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CHEMISTRY AND HUMAN HEALTH DIVISION
MEDICINAL CHEMISTRY SECTION*
COMMISSION ON NOMENCLATURE AND TERMINOLOGY†

GLOSSARY OF TERMS USED IN COMBINATORIAL CHEMISTRY

(Technical Report)

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Glossary of terms used in combinatorial chemistry (Technical Report)

INTRODUCTION

The development of combinatorial chemistry has generated a wide variety of new concepts and much associated terminology. In addition, the nature of research in this area has brought together scientists from diverse backgrounds: statisticians may discuss their work with biologists and heterocyclic chemists; medicinal chemists are talking to engineers, analytical chemists and polymer scientists. In recognition of the potential for confusion and lack of communication in this field, the International Union of Pure and Applied Chemistry (IUPAC) convened a Working Party (within the Division of Human Health, Medicinal Chemistry Section) to attempt to capture and define the terminology at the interface of these endeavours. The following Glossary is the result of their efforts. It is hoped that it will provide a resource for those new to the area encountering terms for the first time, and, perhaps, will increase the clarity of communication between more experienced workers in the field.

The Glossary is not intended as a comprehensive review or encyclopaedia of combinatorial chemistry, although occasional attempts have been made to broaden the scope beyond a strict dictionary-type definition of terms by providing illustrative examples of some terms, and directing readers to literature sources where appropriate. These references have not necessarily been chosen to attribute credit for the discovery or invention of a term; rather they should provide the most pertinent information for the topic. Ideally, this will be an article or review with the Glossary term as its central theme, in which proper accreditation for the seminal contributions to that area may be found.

Because of the intrinsic interdisciplinary nature of this area of research, it has not been possible to provide a comprehensive coverage of each of the sub-fields, neither has this been the intent. Rather, it has been attempted to identify those elements which are particularly pertinent to combinatorial chemistry. Thus, in the analytical sciences, 'magic angle spinning' gains an entry, whereas 'mass spectrometry' does not. The interested reader will readily be able to find more detailed treatments of these specialized areas.

Trademarks have been included where, in the judgement of the authors, their use has become sufficiently widespread that they often do not receive appropriate citation; the implicit assumption being that the reader will understand what is meant. This criterion has been adopted over one of inclusiveness, which would rapidly become extreme in many areas

In a field which is developing as rapidly as combinatorial chemistry, a document such as this Glossary may soon require revision. The authors welcome suggestions for new terms, clarifications, references and other comments which will aid in the development of this resource.

Notes: Italicized words within individual definitions refer to other entries in the Glossary where further information is available.

The 'bead' symbol is used in illustrations to indicate a particle of insoluble material, such as a polystyrene bead.

This simplified representation does not attempt to describe the chemical linkage to pendant functional groups (such as the primary amine in the example above). The reader is directed to the cited literature for more detailed information.

Analytical Construct: Tool for development of chemistry on a *solid support* whereby the desired compound is prepared in a form which facilitates analysis. This may be achieved by the insertion of an additional *orthogonal linker* between the solid support and the standard linker, thus allowing release of the linker-bound compound at any desired point in compound assembly [1–3].

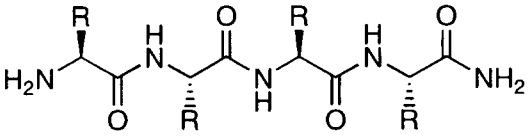
Aptamer: Oligonucleotide which displays specific binding to a protein or other target, often selected by an iterative cycle of affinity-based enrichment [4–6]. See also *SELEX*.

ArgoGel: (Trademark of Argonaut Technologies, San Carlos, California, USA). *Beaded solid support* with a *crosslinked* polystyrene core and grafted linear *poly(ethylene glycol)* (PEG) chains with terminal functional groups [7].

Array Synthesis: Form of *parallel synthesis* in which the reaction vessels are maintained in a specified spatial distribution, e.g. the wells of a 96-well plate or *pins* held in a rack [8–10].

Assay Equivalent: An aliquot of a *library* which will allow the library to be screened in a single assay. Particularly applicable to libraries prepared by *split/pool* procedure, where it pertains to the number of particles required to sample a library. Generally consists of a specified number of *library equivalents*. For statistics related to this, see [11].

Backbone: A *scaffold* of approximately linear configuration. Thus in the *generic structure* of a tetrapeptide shown below, the repeating polyamide core structure (everything except for the R groups—see *Residue*) constitutes the backbone.



Bead: (Normally spherical) particle of *solid support*.

Biased Library: See *Directed Library*.

Binary Code: Relationship between a set of *tags* and their corresponding ligands where *building block* identity is denoted by the presence or absence of a given *tag* or set of tags (i.e. the two 'bits' 1 and 0). Compare quantitative or *Ratio Coding* [13].

Binning: Approach to classifying the diversity of a set of compounds by grouping related members in 'bins' on the basis of common physical or structural features. Commonly applied to the analysis of a set for the completeness of coverage of the desired *property space* [12].

Building Block: One of a number of interchangeable reagents which can be used in *combinatorial library* synthesis, part of the structure of which becomes incorporated into the final product, i.e. its *residue*. See also *Diversity Reagent*.

Capacity: The amount of material which may be attached to a support. May be greater than *loading* due to, for example, steric effects at the solid surface.

Chemset: A collection of two or more library *members*, *building blocks* or reagents; preferred notation in the *Journal of Combinatorial Chemistry* [14] and convenient for describing synthetic procedures on pools of compounds. Thus 'chemset **3**{1–3} denotes three members of the library produced by the reaction of reagents **2**{1–3} with starting material **1**'.

Cleavage: Process of releasing a compound from a *solid support*, thereby permitting assay or analysis of the compound by solution-phase methods. Dissolution of the compound following cleavage, rather than the cleavage step itself, may be rate-limiting.

Cluster: Group of compounds which are related by structural or behavioural properties. Organizing a set of compounds into clusters is often used in assessing the *diversity* of those compounds, or in developing SAR (structure–activity relationship) models. See also *Principal Components Analysis*, *Binning* and *Recursive Partitioning* [15–17].

Combichem: See *Combinatorial Chemistry*.

Combinatorial: '**1**. of, relating to or involving combinations; **2**. of, or relating to the arrangement of, operation on and selection of discrete elements belonging to finite sets.' (*Webster's Collegiate Dictionary*)

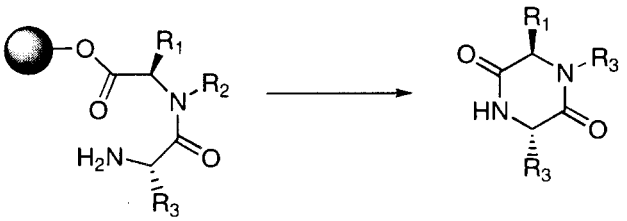
Combinatorial Chemistry: Using a *combinatorial* process to prepare sets of compounds from sets of *building blocks*.

Combinatorial Library: A set of compounds prepared by *combinatorial chemistry*. May consist of a collection of *pools* or *sub-libraries*. Its composition may be described by the *chemset* notation.

Controlled Release: See *Partial Release*.

Crosslinking: Property of a *solid support* prepared from polymeric materials with interconnected strands. Often results from the inclusion of multifunctional monomers in the polymerization reaction, e.g. divinylbenzene in polystyrene production. In such cases, the degree of crosslinking is often quoted as the proportion of the multifunctional monomer in the reaction mixture. The extent of crosslinking is important for physical properties of the solid support, such as the propensity to swell in different solvents [18].

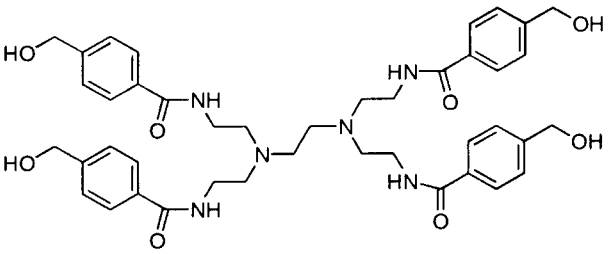
Cyclative Cleavage: *Cleavage* resulting from intramolecular reaction at the linker which results in a cyclized product. The cleavage may also act as a purification if resin-bound side-products are incapable of cyclizing, and thus remain attached to the *solid support* on release of the desired material [9]. Diketopiperazine formation, as shown below, is one well-known example of cyclative cleavage [19,20].



Decode: Use of a surrogate analyte to define the reaction path to which the solid support was exposed, and hence imply the structure of a member of a *combinatorial library* (see also *Encoding*), or the reaction sequence for its preparation [21].

Deconvolute: To render less complex; process of optimizing an activity of interest by fractionating (normally by *resynthesis*, or by elaborating a *partial* library) a *pool* with some level of the desired activity to give a set of smaller pools. Repeating this strategy leads to single members with (ideally) a high level of activity and is termed *iterative deconvolution* [22–24].

Dendrimer: A polymer having a regular branched structure. If suitably functionalized (such as the benzyl alcohol-substituted, four-branch structure shown below) it may be used as a *soluble support*, in which case the desired, dendrimer-supported, material may be isolated by size-exclusion chromatography. Dendrimers may also be attached to a polymer and used as a *solid support*, with significantly increased *loading* over the initial *resin* [25–28].

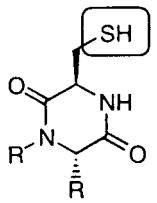


Descriptor: Numerical representation of a molecular property, including bulk properties (e.g. log *P*, molecular weight), two-dimensional (2-D) features (atom connectivities) or three-dimensional (3-D) features (molecular shape). A complete set of descriptors comprises a *fingerprint* [16,29,30]. See also *Binning*, *Clustering*.

Direct Divide: Strategy for the assembly of a *combinatorial library* related to the *pool/split* process in which each portion of solid support is divided into the next set of reaction vessels without an intervening pooling step. The resulting library is (like a pool/split library) *fully combinatorial*, with each particle bearing a single library *member*, but has a reduced standard deviation between the quantity of each library member [34].

Directed Library: (Also *biased* or *focused library*). Library which uses a limited number of *building*

blocks chosen on the basis of pre-existing information or hypothesis which defines the type of functionalities deemed important to obtain a particular activity. For example, every member of the diketopiperazine library shown below contains the thiol *pharmacophore* known to interact with metalloproteinase enzymes [31–33]. See also *Unbiased Library*.



Directed Sorting: Technique for organizing a mixture of solid-supported samples by identifying each particle (for instance, on the basis of its shape, marking or by reading a *radiofrequency code*) and transferring it to an appropriate position in an array. See also *Sort and Combine* [35,36].

Diversity: The 'unrelatedness' of a set of, for example, *building blocks* or members of a *combinatorial library*, as measured by their properties, such as atom connectivity, physical properties, computational measurements or bioactivity [17,37].

Diversity Reagent: One of a set of reagents which introduces *diversity* into the library products, as opposed to one which results in an identical conversion for each member of the library. Similar to *building block* but may be useful to distinguish from other (i.e. 'non-diversity') reagents.

Divide, Couple, Recombine: See *Pool/Split*.

Dynamic Library: Collection of compounds in dynamic equilibrium. If the composition of the library is altered, for instance by the presence of a receptor which selectively binds certain library *members*, then shifting of the equilibrium will lead to an increase in the amount of those components which bind to the target with relatively high affinity [38,39].

Encoding: Strategy for *pool/split* synthesis whereby a surrogate analyte is associated with each *member* of a *combinatorial library*. This is often achieved by the use of *tags* attached to the particle of *solid support* on which the library members are assembled. This allows the determination of the reaction history of an individual particle [21].

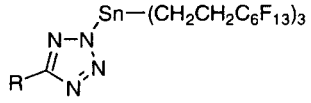
Enumeration: Conceptual process for explicitly describing discrete *members* of a library by elaborating the *generic structure* together with a specified set of *residues*.

Fingerprint: Numerical representation of a compound or library which describes in a computationally simple fashion a set of attributes (*descriptors*), such as atom connectives, 3-D structure or physical properties [29,40].

Flow Cytometry: Technique for characterizing or separating particles such as beads or cells, usually on the basis of their relative fluorescence [41].

Fluidic System: Device for synthesis or screening in which fluids such as reagents or assay buffers may be directed to specified locations by the opening and closing of valves in a stationary network of tubes and wells. See also *Robotic System* [42].

Fluorous Synthesis: Approach for solution phase synthesis which takes advantage of the ability of highly fluorinated groups to partition out of aqueous and most organic solutions into a third phase consisting of a fluorinated solvent. As an example, the compound shown below (with 39 fluorines per molecule) may be isolated by this approach. The fluorinated side-chain acts as a *soluble support* for synthesis [43].



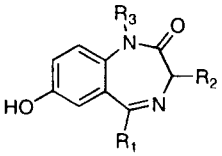
Focused Library: See *Directed Library*.

Frontal Affinity Chromatography: Method for screening mixtures of compounds for affinity against an immobilized target [44].

Fully Combinatorial: Containing, or designed to contain, all possible combinations of *building blocks*. *Pool/split libraries* are generally fully combinatorial while *parallel synthesis libraries* may not be. See also *Reagent Efficiency*.

Gel Phase: Description applied to certain 'solid' supports which display properties intermediate between solid and liquid phases, e.g. in the apparent mobility of the support as determined by nuclear magnetic resonance (NMR) spectroscopy [45].

Generic Structure: The general structural formula of a library, consisting of the *scaffold* plus an indication of the position of attachment of the various *residues*. The diagram below shows the generic structure of a 1,4-benzodiazepin-2-one library [46].



Genetic Algorithm: Method for library design by evaluating the fit of a *parent library* to some desired property (e.g. the level of activity in a biological assay or the computationally determined diversity of the compound set) as measured by a *fitness function*. The design of more optimal *daughter libraries* is then carried out by a *heuristic* process with simularities to genetic selection in that it employs replication, mutation, deletions, etc. over a number of generations [47–49].

Heuristic: 'Providing aid or direction in the solution of a problem but otherwise unjustified or incapable of justification.' (*Webster's Collegiate Dictionary*). Tools such as *genetic algorithms* or *neural networks* employ heuristic methods to derive solutions which may be based on purely empirical information and which have no explicit rationalization.

High-Throughput Screening (HTS): Process for rapid assessment of the activity of samples from a *combinatorial library* or other compound collection, often by running parallel assays in plates of 96 or more wells. A screening rate of 100 000 assays per day has been termed 'Ultra High-Throughput Screening' (UHTS) [50].

Hit: Library component whose activity exceeds a predefined, statistically relevant threshold.

Hit Explosion: Process of establishing structure–activity relationships around a *hit* by preparing new libraries or series of analogues using related *building blocks* and/or *scaffolds* to those employed in the preparation of that hit.

***In Silico* Screening:** See *Virtual Screening*.

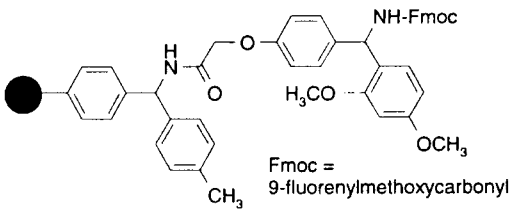
***In Situ* Scaffold Formation:** Process whereby a *scaffold* is formed during library production which contains *residues* of at least two *building blocks*; compare *Preformed Scaffold*.

IR Thermography: Infrared thermography Screening technique where the heat of reaction of a multitude of samples is simultaneously measured. Has been applied in particular to the screening of libraries of potential catalysts [51].

Iterative Deconvolution: Multistep application of *deconvolution* where successively smaller *sub-libraries* are prepared and tested to identify individual active members of a combinatorial library [22–24].

Kaiser Test: Analytical method for the determination of primary amines. Particularly useful for resin-bound analysis as the chromophoric product is released into solution allowing quantitation by colorimetry [52,53].

Knorr Resin: Amide-releasing, acid-cleavable *solid support* [54].



Ladder Synthesis: Strategy for library assembly where a portion of compound is capped following incorporation of each building block, such that the final sample comprises a mixture of all possible truncated products. This may be designed such that approximately equimolar quantities of each truncated form are present as an approach to gain maximal diversity, or such that each truncate is present in a small amount relative to the fully elaborated product. In the latter case, analysis of the pattern of products serves to identify the parent and is termed ladder encoding [55].

Libraries from Libraries: Strategy for accelerating library production, whereby an existing library is subjected to a relatively minor modification in order to generate a new library, thus avoiding the majority of chemical development and *rehearsal* required for a new library [56].

Library: See *Combinatorial Library*.

Library Equivalent: The number of samples which equals the number of compounds in the library. Particularly applied to libraries in which individual beads are *encoded*, where one library equivalent is the number of *beads* which equals the number of compounds in the library. See also *Assay Equivalent*.

Linker: Bifunctional chemical moiety attaching a compound to a *solid support* or *soluble support* which can be *cleaved* to release compounds from the support. A careful choice of linker allows cleaveage to be performed under appropriate conditions compatible with the stability of the compound and assay method [57].

Lipinski's Rules: See *Rules of Five*.

Liquid Phase Chemistry: Synthetic process employing a macromolecular *soluble support* [58,59].

Loading: Characteristic property of a solid support which describes the amount of a specific chemical species per unit mass of the support. See also *Capacity*.

Macroporous Resin: Polymer which contains a permanent network of pores independent of the state of swelling of the resin. This class of resin thus displays much better solvent tolerance than *gel-type* resins [18].

Magic Angle Spinning: NMR strategy in which the tube is rotated at very high speed and at a specific angle which cancels out the line broadening effects of inhomogeneities in the sample. This yields high resolution and high sensitivity which are very useful in trace analysis or in looking at solid phase synthesis resins [60].

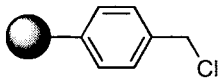
Markush Structure: Similar to a *generic structure*, but more flexible in that the substituents on the core structure need not be precisely enumerated, e.g. 'alkyl' rather than 'CH_3-, CH_3CH_2-, $CH_3(CH_3)CH$-'.

MAS: See *Magic Angle Spinning*.

Mask: Device which acts as a barrier to the passage of a reagent (often light—see *Photolithography*). A pattern of holes in the mask allows selective passage of reagent and results in a corresponding pattern of reagent deposition or photodeprotection on a surface placed behind the mask. This allows the generation of *spatially addressable libraries* [61,62].

Member: (a) Specific compound which is included in a library; (b) the uncharacterized physical product of a library synthesis [14].

Merrifield Resin: *p*-(Chloromethyl) polystyrene [63].



Mesh Size: The density of wires in a sieve. Often used as a measure of particle size, for example, of *solid supports*. A resin whose particle size is quoted as 100–200 mesh will pass through a 100-mesh filter but is trapped by a 200-mesh filter, and consists of particles whose diameter is between 75 and 150 μm. There are, unfortunately, several standard scales for this measurement which differ only very slightly from one another.

Monomer: Member of a *building block* set which can be repeatedly incorporated into a library to give a set of compounds of repeating structure, e.g. amino acids in a peptide library.

MPS: Multiple parallel synthesis (see *Parallel Synthesis*).

Multiple Simultaneous Synthesis: See *Parallel Synthesis.*

Neural Network: Technique for optimizing a desired property given a set of items which have been previously characterized with respect to that property (the 'training set'). Features of members of the training set which correlate with the desired property are 'remembered' and used to generate a model for selecting new items with the desired property or to predict the fit of an unknown member [64,65].

Null Reagent: Concept whereby one of a set of *pools* is subjected to no reaction at a particular stage of a combinatorial synthesis. It is often necessary to record this as a null event to maintain congruence in computational records of the library.

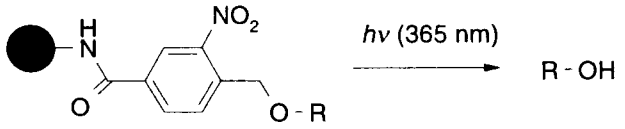
Omission Library: Strategy for identifying active library members by the systematic omission of building blocks from mixtures. Observation of reduced activity in a certain pool suggests that the building block which was omitted in that pool contributes to activity [66].

Orthogonality: (a) Property of protecting groups or *linkers* allowing removal, modification or *cleavage* of one such without affecting others; (b) *pooling* strategy whereby library *members* are incorporated in more than one pool, and are mixed with a different set of other members in each pool. Thus a *hit* results in two or more active pools with only one member in common [67,68].

Parallel Synthesis: Strategy whereby sets of discrete compounds are prepared simultaneously in arrays of physically separate reaction vessels or microcompartments without interchange of intermediates during the assembly process. Contrast *Pool/Split.*

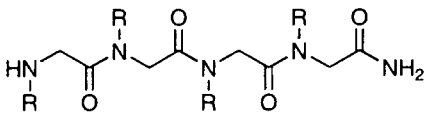
Partial Library: Partly assembled library, or portion thereof, which is reserved to be completed once initial property relationships have been identified. For instance, part of an intermediate *pool* may not be treated with the final *building block* until the optimal *residue* at the final position is known, thus avoiding the need to prepare that pool from the starting materials [69].

Partial Release: *Cleavage* process designed to release a compound from a *solid support* in discrete portions, e.g. by using *orthogonal linkers* or by controlled application of cleavage reagent or condition. Photocleavable linkers, such as that shown below, are a particularly convenient application as cleavage may be controlled by simply turning on or off a lamp [70,71]. Also *Controlled Release, Tiered Release.*



PEG: See *Poly(ethylene glycol).*

Peptoid: Oligomer consisting of repeating *N*-substituted glycine units [72,73].



Phage Display: Use of genetically engineered phage to present peptides as segments of their native surface proteins. Peptide libraries may be produced by populations of phage with different gene sequences [74–76].

Pharmacophore: 'The ensemble of steric and electronic factors which are necessary to ensure supramolecular interactions with a specific biological target structure' [77,78].

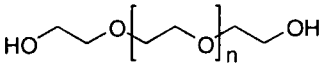
Phase Switch: Strategy for compound isolation, whereby the desired material is rendered sufficiently different from reagents, side-products and other impurities that it may be separated from them by simple physical processes such as filtration or extraction. May be achieved by the attachment of a *tag*, such as a highly fluroinated component (see *Fluorous Synthesis*), or other *sequestration enabling reagent* [43].

Photolithography: Process by which selective *masking* generates light patterns which direct chemical transformations to certain areas of a photosensitive surface. Coupling of different building blocks to discrete sites may give rise to *spatially addressable* arrays of compounds [61].

Pin: An elongated device in which the tip acts as a solid support. An array of pins may typically be held such that sets of pins may be simultaneously inserted or retracted from solvents or reagents allowing library preparation by *parallel synthesis* [8].

Point of Diversity: Portion of a molecule, or step in a synthetic scheme, where different *building blocks* may be introduced.

Poly(ethylene glycol) (PEG): Polymer which has been applied both as a *soluble support* and (as a graft copolymer with a polystyrene matrix) as a *linker* for combinatorial synthesis. See *TentaGel*, *ArgoGel*. The soluble support may have hydroxyls at both termini, or one or both may be capped or modified with additional functionality [59].



Pool: (a) A *sub-library*; (b) process of combining and mixing library components or sub-libraries. See *Pool/Split*.

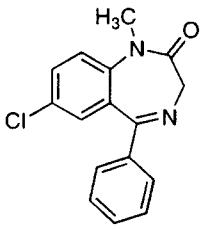
Pool/Split: (*split/pool*; *split&mix*; *divide, couple, recombine*; *portion/mix*) Strategy for assembly of a *combinatorial library*. The solid support is divided into portions, each of which is subjected to reaction with a single *building block*. Pooling of these portions results in a single batch of solid support bearing a mixture of components. Repetition of the divide, couple, recombine processes results in a library where each discrete particle of solid support carries a single library member, and the number of members is equal to the product of the number of building blocks incorporated at each step (i.e. *fully combinatorial*) [79,80].

Positional Scan: Strategy for identifying individual compounds of interest from a library, whereby a collection of *sub-libraries* is prepared, equal in number to the total number of *building blocks* used in the entire library. In each pool, one *point of diversity* is held constant by incorporating a single building block, while the other positions use all possible building blocks [81].

Preformed Scaffold: A *scaffold* which is incorporated into the library as a unit. Compare *In Situ Scaffold*.

Principal Components Analysis: Computational approach to reducing the complexity of, for example, a set of *descriptors*, by identifying those features which provide the major contributions to observed properties, and thus reducing dimensionality of the relevant *property space* [30,82].

Privileged Structure: Substructural feature which confers desirable (often drug-like) properties on compounds containing that feature. Often consists of a semi-rigid *scaffold* which is able to present multiple hydrophobic *residues* without undergoing hydrophobic collapse, e.g. diazepam (below) in which the diphenylmethane moiety prevents association of the aromatic rings [83].



Property Space: Multidimensional representation of a set of compounds in which the axes represent quantifiable properties, such as molecular weight, *c* log *P*, molar refractivity, etc., and individual compounds are represented by a vector or set of coordinates.

Pseudo-Dilution: See *Site Isolation*.

Radiofrequency Encoding: Strategy for identifying library members by physically associating them with a set of electronic devices which emit characteristic radiofrequency signals upon stimulation with a radiofrequency energy source. These signals can be used to track the reaction history of each sample in a synthesis [21,84].

Random Library: See *Unbiased Library*.

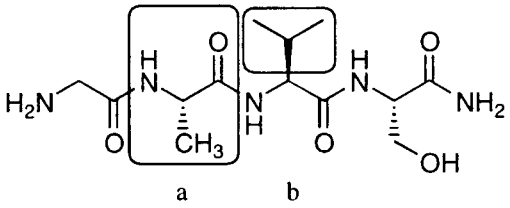
Ratio Coding: *Encoding* strategy in which the relative quantities of *tags* conveys information about compound identity. In comparison to *binary coding*, more information may be obtained from a given tag set, but tag interpretation is more complex [2,85].

Reagent Efficiency: The ratio of the number of library members prepared compared to the number which would have been prepared in a *fully combinatorial* library using the same *building blocks*. Lower reagent efficiency may be desirable in order to reduce the number of compounds to be synthesized or tested, for example by maximizing the number of members expected to have high activity in a library prepared by *parallel synthesis* [86].

Reagent Partitioning: Phenomenon whereby the concentration of a compound within, for instance, a particle of solid support is higher or lower than than of the bulk solution due to the physicochemical properties of the solid support [87].

Recursive Partitioning: Process for identifying complex structure–activity relationships in large sets by dividing compounds into a hierarchy of smaller and more homogeneous sub-groups on the basis of the statistically most significant *descriptors*. See also *Clustering* and *Principal Components Analysis* [88,89].

Residue: (a) Portion of a chemical structure which can be identified as being derived from a particular *building block*, such as the alanine residue in the peptide below; (b) portion of a building block which is incorporated into the final product but is not part of the *scaffold*, such as the valine side-chain below.



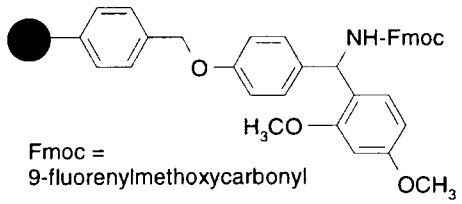
Resin: Insoluble polymeric material which allows ready separation from liquid phase materials by filtration; can be used to carry library members (i.e. *solid support*) or reagents, or to trap excess reagents or reaction by-products (see *Scavenger Resin*) [18].

Resin Capacity: See *Capacity*.

Resin Loading: See *Loading*.

Re-synthesis: Preparation of individual *members* or *pools* of a *combinatorial library*, normally to follow up on some property of interest identified in initial screening, and often in larger scale and/or greater purity than the original preparation.

Rink Resin: Amide-releasing, acid-cleavable *solid support*. 4-(2′,4′-Dimethoxyphenylaminomethyl)-phenoxy polystyrene [90].

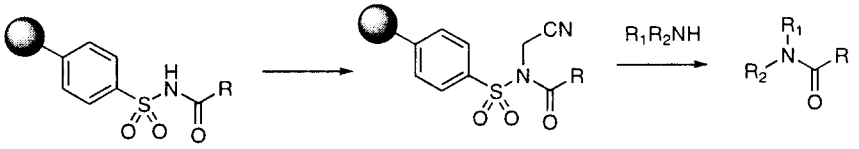


Robotic System: Automated device where materials are transferred by the physical movement of a delivery device relative to the ultimate receptacle, or vice versa. See also *Fluidic System* [42].

Rules of Five: *Lipinski's rules*. Set of criteria for predicting the oral bioavailability of a compound on the basis of simple molecular features (molecular weight, *c* Log *P*, numbers of hydrogen-bond donors and acceptors). Often used to profile a library or *virtual library* with respect to the proportion of drug-like members which it contains [91].

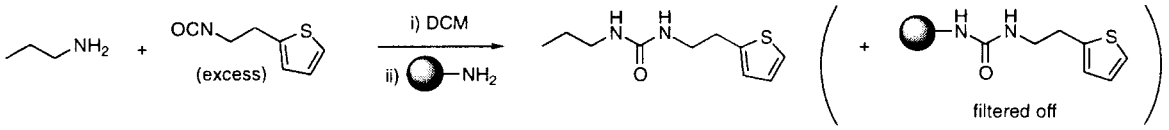
Safety-Catch Linker: A *linker* which is *cleaved* by performing two different reactions instead of the normal single step, thus providing greater control over the timing of compound release. Thus the

sulfonamide resin below must first be alkylated to render it susceptible to cleavage by nucleophilic displacement [92–94].



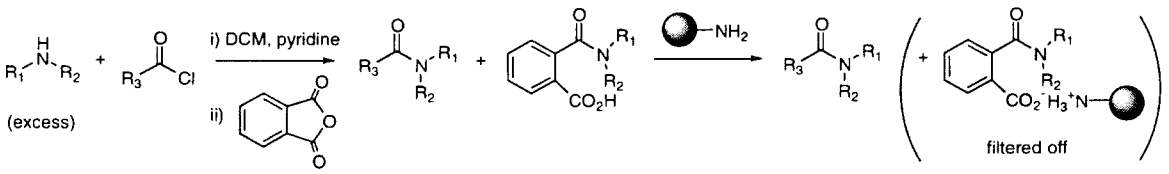
Scaffold: Core portion of a molecule common to all members of a *combinatorial library*.

Scavenger Resin: Solid-supported reagent which will react with undesired materials (such as excess reagents) and remove them from solution. Thus the polymer-supported amine in the example below allows removal of excess isocyanate. See also *Sequestration-Enabling Reagent* [95–98].



SELEX: "Systematic Evolution of Ligands by Exponential Enrichment". Process for identifying *aptamers* by iterative enrichment of oligonucleotide mixtures with respect to their ability to bind a target [4–6].

Sequestration-Enabling Reagent: Reagent which converts undesired by-products or residual starting materials into a form which may more easily be removed from the reaction mixture by, for example, *solid phase extraction* or other *phase switch*. Thus the anhydride (below) will react with residual amine to give an acidic product which is removed by salt formation with an amine *scavanger resin*. Excess anhydride will in turn react with, and be removed from solution by, the same resin [98,99].



Site Isolation: Property of solid supports, whereby functional groups are separated from each other by the polymeric framework, and thus, while they may be physically in close promimity, reduced levels of reaction between sites may be observed. Also referred to as *pseudo-dilution*.

Solid Phase Extraction: Method for sample purification, whereby either the desired or undesired components of a mixture have preferential affinity for a solid material. Adding the mixture to the solid material then allows facile separation of the desired material by filtration. See also *Sequestration-Enabling Reagent* and *Scavenger Resin*.

Solid Support: Insoluble, functionalized, polymeric material to which library members or reagents may be attached (often via a *linker*) allowing them to be readily separated (by filtration, centrifugation, etc.) from excess reagents, soluble reaction by-products or solvents [18,100,101].

Soluble Support: An attachment, common to all library members, which renders the library components soluble under conditions for library synthesis, but which can be readily separated from most other soluble components when desired by some simple physical process. This process has been termed *liquid phase chemistry*. Examples of soluble supports include linear polymers such as *poly(ethylene glycol)*, *dendrimers* or fluorinated compounds which selectively partition into fluorine-rich solvents (see *Fluorous Synthesis*) [59,102].

Sort and Combine: Use of *directed sorting* to facilitate library assembly. Related to *pool/split* protocol, but more commonly applied to macroscopic solid supports (such as *pins* and related carriers) where each library *member* is found on only one, or a small number of carriers.

Spatially Addressable: Having the ability to identify at least part of the structure of a library component or *pool* by noting its physical location in an array [8,10].

SPE: *solid phase extraction.*

Split/Pool: See *Pool/Split.*

Stochastic: 'Aiming, proceeding by guesswork'. (*Websters Collegiate Dictionary.*) Term which is often applied to combinatorial processes involving true random sampling, such as selection of beads from an *encoded library*, or certain methods for library design [103].

Sub-Library: See also *Pool.* A subset of a *combinatorial library*, physically separate from the rest of the library, generally with one or more fixed *building blocks.*

Sub-Monomer Synthesis: Process resulting in an oligomer in which each monomer *residue* is formed from two or more *building blocks.* This approach has been used for *peptoid* synthesis [72].

SURF: 'Synthetic Unrandomization of Randomized Fragments' Strategy for identifying active members of a mixture related to *deconvolution* and *positional scanning* [104].

Tag: (a) One of a set of surrogate analytes which are used in a *decoding* process; (b) pendant function which allows a molecule to be selected from a mixture (see *Phase Switch*) [21,99].

Tea-Bag: A type of reaction vessel consisting of a porous mesh which encloses the *resin* but allows passage of reagents and solvents when immersed in an appropriate secondary container. Several tea-bags may be treated in a single vessel without mixing of the enclosed resins; manipulation of multiple tea-bags allows preparation of libraries by *pool/split* or *directed sorting* techniques [105].

Template: See *Scaffold.*

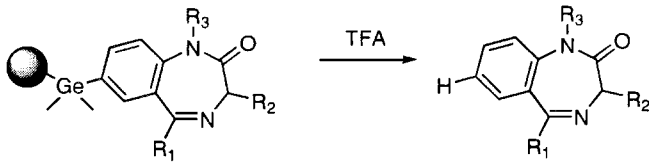
TentaGel: (Trademark of Rapp Polymere GmbH, Tubingen, Germany.) *Beaded solid support* with a *crosslinked* polystyrene core and grafted linear *poly(ethylene glycol)* (PEG) chains with terminal functional groups [106,107].

Tether: See *Linker.*

Thematic Library: See Directed Library.

Tiered Release: See *Partial Release.*

Traceless Linker: Type of *linker* which leaves no residue on the compound after *cleavage*, i.e. is replaced by hydrogen, as in the acid-cleavable germanium-based linker below [108–110].



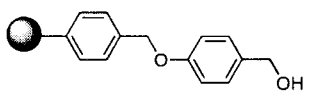
Unbiased Library: Library prepared from *building blocks* and *scaffold* chosen without bias towards a particular target [33].

Universal Library: A hypothetical compound collection which will show activity in all assays; a library with useful activity in many assays.

Virtual Library: A library which has no physical existence, being constructed solely in electronic form or on paper. The *building blocks* required for such a library may not exist, and the chemical steps for such a library may not have been tested. These libraries are used in the design and evaluation of possible libraries [48].

Virtual Screening: Selection of compounds by evaluating their desirability in a computational model. Also termed *in silico screening* [17,111].

Wang Resin: Acid-cleavable resin which generates compounds bearing a carboxylic acid. (4-Hydroxymethyl)phenoxymethyl polystyrene [112].



X-Ray Photoelectron Spectroscopy (XPS): Technique for determining the elemental composition at a

solid surface by measuring the energy of electrons emitted in response to X-rays of different frequency. Has been applied to solid phase combinatorial chemistry by incorporating a tracer atom in the linker [113].

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