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Saccharin Aza Bioisosteres—Synthesis and Preclinical Property Comparisons

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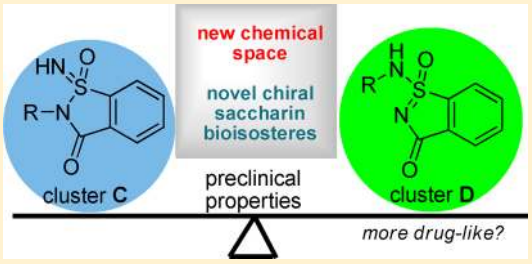
Supporting Information

ABSTRACT: Saccharin is a well-known scaffold in drug discovery. Herein, we report the synthesis and preclinical property comparisons of three bioisosteres of saccharin: aza-pseudosaccharins (cluster **B**), and two new types of aza-saccharins (clusters **C** and **D**). We demonstrate a convenient protocol to selectively synthesize products in cluster **C** or **D** when primary amines are used. Preclinical characterization of selected matched-pair products is reported. Through comparison of two diastereomers, we highlight how stereochemistry affects the preclinical properties. Given that saccharin-based derivatives are widely used in many chemistry fields, we foresee that structures exemplified by clusters **C** and **D** offer new opportunities for novel drug design, creating a chiral center on the sulfur atom and the option of substitution at two different nitrogens.



KEYWORDS: *Pseudosaccharin, Sulfonamide, Sulfonimidamide, Regioselectivity, Chemoselectivity, Telescoping synthesis, Functionalization, Ring-closure, N-Substitution, Chlorinating reagent, Medicinal chemistry*

The saccharin scaffold has been a subject of great interest, especially in the field of medicinal chemistry.[1,2] Since the functionalization of this heterocycle has proved difficult, except for N- and O-alkylation, novel strategic approaches are much sought-after and would be of great value to medicinal chemists.

N- and O-Alkylated saccharin derivatives have been employed as key structural elements in biologically active compounds ranging from enzyme inhibitors to receptor ligands and beyond.[2−4] The saccharin motif can be transformed into 3-N-substituted benzo[d]isothiazole 1,1-dioxide derivatives by derivatization of the carbonyl carbon (aza-pseudosaccharins), and they also have great utility.[5−7]

It is also possible to derivatize at the sulfonamide oxygens to generate a chiral center and two new types of derivatives (Figure 1). These compounds are here categorized into three clusters: cluster **B**, aza-pseudosaccharin; cluster **C**, formed by replacement of sulfonyl oxygen by an imino nitrogen; and cluster **D**, formed by replacement of sulfonyl oxygen with an amino nitrogen. In 1975, Stoss and Satzinger prepared a saccharin analog by replacing one sulfonamide oxygen with alkyl groups to give the cyclic acylsulfoximines.[8] Recently, an aza transformation strategy has been applied for the synthesis of sulfoximines—analogues to sulfones.[9,10]

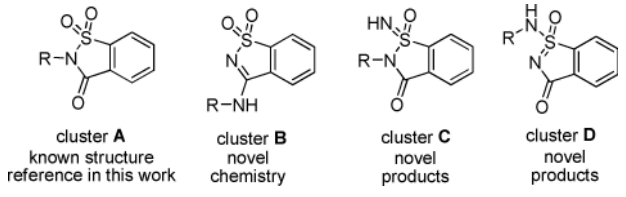


Figure 1. Structures of saccharin (cluster A) and three accessible saccharin aza derivatives (clusters B−D).

Linear chiral sulfonimidamides have been used as chiral ligands in organocatalytic asymmetric chemistry.[11−13] They have

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also been proposed as a bioisosteric replacement of sulfonamides and carboxylic acids.[14−19]

We now report a novel synthetic approach to prepare compounds in cluster **B** from saccharin. The core structure in clusters **C** and **D** was prepared via an intramolecular reaction between the *ortho* ester and the sulfonimidamide group using TBS protected methyl 2-sulfamoylbenzoate as the starting material. The chlorinating agent chloro(triphenyl)phosphonium chloride (Ph_3PCl_2), which we used in our previous work,[20] was employed in this work for both the C═O aza and S═O aza chemistries.

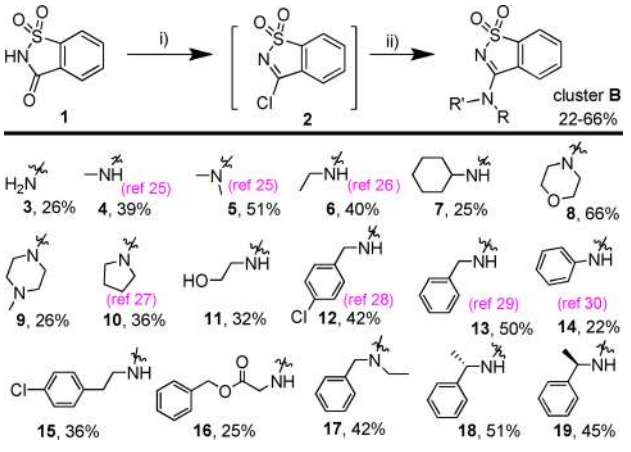
In order to evaluate the potential of these compounds as drug molecules, matched-pair compounds in clusters **B**, **C**, and **D** and three *N*-alkylated saccharin compounds in cluster **A** (R = H, Et, and Bn) were screened in *in vitro* assays. Herein, we report preclinical screening data, including measured pK_a, experimental log D, *in vitro* metabolic stability, plasma protein binding, Caco-2 permeability, aqueous solubility, and hERG inhibition. We also studied the property differences between diastereomers. Although the library of compounds that we have screened is small, the preliminary preclinical characterization results indicate that the functionalization strategy represented in clusters **C** and **D** potentially offers new opportunities for novel drug design, creating a chiral center on the sulfur atom and the option of substitution at two different nitrogens.

CHEMISTRY

1. Cluster B. The traditional method for synthesis of cluster **B** products starts from saccharin **1**. Chlorinating agents such as $SOCl_2$,[21] $POCl_3$,[22] and PCl_5[23,24] have been used as the chlorinating agents. In this work, Ph_3PCl_2 was used as the chlorinating agent to give the intermediate **2**. Nucleophilic substitution of **2** with amines afforded products **3**−**19** in one pot (Scheme 1).[20]

2. Clusters C and D. As shown in Scheme 1, a cluster B product was formed using saccharin as the starting material. In order to prepare an aza analogue on the sulfur atom, i.e. a sulfonimidamide-like product, we have developed a new methodology to prepare the compounds in clusters **C** and **D** in a parallel way as shown in Scheme 2.

Scheme 1. Synthesis of Aza Pseudosaccharin B from Saccharin[a]



[a]Conditions: (i) fresh Ph_3PCl_2 (1.15 equiv), TEA (2 equiv), DCM/$CHCl_3$, 35 °C, 5 h; (ii) various amines (3 equiv), 1.5−6 h, rt (reference numbers of known compounds are in parentheses).[25−30]

First, the sulfonamide group in methyl 2-sulfamoylbenzoate is functionalized to sulfonimidamide (products **22**−**38**) using our previously published protocol;[20] then intramolecular ring-closure occurs between the ester group and a nitrogen from either the amidic nitrogen or the imidic nitrogen in the sulfonimidamide moiety. Acidic treatment of the TBS-protected intermediates gave the final products **48**−**56** in cluster **C**, and **65**−**73** in cluster **D**.

Product **65** was prepared from **22** when the latter was treated with aqueous ammonia.

When cyclohexylamine was used, both the open- and ring-closed products **25** and **41** were found in the reaction mixture in approximately a 1:1 ratio. It was hypothesized that the steric effect of the cyclohexyl group prevented full ring-closure. Treatment of the crude mixture with HCl gave **50** and **66**. No corresponding methyl ester **57** was found.

When an α-branched primary amine, (*S*)- or (*R*)-1-phenylethylamine, was used, only a diastereomeric mixture of esters **32a/b** or **33a/b** was formed, and no cyclized product was observed. NMR indicated the dr ratio of each diastereomeric mixture was about 1:1. Chromatographic separation afforded stereochemically homogeneous isomers. Acidic treatment gave the relevant products **67a**, **67b**, **68a**, and **68b**.

X-ray crystal structures of diastereomers **68a** and **68b** indicated that **68a** had the *RcRs (RR)* and **68b** had the *RcSs* (*RS*) configurations, as shown in Figure 2. Though they only differ in the configuration around the sulfur atom, they display a very different conformation in the solid state with either a face to face or edge to face aromatic interaction, which is also present in solution (see Supporting Information for additional details).

The other ring-closed intermediates (**39**, **40**, **42**−**47**) were obtained during the purification of the relevant precursors (**23**, **24**, **26**−**31**). Finally, acidic treatment of **39**−**47** led to the formation of compounds **48**−**56** in cluster **C**.

When secondary amines were used as nucleophilic agents, intermediates **34**−**38** were obtained. After acidic cleavage of the TBS group, the final compounds **69**−**73** in cluster **D** were formed directly through ring-closure between the imidic nitrogen and the ester group in the corresponding intermediates **60**−**64**.

Besides aliphatic amines, other amino reagents, such as amino alcohols, amino esters, and anilines, are also tolerated under the reaction conditions.

In Scheme 2, when less hindered primary amines, such as methylamine, ethylamine, or benzylamine, were used, only the cluster **C** compounds were obtained. Product **74** in cluster **D** had to be synthesized from the benzylated intermediate **73** (Scheme 3).

Is it possible to prepare a cluster **D** compound directly using a primary amine as the nucleophile?

First, the intermediate **24** was prepared under the same conditions as shown in Scheme 3. Second, without evaporation, a solution of HCl in organic solvents, such as methanol, was added to the reaction mixture to afford **74** exclusively (Scheme 4). In the same manner, products **77**, **79**, and **81** were synthesized, which were not originally formed during the chemistry experiment in Scheme 2.

The chemoselectivity is highlighted in Scheme 5. In general, ring-closure first followed by TBS-deprotection led to a cluster **C** product, while deprotection first followed by ring-closure in one-pot afforded the regioisomer, a cluster **D** product.

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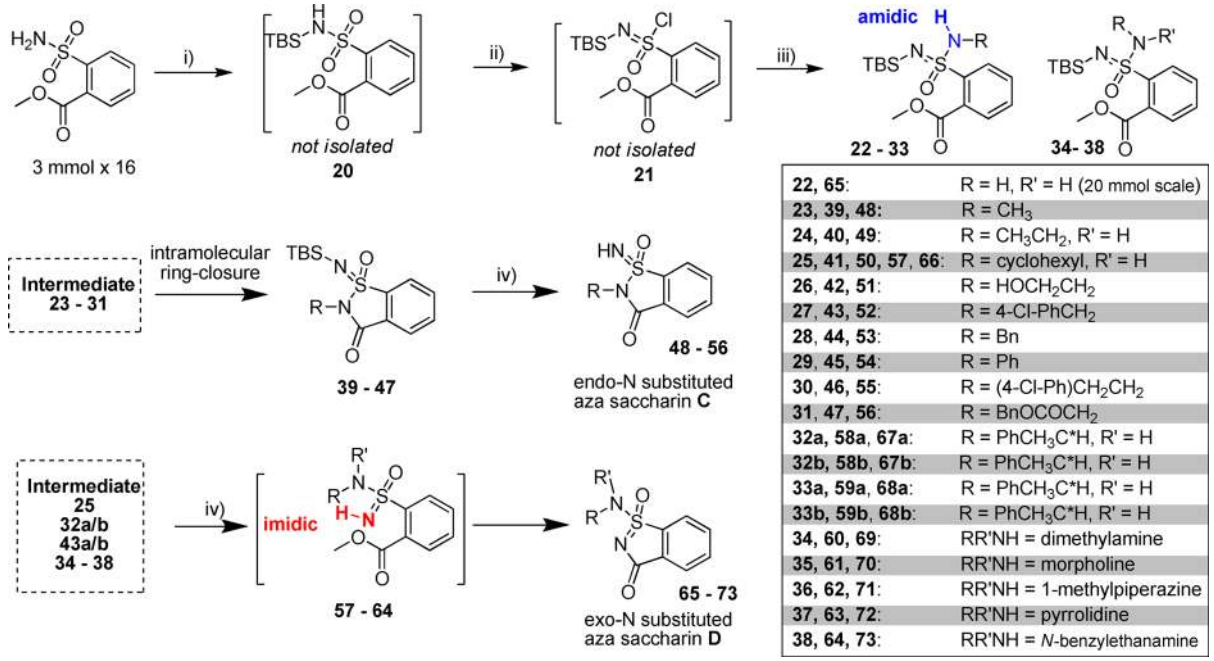
Scheme 2. Synthesis of Aza Saccharin Derivatives in Clusters C and D from Methyl 2-Sulfamoylbenzoate[a]



22, 65:	R = H, R' = H (20 mmol scale)
23, 39, 48:	R = CH_3
24, 40, 49:	R = CH_3CH_2, R' = H
25, 41, 50, 57, 66:	R = cyclohexyl, R' = H
26, 42, 51:	R = $HOCH_2CH_2$
27, 43, 52:	R = 4-Cl-$PhCH_2$
28, 44, 53:	R = Bn
29, 45, 54:	R = Ph
30, 46, 55:	R = (4-Cl-Ph)CH_2CH_2
31, 47, 56:	R = $BnOCOCH_2$
32a, 58a, 67a:	R = $PhCH_3C^*H$, R' = H
32b, 58b, 67b:	R = $PhCH_3C^*H$, R' = H
33a, 59a, 68a:	R = $PhCH_3C^*H$, R' = H
33b, 59b, 68b:	R = $PhCH_3C^*H$, R' = H
34, 60, 69:	RR'NH = dimethylamine
35, 61, 70:	RR'NH = morpholine
36, 62, 71:	RR'NH = 1-methylpiperazine
37, 63, 72:	RR'NH = pyrrolidine
38, 64, 73:	RR'NH = *N*-benzylethanamine

[a]Conditions: (i) TBS-Cl (1.18 equiv), TEA (3 equiv), DCM, rt, 1 d; (ii) fresh Ph_3PCl_2 (1.18 equiv), DCM/$CHCl_3$, 0−35 °C, 10 h; (iii) various amines (3.0 equiv), 10 min −6 h, rt; (iv) HCl/MeOH/water, 1−2 h, rt

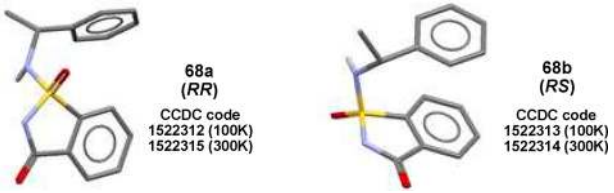
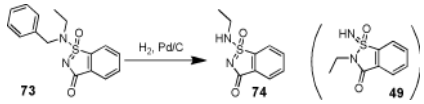
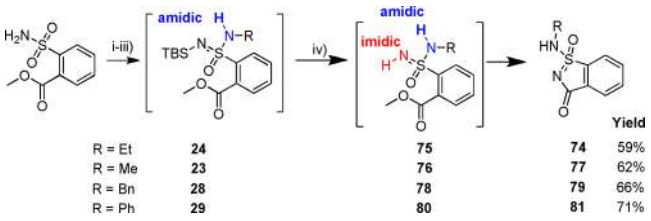


Figure 2. X-ray diffraction structures of **68a** and **68b**.

Scheme 3. Synthesis of 74



Scheme 4. Synthesis of Cluster D Products from Primary Amines[a]

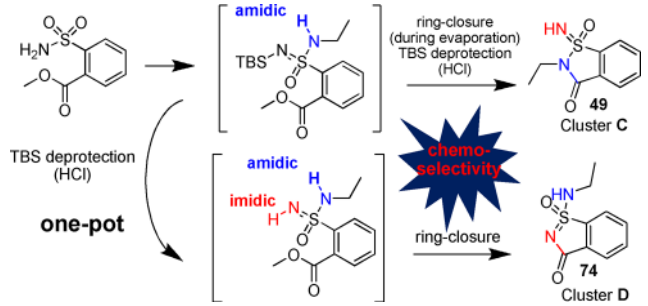


[a]Conditions: (i), (ii), (iii) same as in Scheme 3; (iv) 1.25 N HCl solution in MeOH (6 equiv), 5 min, −10 °C, then warmed up to rt in 16 h, followed by 10 h of stirring at rt.

DMPK

With all products in hand, including three reference products in cluster **A** (Figure 1, compound **1**, R = H; compound **82**, R = Et, and compound **83**, R = Bn), herein we report physicochemical and *in vitro* drug metabolism and pharmacokinetic data on

Scheme 5. Chemoselectivity of 49 and 74



compounds from the four clusters, particularly for those matched pairs where the same substituents appear in different clusters. Comparisons are made between the measured solubility, lipophilicity, pK_a, permeability, metabolic stability, and hERG inhibition (Table 1). All the physicochemical and *in vitro* assays in this work are standard and used to assess preclinical compounds at AstraZeneca.[31]

Compounds **1**, **3**, and **65** bear just a proton as the substituent. Among these three products, Table 1 shows that **3** has excellent permeability (P_{app}), whereas **65** with a lower pK_a (5.7) has a moderate permeability, and **1** is poorly permeable (pK_a 3.1). But they have quite similar profiles in terms of solubility, plasma protein binding (PPB), and *in vitro* metabolic stability (Cl_{int}). Interestingly, when one nitrogen is substituted, Table 1 showed large differences in many DMPK properties.

In general, the results of the substituted products in Table 1 indicate that, with the same substitutents:

- for clogP, compounds in cluster **B** have the highest values;
- for pK_a (acidity), the compounds in cluster **D** are slightly acidic, and pK_a values range from 4.1 to 6.9;
- for logD, compounds in cluster **D** have the lowest logD;

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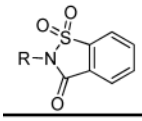
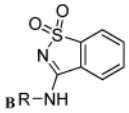
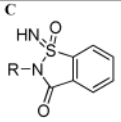
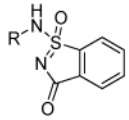
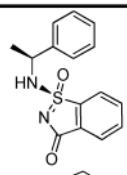
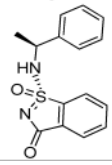
Table 1. *In Vitro* Physicochemical and Pharmacokinetic Properties of Selected Compounds

Cluster	Compd	substitution	clogP	pKa[a]	$logD_{7.4}$[b]	Sol. [μM][c]	PPB fu (%)[d]	Cl_{int} (μL/min/mg)[e]	P_{app} (a→b) x 10^6 (cm/s)[f]	hERG[g] (%)
A 	**1**	H	0.72	3.1[h]	<-0.1	838	37	<3	<0.75	/[i]
	82	Et	1.07	/	/	<13	/	/	125	3.6
	83	Bn	2.31	/	-1.8	<0.01	/	/	/	/
B 	**3**	H	-0.24	11.4	0.2	798	48	<3	7.39	/
	6	Et	1.16	11.7	0.7	971	56	<3	29.3	18.4
	13	Bn	2.40	/	1.9	89	20	<3	/	2.8
	14	Ph	2.49	/	2	7	16	85.4	/	11.1
C 	**49**	Et	0.92	8.9	0.7	512	83	<3	92	-4.7
	53	Bn	2.16	8.7	1.8	946	/	19.2	84.7	-7.4
	54	Ph	1.83	8.3	1.30	578	/	93.5	/	-25.6
D 	**65**	H	-0.49	5.7	<-1.3	>1000	40	<3	1.28	/
	74	Et	0.92	6.9	0.1	947	41	<3	26.8	1.3
	79	Bn	2.16	6.5	0.8	869	12	<3	70.7	-1.9
	81	Ph	1.83	4.1	-1.10	958	8.8	<3	6.57	5.2

[a]Determined by UV. [b]Experimental logD. [c]Dried DMSO solubility. [d]Human plasma protein binding fraction unbound (fu%). [e]Metabolic stability in human liver microsomes. [f]Apparent permeability coefficients (P_{app}) across Caco-2 cell monolayers. [g]The effects in percentage on ion channels by single shot IonWorks assay; test concentration: 11 μM. [h]Determined by potentiometric titration. [i]Not available or not determined.

Table 2. *In Vitro* Physiochemical and Pharmacokinetic Properties of 67a, 67b

Compd	Structure	pKa[a]	$logD_{7.4}$[b]	Sol. [μM][c]	PPB fu (%)[d]	Cl_{int} (μL/min/mg)[e]	P_{app} (a→b) x 10^6 (cm/s)[f]
67a		6.62	1.4	13	1.4	< 3	63
67b		6.55	0.8	107	8.9	< 3	47

[a–f]Same as in Table 1.

- for solubility, compounds in cluster **A** have poor solubility. Compounds in clusters **C** and **D** are rather soluble. This significance may be due to H-bonding between an aza product and the solvent;
- for human plasma protein binding unbound fraction, compounds in cluster **B** have in general a higher unbound fraction;
- for *in vitro* metabolic stability in human liver microsomes, a cluster **D** compound tends to have improved metabolic stability than its analogues in clusters **B** and **C**;
- for intrinsic intestinal Caco-2 permeability, although compounds in cluster **D** generally have lower permeability than the isomers in cluster **C**, they still exhibit moderate to excellent permeability;
- for hERG inhibition, despite different substituents in the tested compounds, the single shot results indicated that the hERG inhibition is usually <25%, and most of the compounds have very low or no significant inhibition (negative values).

Compounds **67a** and **67b** are diastereomeric pairs. The differences of the physiochemical and *in vitro* pharmacokinetic properties between these two compounds are shown in Table 2. The results indicate that the diastereomers have similar pK_a and Cl_{int} values. But they have different profiles, such as logD, unbound PPB, and solubility.

OUTLOOK

We intend to apply the chemistry of clusters **C** and **D** in medicinal chemistry programs, such as fragment-based hit finding. The wide range of commercially available starting materials that could be used means that our chemistry should find easy applictions.[32] Furthermore, it is also possible to install one more variation on the imidic or amidic nitrogen atom. We expect that structures with three possible variations (R, R′, and R″)

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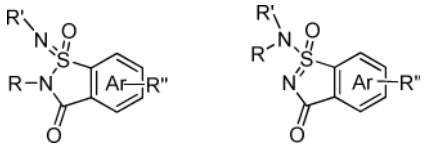

Figure 3. Further derivatization possibilities.

as shown in Figure 3 will expand the application beyond conventional areas in which a saccharin scaffold has been applied in medicinal chemistry and other fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00137.

Synthetic procedures, NMR study of **75a** and **75b**, computational chemistry, NMR spectra (pdf); X-ray data for **68a** and **68b** (PDF)

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Author Contributions

Y.C. conceived the project, Y.C. designed the experiments, Y.C. and C.-J.A. performed the synthetic experiments, C.-J.A. measured melting points for novel solids. A.P. contributed the crystal structure determination and elucidation, M.L. contributed the computational study, R.L. contributed to NMR analysis, M.H. contributed the DMPK characterization, A.J., H.L., and L.T. contributed chiral separation.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CCDC, Cambridge Crystallographic Data Centre; DCM, dichloromethane; FA, formic acid; MeCN, acetonitrile; rt, room temperature; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine

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