Similarity in drugs: reflections on analogue design

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A survey of novel small-molecule therapeutics reveals that the majority of them result from analogue design and that their market value represents two-thirds of all small-molecule sales. In natural science, the term analogue, derived from the Latin and Greek *analogia*, has always been used to describe structural and functional similarity. Extended to drugs, this definition implies that the analogue of an existing drug molecule shares structural and pharmacological similarities with the original compound. Formally, this definition allows the establishment of three categories of drug analogues: analogues possessing chemical and pharmacological similarities (direct analogues); analogues possessing structural similarities only (structural analogues); and chemically different compounds displaying similar pharmacological properties (functional analogues).

The importance of analogue design

In 2002, within the International Union of Pure and Applied Chemistry (IUPAC) Subcommittee for Medicinal Chemistry, a working party on analogue-based drug discovery was formed [1]. A group of us decided to present the subject by editing our collaborative work as a book [2]. Based on our discussions, and given the great importance of analogue design, I felt that some clarifications might be useful. Presenting these clarifications is the purpose of the present perspective.

The process of using marketed drug structures as a basis for investigation (in other words, to practice analogue-based drug design) results in increased efficacy and safety of therapeutic agents, thanks to iterative improvements [3]. For example, 40 years of analogue design allowed progression from the historical antibiotic penicillin G to the modern, orally active, safe, broad-spectrum β-lactams, such as ampicillin and amoxicillin [4]. Similar evolutions are found in the development of neuroleptics, antidepressants and antihypertensive drugs. A survey of the novel small-molecule therapeutics (molecular weight <600 Da) that were launched or approved for the first time in the period 2000–2003 [5,6] reveals that the majority resulted from the continued exploitation of already well-established structural classes (drug analogues) or the rapid expansion of newer structural classes (early-phase analogues) [7,8]. The market value of analogue drugs can be estimated to represent two-thirds of all small-molecule sales. The continued preference for analogue-based approaches has been criticized as being mainly restricted to the synthesis of 'me-too' compounds [9]. In fact, the situation is more subtle and a distinction needs to be established among the three different types of analogues.

What are analogues?

The term analogue, derived from the Latin and Greek *analogia*, has been used in natural science since 1791 to describe structural and functional similarity [10]. Extended to drugs, this definition implies that the analogue of an existing drug molecule shares chemical and pharmacological similarities with the original compound. This definition allows the establishment of three categories of drug analogues:

(i) analogues possessing chemical and pharmacological similarities
(ii) analogues possessing only chemical similarities
(iii) chemically different compounds displaying similar pharmacological properties

The first class of analogues, those that have both chemical and pharmacological similarities, can be considered as direct analogues. These analogues correspond to the category of drugs often referred to as 'me-too' drugs. Usually they are improved versions of a 'pioneer' drug with pharmacological, pharmacodynamic or

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biopharmaceutical advantages over the original. Direct analogue design involves straightforward molecular modifications, such as the synthesis of homologues, vinylogues, isosteres, positional isomers, optical isomers, modified ring systems and twin drugs (homodimers). As a rule, the basic scaffold is conserved or only slightly modified. Fine-tuning can be achieved by means of substituent effects, monitored, for example, using quantitative SAR (QSAR) approaches. Examples are the angiotensin-converting enzyme (ACE) inhibitors derived from captopril, the histamine H_2 antagonists derived from cimetidine and the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors derived from mevinolin. Such analogues are designed for the same industrial and marketing reasons that apply for all other industrial products, such as laptop computers or automobiles, and they offer an advantage to the consumer. In the case of drugs, this means that they provide an advance in therapeutic benefit.

The second class, comprising structural analogues, contains compounds originally prepared as close and patentable analogues of a novel lead, but for which biological assays revealed totally unexpected pharmacological properties. Imipramine provides an historical example of the emergence of such a new activity in that it was originally designed as an analogue of the potent neuroleptic drug chlorpromazine but it revealed antidepressant properties. A more recent example is found with sildenafil, a phosphodiesterase-type-5 (PDE5) inhibitor. Sildenafil was designed as an antihypertensive drug, to capitalize upon the success of other antihypertensive compounds, such as erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA) [11] and zaprinast [12]. Surprisingly, it exhibited particularly good and unexpected activity on male erectile dysfunction during clinical studies. Observation of a new activity can be purely fortuitous but can also result from planned systematic investigations. So, structural analogues originate from those serendipitous discoveries that often happen during clinical investigations. They can also result from a systematic application of multi-target screening a large series of structurally similar compounds.

For the third class of analogues, chemical similarity is not observed; however, they share common biological properties. We propose the term functional analogues for such compounds. Functional analogues were, for a long time, the unpredictable result of fortuitous observations. Examples are the neuroleptics chlorpromazine and haloperidol, and the tranquillizers diazepam and zopiclone. Despite having totally different chemical structures, neuroleptics and tranquillizers show similar affinities for the dopamine and the benzodiazepine receptors, respectively. The design of such drugs is presently facilitated thanks to virtual screening of large libraries of diverse structures.

Are congeners analogues?

The term congener is sometimes used by medicinal chemists instead of the term analogue. However, as already pointed out by Schueller [13], the etymology of the term congener suggests compounds prepared by the same synthetic procedure. He states that, 'congeners are defined in the present context as substances literally con-generated or synthesized by essentially the same synthetic chemical reactions and the same procedures, whereas analogues are substances that are analogous in some respect to the prototype agent in chemical structure. Clearly, congeners can be analogues or vice versa, but not necessarily. Congeners, as defined, are, strictly speaking, usually essentially the same as homologues (i.e. both represent sets of entities arising in essentially the same way). The term congener, although most precisely a synonym for homologue, has today, among various writers, become somewhat more diffuse in meaning so that the terms congener and analogue are frequently used interchangeably in the literature'. According to this definition, most of the antibacterial sulphonamides are congeners, whereas chlorimipramine and chlorpromazine are analogues.

How to design direct analogues

The design of direct analogues starting from a prototype drug (a 'pioneer' drug [7]) is a current practice in the pharmaceutical industry. Among the newer classes to reach the market, the coxibs (Figure 1) represent a recent example of true analogue design.

Generally, the design of true analogues involves straightforward molecular modifications, such as the synthesis of homologues, vinylogues, isosteres, positional isomers, optical isomers, modified ring systems and twin drugs (homodimers) [14,15]. As a rule, the basic scaffold is conserved or only slightly modified. Fine-tuning can be achieved by means of substituent effects, monitored, for example, using QSAR approaches. Drug-like properties are not a major concern because the analogues stem from a starting lead that is already a recognized drug molecule. However, if needed, some filter methods are used, eliminating reactive or toxic groups or accounting for central nervous system (CNS) bioavailabilty or other absorption, distribution, metabolism and excretion (ADME) properties [16].

How to accede to structural analogues

Despite their similar chemical structures, structural analogues exhibit different pharmacological profiles. Typical examples of this type are the steroid hormones estradiol and testosterone (Figure 2a); the antibiotic tetracycline and its analogue; the compound BMS-192548 – a ligand for the central neuropeptide P receptor (Figure 2b) [17]; and the antidepressant minaprine and its cyano analogue SR 95191, a selective inhibitor of type A monoamine oxidase (Figure 2c) [18].

As mentioned previously, most of the structural analogues originate from those serendipitous discoveries that often happen during clinical investigations. For a long time, no straightforward methodologies leading to structural analogues were available. However, presently we can systematically apply multi-target screening to large series of structurally similar compounds. An example is a series of closely related tricyclic isoxazole derivatives in which scientists from Johnson and Johnson [19] observed diverse affinity profiles for the α_{2A}, α_{2C} adrenergic receptors and for the inhibition of the serotonin transporter 5-HTT. Figure 3 shows how relatively modest changes lead to compounds with very different activity profiles.

A particular indication of structural analogues is found in optical isomerism when the two enantiomers present different activity profiles. Such a situation is found for the racemate tetramisole where *S*(−)-levamisole has nematocidal and immunostimulant properties, whereas *R*(+)-dexamisole is an antidepressant [20,21]. Similarly, (−)-3-methoxy-cyproheptadine has anticholinergic properties but (+)-3-methoxy-cyproheptadine exhibits antiserotonin activity [22].

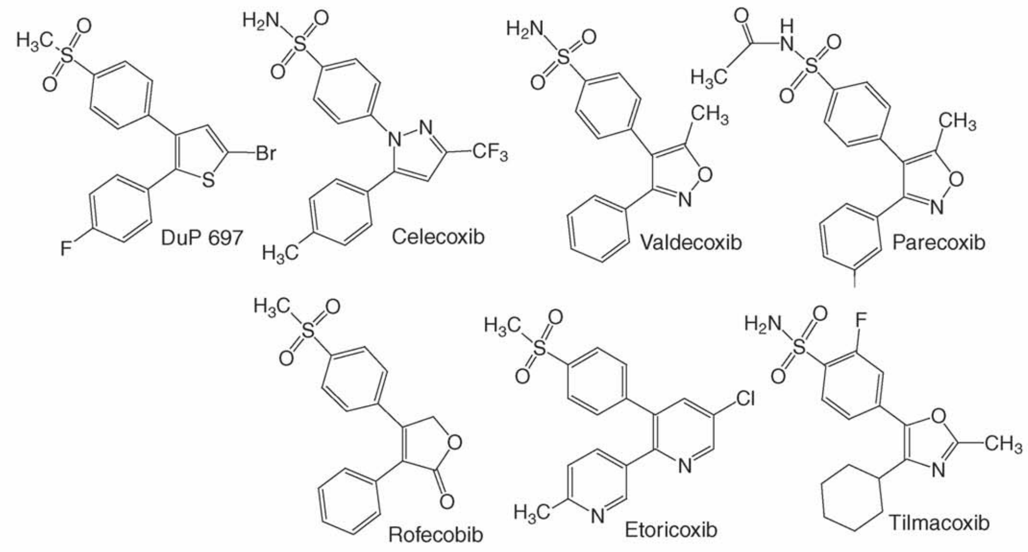


FIGURE 1

Phamacological similarities of coxibs. The coxibs show chemical and pharmacological similarities; thus, they can be considered direct analogues.

How can one design functional analogues?

The design of functional analogues represents the most original method of analogue design. For a long time, discoveries of these analogues were the unpredictable result of fortuitous observations. Presently, the search for functional analogues can be planned, either by using systematic screening or by applying virtual screening or related approaches.

Fortuitous findings

A typical example of a fortuitous finding is the discovery of gabazine, the γ-aminobutyric acid (GABA)-A receptor antagonist [23–25], as the functional analogue of (+)-bicuculline. During a study of minaprine metabolism [26,27], one of its putative metabolites, the hydroxyethyl-amino analogue (Figure 4), was found to present an interesting anticonvulsant profile.

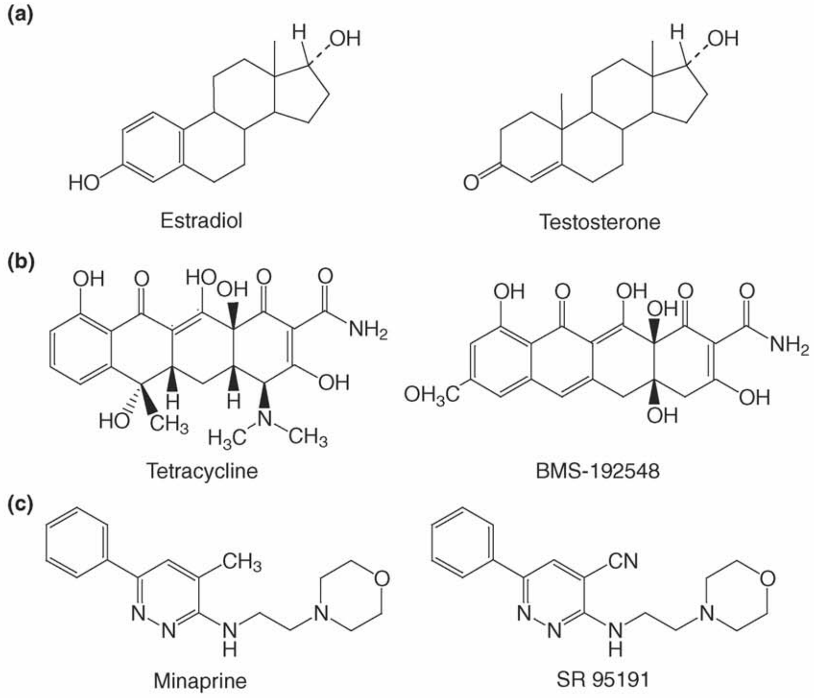
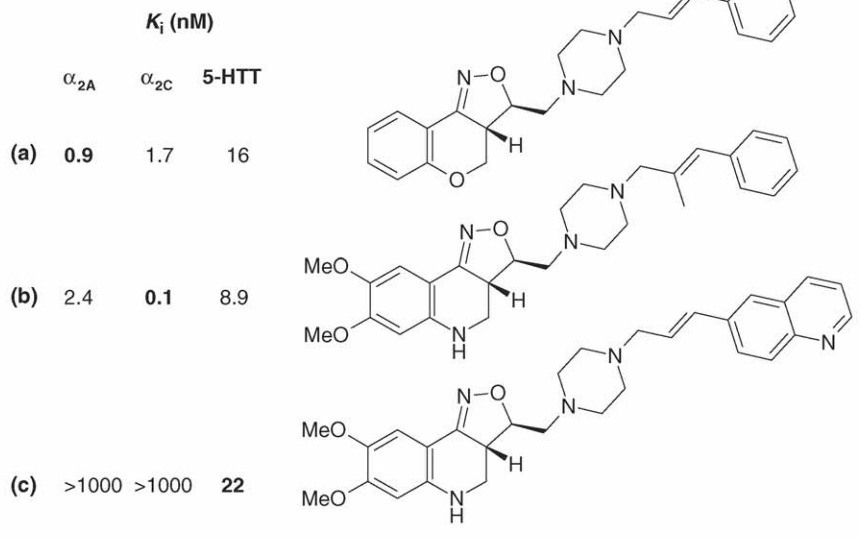


FIGURE 2

Some examples of structural analogues. Despite their structural analogy, these compounds present different pharmacological activities.



	K_i (nM)		
	α_{2A}	α_{2C}	5-HTT
(a)	**0.9**	1.7	16
(b)	2.4	**0.1**	8.9
(c)	>1000	>1000	**22**

FIGURE 3

Similar structures with affinities for different pharmacological targets [19]**.** Despite the structural similarity of the three compounds, compound **(a)** is selective for α_{2A} receptors, whereas compounds **(b)** and **(c)** are selective for α_{2C} and 5-HTT receptors, respectively.

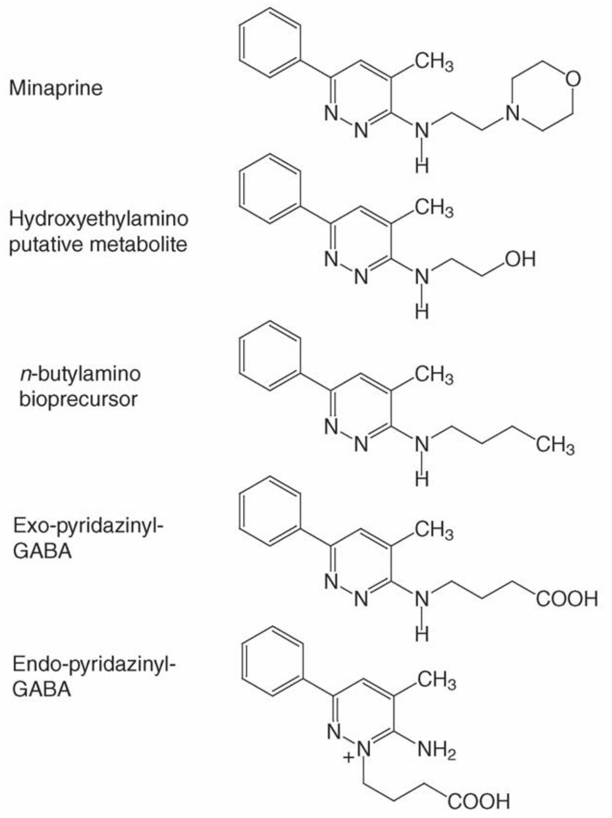


FIGURE 4

Minaprine and endo-pyridazinyl-GABA. The progressive change from the antidepressant minaprine and its putative metabolite to the GABA-A receptor antagonist endo-pyridazinyl-GABA [26,27].

However, the compound was rather short-acting, which suggested the need to synthesize various prodrugs and bioprecursors. Among them, the *n*-butylamino derivative was found to have a much longer duration of action. One of the possible oxidative metabolites (ω-oxidation) of the *n*-butylamino derivative is the exo-pyridazinyl-GABA. In fact, attempts to prepare this compound by direct alkylation of 3-amino-6-arylpyridazines yielded endo-pyridazinyl-GABAs, which surprisingly lost the anticonvulsant properties and proved to be competitive, selective and potent antagonists for the GABA-A receptor.

The exo-pyridazinyl-GABAs prepared later were found to be totally inactive in GABA-A receptor preparations. The resemblance of gabazine, the pyridazinyl-GABA, to the reference antagonist (the alkaloid (+)-bicuculline) is far from obvious (Figure 5). However, computer modeling studies of several GABA-A antagonists revealed the isofunctional nature of gabazine and (+)-bicuculline [28].

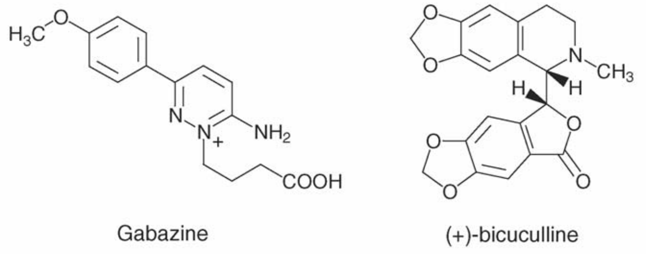


FIGURE 5

Gabazine and (+)-bicuculline. Gabazine, the GABA-A-antagonistic aminopyridazine, is a functional analogue of the alkaloid (+)-bicuculline [24,25].

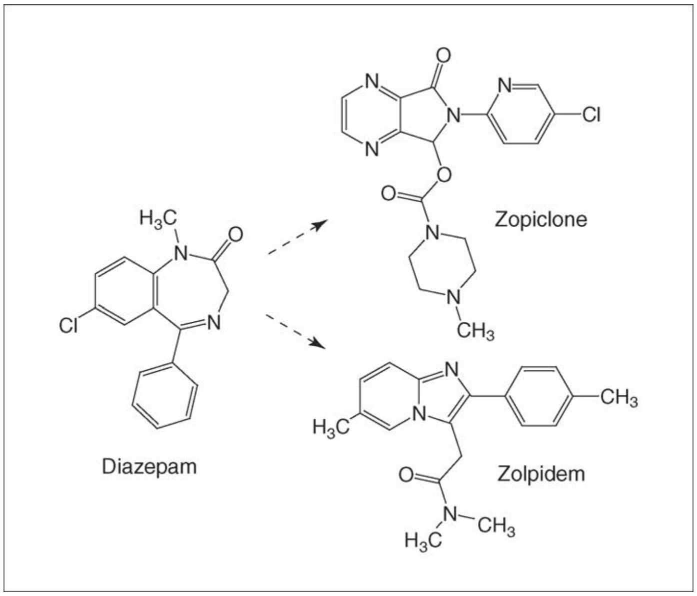


FIGURE 6

Zopiclone and zolpidem. Zopiclone and zolpidem are selective benzodiazepine receptor agonists – not related chemically to benzodiazepines [29,30].

Systematic screening

Functional analogues can be produced deliberately as the result of a screening campaign. Thus, in the early 1970s, after the discovery of the anxiolytic and tranquilizing activity of the benzodiazepines, scientists from Rhône Poulenc initiated a systematic search of other molecules that showed similar binding and *in vivo* pharmacological profiles to the benzodiazepines. The result was the discovery of zopiclone [29], the first non-benzodiazepine showing a pharmacological profile similar to diazepam (Figure 6) [29,30].

Another screening search, performed in the early 1980s by Synthelabo scientists [31], led to an imidazo-pyridine, zolpidem, presently one of the most popular sleep inducers.

Virtual screening

Systematic screening, despite being a fruitful method for identifying functional analogues, must be applied to real libraries made of hundreds or thousands of compounds. This is not the case for virtual screening, an approach based on computer-aided detection in a database of molecules that present similar pharmacophores. In a prospective test (for example, see Ref. [32]), a program called CATS (chemically advanced template search) was applied to the prediction of novel cardiac T-type Ca^{2+}-channel-blocking agents by exploring the Roche in-house compound depository. Mibefradil, a known T-type Ca^{2+}-channel-blocking agent ($IC_{50} = 1.7$ μM, Figure 7), was used as the seed structure for CATS. The 12 highest-ranking molecules were tested, using a cell culture assay for their ability to inhibit cellular Ca^{2+} influx. Nine compounds (75%) showed significant activity ($IC_{50} < 10$ μM) and one of them, clopimozid, had an $IC_{50} < 1$ μM. The IC_{50} values of the next-best structures (not shown in the article) were: 1.7, 2.2, 3.2 and 3.5 μM.

These hits have structural scaffolds that differ significantly from the query structure, mibefradil. However, essential function-determining points are preserved, forming the basis of a relevant pharmacophoric pattern. The use of target-based screening (i.e. high throughput docking) is a major source of discovering functional analogues in modern drug discovery [33].

The degree of analogy

In addition to the direct, the structural or the functional nature of the designed analogues, it also appears worthwhile to consider the degree of relationship between the 'copy' and the original compound.

Isosterism

The search for analogues is, very often, aided by the concept of isosteric replacement and the derived concept of bioisosterism. Isosteric replacement requires substitution of one atom or group of atoms in the parent compound for another with similar electronic and steric configuration. A typical example of isosteric replacement is given in Figure 8 [34], where the oxygen atom of a meperidine analogue is successively replaced by the NH and CH_2 isosteric groups.

The ostensible objective is to produce an improved version of the 'pioneer' drug; however, sometimes compounds with antagonistic properties are obtained.

Bioisosterism

The term bioisosterism is used to describe replacements of fragments of the original molecule that are more significant in terms of overall affinity and function. Thus, the replacement of

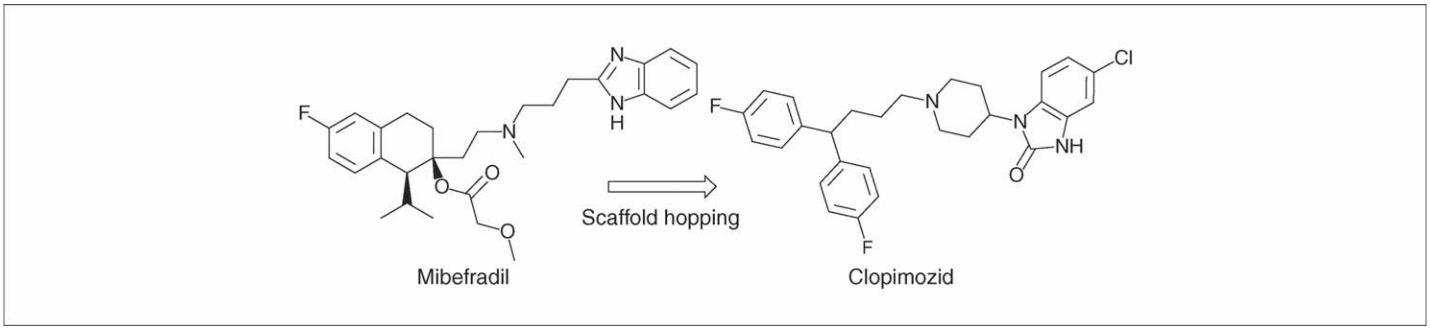


FIGURE 7

Mibefradil, the query structure, and a high-ranking isofunctional structure, clopimozid, derived from mibefradil by CATS.

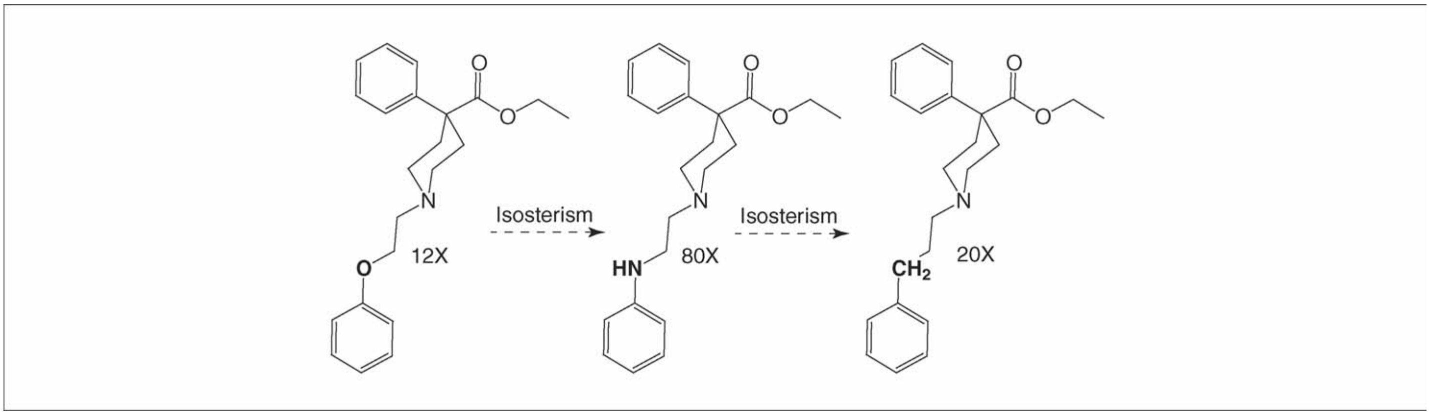


FIGURE 8

Isosteric replacements in meperidine analogues. Analgesic potency relative to meperidine = 1 [34].

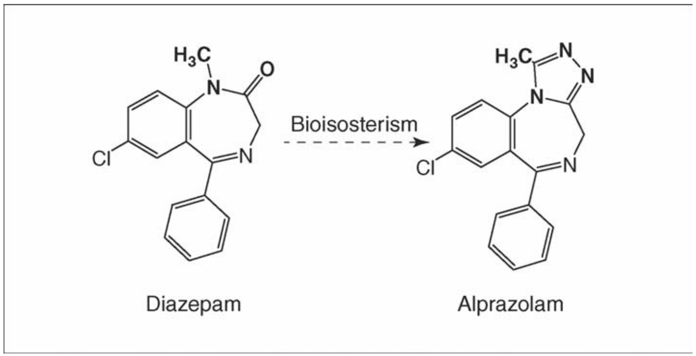


FIGURE 9

The passage from diazepam to alprazolam represents a typical bioisosteric change.

the methylated carboxamide function of diazepam by its bioequivalent methylated triazole group in alprazolam preserves the high affinity for the central benzodiazepinone receptor (Figure 9).

Scaffold hopping

Taken in its broadest meaning, bioisosterism can consist of a complete replacement of the initial molecular structure by another one, resulting in a structure that is isofunctional but based on a different scaffold. This approach, called scaffold hopping [35], can be considered an extreme application of the bioisosterism concept. It is illustrated by the conversion of fluoxetine, a selective serotonin reuptake inhibitor, to its functional analogues, sertraline and paroxetine (Figure 10) [35].

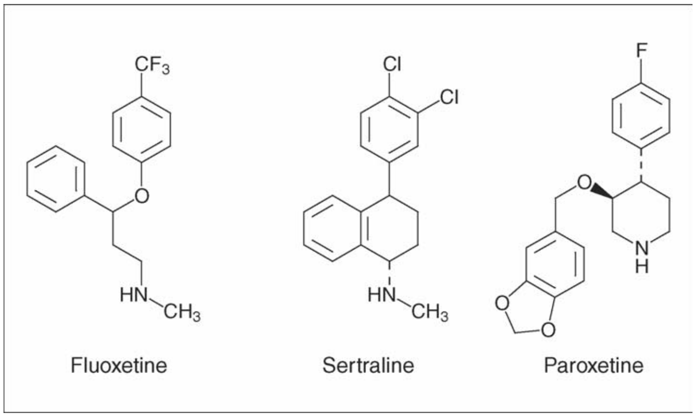


FIGURE 10

Scaffold hopping. An example (from the literature) of scaffold hopping applied to selective serotonin reuptake inhibitors [35].

Fluoxetine and its two analogues have structural scaffolds that differ significantly. Nevertheless, the essential function-determining points are preserved, forming the basis of a relevant serotonin transporter pharmacophore pattern.

TABLE 1

The three categories of drug analogues

Nature of the analogue[*]	Degree of relationship with the original structure	Production and design	Originality and patentability	Result of the design	Likelihood of drug success
S + F: direct analogue	Isosterism Functional exchange	Molecular variations Parallel synthesis	Low	'Me-too'	Medium to high
S: structural analogue	Bioisosterism Fragment exchange	Traditional medicinal chemistry	Medium	Patentable copy	Low
F: functional analogue	Pharmacophore identification Scaffold hopping	Fortuitous discovery Screening Computer-aided design	High	Original back-up	Variable

[*] S = structural, F = functional, S + F = direct.

According to the degree of molecular modifications achieved, the alterations made in drug analoging can focus on exchanges of atoms or small groups (isosterism), exchanges of fragments of molecules (bioisosterism) or on total replacement of the original molecule by a new one (scaffold hopping).

Conclusion

Improvement of an existing active molecule, natural or synthetic (i.e. practicing analogue design) is the typical focus of medicinal chemists. It can be considered as their daily bread. In this context, the objective of the present perspective was to clarify the terminology of analogue design by establishing a clear distinction among three kinds of analogues (Table 1): Direct analogues (i.e. analogues possessing structural and functional similarities); structural analogues (i.e. analogues possessing only chemical similarities but presenting different pharmacological profiles); and functional analogues (i.e. chemically different compounds displaying similar pharmacological properties).

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