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Amino sulfonic acids, peptidosulfonamides and other related compounds

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ABSTRACT

A review with 636 references. The literature on saturated amino sulfonic acids with primary/secondary amino group and their derivatives from XIX century to 2016 is surveyed, focusing mainly on results published in the last two decades. Synthesis of saturated amino sulfonic acids and their derivatives, their occurrence among natural products, as well as their use for design of peptidomimetics, conjugates with various molecules of practical significance, applications as building blocks for drug discovery and for other reasons are discussed.

Contents

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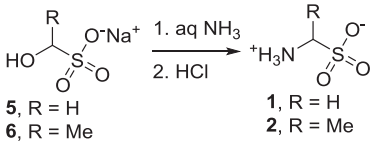
1. Introduction

It is well-known that α-amino acids are basic building blocks of life, and they have found widest application in organic, bioorganic and medicinal chemistry, as well as other related areas.[1,2] A huge number of their (hetero)oligomeric derivatives, *i. e.* peptides are found in Nature and/or approved as marketed drugs.[3] Nevertheless, using peptides in drug discovery has some DMPK issues, mainly related to their metabolic instability and problems with bioavailability.[4] It is not surprising therefore that numerous analogues of amino acids and peptides (the so-called peptidomimetics) are available[5–9]; principles of their design include homologation (e. g. β-amino acids[10–17]), conformational restriction,[18–25] introducing fluorine atom(s)[26–30] or isosteric replacements.[31–34]

Organoelement isosteres of amino acids, *i. e.* compounds where the carboxyl group is replaced by phosphonic, boronic or sulfonic acid moiety, are one of the most straightforward analogues thereof. Whereas amino phosphonic[35–40] and amino boronic[41–43] acids are mostly of synthetic origin, the first representative of saturated amino sulfonic acids (ASAs) was found in Nature almost two centuries ago. In particular, β-aminoethanesulfonic acid, known as taurine (**1**, Fig. 1), was isolated from the bile of an ox (*Bos Taurus*) as early as in 1827.[44] For a long time, it was believed to be a biologically inert end product of sulfur metabolism; currently, taurine is considered as the "conditionally essential" amino acid (despite it does not have classical α-amino acid structure and is not incorporated into the protein molecules).[45] Taurine is found in most mammalian tissues, appears to have multiple functions and plays an important role in many physiological processes, such as osmoregulation, immunomodulation and bile salt formation.[46] The role of amino acid **1** is considered in many diseases such as various central nervous system disorders,[47,48] diabetes and other metabolic disfunctions,[49,50] and retinal diseases.[45] On the other hand, taurine is a major ingredient in popular "energy" drinks.[51,52]

Other simplest representatives of ASAs, α-aminomethanesulfonic acid (**2**), α-aminoethanesulfonic acid (**3**), and γ-aminopropanesulfonic acid, or homotaurine (**4**), have been also known for nearly a century (Fig. 1). α-ASAs **2** and **3** were prepared synthetically *via* reaction of the corresponding bisulfite derivatives **5** and **6** with ammonia (Scheme 1).[53,54] It should be noted that the structure of the products obtained in these reactions was questioned until 1930s, when it was finally accepted that they are α-ASAs.[55] γ-ASA **4** is also known since XIX century[56]; it is a close analogue of well-known neurotransmitter γ-aminobutyric acid (GABA). Homotaurine (**4**) was investigated in a Phase III clinical trial under the name "tramiprosate" as a potential treatment for Alzheimer's disease, but did not show efficacy.[57] *N*-Acetyl derivative of the compound **4**, known as acamprosate (**7**), have become marketed drug used to treat alcohol dependence (Fig. 2).[58] Another marketed drug which can be mentioning here is taurolidine (**8**), a taurine derivative used as an antimicrobial agent.[59]

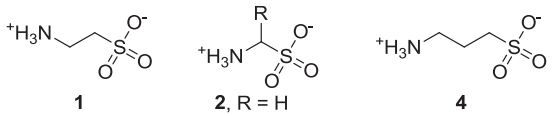
Although being quite a close isosteric replacement for the carboxylic function, the sulfonic acid moiety has several distinct features. First of all, it has much lower pK_a value and hence is almost completely ionized at physiological pH (*e. g.* for taurine $pK_1 \approx 1.5–1.7$, $pK_2 = 9.0$).[60,61] Therefore, the sulfo group can act explicitly as anionic moiety and/or acceptor of hydrogen bond



5, R = H
6, R = Me

1, R = H
2, R = Me

Scheme 1.



1 **2**, R = H **3**, R = Me **4**

Fig. 1. The simplest representatives of saturated ASAs.

7 **8**

Fig. 2. Some marketed drugs – derivatives of saturated ASAs.