CHAPTER THREE

Tales of Drug Discovery

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Contents

1. Prostaglandins 27
2. Cannabinoid Analgesics 28
3. Hypoglycemic Agents 30
4. Opioid Analgesics 30
5. HIV Fusion Inhibitors 31
6. Epithelial Sodium Channel Blockers 32
7. Conclusions and Ramblings 33
Acknowledgments 33
References 34

I'm a Med Chem Junkie. I have a lifelong "addiction" to drug discovery using the tools and concepts of medicinal and organic chemistry. Besides my family, it is the first thing I think about when I wake up and the last thing I remember going to sleep. Looking back, I was excited each and every day because every day carried within it a chance to find a cure for a disease, help ease someone's medical condition, or even save someone's life. There were many research highs and lows along the way, but it helped to believe in my dreams and work hard.

I started off the research phase of my scientific career working for Joe Casanova at LA State University as an NSF undergraduate fellow studying lead tetraacetate oxidations. When I then went on to Berkeley for my BS degree, I worked with the internationally renowned organic chemist Henry Rapoport in natural products synthesis and George Payne (of the "Payne Rearrangement") at Shell Development Company in Emeryville doing sulfur ylid chemistry. After receiving my BS in Chemistry from Berkeley, I went to UCSB for my Ph.D. to work with Bruce Rickborn in physical organic chemistry. Bruce was my mentor and lifelong friend who trained me, not as a medicinal chemist, but as a problem solver. I think this philosophy served me well in the ensuing years in drug discovery. After a short post doc back at Cal with Fritz Jensen in organometallic chemistry, I was hired by

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Pfizer in Groton Connecticut. It was an exciting time for me and my family as we moved East but filled with a little trepidation, since I did not have the slightest idea what I was getting into.

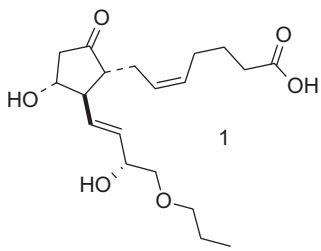
Despite the vast array of tools at one's disposal in the medicinal chemist's armamentarium, it is the way in which one approaches a target and chooses the appropriate tools which will ultimately determine a successful outcome. First of all, I have found it useful to always have a hypothesis—even if it turns out wrong. For example, in the prostaglandin program, we predicted that if we could block major metabolic routes, we would improve duration of action and then influence tissue selectivity by introducing bioisosteres. In the cannabinoids, we postulated a structural similarity between HHC and PGE2 that allowed us to focus on three key interaction points, which led to highly novel cannabinoid structures and beyond. Those first two programs led me to discover just how important natural products can be as prototype leads. In the pursuit of better "glitazones," we postulated that a conformationally rigid structural approach would improve potency. Having a hypothesis also insures you think about the compounds you are about to create. There should be a reason for each and every compound you make!

Once a hypothesis is in place, one can take three basic approaches in designing drugs: (1) The "Soaring Eagle"; (2) The Giant Leap; and (3) Methyl, Ethyl, Butyl, Futile. In practice, successful projects use all three. The Soaring Eagle Approach is akin to an eagle hunting its prey. It starts at the top of the canyon and, with sharp eyes, circles down ever lower to capture its prey. This approach is usually employed in areas where there is already a lot of SAR and mechanism available, and you have many competitors, like we did in the diabetes and opiate analgesic programs. The second approach, The Giant Leap, is used when you have homed in on a group of structures and find key activity parameters in specific regions of the molecule. Rather than defaulting to the third approach, change things radically. In the cannabinoids, we removed rings; in the prostaglandins, we used aryl groups to inhibit oxidation; and in the epithelial sodium channel (ENaC) program, we added additional electrostatic binding regions. Now, as much as every medicinal chemist hates it, there is a role for the third approach. In the short-acting opiate program, we were able to titrate the duration of action simply by varying the alkyl group, thus influencing metabolic inactivation by nonspecific esterases. This latter approach is an end-stage tactic, as there is not much more you can do after this. Once you have successfully generated your target molecule, you will now start to experience the real thrill of discovery: you will get biological feedback from your biological

counterpart. Thus begins the exciting and up-and-down iterative process that will ultimately produce a drug. The following are a few of my own tales of drug discovery.

1. PROSTAGLANDINS

My medicinal chemistry career began in 1971 at Pfizer, where I worked under the direction of Dr. Hans Hess on modifying prostaglandins to improve selectivity for a variety of therapeutic uses. Along with Tom Schaaf, Jasjit Bindra, and Jim Eggler, we focused our research primarily on two areas to increase the potency and duration of action of the natural prostaglandins: the metabolic stabilization of the upper carboxylic side chain to prevent beta-oxidation and modification of the lower side chain to prevent oxidation (15-dehydrogenase). We made extensive contributions to this area that resulted in novel 16-aryl and 16-aryloxy prostaglandin congeners which, when modified in the upper side chain with a bioisostere of carboxylic acids, led to the discovery and ultimate commercialization of sulprostone (Nalador®).[1–4] Up to this point, the widespread use of prostaglandins for a variety of gynecological and obstetric uses was limited by the lack of tissue selectivity and metabolic stability of the natural prostaglandins and simple analogs thereof.



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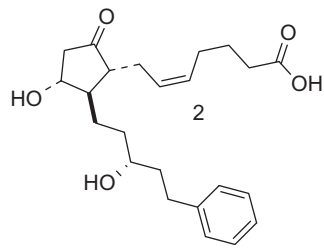

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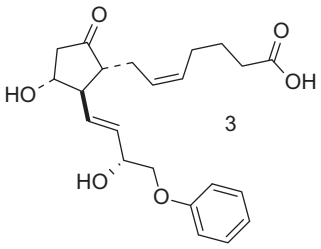

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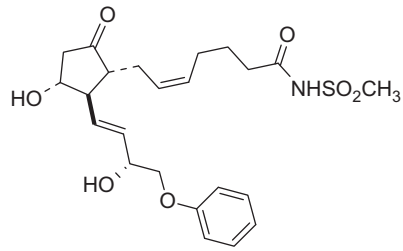


sulprostone/Nalador®

We had increased potency and selectivity by first showing that the 17-oxa and 17-phenyl moieties could be combined to produce 16-phenoxy PGE_2, which enhanced potency *in vivo* due to an increased stability to C_{15}-hydroxyprostaglandin dehydrogenase. Further work showed that tissue selectivity could be enhanced by replacing the carboxylic acid with methane sulfonimide and simultaneously eliminating beta-oxidation. The resultant new chemical entity (sulprostone) incorporated both of these features to produce a drug which was 30 times more selective than PGE_2 and is still used worldwide today for a number of gynecological and obstetric purposes. The 16-phenoxy moiety was subsequently used in a number of marketed prostaglandin and prostanoid drugs. Our work in this field showed the power of using metabolic information and bioisosterism to overcome shortcomings in natural products.

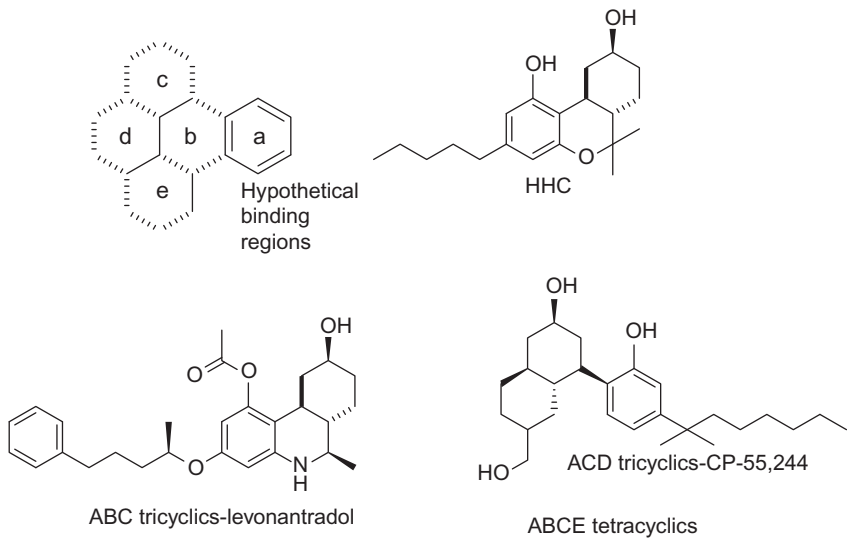
2. CANNABINOID ANALGESICS

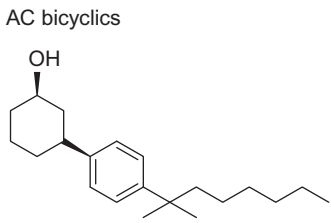
In 1976, I entered CNS research at Pfizer and was assigned the daunting task of producing a nonnarcotic analgesic as potent as morphine. This problem had been studied intensively for nearly 50 years prior to my work by L.F. Small and E.L. May, two giants in the field of opioid analgesics. I was intrigued by the potent, specific analgesic activity of 9-beta-hydroxyhexahydocannabinol (HHC) that was discovered by May.[5] Working with Dr. George Milne at Pfizer, we showed that HHC did not act through opioid receptors. Based on these observations and the molecular differences between morphine and HHC, we proposed a structural hypothesis that highlighted the differences between the planar prostaglandins and T-shaped structure of morphine (the "Prostaglandin Overlap" model).[6] Thus began a program of synthesis and SAR with Dr. Larry Melvin at Pfizer that would have a lasting impact on the cannabinoid field that continues to this day. Not only did this hypothesis provide novel classic cannabinoid structures but also the totally ingenious "non-classical", cannabinoids possessing potent nonnarcotic analgesic activity substantially greater than morphine. These compounds also possessed potent antiemetic activity.

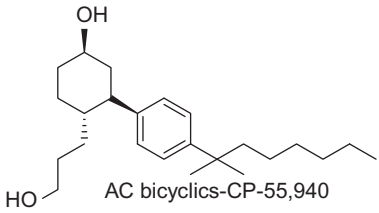
By 1983, our group had amassed a large number of diverse structures exhibiting similar SAR.[7] The exquisite potency, stereospecificity, and lack of a unifying link to existing neurotransmitter system led me to propose that compounds like levonantradol and CP-55,244 bind to a specific (at the time unknown) CNS receptor system. Based on this insight and armed with our structurally diverse novel compounds, including the tritium-labeled drug

[^{3}H]CP-55,940, the elucidation and biochemical identification of the cannabinoid receptor was accomplished in collaboration with A.C. Howlett, then at St. Louis University.[8] Following this landmark work, Miles Herkenham at the NIH, in collaboration with myself, Kenner Rice, and Brian DeCosta,[9] conducted the definitive autoradiographic cannabinoid receptor localization study using [^{3}H] CP-55,940 in several mammalian species, including humans. These anatomical findings explained many of the properties of the cannabinoids, including their almost complete lack of acute toxicity. The studies were central to Lisa Matsuda's subsequent discovery of the cloned human cannabinoid receptor at the NIH. A sequential, quantitative autoradiographic study in 40 regions of the brain and spinal cord with [^{3}H]CP-55,940 provided powerful support for the physiologic and pharmacological relevance of the receptor.[10]

The medicinal chemistry we were able to generate and the excellent work utilizing these tools by my group of collaborators in the cannabinoid area have been a major driving force in the advancement of the field to its present state, emphasizing once again the indispensable role of medicinal chemistry in solving multidisciplinary scientific problems. The compounds and concepts that we advanced over 25 years ago continue to be valuable tools in present-day cannabinoid research. It is well worth noting that these three papers,[8–10] all of which have over 1000 citations each, are all primary research publications. So while I was disappointed that we never got a marketed drug out of this research, we did make an impact on the basic science of the field, and I hope current work based on our earlier findings will yet prove beneficial to mankind.

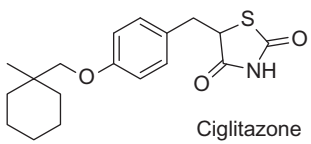




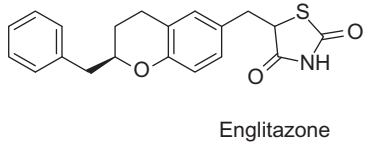


3. HYPOGLYCEMIC AGENTS

In 1985, I became the manager of metabolic diseases at Pfizer. Along with Bob Volkman, Dave Clark, and Jim Eggler, we became involved with the design of second-generation hypoglycemics based on ciglitazone. We proposed and synthesized a series of conformationally restricted dihydrobenzofurans and dihydrobenzopyrans. On the basis of a dramatic increase of *in vivo* potency as a hypoglycemic agent in the *ob/ob* mouse, one of the resolved, conformationally restricted enantiomers was moved into human trials under the name of englitazone.[11] It is worth noting that this class of antidiabetic agents, known collectively as thiazolidinediones (TZDs), or "glitazones," is an important addition to the physician's ability to keep Type II diabetes under control. More recently, these molecules show promise in delaying the onset of Alzheimer's disease. TZDs lower blood glucose levels by stimulating the growth of mitochondria. The theory is that by stimulating mitochondrial growth in the brain, these drugs can delay the ability of Alzheimer's to kill brain neurons. This is an age-old story in medicinal chemistry: Yesterday's discoveries in one therapeutic area often provide the basis for clinical discoveries in other areas.



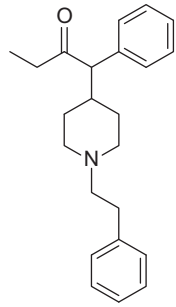
Ciglitazone



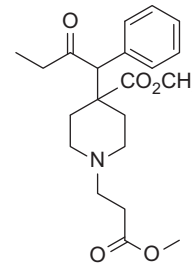
Englitazone

4. OPIOID ANALGESICS

In early 1988, I moved to Glaxo, Inc. in Research Triangle Park, NC as one of the founding scientists of research in the United States. Working out of temporary laboratories at the University of North Carolina, my young group of chemists sought to produce an ultra short-acting opioid analgesic.



Fentanyl



Remifentanyl/Ultiva

We proposed that the ideal analgesic would have a maximum biological half-life of 10–30 min and be biotransformed into inactive metabolites minimizing accumulation and redistribution with prolonged administration, thereby avoiding the respiratory depression and muscle rigidity commonly associated with opiates. Having thus hypothesized the ideal short-acting narcotic analgesic, my protégé, Paul Feldman, and I focused on the synthesis of analogs based on several classes of 4-anilidopiperidines. We circled in on molecules that would be rapidly inactivated enzymatically in plasma and thus be independent of hepatic metabolism, which was of further benefit to renally compromised patients. In one series, we found a compound that possessed potent mu opioid activity with a high degree of analgesic efficacy and an extremely short duration of action.[12] The resultant drug, remifentanyl, showed a profile that could be essentially titrated when used and that completely returns the patient to baseline values in minutes rather than hours when discontinued. Remifentanyl was the first commercial drug marketed by Glaxo Inc. and was sold under the trade name Ultiva®. Since its introduction, this drug has proven to be a major adjunct in surgical anesthesia and is the drug of choice in certain situations. Ultiva® has recently been dubbed "the ultimate opioid."

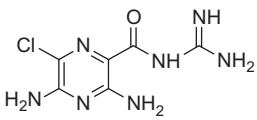
5. HIV FUSION INHIBITORS

In 1995, I decided to enter the biotech industry. I joined Trimeris as its Chief Scientific Officer and subsequently became CEO. Researchers Tom Mathews and Dani Bolognese at Duke University had found that a 36-amino acid peptide (T-20) blocked HIV cell–cell fusion *in vitro*. I was convinced it should work in humans, so we assembled a team at Trimeris to advance this compound into human trials. The group demonstrated very early on that the drug reaches the target lymph and blood compartments *in vivo*, but a huge problem in its development remained. Early versions of the drug required

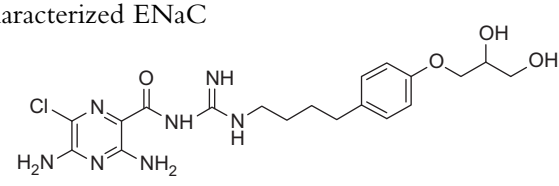
106 steps by traditional solid-state methods, so I assembled some of my old development chemistry team at Glaxo to solve this hurdle. This team of chemists, led by M.C. Kang and inspired by Brian Bray, achieved a vastly more efficient method of manufacturing T-20, which now stands as the most complex synthetic peptide ever manufactured on such a massive scale (>1 metric ton per year). Having solved this important issue, we moved the program into full development. Our first clinical trial, which showed T-20 to lower HIV viral load below detectable levels, is still a landmark study in the field.[13] This program led to the approval of enfuritide, a life-saving drug, sold as Fuzeon®. It is the first and only fusion inhibitor on the market to treat HIV in combination with mechanistically distinct inhibitors. Fuzeon is particularly effective in treating patients who are failing on other drug classes and truly makes the difference between life and death for this patient population. There was no medicinal chemistry magic here—just good old-fashioned organic chemistry and drug development, which carried the day.

6. EPITHELIAL SODIUM CHANNEL BLOCKERS

In 1999, I teamed with the head of the Cystic Fibrosis Center at the University of North Carolina (Dr. Ric Boucher) to design and test drugs to increase mucociliary clearance (MCC) in humans. Early SAR studies had given me unique insights that led to the medicinal chemical conceptualization of the ENaC and the subsequent discovery of auxiliary binding sites resulting in the design of several classes of novel and potent compounds.[14] Compound PS-552 was selected for clinical studies based on the increased potency (100×), reduced reversibility (5×), and increased selectivity for nonrenal elimination (9×) when compared to the prototype ENaC blocker amiloride.[15] PS-552 has shown that it produces MCC in humans and was advanced to Phase II clinical trials for the treatment of cystic fibrosis and xerostomia caused by Sjogren's disease. Following the advancement of PS-552, we continued to improve these potential therapeutics by designing nearly perfect antedrugs based on our earlier hypothesis[14] in the ENaC field. Compared to the well-characterized ENaC



Amiloride



PS-552

blocker amiloride, these new drugs were designed to provide (1) enhanced blocking activity on ENaCs, (2) increased duration of blocking ENaC, (3) decreased rate of absorption across the airway epithelium, (4) enhanced solubility in hypertonic saline, (5) improved retention of ASL (airway surface liquid) volume on airway surfaces, and (6) improved drug safety by incorporating antedrug properties that make it susceptible to epithelial biotransformation which, in turn, produces less active systemic metabolites. Drugs from this class were superior in all these attributes, and clinical trials were initiated as reported in the *C&E News* article, "Breathing Easier" (September 1, 2008).

7. CONCLUSIONS AND RAMBLINGS

To be successful in any life endeavor, I believe one needs to set priorities. I think the three most important things are family, your particular belief system, and your profession. With regard to the latter, drug discovery is a team game, and your mentors, colleagues, and friends are an important part of the success paradigm. As I look back on the breadth and depth of our body of work and the contributions made to medicinal chemistry over a nearly 40-year career, my coworkers' efforts acknowledged below are truly remarkable. My special thanks to Bruce Rickborn, Hans Hess, and Kenner Rice for their lifelong support and mentoring.

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- Englitazone: Dave Clark, Steve Goldstein, Bob Volkmann, Jim Eggler, Jerry Holland, Brett Hulin, Nancy Hudson
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- HIV (Carbovir): Mike Peel, Dan Sternbach
- Insulin Second Messenger: Jeff Cobb, Pedro Cuatrecasas

- HIV (Fuzeon): M.C. Kang, Brian Bray, Bill Lackey, Tom Matthews, Peter Jeffs, Katherine Mader, Dani Bolognesi, Dennis Lambert, Sam Hopkins
- Sodium Channel Blockers: Ric Boucher, Andrew Hirsh, Bill Thelin, Karl Donn, Ann Stevens, John Ansede, Ben Yerxa, Gary Phillips, Bill Baker, Eric Dowdy, Bruce Molino, Bruce Sargent, Jim Zhang, Ron Aungst, Guihui Chen, Don Kuhla

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