Drug Designing: Open Access
ISSN: 2169-0138

Karaman, Drug Des 2013, 2:1
DOI: 10.4172/2169-0138.1000e113

Editorial Open Access

Prodrug Design by Computation Methods: A New Era

Rafik Karaman*

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

Introduction

Prodrugs, soft drugs, targeted drugs, and metabolites of drugs are common terms that are used in the pharmaceutical field. The term "prodrug" was first introduced by Albert to signify pharmacologically inactive chemical moieties that can be used to temporarily alter the physiochemical properties of drugs in order to increase their usefulness and decrease their associated toxicity [1]. The use of the term usually implies a covalent link between a drug and a chemical moiety. Generally, prodrugs can be enzymatically or chemically converted in vivo to provide the parent active drug to exert a therapeutic effect. Ideally, the prodrug should be converted to the parent drug as soon as its goal is achieved, followed by the subsequent rapid elimination of the released linker group [2-5].

On the other hand, soft drugs (antedrugs) are drugs that are readily degraded to inactive derivatives to prevent or reduce activity. Targeted drugs are drugs or prodrugs that exert their biological action only in specific cells or organs such as in the administration of omeprazole and acyclovir. The active metabolite term refers to the degradation of the drug by the body into a modified form that has a biological effect. Usually these effects are similar to those of the parent drug but are weaker yet still significant. Examples of such metabolites are 11-hydroxy-THC and morphine-6-glucuronide. In certain drugs, such as codeine and tramadol, the corresponding metabolites are more potent than the parent drug (morphine and O-desmethyltramadol respectively) [6-8].

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. Development of a prodrug with improved properties may also represent a life-cycle management opportunity. Unfortunately, prodrugs are often considered only when problems are encountered with the parent drug. The design of an appropriate prodrug should be considered in the early stages of preclinical development and should not be viewed as a last resort.

Modifying the ADME properties of the parent drug requires a comprehensive understanding of the physicochemical and biological behavior of the drug candidate. Although prodrug design is very challenging, it can still be more feasible and faster than searching for an entirely new biologically active molecule with suitable ADME properties. The prodrug approach is becoming more popular and successful. To date, prodrugs comprise around 10% of the world's marketed medications and 20% of all small molecular medications approved between 2000-2008 [9,10].

The prodrug approach is a very versatile strategy to increase the utility of biologically active compounds, because one can optimize any of the ADME properties of potential drug candidates. In most cases, prodrugs contain a promoiety (linker) that is removed by an enzymatic or chemical reaction, while other prodrugs release their active drugs after molecular modification such as an oxidation or reduction reaction. The prodrug candidate can also be prepared as a double prodrug, where the second linker is attached to the first promoiety linked to the parent drug molecule. These linkers are usually different and are cleaved by different mechanisms. In some cases, two biologically active drugs can be linked together in a single molecule called a codrug. In a codrug, each drug acts as a linker for the other [9,10]. The prodrug approach has been used to overcome various undesirable drug properties and to optimize clinical drug application. Recent advances in molecular biology provide direct availability of enzymes and carrier proteins, including their molecular and functional characteristics. Prodrug design is becoming more elaborate in the development of efficient and selective drug delivery systems. The targeted prodrug approach, in combination with gene delivery and controlled expression of enzymes and carrier proteins, is a promising strategy for precise and efficient drug delivery and enhancement of the therapeutic effect.

The prodrug design can be utilized in the following: (1) improving active drug solubility and consequently bioavailability; dissolution of the drug molecule from the dosage form may be the rate-limiting step to absorption [10]. It has been reported that more than 30% of drug discovery compounds have poor aqueous solubility [11]. Prodrugs are an alternative way to increase the aqueous solubility of the parent drug molecule by improving dissolution rate via attached ionizable or polar neutral functions, such as phosphates, amino acids, or sugar moieties [2,5,10,12]. These prodrugs can be used not only to enhance oral bioavailability but also to prepare parenteral or injectable drug delivery; (2) increasing permeability and absorption; membrane permeability has a significant effect on drug efficacy [13]. In oral drug delivery, the most common absorption routes are unfacilitated and largely nonspecific passive transport mechanisms. The lipophilicity of poorly permeable drugs can be enhanced by hydrocarbon moiety modification. In such cases, the prodrug strategy can be an extremely valuable option. Improvement of lipophilicity has been the most widely investigated and successful field of prodrug research. It has been achieved by masking polar ionized or non-ionized functional groups to enhance either oral or topical absorption [14]; (3) modifying the distribution profile; before the drug reaches its physiological target and exerts the desired effect, it has to bypass several pharmaceutical and pharmacokinetic barriers.

Today, one of the most promising site-selective drug delivery strategies is the prodrug approach that utilizes target cell- or tissue-specific endogenous enzymes and transporters. One of the few examples that were designed to increase the efficiency of a drug by accumulation into a specific tissue or organ is the antiparkinson agent

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

Received January 17, 2013; **Accepted** January 18, 2013; **Published** January 19, 2013

Citation: Karaman R (2013) Prodrug Design by Computation Methods: A New Era. Drug Des 2: e113. doi:10.4172/2169-0138.1000e113

L-DOPA. Because of its hydrophilic nature, the neurotransmitter dopamine is not able to cross the blood-brain barrier and distribute into brain tissue. However, the prodrug of dopamine, L-DOPA, enables the uptake and accumulation of dopamine into the brain via the L-type amino acid transporter 1 [2,15]. After L-type amino acid transporter 1-mediated uptake, L-DOPA is bioactivated by aromatic L-amino acid decarboxylase to hydrophilic dopamine, which is concentrated in dopaminergic nerves. Because L-DOPA is extensively metabolized in the peripheral circulation, DOPA decarboxylase inhibitors (carbidopa, benserazide, methyldopa) and/or catechol-O-methyltransferase inhibitors (entacapone, tolcapone, nitecapone) are co-administered with levodopa to prevent the unwanted metabolism [16,17]; (4) prevent fast metabolism and excretion; the first-pass effect in the gastrointestinal tract and liver may greatly reduce the total amount of active drug reaching the systemic circulation and consequently its target. This problem has been overcome by sublingual or buccal administration or by controlled release formulations. Fast metabolic drug degradation can also be prevented by a prodrug strategy. This is usually done by masking the metabolically labile but pharmacologically essential functional group(s) of the drug. In the case of the bronchodilator and β2-agonist terbutaline, sustained drug action has been achieved by converting its phenolic groups, which are susceptible to fast and extensive first pass metabolism, into bis-dimethylcarbamate. The prodrug bambuterol is slowly bioactivated to terbutaline predominantly by nonspecific butyrylcholinesterase outside the lungs [18-20]. As a result of the slower release and prolonged action, once-daily administration of bambuterol provides relief of asthma with a lower incidence of adverse effects than terbutaline [21]; (5) reducing toxicity; adverse drug reactions can change the structure or function of cells, tissues, and organs and can be detrimental to the organism. Reduced toxicity can sometimes be accomplished by altering one or more of the ADME barriers but more often is achieved by targeting drugs to desired cells and tissues via site-selective drug delivery. A successful site-selective prodrug must be precisely transported to the site of action, where it should be selectively and quantitatively transformed into the active drug, which is retained in the target tissue to produce its therapeutic effect [2,22]. The ubiquitous distribution of most of the endogenous enzymes that are responsible for bioactivating prodrugs diminishes the opportunities for selective drug delivery and targeting. Therefore, exogenous enzymes are selectively delivered via antibody-directed enzyme prodrug therapy or as genes that encode prodrug activating enzymes. This approach is particularly used with highly toxic compounds such as anticancer drugs to reduce the toxicity of the drugs at other sites in the body [23,24].

There are two major challenges facing the prodrug approach strategy: (a) hydrolysis of prodrugs by esterases; the most common approaches for prodrug design are aimed at prodrugs undergoing in vivo cleavage to the active parent drug by catalysis of hydrolases such as peptidases, phosphatases, and carboxylesterases [14]. The less than complete absorption observed with several hydrolase-activated prodrugs of penicillins, cephalosporins, and angiotensin-converting enzyme inhibitors highlights yet another challenge with prodrugs susceptible to esterase hydrolysis. These prodrugs typically have bioavailabilities of around 50% because of their premature hydrolysis during the absorption process in the enterocytes of the gastrointestinal tract [14]. Hydrolysis inside the enterocytes releases the active parent drug, which in most cases is more polar and less permeable than the prodrug and is more likely to be effluxed by passive and carrier-mediated processes back into the lumen than to proceed into blood, therefore limiting oral bioavailability; (b) bioactivation of the prodrug by cytochrome P450 enzymes. The P450 enzymes are superfamily enzymes that account for up to 75% of all enzymatic metabolisms of drugs, including several prodrugs. There is accumulating evidence that genetic polymorphisms of prodrug-activating P450s contribute substantially to the variability in prodrug activation and thus to the efficacy and safety of drugs using this bioactivation pathway [25,26].

Bioconversion of prodrugs is perhaps the most vulnerable link in the chain, because there are many intrinsic and extrinsic factors that can influence the process. For example, the activity of many prodrug activating enzymes may be decreased or increased due to genetic polymorphisms, age-related physiological changes, or drug interactions, leading to adverse pharmacokinetic, pharmacodynamic, and clinical effects. In addition, there are wide interspecies variations in both the expression and function of the major enzyme systems activating prodrugs, and these can pose challenges in the preclinical optimization phase. Nonetheless, developing a prodrug can still be a more feasible and faster strategy than searching for an entirely new therapeutically active agent with suitable ADMET properties.

An ideal drug candidate needs to have specific properties, including chemical and enzymatic stability, solubility, low clearance by the liver or kidney, permeation across biological membranes, potency, and safety.

The conversion of a prodrug to the parental drug at the target site is crucial for the prodrug approach to be successful. Generally, activation involves metabolism by enzymes that are distributed throughout the body [14,27,28]. The major problem with these prodrugs is the difficulty in predicting their bioconversion rates, and thus their pharmacological or toxicological effects. Moreover, the rate of hydrolysis is not always predictable, and bioconversion can be affected by various factors such as age, health conditions and gender [29-31].

The novel prodrug approach to be reported in this editorial implies prodrug design based on enzyme model (mimicking enzyme catalysis) that has been utilized to understand how enzymes work. The tool used in the design is a computational approach consisting of calculations using molecular orbital and molecular mechanics methods and correlations between experimental and calculated values of intra molecular processes that were used to understand the mechanism by which enzymes might exert their high rates catalysis. In this approach, no enzyme is needed for the catalysis of the intra conversion of a prodrug to its parent drug. The release of the drug from the corresponding prodrug is solely dependent on the rate limiting step for the intra conversion reaction.

In the past few decades, the use of computational chemistry for calculating physicochemical and molecular properties has been a progressive goal of organic, organometallic, inorganic, and pharmaceutical chemists. Thermodynamic and kinetic energy-based calculations for biological systems that have pharmaceutical/medicinal interest are a great challenge to the medical community. Nowadays, quantum mechanics such as ab initio, a semi-empirical and Density Functional Theory (DFT), and Molecular Mechanics (MM) are increasingly being utilized and widely accepted as tools that provide structure-energy calculations for the prediction of potential drugs and prodrugs [32].

The *ab initio* molecular orbital methods (quantum mechanics) such as HF, G1, G2, G2MP2, MP2 and MP3 are based on rigorous utilization of the Schrodinger equation with a number of approximations. Use of the *ab initio* method is restricted to small systems that do not have more than thirty atoms due to the extreme cost of computation time

[33-35]. MINDO, MNDO, MINDO/3, AM1, PM3 and SAM1, are semi-empirical methods based on the Schrodinger equation with the addition of terms and parameters to fit experimental data and have afforded vast information for practical application [36-39]. Calculations of molecules exceeding 50 atoms can be done using such methods. Density functional theory (DFT) is a semi-empirical method used to calculate structures and energies for medium-sized systems of biological and pharmaceutical interest and is not restricted to the second row of the periodic table [40]. Contrary to quantum mechanics, molecular mechanics is a mathematical approach used for the computation of structures, energy, dipole moment, and other physical properties, and is widely used in calculating many diverse biological and chemical systems such as proteins, large crystal structures, and relatively large solvated systems. However, this method is limited by the determination of parameters such as the large number of unique torsion angles present in structurally diverse molecules [41].

Recently we have been investigating the mechanisms for some intramolecular processes that have been used to gain a better understanding of enzyme catalysis and have been exploited for design of novel prodrug linkers [42-60]. Using molecular mechanics, DFT, and *ab initio* methods, we studied various intramolecular processes in order to assign factors affecting the rate-determining step. Among these processes are the following: (1) proton transfer between two oxygen in Kirby's acetals [61] and proton transfer between nitrogen and oxygen in Kirby's enzyme models [61]; (2) intra molecular acid-catalyzed hydrolysis in Kirby's maleamic acid amide derivatives [61]; (3) proton transfer between two oxygen in rigid systems as investigated by Menger [62-65] arriving at the following conclusions: (i) rate accelerations in intra molecular processes are a result of both entropy and enthalpy effects. In intra molecular cyclization processes where enthalpic effects were predominant, steric effects were the driving force for the acceleration, whereas proximity orientation was the determining factor in the case of proton transfer reactions. (ii) The distance between the two reacting centers is the main factor that determines whether the reaction type is intermolecular or intra molecular. In the cases where the distance exceeded 3 Å, an intermolecular engagement was preferred due to the involvement of a water molecule (solvent), whereas an intra molecular engagement prevailed when the distance between the electrophile and nucleophile was less than 3 Å. (iii) The efficiency of proton transfer between two oxygen and between nitrogen and oxygen in Kirby's enzyme models is attributed to relatively strong hydrogen bonding in the products and the transition states leading to them.

The information from our studies on enzyme models was used to design an efficient chemical moiety to be utilized as a prodrug linker with the potential to release the parent drug in a slow or fast manner. Unraveling the mechanism of Kirby's enzyme model (proton transfer in acetals) has led to the design of prodrugs of aza-nucleoside derivatives for the treatment of myelodysplastic syndromes, where the prodrug linker (the acetal moiety) was linked to the hydroxyl group of the nucleoside moiety [66]. In addition, prodrugs of the pain killer paracetamol that are capable of masking the bitter taste of the parental drug were also designed such that the linker is covalently linked to the phenolic group of paracetamol, which is believed to be responsible for the bitter taste of the drug [67].

Different linkers were also investigated for the design of several prodrugs that might be efficient in releasing their corresponding parent drugs at various rates that are dependent on the nature or the structural features of the linkers. Selected examples of these prodrugs include the anti-Parkinson's agent dopamine [68], anti-viral agent acyclovir [69], anti-malarial agent atovaquone [70], antihypertensive atenolol [71], antibacterial cefuroxime [72], ant-psoriasis monomethyl maleate [73], and the anti osteoporosis agents raloxifene and alendronate [74]. Successful synthesis of most of the prodrugs mentioned above was reached and in vitro kinetic results at different pH values have shown promising results for obtaining novel prodrugs that might have enhanced dissolution, membrane penetration, and thus better bioavailability than their corresponding drugs.

In the past, the prodrug approach was viewed as a last resort after all other methods were exhausted. Nowadays, the prodrug approach is being considered in the very early stages of the drug development process. While the classic prodrug approach was focused on altering various physiochemical parameters, the modern computational approach considers using a design of linkers with drugs that have poor bioavailability to release the parent drugs slowly and thus improve their bioavailability. With the possibility of designing prodrugs with different linkers, the rate of release of the parental drugs can be controlled. In addition, since the linkers used in the studies described above are relatively small, it is expected that the prodrugs themselves might have considerable biological effects before intraconversion to their parent drugs. The future of prodrug technology is exciting and yet challenging. Advances must be made in understanding the chemistry of many organic reactions that can be effectively utilized to enable the development of even more types of prodrugs. The understanding of organic reaction mechanisms of certain processes, particularly intramolecular reactions, will be the next major milestone in this field. It is envisioned that the future of prodrug technology holds the ability to create safe and efficacious delivery of a wide range of active small molecules and biotherapeutics.

Acknowledgement

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

References

1. Albert A (1958) Chemical aspects of selective toxicity. Nature 182: 421-422.
2. Stella VJ, Borchardt RT, Hageman M, Oliyai R, Maag H, et al. (2007) Prodrugs: Challenges and Rewards Part 1 and Part 2. Springer Science, New York, USA.
3. Stella VJ, Charman WN, Naringrekar VH (1985) Prodrugs. Do they have advantages in clinical practice? Drugs 29: 455-473.
4. Banerjee PK, Amidon GL (1985) Design of prodrugs based on enzymes-substrate specificity. Bundgaard H ed. Design of Prodrugs. New York, Elsevier: 93-133.
5. Müller CE (2009) Prodrug approaches for enhancing the bioavailability of drugs with low solubility. Chem Biodivers 6: 2071-2083.
6. Haffen E, Paintaud G, Berard M, Masuyer C, Bechtel Y, et al. (2000) On the assessment of drug metabolism by assays of codeine and its main metabolites. Ther Drug Monit 22: 258-265.
7. Raffa RB (1996) A novel approach to the pharmacology of analgesics. Am J Med 101: 40S-46S.
8. Zhou SF, Zhou ZW, Yang LP, Cai JP (2009) Substrates, inducers, inhibitors and structure-activity relationships of human Cytochrome P450 2C9 and implications in drug development. Curr Med Chem 16: 3480-3675.
9. Huttunen KM, Raunio H, Rautio J (2011) Prodrugs--from serendipity to rational design. Pharmacol Rev 63: 750-771.
10. Stella VJ, Nti-Addae KW (2007) Prodrug strategies to overcome poor water solubility. Adv Drug Deliv Rev 59: 677-694.
11. Di L, Kerns EH (2007) Solubility issues in early discovery and HTS. Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics) Springer Science and Business Media, New York, USA.
12. 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.

13. Chan OH, Stewart BH (1996) Physicochemical and drug-delivery considerations for oral drug bioavailability. Drug Discov Today 1: 461–473.

14. 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.

15. del Amo EM, Urtti A, Yliperttula M (2008) Pharmacokinetic role of L-type amino acid transporters LAT1 and LAT2. Eur J Pharm Sci 35: 161-174.

16. Khor SP, Hsu A (2007) The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. Curr Clin Pharmacol 2: 234-243.

17. Hornykiewicz O (2010) A brief history of levodopa. J Neurol 257: S249-252.

18. Svensson LA, Tunek A (1988) The design and bioactivation of presystemically stable prodrugs. Drug Metab Rev 19: 165-194.

19. Tunek A, Levin E, Svensson LA (1988) Hydrolysis of 3H-bambuterol, a carbamate prodrug of terbutaline, in blood from humans and laboratory animals in vitro. Biochem Pharmacol 37: 3867-3876.

20. Sitar DS (1996) Clinical pharmacokinetics of bambuterol. Clin Pharmacokinet 31: 246-256.

21. Persson G, Pahlm O, Gnosspelius Y (1995) Oral bambuterol versus terbutaline in patients with asthma. Curr Ther Res 56: 457-465.

22. Ettmayer P, Amidon GL, Clement B, Testa B (2004) Lessons learned from marketed and investigational prodrugs. J Med Chem 47: 2393-2404.

23. Denny WA (2010) Hypoxia-activated prodrugs in cancer therapy: progress to the clinic. Future Oncol 6: 419-428.

24. Shanghag A, Yam N, Jasti B (2006) Prodrugs as drug delivery systems, in Design of Controlled Release Drug Delivery Systems. The McGraw-Hill Company Inc, New York, USA.

25. Gonzalez FJ, Tukey RH (2006) Drug metabolism, in Goodman and Gilman's The Pharmacological Basis of Therapeutics. The McGraw-Hill Company Inc, New York, USA.

26. Testa B, Krämer SD (2007) The biochemistry of drug metabolism--an introduction: Part 2. Redox reactions and their enzymes. Chem Biodivers 4: 257-405.

27. Gangwar S, Pauletti GM, Wang B, Siahaan TJ, Stella VJ, et al. (1997) Prodrug strategies to enhance the intestinal absorption of peptides. DDT 2: 148-155.

28. Wang W, Jiang J, Ballard CE, Wang B (1999) Prodrug approaches to the improved delivery of peptide drugs. Curr Pharm Des 5: 265-287.

29. Draganov DI, La Du BN (2004) Pharmacogenetics of paraoxonases: a brief review. Naunyn Schmiedebergs Arch Pharmacol 369: 78-88.

30. Ngawhirunpat T, Kawakami N, Hatanaka T, Kawakami J, Adachi I (2003) Age dependency of esterase activity in rat and human keratinocytes. Biol Pharm Bull 26: 1311-1314.

31. Moser VC, Chanda SM, Mortensen SR, Padilla S (1998) Age- and gender-related differences in sensitivity to chlorpyrifos in the rat reflect developmental profiles of esterase activities. Toxicol Sci 46: 211-222.

32. Reddy MR, Erion MD. (2001) Free Energy Calculations in Rational Drug Design. Kluwer Academic/Plenum Publishers, 406 pages.

33. Shrödinger E (1926) Quantisierung als Eignwetproblem. Ann Phys 79: 361.

34. Shrödinger E (1926) Quantisierung als Eignwetproblem. Ann Phys 80: 437

35. Shrödinger E (1926) Quantisierung als Eignwetproblem. Ann Phys 81: 109.

36. Dewar MJS, Thiel W (1977) Ground states of molecules. The MNDO method. Approximations and parameters. J Am Chem Soc 99: 4899-4907.

37. Bingham RC, Dewar MJS, Lo DH (1975) Ground states of molecules. XXV. MINDO/3. An improved version of the MNDO semiempirical SCF-MO method. J Am Chem Soc 97: 1285.

38. Dewar MJS, Zoebisch EG, Healy EF, Stewart JJP (1985) AM1: A new general purpose quantum mechanical molecular model. J Am Chem Soc 107: 3902-3909.

39. Dewar MJS, Jie C, Yu J (1993) The first of new series of general purpose quantum mechanical molecular models. Tetrahedron 49: 5003-5038.

40. Parr RG, Yang W (1989) Density Functional Theory of Atoms and Molecules. Oxford University Press, Oxford.

41. Burkert U, Allinger NL (1982) Molecular Mechanics, American Chemical Society, Washington DC, USA: ACS Monograph 177.

42. Karaman R (2008) Analysis of Menger's spatiotemporal hypothesis. Tetrahedron Lett 49: 5998-6002.

43. 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 THEOCHEM 910: 27-33.

44. Karaman R (2010) The efficiency of proton transfer in Kirby's enzyme model, a computational approach. Tetrahedron Lett 51: 2130-2135.

45. Karaman R, Pascal R (2010) A computational analysis of intramolecularity in proton transfer reactions. Org Biomol Chem 8: 5174-5178.

46. Karaman R (2010) A General Equation Correlating Intramolecular Rates with 'Attack' Parameters: Distance and Angle. Tetrahedron Lett 51: 5185-5190.

47. Karaman R (2011) Analyzing the efficiency of proton transfer to carbon in Kirby's enzyme model- a computational approach. Tetrahedron Lett 52: 699-704.

48. 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.

49. 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.

50. Karaman R (2009) Revaluation of Bruice's Proximity Orientation. Tetrahedron Lett. 50: 452-456.

51. Karaman R (2009) Accelerations in the Lactonization of Trimethyl Lock Systems are Due to Proximity Orientation and not to Strain Effects. Org Chem Int.

52. Karaman R (2009) The gem-disubstituent effect- a computational study that exposes the relevance of existing theoretical models. Tetrahedron Lett 50: 6083-6087.

53. Karaman R (2009) Analyzing Kirby's amine olefin – a model for amino-acid ammonia lyases. Tetrahedron Lett. 50: 7304-7309.

54. Karaman R (2009) The effective molarity (EM) puzzle in proton transfer reactions. Bioorg Chem 37: 106-110.

55. Karaman R (2010) Effects of substitution on the effective molarity (EM) for five membered ring-closure reactions- a computational approach. J Mol Struct (Theochem) 939: 69-74.

56. Karaman R (2010) The Effective Molarity (EM) Puzzle in Intramolecular Ring-Closing Reactions. J Mol Struct (Theochem) 940: 70-75.

57. Menger FM, Karaman R (2010) A singularity model for chemical reactivity. Chemistry 16: 1420-1427.

58. Karaman R (2010) The effective molarity (EM)--a computational approach. Bioorg Chem 38: 165-172.

59. Karaman R (2010) Proximity vs. Strain in Ring-Closing Reactions of Bifunctional Chain Molecules- a Computational Approach. J Mol Phys 108: 1723-1730.

60. Karaman R (2011) The role of proximity orientation in intramolecular proton transfer reactions. Comput Theor Chem 966: 311-321.

61. Kirby AJ (1997) Efficiency of proton transfer catalysis in models and enzymes. Acc Chem. Res 30: 290– 296.

62. Menger FM, Ladika M (1990) Remote enzyme-coupled amine release. J Org Chem 55: 3006-3007.

63. Menger FM, Ladika M (1988) Fast hydrolysis of an aliphatic amide at neutral pH and ambient temperature. A peptidase model. J Am Chem Soc 110: 6794-6796.

64. Menger FM (1985) On the source of intramolecular and enzymatic reactivity. Acc Chem Res 18: 128-134.

65. Menger FM, Chow JF, Kaiserman H, Vasquez PC (1983) Directionality of proton transfer in solution. Three systems of known angularity. J Am Chem Soc 105: 4996-5002.

66. Karaman R (2010) Prodrugs of aza nucleosides based on proton transfer reaction. J Comput Aided Mol Des 24: 961-970.

67. Hejaz H, Karaman R, Khamis M (2012) Computer-assisted design for paracetamol masking bitter taste prodrugs. J Mol Model 18: 103-114.

68. Karaman R (2011) Computational-aided design for dopamine prodrugs based on novel chemical approach. Chem Biol Drug Des 78: 853-863.

69. Karaman R, Dajani KK, Qtait A, Khamis M (2012) Prodrugs of acyclovir--a computational approach. Chem Biol Drug Des 79: 819-834.

70. Karaman R, Hallak H (2010) Computer-assisted design of pro-drugs for antimalarial atovaquone. Chem Biol Drug Des 76: 350-360.

71. 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.

72. Karaman R (2013) Prodrugs for Masking Bitter Taste of Antibacteria Drugs- A Computational Approach. J Mol Model Accepted.

73. 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.

74. Karaman R Unpublished results.