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Search for new sulfonyl-containing glucophores*

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Abstract: A number of sweeteners contain the sulfur atom and a sulfonyl group. In our current search for new glucophores, several new compounds containing a sulfonyl group were obtained. Synthetic targets have been found both by intuitive modifications of the structural motifs of the known sweet compounds and by the use of molecular modeling techniques. We developed the efficient synthetic routes yielding these compounds and obtained a number of these analogs. We have evaluated the taste quality of the amides and sulfonylated amino acids, finding out that almost all of them are bitter actives. We are now performing basic toxicological tests preceding the systematic taste study within the tetrazoles obtained.

INTRODUCTION

Effective synthetic sweeteners are still sought after and are appreciated by industry. However, designing such molecules is far from trivial. Among many different bioeffectors, pharmaceuticals attract the most attention in drug design. Compared to the design of a new pharmaceutical, which is extremely complicated, developing a new sweetener can be even more difficult. The reasons for this are quite obvious. The use of pharmaceuticals is usually restricted to a certain group of patients that use them in small doses. Frequently, even if it is in some sense risky, it is better to take them than to die from the disease. On the contrary, sweeteners must not only be of excellent taste, but they should also be absolutely safe for the consumption by a wide range of people. A number of sweeteners contain the sulfur atom. In particular, the sulfonyl group can be found in many sweeteners, and it is these that are of industrial importance. In our current work, we concentrated on the design of new analogs that contain sulfonyl group.

EXPERIMENTAL

Methods

The Kohonen self-organizing neural network is used to obtain two-dimensional maps of the molecular electrostatic potential of the molecular motifs analyzed. Gasteiger's programs CORINA, PETRA, and SURFACE were used for molecular modeling, and KMAP for simulation of the Kohonen maps. The protocols for these procedures have been discussed elsewhere [1–3]. All the programs were run on a Silicon Graphics O2 workstation.

Synthesis

Below, we specify typical synthetic procedures for the amino acid **1**, amide **2**, and tetrazole **3** series.

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Typical synthesis

A typical procedure described in [4] was used to obtain *N*-(*p*-toluenesulfonyl)glycine **1a**. A mixture of glycine (2.25 g; 0.03 mole), 1 M NaOH (60 ml), 4-methylbenzensulfonylchloride (6 g; 0.03 mole) in diethyl ether was stirred for 2 h. The organic layer was separated, and the aqueous one was acidified with conc. HCl. The solid product was crystallized from 60 % ethanol to give 5 g (72 %), melting point (mp) = 150 °C (literature mp = 150 °C [4]).

2-Phenylsulfonylbutyramide **2h** $SOCl_2$ (18 ml) was added to 2-phenylsulfonylbutyric acid (3.0 g). The mixture was heated under reflux for 30 min. The excess $SOCl_2$ was removed under reduced pressure, and the residue was added to concentrated NH_3 (40 ml). The product was removed by filtration, washed with water, and recrystallized from EtOH/water, to give 1.63 g (55 %), mp 169 °C, lit. mp = 170 °C [20], IR (KBr): 3409, 3175, 1674, 1400, 1143, 1080, 729, 690 cm^{-1}.

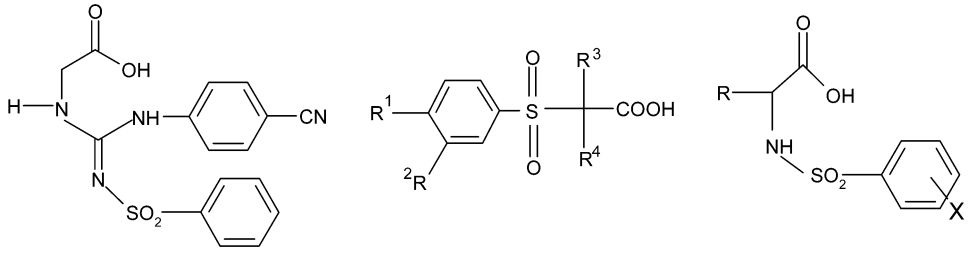
2-(*p*-Toluenesulfonyl)butyronitrile triethylamine (2.18 g) was added to a cooled (ice-water bath) suspension of 2-(*p*-toluenesulfonyl)butyramide **2h** (3.04 g; 0.0126 mole) and $POCl_3$ (23 ml). The mixture was heated under reflux for 30 min with stirring. The excess $POCl_3$ was removed under reduced pressure, and $CHCl_3$ was added. A solution was washed with aqueous K_2CO_3 and water, and dried (Na_2SO_4). The solvent was removed to obtain 2.23 g (80 %) of the oil product, which was used without further purification.

Ethyl(*p*-toluenesulfonyl)methyltetrazole **3d**, a mixture of ethyl(*p*-toluenesulfonyl)acetonitrile (0.89 g; 0.004 mole), NaN_3 (0.45 g; 0.005 mole), NH_4Cl (0.27 g) and dimethylformamide (DMF) (9 ml) was heated with stirring in an oil bath (100–110 °C for 17 h). DMF was removed under reduced pressure, the residue was suspended in cold water (38 ml) and acidified to pH 1–2 with concentrated HCl. The product was filtered and recrystallized from EtOH/water to give compound **3d**; 0.48 g (45 %), mp = 164–165 °C

RESULTS AND DISCUSSION

Synthetic targets

Scheme 1 shows some sweet compounds that include sulfonyl group. Intuitively, we aimed at synthesis of the series **1** that includes some of the motifs of the known active series **A** [6] and **B** [7–9].



A **B** **1**

R^1 = H, Me, Et, i-Pr, Cl, Br, OMe, R^2 = Cl, R, R^3, R^4 = alkyl or H

Scheme 1

Bioisosterism is a strategy consisting of the replacement of a certain group by other groups that are known to preserve or improve biological activity. Although bioisosterism is an interesting concept, we are still far from any quantitative description within this field. Practically, it is an experience that allows selecting potential bioisosteres on the basis of the known patterns of the molecules "usually"

generating active ligands. One of the newest approaches that appears to provide some measure of bioisosterism is the application of the Kohonen maps of the molecular electrostatic potential for so-called bioisosteric design. This was used successfully by the Merck group to design and obtain the endothelin antagonist [10,11]. Therefore, we simulated such maps for some molecules related to arylsulfonylalkanoic acids [12]. Tetrazole and amide functions are possible replacements, and, in fact, both can be found in sweeteners. Figure 1 compares the maps of the molecular electrostatic potential of the carboxylic acid with tetrazole and amide functions. At first sight, it seems quite surprising that the heterocyclic tetrazole moiety mimics the MEP profile much better than the amide one. However, if we analyze the chemistry of the amide and carboxylic function, the differences are quite obvious [13]. On the other hand, it is well known that 5-substituted tetrazoles have similar dissociation constants as carboxylic acids, therefore, such compounds have often been synthesized as potential bioisosteres of carboxylic acids.

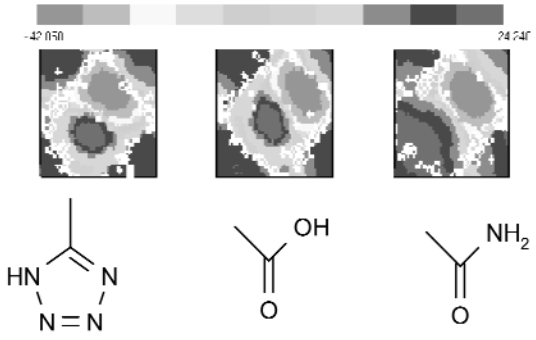
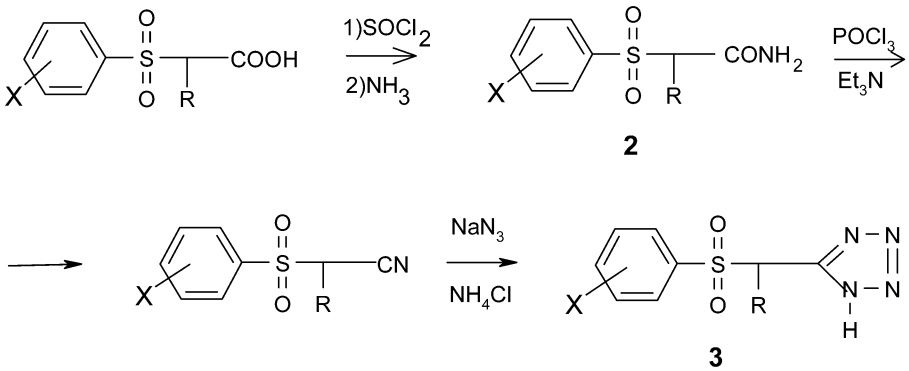


Fig. 1 The Kohonen maps of the molecular electrostatic potential of the motifs shown.

Synthesis

Arylsulfonyl derivatives of amino acids can be obtained easily by sulfonation of the respective amino acid with chlorosulfonic acid. The respective yields and structural data are listed in Table 1. Although all these analogs are described in the literature, their taste quality has not been reported previously.

Scheme 2 illustrates synthetic routes to amides **2** and tetrazoles **3**. Generally, we followed a slightly modified procedure described in the reference [4,5,14]. Therefore, the reaction of arylsulfonyl-



Scheme 2

Table 1 Amides **2** and tetrazoles **3**.

No.	X	R	mp/ lit. mp	yield, %	^{1}HNMR	Analysis, % calculated/found		
						C	H	N
2a	H	H	148/147–148 [17]	50	–	–	–	–
2b	4-CH_3	H	169/166 [18,22]	81	–	–	–	–
2c	4-Br	H	165/166 [17]	27	–	–	–	–
2d	H	CH_3	151/150 [21]	49	–	–	–	–
2e	4-CH_3	CH_3	165/166–168 [22]	52	–	–	–	–
2f	4-Cl	CH_3	185–187/190 [21]	55	–	–	–	–
2g	4-Br	CH_3	192/196 [21]	31	–	–	–	–
2h	H	CH_2CH_3	169/170 [20]	55	–	–	–	–
2i	4-CH_3	CH_2CH_3	170/175 [22]	68	–	–	–	–
2j	4-Cl	C_2H_5	160–161	39	δ[$(CD_3)_2CO$] 0.9(t,3H); 1.7–2.0(m,2H); 3.9–4.0(m,1H); 6.7–7.0(s,1H); 7.1–7.3(s,1H); 7.6–8.0; (m, 4H)	45.71/46.06	4.57/4.69	5.33/5.24
2k	H	*i*-Pr	195	84	δ(DMSO) 0.9(d,3H); 1.1(d,3H); 2.1–2.4(m,1H); 3.9(d,1H); 7.2(s,1H); 7.5(s,1H); 7.6–8.0(m,5H)	54.8/54.51	6.22/6.20	5.80/5.68
2l	4-Cl	*i*-Pr	156–158	39	δ(DMSO) 0.9(d,3H); 1.1(d,3H); 2.1–2.3(m,1H); 3.9(d,1H); 7.2–7.3(s,1H); 7.5–8.0(m,4H)	47.7/47.56	5.40/5.10	5.06/4.92
2m	3,4-diCl	*i*-Pr	175–180	40	δ(DMSO) 0.9(d,3H); 1.1(d,3H); 2.1–2.3(m,1H); 4.0(d,1H); 7.3–7.4(s,1H); 7.5–7.6(s,1H); 7.7–8.1(m,3H)	42.58/42.77	4.19/4.17	–
3a	H	H	181/179–181 [23]	36	δ(DMSO) 5.2(s, 2H); 7.6–7.8(m,5H)	42.86/42.86	3.57/3.56	25.00/24.36
3b	4-CH_3	H	210/211 [14]	79	δ(DMSO) 2.4(s, 3H) 5.2(s,2H); 7.4–7.7(m, 4H)	–	–	–
3c	4-Cl	H	225–226/225–230 [14]	39	δ(DMSO) 5.2(s, 2H); 7.8–7.9(m,4H)	37.14/37.27	2.71/3.56	21.67/21.50
3d	4-CH_3	C_2H_5	164–165	45	δ($CDCl_3$) 1.1–1.2(t,3H); 2.1–2.3(m,2H); 2.5(s,3H); 4.6–4.7(m,1H); 7.5–8.0(m,4H)	49.62/48.16	5.26/4.88	–
3e	4-Br	C_2H_5	181–182	15	δ[$(CD_3)_2CO$] 0.9–1.0(t,3H); 2.1–2.5(m,2H); 4.9–5.1(m,1H); 7.5–7.9(m,4H)	36.25/35.65	3.02/3.42	16.92/16.64

Table 1 (*Continued*).

No.	X	R	mp/ lit. mp	yield, %	^{1}HNMR	Analysis, % calculated/found		
						C	H	N
3f	H	*i*-Pr	205	20	δ[$(CD_3)_2CO$] 1.0(d,3H); 1.2(d,3H); 2.8–3.0(m,1H); 4.9–5.0(d,1H); 7.5–7.8(m,5H)	49.62/50.17	5.26/5.38	–

alkanoic acids (ASAs) with chlorosulfonic acid produced acid chloride that upon treatment with aqueous ammonia gives respective amide **2**. Dehydration of the amide **2** with phosphorous oxychloride and triethylamine results in nitrile that was reacted to the tetrazole using sodium azide and ammonium chloride. Both compound series **2** and **3** were obtained with satisfactory yields. Compounds **2** and **3** obtained are listed in Table 1.

Taste quality

Tasting new compounds is an essential step in any structure-taste study aimed at searching for new glucophores. In practice, such tests are mostly performed by the scientists involved in their synthesis. In the last decade, a number of new sweet compounds have been described, which also means they have been tasted and only very rarely have toxicological tests of any kind been performed, mainly for the analogs that were promising industrial targets.

In order to minimize any potential hazard due to tasting trials, as recommended recently during the discussion on the new ROSTQ proposal [15], we limited our tests to the series **1** and **2** that are close analogs either of the amino acids or the ASA compounds. We decided to delay the evaluation of the taste quality of tetrazoles **3** until the results of the basic toxicological tests of these compounds are known.

The taste quality of the compounds **1a–1f**, as well as **2a–2m**, is given in Table 2. Unfortunately, all of the analogs tested appeared to be "sweet inactives". On the other hand, almost all of them are bitter, while only a few are tasteless. Since bitter compounds are closely related to the sweet ones due to receptor similarities [16] it seems that in fact a sulfonyl group favors bitter/taste activity. We hope that tetrazoles that are highly bioisosteric to the carboxylic acids will taste sweet.

Table 2 Taste quality of analogs **1** and **2**.

Compound number	X	R	Taste quality
1a	H	H	bitter
1b	4-CH_3	H	bitter
1c	4-CH_3	CH_3	bitter
1d	4-CH_3	CH_2Ph	bitter
1e	4-CH_3	$CH_3CHCH_2CH_3$	bitter
1f	4-CH_3	$CH_2CH(CH_3)_2$	bitter
2a	H	H	bitter
2b	4-CH_3	H	bitter
2c	4-Br	H	bitter
2d	H	CH_3	bitter
2e	4-CH_3	CH_3	bitter
2f	4-Cl	CH_3	bitter
2g	4-Br	CH_3	inactive*
2h	H	CH_2CH_3	bitter
2i	4-CH_3	CH_2CH_3	bitter
2j	4-Cl	CH_2CH_3	bitter
2k	H	*i*-Pr	bitter
2l	4-Cl	*i*-Pr	bitter
2m	3,4-diCl	*i*-Pr	bitter

*solid sample

CONCLUSIONS

In a systematic study, we modified the structures of the known sweeteners to obtain a number of the analogs-containing sulfonyl group. Almost all of the analogs tasted so far appeared to have bitter taste. We hope that the tetrazoles, for which we are now performing basic toxicological tests preceding the systematic taste study, will taste sweet.

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