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Amino acidic scaffolds bearing unnatural side chains: An old idea generates new and versatile tools for the life sciences

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ABSTRACT

The unnatural amino acids (UAAs) are members of a class of molecules with relevant impacts in the life sciences. Due to the role of these molecules in the modulation of the chemical and physical properties of biological and inorganic materials, UAAs have attracted increasing interest in recent years. The aim of this review is to highlight (i) the most recent and innovative synthetic routes for the preparation of UAAs, (ii) the recently marketed UAA-based drugs, and (iii) the most promising technological applications involving novel UAA-containing molecular entities.

Proteinogenic amino acids are considered pivotal chiral pool material. In addition to the 20 well-known amino acids, a plethora of analogues with modified side chains and backbones or atypical stereochemistry can also be considered, widening the scope of investigation and increasing the chances for success. Although some of these non-standard amino acids, such as ornithine, which is present in the urea cycle, are naturally occurring, these amino acids are generally termed 'non-natural' or 'unnatural' amino acids (UAAs). Unlike the proteinogenic amino acids, for which the preferred collection method is extraction from natural sources, most non-standard amino acid analogues must be synthesized. For this reason, as well as the growing awareness of the relevance of these molecules in several technological contexts, UAAs have been the subject of a relatively large number of scientific investigations in recent decades (Fig. 1). In addition to the use of amino acid scaffolds as building blocks during drug discovery[1] and the unusual role of amino acids as reactants for important drug-like compounds[2] (e.g., benzodiazepines), the conserved backbones and their variable side chains are potentially relevant for a wide number of applications, which span from probing protein function to adhesive agents and biomedical products. Among the increasing number of publications on this subject, very few general reviews

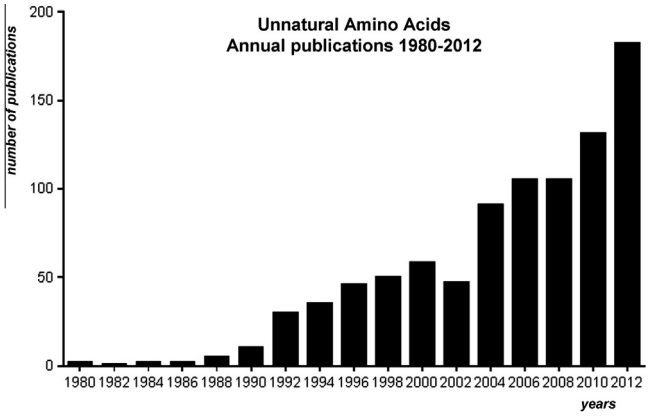

Figure 1. Growing interest towards unnatural amino acids within the last decades (number of annual publications between 1980 and 2012, SciFinder Scholar, research topic search: unnatural amino acids).

Abbreviations: AA, amino acid; UAA, unnatural amino acid; ADC, antibody-drug conjugate; DOPA, L-3,4-dihydroxyphenylalanine; flp, 4-(*R*)-fluoroproline; GnRH, gonadotropin-releasing hormone; hyp, hydroxyproline; LAR, long acting release; MOF, metal–organic framework; 4-DMAP, 4-*N*,*N*-dimethylaminophthalimide; 6-DMN, 6-*N*,*N*-dimethylamino-2,3-naphthalimide; TOAC, 4-amino-1-oxyl-2,2,6,6-tetramethyl-piperidine-4-carboxylic acid; SASA, solvent-accessible surface area; SLP, silk-like properties; 3D, tridimensional.

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addressing UAAs, including their synthesis and their use in diverse fields, are currently available in the literature. The current review will focus on α-UAAs, providing an overview of the most recent and the most innovative synthetic routes for the preparation of these molecules and an overview of recently marketed UAA-based drugs. This review will also include a discussion of the most promising technological applications that involve novel UAA-containing molecular entities in the life science disciplines and beyond.

Synthesis of UAAs: Access to UAAs has attracted attention in recent years.[3] The synthetic routes that are currently available can be reduced to a small number of diversity-oriented transformation categories, which differ from one another with respect to the starting materials employed and the number of bonds formed (see Fig. 2). The most intuitive procedures are based on alkylations that involve glycine equivalents or the widest range of modifications to amino acid side chains. Multicomponent or tandem reactions that proceed via imines or other activated intermediates are likely the most synthetically attractive routes, even though these reactions often lack efficiency or stereoselectivity. Due to the large number of methodologies and examples available, we chose to focus our discussion on only the most innovative approaches, including (but not limited to) the stereoselective multicomponent synthesis of non-proteinogenic α-amino acids.

Several multicomponent access routes to UAAs involving an imine as the key intermediate (see Fig. 2a) were discussed in the literature. The asymmetric Petasis borono–Mannich reaction represents one of the most powerful and straightforward approaches for the stereoselective preparation of α-amino acids. Strategies involving chiral amines, chiral boronate esters, and chiral organocatalysts have been employed, but to date, none of these strategies has yielded satisfactory results in the synthesis of α-amino acids. Li and Xu[4] developed an extremely mild and practical approach for the asymmetric synthesis of β,γ-unsaturated α-amino acids that employs a highly diastereoselective Lewis acid-promoted Petasis three-component-reaction of *N-tert*-butanesulfinamide in the presence of glyoxylic acid and a vinylboronic acid. This reaction was conducted at room temperature and optimized with respect to Lewis acid ($InBr_3$), solvent (CH_2Cl_2), concentration (0.3 M) and time (12 h), with the aim of enhancing diastereoselectivity and yield (Fig. 3a). This method has proven efficient and general with respect to substrate scope and stereocontrol. Not only styryl boronic acids but also alkenyl and benzo-condensed aryl boronic acids performed well under the optimized conditions. After establishing carboxylation reactions of mono-protected *N*-Boc-α-amido stannanes using CO_2 as a C1 source, Mita and Sato[5] developed a one-pot synthesis of α-amino acids based on imine formation, stannylation or silylation, and final carboxylation (Fig. 3b). This reaction was made possible by the combination of CsF and $Me_3Si–SnBu_3$ or $PhMe_2Si–Bpin$ reagents and gave products with yields up to 91%. α,α-Dialkylglycines are sterically constrained amino acids that are of great interest due to their properties when incorporated into peptides. In fact, these amino acids increase proteolytic stability and confer specific conformations. The synthesis of several α,α-dialkylglycines was achieved using a solid phase Ugi reaction performed over isocyanide functionalized resins, with phenyl acetic acid as the acid component, 4-methoxybenzylamine as the amine component and diverse ketones to afford the desired N-acylated α,α-dialkylglycines in good overall yields (60–80%) after acidolytic cleavage from the resin (Fig. 3c).[6] A recent diversity-oriented approach envisaged a solvent/catalyst-free Biginelli condensation to prepare a series of propargylated dihydropyrimidinone scaffolds, which may be considered cyclic β-amino acids.[7] These precursors were further decorated through cycloaddition reactions with small peptide-like azides synthesized from Ugi or Mannich reactions (Fig. 3d). Various hydroxyaldehydes were functionalized via base-catalyzed condensation with propargyl bromide before performing the Biginelli

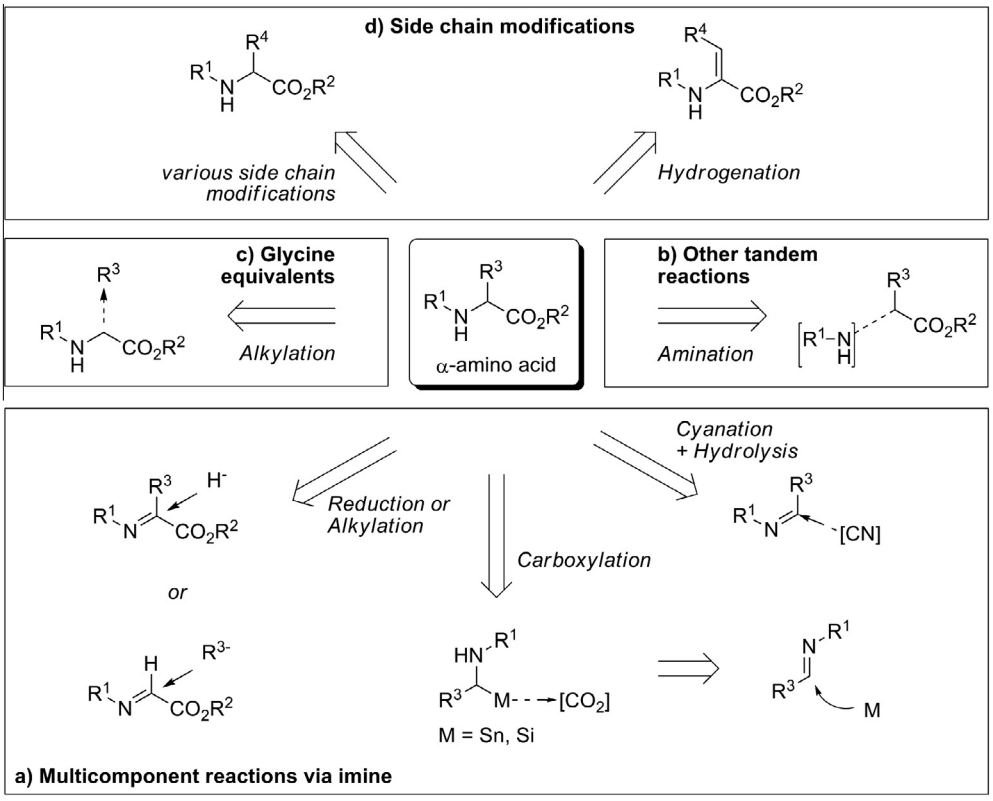

Figure 2. Retrosynthetic approaches to α-amino acids: (a) multicomponent reactions via imine; (b) other tandem reactions; (c) glycine equivalents; (d) side chain modifications.