REVIEW

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Recent advances in retrometabolic drug design (RMDD) and development

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Received January 18, 2010, accepted February 26, 2010

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Pharmazie 65: 395–403 (2010) *doi: 10.1691/ph.2010.0523R*

As a general review for the 7th Retrometabolism-Based Drug Design and Targeting Conference, recent developments within this field are briefly reviewed with various illustrative examples from different therapeutic areas. Retrometabolic drug design incorporates two major systematic approaches: the design of soft drugs and of chemical delivery systems (CDS). Both aim to design new, safe drugs with an improved therapeutic index by integrating structure-activity and structure-metabolism relationships; however, they achieve it by different means: whereas soft drugs are new, active therapeutic agents that undergo predictable metabolism to inactive metabolites after exerting their desired therapeutic effect, CDSs are biologically inert molecules that provide enhanced and targeted delivery of an active drug to a particular organ or site through a designed sequential metabolism that involves several steps.

1. Introduction

Although the drug discovery and development processes have significantly advanced by increasing insight into the molecular/biochemical mechanisms of drug action and by improved and accelerated screening technologies and lead selection methods, the number of approved new chemical entities (NCE) has not increased accordingly. This lack of success underlines the still limited understanding of what makes a good drug, but also the increasing developmental problems caused by stringent regulations. There are still too many "me too" drugs being developed just through limited modifications of known drugs. Highly touted new technologies, such as combinatorial chemistry and high-throughput screening (HTS), still have had no significant impact (Proudfoot 2002). Not enough emphasis is put on the safety issues. This important component is addressed by retrometabolic drug design (RMDD) approaches, a general concept directed toward the design of improved therapeutic index ($TI = TD_{50} / ED_{50}$), which is a reflection of the degree of selectivity or margin of safety. This type of design diverts the metabolism of the drugs to novel, non-toxic pathways avoiding the formation of toxic metabolites. With RMDD, metabolism does not just happen, but the metabolic route is imposed on the new drug by design. As is well known, RMDD involves two basic directions: soft drugs (SD) and targeted chemical delivery systems (CDS).

2. Soft drug examples and recent developments

The soft drug concept was introduced during the 1970 s (Bodor 1977, 1982, 1984), and since then it has been applied by many research groups in a large number of therapeutic areas. Comprehensive reviews of all major aspects have been published (Bodor and Buchwald 2000, 2003b). Our laboratory focused mainly on the design of soft corticosteroids (e.g., loteprednol etabonate, etiprednol dicloacetate) (Bodor and Buchwald 2006c), soft β-blockers (e.g., adaprolol) (Bodor and Buchwald 2005), and soft anticholinergics (e.g., tematropium) (Kumar and Bodor 1996). Detailed quantitative structure-activity relationships were developed in these drug classes (Buchwald 2007a, 2008; Buchwald and Bodor 2002, 2004, 2006) by taking into account, among other things, the size-related effects through a bilinear LinBiExp model (Buchwald 2005, 2007b). A number of soft drug approaches both by our laboratories and by many others already resulted in marketed drugs such as, for example, esmolol and landiolol, soft β-blockers containing easily hydrolyzable ester functions (Fig. 1), or remifentanil, a soft opioid analgesic based on carfentanyl (Fig. 2). Some therapeutic compounds can also be considered as "accidental" soft drugs, i.e., drugs that are, in fact, soft drugs even though they were not intentionally designed as such. For example, methylphenidate, a methyl ester containing piperidine derivative that is structurally related to amphetamine (Fig. 3), which is widely used for the treatment of attention-deficit-hyperactivity disorder (ADHD). As a methyl ester, it is easily hydrolyzed (Markowitz et al. 2000) to the inactive (Patrick et al. 1981) acidic metabolite (ritalinic acid). Thus, methylphenidate can be considered a safe, soft drug, which is why it is used extensively in pediatric patients.

Soft drug design approaches are widely used in both industrial and academic settings. Some more interesting developments include:

1. Soft estradiol analogs developed by Labaree and co-workers at Yale University (Fig. 4) (Labaree et al. 2001, 2003). These compounds, while estrogenic, can be used locally for the treatment of vaginal dispareunia, but are void of systemic estrogenic activity, due to their facile hydrolytic deactivation.
2. Hydrolyzable ester containing soft cyclosporin analogs (Fig. 5) explored at Enanta (Lazarova et al. 2003) for the treatment of autoimmune disorders.

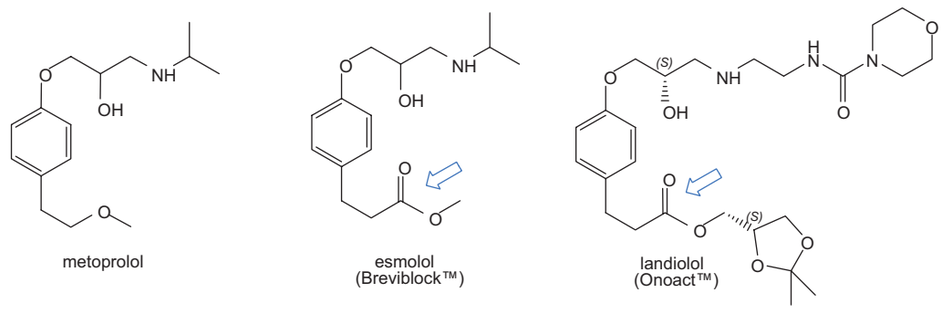

Fig. 1: Soft β-blockers. The deactivating ester functions are structurally removed from the pharmacophore

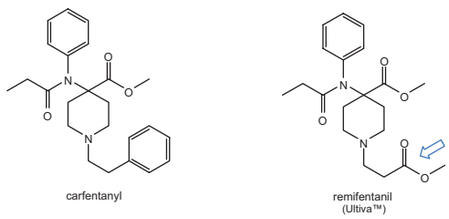

Fig. 2: Soft opioid analgesic, remifentanil

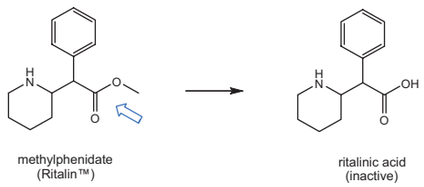

Fig. 3: Methylphenidate and its inactive metabolite, ritalinic acid

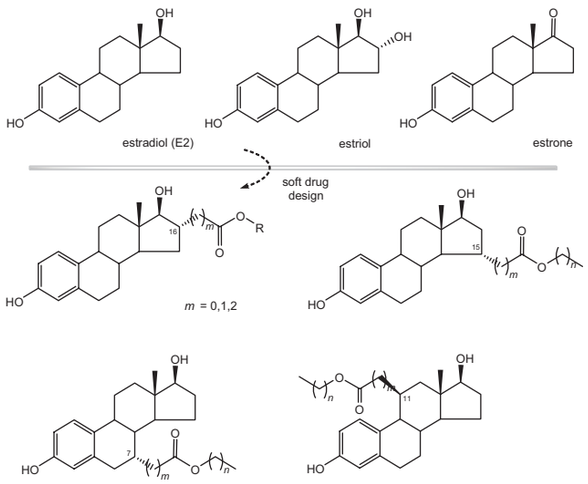

Fig. 4: Soft estradiol analogs

3. Soft tacrolimus analogs (Fig. 6) (e.g., MLD987) investigated at Novartis (Hersperger et al. 2004) for inhalation treatment of asthma.
4. Novel soft cytokine (Fig. 7) analogs developed at Janssen (Freyne et al. 2005) for inhalation therapy of asthma.
5. Some locally acting soft benzodiazepine analogs (CNS7259X, CNS7056) of midazolam and bromazepam, developed at GlaxoSmithKline (Fig. 8) (Kilpatrick et al. 2007; Kilpatrick and Tilbrook 2006; Pacofsky et al 2002; Stafford et al. 2002).
6. Intended soft mometasone furoate analogs (Fig. 9) investigated at Novartis (Sandham et al. 2004) that, however, did not fulfill expectations as the highly hindered 17β-esters did not hydrolyze to the predicted inactive acidic metabolite. A similarly positioned thioester in fluticasone propionate undergoes oxidative and not hydrolytic ester cleavage.
7. Soft amiodarone analogs (Fig. 10) for the treatment of atrial fibrillation were developed by Aryx Therapeutics (Arya et al. 2009; Morey et al. 2001; Raatikainen et al. 2000) using the dedicated software "Computer Assisted Soft Drug Design" (Bodor et al. 1998a) licensed from the University of Florida. Recent Phase II clinical studies demonstrated the superior safety profile of budiodarone (ATI-2042) as compared to amiodarone.
8. Soft cisapride analogs (e.g., ATI-7505) were also developed at Aryx Therapeutics (Fig. 11) and they also demonstrated improved activity and safety in clinical trials for gastroparesis (Camilleri et al. 2007).

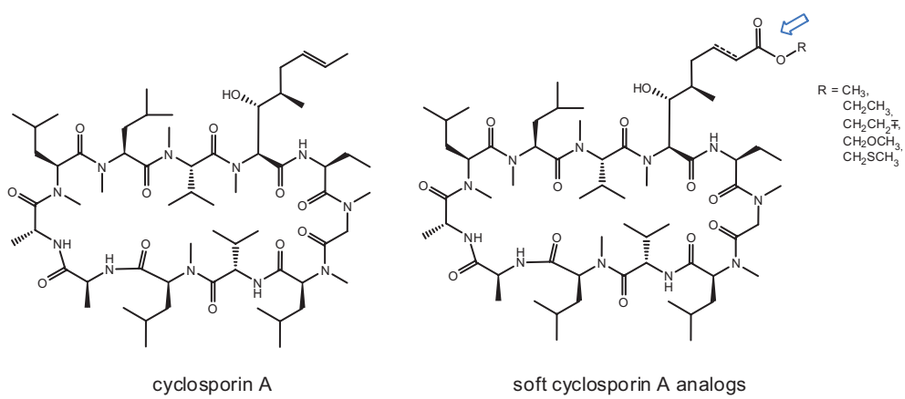

Fig. 5: Soft cyclosporin A analogs

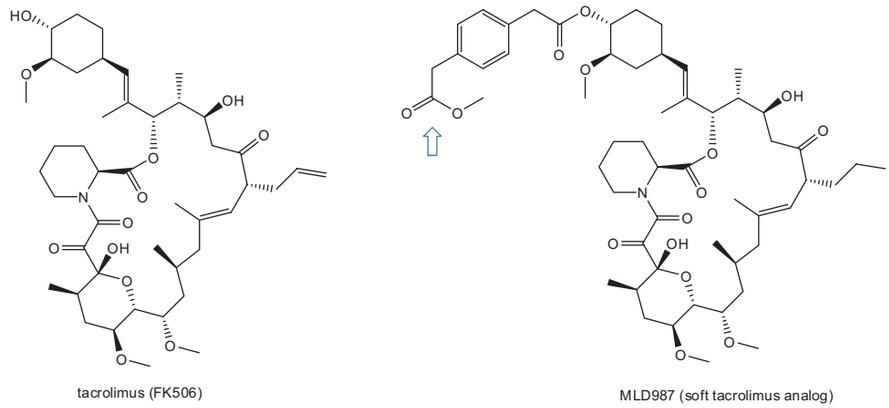

Fig. 6: Soft tacrolimus analog MLD987

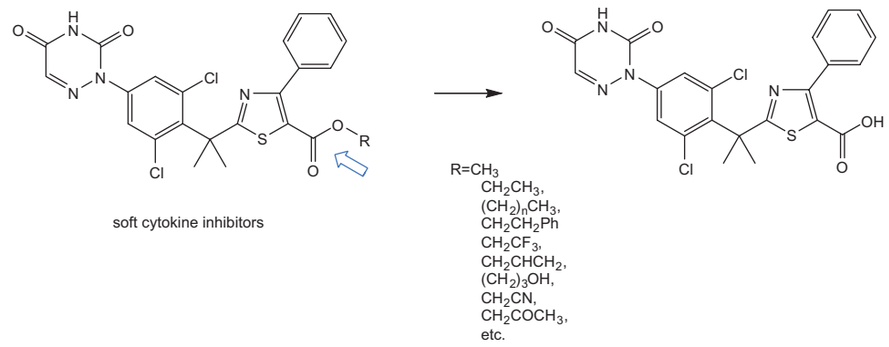

Fig. 7: Soft cytokine inhibitors

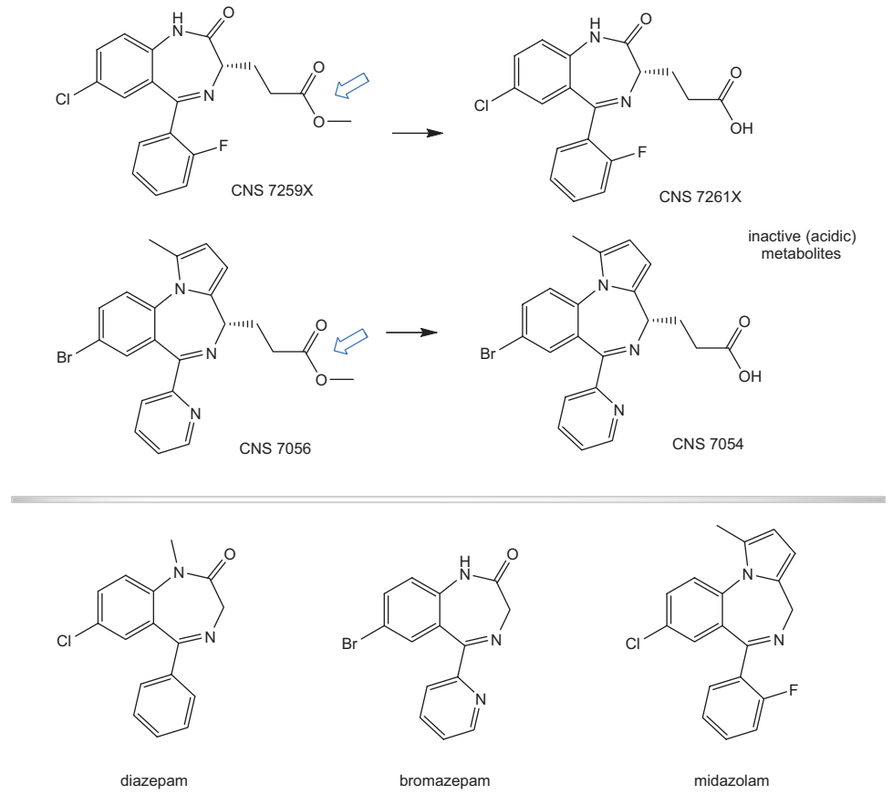

Fig. 8: Soft benzodiazepines, their inactive metabolites, and representative benzodiazepine structures

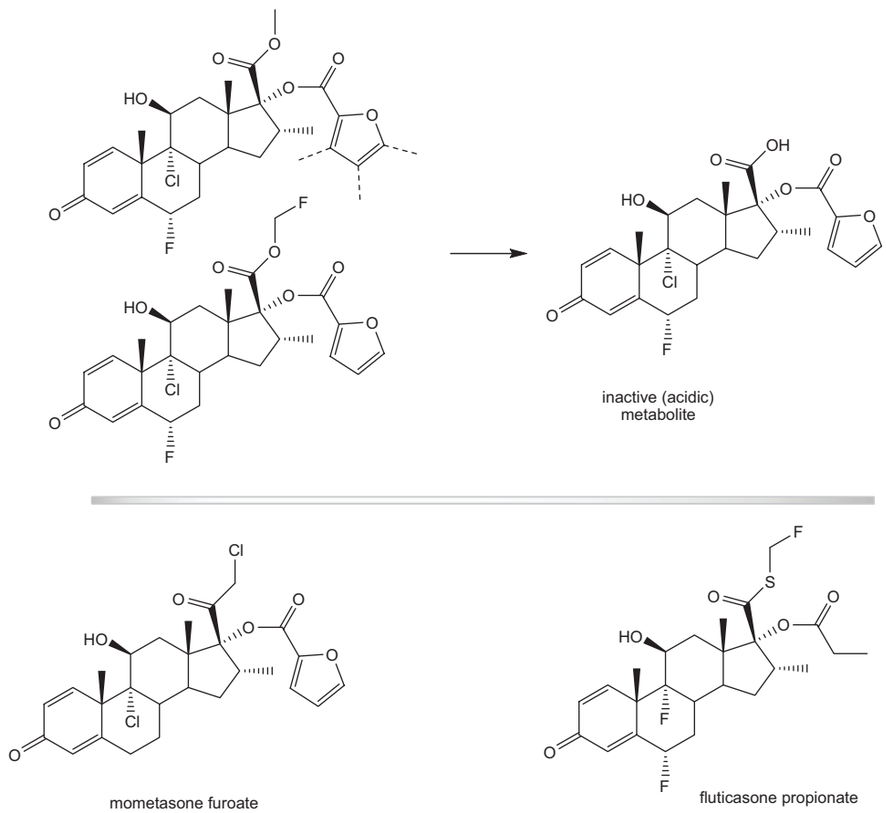

Fig. 9: Soft mometasone furoate analogs, their expected inactive metabolite, and related glucocorticoid structures (mometasone furoate and fluticasone propionate)

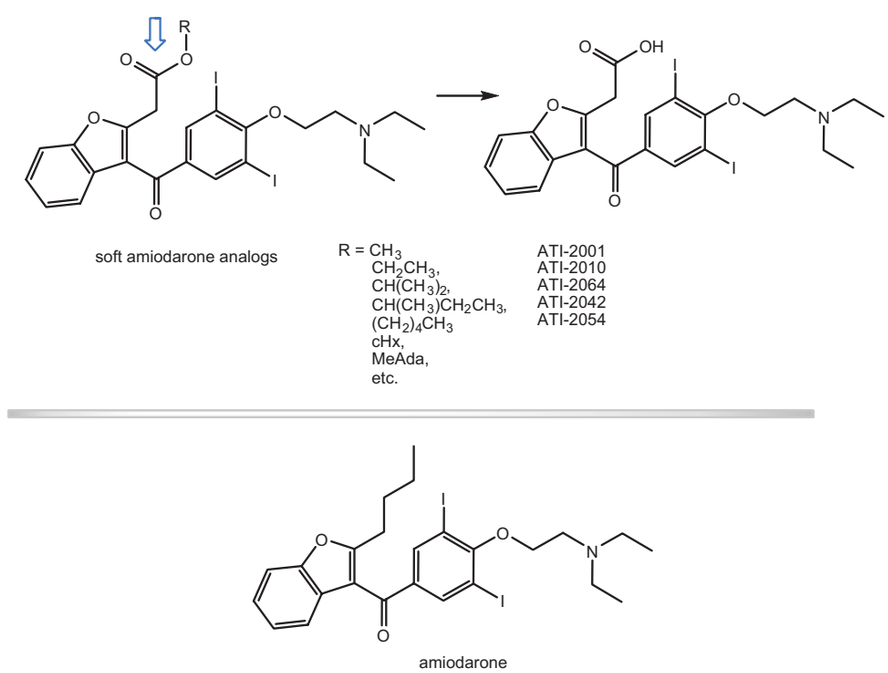

Fig. 10: Soft amiodarone analogs

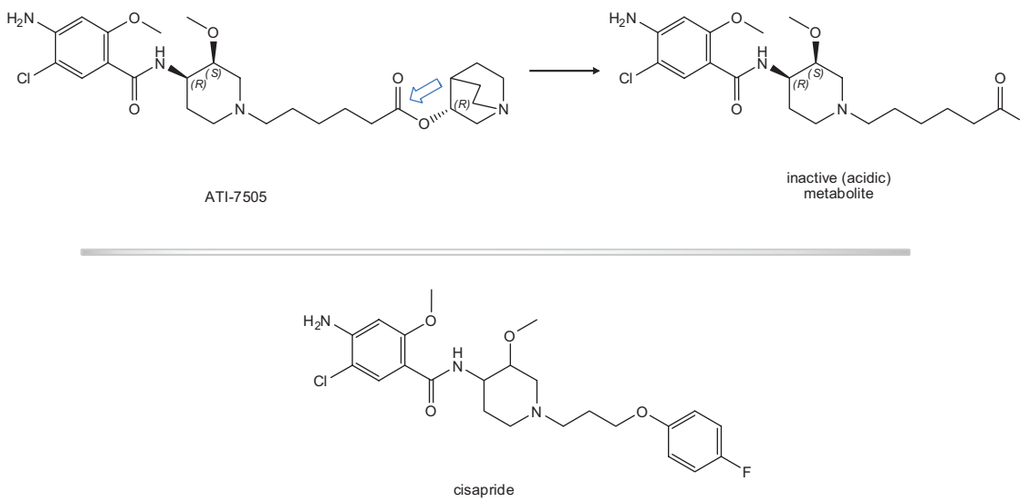

Fig. 11: Soft gastro-prokinetics based on cisapride

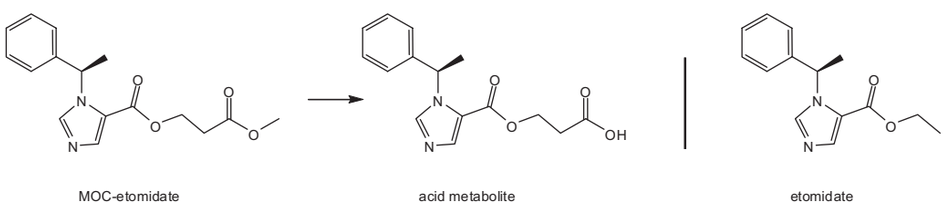

Fig. 12: MOC-etomidate, a soft analog of etomidate, and its inactive acid metabolite

9. The soft drug approach was recently applied in the field of anesthesiology (Cotten et al. 2009). Etomidate, an imidazol-carboxyester type anesthetic is the agent of choice for use in critically ill patients. However, it causes prolonged suppression of adrenocortisol steroid synthesis; consequently, its clinical utility and safety are limited. A soft analog MOC-etomidate, (*R*)-3-methoxy-3-oxopropyl-(1-phenylethyl)-1*H*-imidazole-5-carboxylate (Fig. 12), was strategically designed to undergo ultra-rapid metabolism by esterases. Indeed, the soft analog was metabolized with a half-life of 15.4 min in human liver S9 fraction, while etomidate did not show any significant hydrolysis in 1 hour. MOC-etomidate was effective as a hypnotic, but at equipotent doses of i.v. bolus, its soft analog was ultra-short acting: its duration of activity was one order of magnitude lower than that of etomidate (2.8 ± 0.4 min vs. 27 ± 7 min). On the other hand, MOC-etomidate produced no reduction in the adrenocortical steroid production, whereas an equihypnotic dose of etomidate produced a statistically significant reduction. The acidic metabolite is inactive. An accompanying editorial (Egan 2009) emphasized: "Although the terminology is new, soft drug success stories in anesthesiology date back many years. Perhaps the modern prototype example is the short-acting opioid remifentanil. [. . .] MOC-etomidate is the latest example of a novel soft drug under investigation within anesthesiology. [. . .] The advance of soft drugs [. . .] has made it increasingly possible for us to fulfill the magic switch fantasy. [. . .] the concept certainly makes more precise and accurate titration of anesthetic effect possible. With the soft drug trend clearly established, it can be said that anesthesia is going soft, and it's a good thing."
10. The field of antiinflammatory corticosteroids provides one of the most successful areas for soft drug design (Bodor 1999; Bodor and Buchwald. 2006c). Traditional corticosteroids are very useful drugs because of their ability to exert intense biological effects in almost any organ. They also tend to have multiple adverse effects that seriously limit their usefulness. Not surprisingly, the glucocorticoid receptor represents the target with the most number of approved drugs (together with the histamine H_1 receptor) (Overington et al. 2006). Systemic side effects include, for example, weight gain, fat redistribution, insulin resistance, myopathy, osteoporosis, hypertension, increased intraocular pressure, growth inhibition, and others. Soft drug approaches are particularly well suited for this area and especially for the design of novel inhaled, intranasal, or topically applied

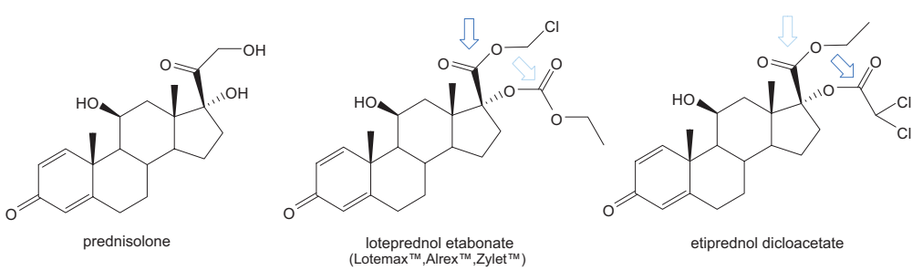

Fig. 13: Two soft steroids, loteprednol etabonate and etiprednol dicloacetate, derived from prednisolone

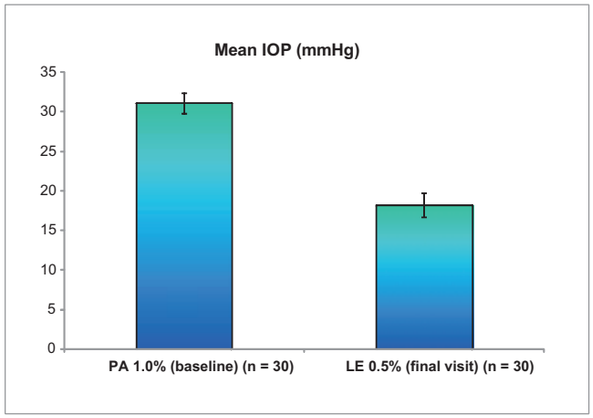

Fig. 14: Mean intraocular pressure (IOP) values of post-corneal transplant patients treated with prednisolone acetate (PA) and after switching to loteprednol etabonate (LE)

corticosteroids. However, to successfully separate the desired local activity from systemic toxicity, it is important to reach an adequate balance between activity/distribution and rate of metabolic deactivation. We followed a classic inactive metabolite-based soft drug approach with cortienic acid, a known inactive metabolite of hydrocortisone, as lead. Starting from this structure, more than 120 first-generation soft steroids have been synthesized by modifications of the 17β ester function and the 17α hydroxy function, together with other changes (introduction of $\Delta^{1,2}$, fluorination at 6α and/or 9α, methylation at 16α or 16β). From these first generation soft analogs, *loteprednol etabonate* (LE, Fig. 13), an analog of prednisolone, has been selected for clinical development on the basis of various considerations including therapeutic index, synthetic availability, and "softness" (the rate and easiness of metabolic deactivation). LE is a safe and effective treatment for seasonal allergic conjunctivitis, post-operative inflammation, contact lens-associated GPC, or uveitis (Howes 2000; Ilyas et al. 2004; Noble and Goa 1998). A very recent paper (Holland et al. 2009) further demonstrates the outstanding safety profile of LE. In these studies, thirty "steroid sensitive" patients who have undergone corneal transplantation were treated, as usual, with prednisolone acetate. This treatment caused an average elevation of intraocular pressure (IOP) to 31.1 mmHg. Increased IOP after corneal transplant can lead to irreversible vision loss through optic nerve damage. For this reason, the patients were switched to LE (Lotemax™). The IOP in all cases was reduced during the 21 weeks treatment to an average of 18.2 mmHg (Fig. 14). It was concluded that switching to loteprednol etabonate from prednisolone acetate in known steroid responders was successful in reducing IOP and did not increase the risk of allograft rejection.

3. Chemical delivery systems

On the other side of retrometabolic design, CDS approaches provide novel, systematic methodologies for targeting active biological molecules to specific target sites or organs based on predictable, multistep enzymatic activation (Bodor and Brewster 1991; Bodor and Buchwald 1997a, 1999). The bioremovable moieties attached to the drug that is the subject of targeted delivery include a *targetor* (T) moiety, which has to achieve the site-specific targeting, and (optional) *modifier functions* ($F_1...F_n$), which serve as lipophilizers, protect certain functions, or fine-tune the necessary molecular properties to prevent premature, unwanted metabolic conversions. The two main classes are represented by the enzymatic physical-chemical-based CDSs, which exploit site-specific traffic properties by sequential metabolic conversions that result in considerably altered transport properties and are used for brain-targeting, and by site-specific enzyme-activated CDSs, which exploit specific enzymes found primarily, exclusively, or at higher activity at the site of action and are used for ocular-targeting.

The brain-targeting redox-type CDS was highly successful in targeting drugs (D) to the brain by exploiting the differential bidirectional movement through the blood-brain barrier (BBB) of a lipophilic dihydrotrigonelline–D construct allowing "lock-in" of the hydrophilic trigonelline$^+$–D in the brain. The positively charged oxidized drug precursor accumulates behind the BBB allowing sustained local release of D and sparing in the same time the whole body from the drug (Bodor and Brewster 1991; Bodor and Buchwald 1997a; Bodor et al. 1975). Among CDS approaches explored to date (Bodor and Buchwald 2003a), estradiol CDS (E_2-CDS) is in the most advanced investigation stage: it has completed Phase I/II studies with a new buccal formulation (Bodor and Buchwald 2006a).

Recently, a group of French researchers (Foucout et al. 2009) have successfully applied our formerly introduced (Bodor et al. 2002) dihydroquinoline ⇆ quinolinium targetor system for GABA: the lipophilic DHQ–D penetrates the BBB, and oxidation locks in the Q$^+$–D precursor (Fig. 15) (Foucout et al. 2009). Further, a modified targetor was reported by Hassan et al. (2009). The 1-malonyl-1,4-dihydropyridine ⇆ pyridinium moiety was successfully applied for brain targeting (Hassan et al. 2009).

4. Molecular packaging

The CDS approach has also been extended to achieve successful brain deliveries of neuropeptides such as Leu-enkephalin, thyrotropin-releasing hormone (TRH), and kyotorphin analogs (Bodor and Buchwald 1999; Bodor and Buchwald 2003b; Bodor et al. 1992; Chen et al. 1998; Wu et al. 2002). Brain delivery of peptides is particularly difficult because of their rapid metabolic degradation by peptidases and their often unfavorable lipophilicity profile (Bodor and Buchwald 2006b). Therefore, the successful brain delivery of peptides requires three issues to be solved simultaneously: enhance passive transport by increasing the lipophilicity, ensure enzymatic stability to prevent premature degradation, and exploit the lock-in mechanism to provide targeting. This has been achieved with a complex *molecular packaging* strategy, in which the peptide unit is part of a bulky molecule dominated by lipophilic modifying groups (L) that direct BBB penetration and prevent recognition by peptidases (Fig. 16). The efficacy of the CDS package was strongly influenced by modifications of the spacer (S) moiety, which consisted of strategically used amino acids that ensured the timely removal of the charged targetor from the peptide, and the lipophilic (L) moiety. The bulkier cholesteryl group used as L showed a better efficacy than the smaller adamantine-ethyl, but the spacer (S) function turned out to be the most important factor for manipulating the rate of peptide release and pharmacological activity: proline, proline-proline, or proline-alanine spacers produced the best *in vivo* pharmacological effects. *Brain-targeting redox analogs* (BTRAs), in which the targetor moiety is not attached to the peptide from outside, but is integrated within novel *redox* amino acid building blocks (Bodor 1997) that replace the original basic amino acid of the active peptide, have also been explored for kyotorphin and its analogs (Chen et al. 1998) as well as for TRH in a copycat design (Prokai-Tatrai et al. 2002; Prokai et al. 2004) (Fig. 17).

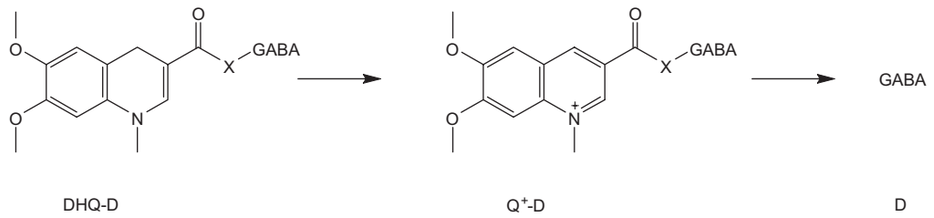

Fig. 15: The dihydroquinoline ⇄ quinolinium redox targetor system as applied to GABA

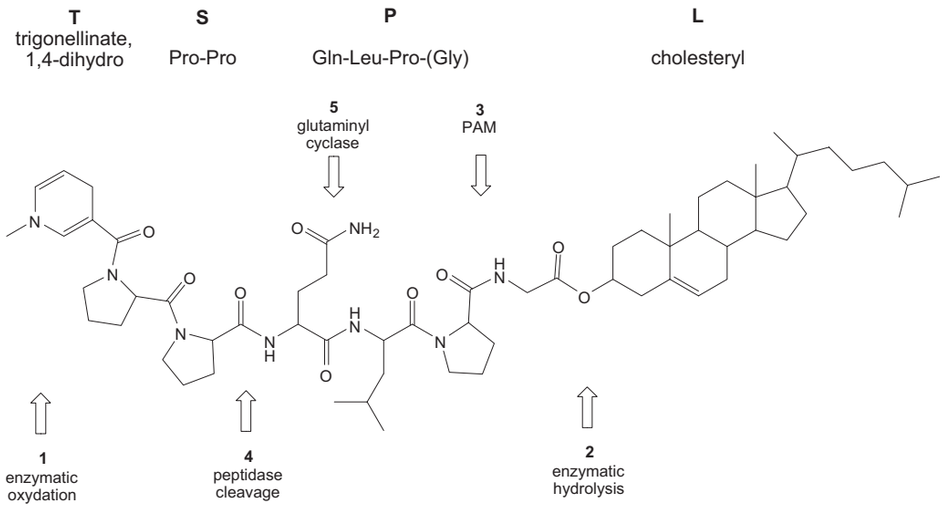

Fig. 16: The peptide brain targeting molecular package construct as applied to TRH

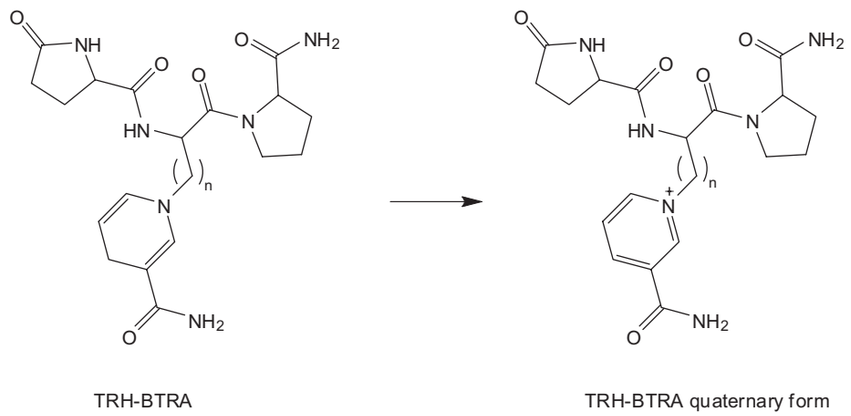

Fig. 17: The brain-targeted redox analogs (BRTA) of TRH

On the other hand, former junior associates of the Center for Drug Discovery at the University of Florida continue to attempt to hijack the original brain targeting concept based on differential sequential metabolism of dihydropyridine ⇆ pyridinium targetor system constructs (Bodor 1997; Bodor et al. 1992) by breaking up the necessary sequence into prodrugs and other units, renaming the original components. For example, the "targetor" is renamed (improperly) as "transport moiety", the "spacer(s)" as "scissile linkers" (Prokai-Tatrai et al. 2008; Prokai-Tatrai and Prokai 2009), and the "brain-targeted redox analog (BTRA)" (Chen et al. 1998) based on 'redox amino acids' (Bodor 1997) as "prodrug-amenable analog" (Prokai-Tatrai and Prokai 2009). They also compare the *in silico* predictions for log *P* values with three different methods, including BLOGP (Bodor et al. 1989) and QLogP (Bodor and Buchwald 1997b), concluding that they "displayed a great array of unrealistic discrepancies within and among the methods" (Prokai-Tatrai and Prokai 2009) and that they were "uninterpretable for the compounds involved in this study" mainly because they "consistently predicted the pyridinium compounds (. . .) to be significantly more lipophilic than the corresponding 1,4-dihydropyridines" (Prokai et al. 2004). However, part of this is because they are using unauthorized software ignoring the existence of updated versions that accurately predict the lipophilicity of peptides (Buchwald and Bodor 1998), even for those that contain the unique dihydropyridine ⇆ pyridinium redox components where there is a large change of several log units (Bodor et al. 1998b, 1999).

5. Conclusion

In conclusion, retrometabolic approaches incorporate two drug design approaches, the soft drugs and CDSs. These achieve their drug targeting roles in opposite ways, but they both rely on

designed metabolism to control drug distribution and action and to increase safety. These approaches are general in nature, and the corresponding specific design principles can be applied to essentially all drug classes.

Acknowledgements: This paper was partially presented during the 7th Conference on Retrometabolism-Based Drug Design and Targeting, May 10–13, 2007, Orlando, Florida, USA.

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