Classification System for Solid Supports Used in Solid-Phase Synthesis[1]

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Abstract

Knowledge and sophistication of solid-phase synthesis of small organic molecules has increased dramatically over the last ten years driven mainly by the growth and the demands of combinatorial chemistry. The need for new and sophisticated synthetic methodologies in this area gave rise to a rapidly growing and increasingly complex collection of solid supports. To keep track of these diverse materials and to facilitate searching in available databases, such as the Solid Phase Organic Reactions (SPORE) database[2], we developed a classification system that identifies the polymeric part and, if required, a linker and/or a spacer fragment. Codes for the polymeric part (including some common spacers) consist of four letters and, if the ligand is separated from this material by a linker, the constitution of the linker is expressed through four digits. The classification has the general format of ABCD or ABCD1234. The solid supports are structurally represented as 'generic' molecules in which the polymeric backbone is represented by the pseudoatom "Pol" and the ligand by "R"; this allows searching a database for all reactions in which a given solid support is involved. Functional groups representing the linkages of the individual fragments are recognized and can be used for specifying a query. In this paper we describe in detail the rules developed for this manually applied classification system.

Contents

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1. Introduction

Solid-phase synthesis is now established as a powerful tool for the preparation of combinatorial libraries of small molecules for lead drug discovery.[3a,b] Various specific solid resins, with and without linkers and spacers, have been designed to adapt to varied reaction conditions required for the preparation of target molecules and to the sensitivities of their functional groups.[4a-d] Increasingly, new methodologies applicable to solid-phase syntheses are being developed and with it new solid supports; frequently the use of specifically designed resins determines the synthetic strategy.

From its inception in 1996, reactions in the SPORE database have risen to about 40,000[5], and more than 1,500 different solid supports (>1,000 of which contain linkers) were used in these reactions. Figures 1 and 2 illustrate the steady growth of solid supports registered in the database (in the 1996-2002 period), as measured by the generic structures (*vide infra*) used for their characterization.
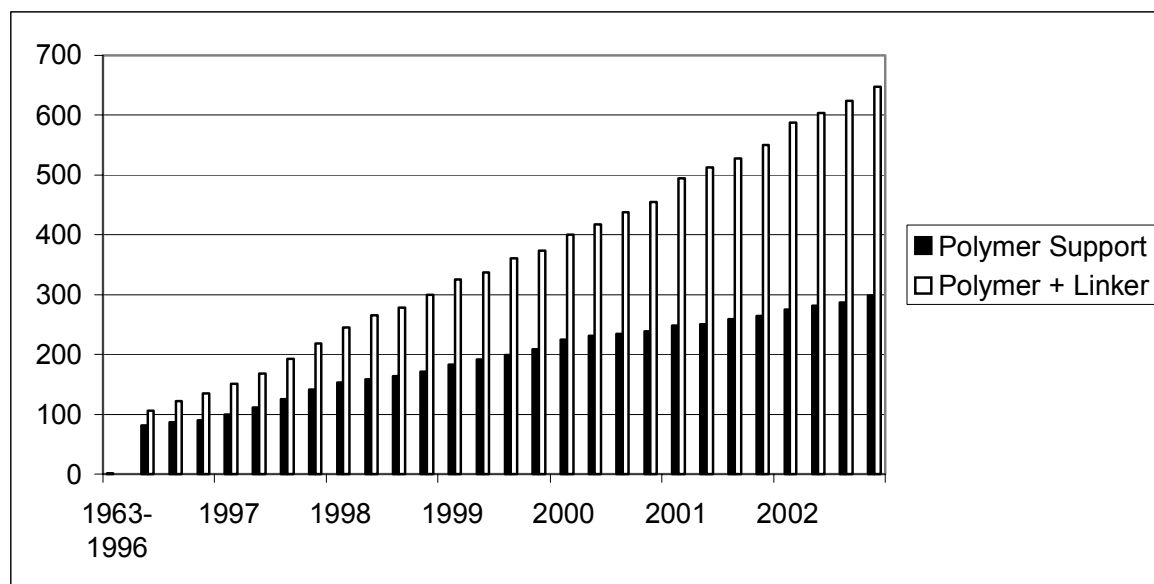
Figure 1. *Increase of different solid supports contained in the SPORE database[5] shown in quarterly intervals from 1996 - 2002.*
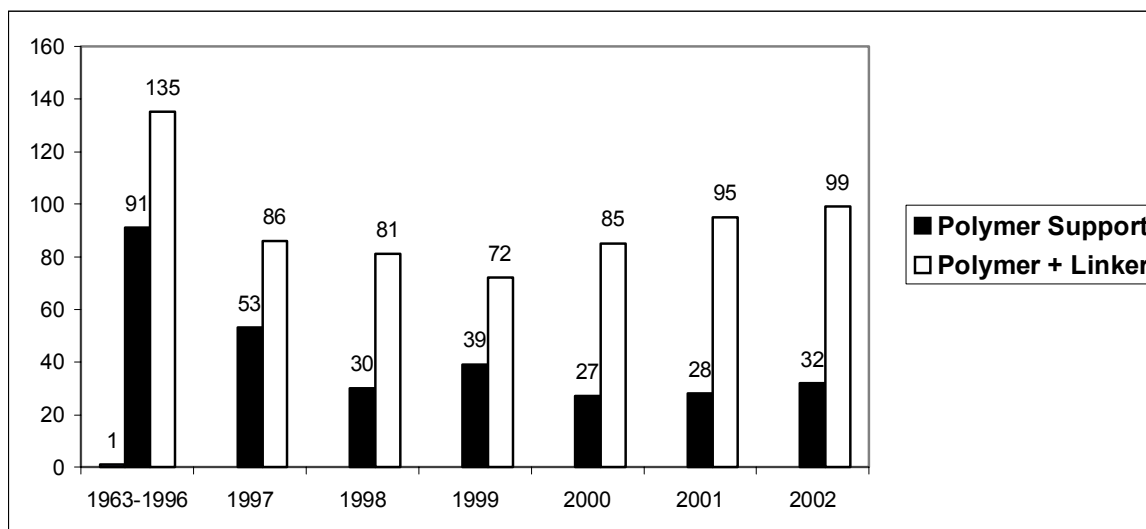
Figure 2. *Number of new solid supports added each year to the SPORE database.*

To facilitate management of solid-support information in the database and to assist users with indexing their proprietary data, we developed a classification system that defines both the individual solid supports and the type of polymer they contain by assigning ID codes to these materials. This classification system was not devised for automatic and unambiguous code assignment to any conceivable type of support, but rather with the aim of creating unique codes for each of the supports used in the database. However, the experiences we have gained during the process of organizing the diverse structural features of solid supports into a coherent overall system may also be of value for any totally systematic approach to rigorously classify the polymeric carriers employed in organic chemistry.

2. General Classification System

Compounds registered in the SPORE database consist of some or all of the components shown in Figure 3. The polymeric part is connected to the linker through the polymer linkage, and the ligand is connected to the linker by the ligand linkage. The linkages are identified in the database as functional group terms, such as 'amide', 'carboxylic ester', 'ether', 'carbamate', etc.
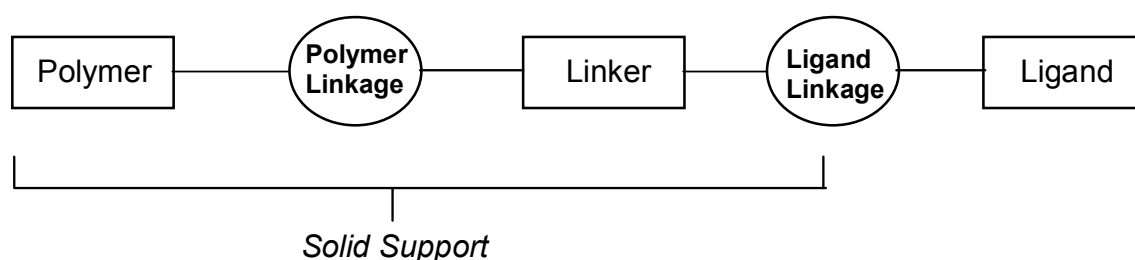
**Figure 3.** *Schematic representation of compounds in the SPORE database*

In the Wang resin-based compound[6] given as an example in Figure 4, the polymer and ligand linkages are 'ether' and 'carboxylic ester', respectively. The solid support part of this compound has been assigned the code PSOX1200 with the four letters describing the polymer (hydroxymethylpolystyrene) and the four digits the linker (p-hydroxybenzyl alcohol). The details of the coding are described below.
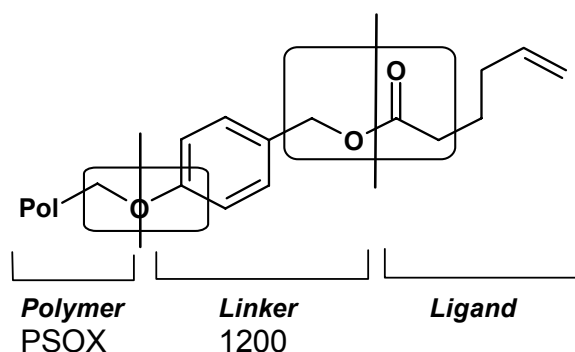
Figure 4. *Schematic illustration of components of a representative compound*

Each polymer and each solid support is stored in the database as a generic-type compound that comprises the particular structure as well as the type of functionalization involved in the neighboring linkage to either the linker or the ligand.

The remainder of the linkage and the ligand or linker attached to this general structure is abbreviated to a generic R-group as shown in Figure 5. This structural representation allows searching by (sub)structure for all reactions in which the particular solid support is attached to a starting material and/or product.


PSOX1200   PSOX
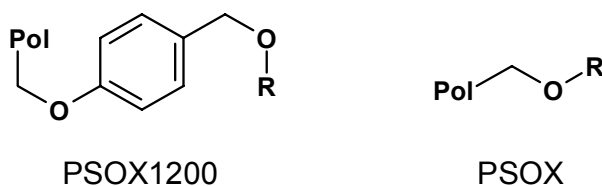
Figure 5. *Structural representations of generic solid supports with and without a linker.*

Many standard synthesis supports, however, do not necessarily contain a linker in the above-mentioned sense, *e. g.* the ester-linked Merrifield resin ("PSOX"; see Figure 5) or the MBHA resin in peptide syntheses. In these cases, polymer and support codes and the generic structures, as well as the polymer and ligand linkage data of a given reaction, have identical entries. Notably, this also applies to some supports of the trityl type, such as the 2-chlorotrityl resin shown in Figure 6[7], which are often regarded as linker-containing supports in the literature. Since there are no separate polymer and ligand linkages, however, these supports have to be regarded as polymers, and not as constructs of a polymer and linker, in our classification system.

PTCX
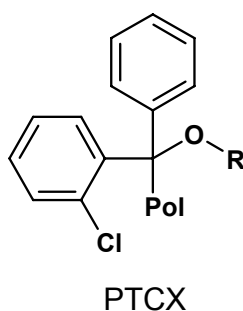
Figure 6. *Generic structure for 2-chlorotrityl resin*

Additionally, ID codes are not assigned if the reaction under consideration describes a functionalization of the polymeric backbone in the absence of a proper 'ligand', as illustrated by the example shown in reaction (1)[8].

$$Pol\frown Cl \;+\; K-C\equiv N \;\longrightarrow\; Pol\frown C\underset{N}{\equiv} \qquad\qquad (1)$$
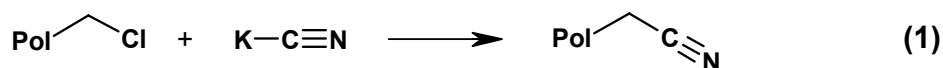
3. The Polymer

In the SPORE database, the term "polymer" comprises both the polymer backbone of a resin and the side-chain extruding from the backbone, up to the point of attachment of the linker or ligand. The codes for the polymers were devised to reflect that concept. Thus, in the polymer code string ABCD, the four characters represent the following elements of the generic polymer:

> A: Polymer backbone specifier
>
> BC: Side chain specifier
>
> D: Additional spacer or "X" for no spacer

The Polymer Backbone Specifier. The first character, relating to the polymer backbone, is linked closely to the structural representations for the different types of polymeric supports commonly used in solid phase synthesis. Initially, we had to select between the varying representations for a given polymer found in the literature. Taking Merrifield resin as the most commonly used polymer support as an example, representations either include or omit the phenyl ring bearing the chloromethyl group. We finally decided to use the most simple representations for the most frequently used structures, *i. e.* to omit the aromatic ring in the case of polystyrene-based supports (see Figure 7).

It should be noted that nearly 80% of all polymer-containing compounds in SPORE are based on polystyrene, another 9% on its PEG-grafted derivatives (TentaGel, ArgoGel etc.). The omission of the phenyl ring had the disadvantage that the benzylic character

of the chlorine or any other substituent was not instantly obvious but, on the other hand, a monovalent "Pol" is roughly equivalent to a "Ph" in our representation of polystyrene-based polymers. Moreover, by using this simple representation, the display is not cluttered and the user can concentrate on the parts of a molecule that really matter, *i. e.* the reaction on the ligand.
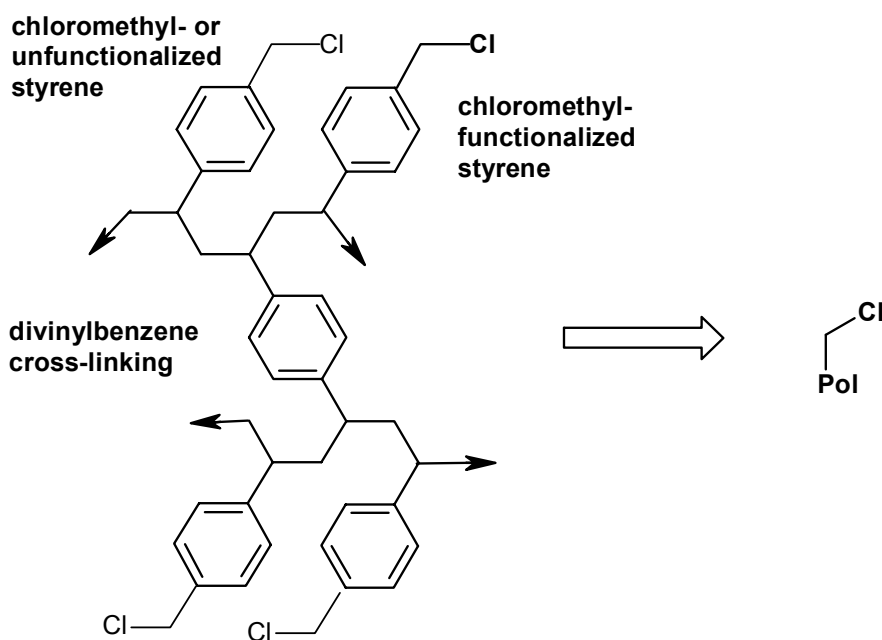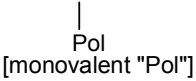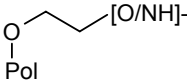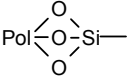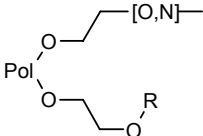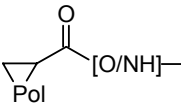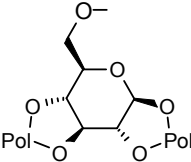

Figure 7. *Full Structure of Merrifield resin and its representation in the SPORE database*

While using only one pseudoatom ("Pol") for all polymers, each type of polymer backbone had to have a distinctive structural representation to allow for structural searches for reactions on a particular polymer and for check routines in the database production. Based on the above-mentioned considerations, polystyrene and its polyethylene glycol-grafted copolymer (the commercial TentaGel or ArgoGel resins) were reduced to the simplest structural representations, whereas less frequently employed polymers were assigned more complex structures roughly describing the polymeric backbone.

These different structural representations and their corresponding polymer codes have proven very valuable as a first filter in searches for a particular polymer type. Currently,

there are 20 different polymer frameworks in the database. The structures of some of the more common polymers are illustrated in Table 1 together with the corresponding backbone specifier of the polymer code.

Table 1. *Structures of polymer backbones in the SPORE database:*

Polymer:	Structure:	Code:
Polystyrene	Pol [monovalent "Pol"]	**P...**
PEG-grafted PS (TentaGel, ArgoGel)	O—[O/NH]- Pol	**T...**
Glass/silica	Pol—O—Si— (with O,O)	**G...**
Polyethylene glycol	Pol—O—[O,N]— O—R—O [R=Me: MeO-PEG]	**E...**

(The "E" group also contains some other soluble polyether supports, such as polyglycerol etc.)

| Polymer:	Structure:	Code:
Polyacryl-type	O, [O/NH]—, Pol	**A...**
Cellulose	O–, Pol–O, O–Pol	**C...**

Further Polymer Backbone Specifiers:
B = PEGA and PEG-MA resins, **D** = Agarose, **F** = Carbon, **I** = Polypyrrole, **J** = Polythiophene, **K** = Dextran (Sephadex), **L** = CLEAR resins, **M** = Polyethylene imine, **N** = Nafion, **O** = POEPOP resin, **R** = ROM polymers, **S** = SPOCC resin, **U** = ChemMatrix/NovaPEG, **V** = other polyvinyl-type resins, **W** = Polyisobutylene.

Since all relevant features of a polymer employed in a particular reaction cannot be included in a structural representation of this kind, the characterization is augmented by textual comments in appropriate reaction datafields. These include, for example, the crosslinking component (other than the standard divinylbenzene crosslinker in the case of polystyrene resins) or additional monomers present in the framework (e.g., in polyacrylamide-type resins), the degree of crosslinking, mesh size, support forms such as in pins, crowns, or lanterns, *etc*. Examples of this kind of information are shown in Table 2.

Table 2. *Additional information about polymers in reaction datafields[9a-d]*

Generic Structure of the Polymer: *(Polymer Code: PSNX)*
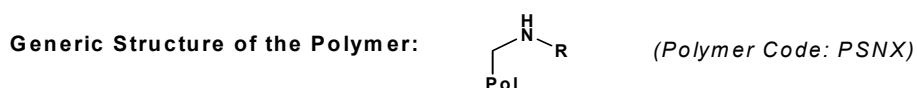
Polymer Name(s):	Polymer loading:	Polymer data:
2% crosslinked polystyrene PS aminomethylpolystyrene Merrifield resin	1.9 mmol/g	200-400 mesh
highly crosslinked polystyrene (ArgoPore) PS aminomethylpolystyrene	0.70 mmol/g	
SynPhase PS lanterns (D-series) PS aminomethylpolystyrene lanterns	35 umol/lantern	
4% TTEGDA-crosslinked polystyrene TTEGDA-PS aminomethyl-(TTEGDA-PS)	0.2 mmol/g	200-400 mesh

The Side Chain Specifier. The second and third characters of the polymer code define the side chain extruding from the polymer backbone. The second character was devised to create classes of polymer supports with similar side chains. (it may also be applied differently, however, in certain cases). The third character has no special meaning in most classifications, unless when indicating the terminal atom of the side chain, such as N, O, or S. The second letter chosen for a particular class is meant to serve as a mnemonic where applicable to provide an instant indication of the type of structure

described by the code. A list of the current[5] entries and their association is given in Table 3.

Ambiguities exist as a look at the entries will show. For example, a long keto-side chain may be F, K, or L, and aminopropyl-functionalized glass may be G or P. A rigorous classification, though possible, is not very practical since the system grows continuously and new, unforeseen entries must be assigned to one or the other group.

Table 3. *Entries for the side-chain type (2nd character of the polymer code)*

|	
A = Anionic or polystyrene-S/Se/Te	**N** = Non-methylated PEG
B = Benzhydryl Type	**O** = Oxygen(PEG)-spacer chain
C = Cationic	**P** = Propylamino, POEPOP, PEGA, etc.
D = Dendrimers	**R** = Rare elements in supports
E = Ethylenediamine chain	**S** = Standard O/N/S derivative
F = Functionalized chain	**T** = Trityl-type resins
G = Glass functionalization/polyglycerol	**U** = Unsual Functionalities
H = Hexamethylenediamine chain	**V** = "Verge-modified" polymers
I = Silyl functionalization	**W** = Linker-type supports without
K = Keto/carbonyl group	a "real" polymer linkage
L = Longer carbon chain	**X** = Bifunctional chains
M = MPEG or MBHA	**Y** = Miscellaneous

Any classification only makes sense when there are at least two species with similar properties. One also has to consider that many side chain variations exist among the >450 polymeric supports currently[5] registered in the database. Given the present system some particular codes invariably will turn out to be more useful than others as exemplified in Table 4.

The first three molecules shown in the first row in Table 4. represent standard Merrifield-type resins, indicated by the first two characters (PS) of the code. The third letters stand for O, S and N functionalization at the terminal of the side chain. The other two examples represent other standard resins with simple amino functionalization. In all these cases the third character could also be considered a mnemonic. The second row contains PEG supports, with the second letter M indicating polyethylene glycol monomethyl ether (MeO-PEG, MPEG) and the letter N bifunctional polyethylene glycol. Examples of trityl-type polymers (PT codes), including fused-ring systems are shown in row three. The fourth row contains less specific solid supports with longer carbon side chains (code = "L").
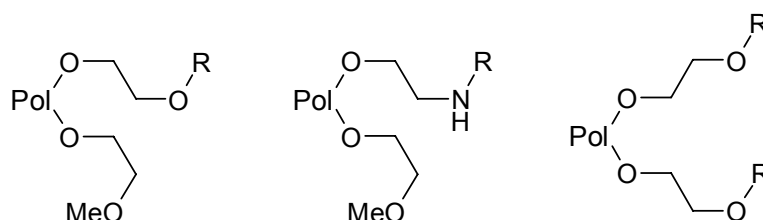
Table 4. *Examples for polymer codes and associated structures.*
"Reactions A": Number of reactions[5] in the database in which the solid support consists of polymer and linker.
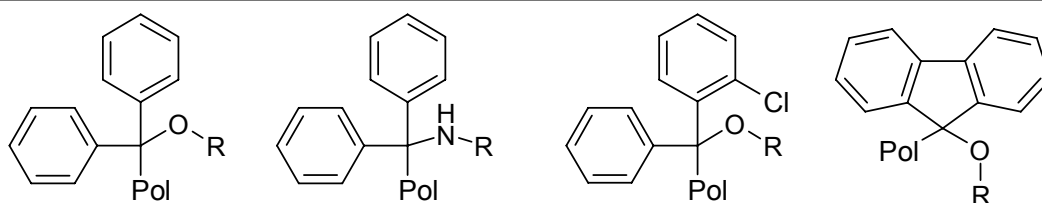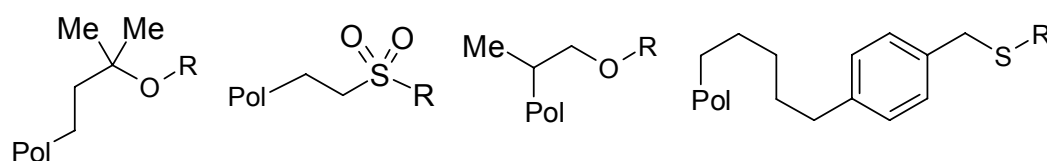*"Reactions B": Number of reactions[5] in which the polymer is directly attached to the ligand*
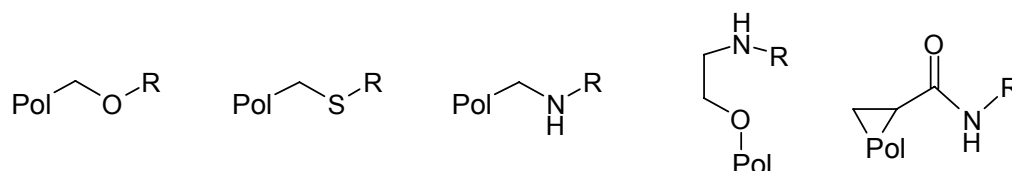
CODE	PSOX	PSSX	PSNX	TSNX	ASNX
Reactions A	12046	244	3160	987	5
Reactions B	2422	444	615	160	9

CODE	EMOX	EMNX	ENOX
Reactions A	209	22	238
Reactions B	463	54	691

CODE	PTRX	PTSX	PTCX	PTUX
Reactions A	18	0	39	0
Reactions B	392	393	605	6

CODE	PLAX	PLDX	PLCX	PLPX
Reactions A	0	0	0	0
Reactions B	20	15	26	8

4. The Linker

The term "linker" is often applied in the literature to the starting material of a solid-phase synthesis prior to the attachment of a ligand. For the purpose of our classification, however, the linker is defined as the structural fragment imbedded between polymer and ligand after attachment of the latter. For example, as shown in Figure 8, an amino-functionalized support can be obtained by nucleophilic substitution reactions of different substrates, or by reductive alkylation of an aldehyde.
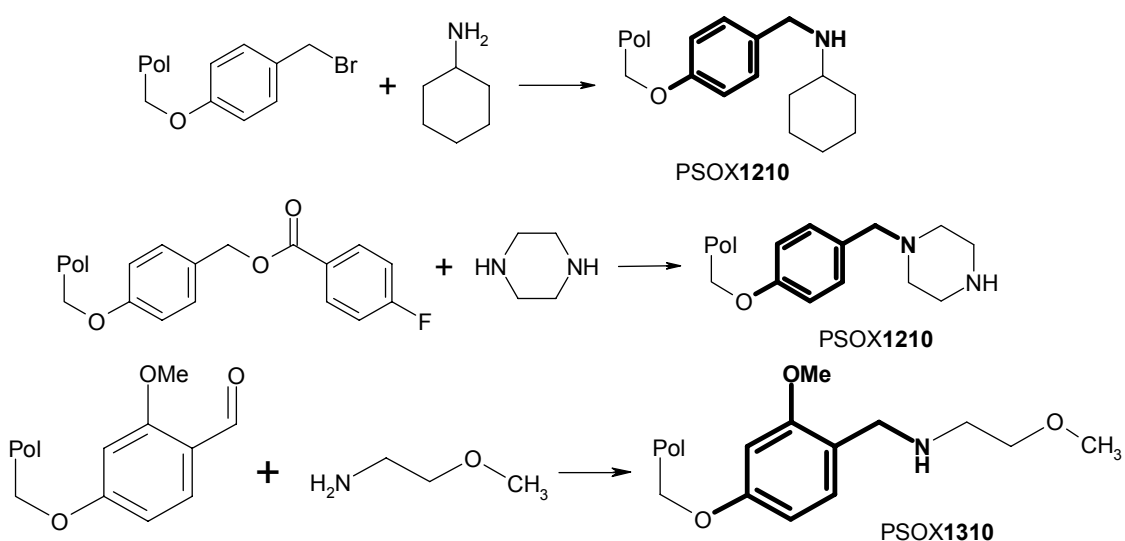
Figure 8. *Amino-functionalized solid supports obtained by different methodologies. The linker fragment is indicated by bold bonds and atoms[10a-c]*

In our classification of a linker, the code consists of four digits. Appropriate codes were devised not with the aim of classifying the multitude of possible chemical structures based on existing systems or algorithms, but rather by taking into account those structural elements that were known to occur in linkers used in solid-phase chemistry.

The first of the four digits divides the different linkers into several groups according to their general structure (acyclic, aromatic, alicyclic, heterocyclic), the second digit is based on the functional groups of the linker, while the third and fourth digit are used for consecutive numbering of individual structures. The specific meaning of the first and second digit is displayed in Tables 5 and 6.
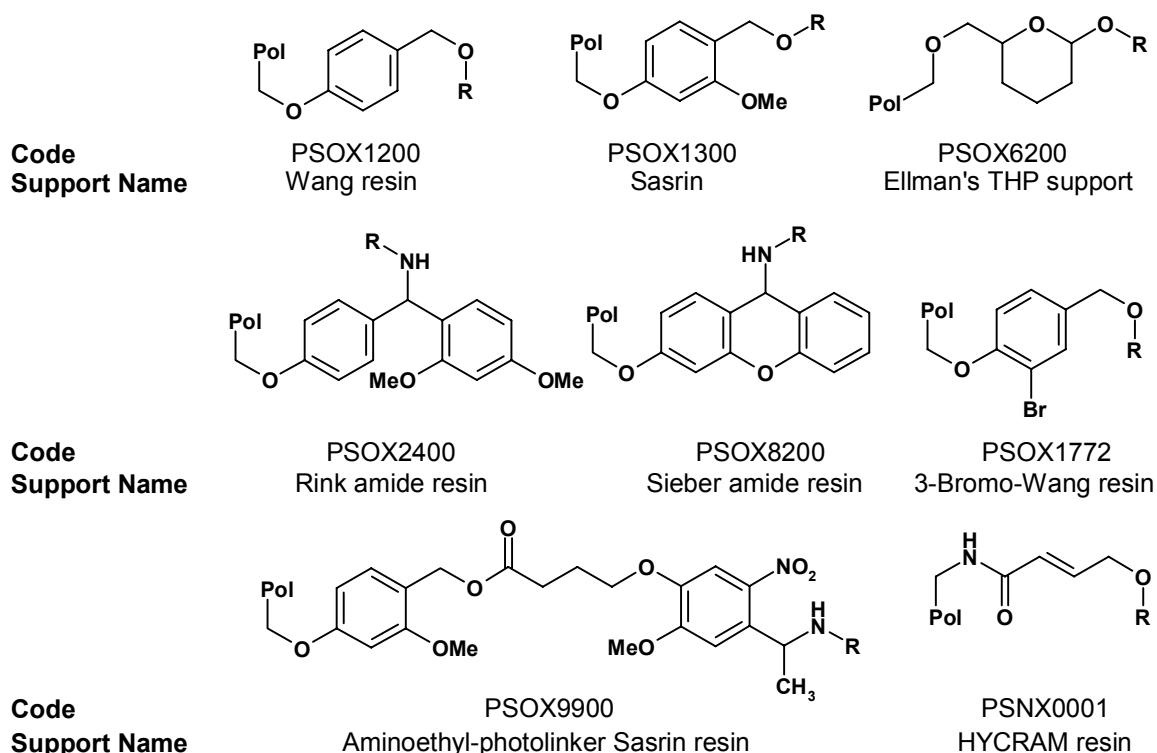
Table 5. *First digit of the linker code: General structural classes*

      0 = Acyclic linkers
  1-3 = Linkers with 1-3 phenyl groups
    4 = Linkers with 4 or more phenyl groups
    5 = Other carbocyclic linkers
    6 = Monocyclic achiral heterocyclic linkers
    7 = Chiral heterocyclic linkers
    8 = Polycyclic achiral heterocyclic linkers
    9 = Special (*e.g.* multi-linker) systems

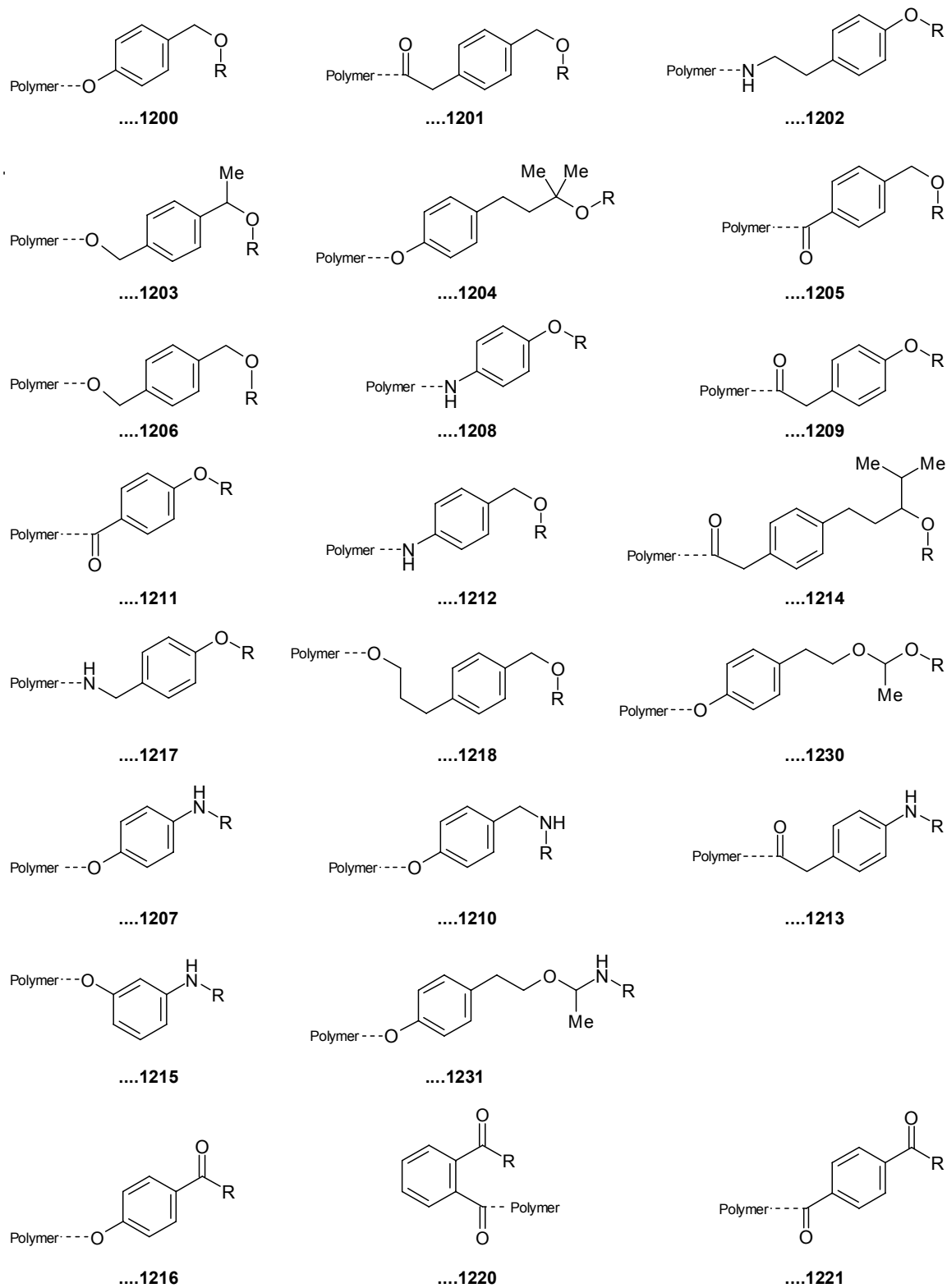**Table 6.** *Second digit of the linker code: Functional groups*

    0 = "Unusual" C/N/O functionalities
      (e.g. NH-NH, N(OMe), oxime, olefin, allyl ether, etc.)
  1-5 = Number of standard N/O functionalities
      (i. e., amine, amide, ketone, ester, ether, acetal)
    6 = 6 or more standard N/O functionalities
    7 = "Rare" linker atoms (such as Si, P, Ge, Bi, Se, halogen)
    8 = Sulfur functionalities
    9 = Nitro groups

Some features of these assignments deserve further comment. Many linkers, *e. g.* those of the Wang or Rink type, consist of phenyl ring systems and amide, ether, or ester functionalities; any other type of basic structure or functionalization is less common. Accordingly, we started by fine-tuning these most frequent elements. Leaving sufficient room for unique code assignments to these structures, we created subdivisions of this large group of structures. The number of phenyl rings and standard functional groups were used as first criteria for classification. Other categories were then added to cover the complete range of possible structures, again taking into account the frequency with which they occur in presently known linker structures. Some examples for the application of this system to several common supports are given in Figure 9.

| Code | PSOX1200 | PSOX1300 | PSOX6200 |
| Support Name | Wang resin | Sasrin | Ellman's THP support |

| Code | PSOX2400 | PSOX8200 | PSOX1772 |
| Support Name | Rink amide resin | Sieber amide resin | 3-Bromo-Wang resin |

| Code | PSOX9900 | PSNX0001 |
| Support Name | Aminoethyl-photolinker Sasrin resin | HYCRAM resin |

Figure 9. *Examples for linker codes and associated structures*

To illustrate the type of structures belonging to a single subgroup, 23 of the linkers assigned to group 1200-1299 (this group currently[5] comprises 37 linkers) are shown in Figure 10. The polymeric part has been generalized in the structures to highlight the linker portion and only the linker part of the code is shown (in conjuction with different polymer components, the group of 37 linkers currently[5] comprises 116 different solid supports). In accordance with Tables 5 and 6, the linkers always incorporate one phenyl group (1st digit = **1**) and two functional groups (2nd digit = **2**). The fact that the diversity and number of linkers described in the literature is large and growing (see Figures 1 and 2) is borne out by the numbers found in the database. Presently[5] there are >1,500 different solid supports (including ca 460 polymer supports without linkers) containing ca. 720 different linkers, as compared to early 1997 when the numbers where 280 and 125, respectively.

....1200

....1201

....1202

....1203

....1204

....1205

....1206

....1208

....1209

....1211

....1212

....1214

....1217

....1218

....1230

....1207

....1210

....1213

....1215

....1231

....1216

....1220

....1221

Figure 10. *Linkers in group 1200-1299*

5. The Spacer Problem

Even though the schematic representation of the individual components of a solid support, as given in Figure 3, looks simple enough, it is often difficult to distinguish between the "polymer" and "linker" part of a molecule.

To determine the codes of individual generic supports based on their structure, three points of reference are required:

        1.) the branching point of a side chain from a given polymer backbone,

        2.) the site where the polymer connects to the linker (polymer linkage), and

        3.) the site where the ligand is attached to the linker (ligand linkage).

The relevance of these criteria for code assignment and some of the inherent problems are illustrated through examples shown in Figure 11.[11a-c] The determination of the branching point of a polymeric side chain has been discussed previously (see Section 3, The Polymer); here we will describe the remaining two points.

Determining the site of the ligand linkage is usually straightforward and in most cases can be easily accomplished by looking at the reaction in which the ligand is cleaved from the support. In order to define the terminal functionality to be used for the generic description of linker structures, we decided to include only the heteroatom on the linker side of the ligand linkage. For the most common linkages, for example carboxylic ester, ether and amide, these structural fragments are oxygen (or carbonyl), oxygen, and nitrogen (or carbonyl), respectively. The application of this principle to the first two examples in Figure 11 results in a thioamide or amide as the ligand linkage and the functionalization NH-R in the generic support structures. At first glance, the third example would also seem to belong to that group. However, the ligand was actually cleaved from the support by nucleophilic substitution at the sulfonate group (see Eq. 2)[11]. Accordingly, the sulfonylphenoxyalkyl moiety must be included in the linker structure leading to a multi-linker system with multiple cleavage sites.
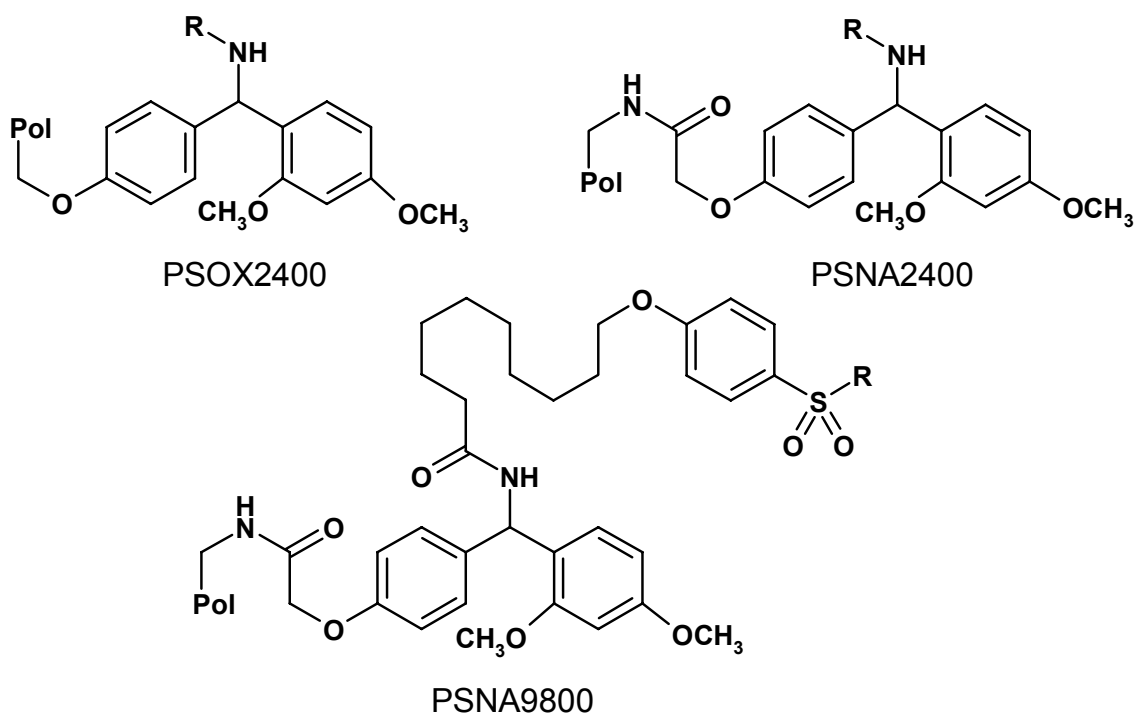
Example 1
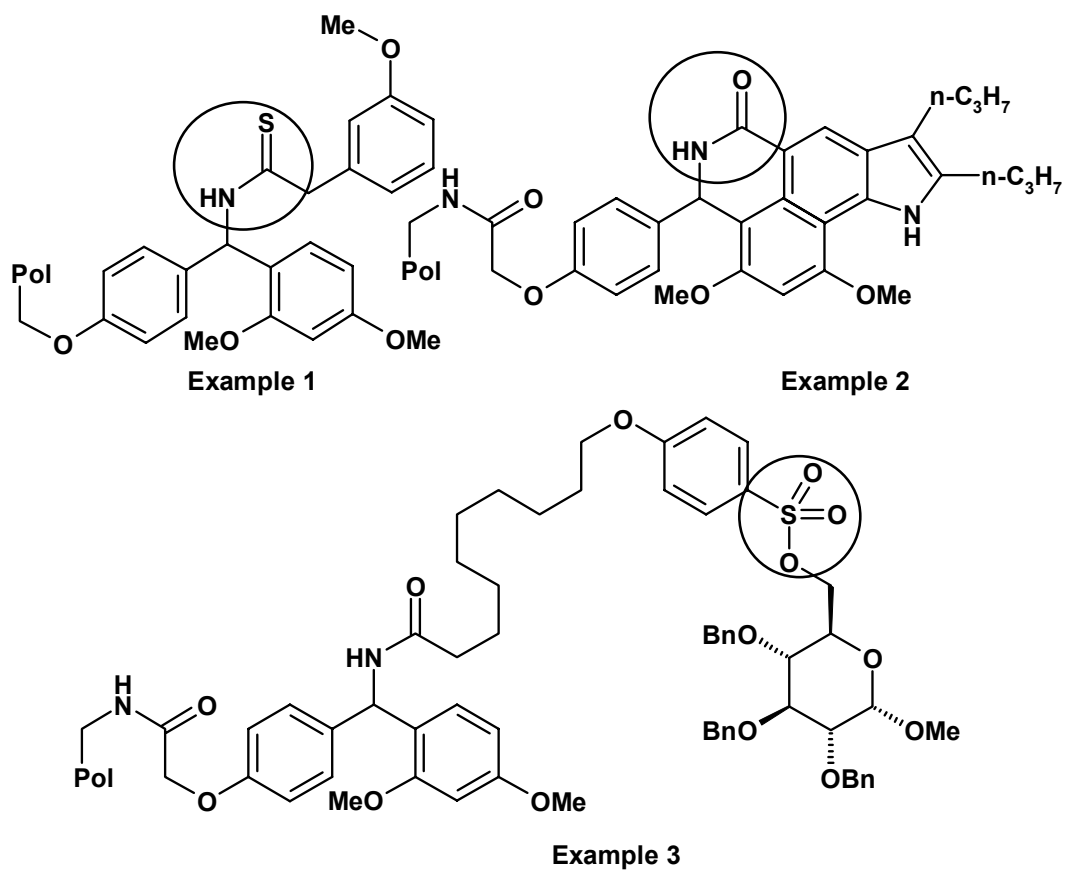
Example 2

Example 3

Figure 11. *Examples for the determination of ligand linkages*

$$ (2) $$
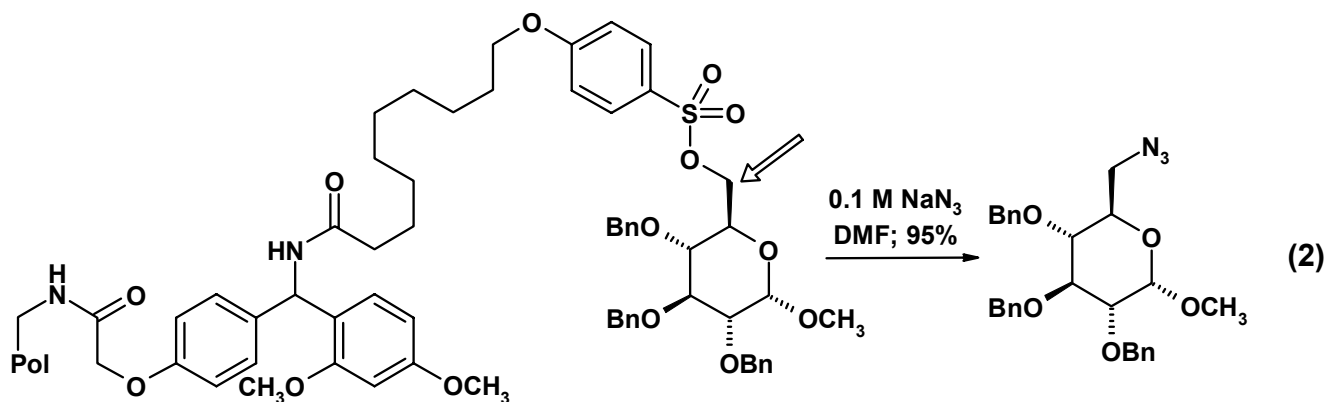
On the basis of these considerations, the three examples shown above are derived from the three generic supports shown in Figure 12.

PSOX2400

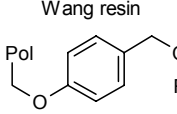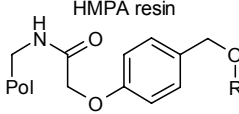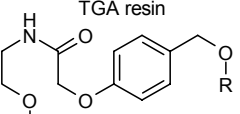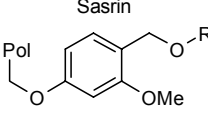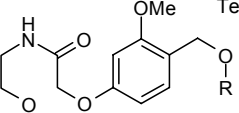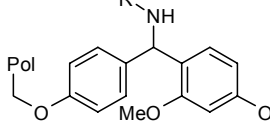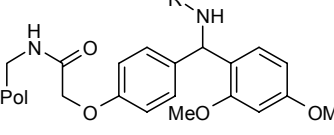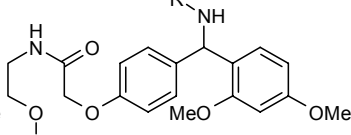**PSNA2400**

PSNA9800

Figure 12. *Generic structures for examples 1-3 in Figure 11*

To complete the classification, the site of the polymer linkage has to be determined. This last step is often problematic. While the ether linkage in the first example in Figure 12 is unambiguous, determination of the linkage in the other two structures is less straightforward. Considering the ether bond as the polymer linkage, the oxyacetyl (glycolyl) group would be included in the structure of the polymer and all three linkers would encompass the basic "Rink-type" structure. If, however, the amide group is taken as the polymer linkage, the linker structure would have to be modified with an additional oxyacetyl group . Both concepts are found in the literature, as evidenced by the different terms "Rink amide AM resin"[12] and "Knorr resin"[13] assigned to supports corresponding to Example 2. We selected the ether functionality as the polymer linkage, thereby regarding both example 1 and 2 as "Rink-type" supports with an identical linker code (2400).

To be able to do this, we employed the fourth character of the polymer code as the "spacer character" to describe common structural groups located between polymer support and linker. Selecting the letter "A" to define the oxyacetyl moiety, we thus arrived at support codes PSOX2400, PSNA2400, and PSNA9800 for the three generic

structures shown in Figure 12. These codes still distinguish between the simple Rink resin (**…X2400**) and the oxyacetyl-modified Knorr support (**….A2400**). The oxyacetyl moiety is a component of several standard solid supports, often co-existing with their corresponding ether-linked counterparts. Some examples are shown in Table 7.

Table 7. *Ether- and Oxyacetyl-amino-linked Supports*

In addition to the oxyacetyl moiety, usually employed to connect oxy-functionalized linkers with amino-functionalized polymers, a large number of structurally diverse bifunctional molecular fragments inserted between polymer and linker can be part of the solid support. Some of these fragments may already be represented by the first three letters of the polymer code, for example in the generic structures POHX and POBX shown in Figure 13.
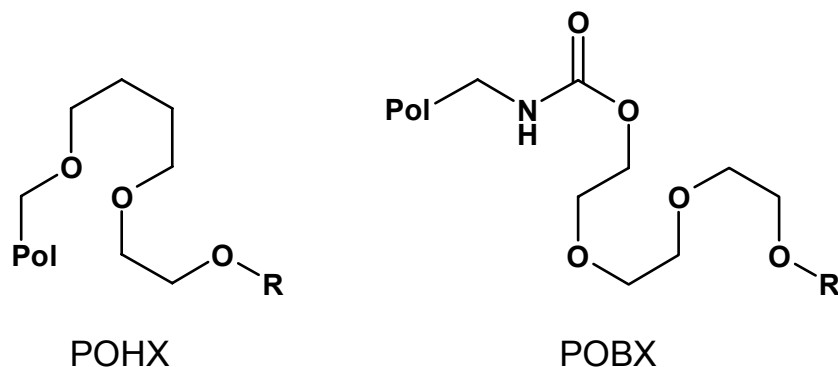
Figure 13. *Polymer supports with no spacer moiety according to Table 4*

In our definition there are only two other groups of spacers in addition to the oxyacetyl group, where the individual members are distinguished by the fourth letter in the polymer code. One of these are dicarbonyl chains, most notably succinyl, which can be used to couple oxy- and/or amino-functionalized polymers and linkers or ligands. Members of this group are often regarded in the literature[14] as "linkers" in themselves, usually in oligonucleotide synthesis. Since they are also used as spacers between polymer and linker, however, we invariably treat them as spacers for reasons of consistency. Thus, the commonly used DNA synthesis support succinyl-LCAA-CPG has the support code GGNS as a polymer support without linker.

The other group of structural fragments treated as spacers consists of amino acids incorporated between polymers and linkers, serving either as connecting units or as reference compounds for analysis. The complete list of structures we regard as spacers is shown in Table 8 and some examples of spacer-containing supports are given in Figure 14.

Table 8. *Fourth letter of the polymer code: Spacers*

**A** = Oxyacetyl (glycolyl)

Amino acids:

B = Beta-alanine
C = 6-Aminocaproyl
E = Isoleucine
F = (free for other amino acids)
G = Glycine
I = Isonipecotic/aminoisobutyric acid
J = Sarcosine
K = Lysine
L = Leucine
M = Alanine
N = Norleucine
P = Phenylalanine

Dicarbonyl chains:

Q = Oxalyl (CO-CO)
T = Malonyl (CO-CH$_2$-CO)
S = Succinyl (CO-CH$_2$-CH$_2$-CO)
R = Glutaryl (CO-(CH$_2$)$_3$-CO)
H = Adipoyl (CO-(CH$_2$)$_4$-CO)
D = Diglycolyl (CO-CH$_2$-O-CH$_2$-CO)

X = No spacer

U/V/W/Y/Z = Reserved for special cases

TSNC1770

PSNG1701

PSNN0815

PSNU1204

GGNR

GGNS5203
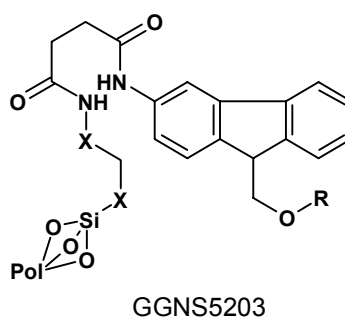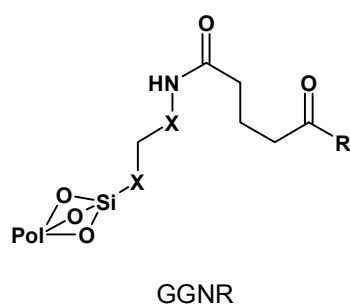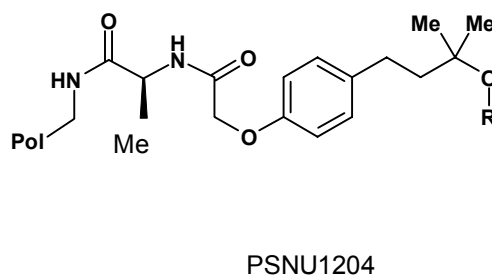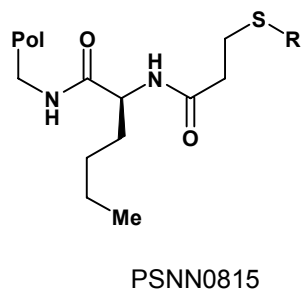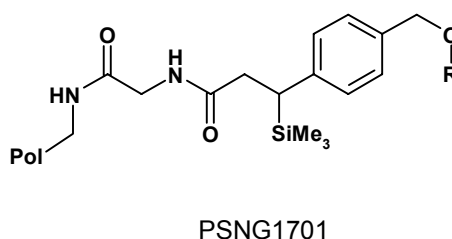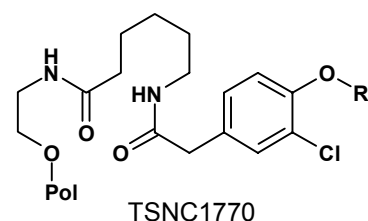
Figure 14. *Examples for applications of the spacer code*

6. Conclusion

We have developed a classification system by which codes of four or eight characters are intellectually assigned to solid supports. The initial four letters of the code represent the polymeric material and the four subsequent digits describe the constitution of any linker fragment, if present. This system provides an efficient way to classify new solid supports and the codes have been used successfully for searching and for clustering existing ones in the SPORE database.

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[1] Presented in part at the 27th National Medicinal Chemistry Symposium in Kansas City, MO, June 13 – 17, 2000, **B-27**.

[2] SPORE had been developed jointly by FIZ CHEMIE Berlin and MDL Information Systems, and is now produced by FIZ CHEMIE and marketed by Symyx Technologies.

[3] a) Dolle, R. E. Comprehensive Survey of Combinatorial Library Synthesis: 2001. *J. Comb. Chem.* **2002**, *4*, 369-418, and references cited therein; b) Felder, E. R.; Poppinger, D. Combinatorial Compound Libraries for Enhanced Drug Discovery Approaches. *Adv. Drug. Res.* **1997**, *30*, 111-199.

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[5] All figures refer to the SPORE database produced in August 2008

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[12] *Novabiochem 2002/3 Catalog,* pp.189, 241.

[13] *Advanced ChemTech Handbook of Combinatorial, Organic & Peptide Chemistry 2003-2004*, p.117.

[14] For example: Pon, R. T.; Yu, S. Efficient and Rapid Coupling of Nucleosides to Amino Derivatized Solid-Phase Supports. *Synlett.* **1999**, 1778-1780.