ELSEVIER

This review seeks to explain some of the common terminology used by medicinal and synthetic chemists. Aimed at the non-specialist, its intent is to help facilitate discussions between chemists and their counterparts from other disciplines.

Drug discovery chemistry: a primer for the non-specialist

Allan M. Jordan and Stephen D. Roughley

Medicinal Chemistry, Vernalis (R&D) Ltd., Granta Park, Cambridge CB21 6GB, UK

Like all scientific disciplines, drug discovery chemistry is rife with terminology and methodology that can seem intractable to those outside the sphere of synthetic chemistry. Derived from a successful in-house workshop, this Foundation Review aims to demystify some of this inherent terminology, providing the non-specialist with a general insight into the nomenclature, terminology and workflow of medicinal chemists within the pharmaceutical industry.

Owing to its multi-disciplinary nature, those working within drug discovery are exposed to a considerable quantity of terminology, drawn from a wide variety of specialisms. From analysts to computational scientists, toxicologists and pharmacologists, each scientific area tends to develop its own dialogue and vocabulary that, to the outsider, can be complex and sometimes overwhelming when trying to collaborate and communicate across disciplines and projects. The synthetic chemist is by no means exempt from this endemic use of jargon. Aside from terminology for the specific chemical entities produced in the laboratory and the functionality these entities contain, chemists make frequent reference to the names of the reactions, techniques and methodology used to assemble them. Though second nature to the practicing chemist, this terminology is frequently referred to with little or no explanation or clarification to those outside the chemistry community.

Within Vernalis, a series of informal discussions clearly highlighted the ways in which different scientists visualise, and thus describe, key candidate compounds. For example, crystallographers would refer to electron densities, while modellers would discuss compounds in terms of their intermolecular interactions with their desired targets. These and other colleagues outside chemistry would often despair as the project chemists discussed seemingly endless lists of functional groups, core ring systems and reaction types. It quickly became apparent that while chemists had, as part of their training, often picked up sufficient biology to allow them to at least partly follow the biological discussions within project meetings, the non-chemists often found chemical discussions considerably more difficult to follow, despite their best efforts. From this starting point, we developed, implemented and evolved an in-house workshop, which we loosely entitled 'chemistry for non-chemists'. This allowed those interested parties to understand a little better the mindset of the synthetic chemist, their terminology, nomenclature and the 'toolbox' of reactions commonly used to construct the molecules of interest.

Corresponding author: Jordan, A.M. (a.jordan@vernalis.com)

Allan Jordan gained his B.Sc. from UMIST, Manchester in 1993. After a short period as a graduate teaching assistant at Arizona State University, he returned to UMIST where he completed his Ph.D. in 1997, investigating taxane-derived anti-cancer agents with Nick Lawrence and Alan McGown. After post-doctoral studies with Helen Osborn at Reading University, he moved to Cambridge to join Ribotargets (which later became part of Vernalis) in 1999. During his time at Vernalis, he has contributed to a number of CNS, oncology and anti-infective programmes and is presently a Team Leader in Medicinal Chemistry.

Stephen Roughley gained his M.A. in 1995 and Ph.D. (with Andrew B. Holmes, on the modelling and application of nitrone cycloadditions to the synthesis of histrionicotoxin alkaloids) in 1999 from the University of Cambridge. During his studies, he undertook placements in Medicinal and Process Chemistry at GlaxoWellcome. In 1999 he joined Ribotargets (later Vernalis), where he has contributed to a broad range of target and technology programmes. After a secondment in NMR-based fragment screening, he has returned to Medicinal Chemistry as a Principal Scientist, where he maintains interests in the development and application of new technologies to drug discovery.

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2009.04.005

BOX 1

Molecular interaction terminology

The interaction of small organic molecules with their biological targets can be loosely divided into four predominant types:

(1) Hydrogen bonds

A hydrogen bond is a weak interaction where a hydrogen atom can be thought of as being shared between two atoms that are frequently heteroatoms [53]. The interaction is formed between two partners, known as a hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA). A HBD is defined as a heteroatom with at least one attached hydrogen whereas a HBA is defined as a heteroatom that bears a partial negative charge. This interaction arises owing to a polarisation of the bond connecting the heteroatom of the HBD and its attached hydrogen. This creates a small partial positive charge on the hydrogen atom that can interact with heteroatoms carrying a partial negative charge. Such interactions are generally much weaker than a covalent bond between atoms.

Though the definitions above are broadly useful, some evidence exists for interactions where the HBD consists of a carbon–hydrogen bond, which is strongly polarised owing to its chemical environment.

(2) Ionic bonds

Unlike hydrogen bonds, which are formed by partial charge interactions between weakly polarised bonds, ionic bonds are formed by the interaction of groups bearing opposite but full charges. Such interactions, sometimes referred to as 'salt bridges', help determine many biological effects, including protein shape and function. Within proteins, five amino acid side chains are fully or partly ionised at physiological pH and thus can carry either a positive or negative charge. Aspartic acid and glutamic acid residues carry a negative charge and can thus interact with positively charged side chains on arginine, lysine or histidine side chains.

Because the majority of drug targets are proteins, these charged residues could also form interactions with suitably charged functional groups on a small molecule. Acidic centres that may lose hydrogen (be *deprotonated*) at physiological pH, and thus yield a negative charge, are primarily provided by carboxylic acids and phosphonic acids. Additionally, alcohols attached directly to a phenyl ring (a *phenol*) and certain heterocycles can also provide a similarly charged centre.

Similarly, many functional groups provide basic centres, which can acquire a hydrogen atom (be *protonated*) at physiological pH. Amines and guanidines are particularly common in this role. However, the presence of charged functional groups within a molecule are not a universal panacea for improving interactions with biological targets: their presence in drug candidates can introduce other unwanted effects, such as poor cell penetration and metabolic issues.

(3) π-Stacking

This form of weak bonding exists between organic compounds containing aromatic moieties that can align themselves in a parallel fashion [54]. Even in apolar, neutral molecules, the distribution of electrons across the functional group is not entirely symmetrical and this results in a slight, transient distribution of partial charges. These partial charges can influence neighbouring functional groups, creating an attractive force between them.

This interaction is important in biological interactions and, though each individual interaction is itself weak, the stacking of multiple heterocyclic rings in DNA creates an enormous stabilising effect within the structure. Such favourable interactions can also be attained between aromatic amino acid side chains, such as those found in tyrosine, phenylalanine and tryptophan, alongside the aromatic and heteroaromatic functionality contained within drug compounds.

(4) The 'Hydrophobic Effect'

Though most of the interactions detailed above concern interactions of polarised bonds contained within drug molecules, these '*polar*' regions are only a small component of the overall molecule that will additionally contain a number of '*apolar*' or '*non-polar*' regions. The interaction of these regions with polar solvents, such as water, is intrinsically unfavourable and highly apolar compounds may display undesirable properties such as poor solubility. This effect is known as '*hydrophobicity*'. Furthermore, though the binding sites of many drug targets are decorated with polar functional groups that allow the formation of hydrogen and ionic bonds, these sites also comprise apolar amino acid side chains, which also interact unfavourably with the surrounding water molecules. The binding of a hydrophobic drug to such a site can displace the resident water molecules and substantially reduce these unfavourable interactions. This beneficial effect can make considerable contribution to binding affinity [55] (Figure 8).

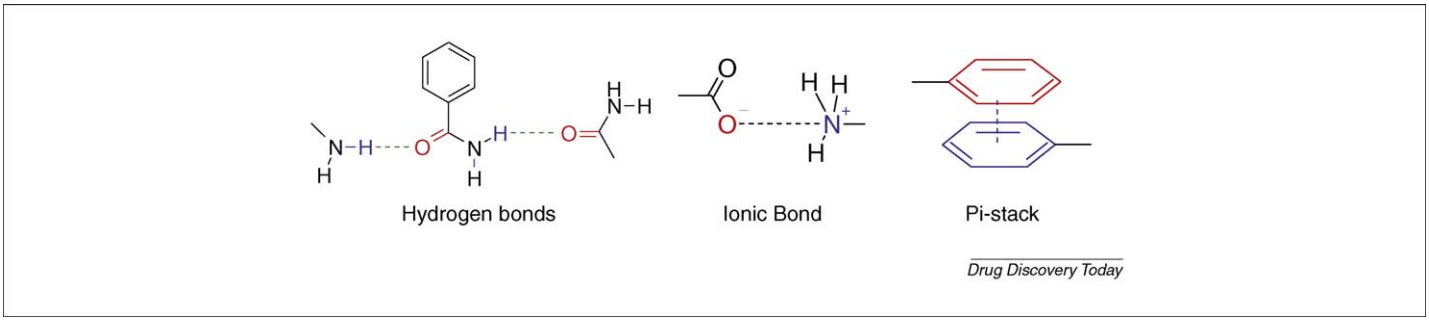

FIGURE 8

Simple schematics of some important molecular interactions. Red atoms signify areas of full or partial negative charge while blue atoms signify full or partial positive charges.

It is from this course and from discussions with those colleagues who have participated that that this primer draws its inspiration and content. The review will focus upon three predominant themes. Firstly, we will examine the nomenclature of compounds and some of the terminology used in the description of their construction ('*synthesis*'). Chemists will often refer to key molecular fragments that are important for the construction of molecules or are involved in their interactions with biological targets. The review will discuss these common biologically relevant fragments, to help the non-chemist identify such entities within their

own compounds and allow some correlation of molecular architecture and biological efficacy.

Secondly, the review will discuss the methodologies and tools used by chemists to construct the molecules required for biological evaluation. The evolution of the apparatus used in the modern synthetic laboratory will be discussed briefly, alongside some of the newer techniques and technologies employed to facilitate compound production. Specific reference will be made to common terminology and explanations of both meaning and applicability will be given.

Finally, the review will summarise those reaction types most commonly employed by the synthetic chemist within the pharmaceutical industry. Special mention will be given to the reasons why each reaction is favoured (for example, synthetic ease or biological relevance), with an aim to provide a basic understanding of the reaction type rather than a comprehensive understanding of the reaction technicalities and underlying mechanistic considerations, which are beyond the scope and limitations of an article such as this.

Molecule-related terminology

Functional groups

In simplistic terms, most drug candidate molecules can be described as a core scaffold, decorated by '*functional groups*', defined as an atom or group of atoms responsible for the characteristic properties of a molecule [1–3]. This group is one that interacts in predictable ways with other molecules. These interactions can be biologically relevant, for example by providing hydrogen bond donors or acceptors (see Box 1), or chemically important, particularly in terms of molecular construction. Many of these functional groups provide 'synthetic handles', facilitating the route used to construct the target compound. A selection of the most common functional groups incorporated in biologically relevant molecules is shown in Figure 1.

Core scaffolds

Functional groups are generally arranged around a central core or scaffold. This core is usually a flat, rigid structure and tends to be '*aromatic*' in nature. Originating from the fragrant (though not always pleasant!) nature of many of these compounds, aromaticity is a concept used to describe cyclic systems that simplistically can be thought of as containing alternating single and double bonds within their core framework. Though this description is not strictly true in an atomic sense, it is sufficient for our purposes and, for the most part, will allow the reader to spot aromatic templates where they arise in the literature and during discussions with their chemistry colleagues. An 'aromatic' framework will often consist of a skeleton of carbon atoms, such as benzene or

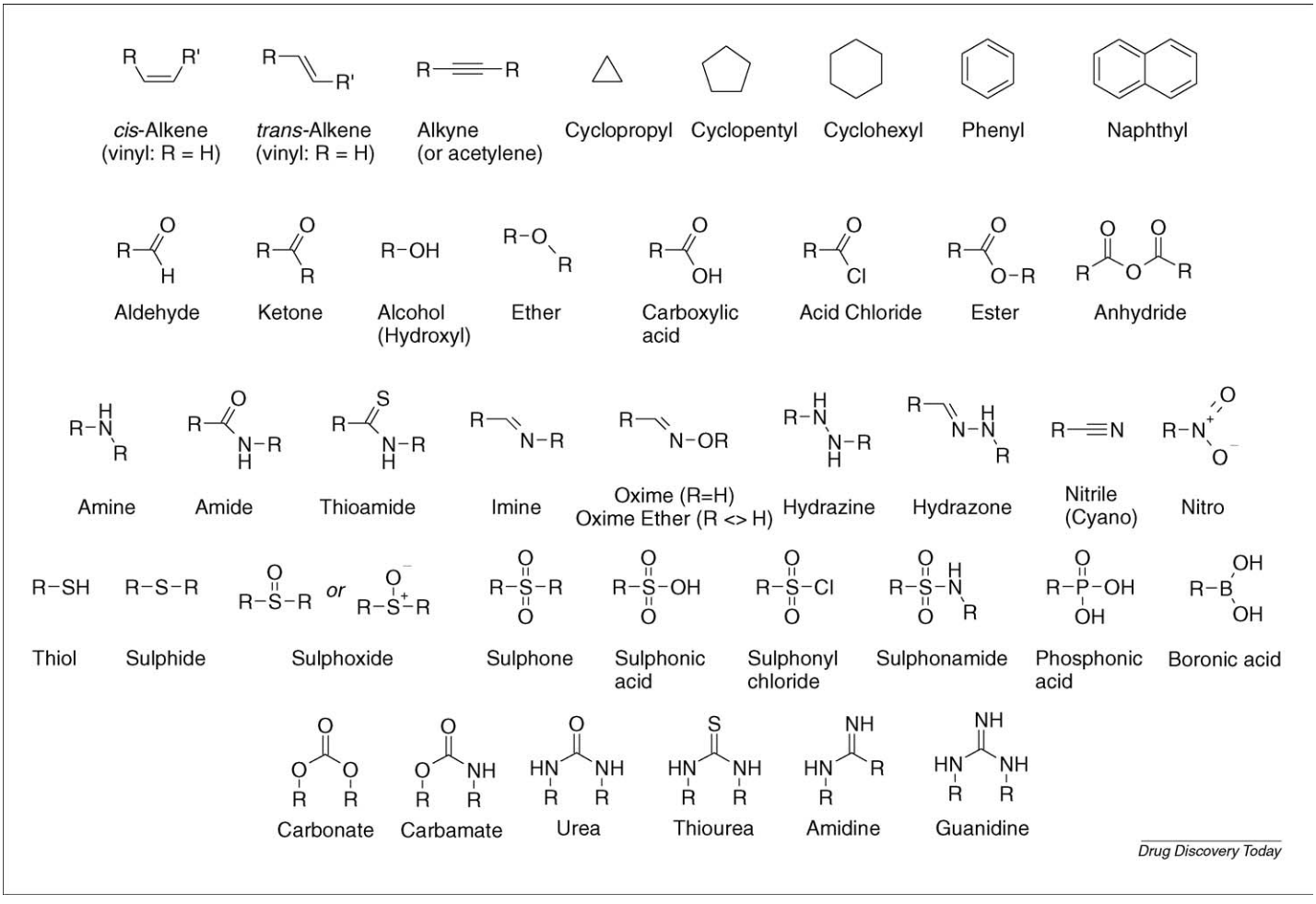

FIGURE 1

Common functional groups.

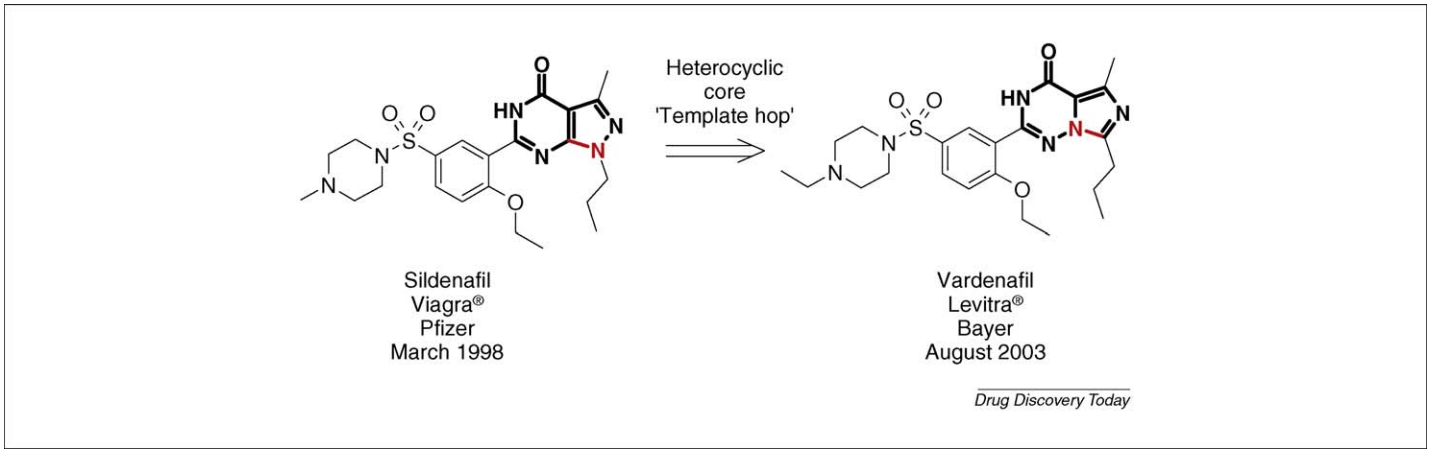

FIGURE 2

An example of a heterocyclic 'template hop' or 'scaffold hop' between the PDE5 inhibitors Sildenafil and Vardenafil. The core heterocyclic template is highlighted in bold, and the atoms changed in red. Note that although the formal positions of the double bonds in the 5-membered ring change, these are both aromatic rings. The dates shown are the respective dates of approval by the FDA. This scaffold hop was predicted by the software described in reference [8].

naphthalene. However, most drug scaffolds incorporate strategically placed '*heteroatoms*' (non-carbon atoms such as oxygen, nitrogen and sulphur). Such systems are known, surprisingly logically, as 'heteroaromatic' ring systems or 'heterocycles'. The incorporation of such ring systems serves several purposes [4–10]. For example, they may:

- Be easy to make or modify
  Heterocyclic systems are much easier to prepare and modify than carbon-based aromatic systems. It is often easier to introduce or modify functional groups attached to these systems.
- Modify the properties of the compound, allowing 'fine-tuning'
  Heterocyclic scaffolds often allow the introduction of hydrogen bond acceptors and donors that, as we have already noted, are important for biological interactions. Additionally, differing heterocyclic templates allow for alterations in the position, number and geometry of such interactions, in an effort to fully optimise the interaction of the drug with its biological target. They also allow the modification of important drug-like properties such as solubility and metabolism.
- Alter reactivity
  Certain heterocycles may offer interesting biological properties and may be found to be biologically reactive. Alternative heterocycles may mimic these important interactions while offering better stability *in vivo*. Alternatively, different heterocycles may be more compatible with the desired synthetic strategy used to investigate the biological activity of a range of compounds, while again offering similar *in vitro* or *in vivo* efficacy.
- Offer novelty
  Given the widespread use of high-throughput chemistry techniques in recent years (see section on Laboratoy Equipment), the chemist is occasionally confronted with the realisation that the compound series they have spent several months optimising has been claimed by a recently published patent application, or the promising hit discovered as part of a high-throughput screen has already been described and therefore cannot be covered by patent protection. Analysis of these documents can offer an opportunity to exploit similar heterocyclic motifs that are outside the coverage of such patents but which may, with a little optimisation, offer similar properties and biologically relevant activity. This concept of 'template hopping' (Figure 2) is of huge commercial value and novel templates generated can be of considerable importance, especially in highly competitive fields such as the inhibition of kinases.

The above points go some way toward demonstrating the importance of heterocyclic templates in medicinal chemistry. Figure 3 details the structures and names of a variety of the most common aromatic and heteroaromatic core scaffolds employed in drug candidates.

Core scaffold nomenclature

Understanding the nomenclature of heteroatomic compounds is not helped by the common usage of many trivial or historical terms. However, the knowledge of a few simple rules can considerably simplify the process [11,12]. For example, a heterocyclic ring system containing an oxygen atom will usually contain either the phrase *oxa-* or be derived from the trivial/historical name for the common five-membered oxygen-containing ring system known as a *furan* (from the Latin *furfur*, meaning bran, from where early furan derivatives were first isolated).

Heteroaromatic derivatives containing a nitrogen atom will often contain specific prefixes or suffixes to denote the presence of the atom such as the *pyr-* prefix. This is most commonly used for compounds derived, or conceptually derived, from pyridine. Additionally, the phrase *aza-* or *azo-* may be contained within the name. Examples of this type depicted in Figure 3 include the triazoles, meaning literally 'three nitrogens'. This nomenclature is derived from azote, meaning 'lifeless', an early name for nitrogen gas as it does not support respiration.

Heterocyclic compounds containing sulphur will often incorporate the phrase *thio-* (from *thios*, the Greek word for elemental sulphur) as exemplified by the thiophenes.

Often, heteroaromatic ring systems will contain multiple heteroatoms (i.e. atoms that are not carbon or hydrogen). Names of these systems are generally found to contain the concatenated phrases for each of the individual heteroatoms. Thus, from the

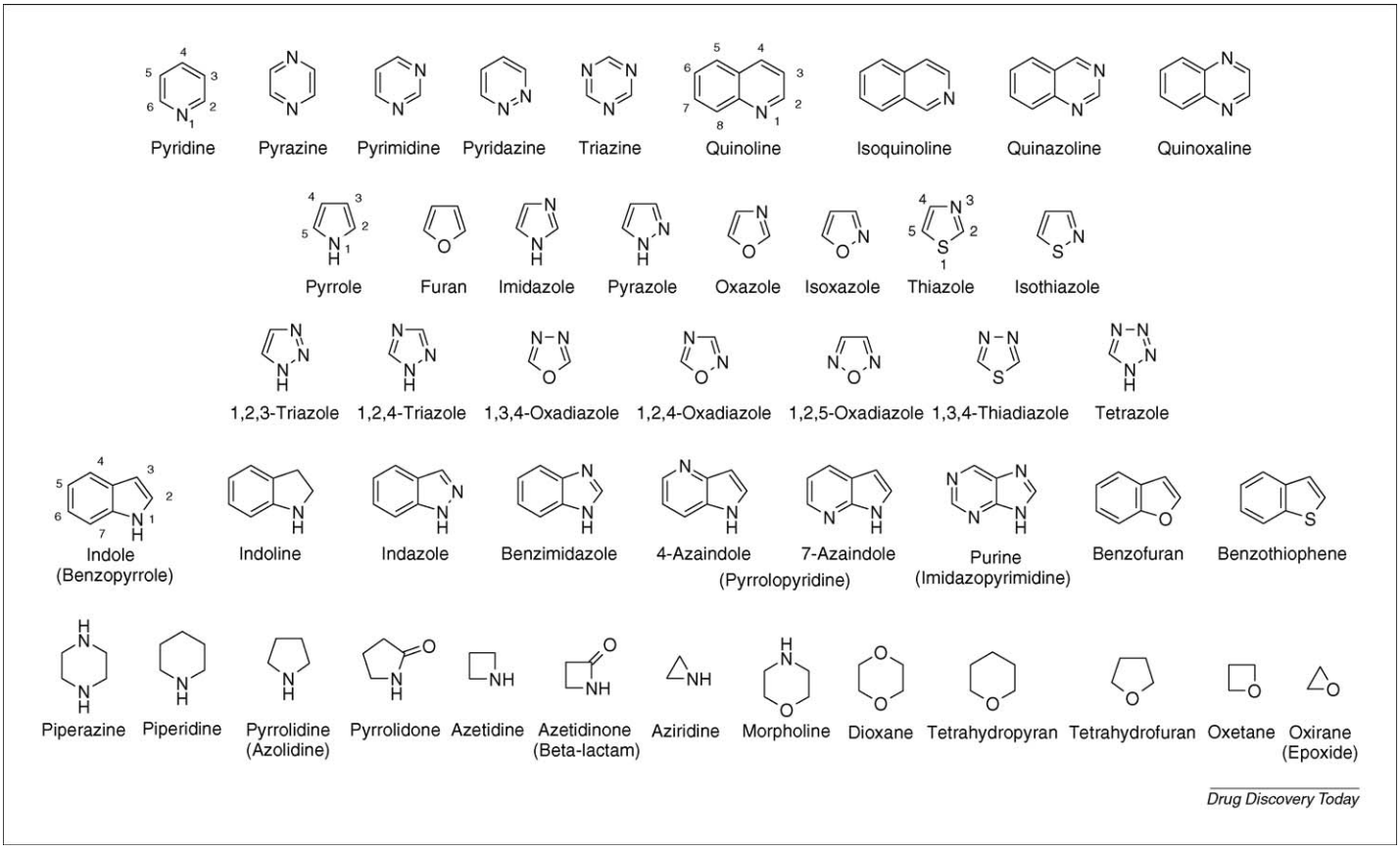

FIGURE 3

Common aromatic and non-aromatic heterocyclic core scaffolds.

guidelines above, a *thiazole* will contain both a sulphur and a nitrogen atom and an *oxadiazole* incorporates both an oxygen and two nitrogen atoms.

Nomenclature of multi-ring systems

This nomenclature also applies where two smaller ring systems are fused to generate a bicyclic system; the names of the two smaller rings are concatentated with an -o- and the smaller ring generally being referred to in the first instance. Thus, a fused pyrrole and pyrimidine becomes a pyrrolopyrimidine and a fused furan and pyridine becomes a furanopyridine. This rule holds true except in those cases where a smaller ring is concatentated to a benzene ring; in these cases, the benzene is usually named first, as in 'benzofuran' (Figure 4).

'Trivial' names

Complexities have arisen where biologically relevant heterocycles were identified and characterised before a more systematic approach to nomenclature was introduced. Particularly relevant are the purines, such as adenine and guanine found in DNA (more correctly, both derivatives are imidazopyrimidines) and indole (a benzopyrrole). Chemists making modifications to these templates often refer back to the trivial name rather than employing the more logical systematic name [12]. For example, the heterocycle formed by the introduction of a nitrogen into the larger ring of an indole will often be referred to as an 'azaindole', rather than the more technically correct pyrrolopyridine.

Although there are many examples similar to the azaindole case that do not follow the guidelines above, these simple notes should allow the reader to overcome many of the complexities of nomenclature present in heterocyclic chemistry.

Numbering protocols

In certain examples in Figure 3, it should be noted that some heterocycles are numbered around the ring. These numbers are

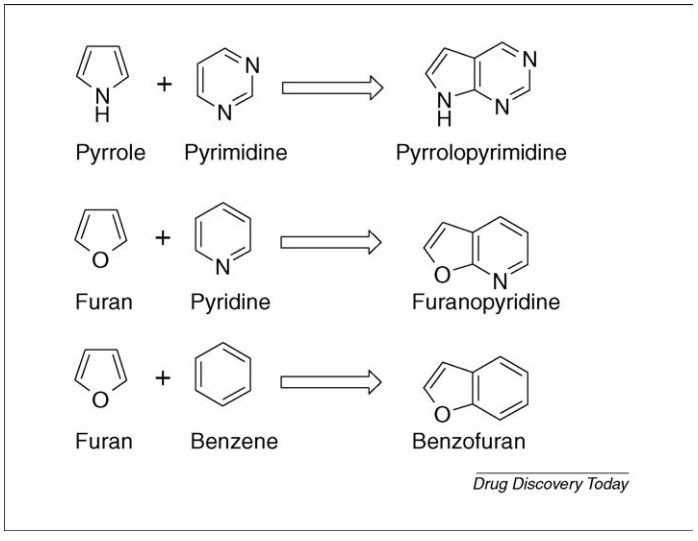

FIGURE 4

Nomenclature of fused heterocycles.

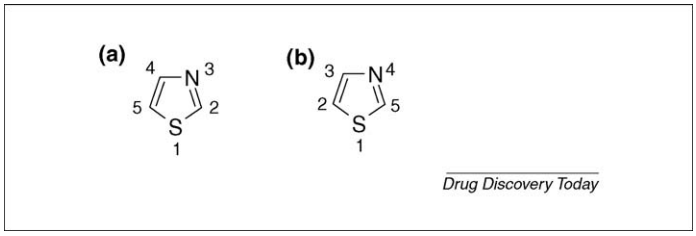

FIGURE 5

Ring numbering conventions. Rings are numbered to ensure heteroatoms bear the lowest possible number. In this instance, numbering anti-clockwise gives the lowest heteroatom numbering (Figure 4a) and is thus correct whilst numbering clockwise (Figure 4b) does not obey the rule.

used as part of the name in order to alleviate confusion as to the atoms to which functional groups are attached. Although only shown for representative systems, this atom numbering scheme can be applied to all core scaffolds. In terms of determining the numbering system the heaviest atom, that is the one with the greatest atomic mass, will carry the lowest number. Therefore, in the case of a thiazole, the heavier sulphur atom will be numbered as atom 1 and numbering continued such that the other heteroatom in the ring carries the lowest possible number. Numbering clockwise around the ring in this example would imply the thiazole nitrogen atom would be denoted as atom 4 in the ring, whereas numbering anticlockwise would denote the nitrogen as atom 3, as required by this rule (Figure 5). This numbering system is useful not only for differentiating between similar heterocyclic templates (such as the 1,2,3-triazoles and 1,2,4-triazoles in Figure 3) but can also define the point of attachment of functional groups around the core template (Figure 6).

Saturated systems

Though the preceding discussion has focused upon aromatic and heteroaromatic templates it is important to note that not all biologically relevant molecules are based around aromatic cores. These non-aromatic cyclic systems are considerably less rigid and, in some cases, allow the molecule some flexibility to adapt the correct spatial arrangement of functional groups to fully optimise the geometry of interactions with the biological target. Fewer in number than their aromatic counterparts, a selection of relevant examples are also detailed in Figure 3. In general, these cores are often less synthetically accessible than their aromatic counterparts and their functionalisation can be much more complex. For these reasons appropriately decorated non-aromatic cores are often purchased, rather than constructed in the laboratory by the chemist.

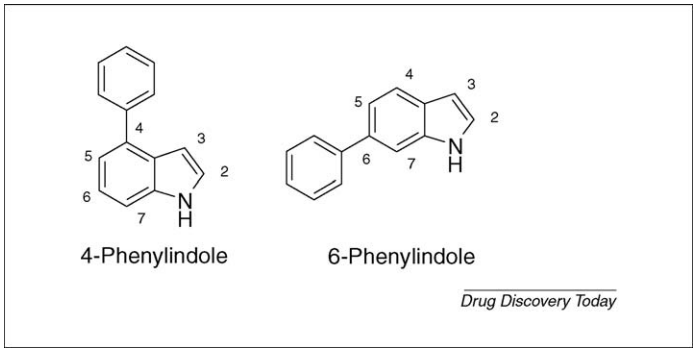

FIGURE 6

Scaffold numbering used to denote points of attachment for functional groups and substituents.

Terminology related to methodology and workflow

Protecting groups

Though the nomenclature associated with the compounds themselves is perhaps used more frequently it is also useful to understand some of the terminology related to the workflow of the chemist. One such term used in this context is the concept of a 'protecting group'. This term refers to a specific functional group introduced not for biological relevance or later synthetic modification, but simply to prevent reactions occurring at a functional group contained within the molecule until the desired time in the reaction sequence. At the relevant point this functional group can then be removed, unmasking the functionality of interest and revealing its reactivity. Though undoubtedly useful, chemists view protecting groups with a degree of frustration and their use requires careful choice. Indeed, the 'protecting group strategy' is often a key part of designing a usable synthetic route.

To be usefully employed, protecting groups must:

- Be easily incorporated and removed.
  The incorporation and removal of protecting groups adds at least two steps to a synthetic route. If these groups are not reliably incorporated and removed cleanly with little purification, their use can have dramatic effects upon the overall yield of a process. While this is more of a frustration at the early research stage, it adds both cost and complexity as more material is needed for proof-of-concept *in vivo* studies. This can also be of commercial significance if the route is to be transferred to a large-scale manufacturing process.
- Be fully compatible with the synthetic route.
  The chosen group must be stable and inert to all the reaction conditions employed in the synthetic route up to its point of removal. The conditions used for removal must also be compatible with the pre-existing functional groups present at that stage in the synthesis. Although the chosen protecting group is carefully selected, it is not unknown for unexpected, premature removal of the protecting group to occur, or for the deprotection conditions to cause unexpected reactions to occur at peripheral sites of the molecule. This generally requires a re-think of the protecting group strategy but in certain circumstances can require a re-think of the entire synthetic route.

In an ideal world synthetic strategies would be designed to entirely negate the requirement for protecting groups and, indeed, many elegant synthetic routes have been designed to achieve this goal [13,14]. These schemes are more prevalent in the context of manufacturing routes for clinical trials or the commercial manufacture of approved drugs. However, despite their drawbacks and limitations, protecting groups form an important part of the chemist's toolkit.

Laboratory equipment

Although many advances in organic chemistry have been made in recent years, the basic tools of the trade generally remain the same. Most syntheses are still conducted in a stepwise manner in glass

vessels, usually connected by means of precision-made conical ground glass joints. This arrangement allows a wide range of synthetic transformations to be conducted without additional specialist set-ups and connection of the apparatus to inert gas feeds (such as nitrogen or argon) allows exclusion of air, facilitating the safe use of reactive reagents that may be moisture-sensitive and/or air-sensitive.

Combinatorial chemistry

While this traditional approach provides great flexibility and scalability, since the 1980s there has been an increasing pressure on chemists to deliver greater numbers of compounds in decreasing timescales. One solution to this increased demand was the advent of combinatorial chemistry. In general employing solid-supported chemistry techniques (see Box 2), synthetic routes were designed to offer as much flexibility and diversity as possible around a central core rather than short, efficient routes to individual compounds designed to test specific hypotheses. In this way, large libraries of related molecules could be rapidly prepared and tested for biological activity [15].

Though combinatorial chemistry delivered many hundreds of thousands of compounds, it suffered from some considerable limitations. Of primary importance was the issue that many early combinatorial libraries were prepared as mixtures of compounds and it was anticipated that, where weak biological activity was noted in a mixture, the individual components of the mixture

BOX 2

Solid-supported chemistry

Many synthetic procedures are undertaken in solution where reagents and reactants are dissolved to form a homogeneous mixture. This has distinct advantages in terms of ease of analysis and handling but also offers some disadvantages. Of general concern to the chemist is how to isolate the desired product, and only the desired product, in high yield from these solutions. This aim is complicated if the reaction is troublesome and requires either a mixture of several reagents or, more commonly, large quantities of a specific reagent to drive the reaction to completion. The desire to surmount these issues has played a significant role in the development of '*solid-phase*' chemistry.

In the early implementation of this idea a starting reagent would be chemically linked to a solid support, often a polymeric bead (Figure 9a). This bead, now coated with the reactant, would be immersed in the reaction mixture and left to form the desired product. At the end of the reaction the beads could be isolated simply by filtration, the unwanted by-products and unused reactants washed off and, finally, the pure product cleaved from the bead [56]. In a multi-step synthesis, these beads could theoretically be carried forward without cleavage, allowing the chemist to construct complex molecules. These could then be isolated at the very end of the synthesis in a pure form, ready for biological assessment. Furthermore, as reagents could now be readily separated from the desired product of each reaction, excess reagents could be added to drive reactions to completion without complicating later synthetic steps or purifications.

As always, such techniques were soon found to have limitations, some of which were easier to overcome than others. For example, the starting material for the synthesis required attachment to its polymeric support and this linker, in a similar manner to a protecting group, had to be tolerant of (and resistant to) all the steps of the synthesis. It then had to be readily cleaved at the correct point in the procedure to release the desired product. Though many elegant chemistries were developed to meet these needs, many of these left part of the linker attached to the target molecule (as denoted by the group 'Y' in Figure 9a). In some cases, this 'stub' could be chosen by design to offer a functional group that conveyed some biological activity in the final molecule. However, this was not always the case and much time was spent developing so-called 'traceless linkers' to alleviate this issue [57–60].

Solid-phase synthesis worked very well when reactions could be driven to completion. However, as most analytical techniques were designed to monitor solution-phase reactions, ensuring complete reaction had occurred was not a trivial undertaking and often required cleavage of a small quantity of product, followed by analysis of the resultant mixture [61]. In addition, much of the available chemistry in the literature has been developed for use in the solution phase and it was found that this chemistry could not always be readily applied to the synthesis of molecules attached to a solid support.

These issues, taken together, somewhat suppressed the enthusiasm for solid-supported chemistry in the average medicinal chemistry laboratory. However, in those laboratories specialising in making large numbers of compounds (for example, those preparing compound libraries for high-throughput screening), the application of solid-supported chemistry by those with the appropriate expertise allowed considerable increases in productivity.

More relevant to the synthetic chemist has been the development of *solid-supported reagents* [62–66]. In this scenario, the reactant remains in solution and it is the reagent that is immobilised (Figure 9b). Being solid-supported, excess reagents can still be added to the reaction and removed easily, allowing reactions to be driven to completion. However, as the starting material and products remain in solution, analysis of the reaction is much more facile and can employ the same techniques used for traditional solution-phase chemistry. Furthermore, the issue of the undesirable 'stub' left on the target molecule after cleavage from the solid support is avoided. A further useful advantage of such reagents is that, owing to their attachment to a bulky support, individual reagent molecules are unlikely to come into close enough contact to react with other similarly supported reagents, thereby reacting only with the compounds in solution. As such, reagents that would be mutually incompatible in solution, such as acids and bases or oxidants and reductants, can be used concomitantly in the same vessel to perform certain transformations [64,66–68]. This is particularly useful in circumstances where an intermediate in a synthesis is unstable and cannot be isolated, but can instead be reacted further (ideally to form a more stable derivative) in the same reaction vessel. A closely related approach is the use of solid-supported scavengers (Figure 9c). In this case, the reaction is performed in solution, using either conventional or solid-supported reagents. Upon completion, the addition of one or more solid-supported reagents (which contain reactive functionality) react with any unused starting material or reagent, allowing for easy removal [65,66].

Though the use of solid-supported reagents is generally easier and requires less specialist knowledge and equipment than solid-supported synthesis, it is worth noting that the final product may still require purification, though this tends to be less complex than would otherwise be the case. It should also be noted that solid-supported reagents are considerably more expensive than their solution-phase counterparts. Despite their usefulness in preparing libraries of compounds for biological assessment, particularly in the early stages of a medicinal chemistry programme, the cost of such reagents often precludes their use in larger scale synthetic endeavours.

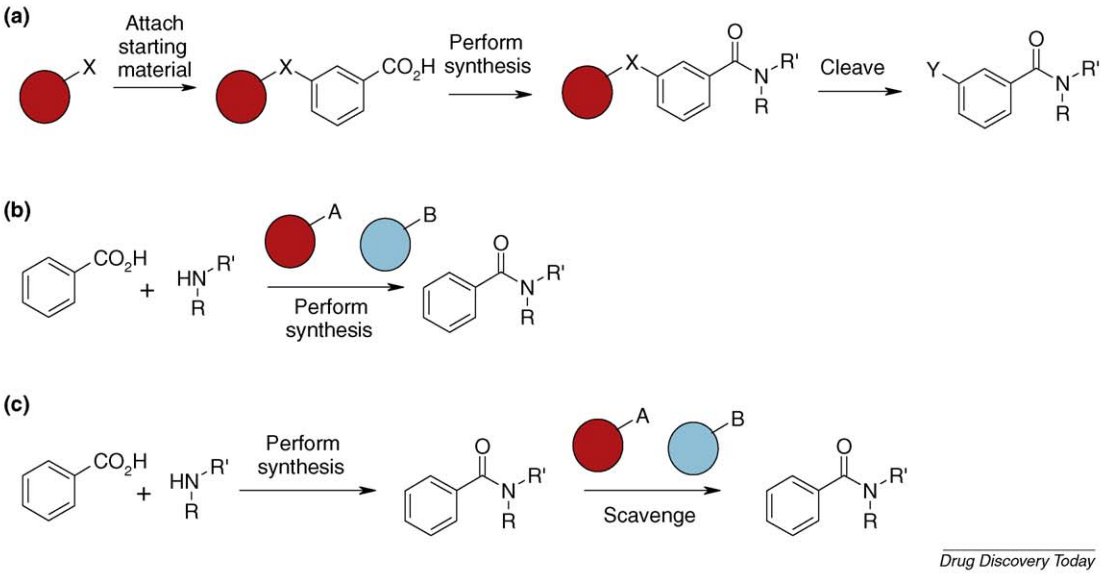

FIGURE 9

Solid-phase chemistries. (a) Solid supported synthesis; (b) solid supported reagents; (c) scavenging reagents.

could be separated out or '*deconvoluted*' to give a single, active compound. However this process, which involved re-synthesising and testing ever smaller mixtures of compounds to track down those responsible for activity, was highly time-consuming and often failed to deliver a single, active molecule. Observed activity in these assays was often confounded by the synergistic interactions of different molecules or the combined effect of many weakly active compounds that could lead to a high false-positive hit rate [16,17]. These issues led to the implementation of methods for tracking the chemical history of each solid-supported particle through its synthesis using methods such as radiofrequency encoding of each particle [18,19]. In this way the mixtures of compounds, still attached to their solid supports, could be deconvoluted before cleavage from the resin, enabling the isolation of single compounds rather than mixtures for screening. Though this approach gave rise to higher quality compounds for screening, it did require additional investments in hardware, further increasing the cost and complexity of such syntheses and limiting its application to dedicated synthetic teams within larger organisations.

Parallel synthesis

The issues surrounding combinatorial chemistry and a desire to put efficient chemistry back into the hands of the bench chemist led to ingenious ways of performing increasing numbers of *discrete* chemical reactions at the same time, an approach referred to as 'parallel synthesis'. The early systems were usually developed in-house, and were often ingenious in design. Some of these systems have been developed commercially and are now commonplace in the laboratory [20]. Simply, these systems comprise drilled aluminium blocks that sit atop a magnetic stirrer/hotplate. The holes in the block are precision machined to allow a snug fit with individual glass reaction tubes. As with traditional apparatus, these tubes can be heated or cooled and placed under an inert atmosphere to exclude oxygen and moisture, lending themselves to parallel reactions requiring air-sensitive reagents. Dependant upon the quantity of product required from the reaction, different system capacities are available, where a trade-off is made between numbers of potential reaction vessels and the working volume of each vessel.

To allow further increases in numbers of compounds synthesised, tools have been developed to allow rapid, parallel synthesis using the solid-phase techniques discussed in Box 2. These systems differ widely in terms of design but tend to offer a very similar set of features, such as:

- efficient shaking of reaction mixtures
- heating and cooling of the reaction vessels
- reagent addition during the reaction
- use of inert atmospheres
- easy access to products, generally by filtration to remove the resin-based reactants and reagents

Automated compound synthesis

A more elaborate extension to these systems is the automated chemical synthesisers. Here, a robotic liquid-handling platform can be programmed to add the desired quantities of reagents and solvents to a pre-determined reaction vessel. The conditions in the reaction vessel can be controlled and, in some cases, the product can be isolated at the end of the reaction. While these machines allow the production of considerable numbers of compounds, for reasons of both cost and complexity they are generally only found in specialist laboratories and not in a 'normal' medicinal chemistry environment. Additional discussions of the design and use of such systems are therefore outside the scope of this overview, though the area has been the subject of recent reviews [21,22].

Microwave chemistry

In the mid 1980s, it was discovered that heating chemical reactions in a conventional microwave oven appeared to greatly

enhance the rate of reaction [23,24]. Unfortunately, the reproducibility (and thus the wider applicability) of these experiments was often poor as it was difficult to standardise an experimental protocol across different domestic microwave ovens. However, over the past ten years microwave devices designed specifically for the conduct of chemical reactions have become commercially available. Such systems employ sealed, pressurised glass vessels that experience controlled heating using high power, focused microwave energy. The use of sealed tubes allows the use of temperatures well above the normal boiling point of the solvent in use, dramatically reducing reaction times from hours to minutes. (There is an oft-quoted rule of thumb that states increasing the temperature of a reaction by 10 °C doubles the rate of the reaction. Therefore, allowing reactions at, for example, 60 °C above the normal boiling point of a solvent can reduce the time needed for a 24-h reaction to just 20 min!) In general, temperatures of 80 °C above normal boiling point are not uncommon in these systems.

This increased rate of reaction naturally allows increases in productivity (the key driver behind most of these innovative technologies) but also offers a positive side effect. Although these reactions are heated to a higher temperature than is normally the case, the fact that they are heated for a much shorter length of time appears to reduce thermal degradation of the reaction mixture. In general, reactions performed under microwave irradiation often appear to have lower impurity profiles than those conducted over longer timescales in traditional apparatus. Furthermore, these higher temperatures and pressures can often force a particularly sluggish reaction to occur on poorly reactive compounds, which cannot be made to react using more conventional means [25–28].

As certain materials, such as metals, are very good absorbers of microwave energy, metal-catalysed reactions (such as the Suzuki reaction, see ''Palladium catalysed processes'') are often enhanced considerably by the use of microwave heating.

Purification of target compounds

Affinity ('column') chromatography

The application of the equipment and technology described above has yielded increases in the productivity of the medicinal chemist, but has served to transfer the bottleneck in compound preparation from synthesis of compounds to their purification. Traditionally, organic compounds have been purified by affinity chromatography in glass columns packed with finely ground silica [29]. This packing has a highly polar surface that forms strong, non-covalent interactions with polar hydrophilic compounds and interacts less strongly with more hydrophobic ones. The desired compound can be selectively eluted from the column and be obtained in a pure form by washing the column with the appropriate choice of solvents. Recently, the health risks associated with fine silica dust have led to the adoption of pre-prepared, sealed silica cartridges for this purpose. These cartridges can be used in the same manner as a traditional affinity column, or can be inserted into one of the many automated or semi-automated purification systems now available, which range in complexity from a simple solvent pump and cartridge holder to devices with on-line detection of eluting components, fraction collectors and multiple pumps allowing gradient elution, which gives better resolution.

High performance liquid chromatography

While the purification systems described above are generally applicable to the majority of organic compounds, in some cases additional purification is required. This may be because the compound remains contaminated with a compound of very similar polarity, which cannot be separated by this method, or because the compound is destined for an assay in which extremely high purity is required, such as an Ames mutagenicity screen [30]. In these cases purification by HPLC (high performance liquid chromatography) is the method of choice [31]. Although analytical HPLC is widely used in the laboratory for monitoring the progress of reactions and assessing purity, its low injection capacity makes it an inappropriate technique for purification. However, preparative or semi-preparative HPLC systems, with their larger column volumes and greater capacity, allow gram quantities of compounds to be readily purified. Alongside the advances in automated column chromatography, preparative HPLC has also evolved considerably in the past 10 years. Modern systems often incorporate 'open-access' software, taking the day-to-day operation of the machines out of the hands of trained analytical chemists and allowing chemists to submit their samples for the machine to purify on an unattended basis. Indeed, some systems will not only pre-analyse the reaction mixture, but can also identify the most suitable purification methodology, purify the submitted sample and even re-analyse the purified material to confirm its level of purity.

Compound analysis

After successful purification, the chemist will confirm both the purity and structure of the compound before registration in corporate databases and submission for biological evaluation.

The use of analytical HPLC has been alluded to in the preceding section as a means of assessing compound purity. However, it gives little indication of the identity of the compound unless it is coupled to a mass spectrometer. In this case, the technique is referred to as 'LC–MS' (Liquid Chromatography–Mass Spectrometry) and, in addition to purity, also provides an indication of molecular weight. Indeed, many preparative HPLC systems now incorporate 'Mass Detection', where a compound is isolated by detection of the desired molecular weight, rather than by retention time.

Whilst mass spectrometry can give some confirmation of molecular identity, more substantial evidence can be obtained from Nuclear Magnetic Resonance (NMR) spectroscopy. The routine 'proton' spectrum gives discrete signals for each hydrogen atom environment in the molecule, along with some information as to those to which it is adjacent. Similarly, 'carbon' NMR experiments provide similar information for the carbon skeleton. However, these are used less routinely as they have longer acquisition times owing to the low natural abundance of the natural ^{13}C isotope which, unlike the more abundant ^{12}C isotope, is observable by NMR spectroscopy. Additionally, there are many more complex NMR experiments giving further information about bond connections and spatial orientation of parts of the molecule to confirm 'difficult' or ambiguous cases. These more advanced experiments are normally acquired and interpreted by an experienced analytical chemist.

Compound synthesis: methodology and terminology

The medicinal chemist will commonly be in the position where the molecule (or family of molecules) to be synthesised has been

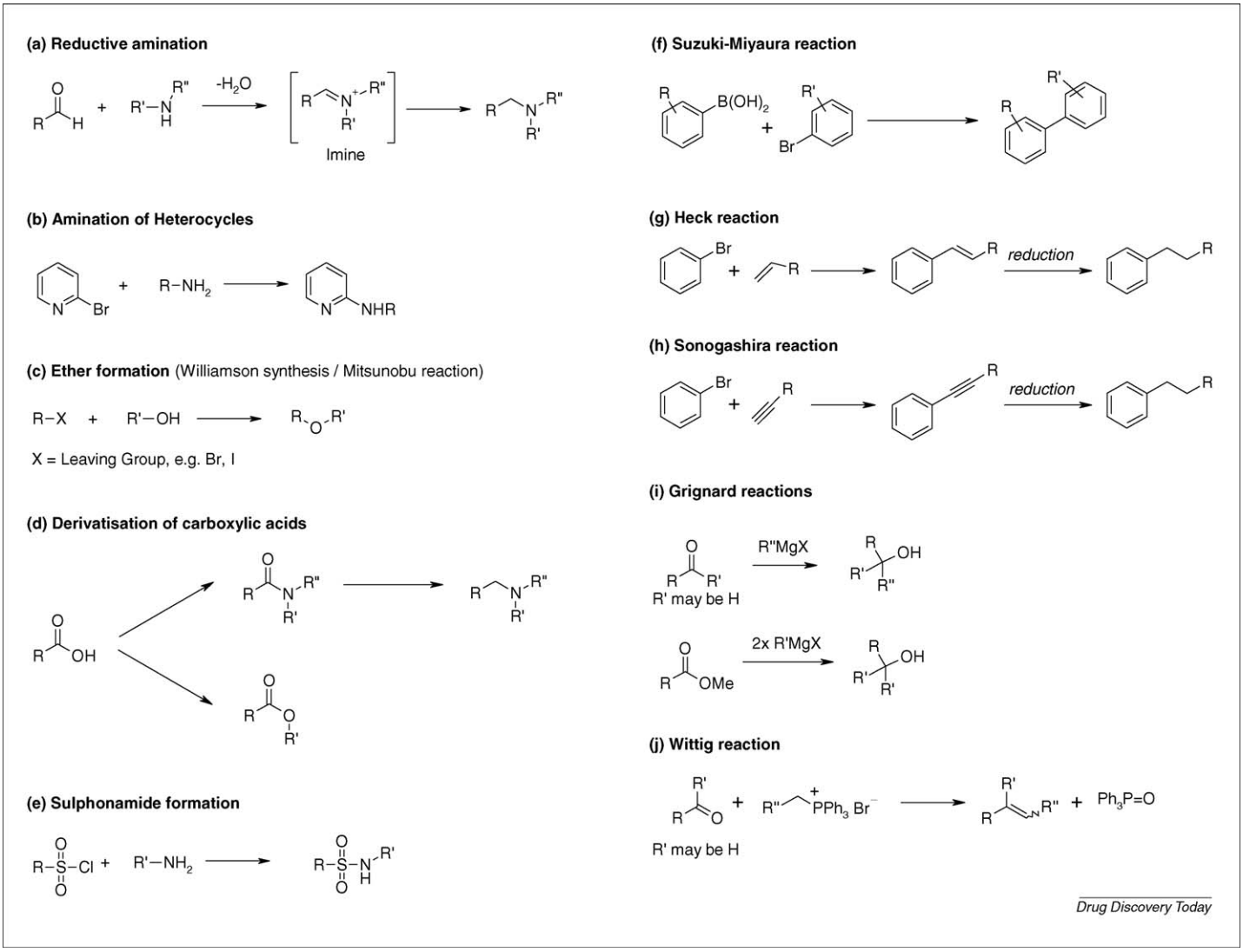

FIGURE 7

An overview of synthetic transformations favoured by medicinal chemists.

identified beforehand. The chemist must then determine the most efficient way to piece the derivatives together, predominantly using a knowledge of which functional groups can be constructed most reliably. The chemist will, in effect, work backwards, deconstructing the compound one functional group at a time until the point is reached where each fragment is available from in-house or commercial sources. This approach is known as *retrosynthetic analysis*, or *retrosynthesis*. It relies upon a good working knowledge of reliable, robust reactions that can be employed in the construction of new functional groups and/or chemical bonds [32,33]. The order of steps in this analysis is then reversed to plan the forward synthetic scheme, from commercial reagents to final product, with the individual reaction conditions used in each step drawn from the chemist's personal experience and those described in the chemical literature over the past century.

This retrosynthetic analysis will generate many possible synthetic pathways and the chemist will select the route that is felt to offer the best balance of expedience, efficiency and safety. Given the inherent dangers of using highly flammable solvents, toxic heavy metal catalysts and reagents that may be explosive, mutagenic or may react violently with atmospheric oxygen or moisture, the chemist must judge whether the potential hazards of a specific route are acceptable and comply with local safety rules and company safety policies. As the scale of a reaction increases, environmental concerns also need to be taken into account, requiring safe disposal of increased quantities of potentially hazardous by-products and large volumes of used solvent. However, these concerns are more likely to be met as a compound passes into development and as such are less crucial in the small-scale synthesis of compounds for biological evaluation.

Often, each chemist will have their own favoured set of reactions and any coverage of the chemistry employed in drug discovery chemistry will naturally display some element of this bias. While a recent review has surveyed the reaction types most commonly used in the large scale manufacture of pharmaceuticals [34], no such review exists for those reactions favoured in the small-scale synthesis of drug candidates. However, informal discussions between the authors and a small number of practicing medicinal chemists defined a number of key reaction types that were almost universally considered to be essential in the rapid synthesis of compounds for bio-assay (Figure 7). With one exception, these involved the formation of new chemical bonds, rather than the

transformation of one functional group into another (known as a *functional group interconversion*). These favoured reactions can be simplified into two types: those involving carbon–heteroatom bond formation and those involving carbon–carbon bond formation. It should be noted that the descriptions of these favoured transformations may describe a particular chemical transformation, such as a '*reductive amination*' while many others are known as '*named reactions*' (such as the Suzuki reaction), named after the lead investigator in the group where they were discovered or popularised.

Carbon–heteroatom bond formation

Carbon–nitrogen (C–N) bond formation

The amine functional group is of particular importance in medicinal chemistry. The group offers both a hydrogen bonding properties and the potential for increasing solubility of the compound, together with a simple and widely applicable method of forming a C–N bond.

The simplest method of C–N bond formation involves the reaction of a pre-existing amine with a carbon atom bearing an easily displaceable moiety known as a '*leaving group*', often a halogen atom such as bromine. This method of direct amination is straightforward, but a major limitation is that the product is more reactive than the starting material and thus over-reaction tends to occur, leading to a mixture of products.

To overcome this issue, the chemist will more frequently undertake a '*reductive amination*' [35,36] (Figure 7a). Here, the amine is reacted with an aldehyde to form an imine. This imine can be isolated, but more often the resultant carbon–nitrogen double bond is immediately converted to a carbon–nitrogen single bond (a '*reduction*'). The intermediate imine does not suffer from the issues of over-reaction described above, offering the chemist greater control over the reaction than the seemingly more straightforward direct approach.

Despite the caveats described above, direct amination can be particularly useful in certain circumstances. One key application of this method is the reaction of amines with heterocycles, particularly those containing a nitrogen atom with a leaving group (usually a chlorine, bromine or, on occasion, fluorine) attached the adjacent carbon atom of the heterocycle [37] (Figure 7b). The chemical nature of such ring systems allows facile displacement of the leaving group to form an aminoheterocycle, in a controllable manner that is not prone to over-reaction. Other functional groups are also able to displace a halogen from a heterocyclic ring system, but the case outlined above is the most likely to be encountered.

This process is known as *Nucleophilic Aromatic Substitution* (or 'S_NAr'), and can be facilitated both by appropriately placed nitrogen atoms within the aromatic ring or by certain functional groups (such as the nitro- and cyano- moieties) attached to the aromatic ring.

Carbon–oxygen (C–O) Bond formation

In a manner analogous to the direct amination method described above for the formation of C–N bonds, the hydroxy group can also displace a leaving group attached to a carbon atom to form a new C–O bond, in a process known as the Williamson ether synthesis (Figure 7c) [38]. In this method, the reacting component containing the oxygen atom is only able to react once and therefore is not prone to over-reaction, making the reaction much more controllable. Though this control makes the ether linkage attractive, it differs from the amine described above in that it lacks hydrogen bond donor functionality and tends to make a lesser contribution toward solubility.

A more recent development of this methodology is the Mitsunobu reaction that allows direct, convenient coupling of two alcohols to form the ether linkage, negating the requirement to first introduce a leaving group to one reagent [39,40]. This reaction is particularly applicable to ethers where the oxygen atom is directly attached to an aromatic system, which can be troublesome to prepare via the Williamson synthesis.

As described in the preceding section relating to amine formation, alcohols can also participate in nucleophillic aromatic substitution processes to form aromatic ethers. Phenols (aromatic alcohols), thiols ('mercaptans', in which the oxygen atom has been replaced by a sulphur atom) and thiophenols (*cf* phenols), also undergo similar reactions to give the corresponding ethers or thioethers.

Derivatisation of carboxylic acids

The conversion of the carboxylic acid functional group into a family of related derivatives is one of the few functional group interconversions mentioned as a favoured reaction by the surveyed chemists (Figure 7d). Functionalisation of a carboxylic acid predominantly involves the formation of either a new C–N or C–O bond, and therefore could be considered in either of the above two sections. However, the versatility and scope of this transformation merits special mention as a separate case.

Direct functionalisation of the carboxylic acid moiety can be rather difficult, as it does not possess a particularly good leaving group. The acid is usually converted into a more reactive form, such as an acid chloride, promoting a much faster reaction. This activated derivative can then be reacted with an alcohol to form an ester, or an amine to form an amide. Indeed, the formation of an amide is probably the most widely employed synthetic transformation in medicinal chemistry. As the basis of peptide and protein chemistry, many routes have been developed to allow the rapid formation of amides. These routes often employ '*coupling agents*' which form '*activated esters' in situ*, which can be prepared under much gentler (and therefore more widely applicable) conditions than those used to form acid chlorides. These conditions allow the tolerance a wide range of functional groups and protecting groups, making this reaction an ideal late-stage step in the preparation of large screening libraries such as those prepared by combinatorial chemistry. In terms of the diversity of commercially available starting materials, ease of synthesis and overall speed of compound production, few reactions allow exploration of structure–activity relationships as expediently as the amide coupling, making it one of the chemist's favourite reaction types.

Amides themselves offer several useful biological properties. They offer both hydrogen bond donors and acceptors and are also relatively stable to metabolism. By comparison, the equivalent oxygen derivative, the ester, is much less metabolically stable and is readily broken down by the body. Few drugs contain ester functionality, though this derivative is often used as a versatile and tolerant protecting group for a carboxylic acid during

synthesis. Additionally, the biological lability of such groups can be advantageous in the formation of pro-drugs [41,42]. In such cases, the ester can be used to temporarily mask the carboxylic acid functionality, overcoming associated issues such as poor cell penetration. The acid itself can then be revealed by cellular processes upon reaching the desired site of action.

It should also be noted that amides could be reduced to the corresponding amine. The versatility and scope of the amide coupling reaction thus allows the controlled formation of an equally wide variety of amines. Alongside reductive amination, this offers an additional method of alleviating the issues of reaction control discussed previously.

In a directly analogous manner to that described for the derivatisation of carboxylic acids, sulphonic acids can be converted to the sulphonamide or sulphonate ester by reaction with an amine or alcohol respectively, via the activated sulphonyl chloride intermediate (Figure 7e). These derivatives offer similar physicochemical properties to the corresponding carboxylic acid derivatives but as their three-dimensional arrangement of atoms is quite different, these sulphonyl derivatives offer alternate geometries for interactions with biological targets. Despite the apparent similarity, sulphonic acid derivatives are structurally very different and typically lead to different structure–activity relationships.

Carbon–carbon (C–C) bond forming reactions

Palladium-catalysed processes

Unlike the formation of carbon–heteroatom bonds, where the different properties of the participating atoms facilitate reaction, it is more difficult to form a bond between two atoms of such similar nature as in a carbon–carbon bond. In most cases, these bonds can only be formed in the presence of some mediating functional group, which modifies the chemical properties of one carbon atom sufficiently to allow a selective reaction to occur. Though a multitude of methods exist for linking two carbon atoms, many of these are only useful in specific circumstances. Furthermore, many of the reagents required for these transformations require special handling, owing to their toxicity, air and/or moisture sensitivity.

One particular type of C–C bond forming reaction has gained overwhelming popularity owing to its wide applicability and reliability. This methodology is the palladium-catalysed C–C bond formation, most usually typified by the Suzuki–Miyaura reaction, often simply known as the Suzuki coupling (Figure 7f) [43,44].

In its simplest form, the Suzuki reaction allows the direct coupling of a halogenated aromatic or heteroatomatic ring to a boronic acid derivative, which is usually an aromatic or heteroaromatic ring, an alkene or, on occasion, a non-aromatic system. These boronic acids are themselves readily prepared from a halogen-containing precursor.

Though the Suzuki reaction sits amongst a family of related palladium-catalysed reactions [45] that are mediated by different metal-based reagents (such as the Negishi coupling [which employs zinc rather than boron] and the Stille coupling [mediated by tin]), the reaction offers several clear advantages over its cousins. Of primary importance is the aforementioned ease of preparation of the boronic acids. Diverse selections of these air-stable and comparatively non-toxic derivatives are widely available from commercial sources and the coupling conditions used are both mild and highly chemoselective, seldom interfering with other functionality present in the molecule. Given these advantages, the Suzuki reaction is a key transformation in the construction of molecular scaffolds in drug discovery.

In certain cases, palladium-mediated reactions can also be effected without the need for the direct incorporation of an additional metallic mediator into one precursor, particularly in cases where an aromatic or heteroaromatic bromide is coupled directly to either an alkene or a terminal alkyne (one in which there are no non-hydrogen substituents at the reacting end of the alkyne). These transformations are known as the Heck [46] and Sonogashira [47–49] couplings respectively and allow the straightforward linkage of molecular fragments with either a carbon–carbon double or triple bond (Figure 7 g, h). Such bonds can be useful in their own right (for example, by introducing molecular rigidity), but can also be readily hydrogenated (reacted with hydrogen) to effect a conversion to a carbon–carbon single bond. Though this two-step process may appear inefficient and cumbersome, its reliability and versatility offers a favoured method of forming a carbon–carbon single bond between two molecular entities.

Use of Grignard reagents

Though palladium-catalysed C–C bond formation reactions are highly prevalent in the synthesis of drug molecules, other metal-mediated processes are commonly encountered in the construction of new molecules. For example, the magnesium-derived Grignard reagents are widely employed owing to their ease of synthesis and versatility. Such reagents are readily prepared by reacting an alkyl, aromatic or, in limited cases, a heteroaromatic system containing a halogen (usually a bromine) with powdered magnesium metal. Though sensitive to both air and moisture, Grignard reagents can be handled with relative ease and are a powerful synthetic reagent.

Most commonly reacted with a functional group containing a carbonyl (a carbon–oxygen double bond) such as an aldehyde or ketone, the reagent appends a new carbon substituent to the carbon of the C=O bond and transforms the carbonyl oxygen to an alcohol (Figure 7i). Reaction of such a reagent with an aldehyde or ketone results in the formation of an alcohol with either two substituents attached (a secondary alcohol) or three substituents (a tertiary alcohol) respectively. Grignard reagents can also be used to modify esters, initially displacing the alcohol moiety of the ester to form a new ketone, which itself reacts with a second molecule of the Grignard reagent to form a tertiary alcohol with two identical substituents.

The Wittig reaction

The final transformation we will consider in this section is the phosphorous-mediated Wittig reaction (Figure 7j). This transformation also acts upon aldehydes and ketones and results in the formation of a new carbon–carbon double bond, in effect directly replacing the oxygen of the carbonyl with the carbon atom of the Wittig reagent [50–52]. Like the Grignard reagents above, the Wittig reagents are formed from alkanes with an attached bromine atom. Reaction of an alkyl bromide with triphenyl phosphine yields an intermediate phosphonium salt, which can then react with the aldehyde or ketone to generate the desired C=C bond. Though synthetically powerful, the reaction has some notable

drawbacks, not least the limited commercial availability of the initial phosphonium salts. Furthermore, the resultant phosphine oxide by-product is often particularly troublesome to remove from the desired product after the completion of the reaction.

Summary

Though this review touches only on a limited selection of terminology, it is hoped that it will enable scientists from other disciplines to understand better the phraseology used by medicinal chemists. The limitations of an article such as this mean that a comprehensive and detailed discussion of the myriad of techniques and reactions employed by synthetic chemists is not possible, nor indeed appropriate. However, the authors hope the content may act as a useful frame of reference for those outside the chemistry laboratory, facilitating more detailed discussions of the techniques and methodology applied to the synthesis of molecules for biological evaluation.

Acknowledgements

The course upon which this primer was based was originally conceived through discussions with our computational colleagues Xavier Barill and Nicolas Foloppe, both of whom deserve due credit for bringing the workshop to fruition. We are also grateful to Karen Benwell, Hollie Blunt, Jenifer Borgognoni, Zoë Daniels, Peter Kierstan and Lisa Wright for their helpful comments and suggestions during the preparation of this manuscript.

References

1 Bemis, G.W. and Murcko, M.A. (1996) The properties of known drugs. 1. Molecular frameworks. *J. Med. Chem.* 39, 2887–2893
2 Bemis, G.W. and Murcko, M.A. (1999) The properties of known drugs. 2. Side chains. *J. Med. Chem.* 42, 5095–5099
3 Shelat, A.A. and Guy, R.K. (2007) Scaffold composition and biological relevance of screening libraries. *Nat. Chem. Biol.* 3, 442–446
4 Furet, P. *et al.* (2008) Entry into a new class of protein kinase inhibitors by pseudo ring design. *Bioorg. Med. Chem. Lett.* 18, 897–900
5 Boehm, M. *et al.* (2008) Similarity Searching and scaffold hopping in synthetically accessible combinatorial chemistry spaces. *J. Med. Chem.* 51, 2468–2480
6 Haubertin, D.Y. and Bruneau, P. (2007) A database of historically-observed chemical replacements. *J. Chem. Inf. Model.* 47, 1294–1302
7 Southall, N.T. and Ajay, (2006) Kinase patent space visualisation using chemical replacements. *J. Med. Chem.* 49, 2103–2109
8 Stewart, K.D. *et al.* (2006) Drug Guru: a computer software program for drug design using medicinal chemistry rules. *Bioorg. Med. Chem.* 14, 7011–7022
9 Lewell, X.Q. *et al.* (2003) Drug rings database with web interface. A tool for identifying alternative chemical rings in lead discovery programs. *J. Med. Chem.* 46, 3257–3274
10 Sheridan, R.P. (2002) The most common chemical replacements in drug-like compounds. *J. Chem. Inf. Comput. Sci.* 42, 103–108
11 (1993) *A Guide to IUPAC Nomenclature of Organic Compounds*. IUPAC/Blackwell Science (Further Reading, below)
12 Eller, G.A. (2006) Improving the quality of published chemical names with nomenclature software. *Molecules* 11, 915–928
13 Baran, P.S. *et al.* (2007) Total synthesis of marine natural products without using protecting groups. *Nature* 446, 404–408
14 Hoffmann, R.W. (2006) Protecting-group-free synthesis. *Synthesis* 3531–3541
15 Dolle, R.E. *et al.* (2008) Comprehensive survey of chemical libraries for drug discovery and chemical biology: 2007. *J. Comb. Chem.* 10, 753–802 (examples of the scope and diversity of combinatorial libraries can be found along with the preceding reviews in this series cited therein)
16 Feng, B.Y. and Shoichet, B.K. (2006) Synergy and antagonism of promiscuous inhibition in multiple-compound mixtures. *J. Med. Chem.* 49, 2151–2154
17 Guintu, C. *et al.* (2006) Just-in-time purification: an effective solution for cherry-picking and purifying active compounds from large legacy libraries. *J. Biomol. Screen.* 11, 933–939
18 Xiao, X.-Y. *et al.* (2000) Solid-phase combinatorial synthesis using microKan reactors, Rf tagging, and directed sorting. *Biotechnol. Bioeng.* 71, 44–50
19 Kiao, X.-Y. and Nicolaou, K.C. (2000) High-throughput combinatorial synthesis of discrete compounds in multimilligram quantities: non-chemical encoding and directed sorting. In *Combinatorial Chemistry: A Practical Approach* (Fenniri, H., ed.), p. 432, Oxford University Press
20 Reader, J.C. (2004) Automation in medicinal chemistry. *Curr. Top. Med. Chem.* 4, 671–686
21 Koppitz, M. and Els, K. (2006) Automated medicinal chemistry. *Drug Discov. Today* 11/12, 561–568
22 Schubert, U.S. *et al.* (2003) Instrumentation for Combinatorial and high-throughput polymer research: a short overview. *Macromol. Rapid Commun.* 24, 33–46
23 Gedye, R. *et al.* (1986) The use of microwave ovens for rapid organic synthesis. *Tetrahedron Lett.* 27, 279–282
24 Giguere, R.J. *et al.* (1986) Application of commercial microwave ovens to organic synthesis. *Tetrahedron Lett.* 27, 4945–4948
25 Dallinger, D. and Kappe, C.O. (2007) Microwave-assisted synthesis in water as solvent. *Chem. Rev.* 107, 2563–2591
26 Alexandre, F.-R. *et al.* (2003) Microwaves in drug discovery and multi-step synthesis. *Mol. Divers.* 7, 273–280
27 Kappe, C.O. (2004) Synthetic Methods. Controlled microwave heating in modern organic synthesis. *Angew. Chem. Int.* 43, 6250–6284
28 Walthey, B. *et al.* (2002) The impact of microwave-assisted organic chemistry on drug discovery. *Drug Discov. Today* 7, 373–380
29 Still, W.C. *et al.* (1978) Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* 43, 2923–2925
30 Mortelmans, K. and Errol Zeiger, E. (2000) The Ames Salmonella/microsome mutagenicity assay. *Mutation research/fundamental and molecular mechanisms of mutagenesis* 455, 29–60
31 Isbell, J. (2008) Changing requirements of purification as drug discovery programs evolve from hit discovery. *J. Comb. Chem.* 10, 150–157 [and references therein]
32 Corey, E.J. and Cheng, X.-M. (1995) *The Logic of Chemical Synthesis*. Wiley
33 Warren, S. (1983) *Organic Synthesis: The Disconnection Approach*. WileyBlackwell
34 Carey, J.S. *et al.* (2006) Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* 2337–2347
35 Baxter, E.W. and Reitz, A.B. (2002) Reductive aminations of carbonyl compounds with borohydride and borane reducing agents. *Org. React.* 59, 1–714
36 Abdel-Magid, A.F. and Mehrman, S.J. (2006) A Review on the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes. *Org. Proc. Res. Dev.* 10, 971–1031
37 Collins, I. (2000) Rapid analogue syntheses of heteroaromatic compounds. *J. Chem. Soc., Perkin Trans.* 1, 2845–2861
38 Williamson, A. (1851) Theory of ether formation. *Liebigs Ann.* 77, 37–49
39 Mitsunobu, O. (1981) The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis* 1–28
40 Hughes, D.L. (1992) The Mitsunobu reaction. *Org. React.* 42, 335–656
41 Ettmayer, P. *et al.* (2004) Lessons learned from marketed and investigational prodrugs. *J. Med. Chem.* 47, 2393–2404
42 Rautio, J. *et al.* (2008) Prodrugs: design and clinical applications. *Nat. Rev. Drug Discov.* 7, 255–270
43 Kotha, S. (2002) Recent applications of the Suzuki-Miyaura cross-coupling reaction in organic synthesis. *Tetrahedron* 58, 9633–9695
44 Miyaura, N. and Suzuki, A. (1995) Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* 95, 2457–2483
45 Stanforth, S.P. (1998) Catalytic cross-coupling reactions in biaryl synthesis. *Tetrahedron* 54, 263–303
46 Heck, R.F. (1982) Palladium-catalyzed vinylation of organic halides. *Org. React.* 27, 345–390
47 Sonogashira, K. (2002) Development of Pd-Cu catalyzed cross-coupling of terminal acetylenes with sp2-carbon halides. *J. Organomet. Chem.* 653, 46–49
48 Negishi, E.-I. (2002) A genealogy of Pd-catalyzed cross-coupling. *J. Organomet. Chem.* 653, 34–40
49 Negishi, E.-I. and Anastasia, L. (2003) Palladium-catalyzed alkynylation. *Chem. Rev.* 103, 1979–2017
50 Maercker, A. (1965) The wittig reaction. *Org. React.* 14, 270–490

51 Boutagy, J. and Thomas, R. (1974) Olefin synthesis with organic phosphonate carbanions. *Chem. Rev.* 74, 87–99
52 Maryanoff, B.E. and Reitz, A.B. (1989) The Wittig olefination reaction and modifications involving phosphoryl-stabilised carbanions. Stereochemistry, mechanism and selected synthetic aspects. *Chem. Rev.* 89, 863–927
53 Kubinyi, H. (2001) Hydrogen bonding, the last mystery in drug design? In *Pharmacokinetic Optimization in Drug Research. Biological, Physicochemical, and Computational Strategies* (Testa, B. *et al.* eds), pp. 513–524, Helvetica Acta and Wiley-VCH
54 Meyer, E.A. *et al.* (2003) Interactions with aromatic rings in chemical and biological recognition. *Angew. Chem. Int. Ed.* 42, 1210–1250
55 Davis, A.M. and Teague, S.J. (1999) Hydrogen bonding, hydrophobic interactions and failure of the rigid receptor hypothesis. *Angew. Chem. Int. Ed.* 38, 736–749
56 Merrifield, R.B. (1963) Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc.* 85, 2149–2154
57 Gil, C. and Bräse, S. (2004) Traceless and multifunctional linkers for the generation of small molecules on solid supports. *Curr. Opin. Chem. Biol.* 8, 230–237
58 Blaney, P. *et al.* (2002) Traceless solid-phase organic synthesis. *Chem. Rev.* 102, 2607–2624
59 Guillier, F. *et al.* (2000) Linkers and cleavage strategies in solid-phase organic synthesis and combinatorial chemistry. *Chem. Rev.* 100, 2091–2157
60 Backes, B.J. and Ellman, J.A. (1997) Solid support linker strategies. *Curr. Opin. Chem. Biol.* 1, 86–93
61 Kay, C. *et al.* (2001) Solid-phase reaction monitoring—chemical derivatisation and off-bead analysis. *Biotechnol. Bioeng.* 71, 110–118
62 Solinas, A. and Taddei, N. (2007) Solid-supported reagents and catch-and-release techniques in organic synthesis. *Synthesis* 2409–2453
63 Ley, S.V. *et al.* (2006) Polymer-supported reagents and scavengers in synthesis. In *Comprehensive Medicinal Chemistry II, vol. 3* (Triggle, D. and Taylor, J., eds), pp. 791–836, Elsevier
64 Ley, S.V. and Baxendale, I.R. (2002) New tools and concepts for modern organic synthesis. *Nat. Rev. Drug Discov.* 1, 573–586
65 Eames, J. and Watkinson, M. (2001) Polymeric scavenger reagents in organic synthesis. *Eur. J. Org. Chem.* 1213–1224
66 Ley, S.V. *et al.* (2000) Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation. *J. Chem. Soc., Perkin Trans.* 1, 3815–4195
67 Oikawa, M. *et al.* (2004) One-pot preparation and activation of glycosyl trichloroacetimidates: operationally simple glycosylation induced by combined use of solid-supported, reactivity-opposing reagents. *Tetrahedron Lett.* 45, 4039–4042
68 Bergbreiter, D.E. and Chandran, R. (1985) Concurrent catalytic reduction/stoichiometric oxidation using oligomerically ligated catalysts and polymer-bound reagents. *J. Am. Chem. Soc.* 107, 4792–4793

Further reading

Terrett, N.K.; 1988 ''*Combinatorial Chemistry*'', Oxford Chemistry Masters Series, Oxford University Press. A readable guide to the benefits, issues and limitations associated with solid-phase and combinatorial synthesis

Clayden, J.P.; Greeves, N.; Warren, S.; Wothers, P D.; 2001 ''*Organic Chemistry*'', Oxford University Press. While there are many good general organic chemistry textbooks available, the authors believe this one to be particularly accessible in its presentation

Joule, J.A.; Mills, K.; Smith, G.F.; ''*Heterocyclic Chemistry*'', Chapman & Hall. A good text on heterocyclic chemistry, covering properties, reactions and synthesis. The book is organised by ring system, and includes some general background chapters on each

Kürti, L.; Czakó, B.; 2005 ''*Strategic Applications of Named Reactions in Organic Synthesis*'', Academic Press. A highly accessible guide to 250 'named reactions', each on a single double spread. Each entry contains background, mechanistic details, modifications and some synthetic applications, along with key references to original papers and seminal reviews

Kappe, C.O.; Stadler, A.; 2005 ''*Microwaves in Organic and Medicinal Chemistry*'', Methods and Principles in Organic Chemistry, Vol. 25, Wiley–VCH. This book starts with three excellent background chapters on the theory and equipment of microwave chemistry, before a detailed review of its application to 'general organic synthesis' and 'Combinatorial chemistry and high-throughput organic synthesis'

Although somewhat technical, the International Union of Pure and Applied Chemistry (IUPAC) nomenclature pages (http://www.chem.qmul.ac.uk/iupac/) contain many tables of so-called 'trivial' names, functional groups, and background chapters on stereochemistry, medicinal chemistry and biological nomenclature. The text of reference [11] can also be found here

While not peer-reviewed, the Internet is a useful source of reference material on chemical reactions and terminology. In particular, Wikipedia (http://en.wikipedia.org) has many articles in a readable format, with literature citations. The site also contains extensive lists of specific compounds (http://en.wikipedia.org/wiki/List_of_organic_compounds) and named reactions (http://en.wikipedia.org/wiki/Named_reactions)

Examples of the bench-top parallel synthesis systems referred to in this review are described on the websites of Radleys (www.radleys.co.uk), Glass Solutions (www.glass-solutions.co.uk) and Asynt (www.asynt.com). These systems can be compared to the more traditional ''Quickfit®'' apparatus, manufactured by Scilabware (www.scilabware.com)

For example microwave systems, see Biotage (http://www.biotage.com) and CEM Corp. (http://www.cem.com).

Alongside their catalogue of solid-supported synthesis reagents, Novabiochem (www.merckbiosciences.co.uk) provide a free ''Polymer Supported Reagents Handbook'', which details example applications