cases the complex inseparable mixtures of di-, tri-, and *O*-sylfonylated side products (Figures S14−S21, S35−S36, in the Supporting Information), while none of the sulfonyl fluorides failed. Only for **3**{*2,12*} and **3**{*5,13*} (entries 3 and 9, in Table 2), the samples with sulfonyl chloride resulted the product in comparable yields to that with the corresponding fluorides.

Table 2. Comparison of Aliphatic Sulfonyl Halides in the Parallel Synthesis with Aliphatic Amines Having Phenol or NH-Heteroaromatic Groups (Subgroup Ib, Figure 4)

entry	sulfonyl halide **1**	amine **2**	sulfonamide **3**	yield[a] (%) for *a*/*b*[b]
1	{1*a*/*b*}	{*17*}	{*1,17*}	<5%[c]: 17
2	{2*a*/*b*}	{*11*}	{*2,11*}	<5%: 19
3		{*12*}	{*2,12*}	20: 30
4		{*15*}	{*2,15*}	8: 20
5		{*16*}	{*2,16*}	<5%: 26
6		{*19*}	{*2,19*}	<5%: 39
7	{3*a*/*b*}	{*17*}	{*3,17*}	<5%: 16
8		{*18*}	{*3,18*}	<5%: 13
9	{5*a*/*b*}	{*13*}	{*5,13*}	18: 31
10		{*14*}	{*5,14*}	<5%: 31
11		{*17*}	{*5,17*}	<5%: 58
12		{*18*}	{*5,18*}	<5%: 40
13		{*19*}	{*5,19*}	<5%: 36

[a]Isolated yield. [b]*a* = yield in experiments with sulfonyl chloride; *b* = yield in experiments with sulfonyl fluorides. [c]Yield of the product in the crude mixture determined by LC-MS or ^{1}H NMR was below 5% or complex mixture of product-byproducts made separation impossible.

Anilines. This subgroup comprises aliphatic amines **2**{*20*−*25*} bearing an additional aromatic amino group (Figure 5).

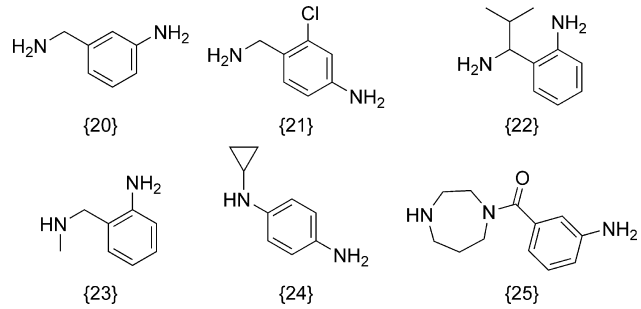

Figure 5. Aliphatic amines **2** with additional aromatic amino group (subgroup **Ic**).

The aromatic amino group is less nucleophilic compared with the aliphatic one, and therefore both the sulfonyl chlorides and fluorides predominantly reacted at the aliphatic amino group showing similar results (Table 3). In most cases for the active benzyl halides, however, the yields were higher for the fluorides than for the chlorides.

Table 3. Comparison of Aliphatic Sulfonyl Halides in the Parallel Synthesis with Aliphatic Amines Having Additional Aromatic Amino Group (Subgroup Ic, Figure 5)

entry	sulfonyl halide **1**	amine **2**	sulfonamide **3**	yield[a] (%) for *a*/*b*[b]
1	{2*a*/*b*}	{*21*}	{*2,21*}	61: 71
2		{*25*}	{*2,25*}	48: 46
3	{3*a*/*b*}	{*20*}	{*3,20*}	30: 48
4		{*21*}	{*3,21*}	60: 63
5	{5*a*/*b*}	{*21*}	{*5,21*}	59: 63
6		{*22*}	{*5,22*}	30: 28
7		{*23*}	{*5,23*}	15: 24
8		{*24*}	{*5,24*}	32: 47
9		{*25*}	{*5,25*}	24: 66

[a]Isolated yield. [b]*a* = yield in experiments with sulfonyl chloride; *b* = yield in experiments with sulfonyl fluorides.

The obtained data for group **I** showed that in 85% of experiments the aliphatic sulfonyl fluorides gave better yields of the products compared with chlorides in the parallel synthesis. The active sulfonyl chlorides mostly failed with aliphatic amines having the additional nucleophilic center: alcohol (**Ia**), phenol, or heteroaromatic NH (**Ib**) groups; but satisfactory worked with amines having an additional aromatic amino function (**Ic**).

Aliphatic Amines with the Easily Accessible Amino Function. For this group, we selected six primary **2**{*26*−*30*} and one secondary amine **2**{*31*} with different nucleophilicity of the amino function (Figure 6) and synthesized fifteen sulfonamides (Table 4). Both, sulfonyl fluorides and chlorides showed similar effectiveness. For halides **1**{*4*} and **1**{*6*}, however, the yields were generally higher with sulfonyl fluorides (entries 6, 8, 10−13, and 15, in Table 4).

Aliphatic Amines with the Sterically Hindered Amino Function. This subgroup comprises seven compounds **2**{*32*−*38*} having only the sterically hindered amino function with the reduced reactivity (Figure 7). We found that sulfonyl chlorides

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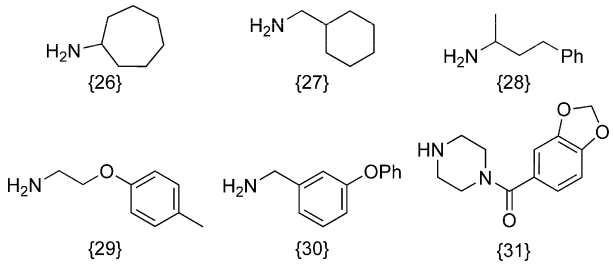

Figure 6. Aliphatic amines **2** with the easily accessible amino function (group **II**).

Table 4. Comparison of Aliphatic Sulfonyl Halides in the Parallel Synthesis with Aliphatic Amines Having the Accessible Amino Function (Group II, Figure 6)

entry	sulfonyl halide **1**	amine **2**	sulfonamide **3**	yield[a] (%) for a/b[b]
1	{1*a*/*b*}	{*28*}	{*1*,*28*}	77: 51
2		{*29*}	{*1*,*29*}	55: 72
3		{*30*}	{*1*,*30*}	81: 62
4		{*31*}	{*1*,*31*}	54: 60
5	{4*a*/*b*}	{*26*}	{*4*,*26*}	47: 45
6		{*27*}	{*4*,*27*}	51: 70
7		{*28*}	{*4*,*28*}	49: 47
8		{*29*}	{*4*,*29*}	69: 82
9		{*30*}	{*4*,*30*}	45: 47
10		{*31*}	{*4*,*31*}	13: 33
11	{5*a*/*b*}	{*27*}	{*5*,*27*}	53: 76
12		{*28*}	{*5*,*28*}	63: 79
13		{*29*}	{*5*,*29*}	65: 82
14		{*30*}	{*5*,*30*}	71: 68
15	{6*a*/*b*}	{*26*}	{*6*,*26*}	53: 65

[a]Isolated yield. [b]*a* = yield in experiments with sulfonyl chloride; *b* = yield in experiments with sulfonyl fluorides.

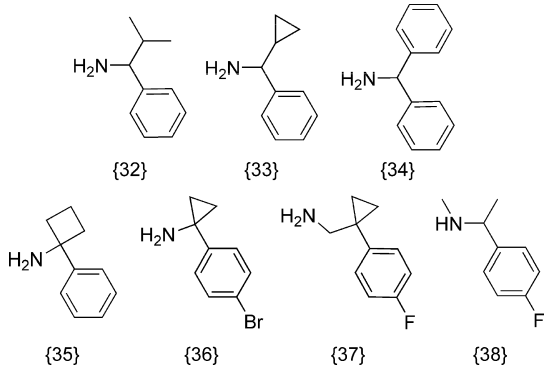

Figure 7. Aliphatic amines **2** with the sterically hindered amino function (group **III**).

gave products in good yields, while the less electrophilic sulfonyl fluorides did not react in ~40% of experiments (Table 5): in some cases complex mixtures were formed (e.g., **3**{3*b*,32}, **3**{7*b*,34}, and **3**{1*b*,36}, Figures S22–S24, in the Supporting Information) or the yields of the crude samples were low despite high purity (e.g, **3**{7*b*,32} and **3**{7*b*,38}, Figures S25–S26, in the Supporting Information). Only active benzylsulfonyl fluoride **1**{5*b*} and its analog **1**{6*b*} gave products in moderate yields comparable to those for the chlorides.

In conclusion, we have studied the efficiency of aliphatic sulfonyl halides (Cl vs F) in the parallel synthesis of 180

Table 5. Comparison of Aliphatic Sulfonyl Halides in the Parallel Synthesis with Aliphatic Amines Having the Sterically Hindered Amino Function (Group III, Figure 7)

entry	sulfonyl halide **1**	amine **2**	sulfonamide **3**	yield[a] (%) for a/b[b]
1	{1*a*/*b*}	{*33*}	{*1*,*33*}	80: 32
2		{*34*}	{*1*,*34*}	52: < 5%[c]
3		{*35*}	{*1*,*35*}	60: 4
4		{*36*}	{*1*,*36*}	68: < 5%
5		{*37*}	{*1*,*37*}	72: 36
6	{3*a*/*b*}	{*32*}	{*3*,*32*}	54: < 5%
7		{*33*}	{*3*,*33*}	69: < 5%
8		{*36*}	{*3*,*36*}	42: < 5%
9		{*37*}	{*3*,*37*}	37: < 5%
10	{4*a*/*b*}	{*32*}	{*4*,*32*}	55: 42
11		{*33*}	{*4*,*33*}	39: 25
12		{*35*}	{*4*,*35*}	64: 4
13		{*36*}	{*4*,*36*}	53: 14
14		{*38*}	{*4*,*38*}	63: < 5%
15	{5*a*/*b*}	{*32*}	{*5*,*32*}	69: 78
16		{*35*}	{*5*,*35*}	57: 64
17		{*36*}	{*5*,*36*}	75: 72
18		{*37*}	{*5*,*37*}	60: 59
19	{6*a*/*b*}	{*32*}	{*6*,*32*}	57: 69
20		{*34*}	{*6*,*34*}	26: 40
21		{*37*}	{*6*,*37*}	84: 70
22		{*38*}	{*6*,*38*}	64: 78
23	{7*a*/*b*}	{*32*}	{*7*,*32*}	27: 22
24		{*34*}	{*7*,*34*}	16: < 5%
25		{*37*}	{*7*,*37*}	63: 15
26		{*38*}	{*7*,*38*}	62: 20

[a]Isolated yield. [b]*a* = yield in experiments with sulfonyl chloride; *b* = yield in experiments with sulfonyl fluorides. [c]Yield of the product in the crude mixture determined by LC-MS or ^{1}H NMR was below 5% or complex mixture of product-byproducts made separation impossible.

aliphatic sulfonamides: Alk–SO_2–NAlk′R (88 examples are reported in the paper). In the reaction with aliphatic amines, the aliphatic sulfonyl chlorides were more active, but less selective compared with the fluorides: (1) Alkyl sulfonyl fluorides gave good results with aliphatic amines bearing additional nucleophilic center, alcohol, phenol, or heterearomatic NH group, while sulfonyl chlorides totally failed because of nonselective reaction at the both nucleophilic centers. (2) Both aliphatic sulfonyl halides worked equally well with the common monofunctional aliphatic amines and those having an additional aromatic amino group. The reaction selectively occurred at the aliphatic amino group. In terms of the synthesis costs, for large compound libraries we advise to use the cheaper sulfonyl chlorides. (3) Aliphatic sulfonyl chlorides reacted with the aliphatic amines bearing the sterically hindered amino group in moderate yields; while the less active fluorides showed no conversion in most cases.

Given the established impact of sulfonamides in drug discovery[3,10] and the recent popularity of saturated compounds,[12] we believe that our results will be useful to scientists dealing with combinatorial synthesis of bioactive molecules, peptidomimetics and medicinal chemistry.

EXPERIMENTAL PROCEDURES

General. All chemicals and solvents were obtained from commercially available sources (Aldrich, Enamine, Ltd.) and

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used without further purification. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer Spectrum BX II. ^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance DRX 500 spectrometer using DMSO-d_6 as a solvent. The spectra were referenced to the peak of DMSO-d_5. LC-MS data were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector Agilent LC-MSD SL, Column, Zorbax SB-C18, 4.6 mm ×15 mm. Eluent, A, acetonitrile−water with 0.1% of TFA (95:5, v/v); B, water with 0.1% of TFA. Flow rate: 1.8 mL/min. Ionization method: Atmospheric Pressure Chemical Ionization (APCI). The purification of the compounds was performed using a Companion Combi-Flash instrument with UV-detector and a reusable LukNova column [eluent, A, $CHCl_3$; B, $CHCl_3$:methanol (7:3, v/v)]. According to HPLC-MS data the synthesized sulfonamides have purity over 95%.

General Procedure for Parallel Synthesis of Aliphatic Sulfonamides. Alkyl sulfonyl halide **1** (1 mmol) was added to a solution of an alkyl amine **2** (1 mmol) and triethylamine (1.1 mmol) in acetonitrile (0.6 mL). The obtained mixture was left staying in a sealed vial at the bench at room temperature overnight. To achieve full conversion, the mixture was then sonicated at 80 °C for 2 or 4 h in experiments with sulfonyl chlorides or the fluorides, respectively (Figure S1, in the Supporting Information). Then, the mixture was cooled down to room temperature, diluted with chloroform (3 mL) and washed with water (3 × 7 mL). The organic phase was separated and the solvent was removed in vacuum. The crude product with purity below 95% was purified by flash chromatography.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental synthetic procedures; analytical and spectroscopic data for selected synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Supuran, C. T.; Casini, A.; Scozzafava, A. Protease Inhibitors of the Sulfonamide Type: Anticancer, Antiinflammatory, and Antiviral Agents. *Med. Res. Rev.* **2003**, *23*, 535−558.

(2) Supuran, C. T.; Innocenti, A.; Mastrolorenzo, A.; Scozzafava, A. Antiviral Sulfonamide Derivatives. *Mini-Rev. Med. Chem.* **2004**, *4*, 189−200.

(3) Wilden, J. The Sulfonamide Motif as a Synthetic Tool. *J. Chem. Res.* **2010**, 541−548.

(4) Knox, C.; Law, V.; Jewison, T.; Liu, P.; Ly, S.; Frolkis, A.; Pon, A.; Banco, K.; Mak, C.; Neveu, V.; et al. DrugBank 3.0: A Comprehensive Resource for "Omics" Research on Drugs. *Nucleic Acids Res.* **2011**, *39*, D1035−D1041.

(5) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 46−58.

(6) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(7) Yang, Y.; Engkvist, O.; Llinàs, A.; Chen, H. Beyond Size, Ionization State, and Lipophilicity: Influence of Molecular Topology on Absorption, Distribution, Metabolism, Excretion, and Toxicity for Druglike Compounds. *J. Med. Chem.* **2012**, *55*, 3667−3677.

(8) Ishikawa, M.; Hashimoto, Y. Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry. *J. Med. Chem.* **2011**, *54*, 1539−1554.

(9) Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; et al. ChEMBL: A Large-Scale Bioactivity Database for Drug Discovery. *Nucleic Acids Res.* **2012**, *40*, D1100−D1107.

(10) Gioiello, A.; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. Building a Sulfonamide Library by Eco-Friendly Flow Synthesis. *ACS Comb. Sci.* **2013**, *15*, 235−239.

(11) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. The Impact of Aromatic Ring Count on Compound Developability: Further Insights by Examining Carbo- and Hetero-Aromatic and -Aliphatic Ring Types. *Drug Discovery Today* **2011**, *16*, 164−171.

(12) Morley, A. D.; Pugliese, A.; Birchall, K.; Bower, J.; Brennan, P.; Brown, N.; Chapman, T.; Drysdale, M.; Gilbert, I. H.; Hoelder, S.; et al. Fragment-Based Hit Identification: Thinking in 3D. *Drug Discovery Today* **2013**, *18*, 1221−1227.

(13) Empfield, J. R.; Mayhugh, D.; Ohnmacht, C. J.; Frank, C. A.; Grant, T.; Li, J. 4-Sulfonamidoanilide Tertiary Carbinols: A Novel Series of Potassium Channel Openers. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 775−778.

(14) Briganti, F.; Scozzafava, A.; Supuran, C. Sulfonylamido Derivatives of Aminoglutethimide and Their Copper(II) Complexes: A Novel Class of Antifungal Compounds. *Eur. J. Med. Chem.* **1997**, *32*, 901−910.

(15) Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J. C.; Boireau, A.; Bour, Y.; Coléno, M. A.; Doble, A.; Doerflinger, G.; Huu, C. D.; et al. Riluzole Series. Synthesis and in Vivo "Antiglutamate" Activity of 6-Substituted-2-Benzothiazolamines and 3-Substituted-2-Imino-Benzothiazolines. *J. Med. Chem.* **1999**, *42*, 2828−2843.

(16) Bebernitz, G. R.; Aicher, T. D.; Stanton, J. L.; Gao, J.; Shetty, S. S.; Knorr, D. C.; Strohschein, R. J.; Tan, J.; Brand, L. J.; Liu, C.; et al. Anilides of (*R*)-Trifluoro-2-Hydroxy-2-Methylpropionic Acid as Inhibitors of Pyruvate Dehydrogenase Kinase. *J. Med. Chem.* **2000**, *43*, 2248−2257.

(17) Cat, A. De; Poucke, R. Van. Sulfonyl Fluorides as Intermediates in Organic Synthesis. I. The Synthesis of Aminobenzenesulfonyl Fluorides and Their Condensation with β-Ketonic Esters. *J. Org. Chem.* **1963**, *28*, 3426−3430.

(18) Brouwer, A. J.; Ceylan, T.; van der Linden, T.; Liskamp, R. M. J. Synthesis of β-Aminoethanesulfonyl Fluorides or 2-Substituted Taurine Sulfonyl Fluorides as Potential Protease Inhibitors. *Tetrahedron Lett.* **2009**, 3391−3393.

(19) Brouwer, A. J.; Ceylan, T.; Jonker, A. M.; van der Linden, T.; Liskamp, R. M. J. Synthesis and Biological Evaluation of Novel Irreversible Serine Protease Inhibitors Using Amino Acid Based Sulfonyl Fluorides as an Electrophilic Trap. *Bioorg. Med. Chem.* **2011**, *19*, 2397−2406.

(20) Lee, I.; Kang, H. K.; Lee, H. W. Nucleophilic Displacement at Sulfur Center. 22. Nucleophilic Substitution Reaction of Phenylmethanesulfonyl Halides with Anilines. *J. Am. Chem. Soc.* **1987**, *109*, 7472−7477.

(21) Harris, P. A.; Cheung, M.; Hunter, R. N.; Brown, M. L.; Veal, J. M.; Nolte, R. T.; Wang, L.; Liu, W.; Crosby, R. M.; Johnson, J. H.; et al. Discovery and Evaluation of 2-Anilino-5-Aryloxazoles as a Novel Class of VEGFR2 Kinase Inhibitors. *J. Med. Chem.* **2005**, *48*, 1610−1619.

(22) Berg, S.; Bergh, M.; Hellberg, S.; Högdin, K.; Lo-Alfredsson, Y.; Söderman, P.; von Berg, S.; Weigelt, T.; Ormö, M.; Xue, Y.; et al. Discovery of Novel Potent and Highly Selective Glycogen Synthase

Kinase-3β (GSK3β) Inhibitors for Alzheimer's Disease: Design, Synthesis, and Characterization of Pyrazines. *J. Med. Chem.* **2012**, *55*, 9107−9119.