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Pharmaceutical "Gold" from Neurostabilizing Agents: Topiramate and Successor Molecules

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Preface

What be this serendipity
that imparts great felicity?
'tis born from perspicacity;
insightful analysis;
sound judgment;
determination; and
perseverance
...the trained and open mind.

Introduction

Like the alchemists of a bygone era, who sought to convert base metals into gold, the medicinal chemists of the 20th century had a comparable aspiration. However, their quest was the conversion of basic chemical elements, such as carbon, hydrogen, nitrogen, oxygen, and sulfur, into the modern-day equivalent of gold: life-saving, life-preserving, life-enhancing drugs. Walking in the footsteps of Paul Ehrlich[1] and other drug discovery pioneers, these latter-day "alchemists" applied their scientific expertise, intellect, and intuition to the invention of magnificent new medicines. Indeed, contemporary medical practice, and the patients that it serves, have benefited enormously from the seminal pharmaceutical discoveries of this remarkable period.[1c,2]

The second half of the 20th century, by virtue of key events, has been characterized in the annals of history as the "Space Age", the "Computer Age", and the "Atomic Age". By the same token, the body of evidence also strongly indicates that this era deserves to be called the "Pharmaceutical Age", despite the apparent absence of this term in the popular lexicon. In the post-1950 world, drug discovery became an institution of the pharmaceutical age and medicinal chemistry became its touchstone. The maturation of medicinal chemistry as a scientific discipline was a critical driving force in the drug discovery process. And because of the rich cornucopia of new drug products, the pharmaceutical industry rocketed to a position of great status and wealth.

The coveted icon ultimately became the "billion-dollar molecule",[3] which some have pinpointed as a prime source for today's problems in the industry.[4] But the difficulty in delivering new, impactful drugs in quantity has much to do with other issues, such as (1) the prior harvesting of the "low-hanging fruit", (2) the lofty demands placed on new clinical candidates to meticulously de-risk them, and (3) the focus on chronic diseases with large, heterogeneous patient populations. Whether the sought-after drug would be blockbuster or not, wishful drug discoverers have never been completely clear on how to do the job right.[5] Arguably, perhaps, there is no guaranteed way to successfully discover marketable drugs, and the rules, conditions, and environment keep on changing. Given the relentlessly shifting landscape over the lengthy time required to discover a drug and advance it to the market, the desirable end result is often derived more from good luck than from any other contributing factor. It is certainly unfortunate that many promising clinical compounds have dissolved into nothingness for reasons ranging from pharmacology to toxicology to economics to corporate psychology. For a medicinal chemist seeking to make the "big score", the odds of success have become decidedly unfavorable. And those odds were fairly lean even in the golden years of drug discovery, in the late 20th century.

TOPAMAX (topiramate) is marketed worldwide for the treatment of epilepsy and the prophylaxis of migraine headache.[6] With annual sales of more than two billion dollars in 2006,[6b]

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[a] Abbreviations: FBPase, fructose-1,6-bisphosphatase; GABA, γ-aminobutyric acid; IND, investigational new drug; MES, maximal electroshock seizure; OTC, over the counter.

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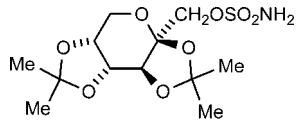


Topiramate (**1**; McN-4853)

topiramate easily qualifies as a "billion-dollar molecule". Given the disabling effects of epileptic seizures and the misery associated with recurrent migraine attacks, this drug has helped millions of patients in need across the globe. While the discovery of this drug was blessed by serendipity, its development was powered by determination, hard work, and heavy capital investment.[7] Topiramate (**1**, McN-4853)[8] actually emanated from a project directed to finding an inhibitor of the enzyme fructose-1,6-bisphosphatase (FBPase[a]) as an antidiabetic agent. Several grams of synthetic intermediate **1** were submitted to our compound library for pharmacological evaluation in animal models. This compound was selected on a hunch for anticonvulsant testing in the maximal electroshock seizure (MES) test in mice and found to be effective. Although the pathway to this drug product was somewhat circuitous, a massive amount of effort from many people in a broad range of functions ultimately accomplished the mission.

In this article I provide a personal perspective on the discovery of topiramate, on our post-topiramate research, and on a class of therapeutic agents that has been referred to as "neurostabilizers".[9] Neurostabilizers work by attenuating the excitability of brain neuronal pathways, essentially by stabilizing the membranes of neurons. Curiously, the potential of neurostabilizers in medicine had gone unappreciated until the 1990s, when they emerged as powerful drugs for treating various neurological and psychiatric disorders. I hope that the events of this three-decades-long "topiramate story" will not only be informative but also convey an understanding of the vagaries and vicissitudes of pharmaceutical research and development.

Sugar Sulfamates for Blocking Seizures

Get a Job. My proposal for a National Institutes of Health (NIH) research grant to extend my postdoctoral work with Prof. Kurt Mislow at Princeton University did not have a chance of being funded because the United States Congress did not provide any budget for fiscal year 1974. So I was seeking to start my career as a synthetic organic chemist at a major drug company. Since my wife, Cyndie, was a second-year graduate student with Prof. Mislow, I had to contend with a geographical constraint. It was very disheartening to receive no positive responses to my many job-seeking letters. Thanks to the painful economic recession of 1973−1974, the job market for chemists was rather bleak! Fortunately, I happened to discover a small drug company called McNeil Laboratories, located in Fort Washington, PA, just outside Philadelphia. Their claim to fame was an analgesic product called Tylenol,[10] which was sold over the counter to treat mild pain, such as headaches, and to reduce fever. The McNeil chemistry department was conducting a second round of interviews for a single opening, as they were not very satisfied with the first five candidates. The available position in process research was not my first choice, as I was more enthused about drug discovery. Nevertheless, I could not afford to be choosy. On the bright autumn day of my interview, I left Princeton quite early and arrived in Fort Washington at 6:30 a.m., although my first appointment was not until 8:30 a.m., which probably sums up my level of nervousness. I sat in my parked car in a service station lot near the company and studied my seminar for a good while.

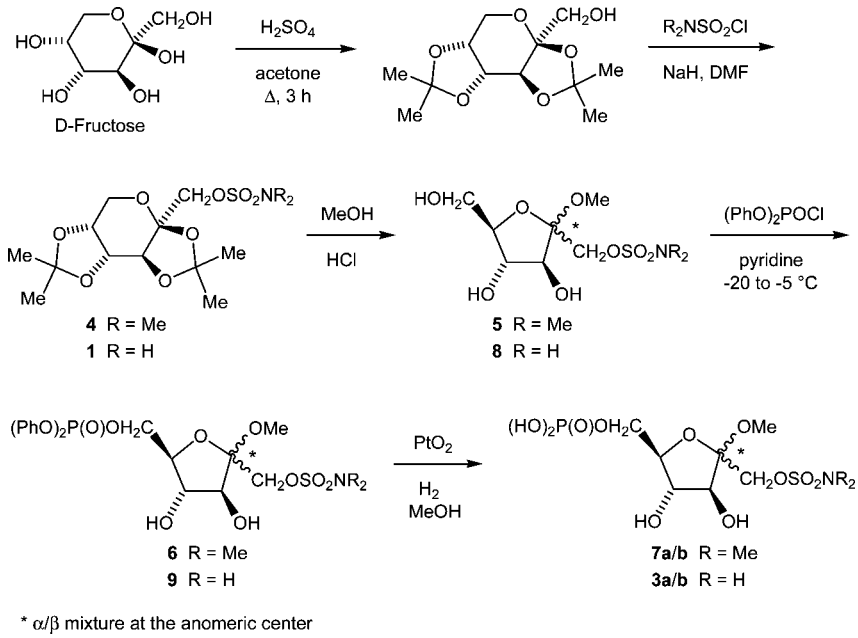
McNeil turned out to be a fairly small operation, but it was a wholly owned subsidiary of Johnson & Johnson. That was good! They had a newly acquired proton nuclear magnetic resonance (NMR) instrument and a decent mass spectrometer. Also good. But I noticed not one single-pan, electric balance in the synthesis laboratories, unlike the situation at Princeton. Not so good. I wondered: How could these people tolerate using two-pan balances with standard weights from a box? My interview went spectacularly well, and the McNeil scientists were really nice. The job offer came and I jumped at the chance, determined to straighten out the balance problem in due course.

I started work doing chemical process research for a new antiarthritic drug called TOLECTIN (tolmetin sodium), which was expected to be approved for marketing shortly.[11] Thus, I developed a love−hate relationship with pyrrole chemistry. My disposition was probably not a good match for a process research job anyway, but I persevered. Gratifyingly, McNeil management had promised me when I joined that I could switch to a drug discovery job after a year or two, if that career path was really my preference. The management was old-school in that they kept their word, and I was able to transfer to medicinal chemistry in 1976.

Opportunity Knocks. Because I had a keen interest in central nervous system (CNS) drugs, I tried to make my mark there first. My early projects dealt with antipsychotic agents (to treat schizophrenia), opioid-like derivatives (to manage severe pain), and antidepressants. One CNS project involved intriguing pyrroloisoquinoline antidepressants, and we nominated McN-5707 and McN-5652-Z, selective inhibitors of reuptake of brain monoamine neurotransmitters, for clinical development in 1984.[12] As a young and eager medicinal chemist, I could not be easily contained. I became interested in potential antidiabetic agents, with Dr. Eugene Tutwiler, an energetic and bright biochemist, acting as a catalyst. In late 1977 Gene presented an intramural lecture on gluconeogenesis, the process by which glucose is biosynthesized de novo in the body, including some known inhibitors and steps in the pathway where they were thought to operate. Although this area was fascinating to me, I was otherwise chemically occupied and had a full plate.

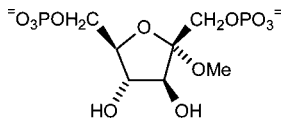
Prof. Roy Olofson from Pennsylvania State University served as a consultant with McNeil, specializing in synthetic and heterocyclic chemistry. When I was entangled with the pyrrole chemistry, I had made several presentations to him in discussion forums. Roy became impressed with me and my work, so he invited me to visit the campus to meet with faculty members and present a seminar. On my trip to Penn State, in the spring of 1978, I had a chance to meet Prof. Stephen Benkovic. Steve described his interest in gluconeogenesis, specifically the penultimate enzymatic step that converts fructose-1,6-bisphosphate to fructose-6-phosphate. His research work dealt with the inhibition of FBPase with substrate-based, carbohydrate materials.[13] I was amazed to be thrust into this situation just a few months after hearing the Tutwiler seminar, which happened to furnish me with the necessary foundation to understand what Steve was saying. Steve and I connected, and I invited him to visit our site. After returning home, I apprised Gene Tutwiler and enlisted him as a cohost. Steve's seminar was brilliant and exciting; furthermore, Steve, Gene, and I just clicked. We signed him on as a consultant and to collaborate on discovering novel inhibitors of FBPase by using monosaccharide derivatives. Steve's laboratory, which included his wife Patty, would conduct the enzymology, and Gene's laboratory would conduct in vivo studies.

Scheme 1. Synthesis of **1** and **7**



In the 1970s, carbohydrate chemistry was generally disfavored across the drug industry. For the most part, researchers sought novel, patentable, biologically active compounds based on molecular structures like those of known drugs or bioactive natural products or endogenous biochemicals with useful pharmacology (e.g., hormones and neurotransmitters). Although novel carbohydrate compounds can meet some of these criteria, they also presented serious concerns. Basically, they would be difficult to purify with the techniques of the day, difficult to isolate as workable solids, and difficult to characterize. Better to avoid carbohydrates entirely. For our intended project, however, there seemed to be no sensible alternative. Many McNeil colleagues were dubious, but Dr. Michael Zelesko, the head of medicinal chemistry, encouraged this foray into a new field. Mike, who had a keen appreciation for new vistas and challenges, was not one to douse the flames of inspiration.

By 1978, we had single-pan, electric balances in most of the synthetic laboratories, as well as a carbon-13 NMR instrument on order. Surprisingly, I and my colleague Dr. Michael Umen had to engage in a Great Debate with the old-timers to justify the value of carbon-13 NMR. The management appreciated our viewpoint and sacrificed the meager capital budget for this purchase. Carbon-13 NMR is essential for the efficient characterization of carbohydrate compounds.



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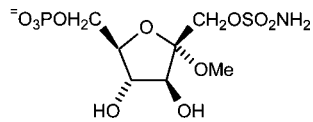


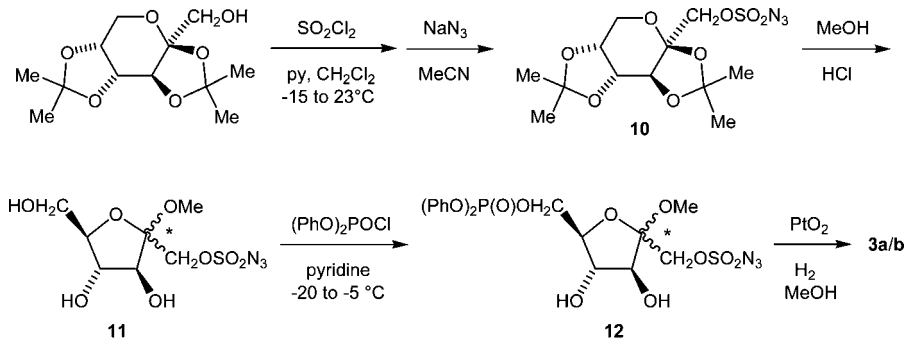
3a (α anomer)

As the lead medicinal chemist on the FBPase inhibitor project, I was expected to come up with the chemical ideas, then synthesize and purify the target molecules. The approach was to use the structural information from substrate-based monosaccharide inhibitors, given the groundwork laid by Steve's published research.[13] These compounds would possess a fructose motif in the furanoside (five-membered ring) format with suitable stereochemistry. One idea was to replace one or two phosphate groups in a prototype structure bearing two phosphate groups (viz. **2**) with sulfamate groups, as isosteres. Although we were worried about the loss of the anionic charges in making this conversion, we did not let such fine details get in the way. After all, we would at least be generating novel, patentable compounds to add to our chemical library for other pharmacological screens. Medicinal chemists in those days commonly pursued chemical lines that just supplied novel molecular entities for general pharmacological screening. So at least there would be a consolation prize for our efforts.

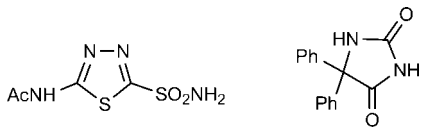
The Big Score. Early on, a target of interest was fructofuranoside-1-sulfamate-6-phosphate **3a** (an α-anomer). I decided to test the chemistry first by employing an *N*,*N*-dimethylsulfamate analogy, which would not pose the potential problem of a reactive SO_2NH_2 group. My research associate, Samuel Nortey, synthesized sulfamate **4**, converted it into methyl fructofuranosides **5** (α/β anomers), introduced a phosphate ester at the 6-position to give **6**, and deprotected the phosphate to yield model compound **7a**/**b** (Scheme 1).[14] This sequence was then applied to the synthesis of **3a**/**b**. Sam prepared **1** and methanolyzed it to methyl fructofuranosides **8**, but attempts to form phosphate ester **9** (en route to **3a**/**b**) were unsuccessful.[14] By installing an azidosulfate group on the 1-position (**10**), we obtained **11**, formed phosphate ester **12**, and produced **3a**/**b**, isolated as a cyclohexylamine salt (Scheme 2).[14] Given the large amounts of the synthetic intermediates on hand, in the spring of 1979 we submitted gram-size samples of sulfamates **1** and **4**, both nice crystalline solids, to the McNeil compound library for biological evaluation.

In those days, library compounds of sufficient quantity were often selected for testing in certain primary animal models that could reflect on possible therapeutic utility. Most of the chemists' compounds were submitted to the collection in the range of 2−5 g, since that quantity would allow for reasonable in vivo examination across the therapeutic categories of interest. Dr. Joseph Gardocki, the head pharmacologist in the CNS area, took an interest in testing **1** for potential anticonvulsant activity. The SO_2NH_2 group suggested to him the sulfonamide that is present in acetazolamide (**13**),[15] a known anticonvulsant. Anticonvulsants, which are generally useful for treating epilepsy, have been identified initially via the MES test in mice. Since

Scheme 2. Synthesis of **3a/b**



antiepileptic drugs were not a priority therapeutic area in McNeil, Joe usually did not perform the MES test as a primary assay. Rather, he used this assay to profile the pharmacological properties of various CNS-active compounds, such as antipsychotics and antidepressants. However, in the case of **1** Joe was very much hoping for something else.



13

14

Joe was an exalted, veteran pharmacologist who rarely visited medicinal chemists in their offices. Occasionally, he would call them down to his office if an interesting result were at hand. But he paid an unexpected visit to me in the autumn of 1979. Joe was very excited about his findings with **1** in the MES test, and he rhapsodized about the compound's potential. Subsequently, he gathered additional data that indicated a profile similar to phenytoin (**14**),[16] a widely prescribed, archetypal antiepileptic drug. Although I was preoccupied with other things and knew that anticonvulsants were not a company priority, Joe's spirited attitude influenced this young, eager medicinal chemist. I had difficulty ignoring such a fortuitous result, and we developed a fruitful working relationship.

Instincts and intuition should never be underestimated in the practice of drug discovery. And Joe's were frequently right on. He acquired more pharmacological data on **1** to position this compound for disclosure to management. However, their reaction was lukewarm, mainly because of reservations relative to business development. The company's business plan simply did not include this therapeutic area because it was not among our important franchises. It occurred to us that we might seek outside support and validation for our novel agent. Thus, an agreement was struck with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS),[17] a branch of the NIH, to investigate this compound. Dr. Harvey Kupferberg, a world-renown expert on antiepileptic agents, received the test substance in June 1981, led its assessment, and expressed strong interest in late 1982. To ignite support for **1**, Joe and I arranged for Harvey to visit McNeil Pharmaceutical, in Spring House, PA, to communicate his findings and viewpoint.

McNeil Pharmaceutical was separated from McNeil Laboratories in 1977−1978 to specialize in prescription medicines, with the other piece becoming McNeil Consumer Products. This business decision was prompted by the fabulous success of Tylenol,[10] our over-the-counter (OTC) product for the management of pain and fever. Around 1977, Bristol-Myers introduced the competing OTC analgesic Datril 500 and mounted a major advertising campaign in print and on television. In TV commercials, their new brand of acetaminophen was supposed to work faster and better than the long-established Tylenol brand. Surprisingly, this head-to-head comparison backfired. McNeil quickly countered the criticism of its regular 250-mg product by introducing an extra-strength (500-mg) product, while the Tylenol brand was receiving free, widespread exposure from the Datril ads. Extra-strength Tylenol became hugely popular, with exploding sales. Perhaps Datril 500 may have suffered from ads that featured John Wayne as a proponent for the headache medicine, since tough guys should not be bothered by such minor pain.[18] Anyway, Johnson & Johnson exercised its legendary wisdom and prowess in the consumer product arena to deflect the challenge. By the spring of 1981, McNeil Pharmaceutical had relocated to a new facility on 170 beautiful acres in Spring House.

The Kupferberg gambit surely struck us as a capital idea. Despite Harvey's vast experience with many anticonvulsant compounds, he considered **1** to be among the *best* that he had ever seen. His opinions carried the day with McNeil management, who became sufficiently impressed to approve a path forward. Consequently, Joe and I organized the data for this compound and made a presentation to management across the various disciplines (at the Research Council) in the summer of 1983, thereby nominating this compound for clinical development. This material was readily synthesized, exhibited a noteworthy pharmacological profile, appeared to be nontoxic, and possessed favorable druglike properties.[18] We got the nod!

To the Market. Although **1** began the long development process in 25th place on the company's priority list of 25 potential products, it rapidly ascended the list and garnered increasing attention. Over time, attrition entered the picture for several higher-priority development projects, while **1** had the staying power to make the top-10 list. The "McN-4853 Development Team", under the leadership of Edith Williams, held its first meeting on May 25, 1984. I was appointed secretary and endured that thankless task for 5 years. Compound **1** proved to be very safe on administration to rats and dogs, forcing us to go to very high doses, as much as 5000 (mg/kg)/day per animal, to detect adverse events. Thus, an abundance of quality drug substance was needed at this stage. Fortunately, its synthesis was short, high-yielding, and economical. A large-scale synthesis involving inexpensive starting materials and reagents (D-fructose, acetone, sulfuric acid, sulfuryl chloride, and ammonia) was eventually developed.[19] Not quite earth, fire, and water but close enough.

At one point, the NIH epilepsy unit[17] was lined up to be a partner with McNeil in conducting clinical studies, but the company eventually decided to proceed on its own. While that course was more costly, it also provided McNeil with greater control. An investigational new drug application (IND) was filed with the U.S. Food and Drug Administration (FDA) in June 1986, the first human volunteer was dosed with **1** in August 1986, and the first epileptic patient was dosed in July 1987. Subsequently, multicenter clinical trials with larger groups of patients were pursued.

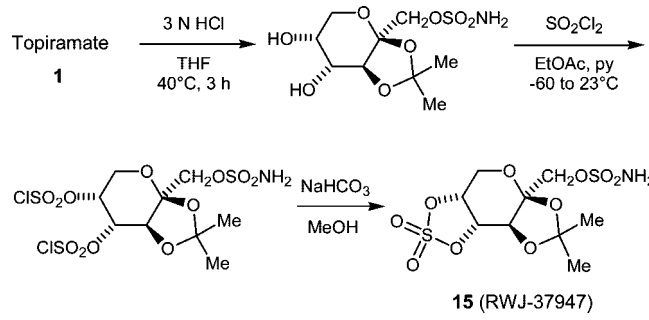
In 1986 the Division of Medicinal Chemistry (MEDI) of the American Chemical Society (ACS) held a symposium on anticonvulsant drugs at the ACS National Meeting in Chicago, IL, and I was one of the speakers. The ACS sponsored a press conference on this topic, and I received permission from McNeil to participate. An atmosphere of excitement permeated the gathering, and some general news services picked up the story. Topiramate (**1**) was described in feature articles in *Medical World News* and *Chemical & Engineering News*. Many epileptic patients or their family members, from all over the country, called my office directly with hopes of obtaining this new medicine. I tried to be calm, collected, and understanding, since topiramate was still a long way from being made available. Obviously, there was an unmet medical need in the community for new antiepileptic drugs, especially those with potential for treating refractory individuals (patients unresponsive to the standard drugs). The last new antiepileptic drug to be introduced into the U.S. market was valproic acid, 8 years earlier (in 1978).

Regulatory filings were submitted to governmental authorities, including the FDA, at the end of 1994. For the U.S. filing of the new drug application (NDA), an 18-wheeler loaded half-full with documents was sent to Washington, DC. The United Kingdom was the first country to confer marketing approval for topiramate, in July 1995, and the FDA came through with approval of the NDA in December 1996. I was pleased to be invited to the official TOPAMAX National Launch Meeting in Scottsdale, AZ, in February 1997. TOPAMAX was introduced to the marketplace as an antiepileptic drug, first for adjunctive therapy and later for monotherapy.[20] There also were clinical trials conducted for other therapeutic indications. A noteworthy result from this clinical effort is topiramate's use in the prophylactic treatment of migraine.[20] Subsequently, numerous clinical researchers and physicians have reported other therapeutic applications.[20]

For Our Next Act. It is natural to seek a backup or follow-up compound in the wake of a clinical candidate. So medicinal chemists try to identify suitable derivatives that might serve this purpose. In the case of topiramate, we also wanted to define the structure−activity relationship further, as our first installment was very limited in scope,[8a] and to protect the chemical space around our intellectual property. Since anticonvulsant medications were not a priority in McNeil, the only medicinal chemists who were preparing molecules for the topiramate project were Sam Nortey and myself. And, I hasten to add, we only worked on a half-time basis because of other project responsibilities. To this day, I am amazed that a billion-dollar molecule could be discovered with such a small amount of medicinal chemistry resources.

In 1987, McNeil's drug discovery unit was absorbed into the Janssen Research Foundation (JRF), a newly created pharma R&D unit under the auspices of the great Dr. Paul A. J. Janssen. As a consequence, we had to cease work on topiramate analogues. However, when my research group became part of the newly formed R. W. Johnson Pharmaceutical Research Institute (RWJPRI) two years later, I was determined to rekindle the project. Drs. Michael Costanzo and Michael Greco joined forces with Sam and me to enhance our medicinal chemistry effort.

Scheme 3. Synthesis of **15**



Mike Costanzo worked on replacing the 4,5-dioxolane ring in **1** with related ring types. One of these analogues contained a sulfur atom in the form of a "cyclic sulfate", such as **15** (RWJ-37947), which was obtained from topiramate (**1**) as depicted in Scheme 3.[21] Compound **15** turned out to be very potent in the MES test with both mice and rats and to have a similar pharmacological profile to topiramate. Indeed, this cyclic sulfate analogue was 8−10 times more potent than topiramate, with a longer duration of action (2−3 times greater in rats). We dubbed this molecule "super-topiramate".

Dr. Richard Shank and I prepared a dossier on **15** to advance this compound for human clinical trials. Richard, a sharp biochemist-cum-pharmacologist, was a strong proponent for its clinical development as an antiepileptic drug and as a neuroprotectant. Interestingly, we received data from an academic collaborator that supported this compound in a neuroprotective capacity (rat model of cerebral ischemia). In the autumn of 1992, Richard and I delivered a presentation to executive management (Research Council) to win entry of **15** into development. However, the compound was rejected because of its lack of differentiation from topiramate. Since its anticonvulsant profile was basically the same as topiramate's, the only clear-cut advantages were markedly increased potency and enhanced duration of action. With topiramate already targeted for once-a-day administration to patients, the second point was not so compelling.

In some drug safety probe studies with **15**, it was found to bind strongly to red blood cells for several days. There was speculation, and concern, that the compound might bind irreversibly with carbonic anhydrase-II (in red blood cells), with the 4,5-cyclic sulfate group facilitating alkylation[22] of the enzyme to form a covalent bond. This adverse finding brought a crisp termination to whatever flickering interest remained, and the anticonvulsant project entered a period of dormancy. About 10 years later, we obtained a crystal structure of the complex formed between carbonic anhydrase-II and **15**, but did not observe any covalent bonds.[23] Sometimes I wonder about this analogue and whether it could have become a second-generation product if given the chance. In this business, we can never know for sure... we just move on.

In November 1997 I was awarded the Johnson Medal for Research & Development, Johnson & Johnson's highest honor, for discovering topiramate. This new-found notoriety brought unexpected attention my way. At a company function in 1998, I was approached by a corporate vice president in business development from Johnson & Johnson headquarters in New Brunswick, NJ, who was very enthused about the commercial

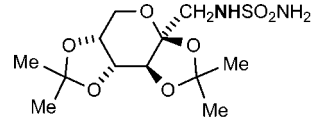
prospects for topiramate. He mentioned that it would be fantastic if I could come up with another compound just like this one. Reluctantly, I had to admit that I only wish I knew how. Without a well-defined molecular mechanism to pursue as a target, it would be difficult to approach discovering new agents of this type. In such a situation, drug design in the true sense is not very feasible, and phenotypic assessment in predictive animal models becomes the order of the day. Besides relying on purely empirical means, coupled with a lot of guesswork, one surely has to get lucky!

Coming Full Circle. Not long after topiramate's market entry, intriguing clinical reports arrived on weight loss and glycemic control in topiramate-treated patients. Of course, one could view such side effects as quite positive, rather than negative. In this respect, meaningful attention, both preclinically and clinically, has been directed at topiramate's potential for treating obesity and type II (noninsulin-dependent) diabetes.[20,24] Interest arose in the company in 2000 as to whether such therapeutic properties could have commercial significance, and various pharmacological and genomics studies were performed. However, the neurological actions of topiramate turned out to be limiting. So we decided to search for a compound that could exert this desirable metabolic action ("antimetabolic dysfunction" activity) more specifically, although it was unclear how to proceed without a distinct molecular target. We considered structurally similar compounds that either would not enter the brain or would not inhibit carbonic anhydrase-II. One idea pertained to the L-enantiomer of topiramate (RWJ-37818, "L-topiramate"),[21] which Mike Costanzo had prepared in 1989, because it was very weak as an anticonvulsant and as an inhibitor of carbonic anhydrase-II. In 2000, chemist Dr. Allen Reitz and CNS biologist Dr. Carlos Plata-Salaman spearheaded this approach, with endocrine biologist Dr. Keith Demarest participating. Since Keith's RWJPRI group in Raritan, NJ, was investigating the metabolic actions of topiramate, he conducted the necessary bioassays to support the desired utility for L-topiramate, or any other compounds. Whereas L-topiramate entered preclinical development in 2001, it did not progress very far because of some adverse toxicology in dogs at elevated doses. Despite this unwelcome event, it was exciting to think that topiramate had come full circle, essentially back to its very origin. That is, an anticonvulsant engendered within a project to find antidiabetic agents in the late 1970s was now perceived to have potential for treating diabetes, but from a completely unexpected direction. What an incredible twist of fate! Clearly, further research in this vein was called for.

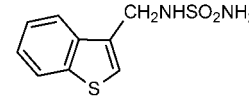
Surprising Sulfamides

Swapping Oxygen for Nitrogen. The sulfamide analogue of topiramate (**16**, RWJ-37082, NH in boldface)[21a] was first prepared in 1987 by Sam Nortey, as a probe of structure vs activity. Even though **16** is a direct isostere of topiramate, it was devoid of anticonvulsant activity and was very weak as an inhibitor of carbonic anhydrase-II.[21a,25] Indeed, we were surprised that such a simple change, from an oxygen atom to an NH group ($-\mathbf{O}SO_2NH_2 \rightarrow -\mathbf{NH}SO_2NH_2$), could cause such a dramatic difference in biological activity. Moreover, **16** did not possess any other CNS activities nor at the time could we detect other useful pharmacology. Thus, we disclosed **16** in our 1998 "magnum opus" in the *Journal of Medicinal Chemistry* to round out the topiramate structure−activity presentation.[21a] Without any utility to support a patent filing, we simply contributed this compound to the public domain.

In our fervor to find topiramate-like antimetabolic dysfunction agents, we selected pharmacologically inert **16** (along with some other compounds) for biological studies. Strangely enough, Keith's group obtained preliminary evidence that this compound exhibits topiramate-like antidiabetic activity. In *db/db* mice, a genetic model of type II diabetes, **16** significantly decreased pathological hyperglycemia in a dose-dependent manner, without affecting body weight. These initial results were noteworthy enough that we assembled a cross-site working group in 2002 to press this issue further, in the new global pharma organization known as Johnson & Johnson Pharmaceutical Research & Development (J&JPRD).



16 (RWJ-37082)



17 (JNJ-26990990)

At first, we synthesized carbohydrate-based sulfamides structurally akin to **16** for biological testing. However, given that we were operating in totally new territory, we decided to pursue simplified sulfamide compounds, with fewer oxygen atoms and less stereochemical complexity. These compounds were screened for an absence of inhibition of carbonic anhydrase-II and then for an absence of CNS behavioral effects. This approach allowed us to be selective with the antidiabetic assays, which are cumbersome because they involve chronic dosing regimes and consume gram quantities of test compounds. To encompass other possible pharmacological opportunities, we also examined compounds in the mouse MES test for anticonvulsant activity.

Silk Purse from Sow's Ear. Unfortunately, the antidiabetic results with sulfamide **16** in animals proved to be irreproducible, so a productive course of action still eluded us. Such confounding situations are encountered more often than one might like in the drug discovery game. To dispel the stench of embarrassment that descended on the project, we swiftly abandoned this compound. Our honor was eventually preserved when we received good news from the MES testing on the simplified sulfamide derivatives. Certain compounds were found to possess worthwhile anticonvulsant activity, thereby providing a potentially fruitful new direction.

At this turning point, we sought to identify broad-spectrum anticonvulsants with a pharmacological profile beyond that of topiramate and even beyond that of currently known antiepileptic drugs. The project was propelled by chemists Dave McComsey and Dr. Michael Parker in collaboration with biologist Dr. Virginia Smith-Swintosky. Because our in-house pharmacology program was missing key animal models to accomplish the goal, we enlisted the assistance of the NINDS[17] and Prof. H. Steve White's laboratory at the University of Utah. Selected novel compounds with suitable activity in the mouse MES test in our laboratories were extensively evaluated as anticonvulsants in the outside laboratories to establish their pharmacological profile and neurotoxicity liability. To overcome some concerns raised by L-topiramate, we needed to perform in vivo tolerability studies at elevated doses in rats and dogs at the outset. This requirement demanded that the first synthesis of the target compounds be at least 5 g. From this effort, two sulfamide derivatives eventually progressed to human clinical studies.[26] One of these molecules is **17** (JNJ-26990990),[26b] but the other cannot be publically disclosed at this time.

Compound **17** exhibited excellent broad-spectrum anticonvulsant activity in rodents against audiogenic, electrically induced, and chemically induced seizures, with very weak

inhibition of human carbonic anhydrase-II (IC_{50} value of 110 μM).[26b] By limiting seizure spread and elevating seizure threshold in preclinical animal models, these compounds promised to be more effective than topiramate (**1**) and several other marketed antiepileptic drugs.[26b] The anticonvulsant profiles and favorable side effect properties of **17** suggest that it may be applicable to treating generalized tonic-clonic, complex partial, and absence seizures, as well as refractory (or pharmacoresistant) epilepsy, at dose levels that allow a good margin of safety (therapeutic index of ≥ 20). The main problem became convincing executive management to move forward with clinical candidates for which we had no clear-cut molecular mechanism(s) of action. It was now the 21st century, and mechanism of action rules. However, a fundamental contradiction exists with such neurostabilizers in that they manifest a complex mixture of different neuronal mechanisms. After considerable review and deliberation, sulfamide **17** was advanced into the development process, while a second sulfamide derivative (not shown) was established as a backup. Although we took great satisfaction from our success with the sulfamide derivatives, especially given the long road traveled, a useful commercial drug is still way off. At this juncture, we can only hope that this recent research will ultimately contribute another important molecule to medicine.

Neurostabilizing Agents

Topiramate, as a broad-spectrum anticonvulsant, turned out to have a robust dimensionality of therapeutic applications beyond the treatment of epilepsy.[20] As mentioned earlier, it also has marketing approval for the prophylaxis of migraine. Moreover, there have been numerous reports in the scientific literature that discuss topiramate's utility in an assortment of CNS conditions, such as eating disorders, alcohol and drug dependence, nerve injury, neuropathies, restless legs syndrome, essential tremor, post-traumatic stress disorder, bipolar disorder, and schizophrenia.[20,27] It is believed that multiple mechanisms of neuronal modulation are responsible for this expanded pharmacology.[20,28] This breadth of CNS-related clinical effects is attributable, at least in part, to the inhibition or stabilization of neuronal hyperexcitability,[9b,29] which has prompted the term "neurostabilizer" or "neurostabilizing agent". This drug class has played an important role in medical practice.

Not Alone in the Universe. Antiepileptic drugs have several pharmacological actions that are responsible for their anticonvulsant and other therapeutic effects. In general, these effects have been categorized into (1) modulation of voltage-gated ion channels, (2) enhancement of neuronal inhibition, and (3) reduction of neuronal excitation.[9b,29a] Nevertheless, other mechanisms, or certain combinations of mechanisms, may contribute to their special qualities. While topiramate has several mechanisms that underpin its action as a neurostabilizing agent,[20] this type of pharmacology is not unique to topiramate. Other antiepileptic drugs have manifested this property,[9b,29,30] with notable examples being gabapentin, valproic acid, lamotrigine, and pregabalin.

Gabapentin, which was introduced into the U.S. market in 1994, is the archetype of this drug category.[31] Although this compound was designed to mimic the inhibitory neurotransmitter γ-aminobutyric acid (GABA), it does not bind directly to GABA receptors in the brain. Rather, gabapentin elevates GABA levels by its effect on a GABA transporter protein. Its noteworthy efficacy in treating neuropathic pain involves decreasing the activity of voltage-gated calcium channels, which is linked to a selective inhibitory effect on calcium channels containing the $\alpha_2\delta$ subunit.[31b] Gabapentin has marketing approval for the treatment of postherpetic neuralgia, but it has also been employed to treat epilepsy and migraine.[31a] Indeed, gabapentin's neurostabilizing actions have been responsible for its therapeutic utility in a range of neurological disorders. The groundbreaking clinical observations with gabapentin engendered widespread appreciation for the diverse therapeutic potential of other broad-spectrum anticonvulsants with neurostabilizing properties.

Pharmaceutical Scope and Impact. Epilepsy is a chronic neurological condition that affects around 1% of the population, which amounts to around 50 million people worldwide.[32] Unfortunately, current medications do not adequately control about 30% of epileptic patients, with 20% suffering from fairly intractable seizures.[32] In seeking next-generation antiepileptic drugs, it has been important to find novel structural classes with broad-spectrum anticonvulsant activity. Interestingly, broad-spectrum anticonvulsants are also effective medications for neuropathic pain and diabetic neuropathy (gabapentin, pregabalin), migraine (topiramate, valproic acid), bipolar disorder (valproic acid, lamotrigine), postherpetic neuraglia (gabapentin, pregabalin), and fibromyalgia (pregabalin).[30] This sizable scope has forged these drugs into powerful therapeutic agents and major revenue generators. As testimony to their widespread utility, the following sales figures were reported in 2007:[33] Depakote (valproate sodium),[33a] $1.5 billion; Lamictal (lamotrigine), £1.1 billion (~$2.2 billion);[33b,34] Lyrica (pregabalin), $1.8 billion; [33c] Neurontin (gabapentin), $0.4 billion;[33c] and TOPAMAX (topiramate), $2.4 billion.[33d] Also, before the patent covering Neurontin (gabapentin) expired, this drug attained peak sales of $2.7 billion in 2004.[35] To be sure, pharmaceutical "gold" was found in them thar neurostabilizers.

Conclusion

TOPAMAX (topiramate), a drug for treating epilepsy and migraine, was derived from a project originally crafted to find an antidiabetic agent. Preclinical and clinical observations have suggested that topiramate possesses antimetabolic dysfunction activity, which could be useful for treating diabetes and obesity. However, the neurological side effects of topiramate pose limitations for chronic therapeutic use in the metabolic arena. With that in mind, we sought to discover agents with topiramate-like antidiabetic and antiobesity actions but without the neurological components. Some leads in this respect were identified and pursued, resulting in the discovery of new broad-spectrum anticonvulsants with therapeutic potential as neurostabilizing agents.

In the execution of drug discovery research, it can be difficult to predict exactly where one will eventually land. For any substantial felicity, such as the discovery and development of a billion-dollar molecule, there is inevitably a chain of events from which no link can be omitted. Key success factors are keen observational powers, effective analysis, flexibility of thought, good common sense, strong determination, and prudent perseverance. I really wish that drug discovery could be much simpler in that a deliberate pathway could be followed toward a well-defined, sought-after end point. On the contrary, history is peppered with examples of accidental or serendipitous discoveries of significant drugs. Unexpected twist and turns.

Many well-intentioned R&D projects succumb to the vicious demon of attrition. Indeed, attrition is pervasive at all stages, from lead generation to preclinical development to human clinical trials. Perversely, fine scientific efforts simply go up in smoke. In that sense, drug discovery can be very frustrating to

the practitioners; yet, these masochists keep coming back for more. Their effusive passion and persistent dedication is a gift to the welfare of humanity.

Acknowledgment. I am truly honored to receive the prestigious Edward E. Smissman Award, which is sponsored by Bristol-Myers Squibb Company. When I joined McNeil Laboratories, Inc., in April 1974, Prof. Smissman served as a company consultant. The researchers at McNeil were very excited to interact with him. I had looked forward to meeting Prof. Smissman, but he died shortly thereafter, on July 14, 1974. Concerning the story at hand, I am indebted to the many excellent scientific colleagues with whom I have collaborated directly over the years. Special thanks go to Samuel O. Nortey, Joseph F. Gardocki, Gene F. Tutwiler, Stephen J. Benkovic, Allen B. Reitz, Michael J. Zelesko, Richard P. Shank, Jeffry L. Vaught, Paulette E. Setler, Michael J. Costanzo, David F. McComsey, Michael N. Greco, Michael H. Parker, Cynthia A. Maryanoff, James J. Schupsky, Susanna P. Dodgson, Virginia L. Smith-Swintosky, Carlos Plata-Salaman, Douglas Brenneman, and Keith T. Demarest. This account is dedicated to my wife, Cyndie, for her sage advice, warm encouragement, and unflinching support.

Biography

Bruce E. Maryanoff earned his B.S. (1969) and Ph.D. (1972) degrees from Drexel University, the latter under the direction of Prof. Robert O. Hutchins. After conducting postdoctoral studies at Princeton University with Prof. Kurt M. Mislow, he joined McNeil Laboratories, a Johnson & Johnson company, in 1974. He advanced to Distinguished Research Fellow, the highest scientific position, and also served as a Team Leader for the past 15 years. Dr. Maryanoff has worked on drugs for central nervous system and cardiovascular disorders and discovered TOPAMAX (topiramate), which is useful for the treatment of epilepsy and migraine. He has published 260 scientific papers and is an inventor on 95 U.S. patents (issued or pending). He has received two ACS national awards, Heroes of Chemistry Award—2000 and Award in Industrial Chemistry—2003, and the 2009 Edward E. Smissman Award from the ACS Division of Medicinal Chemistry. He was inducted into the ACS Division of Medicinal Chemistry Hall of Fame (2008), is a Fellow of the American Association for the Advancement of Science (AAAS), and is a Fellow of the Royal Society of Chemistry.

References

(1) (a) *Nobel Lectures, Physiology or Medicine 1901−1921*; Elsevier: Amsterdam, 1967; http://nobelprize.org/nobel_prizes/medicine/laureates/1908/ehrlich-bio.html (accessed March 2007). (b) Bowden, M. E.; Crow, A. B. *Pharmaceutical Achievers: The Human Face of Pharmaceutical Research*; Chemical Heritage Foundation: Philadelphia, PA, 2005; http://www.chemheritage.org/EducationalServices/pharm/chemo/readings/ehrlich.htm (accessed February 2007). (c) Yarnell, A. Salvarsan. *Chem. Eng. News* **2005**, *83* (25), 116 (issue on The Top Pharmaceuticals that Changed the World; online at http://pubs.acs.org/cen/coverstory/83/8325/8325salvarsan.html; accessed February 2007).

(2) Drews, J. Drug Discovery: A Historical Perspective. *Science* **2000**, *287*, 1960–1963.

(3) (a) Werth, B. *The Billion-Dollar Molecule: One Company's Quest for the Perfect Drug*; Simon & Schuster: New York, 1994. (b) Walsh, V.; Goodman, J. The Billion-Dollar Molecule: Taxol in Historical and Theoretical Perspective. *Clio Med.* **2002**, *66*, 245–267.

(4) Service, R. F. Surviving the Blockbuster Syndrome. *Science* **2004**, *303*, 1796–1799.

(5) Maryanoff, B. E. Adventures in Drug Discovery: Potent Agents Based on Ligands for Cell-Surface Receptors. *Acc. Chem. Res.* **2006**, *39*, 831–840.

(6) (a) For general information on TOPAMAX (topiramate), refer to www.topamax.com. (b) For 2006 sales information on TOPAMAX (topiramate), which is marketed by Ortho-McNeil Neurologics Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., refer to the 2006 Annual Report of Johnson & Johnson (available at http://www.investor.jnj.com/annual-reports.cfm, p 41; accessed in June 2008).

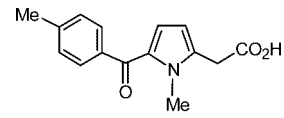
(7) Roberts, R. M. *Serendipity: Accidental Discoveries in Science*; Wiley: New York, 1989.

(8) (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. Anticonvulsant *O*-Alkyl Sulfamates. 2,3:4,5-Bis-*O*-(1-methylethylidene)-beta-D-fructopyranose Sulfamate and Related Compounds. *J. Med. Chem.* **1987**, *30*, 880–887. (b) Shank, R. P.; Gardocki, J. F.; Vaught, J. L.; Davis, C. B.; Schupsky, J. J.; Raffa, R. B.; Dodgson, S. J.; Nortey, S. O.; Maryanoff, B. E. Topiramate: Preclinical Evaluation of a Structurally Novel Anticonvulsant. *Epilepsia* **1994**, *35*, 450–460. (c) Maryanoff, B. E.; Margul, B. L. Topiramate. *Drugs Future* **1989**, *14*, 342–344. (d) Maryanoff, B. E.; Gardocki, J. F. Anticonvulsant Sulfamate Derivatives. U.S. Patent 4,513,006, 1985. This patent was successfully defended in U.S. District Court for the District of New Jersey (Ortho-McNeil Pharmaceutical, Inc. vs Mylan Laboratories Inc., et al.; Civil Action Nos. 04-1689, 06-757, and 06-5166; http://www.orangebookblog.com/files/topamax_opinion.pdf, February 5, 2007; http://www.cafc.uscourts.gov/opinions/07-1223.pdf, March 31, 2008).

(9) (a) For some years, I have had the urge to convey the story of topiramate's discovery and development to the community at large. However, that urge had to be suppressed to shelter the intellectual property. Nowadays, when a proprietary drug product has meaningful market value, generic pharmaceutical houses will attack the key patents in an attempt to invalidate them, usually through some pretext or another. The winning company can acquire a 180-day head start over its competitors in selling the generic version of the branded medicine. To enforce the patent rights, the patent holder must file legal action against the would-be patent infringer for adjudication in a court of law, where any public information that is available can be twisted and bent by the defendant for advantage. Needless to say, one must shy away from contributing any potentially useful ammunition to one's adversary. (b) For insight on agents that attenuate neuronal hyperexcitability (i.e., neurostabilizers), see the following: White, H. S.; Smith, M. D.; Wilcox, K. S. Mechanisms of Action of Antiepileptic Drugs. *Int. Rev. Neurobiol.* **2007**, *81*, 85–110.

(10) (a) Tylenol is Johnson & Johnson's brand of acetaminophen, which is also known as paracetamol and APAP (*N*-acetyl-*p*-aminophenol). (b) For more information on this product, refer to www.tylenol.com.

(11) (a) For information on TOLECTIN, refer to http://www.ortho-mcneil.com/active/janus/en_US/assets/common/company/pi/tolectin.pdf#zoom=100. (b) Carson, J. R.; McKinstry, D. N.; Wong, S. 5-Benzoyl-1-methylpyrrole-2-acetic Acids as Antiinflammatory Agents. *J. Med. Chem.* **1971**, *14*, 646–647. (c) The structure of tolmetin free acid is shown below.



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(12) (a) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. Pyrroloisoquinoline Antidepressants. 2. In-Depth Exploration of Structure−Activity Relationships. *J. Med. Chem.* **1987**, *30*, 1433–1454. Shank, R. P.; Gardocki, J. F.; Schneider, C. R.; Vaught, J. L.; Setler, P. E.; Maryanoff, B. E.; McComsey, D. F. Preclinical Evaluation of McN-5707 as a Potential Antidepressant. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 74–84. Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. Pyrroloisoquinoline Antidepressants. 3. A Focus on Serotonin. *J. Med. Chem.* **1990**, *33*, 2793–2797. Shank, R. P.; Vaught, J. L.; Pelley, K. A.; Setler, P. E.; McComsey, D. F.; Maryanoff, B. E. McN-5652: A Highly Potent Inhibitor of Serotonin Uptake. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1032–1038. Maryanoff, B. E.; Shank, R. P.; Gardocki, J. F. McN-5707 and McN-5652-Z. *Drugs Future* **1986**, *11*, 18–20. (b) For a recent paper on a triple monoamine-uptake inhibitor from this series, see the following: Aluisio, L.; Lord, B.; Barbier, A. J.; Qu, Y.; Fraser, I. C.; Mazur, C.; Wilson, S. J.; Boggs, J.; Pudiak, C. M.; Dvorak, L. K.; Hoey, K.; Everson, A.; Leung, P.; Feinstein, M.; McAllister, H. M.; Tognarelli, D. J.; Letavic, M. A.; Maryanoff, B. E.; Carruthers, N. L.; Bonaventure, P.; Atack, J.; Lovenberg, T. W. In-Vitro and In-Vivo Characterization of JNJ-7925476, a Novel Triple Monoamine Uptake Inhibitor. *Eur. J. Pharmacol.* **2008**, *587*, 141–146. (c) The (+)-enantiomer of McN-5652-Z is a very potent, highly selective inhibitor of serotonin uptake, which became important as a radiolabeled tracer in brain imaging by positron-emission tomography (PET). For example, see the following: Frankle, W. G.; Huang, Y.; Hwang, D.-R.; Talbot, P. S.; Slifstein, M.; van Heertum, R.; Abi-Dargham, A.; Laruelle, M. Comparative Evaluation of Serotonin Transporter Radioligands 11C-DASB and 11C-McN-5652 in Healthy Humans. *J. Nucl. Med.* **2004**, *45*, 682–694.

(13) Benkovic, S. J.; De Maine, M. M.; Kleinschuster, J. J. On the Mechanism of Fructose 1,6-Diphosphatase: Inhibition by Methyl D-Fructoside 1,6-Diphosphate. *Arch. Biochem. Biophys.* **1970**, *139*, 248–251. Benkovic, P. A.; Bullard, W. P.; De Maine, M.; Fishbein, R.; Schray, K. J.; Steffens, J. J.; Benkovic, S. J. Anomeric Specificity of the Alkaline Form of Fructose 1,6-Diphosphatase from Rabbit Liver. *J. Biol. Chem.* **1974**, *249*, 930–931. Frey, W. A.; Fishbein, R.; de Maine, M. M.; Benkovic, S. J. Substrate Form of D-Fructose 1,6-Bisphosphate Utilized by Fructose 1,6-Bisphosphatase. *Biochemistry* **1977**, *16*, 2479–2484. Benkovic, S. J.; Schray, K. J. The Anomeric Specificity of Glycolytic Enzymes. *Adv. Enzymol.* **1976**, *44*, 139–164.

(14) Maryanoff, B. E.; Reitz, A. B.; Nortey, S. O. Synthesis of Phosphate and Phosphate Isosteres of Furanose Sugars as Potential Enzyme Inhibitors. *Tetrahedron* **1988**, *44*, 3093–3106.

(15) (a) Woodbury, D. M. Carbonic Anhydrase Inhibitors. *Adv. Neurol.* **1980**, *27*, 617–633. (b) Woodbury, D. M. Sulfonamides and Derivatives. Acetazolamide. *Antiepileptic Drugs*; Woodbury, D. M., Ed.; Raven Press: New York, 1972; pp 465−475. (c) Millichap, J. G.; Woodbury, D. M.; Goodman, L. S. Mechanism of the Anticonvulsant Action of Acetazole-amide (Diamox), a Carbonic Anhydrase Inhibitor. *J. Pharmacol. Exp. Ther.* **1955**, *115*, 251–258.

(16) (a) Jones, G. L.; Wimbish, G. H.; McIntosh, W. E. Phenytoin: Basic and Clinical Pharmacology. *Med. Res. Rev.* **1983**, *3*, 383–434. (b) Finkel, M. J. Phenytoin Revisited. *Clin. Ther.* **1984**, *6*, 577–591.

(17) The National Institute of Neurological Disorders and Stroke (NINDS), within the NIH.

(18) Roberts, R.; Olson, J. S. *John Wayne: American*; Bison Books: Lincoln, NE, 1997; pp 592−593 (http://www.nebraskapress.unl.edu/bookinfo/3402.html, accessed in March 2007).

(19) Maryanoff, C. A.; Sorgi, K. L.; Scott, L. Preparation of Chlorosulfate and Sulfamate Derivatives of 2,3:4,5-Bis-*O*-(1-methylethylidene)-*β*-D-fructopyranose and (1-Methylcyclohexyl)methanol. Eur. Pat. Appl. EP 533483, 1993. Maryanoff, C. A.; Scott, L.; Sorgi, K. L. Process for the Preparation of Chlorosulfate and Sulfamate Derivatives of 2,3:4,5-Bis-*O*-(1-methylethylidene)-*β*-D-fructopyranose and Cyclohexylmethanol. U.S. Patent 5,387,700, 1995.

(20) Shank, R. P.; Maryanoff, B. E. Molecular Pharmacodynamics, Clinical Therapeutics, and Pharmacokinetics of Topiramate. *CNS Neurosci. Ther.* **2008**, *14*, 120–142.

(21) (a) Maryanoff, B. E.; Costanzo, M. J.; Nortey, S. O.; Greco, M. N.; Shank, R. P.; Schupsky, J. J.; Ortegon, M. E.; Vaught, J. L. Structure−Activity Studies on Anticonvulsant Sugar Sulfamates Related to Topiramate. Enhanced Potency with Cyclic Sulfate Derivatives. *J. Med. Chem.* **1998**, *41*, 1315–1343. (b) Maryanoff, B. E.; Costanzo, M. J. Anticonvulsant Fructopyranose Sulfamate Cyclic Sulfites and Sulfates. U.S. Patent 5,242,942, 1993.

(22) Gao, Y.; Sharpless, K. B. Vicinal Diol Cyclic Sulfates. Like Epoxides Only More Reactive. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.

(23) Recacha, R.; Costanzo, M. J.; Maryanoff, B. E.; Chattopadhyay, D. Crystal Structure of Human Carbonic Anhydrase II Complexed with an Anticonvulsant Sugar Sulphamate. *Biochem. J.* **2002**, *361*, 437–441.

(24) Picard, F.; Deshaies, Y.; Lalonde, J.; Samson, P.; Richard, D. Topiramate Reduces Energy and Fat Gains in Lean (fa/?) and Obese (fa/fa) Zucker Rats. *Obesity Res.* **2000**, *8*, 656–663. Bray, G. A.; Hollander, P.; Klein, S.; Kushner, R.; Levy, B.; Fitchet, M.; Perry, B. H. A 6-Month Randomized, Placebo-Controlled, Dose-Ranging Trial of Topiramate for Weight Loss in Obesity. *Obes. Res.* **2003**, *11*, 722–733. Grady, D. Quest for Weight-Loss Drug Takes an Unusual Turn. *N.Y. Times* **2003**, April 15 (http://query.nytimes.com/gst/fullpage.html?sec= health&res=9906E3DC103BF936A25757C0A9659C8B63; accessed Feb 27, 2007). Liang, Y.; Chen, X.; Osborne, M.; DeCarlo, S. O.; Jetton, T. L.; Demarest, K. Topiramate Ameliorates Hyperglycaemia and Improves Glucose-Stimulated Insulin Release in ZDF Rats and db/db Mice. *Diabetes Obes. Metab.* **2005**, *7*, 360–369. Wilkes, J. J.; Nelson, E.; Osborne, M.; Demarest, K. T.; Olefsky, J. M. Topiramate is an Insulin-sensitizing Compound in Vivo with Direct Effects on Adipocytes in Female ZDF Rats. *Am. J. Physiol.* **2005**, *288* (3, Part 1), E617–E624. Eliasson, B.; Gudbjörnsdottir, S.; Cederholm, J.; Liang, Y.; Vercruysse, F.; Smith, U. Weight Loss and Metabolic Effects of Topiramate in Overweight and Obese Type 2 Diabetic Patients: Randomized Double-Blind Placebo-Controlled Trial. *Int. J. Obes.* **2007**, *31*, 1140–1147. Tremblay, A.; Chaput, J. P.; Berube-Parent, S.; Prud'homme, D.; Leblanc, C.; Almeras, N.; Despres, J. P. The Effect of Topiramate on Energy Balance in Obese Men: A 6-Month Double-Blind Randomized Placebo-Controlled Study with a 6-Month Open-Label Extension. *Eur. J. Clin. Pharmacol.* **2007**, *63*, 123–134.

(25) (a) Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J.; Hochman, C.; Smith-Swintosky, V.; Shank, R. P. Comparison of Sulfamate and Sulfamide Groups for the Inhibition of Carbonic Anhydrase-II by Using Topiramate as a Structural Platform. *J. Med. Chem.* **2005**, *48*, 1941–1947. (b) Klinger, A. L.; McComsey, D. F.; Smith-Swintosky, V.; Shank, R. P.; Maryanoff, B. E. Inhibition of Carbonic Anhydrase-II by Sulfamate and Sulfamide Groups: An Investigation Involving Direct Thermodynamic Binding Measurements. *J. Med. Chem.* **2006**, *49*, 3496–3500. (c) Shank, R. P.; McComsey, D. F.; Smith-Swintosky, V. L.; Maryanoff, B. E. Examination of Two Independent Kinetic Assays for Determining the Inhibition of Carbonic Anhydrases I and II: Structure−Activity Comparison of Sulfamates and Sulfamides. *Chem. Biol. Drug Des.* **2006**, *68*, 113–119. (d) Shank, R. P.; Smith-Swintosky, V. L.; Maryanoff, B. E. Carbonic Anhydrase Inhibition. Insight into the Characteristics of Zonisamide, Topiramate, and the Sulfamide Cognate of Topiramate. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 271–276.

(26) (a) McComsey, D. F.; Parker, M. N.; Reitz, A. B.; Maryanoff, B. E. Preparation of Sulfamates and Sulfamides with Oxygen-Containing Ring Systems Useful for the Treatment of Epilepsy and Related Disorders. PCT Int. Appl. WO 2006007435, 2006. Parker, M. H.; Reitz, A. B.; Maryanoff, B. E. Preparation of Benzo-Fused Heteroaryl Sulfamide Derivatives for the Treatment of Epilepsy and Related Disorders. PCT Int. Appl. WO 2006023861, 2006. McComsey, D. F.; Parker, M. H.; Reitz, A. B.; Maryanoff, B. E. Preparation of Sulfamates and Sulfamides with Oxygen-Containing Ring Systems Useful for the Treatment of Epilepsy and Related Disorders. U.S. Pat. Appl. Publ. US 2005282887, 2005. (b) Parker, M. H.; Smith-Swintosky, V. L.; McComsey, D. F.; Huang, Y.; Brenneman, D.; Klein, B.; Malatynska, E.; Plata-Salaman, C.; White, H. S.; Milewski, M. E.; Herb, M.; Finley, M. F. A.; Liu, Y.; Lubin, M. L.; Qin, N.; Iannucci, R.; Leclercq, L.; Cuyckens, F.; Reitz, A. B.; Maryanoff, B. E. Novel Broad-Spectrum Anticonvulsants Containing a Sulfamide Group: Advancement of *N*-((Benzo[*b*]thien-3-yl)methyl)sulfamide (JNJ-26990990) into Human Clinical Studies. *J. Med. Chem.*, in press.

(27) (a) van Passel, L.; Arif, H.; Hirsch, L. J. Topiramate for the Treatment of Epilepsy and Other Nervous System Disorders. *Expert Rev. Neurother.* **2006**, *6*, 19–31. (b) Tucker, P.; Trautman, R. P.; Wyatt, D. B.; Thompson, J.; Wu, S.-C.; Capece, J. A.; Rosenthal, N. R. Efficacy and Safety of Topiramate Monotherapy in Civilian Posttraumatic Stress Disorder: A Randomized, Double-Blind, Placebo-Controlled Study. *J. Clin. Psychiatry* **2007**, *68*, 201–206. (c) Johnson, B. A.; Capece, J. A.; Wiegand, F.; Mao, L.; Beyers, K.; McKay, A.; Ait-Daoud, N.; Anton, R. F.; Ciraulo, D. A.; Kranzler, H. R.; Mann, K.; O'Malley, S. S.; Swift, R. M. Topiramate for Treating Alcohol Dependence: A Randomized Controlled Trial. *JAMA, J. Am. Med. Assoc.* **2007**, *298*, 1641–1651.

(28) (a) Enhancement of the inhibitory effects of *γ*-aminobutyric acid (GABA);[28b] blockade of excitatory effect of glutamate via non-*N*-methyl-D-aspartate (non-NMDA) receptors;[28c] state-dependent sodium channel blockade;[28d] reduction of calcium channel activity.[28e] (b) Herrero, A. I.; Del Olmo, N.; Gonzalez-Escalada, J. R.; Solis, J. M. Two New Actions of Topiramate: Inhibition of Depolarizing GABA-A-Mediated Responses and Activation of a Potassium Conductance. *Neuropharmacology* **2002**, *42*, 210–220. (c) Skradski, S.; White, H. S. Topiramate Blocks Kainate-Evoked Cobalt Influx into Cultured Neurons. *Epilepsia* **2000**, *41* (Suppl. 1), S45−S47. (d) McLean, M. J.; Bukhari, A. A.; Wamil, A. W. Effects of Topiramate on Sodium-Dependent Action-Potential Firing by Mouse Spinal Cord Neurons in Cell Culture. *Epilepsia* **2000**, *41* (Suppl. 1), S21–S24. (e) Zhang, X.-L.; Velumian, A. A.; Jones, O. T.; Carlen, P. L. Modulation of High-Voltage-Activated Calcium Channels in Dentate Granule Cells by Topiramate. *Epilepsia* **2000**, *41* (Suppl. 1), S52–S60. (f) Waugh, J.; Goa, K. L. Topiramate as Monotherapy in Newly Diagnosed Epilepsy. *CNS Drugs* **2003**, *17*, 985–992. (g) White, H. S. Molecular Pharmacology of Topiramate: Managing Seizures and Preventing Migraine. *Headache* **2005**, *45* (Suppl. 1), S48–S56.

(29) (a) White, H. S. Mechanism(s) of Action of the Antiepileptic Drugs Valproic Acid, Gabapentin, and Topiramate: Implications for Prophylactic Management of Migraine. *Front. Headache Res.* **2004**, *12*, 79–88. (b) Calabresi, P.; Galletti, F.; Rossi, C.; Sarchielli, P.; Cupini, L. M. Antiepileptic Drugs in Migraine: From Clinical Aspects to Cellular Mechanisms. *Trends Pharmacol. Sci.* **2007**, *28*, 188–195. (c) Welch, K. M. Brain Hyperexcitability: The Basis for Antiepileptic Drugs in Migraine Prevention. *Headache* **2005**, *45* (Suppl. 1), S25–S32.

(30) (a) Landmark, C. J. Antiepileptic Drugs in Non-Epilepsy Disorders: Relations between Mechanisms of Action and Clinical Efficacy. *CNS Drugs* **2008**, *22*, 27–47. (b) Ettinger, A. B.; Argoff, C. E. Use of Antiepileptic Drugs for Nonepileptic Conditions: Psychiatric Disorders and Chronic Pain. *Neurotherapeutics* **2007**, *4*, 75–83. (c) Zaremba, P. D.; Bialek, M.; Blaszczyk, B.; Cioczek, P.; Czuczwar, S. J. Non-Epilepsy Uses of Antiepileptic Drugs. *Pharmacol. Rep.* **2006**, *58*, 1–12. (d) Kaniecki, R. Neuromodulators for Migraine Prevention. *Headache* **2008**, *48*, 586–600. (e) Stefan, H.; Feuerstein, T. J. Novel Anticonvulsant Drugs. *Pharmacol. Ther.* **2007**, *113*, 165–183.

(31) (a) http://www.loftusmd.com/Articles/AED/neurontin.html (accessed June 2008). (b) Field, M. J.; Li, Z.; Schwarz, J. B. Ca^{2+} Channel α_2-δ Ligands for the Treatment of Neuropathic Pain. *J. Med. Chem.* **2007**, *50*, 2569–2575.
(32) http://www.who.int/mediacentre/factsheets/fs165/en/ and http://www.ilae.org/docs/GCAEpresentationjec1.ppt (both accessed on November 20, 2008).
(33) (a) The 2007 Annual Report of Abbott. http://phx.corporate-ir.net/phoenix.zhtml?c=94004&p=irol-proxy (p 69; accessed in June 2008). (b) The 2007 Annual Report of GlaxoSmithKline. http://www.gsk.com/investors/reps07/cautionary-report.htm\ (p 37; accessed in June 2008). (c) The 2007 Annual Financial Report of Pfizer Inc. http://www.pfizer.com/investors/financial_reports/financial_report_2007.jsp (p 17; accessed in June 2008). (d) The 2007 Annual Report of Johnson & Johnson. http://www.investor.jnj.com/annual-reports.cfm (p 38; accessed in June 2008).
(34) Based on an exchange rate of about $2.0 (U.S. dollar) per £1.0 (British pound) on July 1, 2007 (http://www.oanda.com/convert/classic; accessed June 2008).
(35) The 2005 Annual Financial Report of Pfizer Inc. http://www.pfizer.com/ investors/financial_reports/financial_report_2005.jsp (p 13; accessed in June 2008).

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