REVIEW

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Recent advances in the design and development of soft drugs

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This paper summarizes recent developments in the field of soft drug development as collected and reviewed for the *9th Retrometabolism-Based Drug Design and Targeting Conference*. Soft drugs are still often confused with prodrugs because they both require metabolic transformations; however, they are conceptual opposites: whereas, prodrugs are pharmacologically inactive and are converted by a predictable mechanism to the active drug, soft drugs are active therapeutic agents as such and are designed to undergo a predictable and controllable metabolic deactivation after exerting their desired therapeutic effect. Several rationally designed soft drug examples including clinically approved ones (e.g., clevidipine, esmolol, landiolol, loteprednol etabonate, and remifentanil) as well as others that have reached clinical investigations within different therapeutic areas (e.g., budiodarone, naronapride, remimazolam, tecarfarine) are briefly summarized. Anesthesiology, which requires a high degree of pharmacologic control during the surgical procedure to maintain the anesthetic state together with a quick return to responsiveness at the end of this procedure, is a particularly well-suited area for soft drug development. Several new initiatives (e.g., MOC-etomidate, AZD3043) are focused in this area; they are also briefly reviewed. Finally, just as there are many 'accidental' prodrugs, there are 'accidental' soft drugs too: i.e., therapeutics that were not intentionally designed to be soft drugs, but turned out to be essentially soft drugs. Some examples, such as articaine or methylphenidate, are briefly reviewed.

1. Introduction

The *soft drug* approach was first introduced more than 35 years ago (Bodor 1977) and reiterated in more detail a few years later (Bodor and Kaminski 1980; Bodor et al. 1980a, b). The concept originated from the realization that metabolic considerations should be an integral part of the drug design process and that this process should focus not on improving activity alone, but on improving the therapeutic index – a measure of the degree of selectivity or margin of safety. The *soft drug* terminology itself was selected to contrast Ariëns's theoretical drug design concept of nonmetabolizable *hard drugs*. Several comprehensive reviews summarizing all major aspects of soft drug design have been published (Bodor and Buchwald 2000, 2010) including a recent book on *retrometabolic drug design*, which incorporates the design of *soft drugs* and *chemical delivery systems* (CDSs) (Bodor and Buchwald 2012). *Soft drugs* (SDs) are new, active therapeutic agents, often isosteric/isoelectronic analogs of a lead compound, with a chemical structure specifically designed to allow predictable metabolism into inactive metabolites after exerting their desired therapeutic effect(s).

In soft drug design, the goal is not to avoid metabolism, but rather to control and direct it. Inclusion of a metabolically sensitive moiety into the drug molecule makes possible to design and predict the major metabolic pathway as well as to avoid the formation of undesired toxic, active, or high-energy intermediates. If possible, inactivation should take place as the result of a single low-energy high-capacity step that yields inactive species subject to rapid elimination. Most critical metabolic pathways are mediated by oxygenases. An analysis of the top 200 drugs found metabolism as the listed clearance mechanism for about 75% of them, and it was predominantly oxidative. Of the drugs cleared *via* metabolism, about 75% are metabolized by cytochrome P450 (CYP) enzymes, mainly CYP3A, CYP2C9, CYP2C19, CYP2D6, and CYP1A (Wienkers and Heath 2005; Williams et al. 2004). Because the rates of hepatic monooxygenase reactions are at least two orders of magnitude lower than the slowest of the other enzymatic reactions (Mannering 1981), and because oxygenases exhibit not only interspecies, but also interindividual variability and are subject to inhibition and induction (Gillette 1979), it is usually desirable to avoid oxidative pathways and these slow, easily saturable oxidase enzymes. Hence, the design of soft drugs should be based on moieties inactivated by hydrolytic enzymes. Rapid metabolism can be carried out more reliably by ubiquitously distributed esterases.

Metabolites formed following administration can contribute significantly toward the overall activity as well as the overall toxicity and side effects of the original drug. Therefore, metabolic considerations should be an integral part of the drug design process, and metabolic pathways should be 'built-in' into the structure. A recent analysis of 68 drugs, which have been recalled or associated with a black box warning due to idiosyncratic toxicity, plus the top 200 U.S. drugs (based on prescription and sales in 2009) found that a significant proportion of drugs associated with toxicity (about 80%) contained structural alerts and that there was evidence indicating reactive metabolite for-

mation as a causative factor for toxicity in approximately 70% of these molecules (Stepan et al. 2011).

For a number of reasons, such as the continuously increasing regulatory burden, the depletion of effective new targets (with possibly no more "low-hanging fruit" remaining), the unrealistic public expectation of no side effects and abuse potential, the unprecedented need for highly multidisciplinary approaches requiring collaborations across very different fields, and many others, the discovery and development of new drugs is becoming an increasingly difficult endeavor. Soft drug approaches might provide viable alternatives in many cases. The increasing difficulty faced by drug developers is well illustrated by the fact that the number of new FDA-approved drugs per each (inflation-adjusted) $1 billion of R&D spending in the drug industry has been halved consistently about every nine years since 1950 – a sort of reverse Moore's law (Scannell et al. 2012). The widely known Moore's law for the electronics industry was originally formulated in the 1960 s by Intel cofounder Gordon Moore (Moore 1965), and it is usually quoted as predicting that the number of transistors that can be integrated into a microchip, and as a result, processor speed too, doubles about every 18 months. Clearly, our understanding of biological systems and their complexities is far from our understanding of physics and electronics – something that often tends to frustrate those working in pure technological fields (Borhani and Butts 2011; Grove 2011). Part of this frustration is supported by a "survivor bias" among R&D projects that creates the illusion of our ability to pursue a much more rational drug discovery and development process than it actually is in reality. News stories on the molecular mechanism of action-based rational design of the few successful drugs overshadow the many more stories of unexpected failures of projects that were also initiated on the basis of just as plausible rationales and that had similarly plausible biological stories until the point of their ultimate failure (Scannell et al. 2012).

2. Prodrugs: 'accidental' and rationally designed prodrugs

Unfortunately, despite clear conceptual differences, *soft drugs* are still often confused with *prodrugs* – mainly, because both approaches rely on metabolic transformations. These two approaches are, however, in fact, conceptual opposites: whereas, prodrugs are pharmacologically inactive and have to be converted by a predictable mechanism into the active form, soft drugs are active therapeutic agents as such and are designed to undergo a predictable and controllable metabolic deactivation after exerting their desired therapeutic effect.

Prodrugs are pharmacologically inactive (or maybe weakly active) compounds obtained by chemical modifications of biologically active species and they are designed to be metabolically transformed into effective drugs following their administration (Balant and Doelker 1995; Beaumont et al. 2003; Bodor and Kaminski 1987; Bundgaard 1985; De Clercq and Field 2006; Ettmayer et al. 2004; Rautio et al. 2008; Stella 1975; Stella 1996; Wermuth et al. 1996). The prodrug concept was introduced by Albert in 1958 (Albert 1958). The rationale is that the structural requirements needed to elicit a desired pharmacological action and those needed to provide optimal delivery to the targeted receptor sites may not be the same. Hence, chemical modifications are made with the goal to improve some deficient physicochemical property, such as membrane permeability, water solubility, or chemical stability or to overcome some other problem, such as rapid elimination, bad taste, a formulation difficulty, or patentability/marketability. After administration, the prodrug, by virtue of its improved characteristics, is expected to be more systemically and/or locally available than the parent drug. However, before exerting its biological effect(s), the prodrug must undergo chemical or biochemical conversion to the active form.

After a relatively slow start and a few early disappointments, prodrug approaches started to gain increasing interest in the last decades, and with several additions (e.g., double or cascade prodrugs (Bundgaard 1987; Wermuth et al. 1996); antibody-, gene-, or virus-directed enzyme prodrug therapies – ADEPT, GDEPT, VDEPT (Niculescu-Duvaz et al. 1999); pronucleotides (Wagner et al. 2000); radiation-activated prodrugs; and others) the field became so wide that it is increasingly difficult to review it in its entirety. According to one estimate (Ettmayer et al. 2004), around 5–8% of the marketed drugs are prodrugs; about one half of them are activated by hydrolysis and about one fourth are bioprecursors activated by a biosynthetic reaction. A more recent and more careful analysis found an even larger proportion of prodrugs: 16% of the small-molecule drugs – 192 out of the 1024 unique small molecules identified from the more than 21,000 FDA-approved products (Overington et al. 2006). Well-known drugs that are in fact prodrugs are, for example, lovastatin (**1**), acyclovir (**2**), enalapril (**3**), clopidogrel (**4**), and omeprazole (**5**) (Fig. 1). Most of these prodrugs, however, are 'accidental' prodrugs in the sense that they were not intentionally designed as prodrugs, but turned out to be prodrugs (i.e., the administered form is inactive and requires metabolic activation). Nevertheless, an increasing number of rational prodrug designs succeeded in developing a marketable product (De Clercq and Field 2006; Rautio et al. 2008). Some of the recent ones include, for example (Fig. 2):

- valacyclovir (Valtrex), the L-valine ester prodrug of acyclovir approved by the FDA in 1995 for the treatment of herpes zoster /shingles/ in immunocompetent adults,
- fosphenytoin sodium (Cerebyx), a phosphonooxy methyl prodrug of phenytoin approved in 1996 for parenteral treatment in epilepsy patients,
- famciclovir (**6**; Famvir), a prodrug of penciclovir approved by the FDA in 1997 for treatment of herpes simplex,
- oseltamivir phosphate (**7**; Tamiflu), the ethyl ester prodrug of oseltamivir carboxylate, a potent and selective inhibitor of influenza A and B neuraminidase, approved by the FDA in 1999 for the treatment of uncomplicated acute illness due to influenza infection in adults,
- balsalazide disodium (Colazal), a sulfa-free prodrug of 5-aminosalicylic acid with 4-aminobenzoyl-β-alanine as carrier and approved by the FDA in 2000 for the treatment of mildly to moderately active ulcerative colitis,
- valganciclovir hydrochloride (Valcyte), an L-valyl ester prodrug of ganciclovir approved by the FDA in 2001 for the treatment of cytomegalovirus, CMV, retinitis in patients with acquired immunodeficiency syndrome, AIDS,
- tenofovir disoproxil fumarate (**8**; Viread), a phosphonate ester prodrug of tenofovir approved by the FDA in 2001 for the treatment of HIV,
- adefovir dipivoxil (Hepsera), a phosphonate ester prodrug of adefovir approved by the FDA in 2002 for the treatment of hepatitis B, and
- ximelagatran (**9**; Exanta), the double /ethyl ester and *N*-hydroxy amidine, amidoxime/ prodrug of melagatran approved for the prevention of recurrent deep vein thrombosis, DVT, in several countries but withdrawn later in 2006 after reports of hepatotoxicity.

Because of their additional complexities (e.g., chemical and/or enzymatic stability, the possibility of species-dependent metabolism, possible toxicity of the pro-moiety), prodrug approaches are worth considering whenever pharmacokineti-

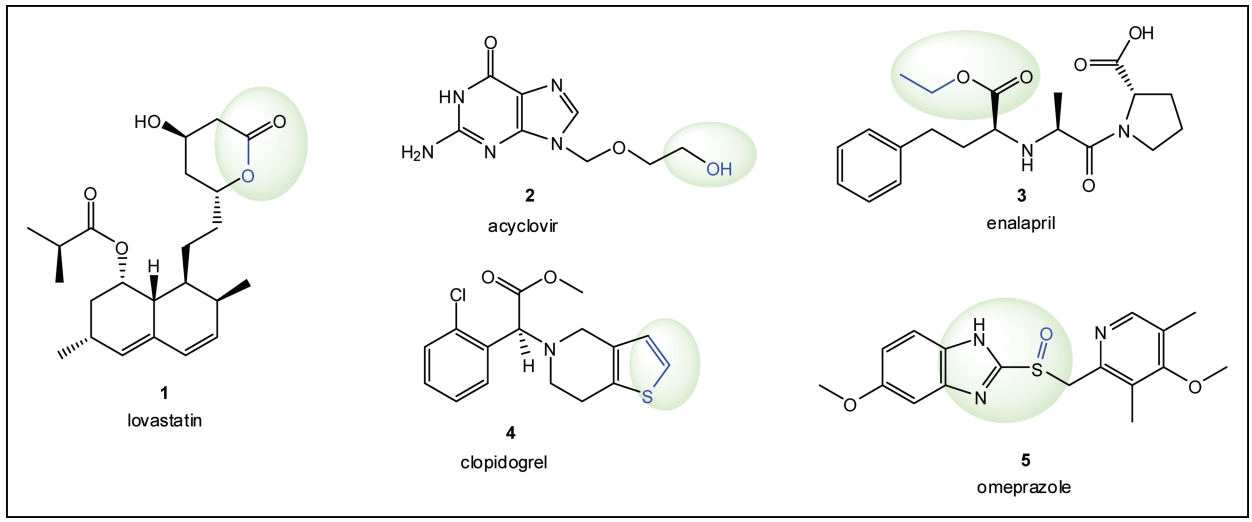

Fig. 1: Structure of some representative 'accidental' prodrugs, i.e., well-known drugs that turned out to be prodrugs, such as lovastatin (**1**), acyclovir (**2**), enalapril (**3**), clopidogrel (**4**), and omeprazole (**5**). Green circles denote the structural moieties where metabolic transformation needs to take place to *activate* these compounds into their pharmacologically active forms.

cally problematic moieties are essential parts of the molecule and are required for the desired biological activity (Ettmayer et al. 2004). However, it has been noted that, in general, prodrug approaches should be used as a last resort only, even when used to improved oral bioavailability, which is one of the most popular uses of this strategy (Beaumont et al. 2003).

3. Soft drugs

Contrary to prodrugs, *soft drugs* are active in their original form. In most typical examples, soft drugs are designed to produce a desired pharmacological activity locally and to be rapidly deactivated metabolically – preferably by a hydrolytic mechanism, following their distribution away from their site of action. Consequently, soft drugs are by no means a universal solution, but they are particularly well suited for a number of cases where local activity is desired at the site of application (eye, lung, skin, intestines) or where well controlled titrated activity and ultrashort action (rapid offset) is desired (e.g., anesthesia). Soft drug design approaches are very general approaches applicable to many therapeutic classes to generate new chemical entities (NCEs). Most soft drug approaches start from a well-known lead structure of confirmed activity and attempt to improve the safety profile. Nevertheless, *de novo* soft drug design is also possible, and the main message of this drug design approach is that metabolism considerations have to be built into the drug structure at the early design phase, not just addressed later when related problems begin to surface. Soft drug approaches are now also aided by computational tools, including an expert system capable of generating new structures and ranking them according to their predicted potential. These expert systems combine

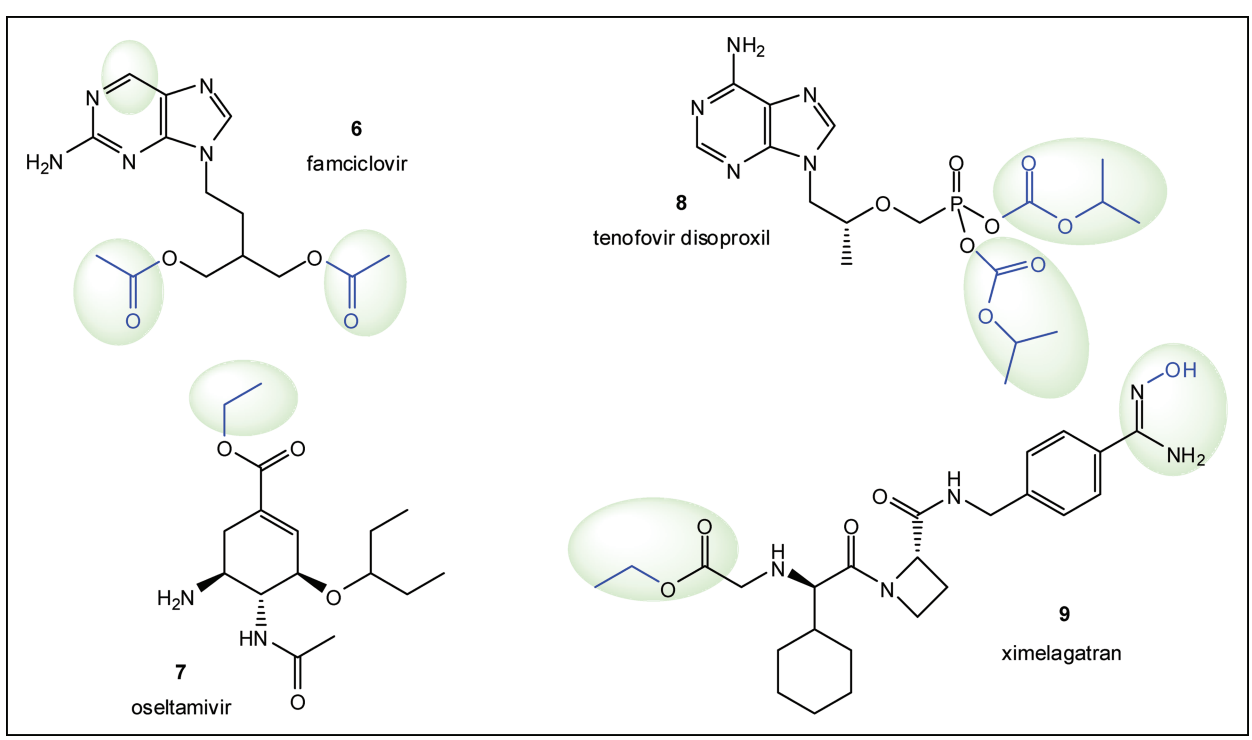

Fig. 2: Structure of some representative rationally designed prodrugs that have recently been approved including famciclovir (**6**), oseltamivir (**7**), tenofovir disoproxil (**8**), and ximelagatran (**9**). As in Fig. 1, green circles denote the structural moieties where metabolic transformation needs to take place to activate these compounds into their pharmacologically active forms.

the various structure-generating rules of soft drug design with the developed quantitative predictive software to provide a ranking order based on isosteric or isoelectronic analogy (Bodor and Buchwald 2000; Bodor et al. 1998, 1999; Buchwald 2007; Buchwald and Bodor 2000).

3.1. Clinically approved soft drugs

During the three decades since the introduction of the concept, soft drug approaches have been explored in numerous academic research centers and almost all major pharmaceutical companies, and several of them already resulted in clinically approved drugs. Our laboratory focused mainly on the design of soft corticosteroids (e.g., loteprednol etabonate and etiprednol dicloacetate) (Bodor and Buchwald 2006), soft β-blockers (e.g., adaprolol) (Bodor and Buchwald 2005), and soft anticholinergics (e.g., tematropium) (Kumar and Bodor 1996). Soft drug approaches initiated by various research groups (including ours) that have already resulted in marketed drugs approved by the corresponding regulatory agencies include, for example (Fig. 3):

- loteprednol etabonate (**10**; Lotemax, Alrex, Zylet), a soft glucocorticoid originating from our own laboratories,
- esmolol (**12**; Breviblock) and landiolol (**13**; Onoact), soft β-blockers containing easily hydrolysable ester functions,
- remifentanil (**15**; Ultiva), a soft opioid analgesic based on carfentanyl, or
- clevidipine (**17**; Cleviprex), an ultrashort-acting soft calcium-channel blocker for intravenous use in the reduction and control of blood pressure in cardiac surgical procedures when oral therapy is not feasible or not desirable.

The structures of these rationally designed soft drugs already approved by regulatory agencies for marketing are summarized in Fig. 3 together with the corresponding lead structures. For detailed reviews of all related aspects, the reader is referred to recent comprehensive reviews by (Bodor and Buchwald (2010, 2012).

3.2. 'Accidental' soft drugs

Just as for prodrugs, there are also examples of 'accidental' soft drugs, i.e., approved drugs that are, in fact, soft drugs even though they were not intentionally designed as such. Obviously, since they were not designed with all the corresponding metabolic aspects considered, they are not always good examples of safe soft drugs, but some of the main aspects are still worth reviewing. Some endogenous compounds, such as steroid hormones or neurotransmitters (e.g., dopamine, GABA, and others) can be considered as natural soft drugs because there are efficient, fast metabolic ways for their disposition without going through highly reactive intermediates.

3.2.1. Etomidate

One of the earliest example of what can be considered an 'accidental' soft drug is etomidate (**26**, see Fig. 5 later), a unique short-acting nonbarbiturate hypnotic agent discovered in the 1960 s (Godefroi et al. 1965). Etomidate is a potent intravenous hypnotic agent with a very rapid onset of action, and it is eliminated by ester hydrolysis in plasma and liver (Lewi et al. 1976). Its acid metabolite is inactive, hence the duration of hypnosis after etomidate administration can be very short (< 5 min) (Janssen et al. 1971). Consequently, the therapeutic index of etomidate (TI = 18.0–32.0) is considerably larger than that of other hypnotic agents, such as thiopental (2.5–4.3) or methohexital (4.9–11.7) (Janssen et al. 1971). Etomidate is one of the most frequently used sedative hypnotic agents in emergency settings for several reasons including its easy dosing profile, limited suppression of ventilation, lack of histamine liberation and protection from myocardial and cerebral ischemia (Hohl et al. 2010). Unfortunately, etomidate inhibits 11β-hydroxylase and can cause suppression of adrenocortical steroid synthesis. Therefore, its use as a continuous infusion to maintain anesthesia or sedation has been mostly abandoned. A soft analog approach to develop an ultrashort-acting alternative (MOC-etomidate) to avoid these problems by incorporating an ester moiety in the structure that is more sensitive to hydrolytic degradation than the relatively hindered one of etomidate is discussed briefly here later.

3.2.2. Local anesthetics: procaine and articaine

Local anesthetics provide other examples of 'accidental' soft drugs. Local analgesia started with the use of cocaine for such purposes at the end of the 1800 s, followed by the development of procaine (**19**) in the early 1900 s. Introduction of the amide-type local anesthetics (lidocaine, **22**) in the late 1940 s revolutionized the field, and by now, local analgesia and dentistry in particular are indeed quite close to having an ideal painless procedure. Structurally, most local anesthetics can be considered as being composed of three main building blocks: a lipophilic (usually aromatic) group and an ionizable (usually tertiary amine) group connected by an alkyl/alylene chain that incorporates either an amide or an ester linkage (Fig. 4) (Nogrady and Weaver 2005). Because of their susceptibility to hydrolytic degradation, ester-type local anesthetics such as procaine (**19**) or benzocaine typically have shorter durations of action than those of amide local anesthetics, such as lidocaine (**22**), bupivacaine, and prilocaine. For example, procaine (**19**) has a very short half-life (≈ 1 min) as it is hydrolyzed to *para*-aminobenzoic acid (PABA, which may cause allergic reactions and inhibit the action of sulfonamides), whereas the analogous procainamide (**20**) has a considerably longer half-life (≈ 3 h). As amides are much less prone than esters to hydrolysis, the major mode of clearance of procainamide is indeed renal and not metabolic, and very little PABA is observed as a metabolite. For some of the amide-type local anesthetics, soft analogs also exist – they incorporate an additional ester side chain that is metabolized to a corresponding inactive acid; such compounds are discussed next focusing on articaine (**21**).

As mentioned, with the introduction of other amide-type local anesthetics (after lidocaine), including mepivacaine, prilocaine, bupivacaine, etidocaine, and articaine, dental practitioners got access to a wide armamentarium of agents that can provide local analgesia from short periods (e.g., ca. 20 min with mepivacaine) to long ones (e.g., ca. 3 h with bupivacaine) as needed. Because amides are much less prone to hydrolysis than esters, amide-type local anesthetics such as lidocaine (**22**) are longer acting than the very short-acting ester types, such as procaine (**19**). As they also have a faster onset of action, in most cases they are the preferred treatment.

This field provides another nice example of an accidental soft drug whose first synthesis predates the concept and was not originally designed as such. Some of the amide-type local anesthetics also incorporate an additional ester side chain that is metabolized to a corresponding inactive acid; these can be considered as (formal) soft analogs of the prototype lidocaine (**22**). For example, tolycaine, which has also been used as a local anesthetic, clearly can be considered a soft analog of lidocaine with a methyl ester in in its structure replacing the methyl functionality in lidocaine. Another, even better example is articaine (**21**; Ultracain, Septocaine), a local anesthetic used in dentistry

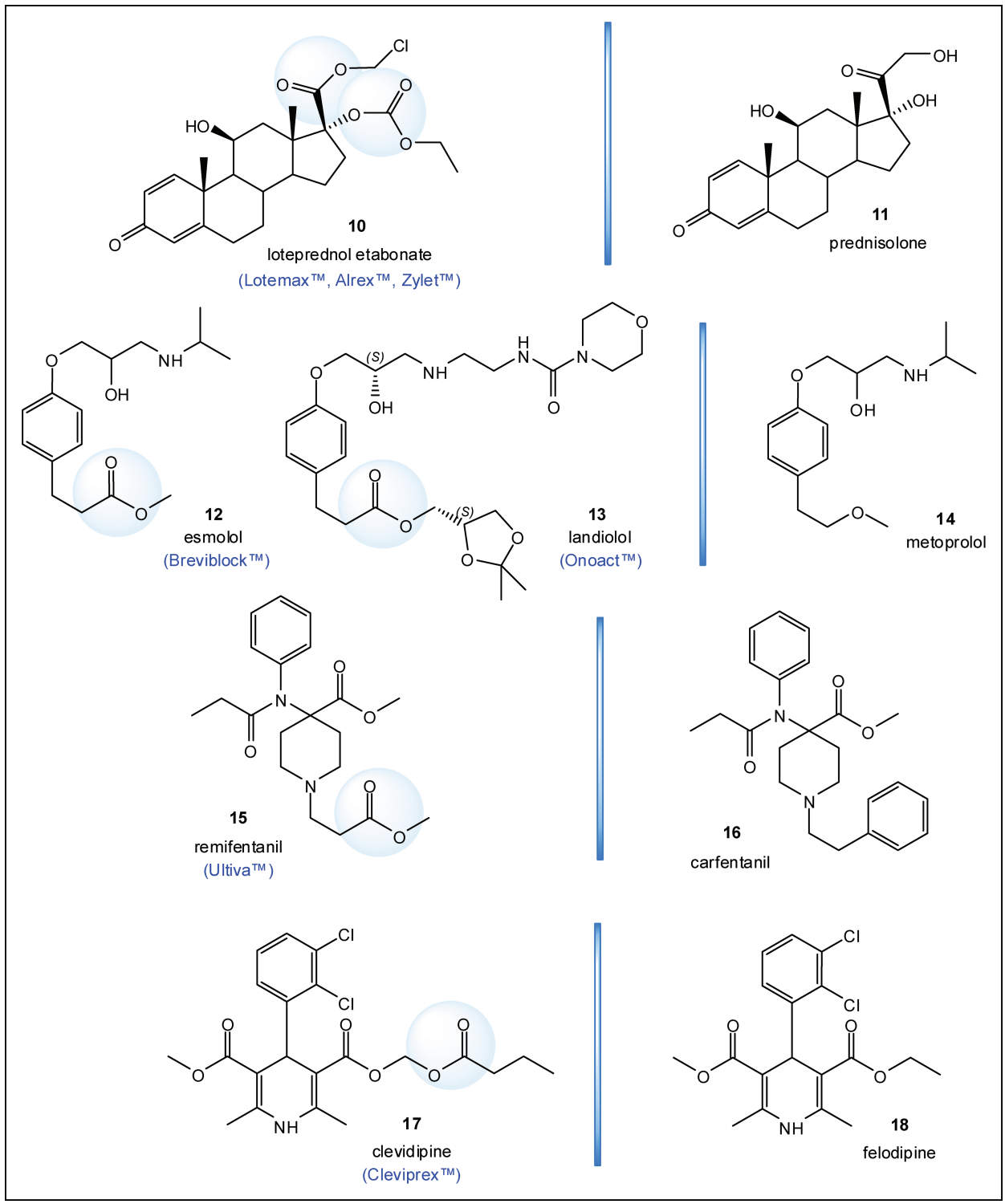

Fig. 3: Structure of rationally designed soft drugs that have already been approved for marketing. Their structures on the left are compared with the corresponding representative leads (on the right), which served as the basis of their designs. Blue circles denote structural moieties where metabolic transformation takes place to *inactivate* these compounds after their exerted their intended pharmacological activity.

(Malamed et al. 2000; Vree and Gielen 2005). Its amide structure is similar to that of other local anesthetics, but it has a thiophene ring instead of the benzene ring, and, similar to tolycaine, it also has an ester group attached to this ring that is susceptible to metabolism by esterases (Malamed et al. 2000; Vree and Gielen 2005). The structural analogy between articaine (**21**) and its nonhydrolyzable counterparts, lidocaine (**22**) and prilocaine, is quite obvious (Fig. 4). Articaine was first prepared in the late 1960 s, and it entered clinical practice in Germany in 1976 (Malamed et al. 2000). Since then, its use has gradually spread, and currently it is the most widely used local anesthetic agent in dentistry in Canada and a number of European countries. It has also been approved by the FDA in the US (2000) as an anesthetic/vasoconstrictor combination with epinephrine. Its wide use is a result of its very fast onset and low degree of toxicity as well as the excellent quality of the anesthesia and the short duration of action it provides. Articaine diffuses better through soft tissue and bone than do other local anesthetics (Vree and Gielen 2005). It is metabolized overwhelmingly *via* hydrolysis into articainic acid, 75% of which is excreted as such and 25% as the glucuronidated form (Vree and Gielen 2005). The articainic acid metabolite is present in the systemic circulation in

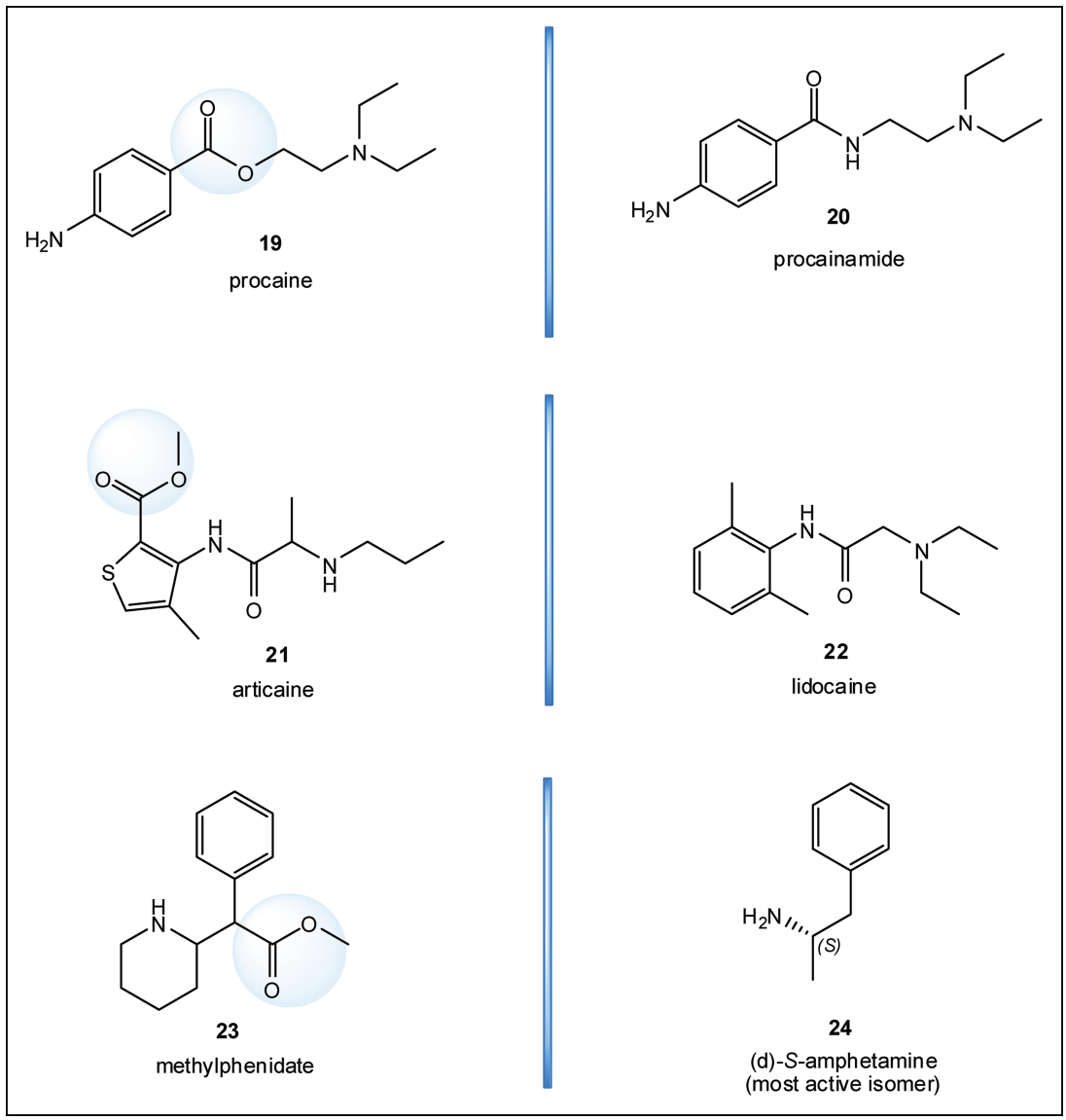

Fig. 4: Structure of some representative 'accidental' soft drugs, i.e., well-known drugs that turned out to be metabolically inactivated soft drugs even though they were not designed as such. They include procaine (**19**), articaine (**21**), and methylphenidate (**23**). As in Fig. 3, blue circles denote structural moieties where metabolic transformation takes place to *inactivate* these compounds after their exerted their intended pharmacological activity.

concentrations higher than the parent articaine (Vree and Gielen 2005); but it is essentially inactive (Van Oss et al. 1988).

3.2.3. Methylphenidate

Finally, methylphenidate (**23**), a methyl ester-containing piperidine derivative structurally related to amphetamine (**24**; Fig. 4) and widely used for the treatment of attention-deficit-hyperactivity disorder (ADHD), can also be considered as a soft psychostimulants. Because methylphenidate is rapidly hydrolyzed (Markowitz et al. 2000) into an inactive acidic metabolite (ritalinic acid) (Patrick et al. 1981), it can be considered a soft drug even if it was not designed as such. This is certainly a main reason behind its relative safety that makes possible its widespread pediatric use. Nevertheless, methylphenidate is still a schedule II drug, just as are amphetamines (i.e., it is considered a medication of high abuse potential). Plasma concentrations of the ritalinic acid metabolite are much higher than those of its parent methylphenidate (e.g., mean AUC values were 23 ± 4 times greater (Markowitz et al. 2000)), and 60 to 80% of methylphenidate is eliminated in urine as its acidic metabolite (Markowitz et al. 2003). In fact, short half-life is one of its main problems, because immediate-release formulations require relatively frequent administration to maintain effectiveness – an inconvenience especially in pediatric populations. Extended-release or transdermal formulations seem to provide good solutions. They also make possible a sort of ideal soft drug therapeutic approach: slow release or infusion to maintain a safe pharmacological effect that disappears rapidly when administration stops.

3.3. Soft drugs in clinical development

Soft drug development is still an expanding area of research and development and is being pursued by various research groups both in industrial and in academic settings for different therapeutic applications. Again, for detailed reviews of all related aspects, the reader is referred to recent comprehensive reviews by Bodor and Buchwald (2010, 2012); here, we will highlight only some of the more recent promising developments.

3.3.1. Soft anesthetics: MOC-etomidate

For several reasons, anesthesiology is one of the best suited areas for soft drug development: it requires a combination of high degree of pharmacologic control during the surgical procedure

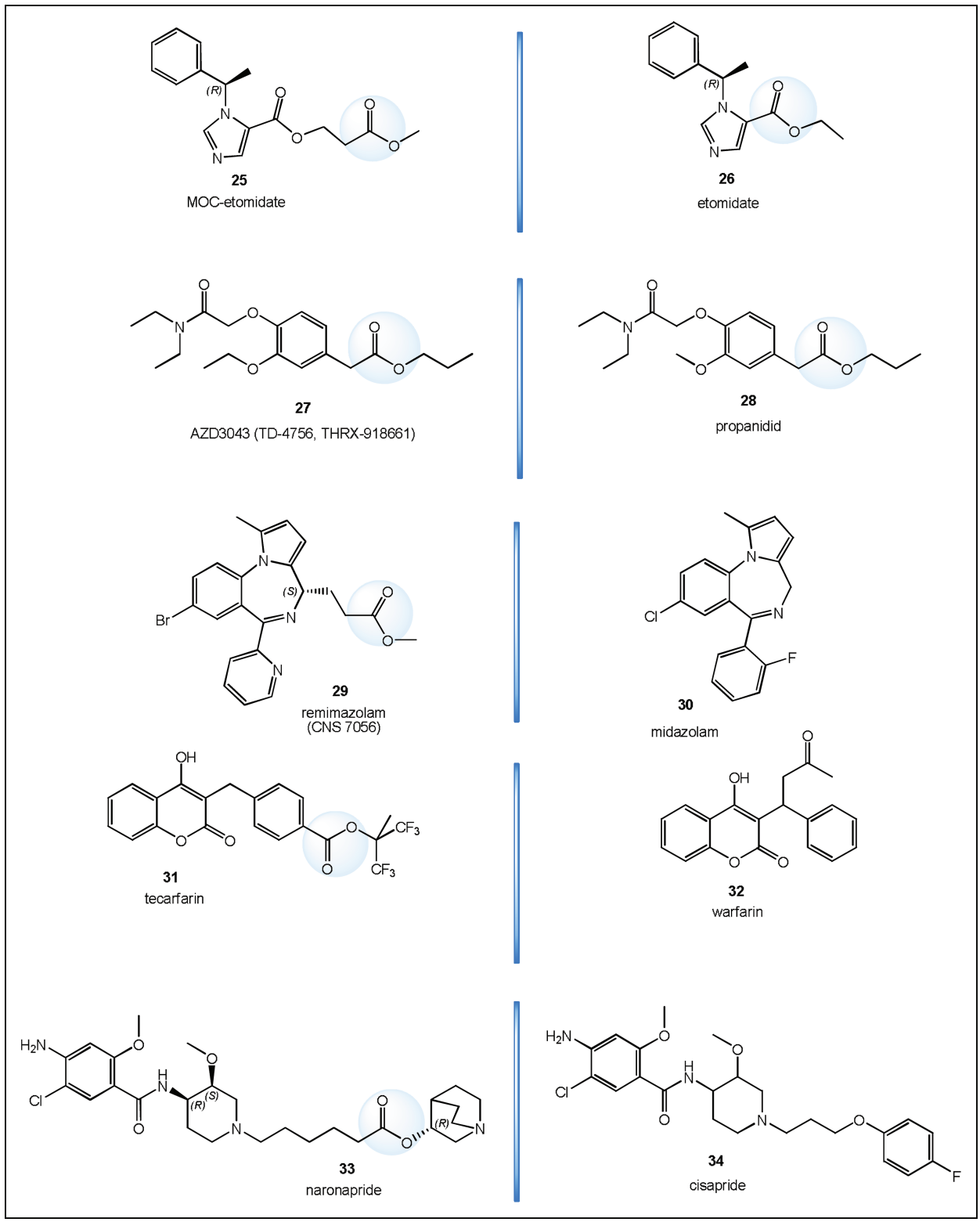

Fig. 5: Structure of some rationally designed soft drugs that have reached clinical investigations. As before, their structures on the left are compared with the corresponding representative leads (on the right), which served as the basis of their designs.

(to maintain the anesthetic state) with a need for quick return to responsiveness, spontaneous ventilation, and other vital functions at the end of this procedure. Soft drugs are ideally suited to provide rapid-on/rapid-off anesthesia: something approaching the "magic switch" type of analgesia so desired by surgeons, which would mean the ability to turn on the state of anesthesia when desired and then simply turn it off when the surgical procedure has been completed. In light of this, it is not surprising that a 2009 editorial in *Anesthesiology* commenting on the introduction of the soft etomidate analog MOC-etomidate was entitled "*Is Anesthesiology Going Soft? Trends in Fragile Pharmacology*" (Egan 2009), and a 2012 editorial introducing four new articles, two on remimazolam and two on MOC-etomidate, was entitled "*New Horizons in Sedative Hypnotic Drug Development: Fast, Clean, and Soft*" (Johnson 2012). We hope that this will indeed be an area of further promising soft drug designs.

As already discussed, etomidate (**26**, Fig. 5) is a short-acting i.v. anesthetic agent that can be considered an accidental soft

drug since it is relatively rapidly deactivated by hepatic and plasma esterases (Lewi et al. 1976). It is an imidazole-based rapidly acting sedative-hypnotic agent commonly used to induce general anesthesia in elderly, critically ill, and hemodynamically unstable patients. Its hypnotic action terminates rapidly after the end of delivery as it redistributes from the brain to other tissues; however, its elimination from plasma has a terminal half-life of 3–5 h as it has a relatively hindered aromatic ester moiety not very susceptible to hydrolysis (Hebron et al. 1983). Although etomidate is used because it maintains hemodynamic stability even in the setting of cardiovascular compromise, it also inhibits 11β-hydroxylase, causing potent and long-lasting suppression of adrenocortical steroid synthesis (de Jong et al. 1984; Wagner et al. 1984). This can persist for more than a day after administration has been discontinued. Therefore, the use of etomidate as a continuous infusion to maintain anesthesia or sedation has been abandoned almost entirely, and the use of even a single dose of etomidate for anesthetic induction is somewhat controversial (Annane 2005; Hohl et al. 2010; Vinclair et al. 2008).

A shorter-acting soft analog can provide a convenient alternative. Along these lines, researchers at the Harvard Medical School proposed methoxycarbonyl-etomidate (MOC-etomidate; **25**, Fig. 5) as a new ultrashort-acting soft anesthetic that is rapidly metabolized due to introduction of an additional, hydrolytically sensitive ester moiety (Cotten et al. 2009, 2011). Accordingly, MOC-etomidate should retain the favorable pharmacological properties of etomidate, but not produce prolonged adrenocortical suppression. Indeed, MOC-etomidate was found to potently enhance $GABA_A$ receptor function and produced loss of righting reflex in tadpoles (EC_{50} = 8 μM *vs*. 2.3 μM for etomidate). Its metabolism in human liver S9 fraction was much faster than that of etomidate, with an *in vitro* half-live of 4.4 min (*vs*. much more than 40 min for etomidate). Its only detected metabolite was the corresponding acid (Cotten et al. 2009). In agreement with its design as a soft drug, MOC-etomidate produced rapid loss of righting reflex in rats (ED_{50} = 5.2 mg/kg *vs*. 1.0 mg/kg for etomidate) that was extremely brief (e.g., 1 min at 20 mg/kg *vs*. 24 min for etomidate at equihypnotic dose) and caused minimal hemodynamic changes. Unlike etomidate, MOC-etomidate produced no adrenocortical suppression 30 min after single bolus administration. Closed-loop continuous infusion studies in rats have also confirmed that following termination of the infusion, serum corticosterone concentrations recovered within 30 min with MOC-etomidate, but persisted beyond 1 h with etomidate (Cotten et al. 2011). The acid metabolite is indeed essentially inactive: in three different biological assays, its potency was approximately 300-fold lower than that of the parent MOC-etomidate (Ge et al. 2012). For example, the median effective concentration (EC_{50}) for direct activation of $GABA_A$ receptors was 3.5 ± 0.6 mM for the metabolite vs. 10 ± 2.5 μM for the parent MOC-etomidate.

Notably, the carboxylic acid metabolite here, just as for a number of other known soft drugs, including esmolol (**12**), remifentanil (**15**), soft anticholinergics, soft TLR7 agonists, or remimazolam (**29**), was about 300-fold less active than the parent ester-containing drug (Bodor and Buchwald 2012). As all these acid moieties have a pK_a value of slightly less than 5.0 /e.g., acetic acid 4.8, propanoic acid 4.9, benzenepropanoic acid 4.7 (Lide 2006–2007)/, at physiological pH the portion of the acidic metabolite molecules that are uncharged (i.e., protonated) is about 1/300 to 1/500 of all metabolite molecules. Therefore, it is conceivable that the pharmacological activity observed results mainly from this uncharged, protonated fraction.

An additional variation, a slightly different soft drug, MOC-carboetomidate, was also explored (Pejo et al. 2012). In a manner very similar to MOC-etomidate, MOC-carboetomidate is a soft analog of carboetomidate, a close structural analog of etomidate (**26**). Carboetomidate is an etomidate analog developed not to inhibit 11β-hydroxylase and, hence, not to cause adrenocortical steroid synthesis suppression by replacing the imidazole ring of etomidate, which is thought to be necessary for high-affinity binding to 11β-hydroxylase, with a pyrrole ring (Cotten et al. 2010). Following synthesis, activity studies have shown that MOC-carboetomidate indeed retains the $GABA_A$ receptor modulatory ability and potent hypnotic activities of etomidate, carboetomidate, and MOC-etomidate upon which its structure is based. Rat studies have also shown that MOC-carboetomidate also maintains hemodynamic stability similar to carboetomidate (and better than propofol) and it does not suppress adrenocortical function. In rat blood, the soft drugs MOC-carboetomidate and MOC-etomidate were indeed rapidly metabolized in an approximately first-order fashion with metabolic half-lives of 1.3 and 0.35 min, respectively (Pejo et al. 2012).

3.3.2. Soft anesthetics: AZD3043

Still within the field of anesthetics, AZD3043 (**27**; Fig. 5), a propanidid analog, is being developed by AstraZeneca as a possible soft drug. Propanidid (**28**) is an ultrashort-acting phenylacetate general anesthetic, originally introduced by Bayer. It also contains an ester and is rapidly inactivated by esterases. Propanidid has been withdrawn due to anaphylactic reactions, which, however, might have been caused primarily by the Cremophor EL solubilizing agent, a polyethoxylated castor oil, used in its formulation (Klockgether-Radke et al. 1995). AZD3043 (**27**), a very close structural analog of propanidid, is being developed by AstraZeneca (originally, TD-4756/THRX-918661 by Theravance) (Sneyd 2004; Sneyd and Rigby-Jones 2010) and can also be classified as a soft anesthetic that is a $GABA_A$ allosteric modulator (Kilpatrick and Tilbrook 2006). AZD3043 has been shown to be a positive modulator and a direct agonist at human $GABA_A$ receptors that is not dependent on the γ2-subunit for its effect (Jonsson Fagerlund et al. 2012). Similar to propofol, the effect of AZD3043 is dramatically reduced by point-mutations in the β2(N289 M) and β3(N290 M) subunits, indicating similar molecular mechanisms of action for propofol and AZD3043 at this receptor (Jonsson Fagerlund et al. 2012). AZD3043 has been shown to produce rapid hypnosis following i.v. bolus administration or infusion in rats, mice, guinea pigs, ferrets, dogs, cats, pigs, and mini-pigs and to hydrolyze rapidly into its acid metabolite both *in vitro* (e.g., half-life of ≈ 10 min in human blood) and *in vivo* (Beattie et al. 2004; Jenkins et al. 2004; Sneyd 2004). It has been shown to be rapidly hydrolyzed by butyrylcholinesterase (BChE, EC 3.1.1.8) present in human plasma and liver microsomes to its pharmacologically inactive carboxylic acid metabolite. Its half-life and clearance are unaffected by the coadministration of butyrylcholinesterase substrate drugs; hence, there is a low risk for *in vivo* PK interactions when administering AZD3043 with other drugs metabolized by the same enzyme, such as remifentanil and succinylcholine (Aasa et al. 2011). Its development was delayed for a while by formulation difficulties, but it has been tested in humans by bolus injection and infusion, with four studies registered at www.clinicaltrials.gov (Sneyd and Rigby-Jones 2010); however, the data are currently still unpublished.

3.3.3. Other soft drugs in clinical development

With the increasingly wide application of these approaches, several other soft drug initiatives have reached the clinical development phase, for example, remimazolam (**29**), budiodarone, tecarfarine (**31**), or naronapride (**33**) (Fig. 5). We will mention

some highlights; details were reviewed by Bodor and Buchwald (2010, 2012).

Remimazolam (**29**) is a soft benzodiazepine resulting from an initiative started originally by GlaxoSmithKline on the basis of the remifentanil experience aiming for intravenous agents with a predictable fast-onset, short duration of action, and rapid recovery profile (Pacofsky et al. 2002; Rogers and McDowell 2010; Stafford et al. 2002). Remimazolam, as a potential i.v. sedative/anesthetic, has recently completed successfully a placebo- and midazolam-controlled, phase I single ascending-dose study evaluating its safety, pharmacokinetics, and pharmacodynamics, showing promising results and no safety concerns (Antonik et al. 2012; Wiltshire et al. 2012).

Tecarfarin (**31**) is a soft drug candidate selected for clinical development form a series of soft analogs of warfarin (**32**) that have been designed at ARYx Therapeutics as possible oral anticoagulants less likely to be subject to such interactions (Bavisotto et al. 2011; Bowersox et al. 2010; Choppin et al. 2009; Druzgala et al. 2006; Ellis et al. 2009). Tecarfarin has reached clinical evaluations in trials for the treatment of patients who are at risk for the formation of blood clots, such as those with atrial fibrillation or those at risk of venous thromboembolism. Naronapride (ATI-7505; **33**, Fig. 5), an investigational 5-HT4 receptor agonist, was also designed at ARYx Therapeutics as a soft analog of cisapride (**34**) and intended to have similar gastro-prokinetic activity without the cardiac adverse effects by avoiding the CYP450 metabolism (Bowersox et al. 2011; Camilleri et al. 2007; Druzgala et al. 2003). Naronapride has successfully completed phase II clinical trials for the treatment of multiple gastrointestinal disorders, including gastroesophageal reflux disease (GERD) and functional dyspepsia. Several other new soft drug initiatives are also under way. For example, some of the most recently published ones include possible soft TLR7 agonists developed at Dainippon Sumitomo Pharma and AstraZeneca (Biffen et al. 2012; Kurimoto et al. 2010) and soft ROCK inhibitors explored at Amakem NV (Boland et al. 2013).

4. Conclusion

In conclusion, soft drug design approaches, which are now part of the more general retrometabolic drug design approaches concept, are very general approaches that can be applied in a wide range of therapeutic classes to generate innovative, new chemical entities. They are particularly well suited where local activity is desired at the site of application or where well controlled titrated activity and ultrashort action is desired (e.g., anesthesia). This is a still expanding area of research, but several soft drugs are now clinically approved drugs. The design of future soft drugs is now also aided by computational tools incorporated into an expert system capable of generating new structures and ranking them according to their predicted potential.

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