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Follow-on drugs: How far should chemists look?

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A major remark made by observers relates to the focus of the pharmaceutical industry on 'me-too' drugs rather than 'first-in-class' drugs, the latter are considered to be 'truly' innovative medicines. Although the subject is heavily debated, chemists in project teams around the globe are routinely following up compounds from competitors. An important strategic consideration is the degree of chemical modification of the original structure required for success. Here, we present an analysis of the DiMasi and Faden set of first-in-class and follow-on drug pairs (n = 74); showing that 70% of them are structurally very similar, meaning that they are characterized by minimal structural variations. This highlights the fact that even simple atomic variations can cause drastic changes in molecular properties responsible for therapeutic advantages.

The pharmaceutical industry continues to face intense scrutiny from investors, regulators and payers, among others. The multiple causes for the reduced number of drug approvals in recent years are periodically reviewed [1,2], and possible solutions are constantly proposed [2,3]. As an example, the development of 'first-in-class' drugs with a novel mode of action (MoA) is the often-advised strategy, as compared with 'follow-on' drugs within an existing MoA [4,5]. However, follow-on drugs might offer advantages in terms of patient segmentation, price competition and, more importantly, therapeutic significance, as widely documented [6–11]. Despite such debate, follow-on of external information remains a vital activity for any drug-hunting project. This is simply caused by the incremental nature of research, where knowledge and insight evolve with time. In fact, throughout the drug discovery process, medicinal chemists spend a considerable amount of time and energy following competitor compounds; from actual organic synthesis of the ligand, as a benchmark for the proprietary chemotype or validation of an *in vitro* and/or *in vivo* assay, to theoretical considerations on ligand structure, scaffold, substituents and SAR. Indeed, competitor compounds represent a vast source of chemical inspiration, and chemists are proficient at 'borrowing' structural elements from them. In addition, several 'scaffold-hopping' tools have been developed to replace a structural moiety on one compound (e.g. a competitor) automatically with a supposedly equivalent structure [12–18].

When following-on a competitor compound a decisive and immediate consideration is the amount of chemical variation one is prepared to explore, mainly for two reasons. The first one is practical. Although patent claims, emerging SAR, computational models and synthetic feasibility might restrict the options, chemists' creativity is notoriously combinatorial and the chemistry program is left with several potential exploration tracks. The second reason is philosophical and revolves around the link (or the lack of) between chemical structure similarity and property (e.g. pharmacological and physicochemical) similarity [19,20]. In a follow-on situation one strives to find chemical modifications that preserve some of the intended properties (e.g. potency) while affording significant advantages in others (e.g. solubility). Is this balance likely to be achieved with minor or major structural variations? In an effort to address this commonly occurring issue we analyzed the structural relationships between the first-in-class and follow-on (second entrant) drugs recently discussed by DiMasi and Faden [21] (Boxes 1 and 2).

Not just copies: same mechanism, different structures

Biology offers significant opportunities for therapeutic innovation within the same therapeutic target (e.g. different binding sites and modulatory mechanisms). Different chemical structures increase the likelihood of therapeutic innovation even further (e.g. affinities

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BOX 1

Dataset and computational details

The first-in-class–follow-on drug dataset recently described by DiMasi and Faden [21] was used as a source for our analysis. The original dataset included 94 drug classes in which the first-in-class compound was approved in the USA between 1960 and 2003. For our purposes, biologics (e.g. the insulin products Humulin™ and Novolin™), medium-sized peptides (MW > 2000 Da) and resins (e.g. the bile acid sequestrants Cuemid™ and Colestid™) were filtered out. Drugs within the same class that acted through different mechanisms were also removed [e.g. the potassium-sparing diuretics Aldactone™ (aldosterone receptor antagonist) and Dyrenium™ (epithelial sodium channel blocker), the leukotriene antagonists Accolate™ (CysLT1 receptor antagonist) and Zyflo™ (5-lipoxygenase inhibitor), and the nonsteroidal antiandrogens Eulexin™ (androgen receptor antagonist) and Proscar™ (type II 5-alpha reductase inhibitor)]. One drug, Vesicar™ (urinary antispasmodic) lacked a US approval date and was consequently left out, leaving a final number of 74 first-in-class–follow-on drug pairs. The chemical structures of the final drug set were retrieved from various sources. The structures were pretreated: covalently bonded salts were split; the smallest fragments were removed; canonical SMILES were calculated [22].

A range of Tanimoto-based similarity values for the pairs were calculated: $Tanimoto_{MCSS}$ [23], $Tanimoto_{Lingo}$ [24], $Tanimoto_{FOYFI}$ [25], $Tanimoto_{ECFI}$ [25], $Tanimoto_{ALFI}$ [25] and $Tanimoto_{Ghose\text{-}Crippen}$ [26,27].

Finally, selected molecular properties were calculated: molecular volume, molecular weight, clog*P* and polar surface area (PSA), as well as several molecular counts: number of heavy atoms, number of rotors, number of rings, number of H-bond donors and acceptors, number of carbon atoms, number of oxygen atoms, number of nitrogen atoms, number of halogens [22].

All of the above reported data are tabulated in Supplementary material.

and selectivities), to the point that unexpected pharmacology and toxicology might be ruling over the intended effect, as is the case with ritonavir (detailed below). Additionally, because physicochemical properties are intrinsic to molecules, different structures might result in ADME differences that can be turned into treatment advantages. Therefore, the pursuit of a completely novel chemotype within a certain MoA not only represents an ideal discovery strategy but also offers an increased likelihood of patentability. Accordingly, 22 (30%) of the pairs in the present analysis contain drugs that are not structurally related. These examples clearly argue against the 'copycat' reputation of second entrants, as described below. A notable case includes verapamil (Isoptin™) and nifedipine (Procardia™), the first and the second L-type calcium channel blockers (CCBs) registered as antihypertensive agents with completely unrelated chemical structures (Fig. 1). The chemistry difference has been used by pharmacologists to classify these CCBs generally (phenylalkylamines and dihydropyridines, respectively) owing to the observed pharmacological and clinical differences, and tissue specificity. These are, in part, attributable to the fact that the two drugs interact with the L-type channel at different sites [29].

Another remarkable example is offered by the structurally distinct acetylcholinesterase (AChE) inhibitors tacrine (Cognex™) and donezepil (Aricept™), see Fig. 1. As observed from crystal structure complexes, they share the same binding site on AChE, but the larger structure of donezepil is occupying more of the active site (PDB: 1eve and 1acj, respectively), resulting in higher (AChE) affinity and selectivity over butyrylcholinesterase (BChE) [30]. Additionally to its effect on affinity and selectivity, the different structure of donezepil is responsible for a pharmacokinetic profile compatible with once-daily dosing, a significant advantage over tacrine [31].

The HIV protease peptide-like inhibitors saquinavir (Invirase™) and ritonavir (Norvir™) are noteworthy in that, although their chemical structures differ significantly in backbone and side-chain composition (Fig. 1), they overlap nicely in the enzyme binding site, and key interactions with the enzyme are conserved (PDB: 3oxc and 2b60, respectively). Ironically, ritonavir is rarely used for its antiviral action but rather as a 'booster' of the exposure of other HIV protease inhibitors, owing to its potent cytochrome P450 3A4 inhibitory activity [32].

Just copies? Same mechanism, similar structures

It is intriguing that, despite all the promises of large structural variations, the second entrant is structurally related to the first-in-class in 70% of the available pairs ($n = 52$), from visual assessment. The structurally related pairs can be further subdivided into two classes, based on the degree of structural modification observed. Here, 72% of the pairs ($n = 38$) are characterized by atomic differences, mainly at a substituent level, whereas the remainder present a more complex structural change although they maintain a large common substructure.

Follow-on settings: distantly registered, similar structure

An interesting subset of the first-in-class–follow-on drug pairs is constituted by those where registration dates are separated by long periods of time (>10 years; $n = 15$). This could be a situation in which a first-in-class drug is just registered and a chemistry team initiates a follow-on program, with a clear rationale for differentiation based on the wealth of preclinical and clinical data available on the pioneer molecule. Apart from considerations on the competition landscape and generics onset, the question arises if they should explore the chemical vicinities of the existing drug or if they should start an independent lead-finding campaign with the aim of affording a completely novel chemotype. In such a subset, 87% of the available pairs are marked by high structural similarity ranging from a *cis–trans* isomeric difference between tretinoin (Retin-A™) and isotretinoin (Accutane™) and side chain and capping group modifications in somatostatin analogs octreotide (Sandostatin™) and lanreotide (Somatuline Depot™), as shown in Fig. 2.

In the following paragraphs some of the most fascinating chemically related pairs are discussed in light of the available discriminating data.

Tamoxifen (Nolvadex™), a selective estrogen receptor modulator approved in 1977 for the treatment of breast cancer, is today's antiestrogen of choice. Almost 20 years later, toremifene (Fareston™) was approved as an alternative to Nolvadex™ for the same

BOX 2

Molecular similarities and trend spotting using calculated data

Molecular similarities

Although similarity methods have proven extremely useful in the pharmaceutical setting over the past three decades it is not straightforward to identify a consistently better method for a particular problem. Different methods will result in different sets of 'similar' compounds, and it is difficult to predict *a priori* which method will produce the best results. Thus, similarity methods are often seen as complementary to each other [28] and all available methods are frequently used. The MAO-B inhibitor pair below (Table I) illustrates this issue. The herein used methods scored this pair as having mediocre similarity (maximum similarity = 1.0; identical molecules). It is our opinion that any experienced medicinal chemist would sort this pair into the structurally related bin. To address this issue we asked a panel of experienced medicinal and computational chemists to refine the first and the second entrant pair classification retrieved by our similarity methods (Figure I). To minimize bias no additional information or purpose other than chemical structures was provided. The reason for using this manual approach was that a few important pairs in the current set would have been misclassified using similarity methods. The panel judged 52 from 74 pairs in the dataset to be structurally related (70%), and 38 of the structurally related pairs were characterized by small structural differences (73%) (Supplementary material, Table 1). A frequency histogram of Tanimoto coefficients, calculated for the 52 similar pairs, underlines the fact that none of the routinely employed similarity methods consistently capture the structural similarity of the pairs.

Intrinsic properties of the first-in-class–follow-on pairs

The analysis of the molecular properties of the pairs was performed with the ultimate goal of discovering trends related to molecular structure. The calculated molecular properties and various counts for the 52 pairs considered as structurally related are shown in Table II. It can be seen that the second entrants, on average, are slightly bigger (Table II: MW and volume). This observation goes hand in hand with the slight increase in number of heavy atoms (more specifically number of carbons, as displayed in Table II). The second entrant is also, on average, slightly more flexible; with one additional rotational bond on average, and displays a modest increase in polar surface area. Nevertheless, the overall differences between the first and the second entrants are undeniably very small and not statistically significant. This supports design strategies such as structural fine-tuning, as compared with more-elaborate methods such as the optimization of new chemotypes.

TABLE I

MAO-B inhibitor pair and calculated similarity coefficients.

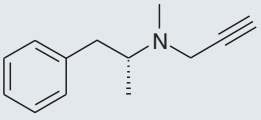
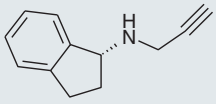
First-in-class	Follow-on	Similarity method	Tanimoto coefficient
 Selegiline (Eldepryl™) 05 June 1989	 Rasagiline (Azilect™) 16 May 2006	ECFI	0.32
		FOYFI	0.49
		ALFI	0.41
		Lingo	0.14
		MCSS	0.50
		GC	0.30

TABLE II

Calculated mean, median, upper and lower quartiles for selected molecular properties of the 52 first-in-class–follow-on pairs considered to be structurally related

Entrant	MW		*c* log *P*		Volume		PSA	
	First	Second	First	Second	First	Second	First	Second
Mean	447.7	480.6	1.5	1.4	371.3	398.1	133.4	144.3
Median	346.4	374.5	1.5	1.5	286.5	310.0	95.0	95.0
Lower quartile (Q1)	266.9	299.1	−0.5	−0.2	223.8	252.0	66.0	74.8
Upper quartile (Q3)	449.1	535.0	3.6	3.2	378.5	434.0	146.5	150.0

Entrant	No. heavyatoms		No. rotors		No. rings		No. H-bond donors and acceptors	
	First	Second	First	Second	First	Second	First	Second
Mean	31.0	33.5	8.8	9.7	3.0	3.3	12.4	13.3
Median	24.0	26.0	6.0	7.0	3.0	3.0	8.5	9.5
Lower quartile (Q1)	19.0	21.0	4.0	5.0	2.0	2.0	6.0	7.0
Upper quartile (Q3)	31.0	37.3	8.8	10.0	4.0	4.0	12.5	14.3

Entrant	No. carbon atoms		No. oxygen atoms		No. nitrogen atoms		No. halogen atoms	
	First	Second	First	Second	First	Second	First	Second
Mean	21.5	23.2	5.4	6.2	3.3	3.3	0.3	0.2
Median	17.0	18.5	4.0	4.0	3.0	3.0	0.0	0.0

TABLE II (*Continued*)

Entrant	No. carbon atoms		No. oxygen atoms		No. nitrogen atoms		No. halogen atoms	
	First	Second	First	Second	First	Second	First	Second
Lower quartile (Q1)	12.8	14.0	2.0	3.0	1.0	1.0	0.0	0.0
Upper quartile (Q3)	24.3	26.0	5.8	7.0	4.3	4.0	0.0	0.0

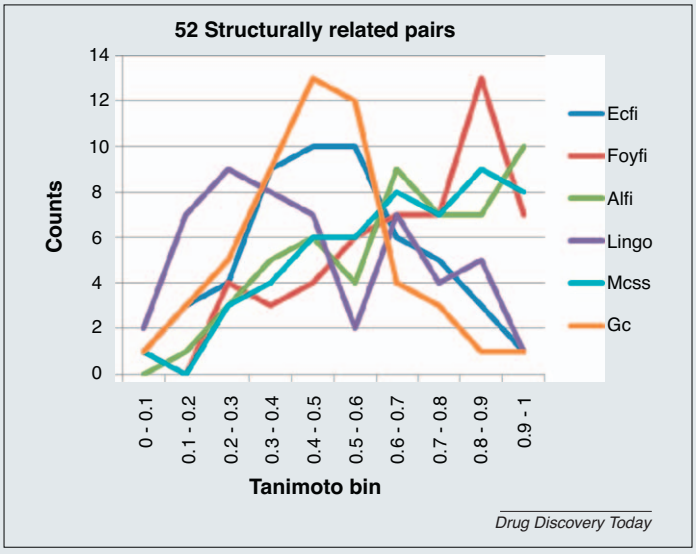


FIGURE I

Frequency distribution of Tanimoto similarity coefficients across the 52 structurally related pairs.

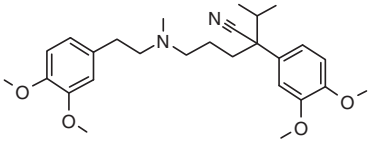
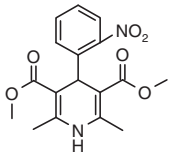
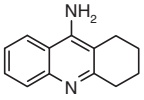
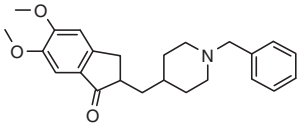
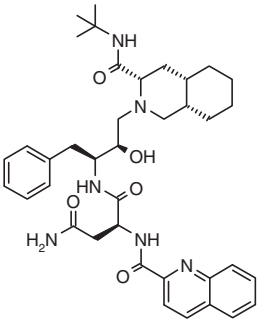
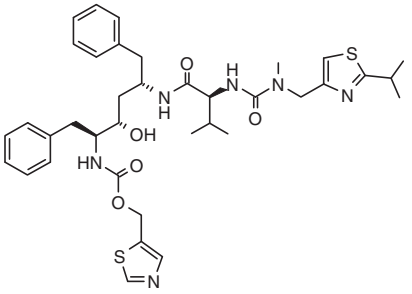
indication. This is one of the most similar pairs of drugs in the set: one chlorine atom difference (Fig. 2). Tamoxifen and toremifene have a similar pharmacologic profile: Phase III clinical trials as well as follow-up analyses showed comparable efficacy on disease and side-effect profile [33]. Chlorine is not a common structural substituent on aliphatic carbon atoms, owing to the potential risk for chemical reactivity. Nevertheless, in contrast to tamoxifen, toremifene is not hepatocarcinogenic in rats [34] and is not associated with severe ocular toxicity [35] and increased stroke incidence [36] in humans. In this case, a one-atom difference within the same chemical class affords a valid and safe alternative to a first-in-class drug, as well as providing a diversified toxicological profile. This contrasts with the widely employed medicinal chemistry tactic of changing the chemical series completely as a means to reduce safety-related risks, and underscores the difficulties in predicting toxicological effects from chemical structure.

Pamidronate disodium (Aredia IV™) is another late second entrant (time between registrations: 14.2 years) with striking structural resemblance to the first-in-class biphosphonate etidronate disodium (Didronel™). They only differ from each other by an addition of two heavy atoms, as shown in Fig. 2. Comparative clinical trials demonstrated that the aminomethyl group introduced on etidronate disodium to yield pamidronate disodium was responsible for significantly superior clinical efficacy in the treatment of cancer-related hypercalcemia, and that this increased efficacy could be achieved without significant toxicity [37,38].

More than 40 years separate the approvals of metronidazole (Flagyl™) and tinidazole (Tindamax™) for the treatment of trichomoniasis, giardiasis and amebiasis, yet the structural difference is minimal. The hydroxyl group on the ethyl side-chain substituting the 2′ position of the 5-nitro-imidazole ring of metronidazole is replaced by an ethylsulfonyl functionality in tinidazole (Fig. 2). This is an interesting substitution for medicinal chemists that design to maintain the polar character of the substituent, while reducing the impact of H-bond donors on permeability as well as removing a soft spot for metabolic conjugation. Accordingly, tinidazole demonstrated an improved pharmacokinetic profile (C_{max}, AUC and $T_{1/2}$) over metronidazole [39]. Additionally, the molecular replacement leads to fewer gastrointestinal side effects and an overall better tolerability profile with tinidazole treatment [40]. Although clinical efficacy is, in general, comparable to metronidazole, the true advantage with tinidazole resides in its ability to affect metronidazole-resistant bacterial strains. Subtle structural variations of existing antibiotics (as well as antineoplastics) that can circumvent drug-resistance will certainly find wider applications in the future as new pathogens (and forms of cancer) evolve.

From a purely structural perspective, it is interesting to note the bioisosterism between propranolol's 1-naphtyloxy and timolol's (4-morpholino-1,2,5-thiadiazol-3-yl)oxy group (Inderal™ and Timoptic™, respectively; Fig. 2). The lower lipophilicity of timolol (*c* log *P*: 1.2 vs 2.8 for propranolol) certainly contributes to several advantages over propranolol: increased bioavailability, reduced clearance and brain uptake. The latter is responsible for a lower incidence of central nervous system side effects, clearer pharmacokinetic–pharmacodynamic (PK–PD) relationships that can be used prospectively for dose selection [41], as well as an improved antitachycardiac effect [42].

Modification of the hybridization state of carbon atoms in a ligand is a useful approach for controlling molecular flexibility and related properties. The prazosin (Minipress™)–terazosin

Drug class	First-in-class International nonproprietary name (brand name), US registration date	Follow-on International nonproprietary name (brand name), US registration date
Calcium channel blocker	 Verapamil (Isoptin™), 1981-08-12	 Nifedipine (Procardia™),1981-12-31
Acetylcholinesterase inhibitor	 Tacrine (Cognex™), 1993-09-09	 Donezepil (Aricept™), 1996-12-18
HIV protease inhibitor	 Saquinavir (Invirase™), 1995-12-06	 Ritonavir (Norvir™), 1996-03-01

Drug Discovery Today

FIGURE 1

Examples of drug pairs with same mechanism but different chemical structures.

(Hytrin™) pair provides an *ad hoc* application of such a strategy (Fig. 2). Here, full saturation of the furane ring in prazosin to yield the follow-on drug terazosin dramatically increases the water solubility of the molecule (28.1 mg/ml for terazosin versus 1.1 mg/ml for prazosin). As a result, improved bioavailability (90% vs 57%) and half-life (2–3 times that of prazosin) afford a longer duration of action and allow the convenience of once-daily administration [43]. Furthermore, the improvement of the physicochemical properties of prazosin via small chemical modifications directly translates in a more homogeneous and predictable PK–PD relationship that is paramount for robust clinical dose titration.

The long time-lag between registrations, as well as the close structural similarity, would certainly demand tangible proof of an inventive step and 'non-obviousness' for the second entrant. Indeed, it is questionable whether a patent office would, today, grant the application disclosing the active ingredient of Fareston™ – toremifen (EP95875) – without any comparative data over tamoxifene (Nolvadex™) or any other prior art. By contrast, the US patent 4026894 claims terazosin (Hytrin™) neatly uses solubility and toxicology data in comparison with prazosin (Minipress™) to support the invention.

Race settings: closely registered, similar structure

Another interesting subset is constituted by those pairs in which the first-in-class and follow-on drugs were registered very close to each other (<2 years; $n = 23$). This category truly reflects the 'race' settings recently described by DiMasi and Faden [21], where the discovery and development of drugs within the same class occur simultaneously. In this context, chemistry teams from different institutions are designing compounds to target the same MoA. The competitors constantly monitor each other for information from patent applications, conferences and publications.

Should they consider modifying the competitor chemotype as a means to deliver their own clinical candidate? Although this decision clearly depends on the quality and maturity of the internal chemical equity, it is noteworthy that 65% of the closely registered pairs are also structurally related, thus providing support for such strategy.

An exceptional example of chemical similarity in this subset is provided by the two macrolides clarithromycin (Biaxin™) and azithromycin (Zithromax™), approved by the FDA in October and November of 1991, respectively. Chemically, whereas clarithromycin is a direct erythromycin derivative that preserves the typical 14-membered lacton ring, azithromycin displays a 15-membered lacton ring (azalide) owing to the replacement of the cyclic ketone group on clarithromycin by an *N*-methylmethanamine fragment, as shown in Fig. 3. Another chemical difference is an ether (clarithromycin) to alcohol (azythromycin) conversion on the macrolide skeleton. Introduction of a basic nitrogen atom in azithromycin greatly increases the volume of distribution (100 l/kg compared with 2.5 l/kg for clarithromycin), thereby

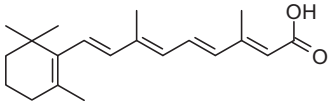
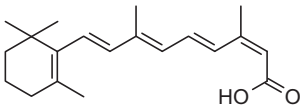
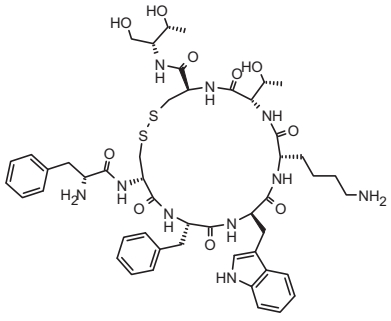
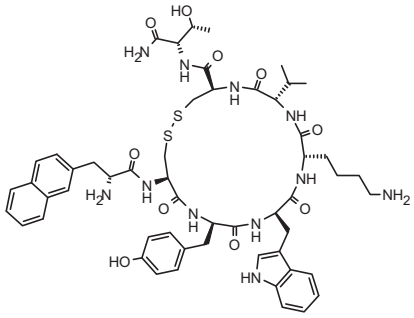
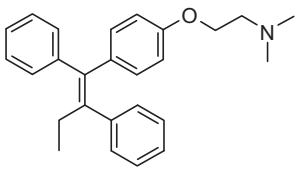
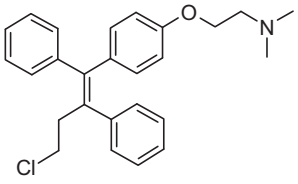
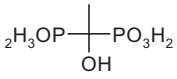
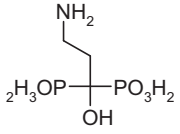
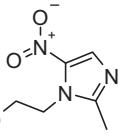
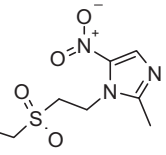
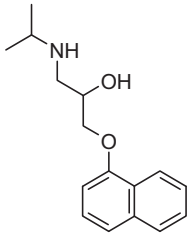
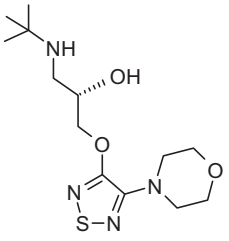
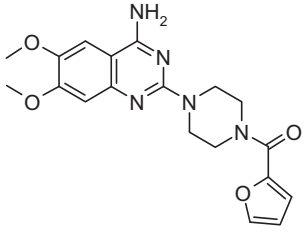
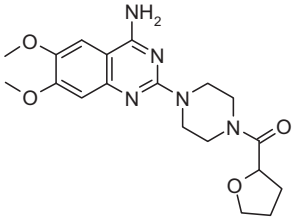
Drug class	First-in-class International nonproprietary name (brand name), US registration date	Follow-on International nonproprietary name (brand name), US registration date	Time to entry (yrs)
Retinoid	 Tretinoin (Retin-A™), 1971-10-20	 Isotretinoin (Accutane™), 1982-05-07	10.6
Antigrowth hormone (somatastatin analogues)	 Octreotide (Sandostatin™), 1988-10-21	 Lanreotide (Somatuline Depot™), 2007-08-30	18.9
Selective estrogen receptor modulator	 Tamoxifen (Nolvadex™), 1977-12-30	 Toremifene (Fareston™), 1997-05-29	19.4
Biphosphonate	 Etinodrate (Didronel™), 1977-09-01	 Pamidronate (Aredia IV™), 1991-10-31	14.2
Nitromindazole derivative (antiprotozoal)	 Metronidazole (Flagyl™), 1963-07-18	 Tinidazole (Tindamax™), 2004-05-17	40.8
Nonselective beta-blocker	 Propranolol (Inderal™), 1967-11-13	 Timolol (Timoptic™), 1978-08-07	10.8
Alpha-blocker	 Prazosin (Minipress™), 1976-06-23	 Terazosin (Hytrin™), 1987-08-07	11.1

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FIGURE 2

Examples of drug pairs with similar chemical structure whose registrations spanned more than 10 years.

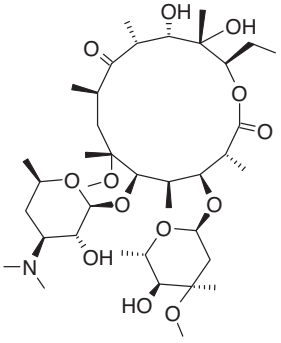
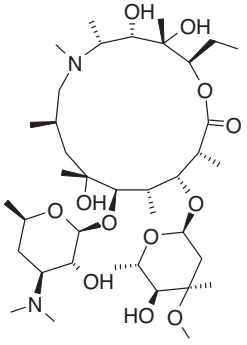
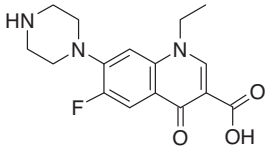
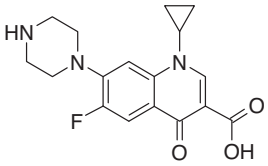
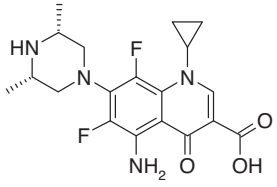
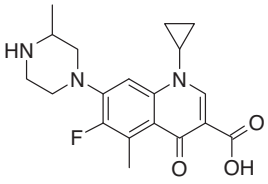
Drug class	First-in-class International nonproprietary name (brand name); US registration date	Follow-on International nonproprietary name (brand name); US registration date	Time to entry (years)
Extended spectrum macrolide	 Clarithromycin (Biaxin™); 31 October 1991	 Azithromycin (Zithromax™); 01 November 1991	0
Second-generation fluoroquinolone	 Norfloxacin (Noroxin™); 31 October 1986	 Ciprofloxacin (Cipro™); 22 October 1987	1
Third-generation fluoroquinolone	 Sparfloxacin (Zagam™); 19 December 1996	 Grepafloxacin (Raxar™); 06 November 1997	0.9

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FIGURE 3

Examples of drug pairs with similar chemical structure registered within two years of each other.

increasing its serum half-life and enabling once-daily dosing [44]. The different lactone cycle on azithromycin also prevents direct interaction with cytochrome P450 enzymes and, contrary to clarithromycin, no significant drug–drug interactions are reported [45].

The fluoroquinolone class of drugs offers another display of follow-on drugs with very high chemical similarity to the corresponding first-in-class. Here, the second-generation fluoroquinolone pair norfloxacin (Noroxin™; 1986) and ciprofloxacin (Cipro™; 1987) is a mere methylene group apart, with a cyclopropyl ring substituting the quinolone nitrogen atom on ciprofloxacin, compared with an ethyl chain on norfloxacin (Fig. 3). The structural variation to cyclopropyl, a medicinal chemistry routine when exploring alkyl chain SAR, identified the optimal substituent for antibacterial potency [46] and, today, still renders ciprofloxacin one of the two most commonly prescribed fluoroquinolones. Third-generation fluoroquinolones, first-in-class sparfloxacin (Zagam™) and follow-on grepafloxacin (Raxar™) were registered about ten years after the second-generation examples previously discussed. They also have very similar chemical structures, differing by three atoms substituting the quinolone core and piperazine side-chain, as shown in Fig. 3. Simple methyl substituents on the piperazine ring and monoatomic substitution on position 5 of the quinolone scaffold provided sparfloxacin and grepafloxacin with activity against gram-positive bacteria [46], an original advantage over previous fluoroquinolones (hence the third-generation classification). However, they also deteriorated the safety profile and this ultimately resulted in the withdrawal of grepafloxacin and severe usage restriction for sparfloxacin.

In a 'race' scenario, chemists will often work on chemical modifications of very similar structures. The goal of finding the best compound is probably to come from subtle structural variations. The race to first-to-register is often settled in the clinic. Careful evaluation of claimed compounds and patent scope is equally important. Exploration and assessment of substituents, ring systems and connecting motifs within the close vicinity of the defined scope are definitely worth the effort of the original applicant, otherwise it could offer opportunities to an opponent.

Similar structures, different properties

In the remainder of the dataset (registration date 2–10 years apart; $n = 36$) 67% of the pairs display striking structural similarity. Here, one finds the follow-on drugs par excellence: ranitidine (Tagamet™), the histamin 2 receptor antagonist, with an improved cytochrome P450 inhibitory profile and reduced risk for drug–drug interactions over the first-in-class cimetidine [47] (Fig. 4); and

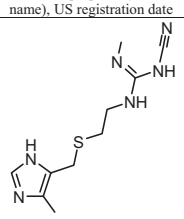
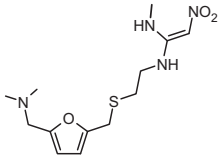
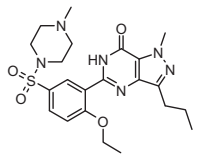
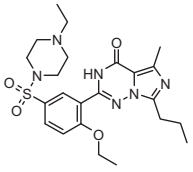
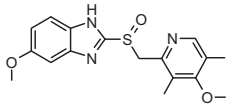
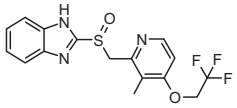
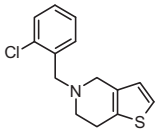
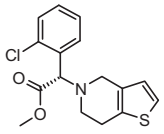
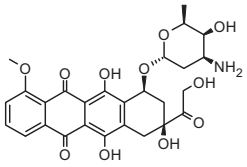
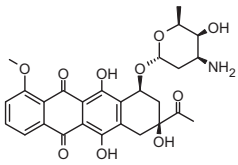
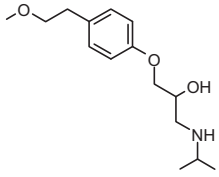
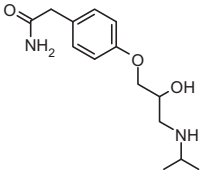
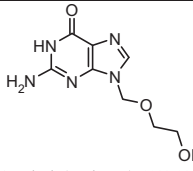
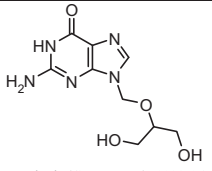
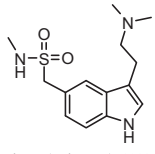
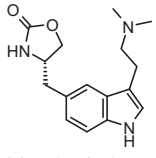
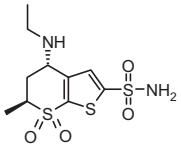
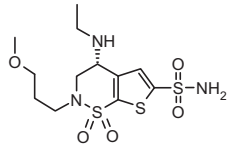
Drug class	First-in-class International nonproprietary name (brand name), US registration date	Follow-on International nonproprietary name (brand name), US registration date	Time to entry (yrs)
H2-antagonist	 Cimetidine (Tagamet™), 1977-08-16	 Ranitidine (Zantac™), 1983-06-09	5.8
cGMP-specific PDE5 inhibitor	 Sildenafil (Viagra™), 1998-03-27	 Vardenafil (Levitra™), 2003-08-19	5.4
Proton pump inhibitor	 Omeprazole (Prilosec), 1989-09-14	 Lansoprazole (Prevacid™), 1995-05-10	5.7
ADP-induced platelet aggregation inhibitor	 Ticlopidine (Ticlid™), 1991-10-31	 Clopidogrel (Plavix™), 1997-11-17	6.1
Anthracycline	 Doxorubicin (Adriamycin™), 1974-08-07	 Daunorubicin (Cerubidine™), 1979-12-19	5.4
Cardioselective β-blocker	 Metoprolol (Lopressor™), 1978-08-07	 Atenolol (Tenormin™), 1981-08-19	3
Guanine derivative	 Acyclovir (Zovirax™), 1982-03-29	 Gancyclovir (Cytovene™), 1989-06-23	3
Triptan	 Sumatriptan (Imitrex™), 1992-12-28	 Zolmitriptan (Zomig™), 1997-11-25	4.9
Carbonic anhydrase inhibitor	 Dorzolamide (Trusopt™), 1994-12-09	 Brinzolamide (Azopt™), 1998-04-01	3.3

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FIGURE 4

Examples of drug pairs with similar chemical structure.

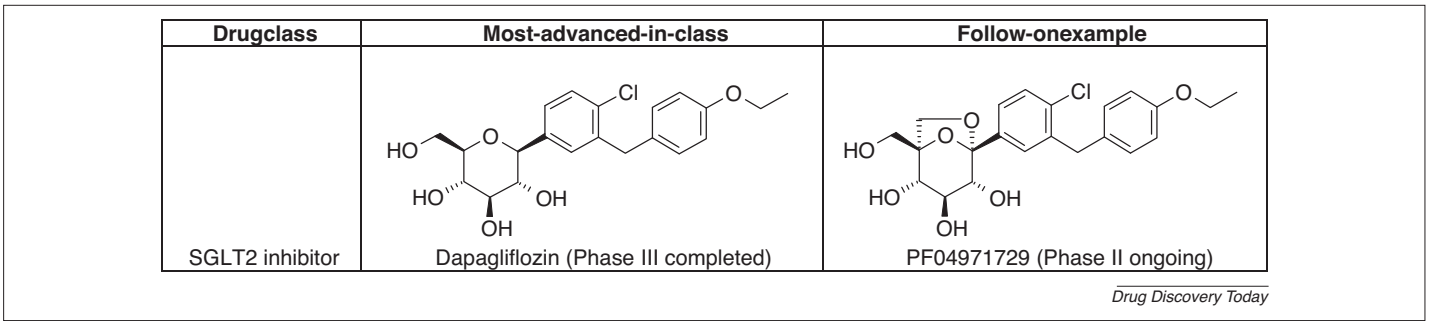

FIGURE 5

Recent example of clinical candidates with similar chemical structure.

vardenafil (Levitra™), the archetypal example of a 'nitrogen-walk' medicinal chemistry strategy (Fig. 4), and lansoprazole (Prevacid™), another remarkable case of substituent fine-tuning (Fig. 4). In addition to these well-known drug pairs, some of the most notable examples are described below, as a source of inspiration for the medicinal chemist tackling the next design.

The introduction of a methyl ester function on the benzylic position of ticlopidine (Ticlid™) afforded clopidogrel (Plavix™), a blockbuster antiplatelet agent with better tolerability and improved safety profile [48], as shown in Fig. 4.

Doxorubicin (Adriamycin™) and daunorubicin (Cerubidine™), the first two anthracycline antibiotics developed, differ by one hydroxyl group (Fig. 4). Despite such a minor change, there are considerable differences in clinical use: daunorubicin is effective in human leukemias, whereas adriamycin is used for a variety of solid tumors [49,50].

In the cardioselective β-blocker class of drugs, metoprolol (Lopressor™) and atenolol (Tenormin™) display a high degree of chemical similarity: the 2-methoxyethyl side-chain of metoprolol is replaced by an acetamide group in atenolol (Fig. 4), in what appears to be a classic attempt at reducing the lipophilicity of the β-blocker (*c* log *P*: 1.5 and −0.1, respectively) and restricting blood–brain barrier permeability (H-bond donors 2 and 4, respectively). Accordingly, the medicinal chemistry exercise resulted in a ten-fold difference in brain concentration between first-in-class and follow-on drug and less incidence of central nervous system (CNS) side effects for atenolol when compared with metoprolol [51].

Acyclovir (Zovirax™) and gancyclovir (Cytovene™), the first two registered guanosine analog antiviral drugs, are almost identical (Fig. 4). They differ in the degree of the sugar ring approximation of guanosine, with the added hydroxymethyl group on gancyclovir mimicking the 4′-hydroxyl of guanosine. Although ganciclovir activity against most DNA herpesviruses is similar to that of acyclovir, it has additional specific potency against cytomegalovirus, as shown clinically after liver transplants [52].

Sumatriptan (Imitrex™) and zolmitriptan (Zomig™) differ in the side-chain, substituting the 5′ position of the *N*,*N*-dimethyl-tryptamine scaffold (Fig. 4). Although the general H-bond properties of the sumatriptan sulfonamide are maintained, the ring-closure to oxazolidin-2-one in zolmitriptan increased lipophilicity and permeability [53]. In line with the intended design, zolmitriptant displayed greater oral bioavailability and a more rapid onset of action [54].

Dorzolamide (Trusopt™) was registered in 1994 as the first carbonic anhydrase inhibitor for the treatment of glaucoma. Brinzolamide, a close structural analog of dorzolamide, represents the second entrant in this class (Fig. 4). Sulfone to sulfonamide replacement, as well as elongation of the methyl substituent to 3-methoxypropyl, drastically increases lipophilicity [log(octanol/water): 6.6 and 1.72 for brinzolamide and dorzolamide, respectively] [55]. The structural change provides several advantages: higher corneal permeability and, thus, greater ocular bioavailability. Additionally, owing to its limited solubility at physiological pH, brinzolamide can be formulated as a suspension therefore reducing the amount of drug in solution and providing superior ocular comfort [56].

Recent example

Among the several examples of published clinical compounds in current years, the recent case of sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors is certainly remarkable from a structural perspective. Dapagliflozin (Fig. 5) was the first SGLT2 inhibitor to demonstrate a significant benefit to type 2 diabetic patients [57] and is currently under FDA scrutiny for regulatory approval. Researchers from Pfizer (http://www.pfizer.com) recently disclosed PF04971729 (Fig. 5), a novel SGLT2 inhibitor being evaluated in Phase II clinical trials for the treatment of type 2 diabetes [58]. The two molecules differ by two atoms: a ketal bridge (Fig. 5). The rigidity and steric hindrance of the ketal system were postulated to increase potency and selectivity while reducing Phase II metabolism over earlier spirocyclic derivatives [59]. Although no preclinical comparison data have been reported so far, it will certainly be interesting to monitor the clinical development of PF04971729 to verify whether such minor structural modifications will translate in a therapeutic differentiation. Pending FDA approval for dapagliflozin and successful progression of PF04971729, a Phase III comparative study would be the ideal and ultimate experiment to answer such question.

How far should chemists look?

To date, there are >50 examples of structurally related first-in-class–follow-on pairs on the market. This analysis illustrates the spectrum of chemical modifications that afforded successful follow-on drugs: from structural fine-tuning to more-radical scaffold-hopping approaches, it is of course arduous to generalize on the best strategy. Nevertheless, whereas it is normally accepted that larger variations in experimental properties occur with drastic changes in structure, we tend to underestimate that the same applies to monoatomic variations as well. This is reinforced by the minimal differences in heavy atom count (median: +2) between structurally related first-in-class and follow-on drugs.

In a hypothetical follow-on scenario, chemists would try to identify the smallest variations that are accessible outside the claims of a competitor's patent. The success of such a strategy rests in their ability to secure a proprietary invention and to demonstrate a therapeutic advantage or differentiation over the competitor. Sound hypotheses, the availability of discriminative experimental models and stringent progression criteria are thus required for such a program.

Despite the controversies around perceived follow-on practices in drug discovery, and their legal and financial aspects, the available first-in-class–follow-on pairs are a sober reminder of the ethereal line connecting chemical structure and experimental properties. While walking that line, chemists can profit from a well-known adage by Sir James Black, 'the most fruitful basis for the discovery of a new drug is to start with an old drug', or at least considering that the next clinical candidate might be closer than one thinks – if not a few atoms away.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2011.05.011.

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