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Safety-Catch and Multiply Cleavable Linkers in Solid-Phase Synthesis

Abstract: *This review article focuses on concepts that incorporate safety-catch and multiply cleavable linkers in solid-phase synthesis. Discussed are specific applications of such linkers in the synthesis of peptides, peptide mimetics, and "small" organic molecules, as well as their limitations for particular chemistries and reaction conditions.* © 1999 John Wiley & Sons, Inc. Biopoly 47: 353–363, 1998

Keywords: *safety-catch linkers; multiply cleavable linkers; solid-phase synthesis; combinatorial chemistry*

INTRODUCTION

The exploding field of combinatorial chemistry was stimulated by the developments in the techniques of solid-phase synthesis, pioneered by Merrifield in 1963.[1] The importance of linkers allowing attachment of organic molecule to the solid support followed by its gentle release in the last step of the synthesis was recognized early on in the synthesis of peptides, and significant effort of hundreds of chemists was devoted to the development of optimal linkers. In this review we would like to focus on two particular types of linkers: (a) safety-catch linkers providing high stability during the synthesis, but capable of chemoselective modification and subsequent labilization for cleavage step; and (b) multiply cleavable linkers allowing release of a defined amount of material from the solid support in several distinct steps.

SAFETY-CATCH LINKERS

To cope with the demands for the synthesis of diverse libraries of small organic molecules, peptide mimetics, and peptides, an access to a broad arsenal of linkers that meet specific requirements of the particular solid-phase synthesis strategy is of great importance. Therefore, the development and refinement of safety-catch linkers continues to be an important element of solid-phase synthesis. In this respect, the benefit of safety-catch linkers that inherently offer an advantage of extended orthogonality further expands the potential for use of a larger repertoire of organic reactions and synthetic protocols.

By definition, the safety-catch principle involves a process based upon conversion of a relatively stable form of a linker to a labile, isolable, and cleavable one.[2] Obviously, the linker has to be entirely inert throughout all operations of the synthesis. Based on

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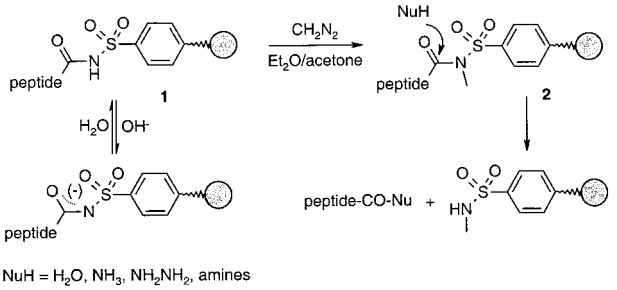


FIGURE 1

the overall cleavage process, two types of safety-catch linkers can be distinguished. For safety-catch type **I**, the stable and labile forms of the linker show a "hidden" orthogonality, i.e., the cleavage mechanism of both forms are different (e.g., alkaline hydrolysis of linker **14** vs. release by intramolecular cyclization of **15**). However, the majority of safety-catch linkers are of type **II**, where the stable and labile form show a kinetic "fine-tuning" effect, i.e., the cleavage mechanism of the stable and labile forms are the same and the stability depends solely upon the "strength" of the cleavage agent (e.g., aq. NaOH or amines at room and higher temperature for phenol-sulfide/sulfone linkers **5** and **6**). Since such a categorization has little practical significance for everyday use of safety-catch linkers, arrangement according to the cleavage mechanism is used in the next section.

ACTIVATION OF CARBONYL GROUP BY THE INDUCTIVE EFFECT (I−) OF AN ADJACENT SUBSTITUENT

The fundamental feature of the following linkers is that their final cleavage step involves an activation of a carbonyl group by the negative inductive effect (I−) of an adjacent substituent. The cleavage occurs after a chemical operation (e.g., oxidation, alkylation) that transforms the stable linker into its labile form.

Among the first carboxyl anchors used to demonstrate the safety-catch principle was the acyl sulfonamide resin **1** (Figure 1) proposed by Kenner and co-workers.[3] Acyl sulfonamides are stable to strong anhydrous acids including HBr/AcOH, as well as to strongly nucleophilic reagents and an aqueous alkali, as the basic attack ionizes the acidic SO_2NH group ($pK_a \sim 2.5$). Safety-catch activation by *N*-methylation with diazomethane in diethyl ether/acetone gives the labile species **2**, which is cleaved by alkali (1 equiv. of 0.5*M* NaOH), by aminolysis (an excess of 0.5*M* ammonia/dioxane) or by hydrazinolysis (3 equiv. of methanolic hydrazine). More recently, Backes and Ellman have adapted the original Kenner's acyl sulfonamide linker for solid-phase synthesis of phenylacetic acid derivatives.[4,5] However, for both peptides and small organic molecule synthesis, the reactivity of the *N*-methyl acylsulfonamide **2** is so poor that less nucleophilic amines (e.g., anilines) do not react at all, while for more nucleophilic alkylamines, an excess of reagent is usually required to ensure successful cleavage. To overcome this problem, haloacetonitrile activation was employed that dramatically increased the reactivity of linker **3** toward a larger variety of amines and other nucleophiles (Figure 2). Hence limiting amounts of even sterically hindered and nonbasic amines can be used to incorporate nucleophiles during the cleavage step and to increase diversity of amide products. The linker was also shown to be compatible with common peptide coupling reagents, enolate alkylation,[4] and Suzuki reaction conditions.[4] One limitation of haloacetonitrile activation was an incomplete alkylation of the acyl sulfonamide when carboxylic acids possessing an α-electron withdrawing group were used. In order to increase the nucleophilicity of the acyl sulfonamide anion, alkyl sulfonamide linker **4** has been suggested and synthesized by the same authors.[5] The overall improvement from the original aryl sulfonamide linker **1** was demonstrated by higher cleavage yields in comparative experiments. However, certain limitations of both sulfamyl linkers, such as incomplete and racemization-free acylation with protected amino acids, still remain to be solved.

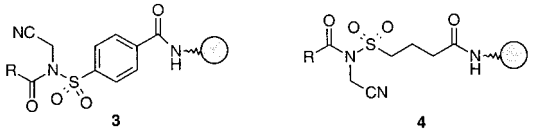
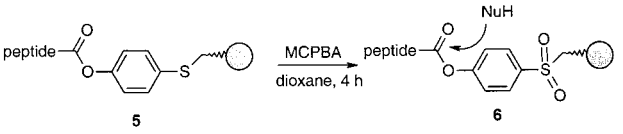


FIGURE 2



NuH = amino acid, amines; MCPBA = 3-Chloroperoxybenzoic acid

FIGURE 3

The oxidative safety-catch linker **5** of Marshall and Liener was originally employed to provide protected peptide fragments.[6,7] The corresponding 4-alkylthiophenyl esters were shown to be sufficiently unreactive toward aminolysis as well as stable to the acid conditions used to remove the Boc, Z, and ^{t}Bu groups (Figure 3). The attractive feature of this linker is its facile conversion to the activated alkylsulfonyl ester **6**. Investigation of corresponding sulfoxides as possible active esters revealed only mild activation toward aminolysis. Illustration of the utility of this phenol-sulfide linker have been reported for the synthesis of both linear[6,7] and cyclic peptides.[7] One obvious limitation preventing practical applicability is related to the oxidation step as sensitive amino acids such as tryptophan, cysteine, cystine, and methionine have to be excluded. In contrast to the above described applications, recent adaptations of the phenol-sulfide linker **5** for the synthesis of tetrahydro-β-carboline-3-carboxamides and piperazine-2-caboxamides suggest that the final cleavage step can be effectively performed even without prior activation of the linker.[8,9] However, in order to avoid long reaction times (5–7 days), authors recommend using pyridine as a solvent of choice and treatment with excess of amines to ensure high cleavage yields across the entire library.

Pascal et al.[10,11] have reported the Dpr(Phoc) safety-catch linker **7** that is cleaved by alkaline hydrolysis (0.03*M* NaOH) or ammonolysis (satd. NH_3 in ^{i}PrOH) after intramolecular cyclization to *N*-acyl-2-imidazolidinone (Figure 4). This linker is a derivative of β-aminophenyloxycarbonyl-2,3-diaminopropionic acid exhibiting high stability under neutral and acidic conditions [1*M* TFMSA in trifluoroacetic acid (TFA) at 0°C, 50% TFA, 6*M* aq. HCl]. Activation is achieved under mild alkaline conditions (2 equiv. of 0.04*M* NaOH for 1 h) by selective intramolecular cyclization of electrophilic isocyanate to the adjacent secondary amide group. Such cyclization leads to *N*-acyl-2-imidazolidinone intermediate **8**. Peptide acids or C-terminal amides are thus formed either concurrently or subsequently depending on conditions used for activation. Linker activation and final cleavage can be conveniently monitored for the presence of released phenol and desired peptide in the hydrolysate by uv spectrophotometry.

ACTIVATION BY THE MESOMERIC EFFECT (M−) OF THE X—Y=Z MOIETY ADJACENT TO A CARBONYL GROUP

An illustrative example of a safety-catch linker where activation of a terminal carbonyl group by the mesomeric effect (M−) of the —X—Y=Z moiety plays a crucial role is a derivative of 2,2-diphenyl-2-hydroxyethyl ester **9** introduced by Wieland and co-workers.[12] Acid-catalyzed dehydration (aq. TFA for 1 h) converts the 2-hydroxyethyl ester into reactive enol ester **10**, which upon reaction with amines affords the corresponding secondary amides (Figure 5). Unfortu-

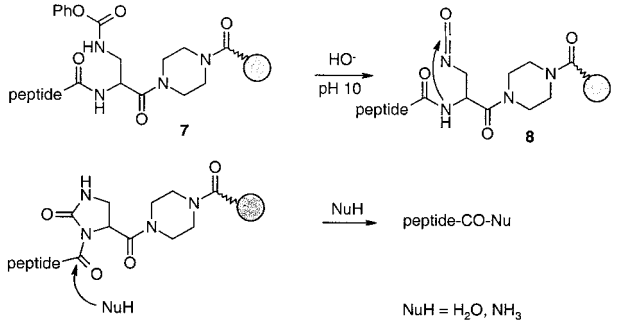


FIGURE 4

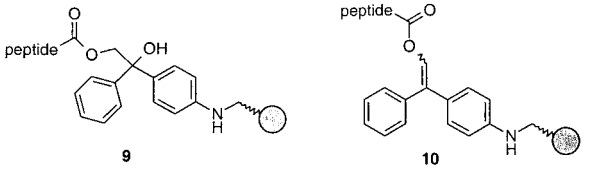


FIGURE 5

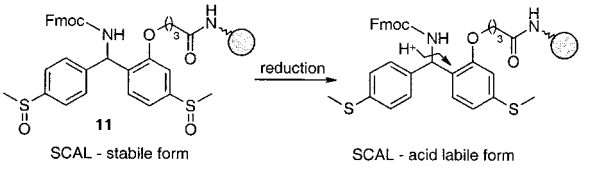


FIGURE 6

nately, the combination of acid-labile groups for side-chain amino acid protection is effectively precluded by the acidic conditions necessary for the generation of the active ester **10**.

ACIDOLYTIC CLEAVAGE OF BENZHYDRYL- OR BENZYL AMIDE AND ESTER TYPES OF LINKERS

In this section, safety-catch linkers will be described that incorporate the well-documented rate dependence in heterolytic benzhydryl- or benzyl-oxygen (nitrogen) cleavage on the electronic character of *ortho* and *para* substituents.[13]

Based on the safety-catch *p*-(methylthio)benzyl and *p*-(methylsulfinyl)benzyl protecting groups of Samanen and Brandeis,[14] new types of linkers have been designed for solid-phase synthesis applications. Pátek and Lebl have introduced safety-catch amide linker **11** (SCAL) for the synthesis of primary amides (Figure 6).[15] In its oxidized form, the linker is extremely stable toward acids [TFA for 24 h, 1*M* thioanisole/TFA for 2 h, TFA/thioanisole/EDT/phenol/water (82.5 : 5 : 2.5 : 5 : 5)] and bases [aq. 0.5% NaOH, 20% piperidine/dimethylformamide (DMF)]. Reductive activation of the SCAL is accomplished by repetitive treatment with either 1*M* PPh_3/Me_3SiCl/DCM or 20% $(EtO)_2P(S)SH$/DMPU (3 × 20 min), followed by washing with DCM and DMF. Acidolytic cleavage of the material from the solid support is then accomplished by treatment with TFA/water (95 : 5) or TFA/DCM/H_2O/$Bu^i{}_3SiH$ (85 : 10 : 2.5 : 2.5) for 1 h. Linker **12** was introduced by Kiso and co-workers[16,17] to demonstrate a new strategy for solid-phase peptide synthesis based on a two-dimensional protection scheme. This strategy involves employing an acid-labile temporary [*tert*-butyloxycarbonyl (Boc)] and acid-stable but reductive acidolysis cleavable (Msob, Msz) semipermanent groups. The core structure of the linker is derived from 4-(2,5-dimethyl-4-methylsulfinyl)-4-hydroxybutanoic (DSB) acid. Peptide synthesis is initiated by attachment of the first amino acid to the linker via an ester bond. The stability of the linker was examined by exposure of the resin-bound Boc–Leu–DSB to TFA/anisole for 24 h. As a result, only 3% of Leu was cleaved whereas 94% of Leu was cleaved by reductive acidolysis [[$SiCl_4$—anisole—thioanisole— EDT (10 equiv. each)/TFA]. Recently, a conceptually similar dialkoxyalkylsulfinylbenzhydrylamine (DSA) type of linker **13** has been described by Kiso et al.[18] The stability was again determined by amino acid analysis of Leu cleaved from the resin after treatment with TFA/anisole for 24 h. In this case, the amount of Leu cleaved from the resin was about 9%, suggesting slightly lower stability toward strongly acid conditions. Reductive acidolysis resulted in 95% cleavage of Leu after 3 h. In this context, it should be emphasized that reductive activation pathways seem, in general, to be more practical than oxidative ones, provided the mild reducing agents are used for such activation.

INTRAMOLECULAR CYCLIZATION

Release by cyclization is another valuable approach to linker strategies. For this particular category of linkers, the cleavage mechanism involves intramolecular cyclization, providing often a heterocyclic side product that stays attached to the solid support. The desired compound is then released at the same time into

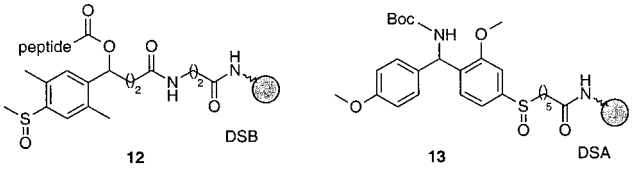


FIGURE 7

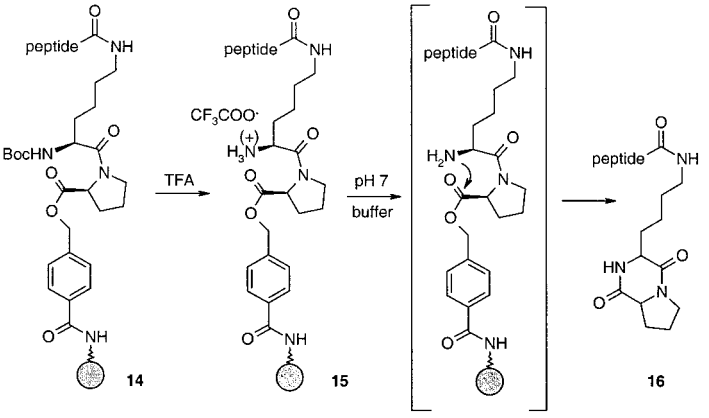


FIGURE 8

the solution. The formation of a five- or six-membered ring provides the driving force for the final cleavage step.

The intramolecular cyclization via diketopiperazine formation has been developed by Geysen and co-workers[19–21] into a method that provides peptide solutions suitable for immediate biological testing. Upon N^{α}-deprotection, linker **14** gives intermediate **15**, which is stable to a protocol designed to remove contaminants from the support-bound peptide before cleavage. Peptide cleavage is then achieved in good yields by treating **15** with a neutral or near neutral buffer to give peptide **16**, which carries a C-terminal diketopiperazine moiety (Figure 8). Recently, Bradley and Atrash[22] have designed a similar diketopiperazine linker, **17**, that after acidic (safety-catch) activation undergoes spontaneous cleavage in buffered (pH 7–8) aqueous media. The diketopiperazine formed during the cleavage remains attached to the solid support while released 4-hydroxybenzyl ester **18** undergoes further 1,6-elimination to give peptide product **19**, accompanied by a stoichiometric amount of quinone methide **20**. Authors have shown that the linker is stable to the base treatment required during (fluorenylmethyl)oxycarbonyl (Fmoc) strategy and is efficiently cleaved in buffered aqueous solution (Figure 9).

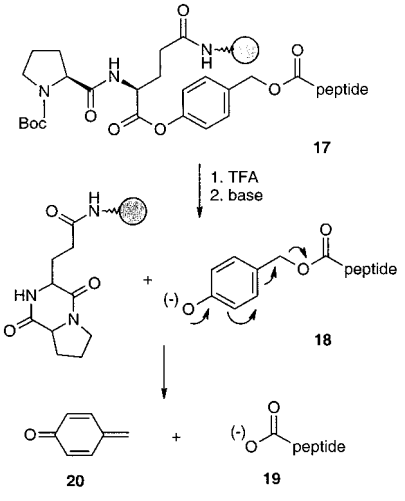


FIGURE 9

PHOTOCLEAVAGE

Photocleavable linkers have been the subject of much interest in recent years since they usually offer an additional dimension of orthogonality. Based on the dithiane-protected 3-alkoxy benzoin tether used by Chen and co-workers in solution synthesis,[23,24] analogous applications for solid-phase synthesis have been reported by Balasubramanian et al.[25] Safety-catch activation of linker **21** can be achieved by treatment with a variety of oxidizing reagents such as bis[(trifluoroacetoxy)iodo]benzene, periodic acid, and mercury (II) perchlorate, the latter being preferred for faster deprotection and higher yields. Photolytical cleavage is accomplished upon irradiation at 350 nm

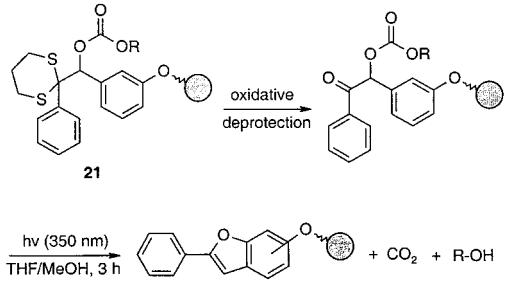


FIGURE 10

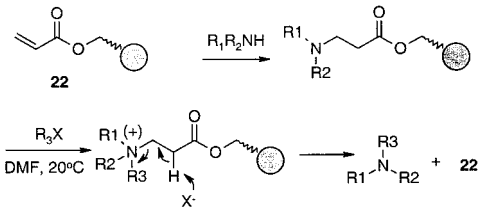


FIGURE 11

in tetrahydrofuran/methanol (3 : 1) for 3 h (Figure 10). As a demonstration of a potential application of this approach, the attachment and subsequent release of cholesterol from the linker was performed on a solid-phase support.[25] Photolysis resulted in release of unmodified cholesterol in 72% yield with a purity $> 95\%$.

FRAGMENTATION BY β-ELIMINATION PROCESS

In order to introduce basic functionality as an inherent feature of exploratory libraries, Rees and co-workers[26,27] have developed traceless REM (regenerated after initial functionalization via a Michael addition) linker **22** that provides tertiary amines (Figure 11). The synthesis is initiated by Michael addition of primary or secondary amines. Quarternization of the tertiary amine introduces an additional point of diversity and activates the linker for the final cleavage. Hofmann elimination is accomplished by treatment with $^{i}Pr_2NEt$ (diisopropylethylamine) at room temperature. Interestingly, the linker is regenerated at the cleavage stage to give resin-bound acrylate ester, available for the next synthesis. The linker was shown to be compatible with esters, anilines, Boc-protected amines, and 50% TFA/DCM for 6 h yielding the tertiary amine products in consistently high purity ($>$95%) even over 5 cycles. Possible limitation includes nonselective alkylation when more nucleophilic nitrogens are present in a molecule. However, although nonselective quarternization may occur, the purity of the final product is not usually reduced as only the ester of 3-trialkylammoniumpropionic acid undergoes the final cleavage.

CLEAVAGE MEDIATED BY NEIGHBORING-GROUP PARTICIPATION

The central feature of the following linker consists in rate enhancement of the ester bond hydrolysis by an intramolecular catalysis established by a properly positioned imidazole moiety. Such intramolecular activation, which presumably involves coordination of a water molecule, has been suggested by Frank and co-workers[28,29] and demonstrated on new linkers **23** and **24**. To reduce basicity of the imidazole ring during the synthesis, the authors conveniently introduced a Boc group into the 1-position of the imidazole ring. Final acidic deprotection of the synthesized peptide simultaneously removes this Boc group and other acid-labile groups, yet maintains the catalytic effect blocked by ring protonation. Upon neutralization to pH $\sim$ 7, the desired peptide product is liberated into the aqueous buffer and becomes immediately available for bioassay (Figure 12). By comparing the reaction rates for both linkers **23** and **24**, the former one was shown to hydrolyze faster (5–7 min at 50°C, pH 7.5) than linker **24**. Both linkers were compatible with Fmoc/^{t}Bu strategy of peptide synthesis.

AROMATIC S_NAR SUBSTITUTION

Quite recently, a new safety-catch linker, **25**, has been described by Hoffmann – La Roche research group.[30,31] This traceless linker strategy involves the use of a 2-thiopyrimidine skeleton that is "activated" by oxidation to the corresponding sulfone. Upon treatment with different nucleophiles, the final products **26** are obtained in high yields and purities. The analogous thio/sulfonyl linkage **27** has been reported later by Suto and Gayo for applications requiring a limiting amount of a nucleophile during the final cleavage.[32] To demonstrate the stability of this linker to common reagents used in solid-phase synthesis, the resin-bound pyrimidine derivatives were subjected to a variety of reaction conditions including saponification, acid chloride formation, ester to alcohol reduction, and Mitsunobu alkylation. After activation with MCPBA in DCM, the desired products were isolated in high yields and purity.

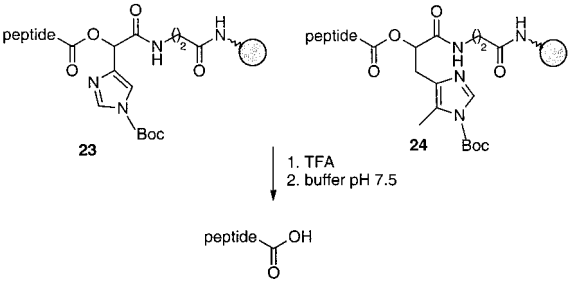


FIGURE 12

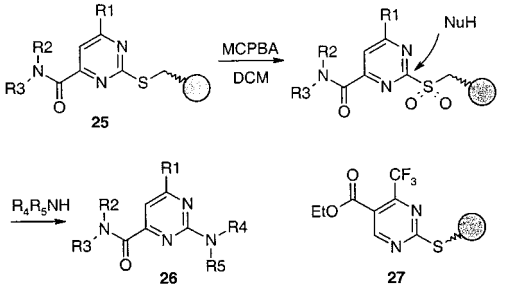


FIGURE 13

The foregoing safety-catch linkers are conveniently summarized in Table I according to the functionality resulting after cleavage.

MULTIPLY CLEAVABLE LINKERS

The application of multiply cleavable linkers is obvious to scientists working with the "one-bead-one-compound" library technique. This elegant method for discovering (biologically) active compounds (drug leads, biological tools, new catalysts, etc.) is based on the synthesis of hundreds of thousands or millions of organic molecules, their screening and determination of structure of the relevant molecule. (Description of this technique was reviewed several times and published elsewhere[33,34]). The multiply cleavable linker allows the release of a fraction of an organic compound load from the individual solid support particle, screening of its activity, isolation of a relevant particle, and confirmation of the activity after the release of the second portion of the compound from the bead. The scheme of the screening process is given in Figure 14. The library is distributed by up to several hundred beads per well into standard 96-well microtiter plates and the first release is performed, generating thus a mixture of up to a hundred compounds in each well. The resulting solution is filtered into a test plate. A biological test is performed and positively reacting wells are identified. The beads from the wells responsible for the biological activity are then individually redistributed into the wells of the microtiter plate, and the second release is performed, now generating a solution of only one compound. After determining which bead was the source of biological activity, the structure of this compound is determined either by the direct sequencing of a compound (peptide) still attached to the bead by the noncleavable linker, or by determining the structure of the appropriate code. An alternative to multiply releasable linkers is the release of compounds from the polymeric carrier after partial cleavage by application of a cleavage reagent that can be delivered in a precise dose. An example of this technique is the application of trifluoroacetic acid vapors[35] to the library synthesized on benzhydrylamine resin. After partial cleavage the library was examined by immobilization of the beads and slow diffusion of released compounds to the surrounding semisolid medium containing melanophore cells expressing bombesin receptor. A partial release by photolysis is the basis of Pharmacopoeia's technology.[36–38] The advantages and disadvantages of various methods of the partial release were discussed previously.[39]

The multiply releasable linkers were originally designed for peptide libraries. During the early development of this technique, the residual functional groups from the linker remaining on a released pep-

Table I Safety-Catch Linkers Arranged by the Resulting Functionality

Resulting Functionality	Linker (**No.**)—[Reference]
Amides	Primary: Kenner's (**1**)—[3]; Dpr(Phoc) (**7**)—[10, 11]; SCAL (**11**)—[15]; DSA (**13**)—[18] Secondary: Kenner's (**3, 4**)—[4, 5]; Dpr(Phoc) (**7**)—[10, 11]; phenyl-sulfide/sulfone (**5**)—[6–9]; (**9**)—[12]; (**14**)—[19–21] Tertiary: Kenner's (**3, 4**)—[4, 5]
Hydrazides	Kenner's (**1**)—[3]
Carboxylic Acids	Kenner's (**1, 3**)—[3, 4]; Dpr(Phoc) (**7**)—[10, 11]; DSB (**12**)—[16, 17]; (**17**)—[22]; (**23, 24**)—[28, 29]
Alcohols	(**21**)—[25]
Aliphatic Amines	Tertiary: REM (**22**)—[26, 27]
Aromatic Amines	Primary: (**27**)—[32] Secondary: (**25**)—[30, 31]; (**27**)—[32] Tertiary: (**25**)—[30, 31]; (**27**)—[32]

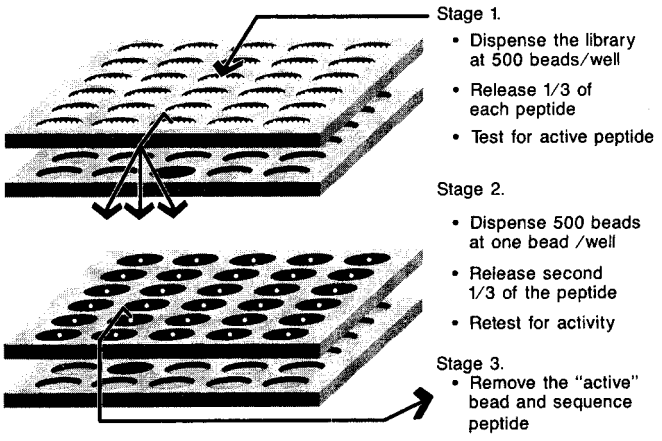


FIGURE 14

tide were not considered to be a critical disadvantage. The general scheme of linker construct **29** allowing multiple release is given in Figure 15. The resin-bound amino groups were branched to produce three independent arms, two of which were used for attaching the test compounds. The third branch linked the compound used for identification, which can be the same compound or a tag encoding the test compound (for coding techniques, see, e.g., Ref. 40–44). Branching the available amino groups allowed to increase the loading of the polymeric beads in order that the amount of compound released in each step was actually identical to the release from the nonmodified bead. Alternative to this approach is the use of a mixture of linkers with different sensitivity to the cleaving agent.[45] In this case, it is difficult to build independently the test and tag compound, and the amount of compound released in each step is lower than the theoretical amount based on the initial resin substitution.

The first generation of multiply cleavable linkers was based on the Glu-Pro motif (Glu provides a side-chain function and Pro enhances the tendency to cyclize) and five independent releases could be realized utilizing selective deprotection of the dipeptide combined with photolytic cleavage and alkaline hydrolysis.[46] The next generations of novel double cleavable linkers were based on the use of iminodiacetic acid (Ida) as a key component.[47] Iminodiacetic

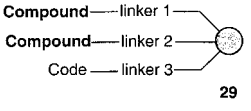


FIGURE 15

acid was found suitable for several reasons: (a) the amino group is in the α-position relative to the carboxyl groups; (b) both carboxyl groups are chemically equivalent; (c) as an *N*-substituted amino acid, it is prone to cyclization via DKP formation with practically any other α-amino acid esters; (d) it is not chiral; (e) it is inexpensive.

Even though the test compounds are attached to two identical (releasable) arms via an ester bond, the cleavage can be accomplished by two unique mechanisms: (i) entropically favored cyclization resulting in diketopiperazine (DKP) formation and (ii) alkaline hydrolysis.[47] In the linker assembly used at Selectide, the compounds were attached to the linker via an ester bond of Fmoc–Gly–NH–$(CH_2)_3$–OH (Fmoc–Gly–HOPA). Upon release into the aqueous solution, the synthesized compounds contained an identical carboxy-terminus, the hydroxypropylamide of glycine (Gly–HOPA).

In general, there are three variations of the Ida-based linker that can be schematically depicted as dipeptides containing Aaa–Ida, Ida–Aaa, or Ida–Ida, where Aaa is any α-amino acid, preferably one that is prone to cyclization via DKP formation. The dipeptide motif Ida-Ida was found particularly suitable for designing double cleavable linkers.[47] The Ida–Ida dipeptide is prone to DKP formation, and it provides three carboxyl groups, one on the amino-terminal Ida and two on the carboxy-terminal. To construct the double cleavable linker, two carboxyl groups are required for the attachment of test compounds, and one carboxyl for anchoring the linker to the resin beads. One possible arrangement of the Ida–Ida based linker **30** and the chemistry of both releases is shown in Figure 16. The linker may be connected to the solid

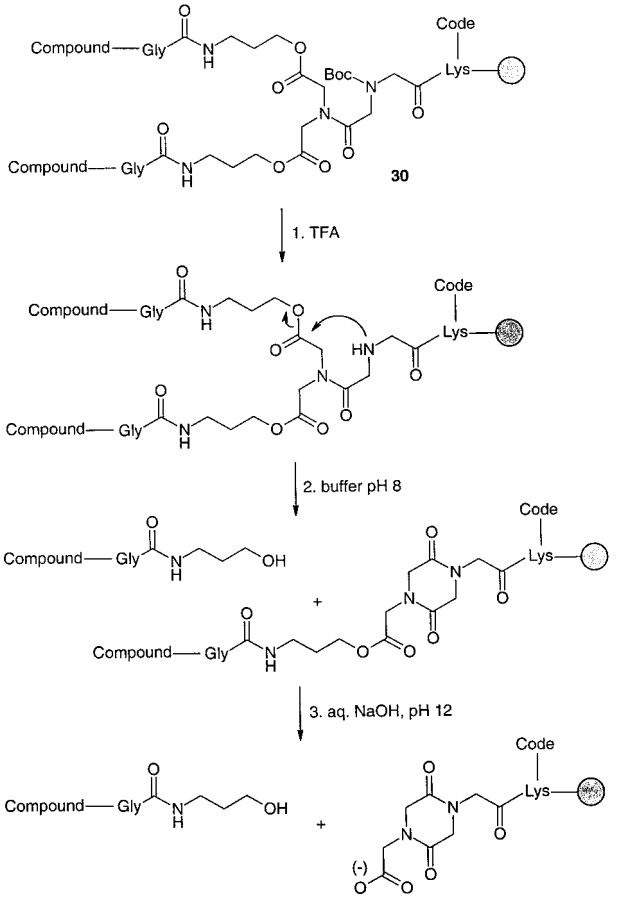


FIGURE 16

support via Lys, which provides one extra amino group for a third, nonreleasable copy of the compound or the tag molecule. Using peptide libraries built on the double cleavable linker, ligands for the anti-β-endorphin antibody and the glycoprotein IIb/IIIa receptor have been identified.[48]

The doubly cleavable linker for the release of alcohols (R = alkyl) is based on the same mechanism (Figure 17) as the release of peptides with carboxy-terminal Gly–HOPA.[49]

It may be desirable to release a compound without the Gly–HOPA and possess a free carboxyl group. A modified linker that incorporates an additional ester linkage was designed[49] (Figure 18). The appended ester bond is introduced into the linker by attaching a hydroxy acid (e.g., 3-hydroxypropylamide of glutaric acid) to both arms of the linker. The first release is accomplished at pH 8 as the DKP formation releases a compound with Gly–HOPA. The beads are then separated from the solution by filtration, the pH is increased to ~13 using aq. NaOH to hydrolyze the ester bond, and the solution is neutralized for biological screening. The second release is performed using NaOH as previously described and directly yields the desired compound with a free carboxyl group.

The practical advantage of this type of linker is that an aqueous buffer for releasing the library compounds is used. The solution of released compounds can be then directly incorporated in a biological assay. The chemical disadvantages are connected with limited chemistry that can be applied during a library synthesis, since the ester bond is labile toward nucleophiles.

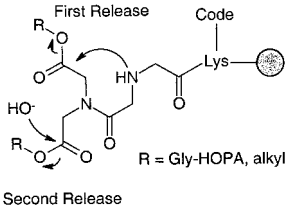


FIGURE 17

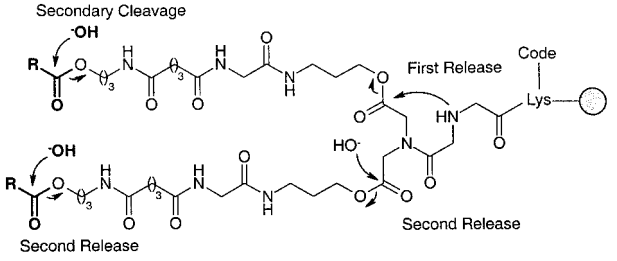


FIGURE 18

CONCLUSIONS

The safety-catch and multiply cleavable linkers are relatively underutilized in the synthetic armamentarium of peptide and solid-phase combinatorial chemists. One of the reasons may involve incompatibility of linkers with a broad spectrum of organic reaction. Another reason may be the relative difficulty in their preparation although some of the linkers are becoming commercially available.[50] (For example, acyl sulfonamide linkers from Calbiochem-Novabiochem Corp. and SCAL linker from CSPS at http://www.5z.com/csps/linker.htm/).

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