Drug Designing: Open Access
ISSN: 2169-0138

Karaman, Drug Des 2013, 2:2
DOI: 10.4172/2169-0138.1000e115

Editorial Open Access

The Prodrug Naming Dilemma

Rafik Karaman*

Bioorganic Chemistry Department, Faculty of Pharmacy, Al-Quds University, P.O. Box 20002, Jerusalem, Palestin

According to Albert's definition, "a prodrug is the inactive form of its parent drug [1]." However, there are few prodrugs that are active before undergoing enzymatic or chemical interconversion themselves. For example, aspirin, acetylsalicylic acid, first made by Felix Hoffmann at Bayer in 1897, is a synthetic prodrug of salicylic acid, however, it was proven that aspirin inhibits Cyclooxygenase (COX-1) via binding to its serine to exert a direct anti-inflammatory activity [2]. This terminology has created widespread confusion among many who study prodrugs. The following discussion aims to clarify the terms associated with prodrugs, understand the history in which the terms came about, and suggest clearer terminology that can be used.

Prodrug is a term that was first introduced in 1958 by Albert in his article in *Nature* to signify a pharmacologically inactive chemical moiety that can be used to temporarily alter the physicochemical properties of a drug to increase its usefulness and decrease its associated toxicity. Others such as Harper also promoted the concept but used the term drug latentiation. The use of the term generally implies a chemical device by which a drug is linked to a chemical promoiety via a covalent bond. Prodrugs can be enzymatically or chemically converted to the parent drug once their goal is achieved, followed by rapid excretion of the released promoiety group. A prodrug is designed to overcome the barriers to utility through a chemical approach rather than a formulation approach. Thus, it is an alternative to the redesign of the drug molecule or what is commonly called an analog approach [1-8].

Prodrug design can be exploited to: (1) improve active drug solubility and consequently bioavailability; dissolution of the drug molecule from the dosage form may be a rate-limiting step to absorption, (2) increase permeability and absorption; membrane permeability has a significant effect on drug efficacy, and (3) modify the distribution profile; before the drug reaches its physiological target and exerts the desired effect. The rationale behind the use of prodrugs is to optimize the Absorption, Distribution, Metabolism, and Excretion Properties (ADME). In addition, the prodrug strategy has been used to increase the selectivity of drugs for their intended target [9-13]. Many prodrugs discovered a long time ago are still in clinical use.

Methenamine was discovered in 1899 by Schering as a prodrug that delivers the antibacterial formaldehyde to treat urinary tract infections. Acetylsalicylic acid (aspirin) was marketed in 1899 as a less irritating replacement of sodium salicylate to treat inflammation. Prontosil was discovered in 1935 as the first sulfa drug and a prodrug of sulfanilamide which ushered in the era of sulfonamide antibiotics. Diacetylmorphine was synthesized in 1874 and subsequently marketed as an over-the-counter drug in 1895 under the name heroin and was used as a morphine substitute for treating coughs and for the treatment of cocaine and morphine addictions. It is still available by prescription in the United Kingdom and other European countries. However, the discovery of the rapid metabolism of heroin into morphine eventually became a historic blunder for Bayer. Acetanilide was used as early as 1886 as a pain killer, but its activity was a result of its metabolism to acetaminophen (paracetamol). Phenacetin, which was removed from the market due to renal toxicity, exhibited its activity due to O-dealkylation to acetaminophen. Acetanilide and phenacetin were originally not designed as prodrugs, but their nature as prodrugs was determined in hindsight. Other such examples include codeine being partially metabolized to morphine, phenylbutazone to oxyphenylbutazone, primadone to phenobarbitone, and diazepam to desmethyldiazepam and oxazepam. More examples of such hindsight recognition are the prodrugs of morphine, heroin and codeine [14].

In these examples such as codeine, phenylbutazone and etc., the prodrugs and their metabolites are active drugs. Albert states in the 1985 edition of his *Selective Toxicity book*,"I apologize for having invented the term, now too widely used to alter, for literary purists tell me they would have preferred 'pre-drug' [13]." Albert essentially gave the prodrug concept legitimacy as a tool to be used in drug discovery to solve issues with problematic drugs. One of the first examples of the application of a prodrug solution to a problematic drug was the work performed at Parke-Davis in the 1950s with the antibiotic chloramphenicol. Chloramphenicol is sparingly water-soluble and has a bitter taste. Parke-Davis developed, after launching chloramphenicol, two prodrugs chloramphenicol hemisuccinate sodium salt for IV, IM, and ophthalmic administration and chloramphenicol palmitate as a suspension for pediatric oral use [15,16]. Paul Ehrlich, in 1908 coined the term "magic bullet" to describe drugs or therapies that selectively acted at their site of action with minimal exposure to the rest of the body. In addition, he also studied the role of drug metabolism in activating drugs in his seminal work on arsenicals. Effectively, Ehrlich's magic bullet concept and his work on arsenicals were the precursors to today's ADEPT, GDEPT, and prodrugs in general [17-21].

In our lab, we have studied a large number of novel prodrugs that were designed based on enzyme models. Some of these prodrugs such as amoxicillin and cephalexin prodrugs were found to be active before interconversion to their parent drugs. Among those are aza-nucleoside derivatives for the treatment of myelodysplastic syndromes, paracetamol as a pain killer, anti-malarial atovaquone, anti-Parkinson dopamine, anti-viral acyclovir, antihypertensive atenolol, antibacterial cefuroxime, anti-psoriasis monomethyl maleate, and phenylephrine as decongestant. In vitro kinetic results at a wide pH range have shown promising results for obtaining novel prodrugs that may have enhanced dissolution, membrane penetration, and thus better bioavailability than their corresponding parent drugs [22-56]. In conclusion, based on the examples discussed, precise terminology can be drawn as follows: inactive prodrugs should be named predrugs and active prodrugs should be named drug-predrugs.

***Corresponding author:** Rafik Karaman, Bioorganic Chemistry Department, Faculty of Pharmacy, Al-Quds University, P.O. Box 20002, Jerusalem, Palestin, Fax: + (972) 2790413; E-mail: dr_karaman@yahoo.com

Received May 26, 2013; **Accepted** May 26, 2013; **Published** May 28, 2013

Citation: Karaman R (2013) The Prodrug Naming Dilemma. Drug Des 2: e115. doi:10.4172/2169-0138.1000e115

Acknowledgement

The author would like to acknowledge funding by the German Research Foundation (DFG, ME 1024/8-1) and Exo Research Organization, Potenza, Italy.

References

1. ALBERT A (1958) Chemical aspects of selective toxicity. Nature 182: 421-422.
2. Burke, Anne; Smyth, Emer; FitzGerald, Garret A (2006) "26: Analgesic Antipyretic and Antiinflammatory Agents". Goodman and Gilman's the pharmacological basis of therapeutics (11thedn). New York: McGraw-Hill. 671-716.
3. Stella VJ, Borchardt RT, Hageman MJ, Oliyai R, Maag H, et al. (2007) Prodrugs: Challenges and Rewards. Springer.
4. Stella VJ, Charman WN, Naringrekar VH (1985) Prodrugs. Do they have advantages in clinical practice? Drugs 29: 455-473.
5. Banerjee PK, Amidon GL (1985) Design of prodrugs based on enzymes-substrate specificity. In: Bundgaard H, ed. Design of Prodrugs. New York: Elsevier 93-133.
6. Müller CE (2009) Prodrug approaches for enhancing the bioavailability of drugs with low solubility. Chem Biodivers 6: 2071-2083.
7. HARPER NJ (1959) Drug latentiation. J Med Pharm Chem 1: 467-500.
8. Harper NJ (1962) Drug latentiation. Progress in Drug Research 4: 221-294.
9. Stella VJ, Nti-Addae KW (2007) Prodrug strategies to overcome poor water solubility. Adv Drug Deliv Rev 59: 677-694.
10. Di L, Kerns EH (2007) Solubility issues in early discovery and HTS, in Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics (AugustijinsP, Brewster M eds) 111–136.
11. Fleisher D, Bong R, Stewart BH (1996) Improved oral drug delivery: solubility limitations overcome by the use of prodrugs. Adv Drug Deliv Rev 19: 115-130.
12. Chan OH, Stewart BH (1996) Physicochemical and drug-delivery considerations for oral drug bioavailability. Drug Discov Today 1: 461-473.
13. Beaumont K, Webster R, Gardner I, Dack K (2003) Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist. Curr Drug Metab 4: 461-485.
14. Albert A (1985) Selective Toxicity: The Physico-Chemical Basis of Therapy. (7thedn). New York, NY: Chapman and Hall 208-214.
15. Glazko AJ, Edgerton WH, Dill WA, Lenz WR (1952) Chloromycetin palmitate: a synthetic ester of chloromycetin. Antibiotics and Chemotherapy 2: 234-242.
16. Glazko AJ, Carnes He, Kazenko A, Wolf LM, Reutner TF (1957) Succinic acid esters of chloramphenicol. Antibiot Annu 5: 792-802.
17. Philpott GW, Shearer WT, Bower RJ, Parker CW (1973) Selective cytotoxicity of hapten-substituted cells with an antibody-enzyme conjugate. J Immunol 111: 921-929.
18. Deonarain MP, Spooner RA, Epenetos AA (1995) Genetic delivery of enzymes for cancer therapy. Gene Ther 2: 235-244.
19. Singhal S, Kaiser LR (1998) Cancer chemotherapy using suicide genes. Surg Oncol Clin N Am 7: 505-536.
20. Aghi M, Hochberg F, Breakefield XO (2000) Prodrug activation enzymes in cancer gene therapy. J Gene Med 2: 148-164.
21. Greco O, Dachs GU (2001) Gene directed enzyme/prodrug therapy of cancer: historical appraisal and future prospectives. J Cell Physiol 187: 22-36.
22. Dahan A, Khamis M, Agbaria R, Karaman R (2012) Targeted prodrugs in oral drug delivery: the modern molecular biopharmaceutical approach. Expert Opin Drug Deliv 9: 1001-1013.
23. Karaman R, Fattash B, Qtait A (2013) The future of prodrugs - design by quantum mechanics methods. Expert Opin Drug Deliv 10: 713-729.
24. Karaman R (2008) Analysis of Menger's spatiotemporal hypothesis. Tetrahedron Lett 49: 5998-6002.
25. Karaman R (2009) Cleavage of Menger's aliphatic amide: a model for peptidase enzyme solely explained by proximity orientation in intramolecular proton transfer. J Mol Struct 910: 27-33.
26. Karaman R (2010) The efficiency of proton transfer in Kirby's enzyme model, a computational approach. Tetrahedron Lett 51: 2130-2135.
27. Karaman R, Pascal R (2010) A computational analysis of intramolecularity in proton transfer reactions. Org Biomol Chem 8: 5174-5178.
28. Karaman R (2010) A General Equation Correlating Intramolecular Rates with Attack" Parameters: Distance and Angle. Tetrahedron Lett 51: 5185-5190.
29. Karaman R (2011) Analyzing the efficiency of proton transfer to carbon in Kirby's enzyme model- a computational approach. Tetrahedron Lett 52: 699-704.
30. Karaman R (2011) Analyzing the efficiency in intramolecular amide hydrolysis of Kirby's N-alkylmaleamic acids - A computational approach. Comput Theor Chem 974: 133-142.
31. Karaman R (2009) A new mathematical equation relating activation energy to bond angle and distance: A key for understanding the role of acceleration in lactonization of the trimethyl lock system. Bioorg Chem 37: 11-25.
32. Karaman R (2009) Revaluation of Bruice's Proximity Orientation. Tetrahedron Lett. 50: 452-458.
33. Karaman R (2009) Accelerations in the Lactonization of Trimethyl Lock Systems are Due to Proximity Orientation and not to Strain Effects. Research Letters in Org. Chem.
34. Karaman R (2009) The gem-disubstituent effect- a computational study that exposes the relevance of existing theoretical models. Tetrahedron Lett 50: 6083-6087.
35. Karaman R (2009) Analyzing Kirby's amine olefin - a model for amino-acid ammonia lyases. Tetrahedron Lett 50: 7304-7309.
36. Karaman R (2009) The effective molarity (EM) puzzle in proton transfer reactions. Bioorg Chem 37: 106-110.
37. Karaman R (2010) Effects of substitution on the effective molarity (EM) for five membered ring-closure reactions- a computational approach. Journal of Molecular Structure 939: 69-74.
38. Karaman R (2010) The Effective Molarity (EM) Puzzle in Intramolecular Ring-Closing Reactions. Journal of Molecular Structure 940: 70-75.
39. Menger FM, Karaman R (2010) A singularity model for chemical reactivity. Chemistry 16: 1420-1427.
40. Karaman R (2010) The effective molarity (EM)--a computational approach. Bioorg Chem 38: 165-172.
41. Karaman R (2010) Proximity vs. Strain in Ring-Closing Reactions of Bifunctional Chain Molecules- a Computational Approach. J Mol Phys 108: 1723-1730.
42. Karaman R (2011) The role of proximity orientation in intramolecular proton transfer reactions. Journal of Computational and Theoretical Chemistry 966: 311-321.
43. Karaman R (2010) Prodrugs of aza nucleosides based on proton transfer reaction. J Comput Aided Mol Des 24: 961-970.
44. Hejaz H, Karaman R, Khamis M (2012) Computer-assisted design for paracetamol masking bitter taste prodrugs. J Mol Model 18: 103-114.
45. Karaman R (2011) Computational-aided design for dopamine prodrugs based on novel chemical approach. Chem Biol Drug Des 78: 853-863.
46. Karaman R, Dajani KK, Qtait A, Khamis M (2012) Prodrugs of acyclovir--a computational approach. Chem Biol Drug Des 79: 819-834.
47. Karaman R, Hallak H (2010) Computer-assisted design of pro-drugs for antimalarial atovaquone. Chem Biol Drug Des 76: 350-360.
48. Karaman R, Dajani KK, Hallak H (2012) Computer-assisted design.
49. Karaman R, Dajani K, Hallak H (2012) Computer-assisted design for atenolol prodrugs for the use in aqueous formulations. J Mol Model 18: 1523-1540.
50. Karaman R (2013) Prodrugs for masking bitter taste of antibacterial drugs-a computational approach. J Mol Model 19: 2399-2412.
51. Karaman R, Dokmak G, Bader M, Hallak H, Khamis M, et al. (2013) Prodrugs of fumarate esters for the treatment of psoriasis and multiple sclerosis--a computational approach. J Mol Model 19: 439-452.
52. Karaman R (2012) The Future of Prodrugs designed by Computational Chemistry. Drug Des 1: e103.

53. Karaman R (2013) Computationally Designed Prodrugs for Masking the Bitter Taste of Drugs. Drug Des 1: e106.

54. Karaman R (2013) Prodrugs Design by Computation Methods-A New Era. Drug Des 2: e113.

55. Karaman R (2013) Computationally Designed Enzyme Models to Replace Natural Enzymes In Prodrug Approaches. Drug Des 1: e111.

56. Karaman R (2013) Prodrug Design vs. Drug Design. Drug Des 2: e114.