Chiral dipeptide mimics possessing a fluoroolefin moiety: a relevant tool for conformational and medicinal studies

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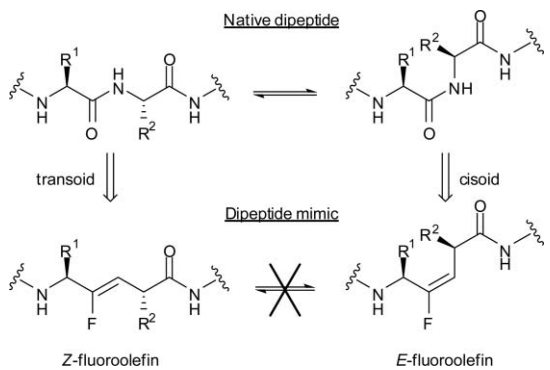
The replacement of the amide bond in a peptide backbone is a promising strategy in peptidomimetic drug research. Over the various amide bond surrogates, the fluoroolefin moiety has been successfully developed as an effective mimic. Today, fluorine-containing compounds account for a large proportion of new active molecules in life sciences. The synthesis of fluoroolefin peptide mimics is not a trivial task and innovative approaches often need to be addressed, in particular for the stereocontrol of the double bond configuration and the chiral centres adjacent to the fluoroalkene. These fluorinated peptidomimetics have been synthesised and evaluated as metabolically stable and/or conformationally constrained analogs of enzyme inhibitors, and as tools for probing the function, structure, and binding process of receptors.

Introduction

Peptides are promising candidates for the development of novel therapeutic agents for the treatment of human diseases. The idea of treating disease with molecules that the body itself synthesises is very attractive, since high activity is expected. Progress in peptide chemistry has made the synthesis of small peptides a routine task but, despite interesting *in vitro* activity, their therapeutic use is often hampered by a poor bioavailability and short physiological half-lives. The design of small protein-like chains to mimic peptides and their development as drug-like compounds is of ongoing interest for both peptide and medicinal chemists. Indeed, peptidomimetics have emerged as valuable tools since they offer significant advantages over peptide-based drugs.[1] In particular, a peptidomimetic that no longer has an enzymatically scissile peptidic bond is not exposed to proteolytic cleavage by enzymes in the digestive system and consequently possesses an extended lifetime. The design of peptidomimetics as potential drugs requires the incorporation of structural elements possessing functionalities able to reproduce favorable geometry, electrostatic interactions, polarity, and hydrogen bonds. The identification of functional groups that can act as bioisosteric replacements of the amide bond led to numerous syntheses of peptidomimetics.[2] Of the functionalities that can effectively mimic the amide bond, the carbon–carbon double bond of alkenes has been the subject of several studies.[3] Peptide bonds exist in cisoid–transoid equilibrium whereas alkene mimics do not isomerise and act either as a cisoid equivalent for *Z*-alkenes or as a transoid equivalent for *E*-alkenes. Peptides with olefin units are conformationally locked peptide bond isosteres and also have increased lipophilicity, however, the olefin bond is of very low polarity and intramolecular hydrogen bonds are lost. Fluorine is the most electronegative atom, its introduction onto the olefin moiety preserves the dipolar nature of the peptide linkage and may participate in hydrogen bonding between the backbone and the peptide bond surrogate even if the interaction energy is weaker than in native peptides.[4] The hydrogen bond notion has been supported by recent studies despite the controversy on the existence of hydrogen bonds between the C–F group and –OH or –NH donors.[5] Advantageously, fluoroolefins have steric and electronic properties that provide closer structural similarities with an amide bond. The electronic distribution significantly differs in fluoroolefins compared to simple alkenes, so the dipole moment of the *trans*-fluoroolefin unit has the same orientation as the amide bond but has a smaller value.[6] In addition, the superior lipophilicity brought by the fluorine atom may facilitate the membrane penetration, in particular the blood–brain barrier passage. For these reasons, the fluoroolefin moiety is considered as an excellent mimic for the peptide bond (Scheme 1).



Scheme 1

In 1990, Allmendinger *et al.* applied this concept.[7a,7b] Their pioneering work led to the synthesis of Gly-Ψ[(*Z*)CF=CH]-Gly and racemic Phe-Ψ[(*Z*) or (*E*)CF=CH]-Gly dipeptide mimics.[7a] They also synthesised both enantiomers of the Phe-Ψ[(*Z*)CF=CH]-Gly dipeptide mimic as fluoroolefin dipeptide isosteres of the Phe-Gly region of the neuropeptide substance P (Fig. 1).[7b]

In this synthetic route, the *Z* configuration of the alkene is brought by the starting fluoroenaldehyde. The construction of the stereogenic centre at the *N*-terminal residue is the result

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Samuel Couve-Bonnaire was born in Maubeuge, France in 1976. He received his Ph.D. in 2001 from the University of Science and Technology of Lille, France. He studied at the Laboratory of Catalysis of Lille, homogeneous section, directed by Professor Andre Mortreux. Then he carried out his post-doctoral studies in Canada in the laboratory of Prof. Prabhat Arya at the Steacie Institute for Molecular Sciences, Ottawa, National Research Council Canada. After returning to France, he was appointed as a post-doctoral researcher with Sanofi-Aventis as an industrial partner. Since February 2005, he has been working in the group of fluorinated biomolecules synthesis as a Maître de Conférences. His current interests are various and deal with organometallic reactions, asymmetric synthesis and fluorinated compounds.

Dominique Cahard was born in 1968 in Fécamp, France. He received his Ph.D. degree in 1994 at the University of Rouen in the laboratory of Pierre Duhamel. He then had post-doctoral experiences as a research associate with Prof. Chris McGuigan at Southampton University and at the Welsh School of Pharmacy in Cardiff, and with Prof. Tadashi Nakata at RIKEN, Tokyo. In 1996, he joined the CNRS at the University of Rouen where he completed his Habilitation in 2001. He is a member of the fluorinated biomolecules synthesis group in the UMR 6014 CNRS. He is interested in electrophilic fluorination and trifluoromethylation with emphasis on asymmetric synthesis and new fluorinated therapeutic agents.

Prof. Xavier Pannecoucke was born in Lille, France in 1967. He got his Ph.D. in BioOrganic Chemistry in 1993 from the University Louis Pasteur of Strasbourg (France), under the supervision of Professors Guy Ourisson and Bang Luu. He then moved to Japan for one year to carry out his first post-doctoral study in the laboratory of Prof. Koichi Narasaka at the University of Tokyo. He moved again, to Great Britain for fourteen months, to carry out his second post-doctoral study in the laboratory of Prof. Steven V. Ley at the University of Cambridge. He then went back to France as a Maître de Conférences at the University of Rouen in the group of Prof. J.-C. Quirion. In 2003, he took up the position of professor at the INSA of Rouen, leading the group of fluorinated biomolecules synthesis. His main research interests are dealing with the development of new methodologies to access fluorinated biomolecules (peptidomimetics, carbohydrates, nucleosides).

Samuel Couve-Bonnaire

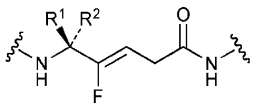
Dominique Cahard

Xavier Pannecoucke

Substance P :
Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

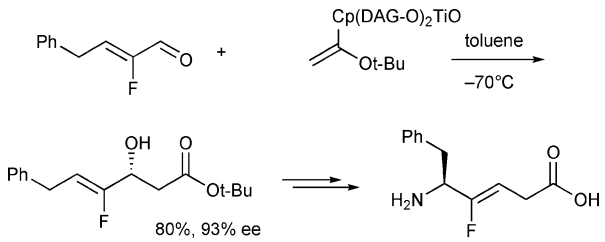
analogues :
Arg-Pro-Lys-Pro-Gln-Gln-Phe-{Phe-Ψ[(*Z*)CF=CH]-Gly}-Leu-Met-NH_2

Phe-Ψ[(*Z*)CF=CH]-Gly :



R^1 = Bn, R^2 = H
R^1 = H, R^2 = Bn

Fig. 1



Scheme 2

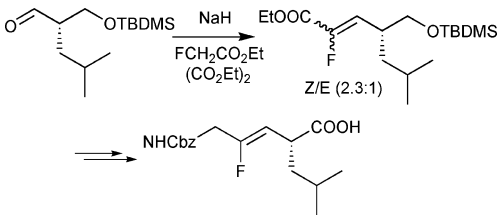
of a diastereoselective aldol reaction at the C-terminal side (in the β-position of the ester moiety) followed by chirality transfer to the N-terminal side through the [3,3] sigmatropic Overman rearrangement (Scheme 2). The substance P analogs were obtained by elongation of the dipeptide mimics by a solid phase approach and receptor binding assays were conducted. The full sequence analog having the natural amino acid (Phe) configuration showed equipotent activity to substance P whereas its diastereoisomer had a 10 times lower binding affinity. This result clearly demonstrated that fluoroolefin peptides can efficiently mimic endogeneous peptides, provided alkene configuration and adequate absolute configuration of stereogenic centres are synthetically controlled.

Consequently, the utilisation of fluoroolefin dipeptide mimics requires the construction of the fluoroolefin with not only regio- and stereocontrol, but also the control of the absolute configuration of the stereogenic centres on both sides of the olefin moiety. This field has become very dynamic in the past few years with the involvement of many research groups, including ours, in fluoroolefin dipeptide mimics. Synthetic methods for fluoroolefin dipeptide mimics are presented in this article as well as results of biological evaluations.

Access to dipeptide mimics containing a fluoroolefin moiety

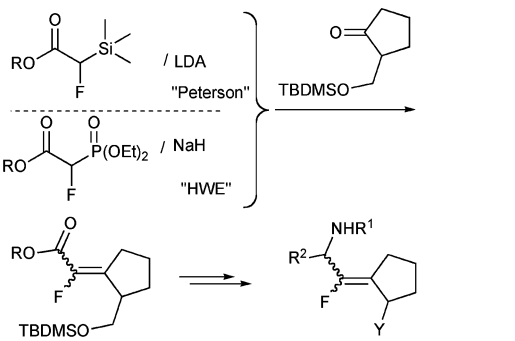
Since Allmendinger's pioneering work, numerous syntheses of molecules bearing a fluoroolefin moiety have been reported in the literature. In this article, only the synthesis of fluoroalkenes as amide bond substitutes will be discussed. Essentially, two methodologies are known to get fluoropeptidomimetics: the olefination reaction pathway that is the most applied and documented one, and the more recent reductive defluorination reaction.

The various olefination reactions produce α-fluoro-α,β-unsaturated esters as common intermediates towards fluoropeptide mimics. Bartlett and Otake have developed a synthesis based on the condensation of the *in situ* generated diethylfluorooxaloacetate with a chiral aldehyde.[8] The stereoisomers of the fluoroacrylate were separated by column chromatography and the *Z* isomer was further transformed into Cbz-Gly-Ψ[(*Z*)–CF=CH]-LeuXaa (Xaa = different amino acids) (Scheme 3).



Scheme 3

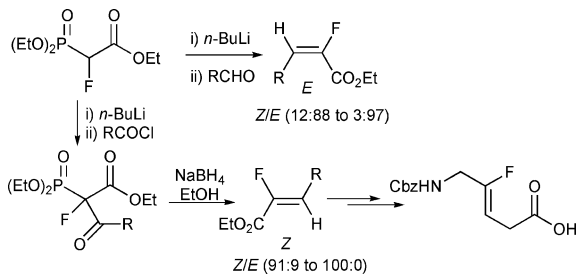
Welch *et al.* used the Peterson olefination to prepare both Ala-Ψ[(*Z*)–CF=CH]-Pro and Gly-Ψ[(*Z*)–CF=CH]-Pro fluoropeptidomimetics (Scheme 4).[9] On similar targets, Augustyns *et al.* applied the Horner–Wadsworth–Emmons (HWE) strategy to form the fluoro skeleton of Gly-Ψ[CF=CH]-Pro analogs (Scheme 4).[10] These two methods gave a mixture of stereoisomers *Z* and *E* that could be separated by column chromatography.



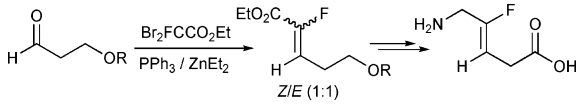
Scheme 4

Sano and Nagao also developed a synthetic route to Gly-Ψ[CF=CH]-Gly based on phosphonate chemistry.[11] Depending on the reaction conditions, the *E* or *Z* fluoroolefins can be obtained selectively. A HWE reaction provided the *E* stereoisomer as a major product whereas a tandem reduction–olefination reaction gave the *Z* stereoisomer predominantly (Scheme 5).

Our group developed another approach to α-fluoro-α,β-unsaturated esters based on a Wittig-type reaction with commercially available ethyldibromofluoroacetate[12] followed by a reduction of the ester group and a Mitsunobu reaction to get the Gly-Ψ[(*Z*)CF=CH]-Gly dipeptide analog (Scheme 6).

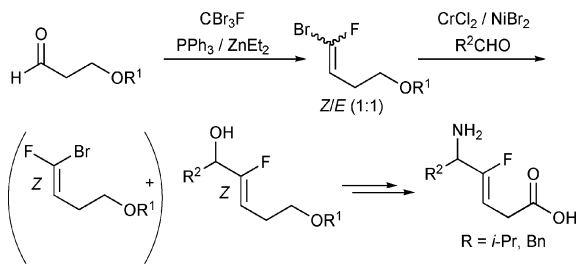


Scheme 5



Scheme 6

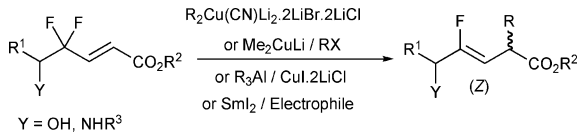
Other useful intermediates in the synthesis of dipeptide mimics could be the *gem*-bromofluoroolefins. A synthetic route towards these compounds was recently developed by our group.[13] The first step, which is the access to bromofluoroolefins, was envisioned through a Wittig-type reaction reported by Burton *et al.*[14] We modified the initial experimental procedure changing the activating agent Zn to the more efficient $ZnEt_2$. This minor change has major consequences as the reaction became efficient for all type of aldehydes as well as for ketones.[12,13] Then, a Nozaki–Hiyama–Kishi (NHK) reaction was conducted on the bromofluoroalkene intermediates.[15] Interestingly, only *E* bromofluoroolefins were reactive under the reaction conditions to get fluorinated allylic alcohol whereas unreactive *Z* bromofluoroolefins could be recovered (Scheme 7). A further Mitsunobu reaction revealed to be difficult, as discussed in the literature,[7c] and allowed us to get two transoid racemic fluoropeptidomimetics, Val-Ψ[(*Z*)CF=CH]-Gly and Phe-Ψ[(*Z*)CF=CH]-Gly) with quite moderate yields. The catalytic and enantioselective version of the NHK reaction is currently under investigation in our group.



Scheme 7

A complementary access to fluorodipeptide mimics was developed independently by the groups of Fujii and Otaka[16] and Taguchi.[17] The method is a so-called reductive defluorination reaction and led quasi-exclusively to *Z* fluoroolefins. The reaction is based on a redox reaction on γ,γ-difluoroacrylates with organometallic reagents: copper complexes, copper-aluminate

derivatives or samarium diiodide (Scheme 8). Based on this chemistry, Fujii and Otaka's group recently developed a synthetic route leading to a cyclic intermediate yielding only the *E* fluoroolefin.[16d]

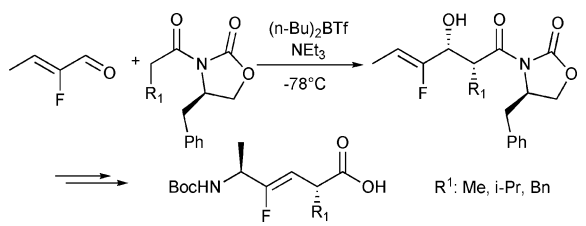


Scheme 8

Recent progress in the asymmetric synthesis of dipeptide mimics

Most of the methodologies described earlier in the text provide achiral or racemic compounds. Nevertheless, some of them lead to chiral non-racemic dipeptide analogs and many recent publications in this area are devoted to the asymmetric synthesis of fluoropeptidomimetics.

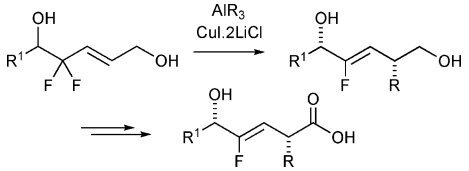
The most studied part of the dipeptide mimics for the stereocontrolled introduction of a chiral centre is the C-terminal moiety. Indeed, we can easily imagine modifying the acid function with a chiral auxiliary to allow diastereoselective reactions. Bartlett and Otake exploited the Evans chiral auxiliary to prepare the α-hydroxymethyl aldehyde that is the substrate in the olefination reaction described in Scheme 3.[8] Then, Waelchli *et al.* combined the same strategy with Allmendinger's work to create two stereocentres at the C-terminal moiety (Scheme 9).[18]



Scheme 9

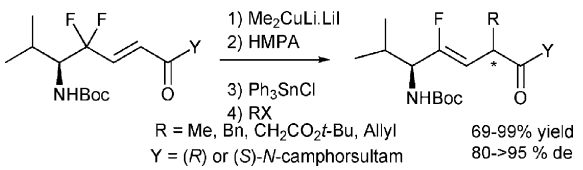
The stereogenic centre β to the carbonyl function was subjected to an Overman rearrangement in order to transfer the chirality to the N-terminal residue. The overall process, although not further illustrated since 1996, is nevertheless a general method to introduce stereocontrolled chiral centres on both sides of the fluoroolefin moiety. About the C-terminal side, the modification of the acid function with a chiral auxiliary could be envisioned as a simple and general method to control a stereocentre α to the C-terminal atom. Indeed, this reaction has been applied successfully by Kelly *et al.* as the key step in the synthesis of a peptide analog bearing a double bond as a peptide bond mimic, Phe-Ψ-[(*E*)CH=CH]-Phe.[19]

As illustrated earlier in the text, the reductive defluorination reaction involves the use of organometallic reagents and so seems to be well-defined for the asymmetric addition of alkyl groups or electrophilic reagents. Unfortunately, the reaction proved to be non-stereoselective in most cases. Nevertheless, one interesting case described by Taguchi about the Cu(I)-mediated reaction of *E*-4,4-difluoro-5-hydroxyallylic alcohol with AlR_3 has to be noted. In this reaction, good yields with diastereoselectivity *syn–anti* superior to 95 : 5 and with the major formation of a *Z* double bond (*Z*–*E* ratio > 95) were obtained allowing the preparation of depsipeptide or dipeptide isosteres after chemical transformations (Scheme 10).[17a,17b]



Scheme 10

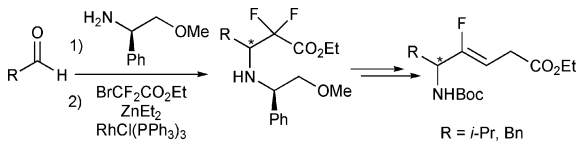
If we now take a closer look at Scheme 8, we see an ester function that could be substituted to a chiral auxiliary allowing asymmetric induction during the reductive defluorination reaction process. Preliminary results in that way were given by Taguchi *et al.* by means of different chiral auxiliaries, including phenylmenthol, camphorsultam and oxazolidinone derivatives.[17c] Only the camphorsultam auxiliary proved to be efficient in terms of asymmetric induction with high diastereoselectivity (dr = 19 : 1) although in a quite low yield. Further developments of this synthetic approach were reported by Fujii *et al.* in 2006.[20] Improved experimental conditions provided a more efficient and general synthetic route to introduce a stereocentre at the C-terminal side. Various electrophiles were introduced at the α-position by a sequence of reduction–transmetalation–alkylation in good yields and with high diastereoselectivities (Scheme 11). In addition, starting from an enantiopure δ-amino-*N*-enoyl sultam, this method provided an access to chiral dipeptide mimics with controlled stereogenic centres on both sides of the molecules. In particular, the synthesis of Val-Ψ[(*Z*)CF=CH]-Phe-OH dipeptide mimic was realised.



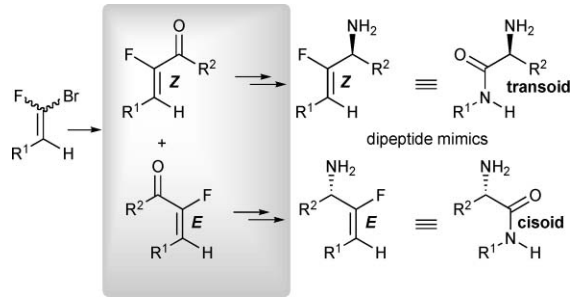
Scheme 11

Concerning the N-terminal moiety, only a few strategies of asymmetric synthesis controlling the creation of a chiral centre on this side of the molecule were described. Allmendinger *et al.* were the first to get a chiral side chain on the N-terminal part of the dipeptide. Nevertheless, as already discussed in the text, this methodology set up initially the chirality at the C-terminal side on the β-position before stereospecific transposition to the N-terminal side by Overman rearrangment.[7b] In 2004, Fujii and Otaka introduced the chirality directly on the N-terminal side of the dipeptide in the first step of the synthetic plan. Ethyl ester derivatives of L-Val-Ψ[(*Z*)CF=CH]-Gly and D-Phe-Ψ[(*Z*)CF=CH]-Gly were synthesised (Scheme 12).[16c]

In the search for an alternative and versatile method to introduce chiral centres at the N-terminal side of the dipeptide mimics, we recently reported the use of a fluoroenone as an advanced intermediate that could be further transformed into the desired dipeptide mimics (Scheme 13).

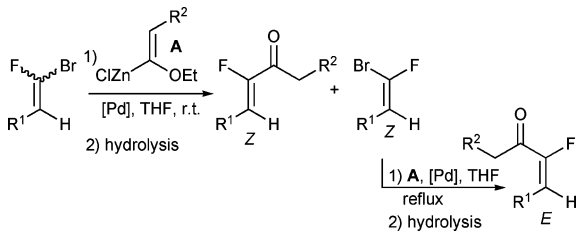


Scheme 12



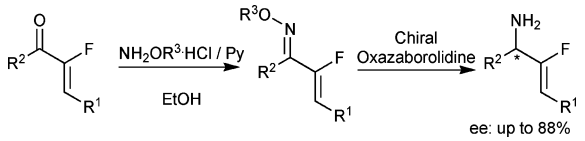
Scheme 13

To obtain the key fluoroenone, we developed a Negishi type coupling reaction between bromofluoroolefins and alkoxyvinylzinc species. The palladium coupling reaction proved to be very efficient and highly chemical tolerant. Moreover, controlling the reaction temperature, this reaction allowed us to get stereospecifically the *Z* (transoid) as well as the *E* (cisoid) fluoroenones (Scheme 14).[21]



Scheme 14

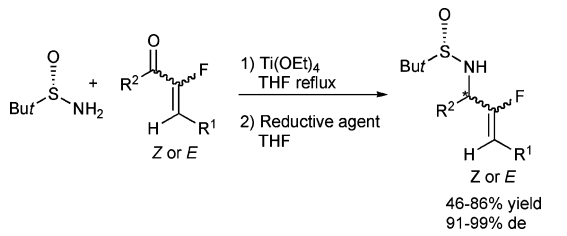
From these fluoroenones, an asymmetric reductive amination was expected to lead to the desired peptide analogs. First, we attempted an enantioselective process using oxazaborolidine reduction of ether ketoxime derivatives (Scheme 15).[22]



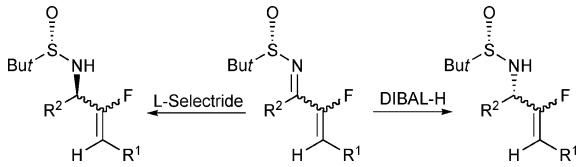
Scheme 15

Unfortunately, the enantioselective reduction was only effective for aromatic substrates but not for aliphatic substrates. We then turned our attention to a diastereoselective process using *tert*-butanesulfinamide as a chiral auxiliary. A one step procedure was developed, involving the formation of *tert*-butanesulfinyl ketimines followed by direct reduction using metal hydrides. This method led to yields of up to 86% and is highly diastereoselective (de up to 99%) (Scheme 16).[23]

An important feature is the possibility to get a complete reversal of stereoselectivity changing the nature of the reducing agent (Scheme 17).[23]

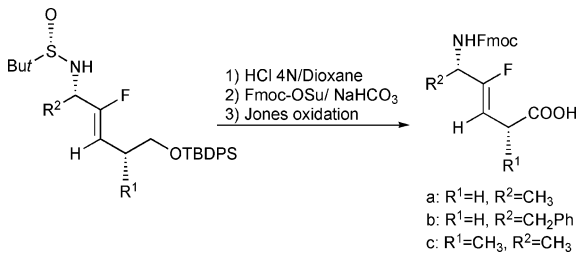


Scheme 16



Scheme 17

The fluoroolefin geometry or the presence of a chiral centre on the C-terminal moiety did not disrupt the reduction process. We applied this methodology to synthesise three chiral dipeptide mimics: Fmoc-Ala-Ψ[(*Z*)CF=CH]-Gly, Fmoc-Ala-Ψ[(*Z*)CF=CH]-Ala and Fmoc-Phe-Ψ[(*Z*)CF=CH]-Gly (Scheme 18).



Scheme 18

Biological results and perspectives

Fluoroolefin-containing compounds could be used in various biological applications such as binding affinity studies, enzyme inhibition, enhancement of bioavailability, improvement of biological activity and conformational studies. Nevertheless, since Allmendinger's work,[7b] there have only been a few biological reports concerning fluoropeptidomimetics essentially because of the lack of general methods leading to these products. Our recent contribution and that from other groups provide new synthetic tools for the rapid development of useful fluoropeptidomimetics.

Most of the reports are devoted to enzyme affinity and biological consequences: agonism or antagonism. Bartlett and Otake studied (some) fluoropeptides Cbz-Gly-Ψ[(*Z*)CF=CH]-Leu-Xaa (with Xaa = Gly, Ala, Leu, Phe and NH_2) in a structure–activity relationship study with zinc peptidase thermolysin. These peptide surrogates were found to be modest inhibitors.[8] In 1996, Waelchli *et al.* studied a series of peptidomimetics of hPTH(1-36), a parathyroid hormone (PTH).[18] They studied the role of the first dipeptide residue Ser-Val of hPTH(1-36)-NH_2 changing the peptidic bond by different isosteres. Among the different analogs tested, a single fluoroolefin-containing compound displayed a better binding affinity than natural substrates and better stimulation of adenylate cyclase production in three different cell lines

constituting highly potent analogs of hPTH(1-36)-NH_2. Welch *et al.* designed new molecules as potent inhibitors of dipeptidyl peptidase IV, an enzyme involved in many biological processes, which could serve as a target for the treatment of diabetes. The Ala-Ψ[(*Z*)CF=CH]-Pro analog (with a cyano group on the pyrrolidine ring) was revealed to have enzyme affinity with a very good inhibition factor and stability.[9,24] Augustyns *et al.* studied the same kind of molecules, Gly-Ψ[(*Z*)CF=CH]-Pro analogs. They demonstrated that the results were not conclusive for dipeptidyl peptidase IV whereas their fluoroolefins were as good an inhibitor of dipeptidyl peptidase II as the native peptides, and with better solution stability.[10]

Leumann and Hollenstein have introduced the fluoroolefin moiety in peptide nucleic acids (PNA's). Decamers containing one modified amide bond as well as fully modified decamers and pentadecamers in the *Z* locked rotameric form were synthesised for evaluation of the base-pairing properties with DNA. The stability of duplexes was found to be highly dependent on the number and the position of the fluoroolefin(s); in particular, fully modified polymeric PNA's have reduced affinity to DNA, probably due to self-aggregation caused by the enhancement of the hydrophobic nature.[25] In 2006, Fujii *et al.* tested some fluoroalkene dipeptide isosteres in a structural study of the di/tri-peptide transporter PEPT1, a membrane protein for which the recognition mechanism is still not fully elucidated. So, they used fluoroalkene and alkene isosteres to find the preferential bioactive conformation and found that, in each case, the transoid-amide analogs were more than 10 times more active than cisoid mimics with a receptor affinity slightly lower than that of the parent peptide.[16e]

In the cases described above, the *in vitro* activity of the fluoropeptides is sometimes lower compared to the activity of the parent peptides. However, the lower biological activity could be compensated for *in vivo* by better stability and greater bioavailability. Research focused in this area is still in progress and further developments are imminent. We recently initiated a research programme aimed at synthesising fluoroanalogs of biologically important peptides, such as the 26RFa neuropeptide, which plays a crucial role in the regulation of appetite and food consumption.[26]

Conclusions

The biological use of dipeptide mimics, although in rapid progression, remains too low with respect to the high potential of small protein-like drugs. This is probably due to non-general and/or non-asymmetric access to dipeptide analogs. Over the past few years, the fluoroalkene moiety as a peptide bond surrogate has gained high interest and should become more and more employed thanks to recent synthetic developments. As a matter of fact, different methodologies are now more efficient and general. The variety of available chiral dipeptides is increasing. It has to be noted that a lot of synthetic challenges are still under investigation. The use of fluoroolefins as amide bond analogs is becoming a tool of choice for different applications owing to their versatility and their potential utility. The fluoroalkene moiety could be used to design new bioactive compounds with promising enzyme/receptor affinity and good bioavailability, not only in the field of peptidomimetics but also as a replacement of the amide bond in any other type of molecule in the pharmaceutical domain. Finally, fluoroolefin-containing molecules could be used as powerful tools in conformational analysis of bioactive peptides and proteins. Indeed, the *cis–trans* isomerisation of peptide bonds, which plays a crucial role in biological activity, could be better studied using fluoroolefins to lock the configuration of the peptide bond mimic.

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