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Amino Acids Modification to Improve and Fine-Tune Peptide-Based Hydrogels

Stefan Loic

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Abstract

Among all the materials used in industry, gels play an increasingly important role. These so-called soft-matter materials are defined by their ability to fix a large amount of solvent, either organic (organogels) or aqueous (hydrogels). The large majority of hydrogels are made of natural or synthetic polymers, or natural proteins. However, a new kind of hydrogel has appeared: the peptide-based hydrogels, developed from short amino acids sequences (<20 amino acids). Due to their exceptional qualities in term of biocompatibility, biodegradability, and atom economy, these peptide-based hydrogels open new horizons in term of applications. They are mainly considered in the biomedical domain as injectable hydrogels, or as an extracellular culture matrix to support cell culture. While important, the possibilities of peptide design can exponentially grow using modified and non-natural amino acids instead of the "only" twenty natural ones. Thus, chemical modifications virtually offer infinite opportunities both to improve applications window and to fine-tune properties of the resulting hydrogels. In this context, this chapter proposes to review peptide and amino acid modifications reported to impact the resulting hydrogel.

Keywords: bioinspired materials, modified amino acids, gelator, peptide-based hydrogel, self-assembly, soft matter, supramolecular chemistry

1. Introduction

1.1. Soft matter and hydrogels as powerful materials

At the tenuous frontier between the solid and the liquid states, soft matter is focusing research interest which has exponentially increased since the beginning of the 1990s (<20 peer-reviewed articles published in 1990 versus >700 for 2014, 2015, and 2016). Interestingly, it is in

perfect accordance with the Nobel Prize in Physics received by Pr. Pierre-Gilles de Gennes in 1991, who merely entitled his Nobel lecture "Soft Matter" [1]. He has definitely contributed to popularize this terminology. Soft matter includes a wide variety of materials, including colloidal suspensions, surfactants, liquid crystals, polymers, or gels. These latter ones constitute the major thread of this chapter.

Interestingly, the gel state can be described both as a solid state, because of the ability of gels to self-support their own weight (which is a solid state characteristic), and as a liquid, on account of the gel composition made of a large majority of a liquid (generally >98% w/w) and only a small amount of solid (<2% w/v) [2–4]. Thus, gels are defined by their ability to fix a large amount of solvent, either organic (organogels) [5] or aqueous (hydrogels) [6, 7]. Hydrogels are of particular interest and find plenty of applications from medical treatments (*e.g.*, wound healing, dental care, cartilage repair, tissue engineering) [8] to cosmetics, agriculture, and water treatments [9]. The commercially available hydrogels are made of several kinds of starting materials, including natural polymers (*e.g.*, xanthan or Arabic gums, agaragar), synthetic polymers (*e.g.*, polyurethane (PU), polyethylene glycol (PEG), polyacrylic acid (PAA)), or natural proteins (*e.g.*, collagen, sink fibroin, elastin) [10].

Depending on the nature of the interactions inside the matter, hydrogels can be discriminated between both chemical gels and physical gels [11]. For the first one, covalent bonds are created to form a network from the starting building block (also termed "gelator"), while for the latter, dynamic cross-links based on non-covalent interactions (mainly hydrogen bonds, π-π interactions, and Van der Waals interactions) control the supramolecular self-assembly of molecules of gelator [2–4].

Physical hydrogels, also called supramolecular hydrogels, draw scientific community's attention due to their ability to be, *in theory*, dynamically assembled and disassembled several times, thanks to the formation and break of non-covalent interactions. However, some examples reveal that some hydrogels are too strong to be broken without degradation of the starting gelator. Regardless, the simplicity of the formation of supramolecular hydrogels, consisting of mixing the gelator and water followed by the application of a stimulus to trigger the gelation process, has made these materials of primary interest for a broad range of applications [8, 12, 13]. The stimuli applied are, depending of the system, of different nature including temperature, ultrasound, salt addition, addition of a specific chemical, pH, enzyme, light, electromagnetic field, etc. [2–4].

In the development of high-efficient hydrogels, the place taken by peptide-based hydrogels drastically increased during the last two decades. Based on the self-assembly of peptides, these hydrogels are particularly interesting for applications in biological and medical contexts [14–19]. Great expectations are placed on these innovative materials by the scientific community, and first commercially available systems have emerged, when others are in clinical research trials.

1.2. Peptide-based hydrogelators as innovative and efficient materials

Smaller than proteins, polypeptides and peptides are comprised of amino acids linked by amide bonds, the terminology depending on the length of the chain (respectively ≥100, <100, and <10 amino acids as generally accepted). In a biological context, common natural amino

acids (α-amino acids to be more specific) are 20 and are characterized by their molecular structures and their physicochemical properties including their isoelectric point, hydrophobicity, pKa, etc. (**Table 1**) [20]. As a function of their sequence and conditions, proteins and peptides have the ability to self-assemble in a non-covalent way, forming secondary structures termed β-sheets (parallel and antiparallel), α-helix, 3_{10} helix, or π-helix. These structures are fundamental for physiological process and are mainly due to specific intra- or inter-molecular hydrogen bond interactions between the carbonyls and the protons of the amide groups. Other types of interactions are also crucial for peptide self-assembly, including van der Waals forces, electrostatic forces, π-π interactions, and hydrophobic affinity [2–4].

An overwhelming majority of the peptide-based hydrogels rests on peptide β-sheet assemblies. Indeed, starting gelators (*i.e.*, peptides) mainly self-assemble into fibrils, which subsequently combine each other via supramolecular interactions to form fibers. Altogether, these fibers form a network acting as the frame of the hydrogel, essentially self-supported by hydrogen bonds (**Figure 1**) [21]. This analogy to building construction is shared with numer-

Name	Three-letter code	One-letter code	M (g.mol^{-1})	Nature (lateral chain)	Isoelectric point (IP)	pKa (lateral chain)	Hydropathy index	P_β
Alanine	Ala	A	89.09	Aliphatic	6.01	N/A	1.8	0.76
Glycine	Gly	G	75.07	Aliphatic	5.97	N/A	−0.4	0.71
Isoleucine	Ile	I	131.17	Aliphatic	6.02	N/A	4.5	1.73
Leucine	Leu	L	131.17	Aliphatic	5.98	N/A	3.8	1.23
Proline	Pro	P	115.13	Aliphatic	6.48	N/A	1.6	0.43
Valine	Val	V	117.15	Aliphatic	5.97	N/A	4.2	1.82
Phenylalanine	Phe	F	165.19	Aromatic	5.48	N/A	2.8	1.48
Tryptophan	Trp	W	204.23	Aromatic	5.89	N/A	−0.9	1.24
Tyrosine	Tyr	Y	181.19	Aromatic	5.66	10.07	−1.3	1.43
Aspartic acid	Asp	D	133.10	Acid	2.77	3.65	−3.5	0.52
Glutamic acid	Glu	E	147.13	Acid	3.22	4.25	−3.5	0.67
Asparagine	Asn	N	132.12	Amide	5.41	N/A	−3.5	0.53
Glutamine	Gln	Q	146.15	Amide	5.65	N/A	−3.5	0.78
Arginine	Arg	R	174.20	Basic	10.76	12.48	−4.5	0.86
Histidine	His	H	155.16	Basic	7.59	6.00	−3.2	1.01
Lysine	Lys	K	146.19	Basic	9.74	10.53	−3.9	0.82
Serine	Ser	S	105.09	Hydroxyl	5.68	N/A	−0.8	0.92
Threonine	Thr	T	119.12	Hydroxyl	5.87	N/A	−0.7	1.19
Cysteine	Cys	C	121.16	Sulfur-containing	5.07	8.18	2.5	1.26
Methionine	Met	M	149.21	Sulfur-containing	5.74	N/A	1.9	1.26

Table 1. Key properties of the main amino acids (with P_β for amino acids β-sheet propensity).
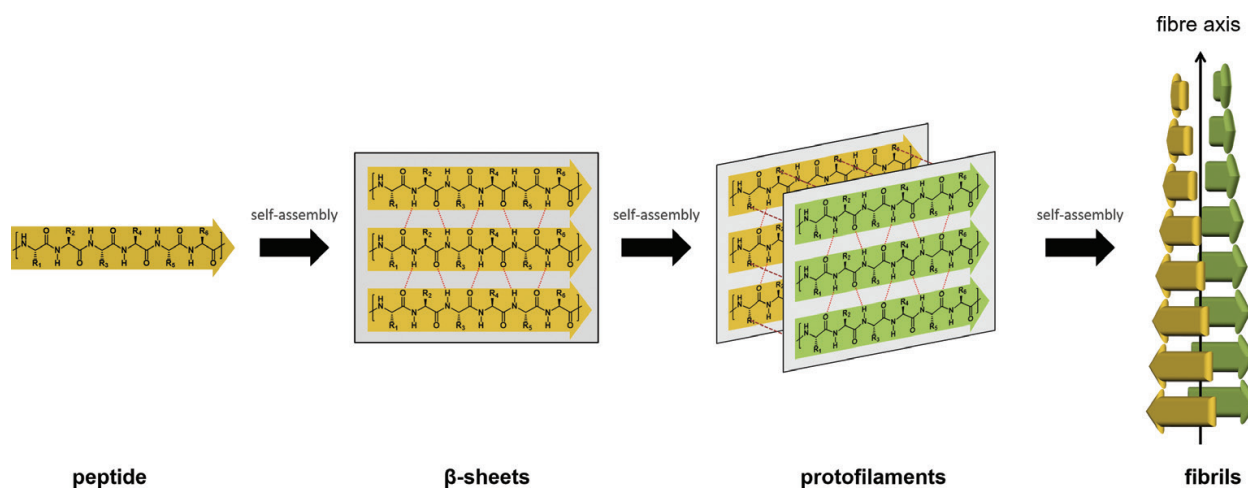
Figure 1. Schematic representation of peptide self-assembling to form fibrils.

ous vital biological self-assemblies (*e.g.*, antibody/antigen, RNA/protein, DNA/DNA, etc.), showing the pivotal role of supramolecular assemblies. Because peptides (*i.e.*, short proteins) natively self-assemble each other, peptide-based hydrogels can be considered as Nature-inspired materials [22].

While β-sheet assemblies are the predominant way peptides interact to form hydrogels, a handful of these soft matter materials are based on α-helical coiled-coil structures [23, 24]. Briefly, these architectures involve repeating heptapeptides (or heptads) mainly based on the sequence (HPPHPPP) in which H is a hydrophobic amino acid and P a polar one. Among them, few examples of coiled-coil-based hydrogels can be cited, including the tri heptad repeats **(Ile-Lys-Gln-Leu-Glu-Ser-Glu)$_3$** and **(Ile-Ala-Gln-Leu-Glu-Tyr-Glu)$_3$** [25], a 34-mer based on the **Gln-Leu-Ala-Arg-Glu-Leu(Gln-Gln-Leu-Ala-Arg-Glu-Leu)$_4$** [26], a 19-mer (**Ac-Leu-Lys-Glu-Leu-Ala-Lys-Val-Leu-His-Glu-Leu-Ala-Lys-Leu-Val-Ser-Glu-Ala-Leu-His-Ala-NH$_2$**) [27], and the hydrogel formed by two 28-residue peptides termed hSAF$_{AAA}$ used as substrate for cell growth [28]. However, these gels based on coiled-coil peptide architecture are limited by both the length of the sequence (from ~20 to 40 amino acid residues) and the concentration of peptide (from 1 to 12% w/v) required. Comparatively, hydrogels based on peptide self-assembling via β-sheet formation can be formed with ultrashort peptides (≤7 amino) and with smaller concentrations (≤0.1% w/v), making those indubitably better candidates in terms of efficiency and atom economy. Thus, the large majority of peptide-based hydrogels developed in the last two decades are based on β-sheet assemblies [2–4].

Contrastingly to the use of polymers in hydrogel formation, peptides have indisputable advantages making them remarkably more attractive. In particular, they are both biocompatible and easily metabolized by proteolysis, making them perfect candidates for biomedical and therapeutic applications [15]. Unlike polymers, peptides are chemically defined and synthesized in a high-purity with high reproducibility. Moreover, due to their own structure, peptides are perfectly biodegradable and seem to be an *ad hoc* alternative to polymers when suitable. Nonetheless, it is fair to remind that polymer science still has an indisputable

advantage because of its in-depth knowledge, while peptide-based hydrogels are still at their infancy. Fundamental research strongly supports the interest of these innovative peptide-based materials, trying to decipher the subtle mechanisms of self-assembly and the way(s) to optimize and fine-tune their thermodynamic and kinetic properties. Following this trend, applications have substantially increased and first commercially available peptide-based hydrogels have started to be sold, demonstrating their real interest [29].

1.3. Applications, commercial innovations, and outlook of peptide-based hydrogels

Due to their bioinspired architecture, peptide-based hydrogels are biocompatible, non-immunogenic, and potentially non-inflammatory [30], making them perfect materials for biomedical applications [31]. As a result, several systems were developed:

- as extracellular culture medium (or ECM) for cancer cells [16], stem cells, or neuronal SN4741 cells [32].

- as ECM to control $\alpha_5\beta_1$ integrin expression of endothelial cells [33].

- as injectable hydrogel for controlled-release of opioids [34] or of embryonic stem cell secretome [35].

- as implanted hydrogel-containing stem cells to treat spinal cord injury [36] or for nerve repair after traumatic injury in the nervous system [37]. *In vivo* implantation of RADA-16 peptide derivatives enhances extensive bone regeneration of mice femurs [38].

- as injectable hydrogel incorporating a Gadolinium MRI agent to follow its degradation *in vivo* [35].

- as adjuvant for vaccines, for instance against West Nile virus [39].

- for rapid hemostasis [40].

- for controlled-release of growth factor [41], pindolol, quinine, timolol [42], 5-fluorouracil [43], vancomycin and vitamin B12 [44], tanshinones [45], microRNA [46], or proteins (*e.g.*, BSA, IgG) [47].

- for immobilization of biocatalysts for chemical transformations [48].

- for removal of toxic dyes and heavy metal ions from waste water [49].

- to produce nanostructured silica [50] or to encapsulate carbon nanotubes [51].

- as antibacterial hydrogels [52], like the 20-mer MARG1 against methicillin-resistant *Staphylococcus aureus* [53], or **(Lys-Ile-Gly-Ala-Lys-Ile)$_3$-NH$_2$**, #1 **Figure 2**) against *E. coli* [54].

This laundry list clearly illustrates the potential of peptide-based hydrogels and puts out a new avenue in term of polyvalence, mainly in the biomedical domain. It has not escaped the attention of generalist media, like for instance Times of India [55], Asian Scientist [56], LaboratoryNews [57], Phys Org [58], Medical News Today [59], Medical Daily [60], and so forth.
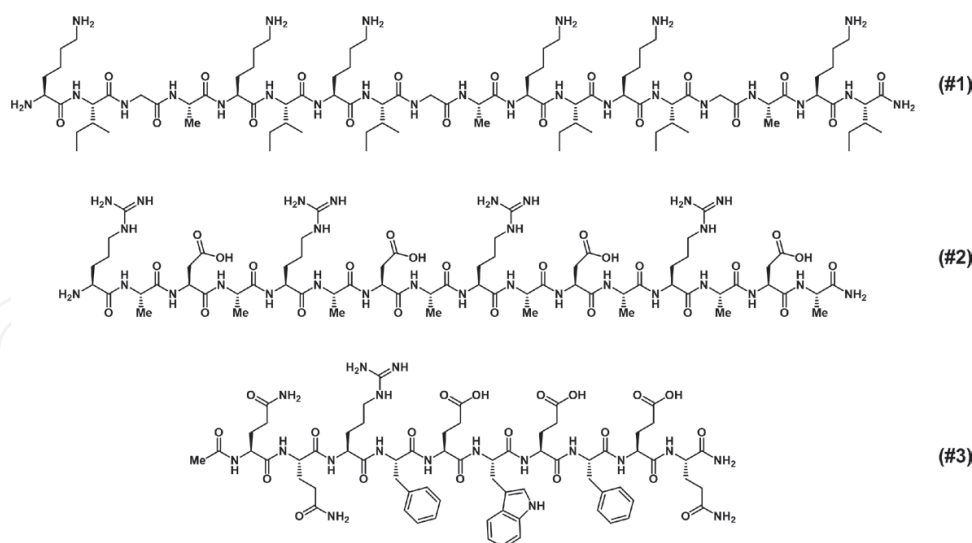
Figure 2. Chemical structures of peptides forming hydrogels.

Undoubtedly, peptide-based hydrogels are far from the laboratory curiosity, as evidenced by the new commercial market concerning these innovative materials. To the best of our knowledge, five products are commercially available:

- Hydromatrix™, developed by Sigma-Aldrich® (Saint Louis, USA) as medium for cell culture. The average price to prepare a 5 mL solution (0.1% w/v) is around 270 USD [61].

- PuraMatrix®, developed by 3-D Matrix Group (Tokyo, Japan) as medium for cell culture is a 16-mer (sequence **Ac-(Arg-Ala-Asp-Ala)$_4$-NH$_2$**, #2 **Figure 2**). The average price to prepare a 5 mL solution (0.1% w/v) is around 230 USD [62].

- Peptigel, developed by PeptiGel Design (Cheshire, UK) as medium for cell culture. The average price to prepare a 1 mL solution is around 130 USD [63].

- PGmatrix™, developed by PepGel LLC (Manhattan, USA) as medium for cell culture. The average price to prepare a 6 mL solution (0.1% w/v) is 375 USD [64].

- Curolox® technology, developed by Credentis (Windisch, Switzerland) as professional dental product for regeneration of enamel. It is not sold as it is, but as both toothpaste and a formulated product. The peptide used is an 11-mer termed P$_{11}$-4 (sequence **Ac-Gln-Gln-Arg-Phe-Glu-Trp-Glu-Phe-Glu-Gln-NH$_2$**, #3 **Figure 2**) [65].

It is a good bet that the number of commercially available peptide-based hydrogelator will increase in a near future.

As described hereinbefore, although the 20 natural amino acids offer a multitude of combinations, *i.e.*, a multitude of peptide-based hydrogel designs, the use of modified and non-canonical amino-acids drastically shoots up the possibilities and offers infinite opportunities both to improve the application window and to fine-tune properties of the resulting hydrogels. The next parts of this chapter are dedicated to the modifications developed to this end and illustrate the tremendous modularity of these materials.

2. Addition or insertion of organic moieties at the extremities or inside the amino acids sequences

2.1. Modifications at both N- and C-terminal ends

As discussed hereinbefore, gelation process is due to peptide self-assembly, driven by hydrogen bonds, electrostatic interactions, etc. In particular, π-π interactions and hydrophobic affinity are key parameters to design efficient hydrogelators, along with the subtle ability of the peptide to be partially soluble in water (mainly thanks to the presence of charged amino acids), and partially insoluble to form fibers. Thus, aromatic amino acids, mainly phenylalanine (**Phe**) and tyrosine (**Y**), are perfect candidates to balance these constraints. This is why a large majority of the peptide-based gelators are comprised of either these aromatic amino acids or other aromatic moieties.

Among them, it is not uncommon to observe the presence of a protecting group at the N-terminus. Indeed, protecting groups are widely used in both liquid and solid phase peptide synthesis (SPPS), and the easiest way to have them is simply by skipping the deprotection step at the end of the synthesis. Undoubtedly, Fmoc (fluorenylmethoxycarbonyl) is the more reported one, functionalizing peptide chains from one amino acid (*e.g.*, Fmoc-**Phe**, #4 **Figure 3**), to two (*e.g.*, **Fmoc-Gly-Ser**, #5 **Figure 3**), four (*e.g.*, **Fmoc-Phe-Arg-Gly-Asp**, #6 **Figure 3**), and more. Contrastingly, the other classic Cbz (carboxybenzyl) protecting group has not been well adopted, due to its smaller aromatic area leading to weaker π-π interactions compared to the Fmoc moiety [66, 67]. Another phenyl group was introduced via a cinnamoyl at the N-terminus of a phenylalanine amino acid, but it required higher concentration to form a gel in water, compared to the **Fmoc-Phe** analog (1.0% versus 0.3% w/v, respectively) [67]. Addition of naphthyl (Nap) derivatives (*e.g.*, 6-bromo-naphthyl (**6Br-Nap**) or 6-cyano-naphthyl (**6CN-Nap**)) has demonstrated high efficiency for several dipeptide gelators, like **Nap-Ala-Ala** (#7 **Figure 3**) or **Nap-Phe-Phe** (#8 **Figure 3**), **(6Br-Nap)-Phe-Phe** (#9 **Figure 3**), or **(6CN-Nap)-Ala-Val** (#10 **Figure 3**) [68]. Interestingly, **Nap-Gly-Ala** (#11 **Figure 3**) is able to form a stable hydrogel at acidic pH (pH = 2) at a concentration as low as 0.07% w/v [69]. Other moieties with larger aromatic areas are reported, even if they are much less common, like phenothiazine (e.g., #12 **Figure 3**) [66], pyrene (e. g., #13 **Figure 3**) [70, 71], spiropyran (e.g., #14 **Figure 3**) [72], or pyridine (#15 **Figure 3**) [73]. In addition, few exotic aromatic groups were used to add specific properties to the peptide, including a fluorescent stilbene chromophore (#16 **Figure 3**) [74] or a photosensitive azobenzene (#17 **Figure 3**) [75]. In this latter, an E conformation leads to hydrogel formation, while the photo-induced isomerization of the double-bond to a Z one triggers a phase change (*i.e.*, a liquid is thus obtained).

Another approach consists to graft a long alkyl chain at the N-terminus to form an amphiphilic hybrid molecule comprised of both a hydrophilic (peptide head) and a hydrophobic parts (alkyl tail). For instance, $CH_3(CH_2)_{14}$**-CO-Gly-Gly-Gly-Ser-Ser-Pro-His-Ser-Arg-Asn-(Ser-Gly)$_5$-Arg-Gly-Asp-Ser-Pro** forms a stable hydrogel from a minimum gelation concentration of ~1.4% w/v [76]. This latter contains a cell attachment site, the so-called **Arg-Gly-Asp** (or RGD) tripeptide, making the resulting hydrogel a good candidate for long-term human umbilical vein endo-
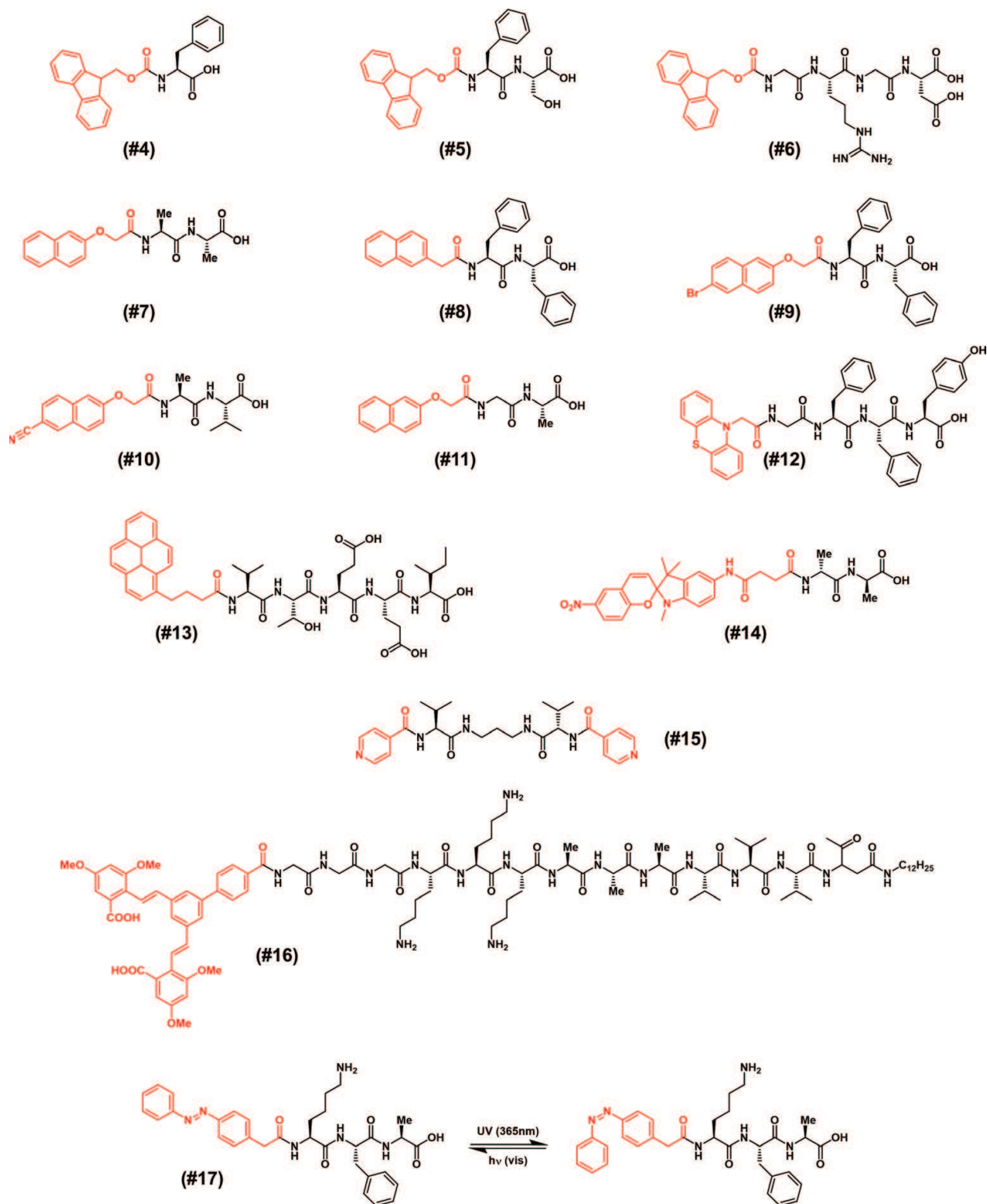
Figure 3. Chemical structures of hydrogel-forming peptides with N-terminal modifications.

thelial cell adhesion and proliferation. According to this model, other amphiphilic peptides containing alkyl chains were designed [77, 78], including **CH$_3$(CH$_2$)$_{14}$-CO-Gly-Thr-Ala-Gly-Leu-Ile-Gly-Gln-Glu-Arg-Gly-Asp-Ser** (#18 **Figure 4**) [79] and **CH$_3$(CH$_2$)$_{14}$-CO-Val-Val-Val-Ala-Ala-Ala-Glu-Glu-Glu** (#19 **Figure 4**) [80]. In parallel, innovative antibacterial hydrogels

were developed from peptides in which the nitrogen of the N-terminus was quaternalized, promoting the *in situ* synthesis of gold nanoparticules (#20, 21 **Figure 4**) [78, 81–83]. In order to favor self-assembly of peptides, addition of nucleobases was investigated and demonstrated promising results to develop biocompatible hydrogels (#22, 23 **Figure 4**) [84, 85]. Acetylation of the terminal primary amine is applied in some cases [86], such as for the design of the efficient KLD12 for cartilage tissue repair (#24 **Figure 4**) [87, 88]. Last of all, several hydrogelators are composed of a non-aromatic *tert*-butyloxycarbonyl (Boc) protecting group at their N-terminus, annihilating the charge of the amine group. In this case, the resulting peptides are weakly water soluble and often find applications as organogels instead of hydrogels [89–92]. However, Baral et al. show its interest in the formation of stable antibacterial hydrogels (#25 **Figure 4**) [93]. Functionalizations with tetraethylene glycol [94] or polyethylene glycol [95] are also reported and increase significantly the global water solubility of the peptide (#26 **Figure 4**).

Regarding the C-terminus, while neutralization of the carboxylic acid thanks to its substitution by an ester (mostly methyl and ethyl esters) [89–92] is widely used to favor organogels, only few modifications are reported for hydrogels. Indeed, the acidic group plays a pivotal role in the peptide self-assembly and solubilization in aqueous solvent. Conversion of the carboxylic acid to the corresponding amide (*i.e.*, amidation) is well documented and tends toward faster hydrogel formation [96–99], but with weaker rigidity [100]. Peptides P_{11}-I (#27 **Figure 5**) [101] and **Ac-Cys-(Phe-Lys-Phe-Glu)$_2$-Cys-Gly-NH$_2$** (#28 **Figure 5**) [102] can be cited as examples.
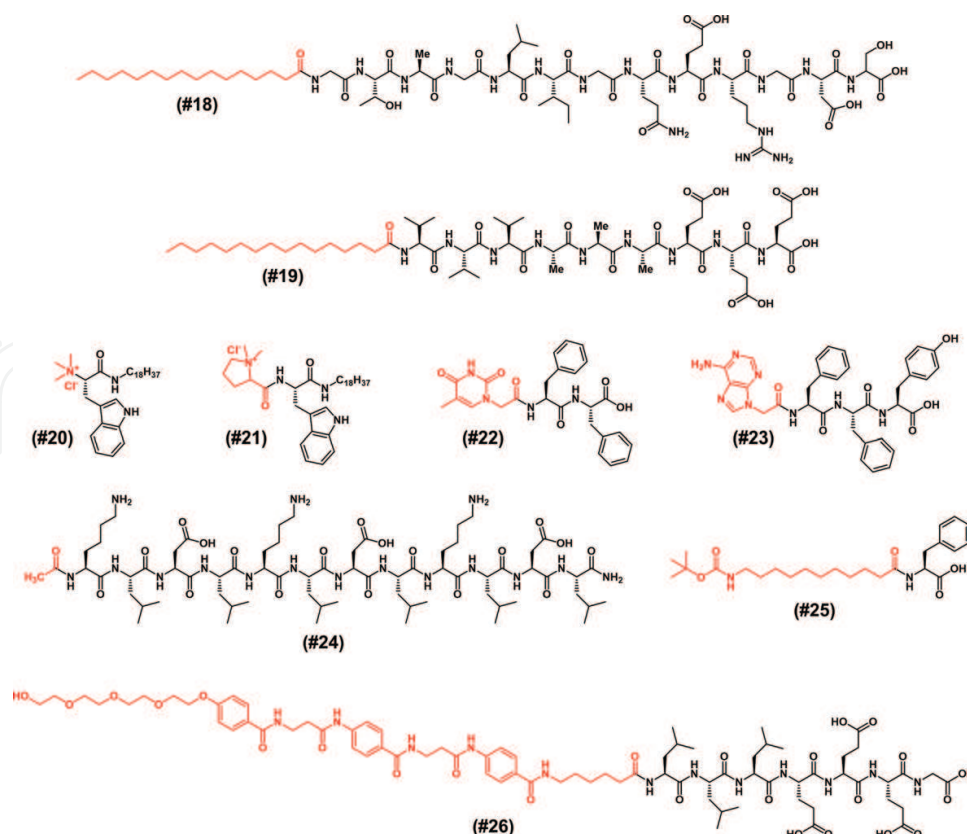

Figure 4. Chemical structures of hydrogel-forming peptides with N-terminal modifications (panel two).
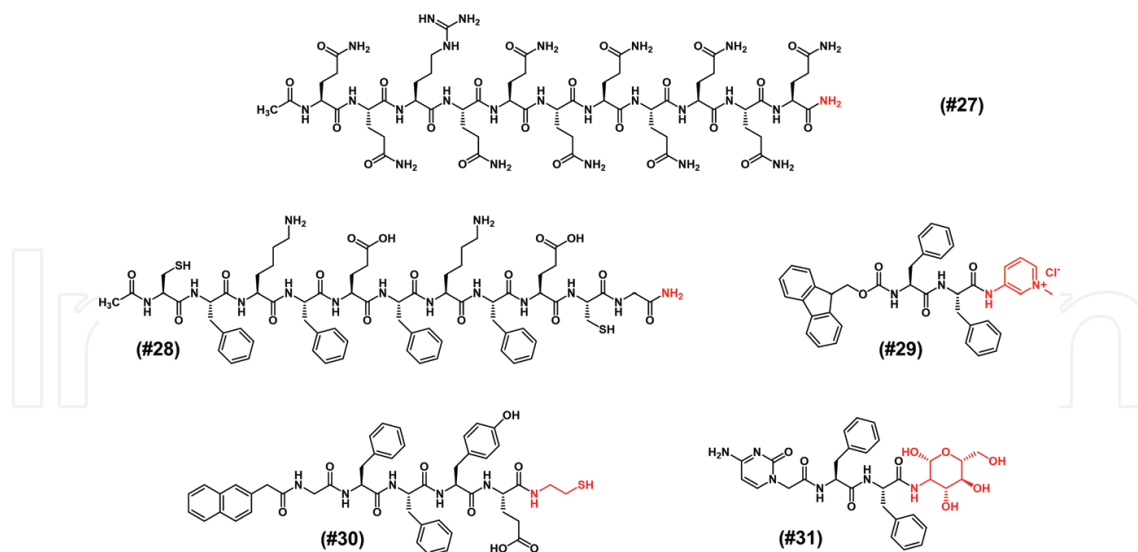
Figure 5. Chemical structures of hydrogel-forming peptides with C-terminal modifications.

Besides, more anecdotal C-terminus modifications were experimented, including pyridinium moieties (*e.g.*, #29 **Figure 5**) [103], thiol ethyl amides (#30 **Figure 5**) [104], tetraethylene glycol [94] or polyethylene glycol [95], kanamycin (an aminoglycoside antibiotic), or glycoside (#31 **Figure 5**) [85].

2.2. Insertion of organic moieties inside the amino acid sequences

Another way to improve hydrogelation and/or to add properties to the resulting gel consists to introduce an organic moiety inside the amino acid sequence. Thus, alkyl chains were inserted between two sequences of one or two amino acids to form a bolaamphiphilic molecule [73]. Indeed, these systems are comprised of a hydrophobic core (*i.e.*, the alkyl chain), twice functionalized at both extremities by hydrophilic amino acids (#32 **Figure 6**) [105]. While several kinds of aggregates are observed for short alkyl chains (*e.g.*, vesicles), longer ones favor hydrogel formation. For instance, with the presence of two histidines on each side (#33 **Figure 6**), optimal length of the alkyl spacer is of 20 methylene groups; in contrast, a length of 10 or 12 methylene leads to too soluble molecules unable to self-assemble to form a gel [106]. Similarly, unsaturated hydrocarbon chains were used, like diacetylene units functionalized by two tetrapeptides on each extremity. This strategy is ingenious because it offers the possibility to add covalent links between the peptide-forming hydrogels (#34, 35 **Figure 6**). Indeed, these materials are simultaneously physical (*i.e.*, by peptide self-assembly) and chemical (*i.e.*, chemical bonds obtained after polymerization) hydrogels, simply obtained by UV radiations (254 nm, 4 W, 30 min) [107].

As described hereinbefore, aromatic moieties play a pivotal role in the peptide self-assembly mechanism and were considered as efficient organic blocks to be inserted inside an amino acid chain. Among them, both naphthalene and perylene (#36 **Figure 6**) diimines demonstrated good results, even if their syntheses were limited by modest yields [108]. However, the same authors described efficient peptide-based hydrogelators comprised of oligophenylenes, oligophenylene vinylenes (#37 **Figure 6**) [109], or oligothiophenes (#38 **Figure 6**).
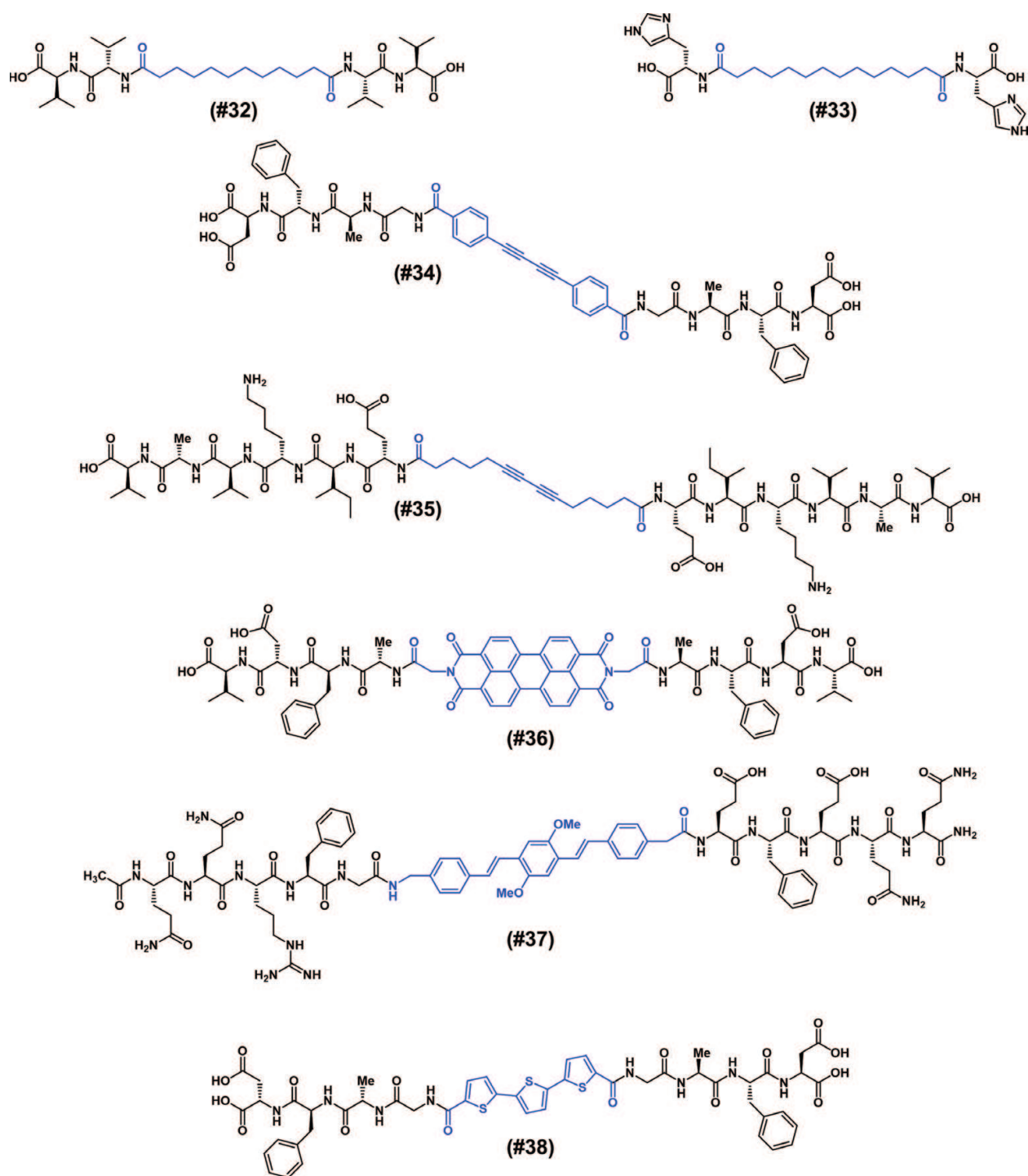
Figure 6. Chemical structures of hydrogel-forming peptides with organic moieties inserted into.

These systems are also very interesting specimens thanks to their photoluminescence properties due to their large π-conjugated surfaces [108, 110, 111]. Last of all, formation of a disulfide bond inside a sequence, mainly between two cysteines, is an easy way to functionalize hydrogelators. Besides, disulfite bond is often associated with protein and peptide self-assembly [112, 113], which plays a fundamental role in the peptide-based gelation process.

3. Using non-canonical and modified amino acids to tune peptide-based hydrogel properties

3.1. Impact of D-amino acids on the peptide-based hydrogel properties

In biological organism, the overwhelming majority of the natural proteins are exclusively composed of amino acids in their L-enantiomer forms. However, the chiral equivalents, *i.e.*, D-enantiomers with a reverse chemical configuration (**Figure 7A**), are present in several cases. For instance, the D-amino acids are found in bacteria in which D-alanine, D-aspartic, and D-glutamic acids are essential constituents for the synthesis of the peptidoglycan, forming the bacteria cell wall. Several antibiotics also contain a D-amino acid, like penicillin G (**δ-(L-α-aminoadipyl)-L-Cys-D-Val**), gramicidin, actinomycin, or polymyxins [114]. Not limited to prokaryotes, D-amino acids were also isolated from eukaryotic tissue, including dermophin from frogs, venom toxins from spiders or platypus, or neurohormones from crustaceans. More recently, these D-amino acids have been discovered in various human tissues, especially due to the presence of D-aspartic acid. It is the case for elastin, β-amyloid, α-synuclein, or AB-crystallin. Interestingly, these proteins are involved in several pathologies: arteriosclerosis, Alzheimer's and Parkinson's diseases, and cataract, respectively, demonstrating the undisputable importance of chirality in physiological process [115]. Research on amino acid role *in vivo* (as signaling molecules in the brain or endocrine glands [116], or in age-related diseases) [117] is a current fascinating hot topic, far from the scope of this chapter, and author incites curious readers to have a look to some reviews cited in this paragraph.

Inspired by the existence of D-amino acids, several groups used them to design efficient peptide-based hydrogels. The shorter one is undoubtedly **Fmoc-D-Glu**, which forms right-handed helical nanofibers in the presence of **D-Lys** (equimolar, #39 **Figure 7B**), while the same mixture with the L-enantiomer equivalents (*i.e.*, **Fmoc-L-Glu + L-Lys**) leads to left-handed helical nanofibers. Interestingly, the hydrogel containing D-enantiomers has slightly better viscoelastic properties than the levorotatory one [118]. This example clearly highlights that the organization at the molecular level (*i.e.*, the chirality) impacts the organization at the micro (*i.e.*, the fibers) and macroscopic scales (*i.e.*, the hydrogel). Series of dipeptides containing D-amino acids were also developed, one with Fmoc N-protecting group, and one with a naphtyl group (Nap). For the first instance, **Fmoc-D-Ala-D-Ala** (#40 **Figure 7B**) can be cited to be highly efficient to form a hydrogel (>0.13% w/v), slightly better than the corresponding **Fmoc-L-Ala-L-Ala** (>0.15% w/v), whereas **Fmoc-Gly-D-Ala** (#41 **Figure 7B**) required concentration >1.7% w/v [119]. Interestingly, **Nap-Gly-D-Ala** (#42 **Figure 7B**) displays exceptional properties with a minimum gelation concentration of only 0.07% w/v in water [69]. In this specific case, hydrogel characteristics are similar to the ones obtained with **Nap-Gly-Ala**, but the circular dichroism signature of each other is the perfect reverse, illustrating the opposite helical fibril structure. Tripeptides are also represented in this list with other Fmoc-derivatized structures containing three phenylalanine: **Fmoc-Phe-Phe-Phe** (#43 **Figure 7B**), **Fmoc-D-Phe-D-Phe-D-Phe** (#44 **Figure 7B**), **Fmoc-Phe-D-Phe-D-Phe** (#45 **Figure 7B**), and **Fmoc-D-Phe-Phe-Phe** (#46 **Figure 7B**) [120]. Interestingly, the fibers obtained in water
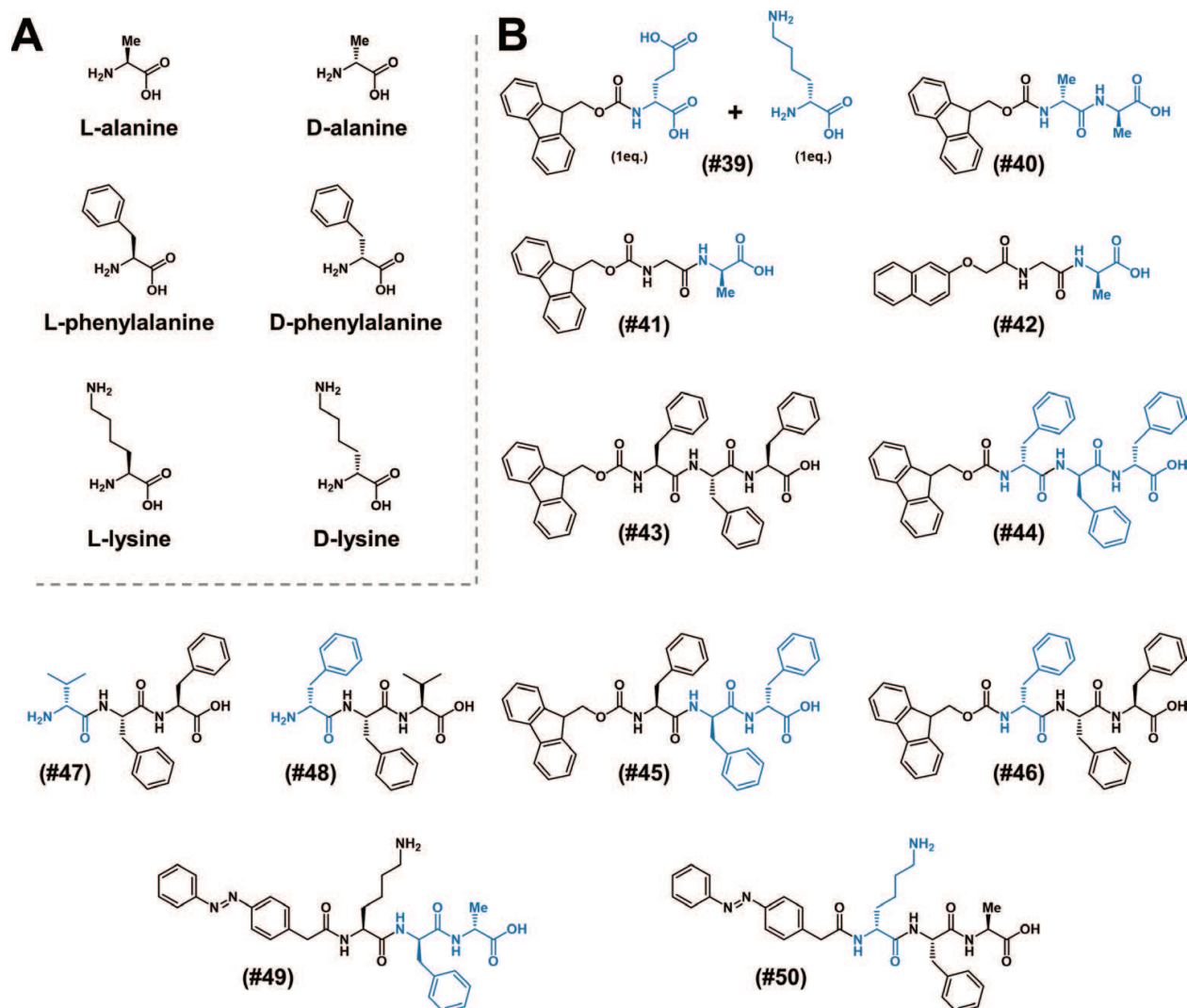
Figure 7. Chemical structures of L- and D-amino acids (A), and chemical structures of hydrogel-forming peptides incorporating D-amino acid(s) (B).

are right-handed for **Fmoc-Phe-Phe-Phe** and **Fmoc-Phe-_{D-}Phe-_{D-}Phe** and left-handed for the two others. Their viscoelastic properties are also improved by the addition of D-enantiomers, with **Fmoc-_{D-}Phe-_{D-}Phe-_{D-}Phe** about 23% higher than **Fmoc-Phe-Phe-Phe** in terms of storage and loss moduli. Without protecting group at the N-terminus, **Val-Phe-Phe** and **Phe-Phe-Val** peptides were unable to from hydrogels at neutral pH, while the _{D-}**Val-Phe-Phe** (#47 **Figure 7B**) and _{D-}**Phe-Phe-Val** (*i.e.*, both with the D-amino acid at the N extremity, #48 **Figure 7B**) equivalents did [121]. Another tripeptide, protected with an azobenzene moiety at the N-terminus, was developed from the sequence **Azo-Lys-Phe-Ala**, with D-enantiomers in different positions. Contrary to **Azo-Lys-Phe-Ala** which forms a hydrogel from 3.1% w/v, **Azo-Lys-_{D-}Phe-_{D-}Ala** (#49 **Figure 7B**) and **Azo-_{D-}Lys-Phe-Ala** (#50 **Figure 7B**) require 6.8% w/v, more than twice. Interestingly, the all D-amino acid-containing peptide gel is a little bit more efficient, with a minimum concentration of 3.0% w/v [75].

The last, but clearly not the least, example of the use of D-amino acids to improve hydrogelation is definitively the introduction of the sequence $_D$**Pro-Pro**. Indeed, this latter confers a type II' turn (a β-hairpin), favoring the contact between the two peptide strands on both sides. This decrease of degrees of freedom drastically favors the hydrogel formation efficiency. Thus, plenty of sequences were developed [122, 123], including the 20-mers MAX1 (sequence **(Val-Lys)₄-Val-$_D$Pro-Pro-Thr-(Lys-Val)₄-NH₂**, #51 **Figure 8**) [124–129] and MAX8 (**(Val-Lys)₄-Val-$_D$Pro-Pro-Thr-Lys-Val-Glu-Val-(Lys-Val)₂-NH₂**) [128, 130], in which the $_D$**Pro-Pro** sequence is just in the middle, contrary to SSP1 (**(Val-Lys)₂-Val-$_D$Pro-Pro-Thr-(Lys-Val)₆-NH₂**, #52 **Figure 8**) or SSP2 (**(Val-Lys)₃-Val-$_D$Pro-Pro-Thr-(Lys-Val)₅-NH₂**) [131, 132]. More complex, a series of three-stranded peptides was developed, including TSS1 (sequence **(Val-Lys)₄-Val-$_D$Pro-Pro-Thr-(Lys-Val)₃-Lys-$_D$Pro-Pro-(Lys-Val)₄-NH₂**) [133].

Finally, derivatives from EAK-16 (sequence **Ac-(Ala-Glu-Ala-Glu-Ala-Lys-Ala-Lys)₂-NH₂**) incorporating D-amino acids were designed. Interestingly, the enantiomers EAK-16 and $_D$-EAK-16 (sequence **Ac-($_D$Ala-$_D$Glu-$_D$Ala-$_D$Glu-$_D$Ala-$_D$Lys-$_D$Ala-$_D$Lys)₂-NH₂**, #53 **Figure 8**) have shown similar hydrogel thermodynamic properties (*e.g.*, storage moduli ≈1 kPa at 1% w/v) [134–136]. In contrast, the corresponding diastereoisomers E$_D$AK-16 (sequence **Ac-($_D$Ala-Glu-$_D$Ala-Glu-$_D$Ala-Lys-$_D$Ala-Lys)₂-NH₂**, #54 **Figure 8**) and $_D$EA$_D$K (sequence **Ac-(Ala-$_D$Glu-Ala-$_D$Glu-Ala-$_D$Lys-Ala-$_D$Lys)₂-NH₂**) appear to have extremely modest capability to form stable hydrogels [137].
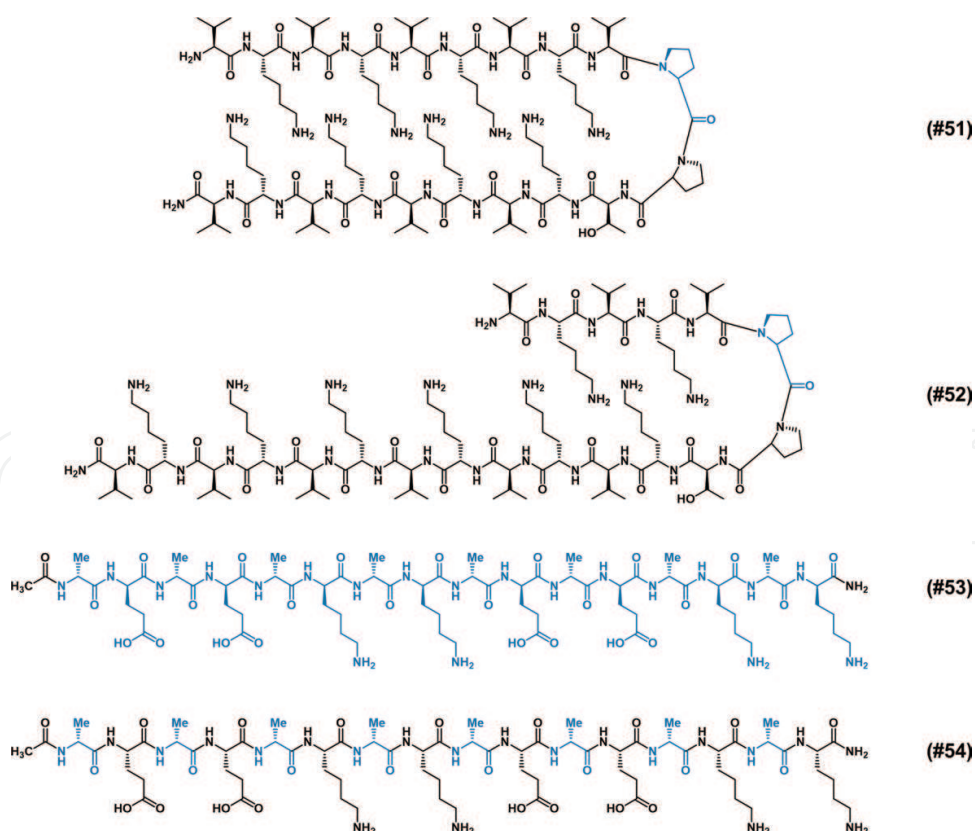

Figure 8. Chemical structures of hydrogel-forming peptides incorporating D-amino acid(s).

3.2. Using non-canonical amino acids to design peptide-based hydrogels

As described before, modifications of the peptide may be induced by functionalization of the N- and C-termini, along with the insertion of an organic moiety inside the sequence, or by inversion of the amino acids chirality, using D-amino acids. Furthermore, introduction of non-canonical amino acids (*i.e.*, not from the 20 encoded proteinogenic ones) offers broad new possibilities and has been exploited by researchers to improve and fine-tune hydrogel formation.

Among them, the cyclohexylalanine (**Cha**), a hydrogenated phenylalanine, prevents the formation of π-π interactions and significantly increases the global hydrophobicity of the peptide in which it is inserted. For instance, using the octapeptide **Ac-(Phe-Lys-Phe-Glu)$_2$-NH$_2$**, the substitution of both phenylalanine by two cyclohexylalanine (*i.e.*, **Ac-(Cha-Lys-Cha-Glu)$_2$-NH$_2$**, #55 **Figure 9**) leads to a less soluble peptide requiring a few percentage of HFIP (for hexafluoroisopropanol) to ensure a gelation. However, while a self-supporting hydrogel was obtained at 0.23% w/v for this latter, the Phe-containing peptide necessitates 0.46% w/v [138]. In parallel, experiments on **Ac-(Cha-Lys-Cha-Lys)$_2$-NH$_2$** demonstrate that at the same concentration, **Ac-(Phe-Lys-Cha-Phe)$_2$-NH$_2$** (#56 **Figure 9**) forms a more rigid hydrogel (G′ ≈ 1800 kPa versus 76 Pa) [139]. These experiments have illustrated the pivotal role of hydrophobicity in peptide self-assembly and consequently in the gelation process.

Another non-usual amino acid used is the ornithine (**Orn**), comprised of an aminopropyl lateral chain. It can be considered as a lysine but with only three methylenes in the side chain instead of four. Derived from P$_{11}$ family [101, 140], an 11-mer containing three ornithine, positively charged, was synthesized (sequence **Ac-Gln-Gln-Orn-Phe-Orn-Trp-Orn-Phe-Gln-Gln-Gln-NH$_2$**, #57 **Figure 9**) and mixed with a close sequence, negatively charged, in which Orn were substituted by glutamic acids (sequence **Ac-Gln-Gln-Glu-Phe-Glu-Trp-Glu-Phe-Gln-Gln-Gln-NH$_2$**, #58 **Figure 9**). The equimolar mixture revealed both nematic gels and solutions properties. The assembly is favored by electrostatic interactions between charges carried by the primary amines (**Orn**) and the carboxylic acids (**Glu**) [96]. Other Orn-containing hydrogelators were developed from a decapeptide. More specifically, an oligo(p-phenylvinylene) (termed *OPV*) was functionalized by two pentapeptides on both sides: **Ac-Gln-Gln-Orn-Phe-Orn-*OPV*-Orn-Phe-Gln-Gln-Gln-NH$_2$** and **Ac-Gln-Gln-Arg-Phe-Glu-*OPV*-Glu-Phe-Gln-Gln-Gln-NH$_2$**. They both form a stable hydrogel, the first been more robust than the second one [109]. Working with short sequences of two amino acids without protection either at the N- or at the C-termini, the use of α,β-dehydrophenylalanine (**ΔPhe**) provides distinguished results [141, 142]. Compared to canonical **Phe, ΔPhe** has no chirality on its C$^\alpha$ and favors π-π stacking due to its extended electron delocalization. Indeed, while **Phe-Phe** lacks to form a hydrogel, **Phe-ΔPhe** is drastically more efficient forming a stiff one with G′ ≈ 210,000 Pa for only 1% w/v. However, after a full study on **Xxx-ΔPhe** (in which **Xxx** = 1 of the 20 canonical amino acids), only 2 dipeptides were reported as able to gelify: **Leu-ΔPhe** (#59 **Figure 9**) and **Phe-ΔPhe** (#60 **Figure 9**). Recently, the first one was applied *in vivo* in a mouse model as a drug delivery platform for mitoxantrone, an anticancer drug, and seems to be very promising [141].
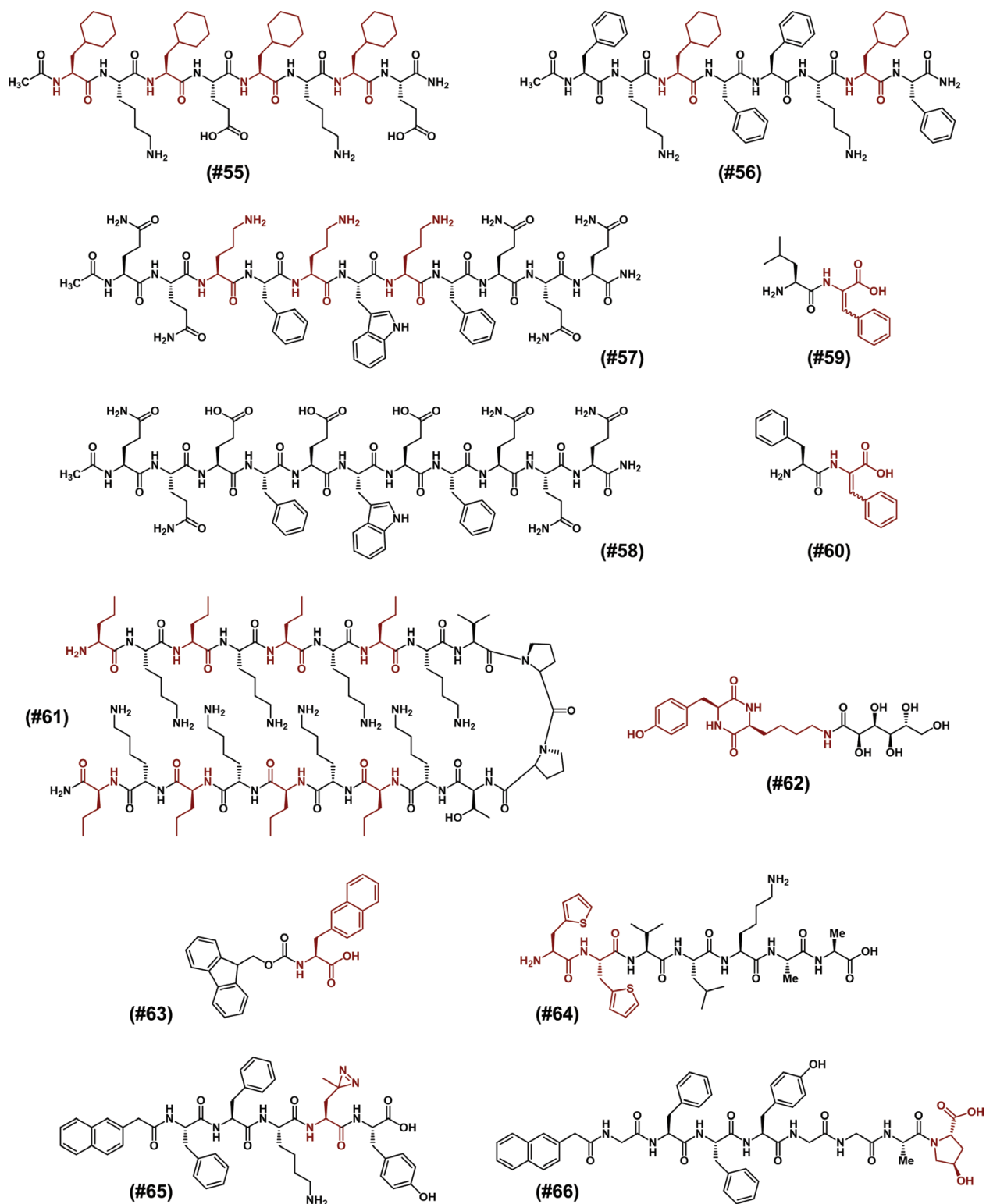
Figure 9. Chemical structures of hydrogel-forming peptides incorporating non-canonical amino acid(s).

Recently, based on the 20-mers MAX1 (sequence **(Val-Lys)$_4$-Val-$_D$Pro-Pro-Thr-(Lys-Val)$_4$-NH$_2$**, see hereinbefore) [124–129], other derivatives were synthesized in which eight valines (excluding the **Val** adjacent to the $_D$**Pro**) were substituted by non-canonical aminobutyric acid (**Abu**), norvaline (**Nva**, #61 **Figure 9**), or norleucine (**Nle**). Results have highlighted

that, at 1% w/v, only the peptide-containing norvaline forms a stiffer material than the original MAX1, with G′ ≈ 3300 Pa versus 1800 Pa, respectively [143]. The use of cyclodipeptide was also reported as an efficient method. Indeed, **cyclo(L-Tyr-L-Lys)** (#62 **Figure 9**) and **cyclo(L-Phe-L-Lys)** N^ε-acetylated by gluconic acid lead to thixotropic hydrogels, which can be stored for a long period of time as a solution. The gelation is simply triggered by a short and vigorous stirring [144]. In order to increase the aromatic surface available from an ultra-short peptide, Fmoc-β-(2-naphthyl)-L-alanine (#63 **Figure 9**) was evaluated and the resulting hydrogel has exhibited good stability in a large range of pH, from 3 to 12 [145]. Inspired by the pentapeptide fragment **Lys-Leu-Val-Phe-Phe** from the 16 to 20 region of the Aβ protein (involves in Alzheimer's disease) and well-known for its ability to form amyloid fibers, effects of β-2-thienyalanine (**2-Thi**) were evaluated. The obtained **(2-Thi)-(2-Thi)-Val-Leu-Lys-Ala-Ala** (#64 **Figure 9**) has displayed high efficiency in hydrogel formation and liquid crystal properties [146].

Ingeniously, photoleucine, a diazirine-based photo-reactive analog of leucine, was introduced inside a pentapeptide protected with a naphthalene moiety at its N-terminus (#65 **Figure 9**). Thus, the system is applied for protein complex immunoprecipitation (also termed "pull-down" method) and interacts with proteins from 42 to 55 kDa [147].

Derived from the L-proline, the L-4-hydroxyproline (**Hyp**) is one of the amino acids constituting the tropocollagen and, *in fine*, the collagen. Indeed, collagen fibers are composed of the repeating sequence **Gly-Xxx-Hyp** in which **Xxx = Lys, Glu, Ser, Ala**, and **Pro** [148]. Based on that, **Nap-Gly-Phe-Phe-Tyr-Gly-Gly-Xxx-Hyp** peptides were studied (#66 **Figure 9**). Depending on the amino acid at the seventh position (*i.e.*, **Xxx**), the minimum gelation concentrations are between 0.04% and 0.10% w/v, demonstrating the assets of this bio-mimicking approach [149].

One of the last categories of modification this part would like to highlight is the functionalization of phenylalanine. Indeed, a convincing body of work has been focused on this pivotal amino acid playing a central role in peptide self-assembly and *in fine*, in hydrogel formation. Thus, working on the short **Fmoc-Phe**, the group of Bradley L. Nilsson studied the impact of the substitution of the hydrogen in the para position by a nitro (-NO_2, #67 **Figure 10**), a cyano (-CN, #68 **Figure 10**), an amino (-NH_2), a hydroxyl (-OH, in this case the amino acid corresponds to a tyrosine), a methoxy (-OMe, #69 **Figure 10**), a trifluoromethyl (-CF_3, #70 **Figure 10**), or a methyl group [100, 150–152]. This modification leads to a redistribution of the electron density of the aromatic ring, influencing the π-π and dipolar interactions between benzyl groups. While **Fmoc-Phe** forms a weak hydrogel at 0.6% w/v (G′ ≈ 40Pa), all these *para* substitutions improve the mechanical behavior of the resulting gels, especially for **Fmoc-(pNO2-Phe), Fmoc-Tyr**, and **Fmoc-(pNH2-Phe)**, with storage moduli of ≈410 Pa, 506 Pa, and 527 Pa, respectively. However, the gelation time is not directly linked to the mechanical properties, with t_{gel} ≈ 0.5 min, 5 min, and 10 min for **Fmoc-(pNO2-Phe), Fmoc-(pCN-Phe)**, and **Fmoc-(pCH3-Phe)**, respectively.

The effect of halogenation was also investigated on **Fmoc-Phe**, with substitutions on the *ortho*, *meta*, and *para* positions, by fluorine, chlorine, or bromine [153]. In this work, in terms of gelation time, halogenation on the *para* position is drastically shorter (t_{gel} ≈ 0.5 min) compared to both *meta* (t_{gel} ≈ 3–15 min) and *ortho* (t_{gel} ≈ 30–50 min) positions. However, regarding the
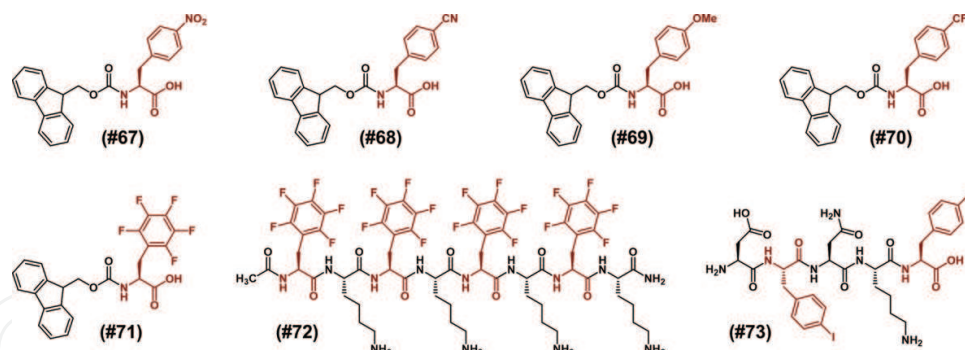
Figure 10. Chemical structures of hydrogel-forming peptides incorporating non-canonical amino acid(s) (panel two).

mechanical properties, the presence of a halogen in the *meta* position is the more efficient, followed by the *ortho* and finally the *para* positions. In parallel, the impact of the atom seems to be determined by its polarizability, with the formation of more rigid hydrogels with fluorine, better than chlorine and then bromine. In this way, the use of a pentafluorinated phenylalanine **Fmoc-(F$_5$-Phe)** (#71 **Figure 10**) was considered [100, 151]. This perfluorination drastically increases the hydrophobicity of the molecule and drops down the minimum gelation concentration to 0.1% w/v. At 0.2% w/v, the gel has good rheological results, with G′ ≈ 3100 kPa and G″ ≈ 320 Pa, confirming its efficiency compared to the classic **Fmoc-Phe**. Incorporation of (F$_5$-Phe) in a longer peptide chain was a success, as attested by the studies involving **Ac-[(F$_5$-Phe)-Lys-(F$_5$-Phe)-Lys]$_2$-NH$_2$** (#72 **Figure 10**) [139].

In the same way was reported the impact of a single-atom replacement of hydrogen with halogen in the human calcitonin-derived amyloidogenic fragment **Asp-Phe-Asn-Lys-Phe**. Mainly, the substitution of phenylalanine(s) by para-X-Phe (X = Cl, Br, I) led to a drastic improvement of the thermodynamic and kinetic properties. Amyloid structures were confirmed by Atomic Force Microscopy (AFM) and cryo-Transmission Electron Microscopy (cryo-TEM) measurement, and by their green birefringence upon staining with Congo Red, highlighting the **Asp-(pI-Phe)-Asn-Lys-(pI-Phe)** derivative (#73 **Figure 10**) as the most fibrilogenic peptide monomer. As reported in the literature, it was attested that these amyloid fibrils had the ability to form hydrogels with more efficiency compared to the wild-type **Asp-Phe-Asn-Lys-Phe**, illustrated by the 30-fold lower concentration required for the gelification of **Asp-(pI-Phe)-Asn-Lys-Phe**. However, best thermal stability (*T* = 116°C), lowest gelification time (<10 min), and highest stiffness (storage modulus G′ > 10^4 Pa) were observed for the same bis-iodinated sample (at 15 mM), far better than the bis-bromo and bis-chloro derivatives, respectively. All these results emphasize the positive role of halogenation of peptides, especially iodination, for supramolecular amplification of amyloid self-assembly [154].

3.3. Functionalization of amino acids on their side chain

Among the 20 canonical amino acids, a mere fraction contains a reactive organic group on its lateral chain. These amino acids are mainly the ones with a carboxylic acid: **Asp** and **Glu**, an amine (**Lys**), a guanidine (**Arg**), or a thiol group (**Cys**). Thus, modifications and

post-modifications (*i.e.*, after the peptide synthesis) of the hydrogel-forming peptides can be carried out by chemical reactions between the amino acid cited above and an organic compound.

Following this rule, several structures have been developed, offering a new myriad of possibilities to enhance the versatility of the peptide-based hydrogels. Functionalization of lysine is clearly the more often used method. This amino acid has been grafted to a naphthalene diimine (NDI) moiety to increase the aromatic surface available on the peptide in order to favor π-π interactions and subsequently, hydrogelation. The resulting **Fmoc-Lys-Lys(NDI)** (#74 **Figure 11**) self-assembles at low concentration (<1.5% w/v) and can act as a semiconductor [155]. Similarly, lysines were modified by addition of an azobenzene moiety, leading to photoswitchable hydrogels (#75 **Figure 11**) [156, 157]. Presence of a sorbamide group on the Lys side chain offers the possibility to photopolymerize the physical hydrogel obtained by non-covalent interactions in order to create chemical bonds rigidifying the network. This second step improves the mechanical rigidity by 2.5 [158]. Using the same approach, an amphiphilic peptide was developed, composed of a lysine functionalized with an alkyl chain containing a diacetylene segment (#76 **Figure 11**). The subsequent polymerization leads to polyacetylene-containing hydrogel applied for cell culture [159]. Furthermore, substituting the primary amine by an acrylamide group to secondly form polyacrylamide is also an adopted approach (#77 **Figure 11**) [160].

Addition of a hydrazine-containing arm to an amphiphilic peptide was proposed to control the release of ketones. Indeed, ketones can react with hydrazine to form a hydrazone. The high hydrolytic stability of this chemical function leads to a slow release of the ketone-containing compound from the hydrogel (#78 **Figure 11**) [161]. The presence of Boc protecting groups at the N^ε of **Lys**, originating from the peptide synthesis, definitely improves the hydrogel properties, as described for **Fmoc-Val-Leu-Lys(Boc) and Fmoc-Lys(Boc)-Leu-Val** (#79 **Figure 11**). The first one is the weakest with G′ ≈ 4000 Pa (at 2% w/v), while the latter is the stiffest with G′ > 100,000 Pa [162]. The same approach was reported with Fmoc protecting-group simply using **Lys(N^ε-Fmoc)**. However, the hydrogelation was triggered by addition of one equivalent of either **Fmoc-Phe** or **Fmoc-Leu** and both with two equivalents of Na_2CO_3. Comparing the two mixtures, the hydrogel formulated from **Lys(N^ε-Fmoc) + Fmoc-Phe** (#80 **Figure 11**) is drastically more rigid than the one with **Fmoc-Leu**, with storage moduli of 25,000 Pa and 3000 Pa, respectively [163, 164]. Lastly, a lysine-functionalized peptide reported concerns a linear amphiphilic nonapeptide N^ε-functionalized in second and last position by a histine and a palmitoyl (including a C_{15} alkyl chain). Gelation properties are interesting, with a minimum concentration required of 0.1% w/v and pH > 6.5 [165].

Working on a 20-mer derived from MAX1, an ingenious zinc-triggered hydrogelation was designed using a 3-amidoethoxyaminodiacetoxy-2-aminopropionic acid instead of a valine at the last position of the peptide sequence. Thus, the two incorporated acid groups perfectly fit to bind metals, in particular Zn^{2+}. While no gelation occurs for peptide alone in solution, addition of $ZnCl_2$ triggers the formation of the hydrogel (#81 **Figure 11**) [166]. In order to produce composite materials comprised of peptide fibers mineralized by calcium, an amphiphilic
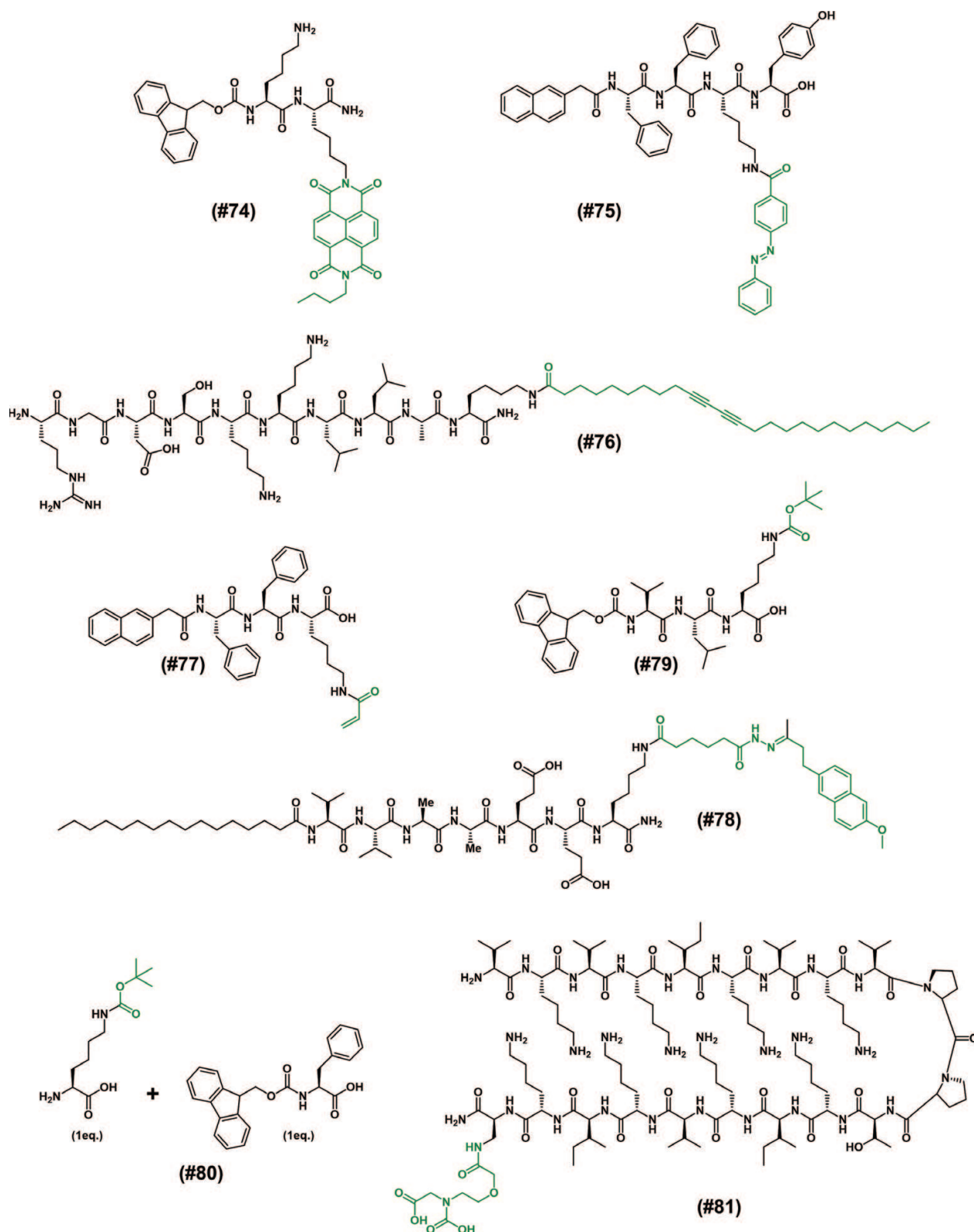
Figure 11. Chemical structures of hydrogel-forming peptides incorporating functionalized side chains.

molecule of 11 amino acids and a long alkyl chain of 15 methylene groups were designed. The key amino acid is a phosphorylated serine, playing a pivotal role in the formation of calcium phosphate minerals. After the self-assembly of the fibers, cysteine thiol groups are

oxidized to disulfides before being treated by $CaCl_2$. After 20 min, the fibers start to be coated by crystalline minerals. These composite materials mimic the collagen fibrils and hydroxy-apatite crystals in bone [167]. Concerning the phosphorylated serine, another peptide with the same global structure (alkyl chain and 11-mer) but with a different peptide sequence is able to form hydrogels for which the mechanical properties can be modulated by the cation added (#82 **Figure 12**). Indeed, while a viscous liquid is obtained with Na^+ or K^+, Mg^{2+} and Ca^{2+} lead to hydrogels with moderate storage moduli (around 500 Pa), while with Zn^{2+} or Cu^{2+}, the gels are drastically stiffer (G′ ≈ 10,000 Pa) [168].

Working on **Fmoc-Phe-Phe-Gly-Gly-Gly-Tyr**, an innovative approach was experimented, based on $Ru(bpy)_3^{2+}$-catalyzed photo-crosslinking of two tyrosine residues to give dityrosine adduct. The obtained dimer acts as an efficient hydrogelator, while the monomer does not, with an increase of the mechanical stability up to 10,000 times (#83 **Figure 12**) [169]. Interestingly, formation of dityrosine is a strategy used by Nature to improve elastic properties of biomaterials, including the well-known resilin, first identified in *Drosophilia melanogaster* [170].

Last of all, some peptide drugs are able of hydrogelating, offering undoubted perspectives for biomedical applications. Among them, analogs of gonadotropin-releasing hormone (or GnRH) were developed. GnRH is a peptide hormone composed of 10 amino acids (sequence **pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH$_2$**) and discovered by Guillemin [171] and Schally [172] who received the Nobel Prize in Physiology and Medicine in 1977 with Yalow [173]. Analogs have been continuously and slowly releasing during a long period of time, up to 35 days. In particular, both ganirelix and degarelix show efficient gelation properties, and are composed of non-canonical amino acids (#82 **Figure 12**), including a **pCl-Phe**, a **NaI**, a $N^G,N^{G'}$-diethyl arginine, a (3-pyridyl)-alanine, an N^ε-isopropyl lysine, a para-urea phenylalanine, and a para-6-amido dihydroxyuracil [174]. Finally, the example of vancomycin,
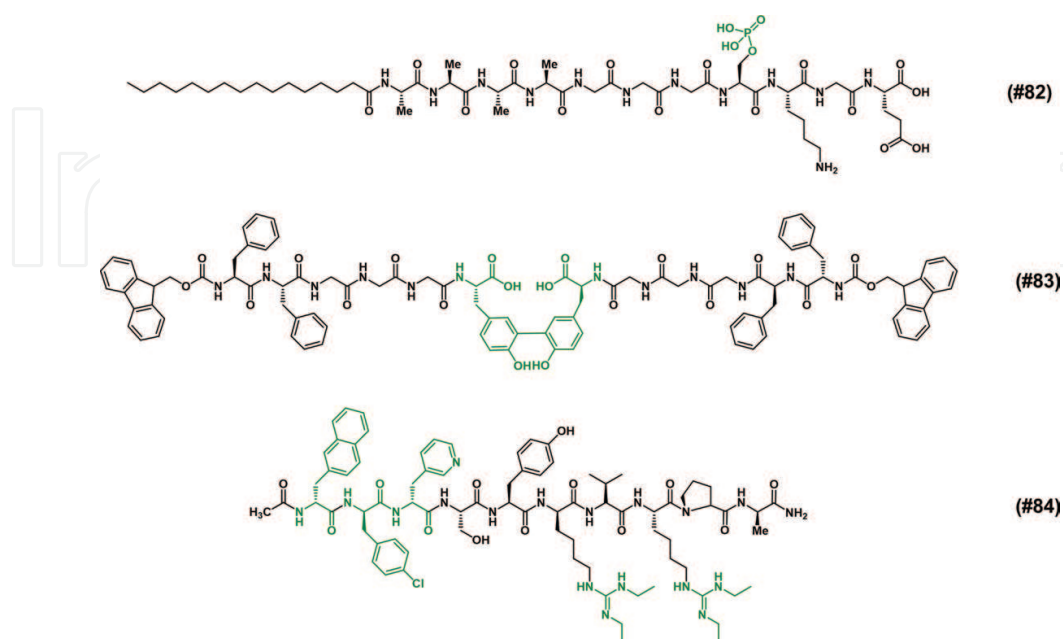

Figure 12. Chemical structures of hydrogel-forming peptides incorporating functionalized side chains (panel two).

a glycopeptide with antibiotic properties, demonstrates the degree of complexity which can be reached. The minimum concentration of this perplexing molecule is around 0.36% w/v and offers new perspective in term of materials for biomedical applications [175]. However, due to the complexity of the system, it has to be considered as a special case, far from the initial idea to develop short peptide-based hydrogels synthesized in a straightforward and fast way.

4. Development of pseudo-peptides and peptidomimetics

4.1. A brief description of peptide analogs

Research on peptide analogs mainly refers to the development of metabolically stable peptide-like structures for biomedical and therapeutic applications. Indeed, the rapid proteolysis of native peptides and their inability to cross cellular membranes have required modifications of their intrinsic structure. Thus, changes of the peptide bond structure have been deeply studied and have led to efficient drugs commercialized by pharmaceutical company. For instance, Ziconotide (brand name Prialt®, sold by Elan Pharms) is a 25-mer indicated for severe chronic pains, Icatibant acetate (brand name Firazyr®, sold by Jerini AG) is a decapeptide indicated for hereditary angioedema, and Afamelanotide (brand name Scenesse®, sold by Clinuvel Pharmaceuticals) is a 13-mer indicated for erythropoietic prophyries [176].

Thus, two terminologies were introduced. The term "pseudopeptide" proposed by Spatola in 1981 strictly refers to peptide analogs in which the peptide backbone has been modified [177, 178]. Briefly, their nomenclature is quite simple, with the use of the Greek letter psi "ψ[…]" in which the term under bracket refers to the "new" peptide link introduced. For example, the dipeptide #85 (**Figure 13A**) is represented as **Phe-Leu** (#85 **Figure 13A**), while **Phe-ψ[CH$_2$O] Leu** represents the pseudopeptide #86 (**Figure 13A**). In parallel, the term "peptidomimetic" refers to any compound able to mimic the specific action of a peptide (*i.e.*, inhibition, activation, etc.) [179]. Thus a "peptidomimetic" can be an organic molecule without any similarities to a peptide. It is the case of morphine, a "non-peptide" molecule mimicking the opioid peptides [177]. However, the word "pseudopeptide" has become obsolete years after years, and the generic term "peptidomimetic" is used to speak about both [180].

4.2. Peptidomimetics as efficient hydrogelators

First and foremost, the most represented peptidomimetics able to form hydrogels are undoubtedly the ones comprised of one or several β-amino acids. These latter differ from the native α-amino acids due to the presence of an additional carbon atom in the amino acid backbone. Besides, two regioisomers exist, depending on the position of the additional methylene group, termed β^2 or β^3-amino acids (**Figure 13A**, right panel) [181]. With this in mind, a series of β^3-dipeptides was synthesized, protected at the N-terminus by a naphthalene (**Nap**) derivative. Peptidomimetics #87 (**Nap-OCH$_2$CO-αGly-β^{3}HAla**, **Figure 13B**) and #88 (**Nap-CH$_2$CO-β^{3}Phg-β^{3}Phg**, with **Phg** = phenylglycine, **Figure 13B**) have reasonable mechanical properties,
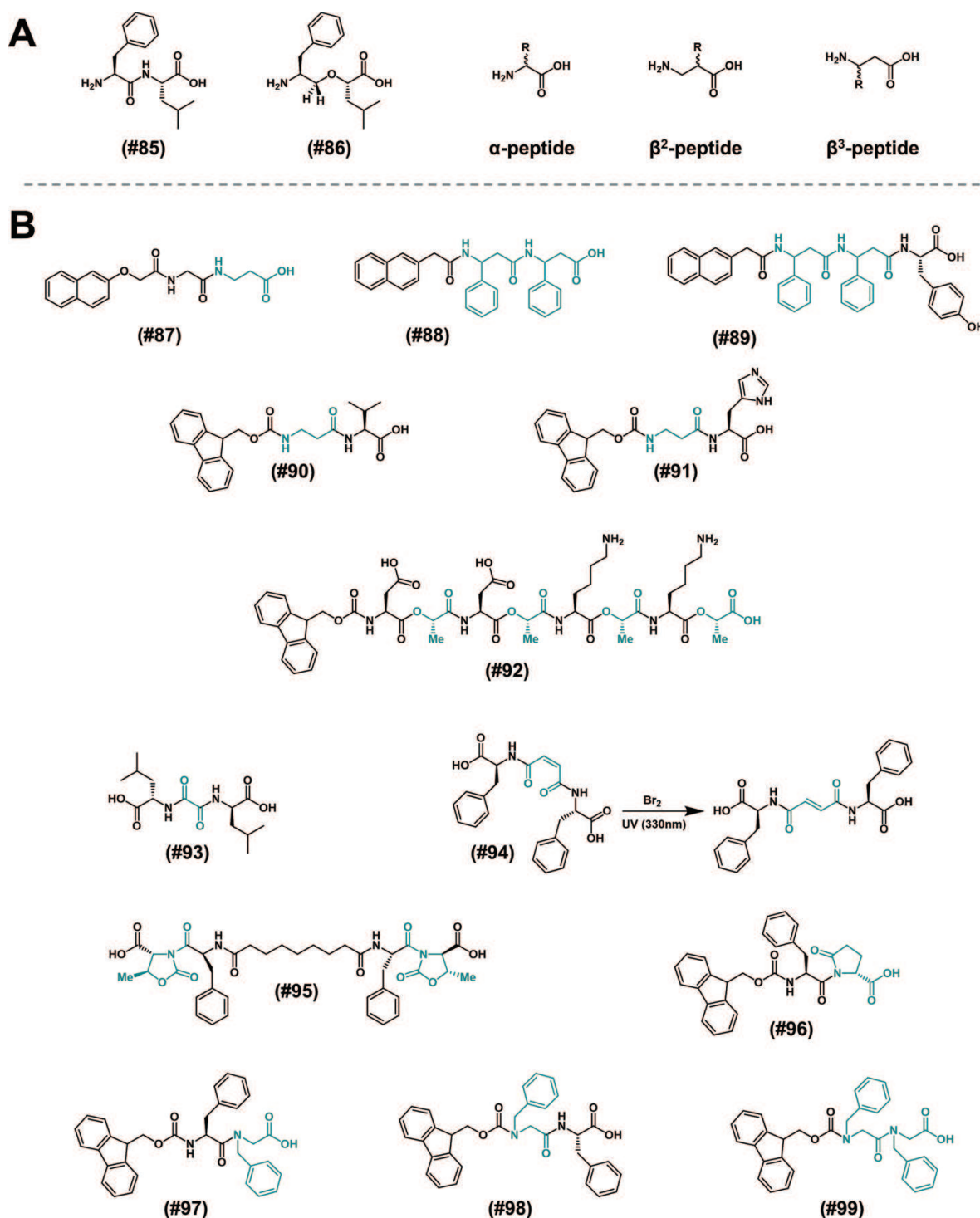
Figure 13. Chemical structures of peptidomimetics (A), and chemical structures of hydrogel-forming peptides incorporating peptidomimetics (B).

the first one being stiffer than the second one [182]. With the same **β³Phg** and naphthalene extremity, a tripeptide (**Nap-CH₂CO-β³Phg-β³Phg-αTyr**, #89 **Figure 13B**) was studied as injectable hydrogel *in vitro* and *in vivo*, and offers longer biostability than the corresponding all α-containing-amino acids peptide **Nap-CH₂CO-αPhe-αPhe-αTyr** [183]. Other compounds with a Fmoc N-protected group were developed and demonstrated ability to encapsulate and

release both vitamins B$_2$ and B$_{12}$ over a period of more than 48 hours, at physiological pH and temperature. Their structures are **Fmoc-βAla-αVal** (#90 **Figure 13B**) and **Fmoc-βAla-αPhe** and have comparable mechanical properties and release profiles [184]. In parallel, hydrogelation of **Fmoc-βAla-αHis** (#91 **Figure 13B**) is triggered by addition of Zn^{2+} cations [185].

In a peptide, substitution of the native amide function by an ester leads to structures called depsipeptides. The octapeptide Fmoc-DAKA-8 (sequence **Fmoc-Asp-Ala-Asp-Ala-Lys-Ala-Lys-Ala**) was modified, *inter alia*, by the introduction between the first and the second amino acids of an ester bond. Thus, **Fmoc-Asp-ψ[CO-O]Ala-Asp-ψ[CO-O]Ala-Lys-ψ[CO-O]Ala-Lys-Ala]** (#92 **Figure 13B**) self-assembles and forms a hydrogel, with hydrolytic susceptibility (hydrolysis at the ester bond sites), which offer opportunities for applications such as tissue scaffold or drug delivery system [186]. Anecdotally, two peptidomimetics containing an oxalyl function are reported for their ability to form organogel as well as hydrogel, including #93 (**Figure 13B**) [187, 188]. As well, a molecule containing a maleic acid-like function is able to gelify in the presence of light and bromine. Indeed, starting with the Z configuration, UV irradiation (330 nm, 400 W, 30 s) and bromine trigger the photochemical isomerization (formation of a fumaryl-like group). The obtained diastereoisomer is then able to self-assemble (#94 **Figure 13B**) [189].

In parallel, a constrained amino acid derived from oxazolidine was used by the group of C. Tomasini, named (*4R,5S*)-4-carboxy-5-methyl oxazolidin-2-one (3-letter code **Oxd**). The first hydrogelator including an **Oxd** (#95 **Figure 13B**) was composed of a central alkyl chain, two **Phe** (one on each side), and two terminal **Oxd** (one on each side). However, hydrogelation can only occur in a 50/50 water/MeOH mixture [190, 191] or 90/10 water/EtOH [192]. The second system (#96 **Figure 13B**) is definitively more efficient (cpd xx) and exhibits properties of entrapment of aromatic dyes methylene blue (cationic) and eosin Y (anionic) [193].

Last of all, functionalization of the nitrogen of the amide group was proposed as a way to improve hydrogelation. Because of the high efficiency of phenylalanine, N-benzyl glycine (**Nphe**) derivatives synthesized were the following: **Fmoc-Phe-Phe, Fmoc-Phe-Nphe** (#97 **Figure 13B**), **Fmoc-Nphe-Phe** (#98 **Figure 13B**), and **Fmoc-Nphe-Nphe** (#99 **Figure 13B**). While the latter failed to form a hydrogel, the two peptides with one **Nphe** inside turned out to be less stiff than **Fmoc-Phe-Phe** in the same conditions. However, these experiments provide new molecular tools to fine-tune the properties of peptide self-assembly and gelation process [194].

5. Conclusion

Peptide-based hydrogels are innovative materials able to efficiency tackle the challenges of biocompatible and biodegradable soft matter. Mainly, they pave the way to promising medical and biological applications, and it is a safe bet that in the next years, their market share will increase drastically. Furthermore, the first commercially available peptide-based hydrogel has been launched, and new companies have emerged. Nevertheless, all these applications are possible thanks to the plentiful body of work accomplished in fundamental research during the last decades.

In order to improve and fine-tune the hydrogelation process, a critical point to broaden the application window, several strategies have been envisaged, described all along this chapter. Among them, addition of aromatic groups at the N-terminus, mainly via the presence of protecting groups (*e.g.*, Fmoc, Cbz, etc.), clearly favors the hydrogel formation, thanks to the increase of π-π interactions. Introduction of organic moieties inside the peptide sequence is also an efficient strategy, whether they are aromatic or unsaturated. In this latter case, introduction of acetylene groups offers the opportunity to add to the peptide self-assembly polymerization, which reinforces the mechanical properties of the gel. Furthermore, introduction of non-canonical D-amino acids is an efficient approach and leads to more stable hydrogels in term of proteolytic resistance. The development of new amino acids, including α,β-dehydrophenylalanine, β-thienylalanine, or functionalized phenylalanine, especially designed to influence the peptide self-assembly, drastically impacts the final properties of the obtained hydrogel. Functionalization on the lateral chains is another opportunity to support interactions between peptides, and to include new properties, like photoswitchable ones thanks to the introduction of azobenzene moieties. Creation of additional bonds via dityrosine formation or subsequent polymerization is a smart strategy combining both the physical and chemical gels worlds. Last of all, substitution of the inner peptide bond by another one leads to the development of peptidomimetics which are burgeoning and promise a bright future.

This chapter has reviewed the recent advances in peptide-based hydrogel development using modified peptide structures.

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